BIOL 440: GENERAL MICROBIOLOGY



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BIOL 440: General Microbiology (Panoutsopoulos)

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Licensing

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1.1.1: Why It Matters- Important Biological Macromolecules

Why learn about the four main classes of important biological macromolecules?

Fad diets: we've all heard about them and maybe followed one or two in our lives. These diets have strict rules, and often have restrictions on eating a certain thing like fats or carbs (carbohydrates).

There are several things to critically consider about this type of diet. First off, is it even possible for a person to cut all carbs out of his or her diet? More importantly, is it actually healthy to remove an entire class of molecules from the diet? Fats aren't really important right? Certainly cholesterol is bad—right?

Before you decide to swear off carbs or fats, you should know that these types of foods are named after the kind of molecules that build them. Then you should learn what they actually do in cells.

Biological macromolecules are large molecules, necessary for life, that are built from smaller organic molecules. There are four major classes of biological macromolecules: carbohydrates, lipids, proteins, and nucleic acids (found in DNA and RNA). Each is an important component of the cell and performs a wide array of functions. Combined, these molecules make up the majority of a cell's mass. Biological macromolecules are organic, meaning that they contain carbon. In addition, they may contain hydrogen, oxygen, nitrogen, phosphorus, sulfur, and additional minor elements. We'll discuss each class and how they compare to each other.

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1.1.2: Carbon

What you'll learn to do: Discuss why it is said that life is carbon-based and the bonding properties of carbon

You've probably heard the term *carbon-based life* thrown about in scientific conversations before. But what exactly does the term mean? Possibly the quickest answer to this question is simply that all living things are reliant on molecules that include carbon. There are no living things on our planet that do not have carbon (however, there are nonliving things made up of carbon as well: e.g, diamonds and, well, carbon itself).

In this outcome we'll learn about the importance of carbon to every living thing on earth and its unique properties that make it particularly suited for its role in living things.

Learning Objectives

Discuss why it is said that life is carbon-based and the bonding properties of carbon.

Carbon

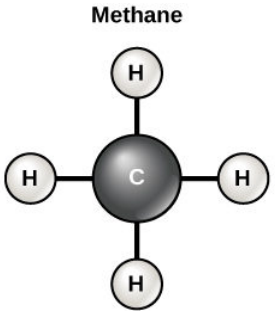


Figure 1. Carbon can form four covalent bonds to create an organic molecule. The simplest carbon molecule is methane (CH_4), depicted here.

Living things are carbon-based because carbon plays such a prominent role in the chemistry of living things. This means that carbon atoms, bonded to other carbon atoms or other elements, form the fundamental components of many, if not most, of the molecules found uniquely in living things. Other elements play important roles in biological molecules, but carbon certainly qualifies as the "foundation" element for molecules in living things. It is the bonding properties of carbon atoms that are responsible for its important role.

Carbon Bonding

The four covalent bonding positions of the carbon atom can give rise to a wide diversity of compounds with many functions, accounting for the importance of carbon in living things.

Carbon contains four electrons in its outer shell. Therefore, it can form four covalent bonds with other atoms or molecules. The simplest organic carbon molecule is methane (CH_4), in which four hydrogen atoms bind to a carbon atom (Figure 1).

However, structures that are more complex are made using carbon. Any of the hydrogen atoms can be replaced with another carbon atom covalently bonded to the first carbon atom. In this way, long and branching chains of carbon compounds can be made (Figure 2**a**). The carbon atoms may bond with atoms of other elements, such as nitrogen, oxygen, and phosphorus (Figure 2**b**). The molecules may also form rings, which themselves can link with other rings (Figure 2**c**). This diversity of molecular forms accounts for the diversity of functions of the biological macromolecules and is based to a large degree on the ability of carbon to form multiple bonds with itself and other atoms.

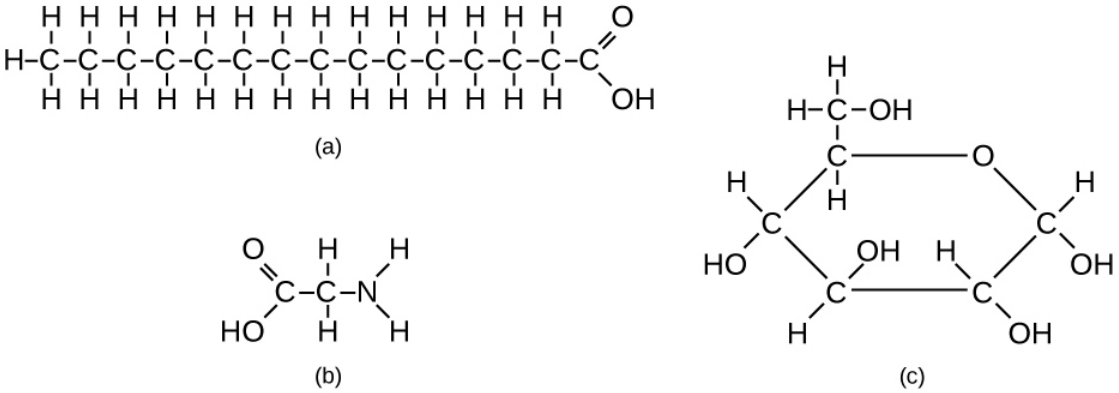


Figure 2. These examples show three molecules (found in living organisms) that contain carbon atoms bonded in various ways to other carbon atoms and the atoms of other elements. (a) This molecule of stearic acid has a long chain of carbon atoms. (b) Glycine, a component of proteins, contains carbon, nitrogen, oxygen, and hydrogen atoms. (c) Glucose, a sugar, has a ring of carbon atoms and one oxygen atom.

Check Your Understanding

Answer the question(s) below to see how well you understand the topics covered in the previous section. This short quiz does **not** count toward your grade in the class, and you can retake it an unlimited number of times.

Use this quiz to check your understanding and decide whether to (1) study the previous section further or (2) move on to the next section.

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1.1.3: Carbohydrates

What you'll learn to do: Summarize the roles carbohydrates play in biological systems

Are carbohydrates good for you? People who wish to lose weight are often told that carbohydrates are bad for them and should be avoided. Some diets completely forbid carbohydrate consumption, claiming that a low-carbohydrate diet helps people to lose weight faster. However, carbohydrates have been an important part of the human diet for thousands of years; artifacts from ancient civilizations show the presence of wheat, rice, and corn in our ancestors' storage areas.

Carbohydrates should be supplemented with proteins, vitamins, and fats to be parts of a well-balanced diet. Calorie-wise, a gram of carbohydrate provides 4.3 Kcal. For comparison, fats provide 9 Kcal/g, a less desirable ratio. Carbohydrates contain soluble and insoluble elements; the insoluble part is known as fiber, which is mostly cellulose. Fiber has many uses; it promotes regular bowel movement by adding bulk, and it regulates the rate of consumption of blood glucose. Fiber also helps to remove excess cholesterol from the body. In addition, a meal containing whole grains and vegetables gives a feeling of fullness. As an immediate source of energy, glucose is broken down during the process of cellular respiration, which produces ATP, the energy currency of the cell. Without the consumption of carbohydrates, the availability of "instant energy" would be reduced.

Eliminating carbohydrates from the diet is not the best way to lose weight. A low-calorie diet that is rich in whole grains, fruits, vegetables, and lean meat, together with plenty of exercise and plenty of water, is the more sensible way to lose weight.

Learning Objectives

- Distinguish between monosaccharides, disaccharides, and polysaccharides
- Identify several major functions of carbohydrates

Most people are familiar with carbohydrates, one type of macromolecule, especially when it comes to what we eat. To lose weight, some individuals adhere to "low-carb" diets. Athletes, in contrast, often "carb-load" before important competitions to ensure that they have enough energy to compete at a high level. Carbohydrates are, in fact, an essential part of our diet; grains, fruits, and vegetables are all natural sources of carbohydrates. Carbohydrates provide energy to the body, particularly through glucose, a simple sugar that is a component of starch and an ingredient in many staple foods. Carbohydrates also have other important functions in humans, animals, and plants.

Molecular Structures

Carbohydrates can be represented by the formula $(CH_2O)_n$, where n is the number of carbons in the molecule. In other words, the ratio of carbon to hydrogen to oxygen is 1:2:1 in carbohydrate molecules. This formula also explains the origin of the term "carbohydrate": the components are carbon ("carbo") and the components of water (hence, "hydrate"). Carbohydrates are classified into three subtypes: monosaccharides, disaccharides, and polysaccharides.

Monosaccharides

Monosaccharides (*mono–* = "one"; *sacchar–* = "sweet") are simple sugars, the most common of which is glucose. In monosaccharides, the number of carbons usually ranges from three to seven. Most monosaccharide names end with the suffix *–ose*. If the sugar has an aldehyde group (the functional group with the structure R-CHO), it is known as an aldose, and if it has a ketone group (the functional group with the structure RC(=O)R′), it is known as a ketose. Depending on the number of carbons in the sugar, they also may be known as trioses (three carbons), pentoses (five carbons), and or hexoses (six carbons). See Figure 1 for an illustration of the monosaccharides.

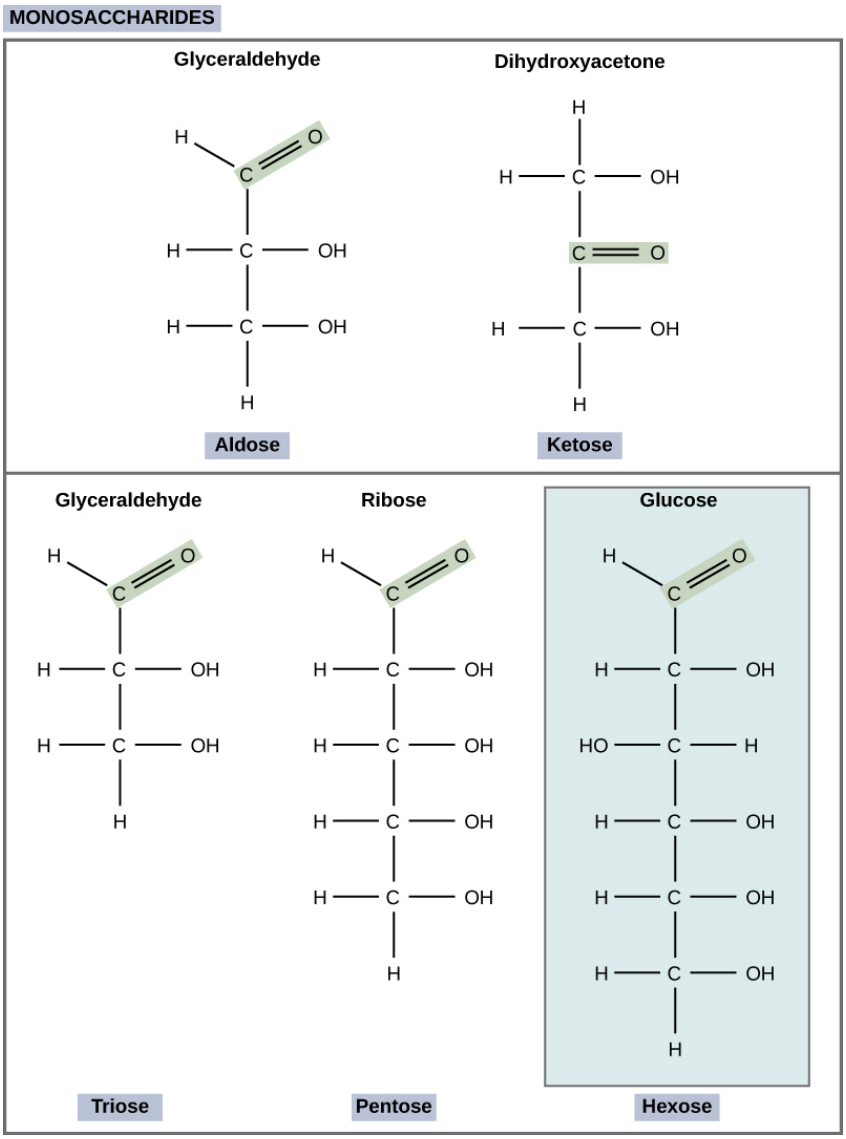


Figure 1. Monosaccharides are classified based on the position of their carbonyl group and the number of carbons in the backbone. Aldoses have a carbonyl group (indicated in green) at the end of the carbon chain, and ketoses have a carbonyl group in the middle of the carbon chain. Trioses, pentoses, and hexoses have three, five, and six carbon backbones, respectively.

The chemical formula for glucose is $C_6H_{12}O_6$. In humans, glucose is an important source of energy. During cellular respiration, energy is released from glucose, and that energy is used to help make adenosine triphosphate (ATP). Plants synthesize glucose using carbon dioxide and water, and glucose in turn is used for energy requirements for the plant. Excess glucose is often stored as starch that is catabolized (the breakdown of larger molecules by cells) by humans and other animals that feed on plants.

Galactose and fructose are other common monosaccharides — galactose is found in milk sugars and fructose is found in fruit sugars. Although glucose, galactose, and fructose all have the same chemical formula ($C_6H_{12}O_6$), they differ structurally and chemically (and are known as isomers) because of the different arrangement of functional groups around the asymmetric carbon; all of these monosaccharides have more than one asymmetric carbon.

Monosaccharides can exist as a linear chain or as ring-shaped molecules; in aqueous solutions they are usually found in ring forms.

Disaccharides

Disaccharides (*di–* = "two") form when two monosaccharides undergo a dehydration reaction (also known as a condensation reaction or dehydration synthesis). During this process, the hydroxyl group of one monosaccharide combines with the hydrogen of another monosaccharide, releasing a molecule of water and forming a covalent bond (Figure 2).

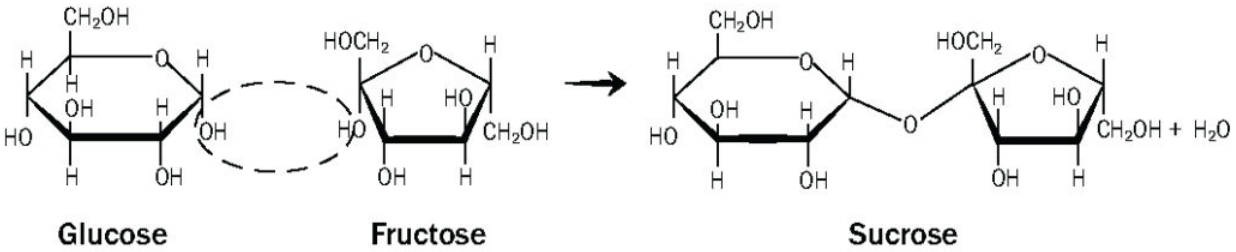


Figure 2. Sucrose is produced from the chemical reaction between two simple sugars called glucose and fructose.

Common disaccharides include lactose, maltose, and sucrose. Lactose is a disaccharide consisting of the monomers glucose and galactose. It is found naturally in milk. Maltose, or malt sugar, is a disaccharide formed by a dehydration reaction between two glucose molecules. The most common disaccharide is sucrose, or table sugar, which is composed of the monomers glucose and fructose.

Polysaccharides

A long chain of monosaccharides linked by covalent bonds is known as a polysaccharide (*poly–* = “many”). The chain may be branched or unbranched, and it may contain different types of monosaccharides. Polysaccharides may be very large molecules. Starch, glycogen, cellulose, and chitin are examples of polysaccharides.

Starch is the stored form of sugars in plants and is made up of amylose and amylopectin (both polymers of glucose). Plants are able to synthesize glucose, and the excess glucose is stored as starch in different plant parts, including roots and seeds. The starch that is consumed by animals is broken down into smaller molecules, such as glucose. The cells can then absorb the glucose.

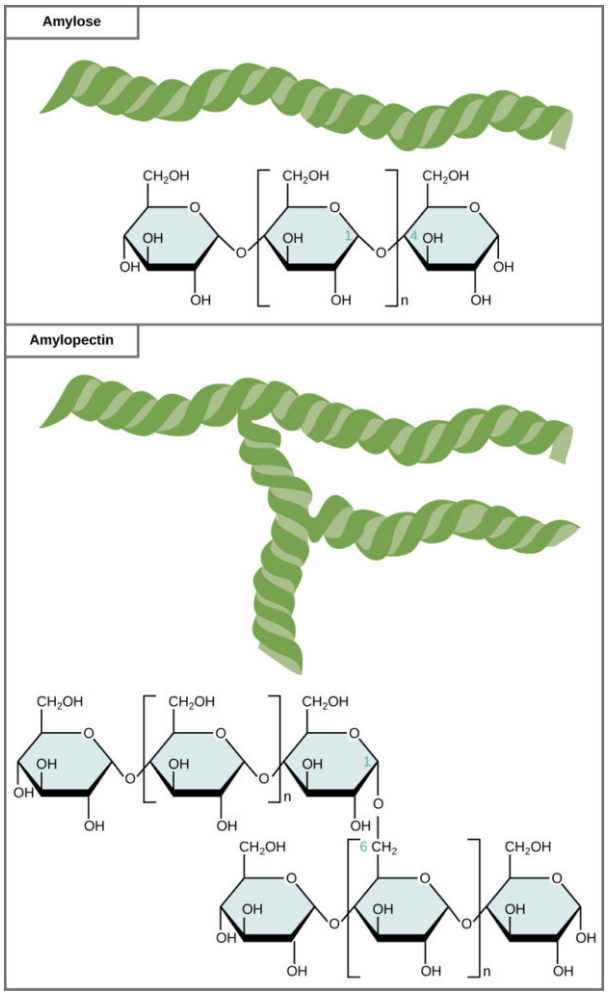


Figure 3. Amylose and amylopectin are two different forms of starch. Glycogen is the storage form of glucose in humans and other vertebrates and is made up of monomers of glucose.

Glycogen is the storage form of glucose in humans and other vertebrates, and is made up of monomers of glucose. Glycogen is the animal equivalent of starch and is a highly branched molecule usually stored in liver and muscle cells. Whenever glucose levels decrease, glycogen is broken down to release glucose.

Cellulose is one of the most abundant natural biopolymers. The cell walls of plants are mostly made of cellulose, which provides structural support to the cell. Wood and paper are mostly cellulosic in nature. Cellulose is made up of glucose monomers that are linked by bonds between particular carbon atoms in the glucose molecule.

Every other glucose monomer in cellulose is flipped over and packed tightly as extended long chains. This gives cellulose its rigidity and high tensile strength—which is so important to plant cells. Cellulose passing through our digestive system is called dietary fiber. While the glucose-glucose bonds in cellulose cannot be broken down by human digestive enzymes, herbivores such as cows, buffalos, and horses are able to digest grass that is rich in cellulose and use it as a food source. In these animals, certain species of bacteria reside in the rumen (part of the digestive system of herbivores) and secrete the enzyme cellulase. The appendix also contains bacteria that break down cellulose, giving it an important role in the digestive systems of ruminants. Cellulases can break down cellulose into glucose monomers that can be used as an energy source by the animal.

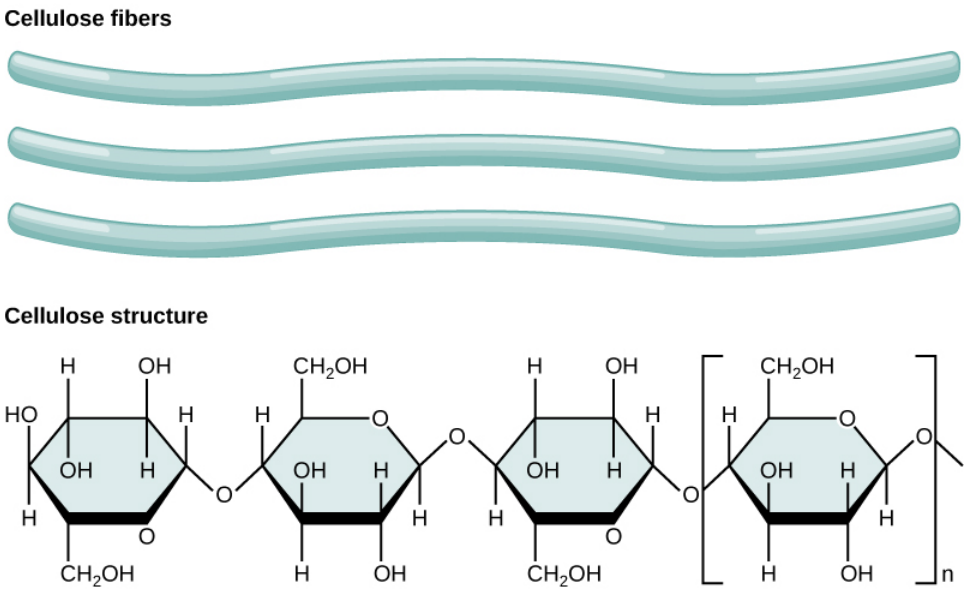


Figure 4. In cellulose, glucose monomers are linked in unbranched chains by β 1-4 glycosidic linkages. Because of the way the glucose subunits are joined, every glucose monomer is flipped relative to the next one resulting in a linear, fibrous structure.



Figure 5. Insects have a hard outer exoskeleton made of chitin, a type of polysaccharide.

As shown in Figure 4, every other glucose monomer in cellulose is flipped over, and the monomers are packed tightly as extended long chains. This gives cellulose its rigidity and high tensile strength—which is so important to plant cells.

Carbohydrates serve other functions in different animals. Arthropods, such as insects, spiders, and crabs, have an outer skeleton, called the exoskeleton, which protects their internal body parts. This exoskeleton is made of the biological macromolecule chitin, which is a nitrogenous carbohydrate. It is made of repeating units of a modified sugar containing nitrogen.

? Try It

Obesity is a worldwide health concern, and many diseases, such as diabetes and heart disease, are becoming more prevalent because of obesity. This is one of the reasons why registered dietitians are increasingly sought after for advice. Registered dietitians help plan food and nutrition programs for individuals in various settings. They often work with patients in health-care facilities, designing nutrition plans to prevent and treat diseases. For example, dietitians may teach a patient with diabetes how to manage blood-sugar levels by eating the correct types and amounts of carbohydrates. Dietitians may also work in nursing homes, schools, and private practices.

To become a registered dietitian, one needs to earn at least a bachelor's degree in dietetics, nutrition, food technology, or a related field. In addition, registered dietitians must complete a supervised internship program and pass a national exam. Those who pursue careers in dietetics take courses in nutrition, chemistry, biochemistry, biology, microbiology, and human physiology. Dietitians must become experts in the chemistry and functions of food (proteins, carbohydrates, and fats).



Figure 6. Registered Dietitian Nutritionist (RDN) Chef Brenda Thompson works with foodservice staff to assemble her breakfast burrito recipe during the chef designed school taste testing in Idaho. Thanks to a U.S. Department of Agriculture (USDA) Team Nutrition grant RDN Chef Brenda Thompson, developed recipes for the Chef Designed School Lunch cookbook.

Learning Objectives

Carbohydrates are a group of macromolecules that are a vital energy source for the cell and provide structural support to plant cells, fungi, and all of the arthropods that include lobsters, crabs, shrimp, insects, and spiders. Carbohydrates are classified as monosaccharides, disaccharides, and polysaccharides depending on the number of monomers in the molecule. Monosaccharides are linked by glycosidic bonds that are formed as a result of dehydration reactions, forming disaccharides and polysaccharides with the elimination of a water molecule for each bond formed. Glucose, galactose, and fructose are common monosaccharides, whereas common disaccharides include lactose, maltose, and sucrose. Starch and glycogen, examples of polysaccharides, are the storage forms of glucose in plants and animals, respectively. The long polysaccharide chains may be branched or unbranched. Cellulose is an example of an unbranched polysaccharide, whereas amylopectin, a constituent of starch, is a highly branched molecule. Storage of glucose, in the form of polymers like starch of glycogen, makes it slightly less accessible for metabolism; however, this prevents it from leaking out of the cell or creating a high osmotic pressure that could cause excessive water uptake by the cell.

Check Your Understanding

Answer the question(s) below to see how well you understand the topics covered in the previous section. This short quiz does **not** count toward your grade in the class, and you can retake it an unlimited number of times.

Use this quiz to check your understanding and decide whether to (1) study the previous section further or (2) move on to the next section.

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1.1.4: Lipids

What you'll learn to do: Illustrate different types of lipids and relate their structure to their role in biological systems

Fats and oils are probably the type of lipid that you're most familiar with in your everyday life. The word *fat* typically brings up a negative picture in our minds. In diets, we're advised to stay away from fatty foods. However, our bodies require some fat in order to survive. There are also other lipids essential to human life, including phospholipids, steroids, and waxes.

While an excess of any substance can be a problem, all of these lipids play essential roles in living things.

In this outcome, we will discuss lipids and the role they plan in our bodies.

Learning Objectives

- Distinguish between the different kinds of lipids
- Identify several major functions of lipids



Figure 1. Hydrophobic lipids in the fur of aquatic mammals, such as this river otter, protect them from the elements. (credit: Ken Bosma)

Lipids include a diverse group of compounds that are largely nonpolar in nature. This is because they are hydrocarbons that include mostly nonpolar carbon–carbon or carbon–hydrogen bonds. Non-polar molecules are hydrophobic ("water fearing"), or insoluble in water. Lipids perform many different functions in a cell. Cells store energy for long-term use in the form of fats. Lipids also provide insulation from the environment for plants and animals (Figure 1). For example, they help keep aquatic birds and mammals dry when forming a protective layer over fur or feathers because of their water-repellant hydrophobic nature. Lipids are also the building blocks of many hormones and are an important constituent of all cellular membranes. Lipids include fats, oils, waxes, phospholipids, and steroids.

Fats and Oils

A fat molecule, such as a triglyceride, consists of two main components—glycerol and fatty acids. Glycerol is an organic compound with three carbon atoms, five hydrogen atoms, and three hydroxyl (–OH) groups. Fatty acids have a long chain of hydrocarbons to which an acidic carboxyl group is attached, hence the name "fatty acid." The number of carbons in the fatty acid may range from 4 to 36; most common are those containing 12–18 carbons. In a fat molecule, a fatty acid is attached to each of the three oxygen atoms in the –OH groups of the glycerol molecule with a covalent bond (Figure 2).

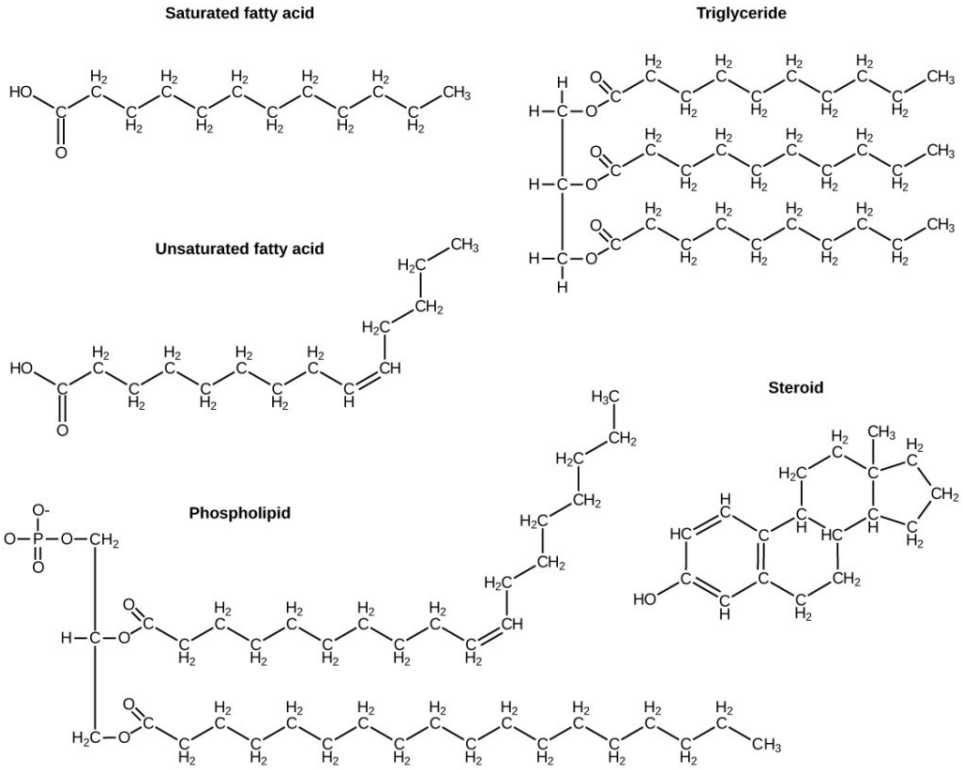


Figure 2. Lipids include fats, such as triglycerides, which are made up of fatty acids and glycerol, phospholipids, and steroids.

During this covalent bond formation, three water molecules are released. The three fatty acids in the fat may be similar or dissimilar. These fats are also called triglycerides because they have three fatty acids. Some fatty acids have common names that specify their origin. For example, palmitic acid, a saturated fatty acid, is derived from the palm tree. Arachidic acid is derived from *Arachis hypogaea*, the scientific name for peanuts.

Fatty acids may be saturated or unsaturated. In a fatty acid chain, if there are only single bonds between neighboring carbons in the hydrocarbon chain, the fatty acid is saturated. Saturated fatty acids are saturated with hydrogen; in other words, the number of hydrogen atoms attached to the carbon skeleton is maximized.

When the hydrocarbon chain contains a double bond, the fatty acid is an unsaturated fatty acid.

Most unsaturated fats are liquid at room temperature and are called oils. If there is one double bond in the molecule, then it is known as a monounsaturated fat (e.g., olive oil), and if there is more than one double bond, then it is known as a polyunsaturated fat (e.g., canola oil).

Saturated fats tend to get packed tightly and are solid at room temperature. Animal fats with stearic acid and palmitic acid contained in meat, and the fat with butyric acid contained in butter, are examples of saturated fats. Mammals store fats in specialized cells called adipocytes, where globules of fat occupy most of the cell. In plants, fat or oil is stored in seeds and is used as a source of energy during embryonic development.

Unsaturated fats or oils are usually of plant origin and contain unsaturated fatty acids. The double bond causes a bend or a “kink” that prevents the fatty acids from packing tightly, keeping them liquid at room temperature. Olive oil, corn oil, canola oil, and cod liver oil are examples of unsaturated fats. Unsaturated fats help to improve blood cholesterol levels, whereas saturated fats contribute to plaque formation in the arteries, which increases the risk of a heart attack.

Margarine, some types of peanut butter, and shortening are examples of artificially hydrogenated *trans*-fats. Recent studies have shown that an increase in *trans*-fats in the human diet may lead to an increase in levels of low-density lipoprotein (LDL), or “bad” cholesterol, which, in turn, may lead to plaque deposition in the arteries, resulting in heart disease. Many fast food restaurants have recently eliminated the use of *trans*-fats, and U.S. food labels are now required to list their *trans*-fat content.In the food industry, oils are artificially hydrogenated to make them semi-solid, leading to less spoilage and increased shelf life. Simply speaking,

hydrogen gas is bubbled through oils to solidify them. During this hydrogenation process, double bonds of the *cis*-conformation in the hydrocarbon chain may be converted to double bonds in the *trans*-conformation. This forms a *trans*-fat from a *cis*-fat. The orientation of the double bonds affects the chemical properties of the fat (Figure 3).

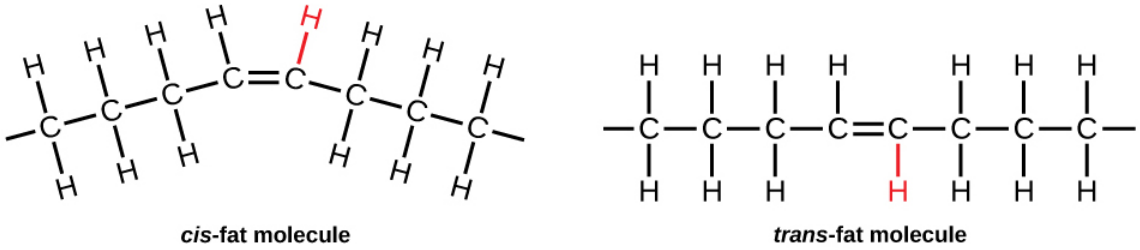


Figure 3. During the hydrogenation process, the orientation around the double bonds is changed, making a trans-fat from a cis-fat. This changes the chemical properties of the molecule.

Essential fatty acids are fatty acids that are required but not synthesized by the human body. Consequently, they must be supplemented through the diet. Omega-3 fatty acids fall into this category and are one of only two known essential fatty acids for humans (the other being omega-6 fatty acids). They are a type of polyunsaturated fat and are called omega-3 fatty acids because the third carbon from the end of the fatty acid participates in a double bond.

Salmon, trout, and tuna are good sources of omega-3 fatty acids. Omega-3 fatty acids are important in brain function and normal growth and development. They may also prevent heart disease and reduce the risk of cancer.

Like carbohydrates, fats have received a lot of bad publicity. It is true that eating an excess of fried foods and other “fatty” foods leads to weight gain. However, fats do have important functions. Fats serve as long-term energy storage. They also provide insulation for the body. Therefore, “healthy” unsaturated fats in moderate amounts should be consumed on a regular basis.

Phospholipids

Phospholipids are the major constituent of the plasma membrane. Like fats, they are composed of fatty acid chains attached to a glycerol or similar backbone. Instead of three fatty acids attached, however, there are two fatty acids and the third carbon of the glycerol backbone is bound to a phosphate group. The phosphate group is modified by the addition of an alcohol.

A phospholipid has both hydrophobic and hydrophilic regions. The fatty acid chains are hydrophobic and exclude themselves from water, whereas the phosphate is hydrophilic and interacts with water.

Cells are surrounded by a membrane, which has a bilayer of phospholipids. The fatty acids of phospholipids face inside, away from water, whereas the phosphate group can face either the outside environment or the inside of the cell, which are both aqueous.

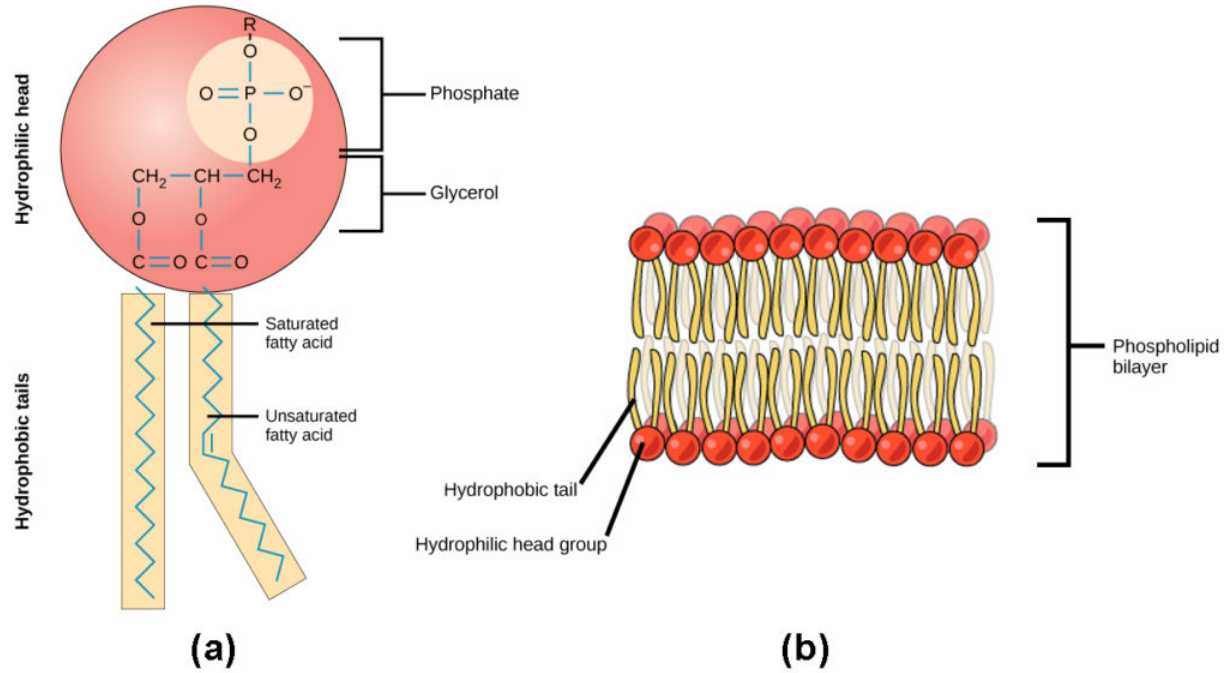


Figure 4. (a) A phospholipid is a molecule with two fatty acids and a modified phosphate group attached to a glycerol backbone. The phosphate may be modified by the addition of charged or polar chemical groups. Two chemical groups that may modify the phosphate, choline and serine, are shown here. Both choline and serine attach to the phosphate group at the position labeled R. (b) The phospholipid bilayer is the major component of all cellular membranes. The hydrophilic head groups of the phospholipids face the aqueous solution. The hydrophobic tails are sequestered in the middle of the bilayer.

Steroids and Waxes

Unlike the phospholipids and fats discussed earlier, steroids have a ring structure. Although they do not resemble other lipids, they are grouped with them because they are also hydrophobic. All steroids have four, linked carbon rings and several of them, like cholesterol, have a short tail.

Cholesterol is a steroid. Cholesterol is mainly synthesized in the liver and is the precursor of many steroid hormones, such as testosterone and estradiol. It is also the precursor of vitamins E and K. Cholesterol is the precursor of bile salts, which help in the breakdown of fats and their subsequent absorption by cells. Although cholesterol is often spoken of in negative terms, it is necessary for the proper functioning of the body. It is a key component of the plasma membranes of animal cells.

Waxes are made up of a hydrocarbon chain with an alcohol (–OH) group and a fatty acid. Examples of animal waxes include beeswax and lanolin. Plants also have waxes, such as the coating on their leaves, that helps prevent them from drying out.

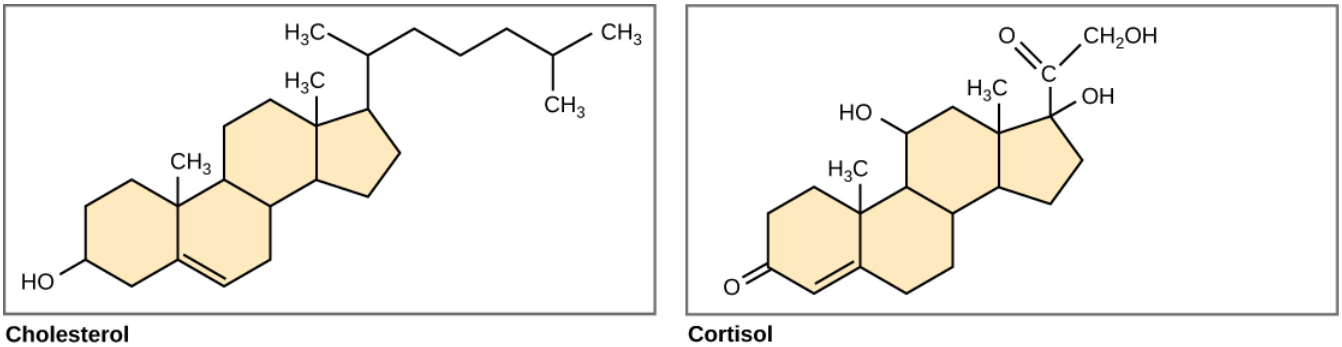


Figure 5. Steroids such as cholesterol and cortisol are composed of four fused hydrocarbon rings

For an additional perspective on lipids, explore this interactive animation.

Learning Objectives

Lipids are a class of macromolecules that are nonpolar and hydrophobic in nature. Major types include fats and oils, waxes, phospholipids, and steroids. Fats are a stored form of energy and are also known as triacylglycerols or triglycerides. Fats are made up of fatty acids and either glycerol or sphingosine. Fatty acids may be unsaturated or saturated, depending on the presence or absence of double bonds in the hydrocarbon chain. If only single bonds are present, they are known as saturated fatty acids. Unsaturated fatty acids may have one or more double bonds in the hydrocarbon chain. Phospholipids make up the matrix of membranes. They have a glycerol or sphingosine backbone to which two fatty acid chains and a phosphate-containing group are attached. Steroids are another class of lipids. Their basic structure has four fused carbon rings. Cholesterol is a type of steroid and is an important constituent of the plasma membrane, where it helps to maintain the fluid nature of the membrane. It is also the precursor of steroid hormones such as testosterone.

Check Your Understanding

Answer the question(s) below to see how well you understand the topics covered in the previous section. This short quiz does **not** count toward your grade in the class, and you can retake it an unlimited number of times.

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1.1.5: Proteins

What you'll learn to do: Describe the structure and function proteins

Proteins are polymers of amino acids. Each amino acid contains a central carbon, a hydrogen, a carboxyl group, an amino group, and a variable R group. The R group specifies which class of amino acids it belongs to: electrically charged hydrophilic side chains, polar but uncharged side chains, nonpolar hydrophobic side chains, and special cases.

Proteins have different "layers" of structure: primary, secondary, tertiary, quaternary.

Proteins have a variety of function in cells. Major functions include acting as enzymes, receptors, transport molecules, regulatory proteins for gene expression, and so on. Enzymes are biological catalysts that speed up a chemical reaction without being permanently altered. They have "active sites" where the substrate/reactant binds, and they can be either activated or inhibited (competitive and/or noncompetitive inhibitors).

Learning Objectives

- Identify the component parts of proteins
- Define the different layers of protein structure
- Identify several major functions of proteins

Components of Proteins

Proteins are one of the most abundant organic molecules in living systems and have the most diverse range of functions of all macromolecules. Proteins may be structural, regulatory, contractile, or protective; they may serve in transport, storage, or membranes; or they may be toxins or enzymes. Each cell in a living system may contain thousands of different proteins, each with a unique function. Their structures, like their functions, vary greatly. They are all, however, polymers of amino acids, arranged in a linear sequence.

Proteins have different shapes and molecular weights; some proteins are globular in shape whereas others are fibrous in nature. For example, hemoglobin is a globular protein, but collagen, found in our skin, is a fibrous protein. Protein shape is critical to its function. Changes in temperature, pH, and exposure to chemicals may lead to permanent changes in the shape of the protein, leading to a loss of function or denaturation (to be discussed in more detail later). All proteins are made up of different arrangements of the same 20 kinds of amino acids.

Amino acids are the monomers that make up proteins. Each amino acid has the same fundamental structure, which consists of a central carbon atom bonded to an amino group ($–NH_2$), a carboxyl group (–COOH), and a hydrogen atom. Every amino acid also has another variable atom or group of atoms bonded to the central carbon atom known as the R group. The R group is the only difference in structure between the 20 amino acids; otherwise, the amino acids are identical.

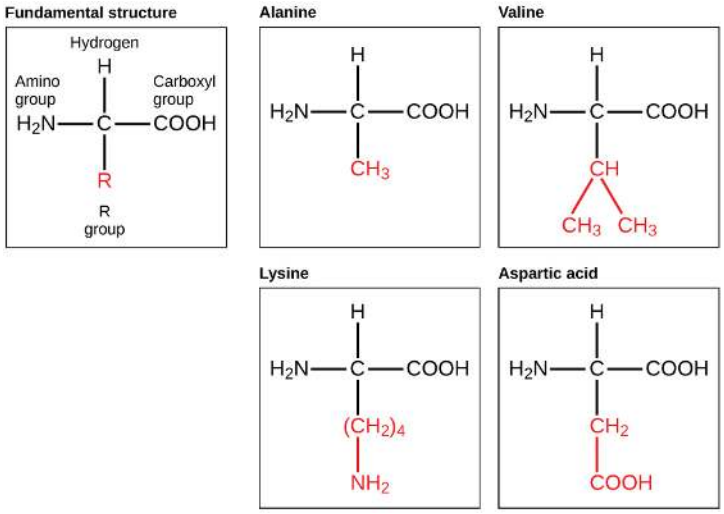


Figure 1. Amino acids are made up of a central carbon bonded to an amino group ($–NH_2$), a carboxyl group (–COOH), and a hydrogen atom. The central carbon's fourth bond varies among the different amino acids, as seen in these examples of alanine, valine, lysine, and aspartic acid.

The chemical nature of the R group determines the chemical nature of the amino acid within its protein (that is, whether it is acidic, basic, polar, or nonpolar).

The sequence and number of amino acids ultimately determine a protein's shape, size, and function. Each amino acid is attached to another amino acid by a covalent bond, known as a peptide bond, which is formed by a dehydration reaction. The carboxyl group of one amino acid and the amino group of a second amino acid combine, releasing a water molecule. The resulting bond is the peptide bond.

The products formed by such a linkage are called polypeptides. While the terms polypeptide and protein are sometimes used interchangeably, a **polypeptide** is technically a polymer of amino acids, whereas the term protein is used for a polypeptide or polypeptides that have combined together, have a distinct shape, and have a unique function.

? Try It

Cytochrome c is an important component of the electron transport chain, a part of cellular respiration, and it is normally found in the cellular organelle, the mitochondrion. This protein has a heme prosthetic group, and the central ion of the heme gets alternately reduced and oxidized during electron transfer. Because this essential protein's role in producing cellular energy is crucial, it has changed very little over millions of years. Protein sequencing has shown that there is a considerable amount of cytochrome c amino acid sequence homology, or similarity, among different species — in other words, evolutionary kinship can be assessed by measuring the similarities or differences among various species' DNA or protein sequences.

Scientists have determined that human cytochrome c contains 104 amino acids. For each cytochrome c molecule from different organisms that has been sequenced to date, 37 of these amino acids appear in the same position in all samples of cytochrome c. This indicates that there may have been a common ancestor. On comparing the human and chimpanzee protein sequences, no sequence difference was found. When human and rhesus monkey sequences were compared, the single difference found was in one amino acid. In another comparison, human to yeast sequencing shows a difference in the 44th position.

Protein Structure

As discussed earlier, the shape of a protein is critical to its function. To understand how the protein gets its final shape or conformation, we need to understand the four levels of protein structure: primary, secondary, tertiary, and quaternary (Figure 3).

The unique sequence and number of amino acids in a polypeptide chain is its primary structure. The unique sequence for every protein is ultimately determined by the gene that encodes the protein. Any change in the gene sequence may lead to a different amino acid being added to the polypeptide chain, causing a change in protein structure and function. In sickle cell anemia, the hemoglobin β chain has a single amino acid substitution, causing a change in both the structure and function of the protein. What is

most remarkable to consider is that a hemoglobin molecule is made up of two alpha chains and two beta chains that each consist of about 150 amino acids. The molecule, therefore, has about 600 amino acids. The structural difference between a normal hemoglobin molecule and a sickle cell molecule—that dramatically decreases life expectancy—is a single amino acid of the 600.

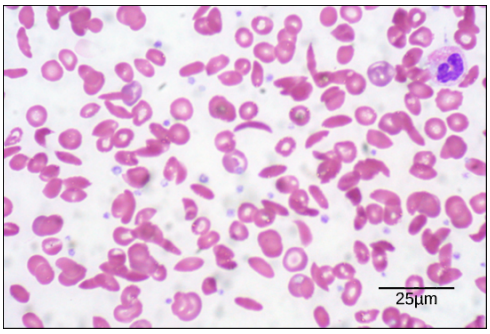


Figure 2. In this blood smear, visualized at 535x magnification using bright field microscopy, sickle cells are crescent shaped, while normal cells are disc-shaped. (credit: modification of work by Ed Uthman; scale-bar data from Matt Russell)

Because of this change of one amino acid in the chain, the normally biconcave, or disc-shaped, red blood cells assume a crescent or "sickle" shape, which clogs arteries. This can lead to a myriad of serious health problems, such as breathlessness, dizziness, headaches, and abdominal pain for those who have this disease.

Folding patterns resulting from interactions between the non-R group portions of amino acids give rise to the **secondary structure** of the protein. The most common are the alpha (α)-helix and beta (β)-pleated sheet structures. Both structures are held in shape by hydrogen bonds. In the alpha helix, the bonds form between every fourth amino acid and cause a twist in the amino acid chain.

In the β-pleated sheet, the "pleats" are formed by hydrogen bonding between atoms on the backbone of the polypeptide chain. The R groups are attached to the carbons, and extend above and below the folds of the pleat. The pleated segments align parallel to each other, and hydrogen bonds form between the same pairs of atoms on each of the aligned amino acids. The α-helix and β-pleated sheet structures are found in many globular and fibrous proteins.

The unique three-dimensional structure of a polypeptide is known as its **tertiary structure.** This structure is caused by chemical interactions between various amino acids and regions of the polypeptide. Primarily, the interactions among R groups create the complex three-dimensional tertiary structure of a protein. There may be ionic bonds formed between R groups on different amino acids, or hydrogen bonding beyond that involved in the secondary structure. When protein folding takes place, the hydrophobic R groups of nonpolar amino acids lay in the interior of the protein, whereas the hydrophilic R groups lay on the outside. The former types of interactions are also known as hydrophobic interactions.

In nature, some proteins are formed from several polypeptides, also known as subunits, and the interaction of these subunits forms the **quaternary structure**. Weak interactions between the subunits help to stabilize the overall structure. For example, hemoglobin is a combination of four polypeptide subunits.

Each protein has its own unique sequence and shape held together by chemical interactions. If the protein is subject to changes in temperature, pH, or exposure to chemicals, the protein structure may change, losing its shape in what is known as **denaturation** as discussed earlier. Denaturation is often reversible because the primary structure is preserved if the denaturing agent is removed, allowing the protein to resume its function. Sometimes denaturation is irreversible, leading to a loss of function. One example of protein denaturation can be seen when an egg is fried or boiled. The albumin protein in the liquid egg white is denatured when placed in a hot pan, changing from a clear substance to an opaque white substance. Not all proteins are denatured at high temperatures; for instance, bacteria that survive in hot springs have proteins that are adapted to function at those temperatures.

The four levels of protein structure (primary, secondary, tertiary, and quaternary) are illustrated in Figure 3.

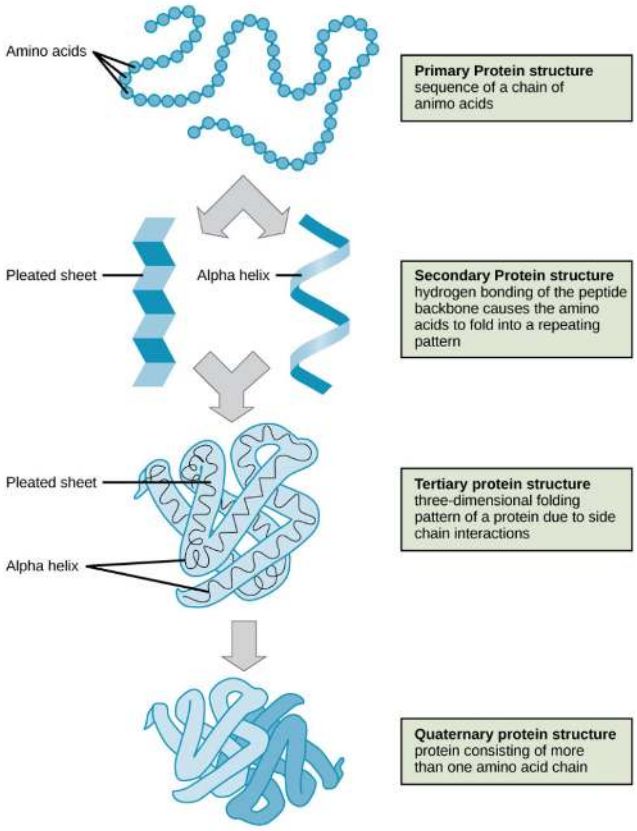


Figure 3. The four levels of protein structure can be observed in these illustrations. (credit: modification of work by National Human Genome Research Institute)

For an additional perspective on proteins, view this animation called "Biomolecules: The Proteins."

Function of Proteins

The primary types and functions of proteins are listed in Table 1.

Table 1. Protein Types and Functions

Type	Examples	Functions
Digestive Enzymes	Amylase, lipase, pepsin, trypsin	Help in digestion of food by catabolizing nutrients into monomeric units
Transport	Hemoglobin, albumin	Carry substances in the blood or lymph throughout the body
Structural	Actin, tubulin, keratin	Construct different structures, like the cytoskeleton
Hormones	Insulin, thyroxine	Coordinate the activity of different body systems
Defense	Immunoglobulins	Protect the body from foreign pathogens
Contractile	Actin, myosin	Effect muscle contraction
Storage	Legume storage proteins, egg white (albumin)	Provide nourishment in early development of the embryo and the seedling

Two special and common types of proteins are enzymes and hormones. **Enzymes**, which are produced by living cells, are catalysts in biochemical reactions (like digestion) and are usually complex or conjugated proteins. Each enzyme is specific for the substrate

(a reactant that binds to an enzyme) it acts on. The enzyme may help in breakdown, rearrangement, or synthesis reactions. Enzymes that break down their substrates are called catabolic enzymes, enzymes that build more complex molecules from their substrates are called anabolic enzymes, and enzymes that affect the rate of reaction are called catalytic enzymes. It should be noted that all enzymes increase the rate of reaction and, therefore, are considered to be organic catalysts. An example of an enzyme is salivary amylase, which hydrolyzes its substrate amylose, a component of starch.

Hormones are chemical-signaling molecules, usually small proteins or steroids, secreted by endocrine cells that act to control or regulate specific physiological processes, including growth, development, metabolism, and reproduction. For example, insulin is a protein hormone that helps to regulate the blood glucose level.

Proteins have different shapes and molecular weights; some proteins are globular in shape whereas others are fibrous in nature. For example, hemoglobin is a globular protein, but collagen, found in our skin, is a fibrous protein. Protein shape is critical to its function, and this shape is maintained by many different types of chemical bonds. Changes in temperature, pH, and exposure to chemicals may lead to permanent changes in the shape of the protein, leading to loss of function, known as denaturation. All proteins are made up of different arrangements of the same 20 types of amino acids.

Learning Objectives

Proteins are a class of macromolecules that perform a diverse range of functions for the cell. They help in metabolism by providing structural support and by acting as enzymes, carriers, or hormones. The building blocks of proteins (monomers) are amino acids. Each amino acid has a central carbon that is linked to an amino group, a carboxyl group, a hydrogen atom, and an R group or side chain. There are 20 commonly occurring amino acids, each of which differs in the R group. Each amino acid is linked to its neighbors by a peptide bond. A long chain of amino acids is known as a polypeptide.

Proteins are organized at four levels: primary, secondary, tertiary, and (optional) quaternary. The primary structure is the unique sequence of amino acids. The local folding of the polypeptide to form structures such as the α helix and β-pleated sheet constitutes the secondary structure. The overall three-dimensional structure is the tertiary structure. When two or more polypeptides combine to form the complete protein structure, the configuration is known as the quaternary structure of a protein. Protein shape and function are intricately linked; any change in shape caused by changes in temperature or pH may lead to protein denaturation and a loss in function.

Check Your Understanding

Answer the question(s) below to see how well you understand the topics covered in the previous section. This short quiz does **not** count toward your grade in the class, and you can retake it an unlimited number of times.

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1.1.6: Nucleic Acids

What you'll learn to do: Discuss nucleic acids and the role they play in DNA and RNA

Humans have two types of nucleic acids in their bodies: DNA and RNA. These molecules contain the set of instructions for our cells: they determine who and what we are. But what makes up our DNA?

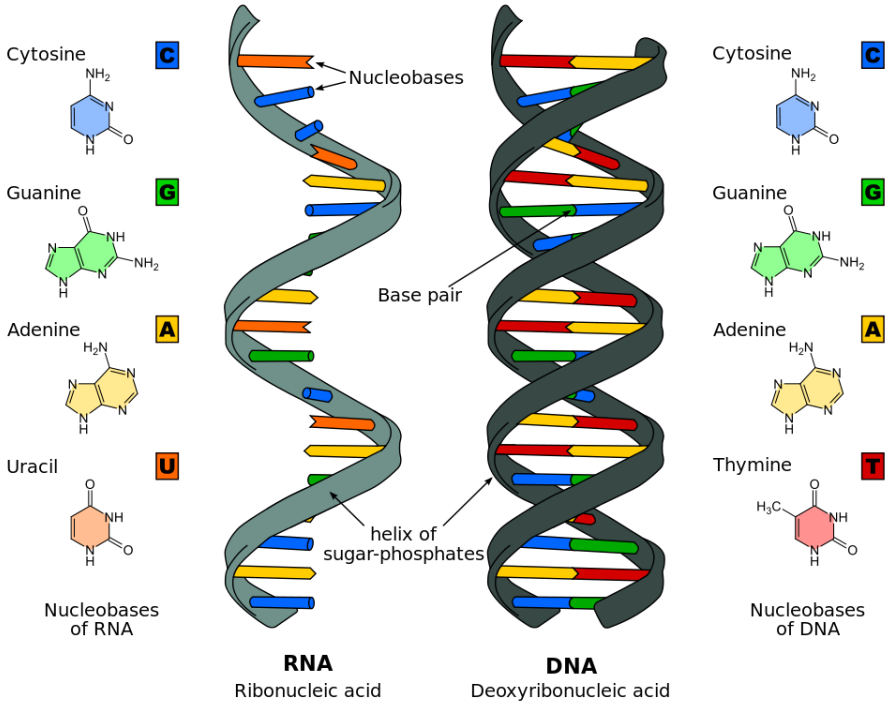


Figure 1. Spot the differences between DNA and RNA

In this outcome, we'll learn about the components of DNA and RNA and get a brief introduction to how they work.

Learning Objectives

- Describe the basic structure of nucleic acids
- Compare and contrast the structure of DNA and RNA

Structure of Nucleic Acids

Nucleic acids are key macromolecules in the continuity of life. They carry the genetic blueprint of a cell and carry instructions for the functioning of the cell.

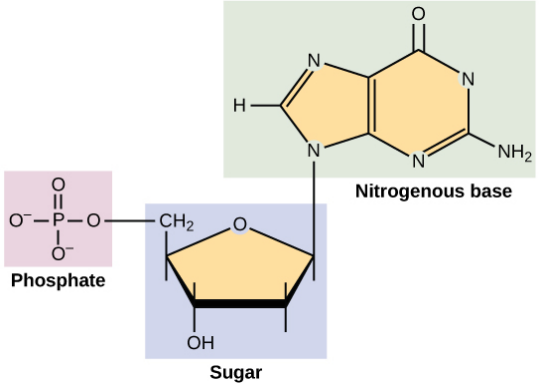


Figure 2. A nucleotide is made up of three components: a nitrogenous base, a pentose sugar, and a phosphate group.

The two main types of nucleic acids are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is the genetic material found in all living organisms, ranging from single-celled bacteria to multicellular mammals.

The other type of nucleic acid, RNA, is mostly involved in protein synthesis. The DNA molecules never leave the nucleus, but instead use an RNA intermediary to communicate with the rest of the cell. Other types of RNA are also involved in protein synthesis and its regulation.

DNA and RNA are made up of monomers known as nucleotides. The nucleotides combine with each other to form a polynucleotide, DNA or RNA. Each nucleotide is made up of three components: a nitrogenous base, a pentose (five-carbon) sugar, and a phosphate group (Figure 2). Each nitrogenous base in a nucleotide is attached to a sugar molecule, which is attached to a phosphate group. The nucleotides link together by phosphodiester bonds to form the polynucleotide.

DNA Double-Helical Structure

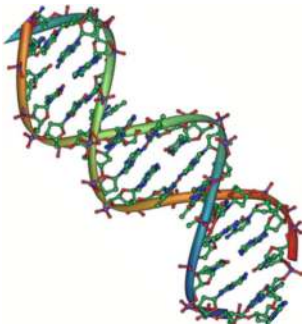


Figure 3. The double-helix model shows DNA as two parallel strands of intertwining molecules. (credit: Jerome Walker, Dennis Myts)

DNA has a double-helical structure (Figure 3). It is composed of two strands, or polymers, of nucleotides. The strands are formed with covalent bonds between phosphate and sugar groups of adjacent nucleotides.

The two strands are bonded to each other at their bases with hydrogen bonds, and the strands coil about each other along their length, hence the “double helix” description, which means a double spiral.

The alternating sugar and phosphate groups lie on the outside of each strand, forming the backbone of the DNA. The nitrogenous bases are stacked in the interior, like the steps of a staircase, and these bases pair; the pairs are bound to each other by hydrogen bonds. The bases pair in such a way that the distance between the backbones of the two strands is the same all along the molecule.

DNA and RNA

While DNA and RNA are similar, they have very distinct differences. Table 1 summarizes features of DNA and RNA.

Table 1. Features of DNA and RNA

	DNA	RNA
Function	Carries genetic information	Involved in protein synthesis
Location	Remains in the nucleus	Leaves the nucleus
Structure	DNA is double-stranded “ladder”: sugar-phosphate backbone, with base rungs.	Usually single-stranded
Sugar	Deoxyribose	Ribose
Pyrimidines	Cytosine, thymine	Cytosine, uracil
Purines	Adenine, guanine	Adenine, guanine

One other difference bears mention. There is only one type of DNA. DNA is the heritable information that is passed along to each generation of cells; its strands can be “unzipped” with small amount of energy when DNA needs to replicate, and DNA is transcribed into RNA. There are mutliple types of RNA: Messenger RNA is a temporary molecule that transports the information

necessary to make a protein from the nucleus (where the DNA remains) to the cytoplasm, where the ribosomes are. Other kinds of RNA include ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), and microRNA.

Even though the RNA is single stranded, most RNA types show extensive intramolecular base pairing between complementary sequences, creating a predictable three-dimensional structure essential for their function.

As you will learn later, information flow in an organism takes place from DNA to RNA to protein. DNA dictates the structure of mRNA in a process known as transcription, and RNA dictates the structure of protein in a process known as translation. This is known as the Central Dogma of Life, which holds true for all organisms; however, exceptions to the rule occur in connection with viral infections.

Learning Objectives

Nucleic acids are molecules made up of nucleotides that direct cellular activities such as cell division and protein synthesis. Each nucleotide is made up of a pentose sugar, a nitrogenous base, and a phosphate group. There are two types of nucleic acids: DNA and RNA. DNA carries the genetic blueprint of the cell and is passed on from parents to offspring (in the form of chromosomes). It has a double-helical structure with the two strands running in opposite directions, connected by hydrogen bonds, and complementary to each other. RNA is single-stranded and is made of a pentose sugar (ribose), a nitrogenous base, and a phosphate group. RNA is involved in protein synthesis and its regulation. Messenger RNA (mRNA) is copied from the DNA, is exported from the nucleus to the cytoplasm, and contains information for the construction of proteins. Ribosomal RNA (rRNA) is a part of the ribosomes at the site of protein synthesis, whereas transfer RNA (tRNA) carries the amino acid to the site of protein synthesis. microRNA regulates the use of mRNA for protein synthesis.

Check Your Understanding

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1.1.7: Comparing Biological Macromolecules

What you'll learn to do: Discuss macromolecules and the differences between the four classes

As we've learned, there are four major classes of biological macromolecules:

- Proteins (polymers of amino acids)
- Carbohydrates (polymers of sugars)
- Lipids (polymers of lipid monomers)
- Nucleic acids (DNA and RNA; polymers of nucleotides)

Let's take a closer look at the differences between the difference classes.

Learning Objectives

Distinguish between the four classes of macromolecules

Carbohydrates are a group of macromolecules that are a vital energy source for the cell, provide structural support to many organisms, and can be found on the surface of the cell as receptors or for cell recognition. Carbohydrates are classified as monosaccharides, disaccharides, and polysaccharides, depending on the number of monomers in the molecule.

Lipids are a class of macromolecules that are nonpolar and hydrophobic in nature. Major types include fats and oils, waxes, phospholipids, and steroids. Fats and oils are a stored form of energy and can include triglycerides. Fats and oils are usually made up of fatty acids and glycerol.

Proteins are a class of macromolecules that can perform a diverse range of functions for the cell. They help in metabolism by providing structural support and by acting as enzymes, carriers or as hormones. The building blocks of proteins are amino acids. Proteins are organized at four levels: primary, secondary, tertiary, and quaternary. Protein shape and function are intricately linked; any change in shape caused by changes in temperature, pH, or chemical exposure may lead to protein denaturation and a loss of function.

Nucleic acids are molecules made up of repeating units of nucleotides that direct cellular activities such as cell division and protein synthesis. Each nucleotide is made up of a pentose sugar, a nitrogenous base, and a phosphate group. There are two types of nucleic acids: DNA and RNA.

Practice Questions

Explain at least three functions that lipids serve in plants and/or animals.

Show Answer

Fat serves as a valuable way for animals to store energy. It can also provide insulation. Phospholipids and steroids are important components of cell membranes.

Explain what happens if even one amino acid is substituted for another in a polypeptide chain. Provide a specific example.

Show Answer

A change in gene sequence can lead to a different amino acid being added to a polypeptide chain instead of the normal one. This causes a change in protein structure and function. For example, in sickle cell anemia, the hemoglobin β chain has a single amino acid substitution. Because of this change, the disc-shaped red blood cells assume a crescent shape, which can result in serious health problems.

Check Your Understanding

Answer the question(s) below to see how well you understand the topics covered in the previous section. This short quiz does **not** count toward your grade in the class, and you can retake it an unlimited number of times.

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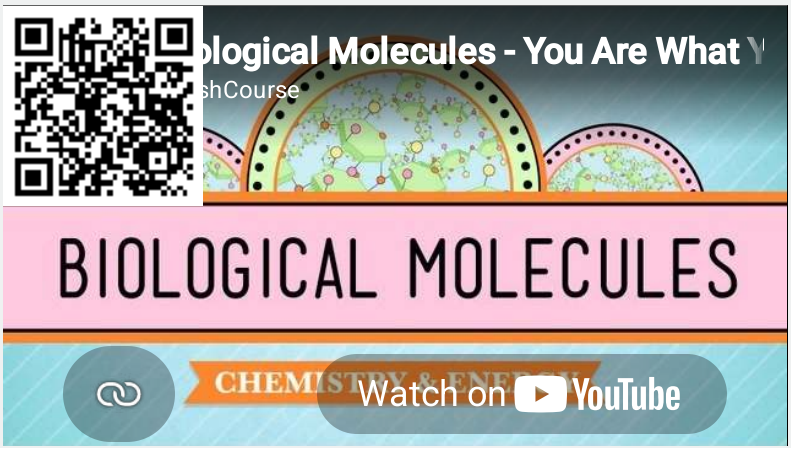
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1.1.8: Putting It Together- Important Biological Macromolecules

Watch This Video



Now that we've learned about the different macromolecules our bodies need and use, let's return to our the questions we asked at the beginning of the chapter about healthy diets:

Think about It

- Is it even possible for a person to cut all carbs out of his or her diet?
- Is it actually healthy to remove an entire class of molecules from the diet?
- Fats and cholesterol are strictly bad—right?

See Our Thoughts

It is, in fact, impossible to have a no carb or no fat diet. These molecules are in all cells and cells makes up what we eat. More importantly though, each of these biological macromolecules has a very important role to play. If you cut too much fat from your diet, for example, it is possible for your fat stores dip low enough that your hair will fall out!

Even the much maligned cholesterol is a requirement for a healthy body and lifestyle: without sufficient cholesterol, your body doesn't make enough sex hormones (estrogen or testosterone depending on if you're male or female). The trick is to make healthy choices overall without too much of any biological macromolecules—after all, there can certainly be too much of a good thing.

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1.1.9: Assignment- Nutritionist for a Day

You have been hired as a high school nutritionist and your first big task is to carry out a “Healthy Lifestyles” nutrition campaign. You want the students you work with to understand the relationship between the four categories of biological macromolecules and the food they eat.

Prepare a brochure or flyer that clearly and accurately educates your students about lipids, carbohydrates, proteins, and nucleic acids. Your flyer should include the following information about each type of macromolecule:

- overall function in the body
- types of food where each biomolecule can be found

Your flyer should also include an overall theme that emphasizes the importance of a healthy diet.

Take a look at the hints in this worked example for help completing this assessment.

Basic Requirements (the assignment will not be accepted or assessed unless the follow criteria have been met):

- Assignment has been proofread and does not contain any major spelling or grammatical errors
- Assignment includes appropriate references
- Assignment includes a food source for each biomolecule illustrated.
- Assignment emphasizes an overall healthy diet.

Rubric

Nutritionist for a Day
Outcome: Identify and describe the main features of the four main classes of important biomolecules

Nutritionist for a Day				
Criteria	Ratings			Pts
The role of carbohydrates in the body is identified and their structural makeup summarized.	Carbohydrates and their role in the body identified; structural makeup discussed/illustrated in detail in connection to role in the body. 5.0 pts	Carbohydrates and their basic role in the body identified; structural makeup summarized/illustrated. 4.0 pts	Carbohydrates are not discussed sufficiently. 0.0 pts	5 pts
The role of lipids in the body is identified and the structural makeup of each type is summarized.	Lipids and their role in the body identified; structural makeup discussed/illustrated in detail in connection to role in the body. 5.0 pts	Lipids and their basic role in the body identified; structural makeup summarized/illustrated. 4.0 pts	Lipids are not discussed sufficiently. 0.0 pts	5 pts
The role of proteins in the body is identified and their structural makeup summarized.	Proteins and their role in the body identified; structural makeup discussed/illustrated in detail in connection to role in the body. 5.0 pts	Proteins and their basic role in the body identified; structural makeup summarized/illustrated. 4.0 pts	Proteins are not discussed sufficiently. 0.0 pts	5 pts
The role of nucleic acids in the body is identified and the structural makeup of DNA and RNA summarized.	Nucleic acids and their role in the body identified; structural makeup discussed/illustrated in detail in connection to role in the body. 5.0 pts	Nucleic acids and their basic role in the body identified; structural makeup summarized/illustrated. 4.0 pts	Nucleic acids are not discussed sufficiently. 0.0 pts	5 pts
				Total points: 20

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SECTION OVERVIEW

1.2: The Origins of Life

1.2.1: Introduction

1.2.2: Thinking about Life's Origins- A Short Summary of a Long History

1.2.3: Formation of Organic Molecules in an Earthly Reducing Atmosphere

1.2.4: Origins of Organic Molecules in a Non-Reducing Atmosphere

1.2.5: Origins of Life Chemistries in an RNA World

1.2.6: Molecules Talk- Selecting Molecular Communication and Complexity

1.2.7: A Summary and Some Conclusions

1.2.8: Key Words and Terms

Thumbnail: 3D structure of a hammerhead ribozyme. (CC BY-SA 3.0; William G. Scott via Wikipedia)

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1.2.1: Introduction

It is nearly universally accepted that there was a time, however brief or long, when the earth was a lifeless planet. Given that the cell is the basic unit of life, and that to be alive is to possess all of the **properties of life**, any cell biology textbook would be remiss without addressing the questions of **when** and **how** the first cells appeared on our planet. **Abiogenesis** is the origin of life from non-living matter. Of course describing abiogenesis is no longer possible by observation! Through experiment and educated guesswork, it has been possible to construct reasonable (if sometimes conflicting) scenarios to explain the **origins of life**, and hence our very existence.

In this chapter, we will see that different scenarios share at least one feature, namely a set of geologic, thermodynamic and chemical conditions that favored an accumulation of organic molecules and proto-structures that would eventually become a cell. Those permissive conditions would have been an ecological, climatological, and environmental **prebiotic laboratory** in which *many* experimental cells might have formed and competed. Hence the chapter title “Origins of Life”! Multiple origins were not only possible under these conditions, but also probable! According to Jeremy England, of MIT, the laws of thermodynamics dictate that "... when a group of atoms is driven by an external source of energy (like the sun or chemical fuel) and surrounded by a heat bath (like the ocean or atmosphere), matter inexorably acquires the key physical attribute(s) associated with life”. (Statistical Physics of Self Replication). Here is a reminder of those key attributes, or properties of life.

Properties of Life

1. **Evolution**: long term adaptation/speciation
2. **Cell-based**: Cells are the fundamental unit of life
3. **Complexity**: allows physical/biochemical changes (dynamic order)
4. **Homeostasis**: maintains balance between change and order
5. **Requires Energy**: needed to do *work* (cellular functions)
6. **Irritability**: immediate sensitivity and response to stimuli
7. **Reproduction**: the ability to propogate life
8. **Development**: programmed change, most obvious in multicellular organisms

Remember, to be alive is to possess not just some, but all of these properties! If entities with all of the properties of life (i.e., cells) did originate independently, they would have reproduced to form separate populations of cells. In this scenario, less successful populations go extinct while successful ones become dominant. Successful organisms would have spread, spawning populations and generating new species. The **take-home message** is that if conditions on a prebiotic earth favored the formation of the ‘first cell’, then why not the formation of two, or dozens or even hundreds of ‘first cells’? However, we will see that only one successful population of cells would survive to become the source of the common ancestor of all life on earth, while other populations became extinct.

As to the question of **when** life began, geological and geochemical evidence suggests the presence of life on earth as early as 4.1 billion years ago. As for **how** life began, this remains the subject of ongoing speculation. *All* of the scenarios described below attempt to understand the physical, chemical and energetic conditions that might have been the ideal laboratory for prebiotic “*chemistry experiments*”. What all the scenarios share are the following requirements.

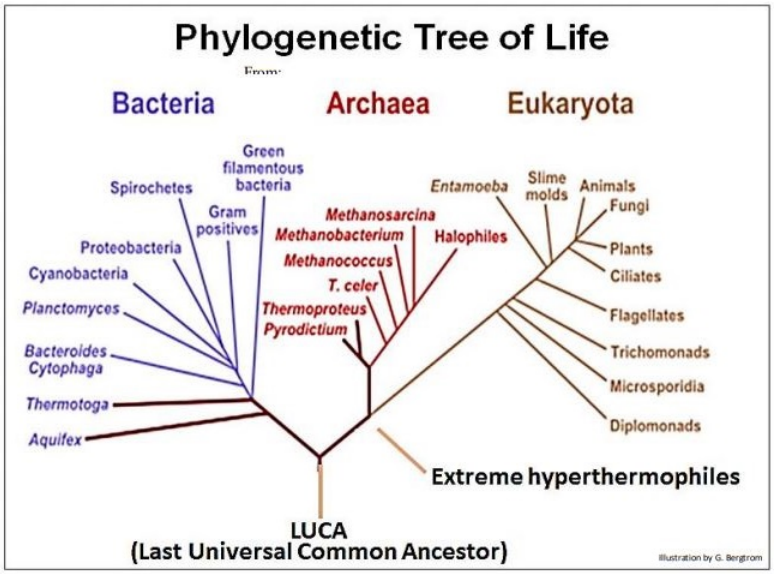
All Origins of Life Scenarios Must Explain:

- **Prebiotic Synthesis** of organic molecules and polymers
- the origins of **catalysis** and **replicative biochemistry**
- the **sources of free energy** to sustain prebiotic biochemistry
- the beginnings of **metabolism** sufficient for life
- the origins of **molecular information storage and retrieval**
- enclosure of life's chemistry by a semipermeable membrane

Let’s consider some tricky definitions. If one believes the origin of life was so unlikely that it could only have happened once (still a common view), then the very first cell (defined as the **progenote**, the progenitor of us all) is our common genetic ancestor.

On the other hand, what if there were many origins of life? Then there must have been more than one 'first cell', generating multiple populations of cells. Each such population, starting with its own 'progenote' would have evolved. In this scenario, only one cell population would survive; its evolved cells would have been the source of our **Last Universal Common Ancestor**, or **LUCA**. All populations of other first cells went extinct. The LUCA remains defined as the highly evolved cell(s) with genome, biochemistry and basic metabolic infrastructure that is shared among all things alive today.

Whatever the pathway to the first living cells on earth, molecular studies over the last several decades support the common ancestry of all life on earth, in the form of the LUCA. Look at the phylogenetic tree below showing the domains of life that we have seen before, with the *LUCA* at its root.



Regardless of the number of 'first cells', the LUCA's ancestors still descended from a progenote! So, how did we get to our own progenote, or first cell? Consider these common features of any life-origins scenario:

- reduction of inorganic molecules to form organic molecules
- a source of free energy to fuel the formation of organic molecules
- a scheme for catalytic acceleration of biochemical reactions
- separation of early biochemical 'experiments' by a semipermeable boundary

Next, consider some proposed scenarios for the creation of organic molecules:

- import of organic molecules (or even life itself) from **extraterrestrial** sources
- organic molecule synthesis on an earth with a **reducing atmosphere**
- organic molecule synthesis on an earth with a **non-reducing atmosphere**

Here we explore alternate free-energy sources and pathways to the essential chemistry of life dictated by these different beginnings. Then we look at possible scenarios of chemical evolution that must have occurred before life itself. Finally, we consider how primitive (read "simpler") biochemistries could have evolved into the present-day metabolisms shared by all existing life forms.

347 What any Life Origins Scenario Must Explain

Learning Objectives

When you have mastered the information in this chapter, you should be able to:

1. Explain how organic molecules would capture chemical energy on a *prebiotic earth*.
2. List the essential chemistries required for life and why they might have been *selected* during chemical evolution.
3. Discuss the different fates of prebiotically synthesized organic *monomers* and *polymers* and how these fates would influence the origins of the first cells on earth.
4. Compare and contrast two scenarios for *extraterrestrial origins* of organic molecules.

5. Summarize the arguments against Oparin's *primordial soup* hypothesis.
6. Summarize the evidence supporting origins of life in a *non-reducing* earth atmosphere.
7. Compare the *progenote* and the *LUCA*.
8. Discuss the evidence suggesting an origin of cellular life in the *late Hadean eon*.
9. Describe how life might have begun in deep ocean vents – compare the possibilities of life beginning in *black smokers* vs. *white smokers*.
10. Argue for and against an *autotroph-first* scenario for cellular origins.
11. Explain why some investigators place significance on the early origins of free energy storage in *inorganic proton gradients*.
12. Define *autocatalysis*, co-catalysis and co-catalytic sets; provide examples.
13. Define *coevolution*.
14. Describe the significance and necessity of *coevolution* before life. In what ways is coevolution a feature of living things? Explain.

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1.2.2: Thinking about Life's Origins- A Short Summary of a Long History

By all accounts, the earth must have been a very unpleasant place soon after its formation! For that reason, the period from 4.8 to 4.0 billion years ago is called the Hadean Eon, after Hades, the hell of the ancient Greeks! Until recently, geological, geochemical and fossil evidence suggested that life arose between 3.8 and 4.1 billion years ago. The 2017 discovery of 3.95 billion year-old sedimentary rocks in Labrador with evidence of life, points to an even earlier origin of life, (see From Canada Comes the Oldest Evidence of Life on Earth). In fact, questions about life's origins are probably "as old as the hills…" or at least as old as the ancient Greeks! We only have records of human notions of life's origins dating from biblical accounts and, just a bit later, from Aristotle's musings. While Aristotle did not suggest that life began in hell, he and other ancient Greeks did speculate about life's origins by *spontaneous generation*, in the sense of *abiogenesis* (*life* originating from *non-life*). He further speculated that the origins of life were gradual.

Later, the dominant theological accounts of creation in Europe in the middle ages muted any notions of origins and evolution. While a few mediaeval voices ran counter to strict biblical readings of the creation stories, it was not until the Renaissance in the 14th-17th century that an appreciation of ancient Greek *humanism* was reawakened, and with it, scientific curiosity and the ability to engage in rational questioning and research.

Many will recall that Louis Pasteur in the mid-19th century put to rest any lingering notions of life forming from dead (e.g., rotten, or fecal) matter. He showed that life would not form in sterilized nutrient solutions unless the broth was exposed to the air. Fewer know that much earlier, Anton Van Leeuwenhoek, the 17th century microscopist who first described bacteria and *animalcules*, mostly protozoa in pond water, had already tested the notion of spontaneous generation. By observing open and sealed containers of meat over time, he became convinced that 'large' animals like fleas and frogs do not arise *de novo* from putrid meat or slime. He also declared that insects come from other insects, and not from the flowers that they visited.

No lesser light than Charles Darwin suggested in 1859 that life might have begun in a "*warm little pond, with all sorts of ammonia and phosphoric salts, light, heat, electricity, &c., present, that a proteine compound was chemically formed ready to undergo still more complex changes.*" He even realized that these chemical constituents would not have survived in the atmosphere and waters of his day, but must have done so in a prebiotic world. In *On the Origin of Species*, he referred to life having been 'created'. There, Darwin was not referring to a biblical basis of creation; he clearly meant that life originated "*by some wholly unknown process*" at a time before which there was no life. Finally, Pasteur's 1861 contribution was the irrefutable, definitive proof that 'invisible' *microbial life* likewise did not arise by spontaneous generation. Thus for creatures already on earth, they could only arise by **biogenesis** (*life-from-life*), the opposite of *abiogenesis*, a term that now applies to only the first origins of life!

Among Darwin's friends and contemporaries were Charles Lyell and Roderick Murchison, both geologists who understood much about the slow geological changes that shaped the earth. Darwin was therefore familiar with the concept of extended periods of geological time, amounts of time he believed was necessary for the natural selection of traits leading to species divergence.

Fast-forward to the 1920s when J.H.B.S. Haldane and A. Oparin offered an hypothesis about the life's origins based on notions of the chemistry and physical conditions that might have existed on a **prebiotic earth**. Their proposal assumed that the earth's atmosphere was hot, hellish and reducing (i.e., filled with inorganic molecules able to give up electrons and hydrogens). There are more than a few hypotheses for which chemicals were already present on earth, or that formed when the planet formed about 4.8 billion years ago. We'll start our exploration with Oparin and Haldane's *reducing atmosphere*. Then we look at the possibility that life began under *non-reducing conditions* (with passing reference to a few other ideas).

348 Early Ideas to Explain the Origins of Life

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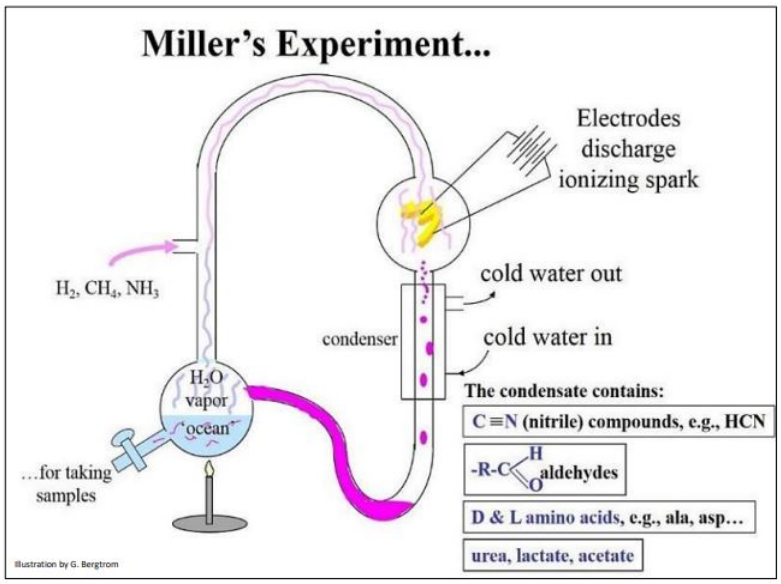
1.2.3: Formation of Organic Molecules in an Earthly Reducing Atmosphere

A prerequisite to the prebiotic chemical experimentation is a source of organic molecules. Just as life requires energy (to do anything and everything!), converting inorganic molecules into organic molecules requires an input of *free energy*. As we have seen, most living things today get free energy by oxidizing nutrients or directly from the sun by photosynthesis. Recall that in fact all the chemical energy sustaining life today ultimately comes from the sun. But, before there were cells, how did organic molecules form from inorganic precursors? Oparin and Haldane hypothesized a reducing atmosphere on the prebiotic earth, rich in inorganic molecules with *reducing power* (like H_2, NH_3, CH_4, and H_2S) as well as CO_2 to serve as a carbon source. The predicted physical conditions on this prebiotic earth were:

- lots of water (oceans).
- hot (no free O_2).
- lots ionizing (e.g., X, γ) radiation from space, (no protective ozone layer).
- frequent ionizing (electrical) storms generated in an unstable atmosphere.
- volcanic and thermal vent activity.

A. Origins of Organic Molecules and a Primordial Soup

Oparin suggested that abundant sources of free energy fueled the reductive synthesis of the first organic molecules to create what he called a “primeval soup”. No doubt, he called this primeval concoction a “soup” because it would have been rich in chemical (nutrient) free energy. The Oparin/Haldane proposal received strong support from the experiments of Stanley Miller and Harold Urey (Urey had already won the 1934 Nobel Prize in Chemistry for discovering deuterium). Miller and Urey tested the prediction that, under Haldane and Oparin’s prebiotic earth conditions, inorganic molecules could produce the organic molecules in what came to be known as the *primordial soup*. Their famous experiment, in which they provided energy to a mixture of inorganic molecules with reducing power, is illustrated below.



Miller’s earliest published data indicated the presence of several organic molecules in their *ocean* flask, including a few familiar metabolic organic acids (lactate, acetate, several amino acids…) as well as several highly reactive *aldehydes* and *nitriles*. The latter can interact in spontaneous chemical reactions to form organic compounds. Later analyses further revealed purines, carbohydrates and fatty acids in the flask. Later still, 50 years after Miller’s experiments (and a few years after his death), some un-analyzed sample collection tubes from those early experiments were discovered.

When the contents of these tubes were analyzed with newer, more sensitive detection techniques, they were shown to contain additional organic molecules not originally reported, including 23 amino acids (to read more, click Surprise Goodies in the Soup!).

Clearly, the thermodynamic and chemical conditions proposed by Oparin and Haldane could support the *reductive synthesis* of organic molecules. At some point, Oparin and Haldane's evolving chemistries would have to have been internalized inside of semipermeable aggregates (or boundaries) destined to become cells. Examples of such structures are discussed below. A nutrient-rich primordial soup would likely have favored the genesis of *heterotrophic* cells that could use environmental nutrients for energy and growth, implying an early evolution of fermentative pathways similar to glycolysis. But, these first cells would quickly consume the nutrients in the soup, quickly ending the earth's new vitality!

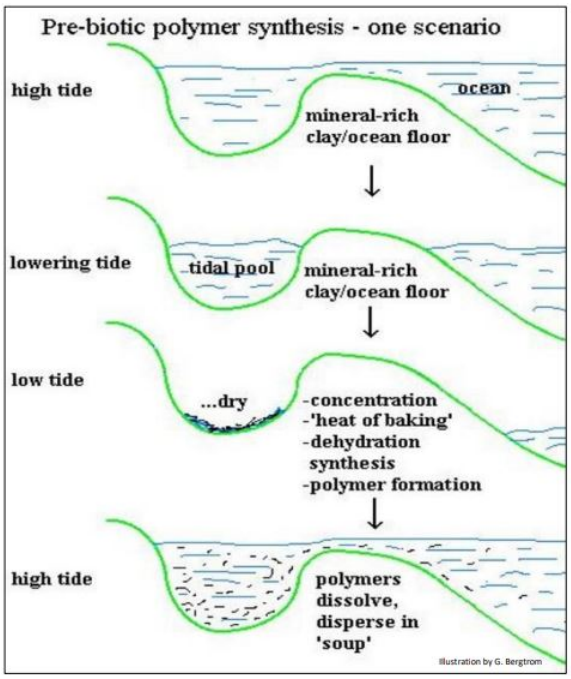
So, one must propose an early evolution of least small populations of cells that could capture free energy from inorganic molecules (**chemoautotrophs**) or even sunlight (**photoautotrophs**). As energy-rich organic nutrients in the 'soup' declined, autotrophs (notably photoautotrophs that could split water using solar energy) would be selected. Photoautotrophs would *fix* CO_2, reducing it with H^- ions from water. Photoautotrophy (**photosynthesis**) would thus replenish carbohydrates and other nutrients in the oceans and add O_2 to the atmosphere.

Oxygen would have been toxic to most cells, but a few already had the ability to survive oxygen. Presumably these spread, evolving into cells that could *respire*, i.e., use oxygen to *burn* environmental nutrients. Respiratory metabolism must have followed hard on the heels of the spread of photosynthesis.

Photosynthesis began between 3.5 and 2.5 billion years ago (the Archaean Eon). Eventually, photosynthetic and aerobic cells and organisms achieved a natural balance to become the dominant species in our oxygen-rich world.

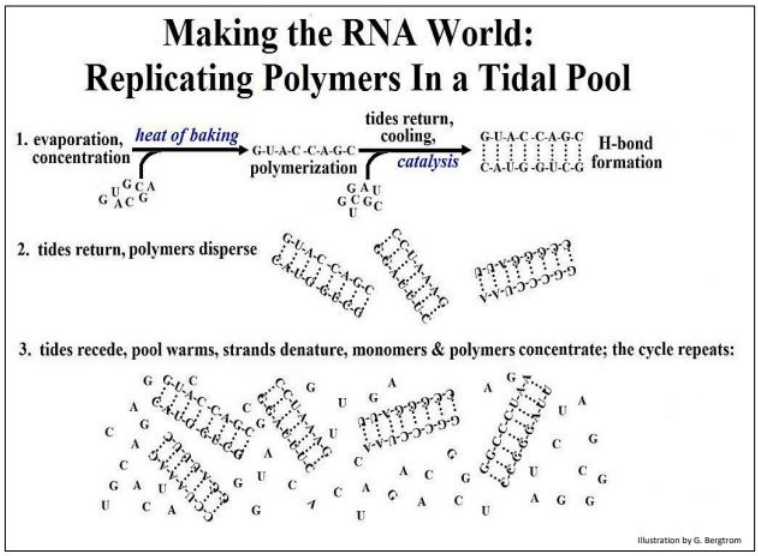
B. The Tidal Pool Scenario for an Origin of Polymers and Replicating Chemistries

In this scenario, prebiotic organic monomers would concentrate in tidal pools in the heat of a primordial day, followed by polymerization by dehydration synthesis. The formation of polymer linkages is an 'uphill' reaction requiring free energy. Very high temperatures (the **heat of baking**) can link monomers by dehydration synthesis in the laboratory, and may have done so in tidal pool sediments to form random polymers. This scenario further assumes the dispersal of these polymers from the tidal pools with the ebb and flow of high tides. The tidal pool scenario is illustrated below.



The concentration of putative organic monomers at the bottom of tidal pools may have offered opportunities to catalyze polymerization, even in the absence of very high heat. Many metals (nickel, platinum, silver, even hydrogen) are inorganic catalysts, able to speed up many chemical reactions. The heavier metals were likely to exist in the earth's crust as well as in the sediments of primordial oceans, as they do today. Such mineral aggregates in soils and clays have been shown to possess catalytic properties. Furthermore, metals (e.g., magnesium, manganese…) are now an integral part of many enzymes, consistent with an origin of biological catalysts in simpler aggregated mineral catalysts in ocean sediments.

Before life, the micro-surfaces of mineral-enriched sediment, if undisturbed, could have been able to catalyze the same or at least similar reactions repeatedly, leading to related sets of polymers. Consider the possibilities for RNA monomers and polymers, based on the assumption that life began in an RNA world. The possibilities are illustrated below.



The result predicted here is the formation not only of RNA polymers (perhaps only short ones at first), but of H-bonded double-stranded RNA molecules that might effectively replicate at each cycle of concentration, polymerization and dispersal. Heat and the free energy released by these same reactions could have supported polymerization, while catalysis would have enhanced the fidelity of RNA replication.

Of course, in the tidal pool scenario, repeated high heat or other physical or chemical attack might also degrade newly formed polymers. But what if some RNA double strands were more resistant to destruction. Such early RNA duplexes would accumulate at the expense of the weaker, more susceptible ones. Only the *fittest* replicated molecules would be selected and persist in the environment! The environmental accumulation of structurally related, replicable and stable polymers reflects a prebiotic chemical **homeostasis** (one of those properties of life!)

349 Life Origins in a Reducing Atmosphere

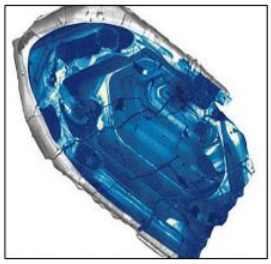
Overall, this scenario hangs together nicely, and has done so for many decades. However, there are now challenging questions about the premise of a prebiotic reducing environment. Newer evidence points to an earth atmosphere that was not at all reducing, casting doubt on the idea that the first cells on the planet were heterotrophs. Recent proposals posit alternative sources of prebiotic free energy and organic molecules that look quite different from those assumed by Oparin, Haldane, Urey and Miller.

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1.2.4: Origins of Organic Molecules in a Non-Reducing Atmosphere

A prebiotic non-reducing atmosphere is based on several assumptions: (1) The early earth would have had insufficient gravity to hold H_2 and other light gasses; thus "outgassing" would have resulted in a loss of H_2 and other reducing agents from the atmosphere. (2) Geological evidence suggests that the earth's oceans and crust formed early in the Hadean Eon, just a few hundred million years after formation of the planet. (3) Studies of 4.4 billion year old (early Hadean Eon) Australian *zircon* crystals suggest that their oxidation state is the same as modern day rocks, meaning that the early Hadean atmosphere was largely N_2 and CO_2, a distinctly *non-reducing* one! A colorized image of this Australian zircon is shown below.



So life might have begun in a non-reducing environment. Nevertheless, how far back can we date the appearance of the first actual cells on earth? Solid geological evidence of actual life dates to 3.5-3.95 billion years ago (i.e., the *Archaean Eon*). Softer evidence of microbial life exists in the form of graphite and other 'possible' remains as old as 4.1 billion years ago, near the end of the Hadean Eon. Thus, regardless of whether life began 3.5 or even 4.1 billion years ago, the evidence suggests that life's beginnings had to contend with a non-reducing environment.

Before we look more closely at other evidence of life origins under non-reducing conditions, let's consider the **Panspermia**, the possibility that life came to earth from **extraterrestrial** sources and a related hypothesis that prebiotic organic molecules came from extraterrestrial sources. Then we will examine how cells might have formed in localized, favorable **terrestrial** environments.

A. Panspermia - an Extraterrestrial Origin of Earthly Life

Panspermia posits that life itself arrived on our planet on comets or meteorites. Since these are unlikely to have sustained life in space, they must have been a kind of interstellar 'mailbox' into which dormant life forms were deposited. The cells in the mailboxes must have been *cryptobiotic*. Examples of cryptobiosis exist today (e.g., bacterial spores, brine shrimp!). Once delivered to earth's life-friendly environment, such organisms would emerge from dormancy, eventually populating the planet. There is however, no evidence of dormant or cryptobiotic life on comets or meteorites, and no hard evidence to support *Panspermia*. On the other hand, there is evidence at least consistent with an extraterrestrial source of organic molecules, and plenty to support more terrestrial origins of life. In any case, notions of *Panspermia* (and even extraterrestrial sources of organic molecules) simply beg the question of the conditions that would have led to the origin of life elsewhere!

While panspermia is not a favored scenario, it is nevertheless intriguing, in the sense that it is in line the likelihood that organic molecules formed soon after the *Big Bang*. Moreover, if ready-made organic molecules and water were available, we can expect (and many do!) that there is life on other planets. This expectation has stimulated serious discussion and funding of programs looking for signs of life on other planets. For example, NASA funded *Rover*'s search for (and discovery of) signs of water on Mars. It even supported the more earth-bound *Search for Extraterrestrial Intelligence* (the SETI program), based on the assumption that life not only exists elsewhere, but that it evolved high level communication skills (and why not?)! For a fascinating story about meteorites from Mars that contain water and that are worth more than gold, click Martian Obsession.

B. Extraterrestrial Origins of Organic Molecules

Even if life did not come to us ready-made, could organic molecules have arrived on earth from outer space? They are abundant, for example in *interstellar clouds*, and could have become part of the earth as the planet formed around 4.8 billion years ago. This suggests that there was no need to create them *de novo*. One hypothesis suggests meteorites, comets and asteroids, known to contain organic molecules, brought them here during fiery impacts on our planet. Comet and meteorite bombardments would have

been common 3.8 or more billion years ago. In this scenario the question of how (*not on earth!*) free energy and inorganic molecular precursors reacted to form organic molecules is moot!

A related hypothesis suggests that those fiery hits themselves provided the free energy necessary to synthesize the organic molecules from inorganic ones- a *synthesis-on-arrival* scenario. With this hypothesis on the one hand, we are back to an organic oceanic primordial soup. On the other, some have suggested that organic molecules produced in this way (not to mention any primordial life forms) would likely have been destroyed by the same ongoing impacts by extraterrestrial bodies; witness the relatively recent dinosaur extinction by an asteroid impact off the coast of Mexico some 65.5 million years ago.

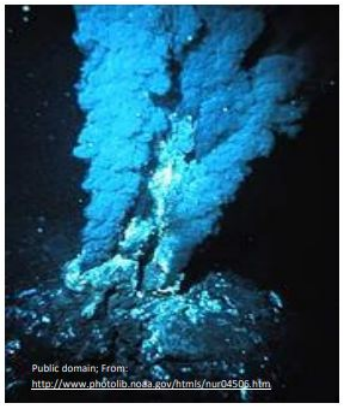
350 Life Origins in a Non-reducing Atmosphere?

C. Organic Molecular Origins Closer to Home

Deep in the oceans, far from the meteoric bombardments and the rampant free energy of an oxygen-free and ozone-less sky, deep-sea hydrothermal vents would have been spewing reducing molecules (e.g., H_2S, H_2, NH_4, CH_4), much as they do today. Some vents are also high in metals such as lead, iron, nickel, zinc copper, etc. When combined with their clay or crustal substrata, these minerals could have provided catalytic surfaces to enhance organic molecule synthesis. Could such localized conditions have been the focus of prebiotic chemical experimentation leading to the origins of life? Let's look at two kinds of deep-sea hydrothermal vents recognized today: **volcanic** and **alkaline**.

1. Origins in a High-Heat Hydrothermal Vent (Black Smoker)

The free energy available from a volcanic hydrothermal vent would come from the high heat (temperatures ranging to 350^oC) and the minerals and chemicals expelled from the earth's mantle. A volcanic hydrothermal vent is illustrated below.



Conditions assumed for prebiotic volcanic hydrothermal vents could have supported catalytic syntheses of organic molecules from inorganic precursors (see Volcanic Vents and organic molecule formation). The catalysts would have been metallic (nickel, iron, etc.) minerals. Chemical reactions tested include some that are reminiscent of biochemical reactions in chemoautotrophic cells alive today. Günter Wächtershäuser proposed the Iron-sulfur world theory of life's origins in these vents, also called "black smokers". These vents now spew large amounts of CH_4 and NH_4 and experiments favor the idea that iron-sulfur aggregates in and around *black smokers* could provide catalytic surfaces for the prebiotic formation of organic molecules like methanol and formic acid from dissolved CO_2 and the CH_4 and NH_4 coming from the vents. Wächtershäuser is also credited with the idea that prebiotic selection acted not so much on isolated chemical reactions, but on aggregates of *metabolic reactions*.

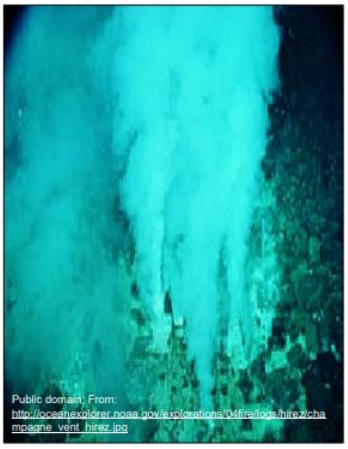
We might think of such metabolic *aggregates* as biochemical pathways or multiple integrated pathways. Wächtershäuser proposed the selection of cyclic chemical reactions that released free energy usable by other reactions. This prebiotic **metabolic evolution** of reaction chemistries (rather than a simpler chemical evolution) would have been essential to the origins of life. A variety of extremophiles (e.g., thermophilic archaea) now living in and around *black smokers* seems to be testimony to black smoker origins of life.

While the idea of selecting metabolic pathways has great merit, there are problems with a life-origins scenario in volcanic hydrothermal vents. For one thing, their high temperatures would have destroyed as many organic molecules as were created. Also, the extremophilic archaea now found around these volcanic vents cannot be the direct descendants of any cells that might have

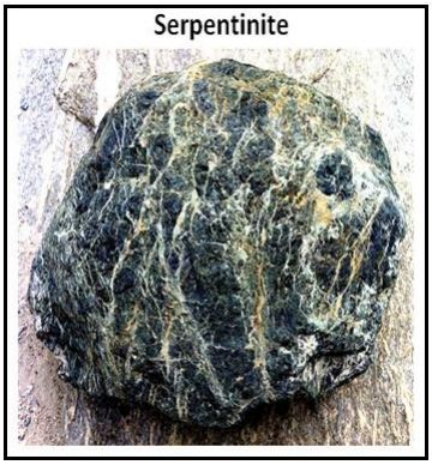
originated there. Woese's phylogeny clearly shows that archaea share a lineage with eukaryotes (not eubacteria - see above). Therefore, extremophilic cellular life originating in the vents must have first have given rise to a more moderate LUCA before then dying off themselves, after which extremophiles would once again evolve independently to re-colonize the vents! This mitigates against an extremophiles- first origins scenario. Given these concerns, recent proposals focus on life origins in less extreme **alkaline hydrothermal vents**.

2. Origins in an Alkaline Deep-Sea Vent (White Smoker)

Of the several scenarios discussed here, an origin of autotrophic life in *alkaline vents* is one of the more satisfying alternatives to a soupy origin of heterotrophic cells. For starters, at temperatures closer to 100°C-150°C, alkaline vents (**white smokers**) are not nearly as hot as are black smokers. An *alkaline vent* is shown below.



Other chemical and physical conditions of alkaline vents are also consistent with an origins-of-life scenario dependent on *metabolic evolution*. For one thing, the interface of alkaline vents with acidic ocean waters has the theoretic potential to generate many different organic molecules [Shock E, Canovas P. (2010) *The potential for abiotic organic synthesis and biosynthesis at seafloor hydrothermal systems*. Geofluids 10 (1-2):161-92)]. In laboratory simulations of alkaline vent conditions, the presence of dissolved CO_2 favors **serpentinization**, a reaction of water and heat with *serpentinite*, an iron-containing mineral found on land and in the oceanic crust. A sample of serpentinite is shown below.



Experimental serpentinization produces hydrocarbons and a warm aqueous oxidation of iron produces H_2 that could account for abundant H_2 in today's *white smoker* emissions. Also, during serpentinization, a mineral called *olivine* [$(Mg^{+2}, Fe^{+2})_2SiO_4$] reacts with dissolved CO_2 to form methane (CH_4). So, the first precondition of life, the energetically favorable creation of organic molecules, is possible in alkaline vents.

Proponents of cellular origins in a late-Hadean non-reducing ocean also realized that organic molecules formed in an alkaline (or *any*) vent would disperse and be rapidly neutralized in the wider acidic oceans waters. Somehow, origins on a nonreducing planet

had to include some way to contain newly formed organic molecules from the start, and to power further biochemical evolution. What then, were the conditions in an alkaline vent that could have contained organic molecules and led to metabolic evolution and ultimately, life's origins? Let's consider an intriguing proposal that gets at an answer!

The porous rock structure of today's alkaline vents provides micro-spaces or micro-compartments that might have captured alkaline liquids emitted by *white smokers*. It turns out that conditions in today's alkaline vents also support the formation of hydrocarbon **biofilms**. Micro-compartments lined with such biofilms could have formed a primitive prebiotic membrane against a rocky "cell wall", within which alkaline waters would be trapped. The result would be a natural *proton gradient* between the alkaline solutions of organic molecules trapped in the microcompartments and the surrounding acidic ocean waters. Did all this happen?

Perhaps! Without a nutrient-rich environment, **heterotrophs-first** is not an option. That leaves only the alternate option: an **autotrophs-first** scenario for the origins of life. Nick Lane and his coworkers proposed that proton gradients were the selective force behind the evolution of early metabolic chemistries in the alkaline vent scenario (Prebiotic Proton Gradient Energy Fuels Origins of Life). Organized around biofilm compartments, prebiotic structures and chemistries would have harnessed the *free energy* of the *natural proton gradients*. In other words, the first protocells, and then cells, may have been **chemoautotrophs**.

Last but not least, how might chemoautotrophic chemistries on a non-reducing planet have supported polymer formation, as well as polymer replication? Today we see storage and replication of information in nucleic acids as separate from enzymatic catalysis of biochemical reactions. But are they all that *separate*? If replication is the faithful reproduction of the information needed for a cell, then enzymatic catalysis ensures the redundant production of all molecules essential to make the cell! Put another way, if catalyzed *polymer* synthesis is the replication of the workhorse molecules that accomplish cellular tasks, then what we call 'replication' is nothing more than the replication of nucleic acid *information* needed to faithfully reproduce these workhorse molecules. So, was there an early, coordinated, concurrent selection of mechanisms for the catalyzed metabolism as well as catalyzed polymer synthesis and replication? We'll return to these questions shortly, when we consider the origins of life in an RNA world.

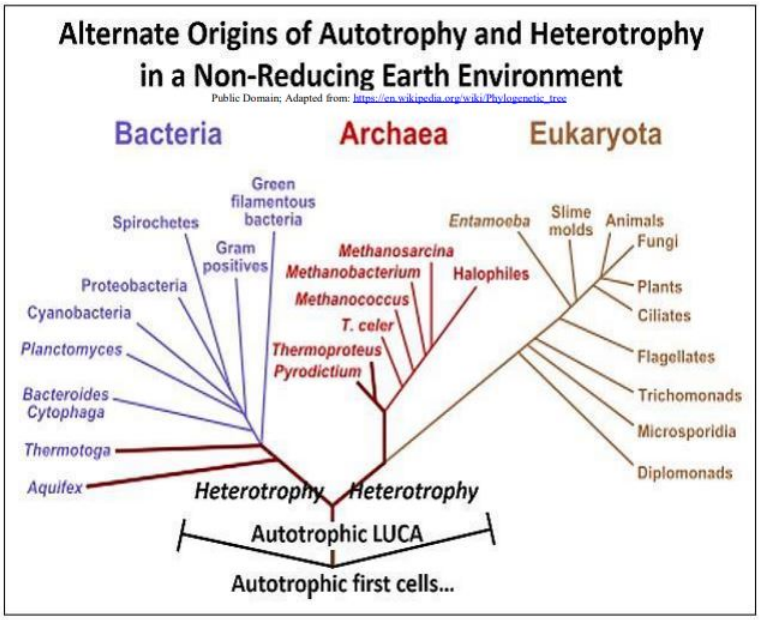
Life-origins in a non-reducing (and oxygen-free) atmosphere raise additional questions. Would proton gradients provide enough free energy to fuel and organize life's origins? If so, how did cells arising from prebiotic chemiosmotic metabolism actually harness the energy of a proton gradient? Before life, were protocells already able to transduce gradient free energy into chemical free energy? And was ATP selected to hold chemical free energy from the start? Alternatively, was the relief of the gradient coupled at first to the synthesis of other high-energy intermediate compounds with e.g., thioester linkages? Later on, how did cells formed in alkaline vents escape the vents to colonize the rest of the planet?

Regardless of how proton gradient free energy was initially captured, the **chemoautotrophic LUCA** must have already have been using membrane-bound proton pumps and an ATPase to harness gradient free energy to make ATP, since all of its descendants do so. Finally, when did photoautotrophy (specifically **oxygenic photoautotrophy**) evolve? Was it a late evolutionary event? Is it possible that photosynthetic cells evolved quite early among some of the chemoautotrophic denizens of the white smokers, biding their time before exploding on the scene to create our oxygenic environment?

3. Heterotrophs-First vs. Autotrophs-First: Some Evolutionary Considerations

In the alkaline vent scenario, chemiosmotic metabolism predated life. Therefore, the first chemoautotrophic cells did not need the fermentative reactions required by cells in a heterotrophs-first origin scenario. Even though all cells alive today incorporate a form of glycolytic metabolism, *glycolysis may not be the oldest known biochemical pathway*, as we have thought for so long.

In support of a later evolution of glycolytic enzymes, those of the archaea show little structural resemblance to those of bacteria. If fermentative heterotrophy was a late evolutionary development, then LUCA and its early descendants would lack a well-developed glycolytic pathway. Instead, the LUCA must have been one of many 'experimental' autotrophic cells, most likely a chemoautotroph deriving free energy from inorganic chemicals in the environment. To account for heterotrophy in the three domains of life, it must have evolved separately in the two antecedent branches descending from the last universal common ancestor of bacterial, archaeal and eukaryotic organisms. The phylogeny shown below illustrates the *autotrophs-first* scenario.



4. Summing Up

Speculation about life's origins begins by trying to identify a source of free energy with which to make organic molecules. The first cells might have been heterotrophs formed in a reducing earth environment, from which autotrophs later evolved. On the other hand, the earliest cells may have been autotrophs formed under non-reducing conditions in the absence of a primordial soup. Then, only after these autotrophs had produced enough nutrient free energy to sustain them did heterotrophs belatedly emerge. Discoveries suggesting that the earth's atmosphere was a non-reducing one more that 4 billion years ago (soon after the formation of the planet), and that there was life on earth 3.95 billion years ago favor metabolic origins of autotrophic life in a thermal vent, likely an alkaline vent. Questions nevertheless remain about life-origins under non-reducing conditions. Even the composition of the prebiotic atmosphere is still in contention (see Non-reducing earth- Not so fast!).

For now, let us put these concerns aside for a moment and turn to events that get us from the LUCA and its early descendants to the elaborated chemistries common to all cells today. The descriptions that follow are educated guesses about pathways taken early on towards the familiar cellularity now on earth. They mainly address the selection of catalytic mechanisms, replicative metabolism, the web of intersecting biochemical pathways, and the even more intricate chemical communication that organized cell function and complexity.

352 Phylogenetic Support for Autotrophs-First Origins of Life

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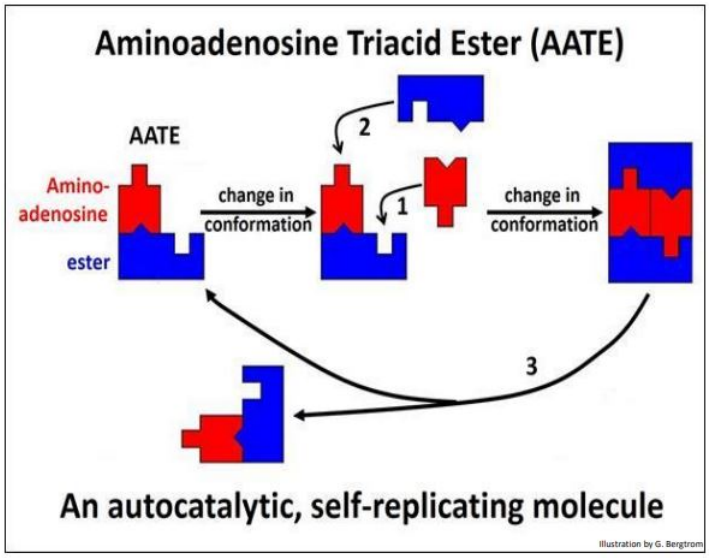
1.2.5: Origins of Life Chemistries in an RNA World

In the tidal pool scenario, with its feel of 'best-fit' with origins of life in a reducing environment, the energy for polymer formation from organic monomers came from an overheated earth environment. In that scenario, we considered the possibility that chains of nucleotides might have been synthesized, and then even replicated to form populations of nucleic acids. But if the prebiotic environment was non-reducing, where would the energy have come from to make any polymers, let alone ones that could replicate themselves? If you guessed that the energy was provided by a proton gradient between biofilm-enclosed acidic proto-cells and an alkaline ocean…, you would have been right! In this case, then polymers would have been synthesized in enclosed spaces, and not in tidal pools only to be dispersed and diluted in the wider oceans. And then, how would replicative, informational and catalytic chemistries have arisen from these organic monomers and polymers? Polypeptides would have formed, but they have no inherent chemical or structural basis for self-replication. Unlike polypeptides, we saw in describing the tidal pool scenario that polynucleotides (nucleic acids) do! In fact, evidence is accumulating to support the increasingly accepted hypothesis that life originated in a **RNA world**:

- Today's RNAs include ribozymes that catalyze their own replication (e.g., self-splicing introns).
- Some RNAs are part of **ribonucleoproteins** with at least **co-catalytic activity** (recall ribosomes, spliceosomes and the secretory signal recognition particle).
- **Retroviruses** (e.g., HIV) store their genetic information in *RNA genomes* that may have been integral to the emergence of cellular life.

Ribozymes, ribonucleoprotein structures and retroviruses may be legacies of a prebiotic RNA world. In fact, in an '*in vitro* evolution study', self-replicating ribozyme polymerases in a test tube become more efficient at replicating a variety of increasingly longer and more complex RNAs over time. For more about these autocatalysts, click Artificial Ribozyme Evolution Supports Early RNA World.

There are hypothetical *RNA world scenarios* for the origins of replicating, catalytic polymers, and even a real organic chemical **autocatalyst** that can catalyze its own synthesis. So, which may have come first? A self-replicating RNA or some other selfreplicating molecule, even a self-replicating organic molecule? Arguably, chemical evolution of an autocatalytic RNA is a stretch, but at least one organic molecule, **A**mino-**A**denosine **T**riacid-**E**ster (AATE), is a present-day self-replicating *autocatalyst*. Could an organic molecule like AATE have been a prebiotic prelude to the RNA world? The structure and replication of AATE are described below.



The replicative reaction proceeds in the following steps:

- The aminoadenosine triacid ester binds another molecule of aminoadenosine.
- The two aminoadenosines, now in opposite orientations, can attract and bind a second ester.
- After bond-rearrangements, the molecule separates into two molecules of AATE.

This reaction is catalytic because the stereochemistry of the reacting molecules creates an affinity of the aminoadenosine ester molecule first for an additional free aminoadenosine molecule, and then for a second free ester. The structure formed allows (i.e., catalyzes) linkage of the second aminoadenosine and ester followed by the separation of both AATE molecules. Subtle, sequential changes in the molecular conformation of the molecules result in the changes in affinities of the molecules for each other. In the replicative reaction, the AATE, free ester and free aminoadenosine concentrations would drive the reaction. Could AATE-like molecules have been progenitors of autocatalyzed polymer replication? *Could replication of a prebiotic AATElike molecule have led to an RNA world*? Could primitive RNAs have been stabilized by binding to short prebiotic peptides, becoming forerunners of ribozymes? The possibility of a prebiotic AATE-like molecule is intriguing because the 'triacid' includes a nucleotide base, the purine adenosine! On the other hand, the possibility of prebiotic replicating RNA-peptide complexes implies the origins of life in an **RNA-Protein world** (rather than exclusively RNA-world)! Whether life began in an RNA world or an RNA-protein world, catalyzed replication is of course another property of life.

353 AATE: An Autocatalytic, Self-Replicating Organic Molecule

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1.2.6: Molecules Talk- Selecting Molecular Communication and Complexity

In our complex human society, we define communication by its **specificity**. Without a careful choice of words, our speech would be at best, a source of magnificent misunderstanding, or just plain babel! What does this mean for prebiotic chemistries?

In terms of prebiotic chemical evolution, selection by definition would have favored protective accumulation of longer-lived molecular aggregates. Over time, the same selective imperatives would create webs of such aggregates, increasing the *range and specificity* of molecular interactions in a challenging environment. If this were to have occurred in an enclosed proto-cellular space, it should have resulted in a primitive *molecular communication* and a growing **complexity** (another property of life!). In fact, alof the properties of life must have accompanied the achievement of more and more complex intermolecular communication. Simply put, a prebiotic (or for that matter a cellular) genetic change that alters the rate of one catalytic reaction (if not destructive) will drive the selection of changes in components of other, interconnected metabolic chemistries. If *molecular communication* required the evolution of catalytic specificity, then the final elaboration of complexity and order as a property of life further requires the selection of mechanisms of **regulation** and **coordination**.

A. Intermolecular Communication Leads to an Early Establishment of Essential Interconnected Chemistries

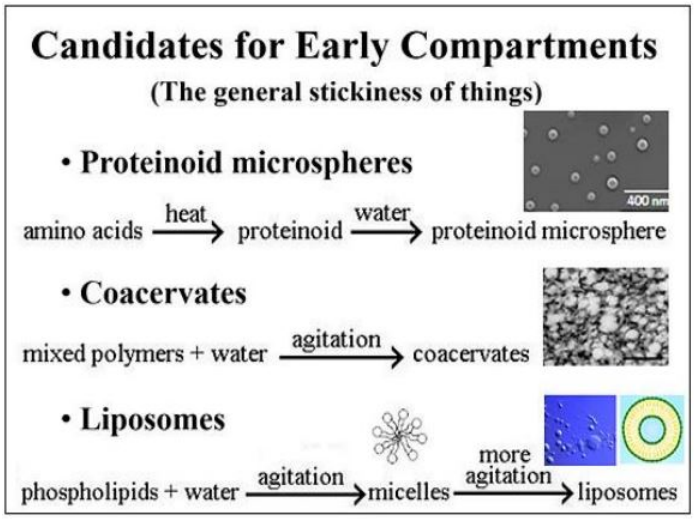
Earlier, we suggested that inorganic catalyst precursors to biological enzymes were probably minerals embedded in clay or other substrata, providing surfaces that would naturally aggregate organic molecules and catalyze repetitive reactions. Either the initial objects of prebiotic selection included external stable monomers and polymers, outside or as seems more likely, inside proto-cells. Later, selection would have favored polymers that enhanced growth and reproduction of successful aggregates. These polymers were likely those that catalyzed their own synthesis, perhaps collaborating with inorganic catalytic minerals. The result would be the elaboration of a web of *interconnected chemical reactions* between molecules with high affinity for each other, thereby increasing the specificity of those reactions. In the context of life origins and evolution, **co-catalysis** describes the activities of these interconnected metabolic reactions.

As noted, high-affinity interactions are inherently **protective**. During prebiotic chemical/metabolic evolution, protected stable **molecular assemblies** would be targets of selection. Continuing co-evolution of catalysts, substrates and co-catalytic reaction sets would lead to more and more sophisticated *molecular communication*. Once established, efficient biochemical reaction sets would be constrained against significant evolutionary change. Any change (mutation) that threatened this efficiency would mean the end of a prebiotic chemical (or for that matter, cell) lineage! This explains why we find common pathways for energy-generation (e.g., autotrophic and fermentative), reproduction (replication), and information storage and retrieval (DNA, RNA, protein synthesis) in all of LUCA's descendants.

Sophisticated, effective communication requires coordination. In fact, effective communication is defined by **coordination**, the capacity to make *chemical decisions*. Selection of molecular aggregates that sequestered metabolic reactions behind a semipermeable membrane ensure that only certain molecules communicate with each other. This sequestration is likely to have occurred repeatedly during chemical evolution, beginning with the synthesis of larger, polymeric molecules and possibly, an aggregation of primitive lipoidal molecules. We can think of increasingly effective catalysis in an enclosed environment as a **conversation mediated by good speakers**! *Coordination* is a property that likely co-evolved with life itself!

B. Origins of Coordination

Let's look some possible structures churning around in the prebiotic chemistry set that might have self-assembled, or sequestered compatible chemistries of life. Along with the alkaline vent *biofilm compartment*, **coacervates**, **proteinoid microspheres** and **liposomes** have been considered as possible progenitors of biological membranes. Each can be made in the laboratory. They are demonstrably semipermeable, and in some cases can even replicate! Micrographs and the production of coacervates, proteinoid microspheres and liposomes are shown below



Oparin had proposed that the action of sunlight in the absence of oxygen could cause ionized, oppositely charged organic molecules (e,g, amino acids, carbohydrates, etc.) to form droplets from organic molecules in his primordial soup. These **coacervates** were actually produced in 1932, visualized by microscopy and demonstarted to be a semi-permeable compartment. They even behaved as if they were able to grow and reproduce (also as Oparin originally suggested they might).

In the 1950s, Sidney Fox produced **proteinoid microspheres** from short peptides that formed spontaneously from aqueous amino acid solutions heated to dryness (not unlike what happens in the tidal pool scenario of polymer formation from organic monomers). These can be seen by light and electron microscopy.

While **liposomes** are easily made in a laboratory, it isn't clear that they existed on a pre-biotic earth. Nevertheless, cell membranes must have had acquired their phospholipid bilayer structure by the time of LUCA since we all have them! Prior to LUCA, chemical rearrangenments must have occurred to enable incorporation of a phospholipid bilayer into whatever starting boundary life started with.

We have already considered the **biofilm** proposed for cellular origins in an alkaline vent. The formation of such biofilms would have separated acidic ocean protons from the interior of such protocells, creating a proton gradient. Such a gradient could have driven the early evolution of chemiososis as a means to create chemical energy, complete with the eventual selection of ATP synthases and the enzymes of proton transport, again because all cells descendent from LUCA's posess these biochemistries. Of course, proteinoid microspheres, coacervates, biofilm-based 'membranes and liposomes are not alive, and are therefore not cells. But one or another of them must have been where the enhanced **coordination of molecular communication** required for life began.

354 Protected Molecular Communication: Semipermeable Membranes

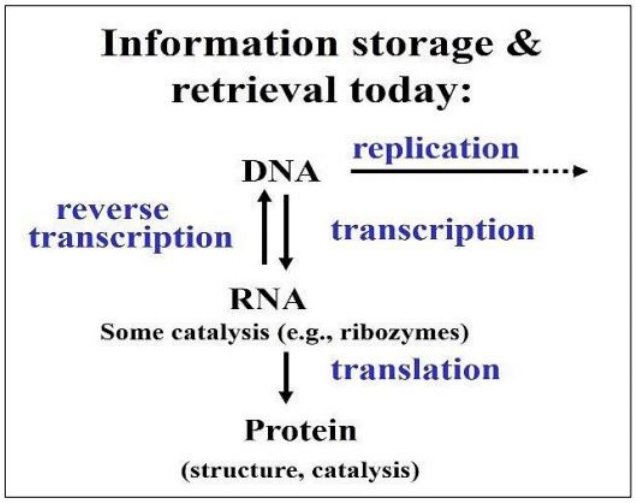
An important **take-home message** here is that whatever the original structure of the first cells, they arose soon after the organic chemical prerequisites of life began to acquire familiar metabolic functions. We need to see chemical and structural progress to cellularity as concurrent metabolic evolutionary events. At some point, selection of sequestered biochemistries led to **protocells**, then to the first cells, each with all of the properties of life.

Finally, selection of highly specific communication between cellular molecules allowed cells themselves to talk to one another, engage in group activities, and eventually join together to form multicellular organisms. Multicellularity is of course a characteristic of many if not most eukaryotes. But watch a great TED Talk on bacterial intercellular communication by Dr. Bonnie Bassler at Intercellular Communication in Bacteria.

C. Origins of Information Storage and Retrieval in an RNA World

Let us accept for now that molecular communication began concurrently with the packaging of interconnected co-catalytic sets into semipermeable structures. Then the most 'fit' of these structures were selected for efficient coordination of meaningful, timely chemical messages. Ultimately, coordination requires **information processing**, **storage** and **retrieval**, something we recognize in

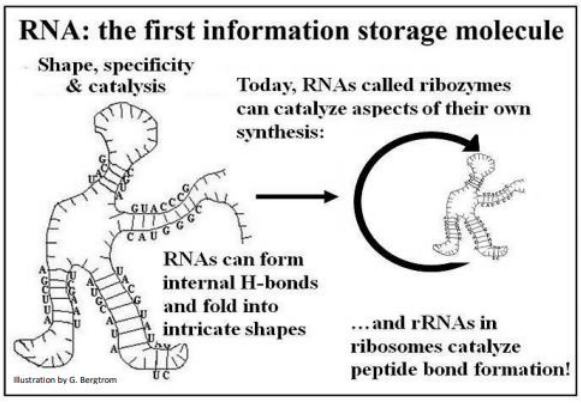
Francis Crick's Central Dogma of information flow from DNA to RNA to protein. Cells and organisms do coordination quite well, but what do its beginnings look like? The answer may lie in the pre-biotic RNA world we discussed earlier. The Central Dogma, modified to account for reverse transcription and the behavior of retroviruses, is shown below.



We do not really know how cells came to rely on DNA to store, pass on and mobilize genetic information, but we have presented reasons to believe that the first replicating nucleic acid was RNA, creating an *RNA world*. Here is the evidence that leads us to this conclusion.

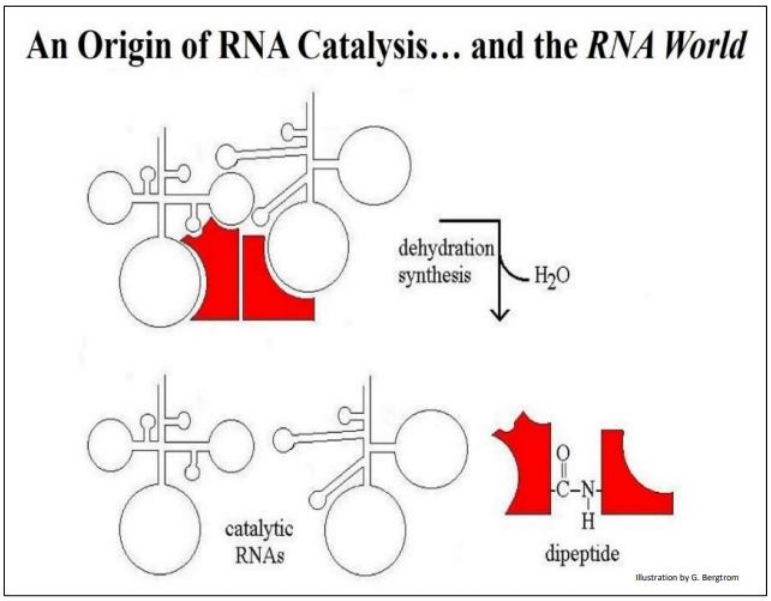
- Based on the stem-and-loop and other structures that form when RNA molecules undergo internal H-bonding, we know that RNAs can take on varied and intricate shapes.
- Diverse conformations are consistent with the evolution of specificity in the interaction of RNAs with themselves and/or with other molecules in the prebiotic environment.
- RNAs, either alone as *autocatalysts* (for example, self-splicing mRNAs) or in catalytic ribonucleoprotein complexes (e.g., ribosomes) exist in cells today.
- Some of these RNAs (specifically rRNAs), have a long phylogenetic heritage, shared by cells in all three domains of life.

The propensity of single stranded RNA molecules to fold based on internal H-bonding can lead to those diverse three-dimensional shapes (tertiary structure). These structures could have interacted with other molecules in a environment. Because they could be replicated according to different prebiotic scenarios, the same RNAs could also pass on simple genetic information contained in their base sequences. The combination of informational and catalytic properties in a single molecule is illustrated below.



The capacity of RNAs as catalysts and warehouses of genetic information speaks to an efficient candidate for the first *dual* or *multi-purpose* polymer, a property that is not known and cannot be demonstrated for DNA. Read more about the proposed 'RNA worlds' in which life may have begun in Cech TR (2012) [*The RNA Worlds in Context*. In *Cold Spring Harbor Perspectives in Biology* (Cold Spring Harbor, NY: Cold Spring Harbor press) 4(7):a006742e].

What might RNA catalysis beyond self-replication have looked like in simpler times? Consider the interaction between a two hypothetical RNAs and different hypothetical amino acids bound to each, shown below.



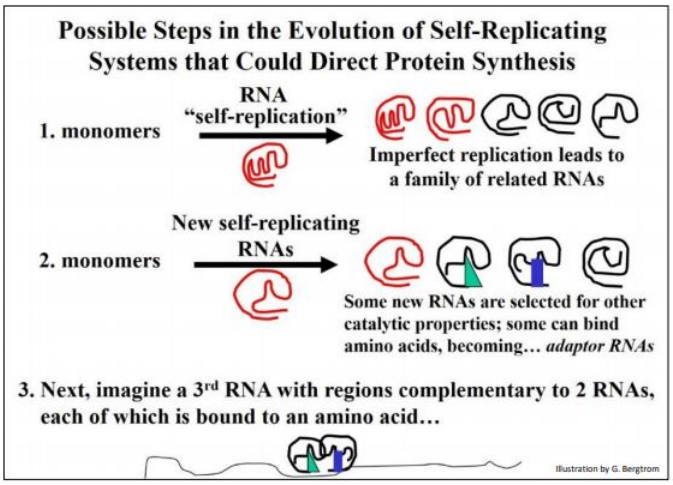
The binding of each RNA to its amino acid would be a high affinity, specific interaction based on charge and shape complementarity. Likewise, the two RNAs seen in the illustration must have a high affinity for each other, also based on chemical and physical complementarities. One can even envision some strong H-bonding between bases in the two RNAs that might displace intra-strand H-bonding (not shown here). The result is that the two amino acids are brought together in a way that catalyzes peptide bond formation. This will require an input of free energy (recall that peptide bond is one of the most energy intensive reaction in cells). For now, assume a chemical energy source and let us focus on the specificities required for RNA catalytic activity.

We know now that tRNAs the intermediaries between nucleic acids and polypeptide synthesis. So it's fair to ask how the kind of activity illustrated above could have led to the tRNA-amino acid interactions we see today. There is no obvious binding chemistry between today's amino acids and RNAs, but there may be a less obvious legacy of the proposed bindings. This has to do with the fact that the genetic code is universal, which means that any structural relationship between RNA and amino acids must have been selected early (at the start!) of cellular life on earth. Here is the argument.

1. The code is indeed universal (or nearly so)
2. There is a correlation between the chemical properties of amino acids and their codons, for example
    - Charged (polar) amino acids are encoded by triplet codons with more G (guanine) bases.
    - Codons for uncharged amino acids more often contain a middle U (uracil) than any other base.

These correlations would mean that an early binding of amino acids to specifically folded RNAs was replaced in evolution by enzyme-catalyzed covalent attachment of an amino acid to a 'correct' tRNA, such as we see today.

What forces might have selected separation of the combined template/informational functions from most of the catalytic activities of RNAs? Perhaps it was the selection of the greater diversity of structure (i.e., shape) that folded polypeptides can achieve, compared to folded RNAs. After all, polypeptides are strings of 20 different amino acids compared to the four bases that make up nucleic acids. This potential for molecular diversity would in turn accelerate the pace of chemical (and ultimately cellular) evolution. A scenario for the transition from earlier self-replicating RNA events to the translation of proteins from mRNAs is illustrated here.



Adaptor RNAs in the illustration will become tRNAs. The novel, relatively unfolded RNA depicts a presumptive mRNA. Thus, even before the entry of DNA into our RNA world, it is possible to imagine the selection of the defining features of the genetic code and mechanism of translation (protein synthesis) that characterizes all life on the planet. Next, we consider "best-speculations" of how RNA-based information storage and catalytic chemistries might have made the evolutionary transition to DNA-based information storage and predominantly protein based enzyme catalysis.

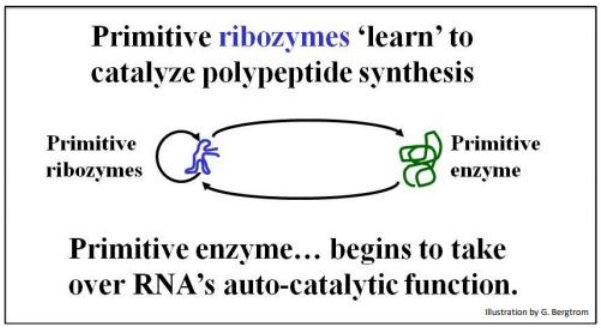
D. From Ribosomes to Enzymes; From RNA to DNA

The term *co-catalysis* could very well describe biochemical reactions in which a catalyst accelerates a chemical reaction whose product feeds back in some way on its own synthesis. We saw this in action when we discussed allosteric enzyme regulation and the control of biochemical pathways. Catalytic feedback loops must have been significant events in the evolution of the *intermolecular communication* and *metabolic coordination* required for life.

Here we will consider some scenarios for the transition from an RNA world to something more recognizable as today's nucleic acid information storage and proteinbased catalytic metabolism.

1. Ribozymes Branch Out: Replication, Transcription, and Translation

If RNAs catalyzed their own replication, it may have resembled the autocatalytic replication of AATE. At the same time, some RNAs may also have attracted amino acids to their surfaces and catalyzed peptide bond formation, as already described. Shapely prebiotic RNAs may therefore have catalyzed synthesized peptides, some of which would eventually take over catalysis of RNA synthesis! The scenario is summarized below.

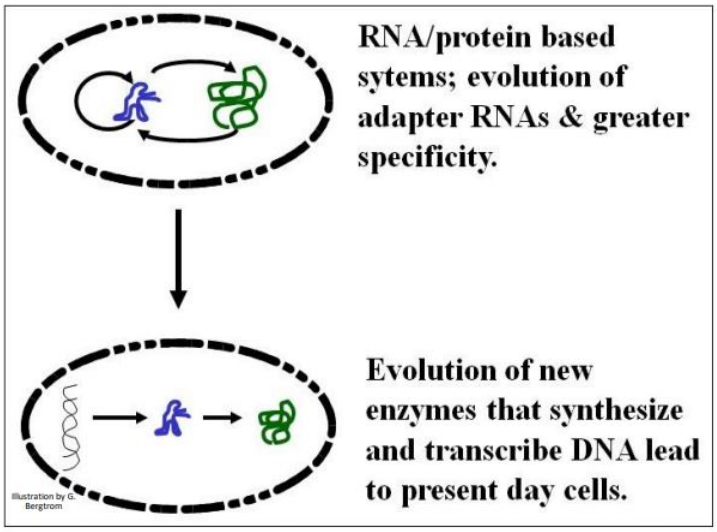


Selection favoring the synthesis of short oligopeptides and polypeptides is consistent with a catalytic diversification that led to the dominance of protein catalysts, i.e., enzymes. The primitive enzyme shown here must have been selected because at first, it assisted the autocatalytic replication of the RNA itself! Over time, the enzyme would evolve along with the RNA. This co-evolution then eventually replaced autocatalytic RNA replication with the enzyme-catalyzed RNA synthesis we recognize as transcription today. In this scenario, self-splicing premRNAs and ribozymes are surviving remnants of an RNA world!

Let’s turn now to some ideas about how an RNA world could make the transition to the DNA-RNA-protein world we have today

2. Transfer of Information Storage from RNA to DNA

The transfer of function from RNA to DNA is by no means a settled issue among students of life origins and early evolution. A best guess is that the elaboration of protein enzymes begun in the RNA world would lead to reverse transcriptase-like enzymes that copied RNA information into DNA molecules. DNA information may have been selected because DNA is chemically more stable than RNA. The basic transfer scenario is illustrated below.



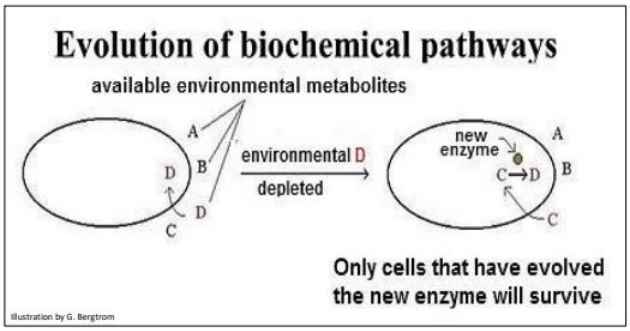
All cells alive today store information in DNA (only some viruses have an RNA genome). Therefore, transition to the use of DNA as an information molecule must have preceded the origin of life. At least, it must have occurred in the cells from which the LUCA arose. Details of this key change involve evolutionary steps yet to be worked out to everyone’s satisfaction!

357 The Transition from an RNA World to a DNA World

E. The Evolution of Biochemical Pathways

The tale of the evolution of enzymes from ribozymes and of informational DNA from RNA, and the other metabolic chemistries behind prebiotic semipermeable boundaries is ongoing in cells today. Undoubtedly, early cellular metabolism involved only reactions crucial to life, catalyzed by a limited number of enzymes. But, if evolution inexorably trends towards greater complexity of molecular communication and coordination, in other words, towards increasingly refined regulation of metabolism, how did the repertoire of enzymes get larger, and how did biochemical pathways become more elaborate? We answered the first question elsewhere, when we discussed gene duplication (e.g., by unequal crossing over). The duplicate genes encoding the same enzyme provided the raw material for new enzymes and new enzymatic functions.

Whether in cells or in prebiotic structures, we can hypothesize how a new chemical reaction could evolve. For example, assume that a cell acquires molecule **D** required for an essential function, from an external, environmental source. What happens if levels of **D** in the environment become *limiting*? Clearly, cells would die without enough **D**. That is, unless cells that already have a duplicated, redundant gene that has mutated and now encodes an enzyme with the ability to make **D** in the cell. Such a cell might have existed with other cells without the mutation, but a D-limited environment would select the mutant cell for survival and reproduction. Imagine the scenario illustrated below.



358 Origins and Evolution of Biochemical Pathways

In a similar scenario, a mutation in a duplicated gene could result in a novel enzyme activity that can convert some molecule (e.g., C or D) in the cell into a new molecular product. If the new enzyme and molecular product do not kill or debilitate the cell, the cell might survive to be selected by some future exigency.

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1.2.7: A Summary and Some Conclusions

Our consideration of how life began on earth was intentionally placed at the end of this textbook, after we tried to get a handle on how cells work. Clearly any understanding of life origins scenarios is very much a matter of informed, if divergent speculations. Alternative notions for the origins of life entertained here all address events that presaged life under 'best-guess' hypothetical conditions. After trying to get a grip on prebiotic events, we asked how we got from what could have happened under a given set of prebiotic conditions to the cellular life we recognize today. All proposals recognize that the first cells had all of the properties of life (including evolution itself). Starting with that common understanding, all arguable scenarios try to navigate pathways from primitive, less controlled chemistries to more regulated and coordinated metabolisms, in other words from chemical simplicity to biochemical complexity. The chemical and metabolic evolution that began before life may have overlapped in time with cellular evolution, at least until the LUCA. While chemical evolution was mainly a series of selections by the physicality of a prebiotic world, the evolution of life contends with both that physical world, and with life itself. LUCA, the universal common ancestor, had already escaped the RNA world, replicating DNA, transcribing RNA and translating mRNAs into polypeptides, all behind a semipermeable phospholipid bilayer. Whether a heterotroph or (increasingly more likely) an autotroph, LUCA used the energy of ATP to power all of its cellular work, as do its descendants. Thus, cellular evolution, in fact all life after the LUCA, is focused on continued selection of the complexities of metabolism that enables the spread and diversification of life from wherever it started.

The selection of chemistries and traits encoded by already existing, accumulated random, neutral genetic changes, continue to this day, increasing the diversity of species and their spread to virtually every conceivable ecological niche on the planet. The overall takehome message of this chapter should be an understanding of how the molecular basis of evolution can help us understand how life may have begun on earth (or anywhere for that matter!). In turn, speculation about life's origins informs us about how the properties of life were selected under a set of prebiotic physical and chemical conditions.

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1.2.8: Key Words and Terms

AATE	deep sea hydrothermal vent	progenote
abiogenesis	Hadean eon	proteinoid microsphere
adapter RNA	heat of baking	protocell
alkaline hydrothermal vent	heterotrophs-first	reducing atmosphere
aminoadenosine triacid ester	ionizing radiation	retroviruses
Archean eon	last universal common ancestor	ribonucleoproteins
autocatalysis	liposome	ribozymes
autotrophs-first	LUCA	RNA world
biofilm	metabolic environment	Serpentinite
biogenesis	molecular communication	serpentinization
black smoker	non-reducing atmosphere	spontaneous generation
chemoautotrophs	ozone layer	tidal pool scenario
coacervate	Panspermia	white smoker
co-catalysis	photoautotrophs	zircon
	primordial soup	

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SECTION OVERVIEW

1.3: The Cell

Life takes many forms, from giant redwood trees towering hundreds of feet in the air to the tiniest known microbes, which measure only a few billionths of a meter. Humans have long pondered life's origins and debated the defining characteristics of life, but our understanding of these concepts has changed radically since the invention of the microscope. In the 17th century, observations of microscopic life led to the development of the cell theory: the idea that the fundamental unit of life is the cell, that all organisms contain at least one cell, and that cells only come from other cells.

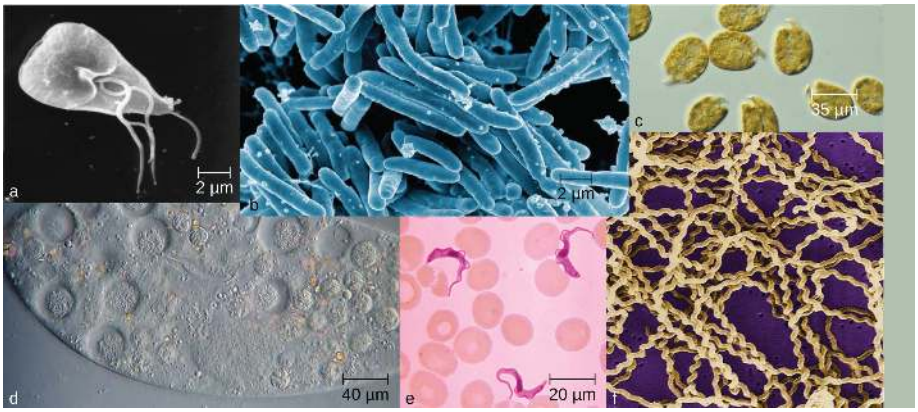


Figure 1.3.1: Microorganisms vary visually in their size and shape, as can be observed microscopically; but they also vary in invisible ways, such as in their metabolic capabilities. (credit a, e, f: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by NIAID; credit c: modification of work by CSIRO; credit d: modification of work by "Microscopic World"/YouTube)

Despite sharing certain characteristics, cells may vary significantly. The two main types of cells are prokaryotic cells (lacking a nucleus) and eukaryotic cells (containing a well-organized, membrane-bound nucleus). Each type of cell exhibits remarkable variety in structure, function, and metabolic activity. This chapter will focus on the historical discoveries that have shaped our current understanding of microbes, including their origins and their role in human disease. We will then explore the distinguishing structures found in prokaryotic and eukaryotic cells.

1.3.1: Spontaneous Generation

1.3.2: Foundations of Modern Cell Theory

1.3.E: The Cell (Exercises)

Thumbnail: A 3D rendering of an animal cell cut in half. (CC -BY-SA 4.0; Zaldua I., Equisoain J.J., Zabalza A., Gonzalez E.M., Marzo A., Public University of Navarre).

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1.3.1: Spontaneous Generation

Learning Objectives

- Explain the theory of spontaneous generation and why people once accepted it as an explanation for the existence of certain types of organisms
- Explain how certain individuals (van Helmont, Redi, Needham, Spallanzani, and Pasteur) tried to prove or disprove spontaneous generation

Clinical Focus: Part 1

Barbara is a 19-year-old college student living in the dormitory. In January, she came down with a sore throat, headache, mild fever, chills, and a violent but unproductive (i.e., no mucus) cough. To treat these symptoms, Barbara began taking an over-the-counter cold medication, which did not seem to work. In fact, over the next few days, while some of Barbara's symptoms began to resolve, her cough and fever persisted, and she felt very tired and weak.

Exercise 1.3.1.1

What types of respiratory disease may be responsible?

Humans have been asking for millennia: Where does new life come from? Religion, philosophy, and science have all wrestled with this question. One of the oldest explanations was the theory of spontaneous generation, which can be traced back to the ancient Greeks and was widely accepted through the Middle Ages.

The Theory of Spontaneous Generation

The Greek philosopher Aristotle (384–322 BC) was one of the earliest recorded scholars to articulate the theory of spontaneous generation, the notion that life can arise from nonliving matter. Aristotle proposed that life arose from nonliving material if the material contained *pneuma* ("vital heat"). As evidence, he noted several instances of the appearance of animals from environments previously devoid of such animals, such as the seemingly sudden appearance of fish in a new puddle of water.[1]

This theory persisted into the 17th century, when scientists undertook additional experimentation to support or disprove it. By this time, the proponents of the theory cited how frogs simply seem to appear along the muddy banks of the Nile River in Egypt during the annual flooding. Others observed that mice simply appeared among grain stored in barns with thatched roofs. When the roof leaked and the grain molded, mice appeared. Jan Baptista van Helmont, a 17th century Flemish scientist, proposed that mice could arise from rags and wheat kernels left in an open container for 3 weeks. In reality, such habitats provided ideal food sources and shelter for mouse populations to flourish.

However, one of van Helmont's contemporaries, Italian physician Francesco Redi (1626–1697), performed an experiment in 1668 that was one of the first to refute the idea that maggots (the larvae of flies) spontaneously generate on meat left out in the open air. He predicted that preventing flies from having direct contact with the meat would also prevent the appearance of maggots. Redi left meat in each of six containers (Figure 1.3.1.1). Two were open to the air, two were covered with gauze, and two were tightly sealed. His hypothesis was supported when maggots developed in the uncovered jars, but no maggots appeared in either the gauze-covered or the tightly sealed jars. He concluded that maggots could only form when flies were allowed to lay eggs in the meat, and that the maggots were the offspring of flies, not the product of spontaneous generation.

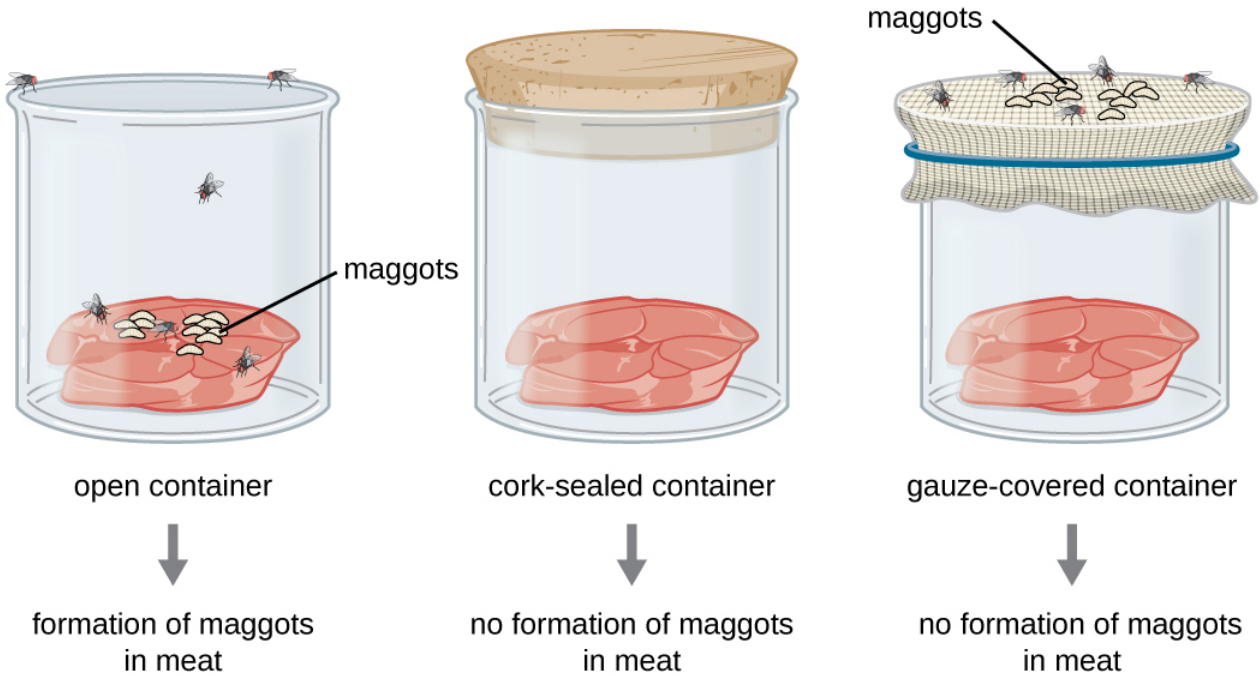


Figure 1.3.1.1: Francesco Redi's experimental setup consisted of an open container, a container sealed with a cork top, and a container covered in mesh that let in air but not flies. Maggots only appeared on the meat in the open container. However, maggots were also found on the gauze of the gauze-covered container.

In 1745, John Needham (1713–1781) published a report of his own experiments, in which he briefly boiled broth infused with plant or animal matter, hoping to kill all preexisting microbes.[2] He then sealed the flasks. After a few days, Needham observed that the broth had become cloudy and a single drop contained numerous microscopic creatures. He argued that the new microbes must have arisen spontaneously. In reality, however, he likely did not boil the broth enough to kill all preexisting microbes.

Lazzaro Spallanzani (1729–1799) did not agree with Needham's conclusions, however, and performed hundreds of carefully executed experiments using heated broth.[3] As in Needham's experiment, broth in sealed jars and unsealed jars was infused with plant and animal matter. Spallanzani's results contradicted the findings of Needham: Heated but sealed flasks remained clear, without any signs of spontaneous growth, unless the flasks were subsequently opened to the air. This suggested that microbes were introduced into these flasks from the air. In response to Spallanzani's findings, Needham argued that life originates from a "life force" that was destroyed during Spallanzani's extended boiling. Any subsequent sealing of the flasks then prevented new life force from entering and causing spontaneous generation (Figure 1.3.1.2).



Figure 1.3.1.2: (a) Francesco Redi, who demonstrated that maggots were the offspring of flies, not products of spontaneous generation. (b) John Needham, who argued that microbes arose spontaneously in broth from a "life force." (c) Lazzaro Spallanzani, whose experiments with broth aimed to disprove those of Needham.

? Exercise 1.3.1.2

1. Describe the theory of spontaneous generation and some of the arguments used to support it.
2. Explain how the experiments of Redi and Spallanzani challenged the theory of spontaneous generation.

Disproving Spontaneous Generation

The debate over spontaneous generation continued well into the 19th century, with scientists serving as proponents of both sides. To settle the debate, the Paris Academy of Sciences offered a prize for resolution of the problem. Louis Pasteur, a prominent French chemist who had been studying microbial fermentation and the causes of wine spoilage, accepted the challenge. In 1858, Pasteur filtered air through a gun-cotton filter and, upon microscopic examination of the cotton, found it full of microorganisms, suggesting that the exposure of a broth to air was not introducing a "life force" to the broth but rather airborne microorganisms.

Later, Pasteur made a series of flasks with long, twisted necks ("swan-neck" flasks), in which he boiled broth to sterilize it (Figure 1.3.1.3). His design allowed air inside the flasks to be exchanged with air from the outside, but prevented the introduction of any airborne microorganisms, which would get caught in the twists and bends of the flasks' necks. If a life force besides the airborne microorganisms were responsible for microbial growth within the sterilized flasks, it would have access to the broth, whereas the microorganisms would not. He correctly predicted that sterilized broth in his swan-neck flasks would remain sterile as long as the swan necks remained intact. However, should the necks be broken, microorganisms would be introduced, contaminating the flasks and allowing microbial growth within the broth.

Pasteur's set of experiments irrefutably disproved the theory of spontaneous generation and earned him the prestigious Alhumbert Prize from the Paris Academy of Sciences in 1862. In a subsequent lecture in 1864, Pasteur articulated "*Omne vivum ex vivo*" ("Life only comes from life"). In this lecture, Pasteur recounted his famous swan-neck flask experiment, stating that "…life is a germ and a germ is life. Never will the doctrine of spontaneous generation recover from the mortal blow of this simple experiment."[4] To Pasteur's credit, it never has.

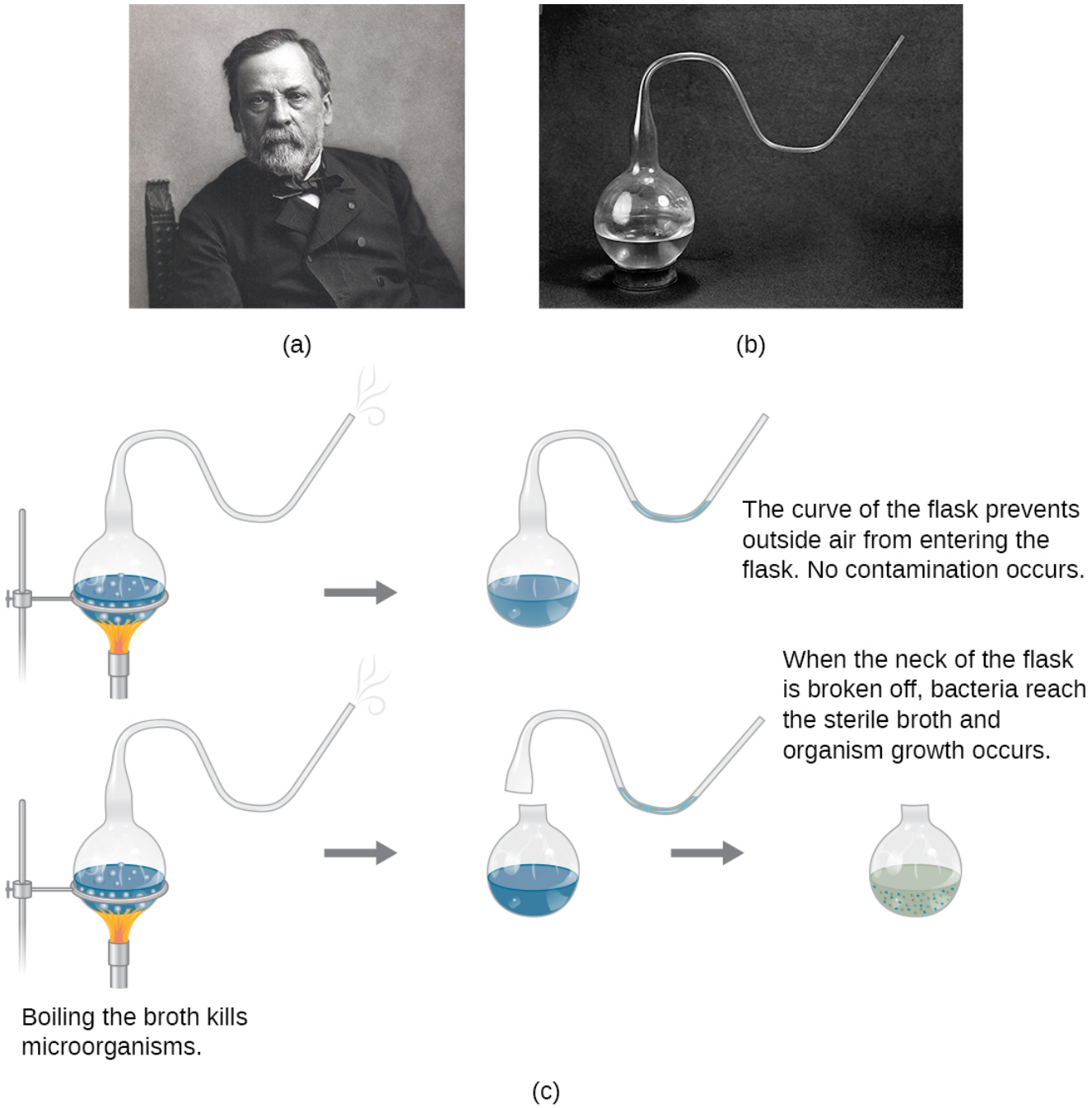


Figure 1.3.1.3: (a) French scientist Louis Pasteur, who definitively refuted the long-disputed theory of spontaneous generation. (b) The unique swan-neck feature of the flasks used in Pasteur's experiment allowed air to enter the flask but prevented the entry of bacterial and fungal spores. (c) Pasteur's experiment consisted of two parts. In the first part, the broth in the flask was boiled to sterilize it. When this broth was cooled, it remained free of contamination. In the second part of the experiment, the flask was boiled and then the neck was broken off. The broth in this flask became contaminated. (credit b: modification of work by "Wellcome Images"/Wikimedia Commons)

? Exercise 1.3.1.3

1. How did Pasteur's experimental design allow air, but not microbes, to enter, and why was this important?
2. What was the control group in Pasteur's experiment and what did it show?

Summary

- The theory of **spontaneous generation** states that life arose from nonliving matter. It was a long-held belief dating back to Aristotle and the ancient Greeks.
- Experimentation by Francesco Redi in the 17th century presented the first significant evidence refuting spontaneous generation by showing that flies must have access to meat for maggots to develop on the meat. Prominent scientists designed experiments and argued both in support of (John Needham) and against (Lazzaro Spallanzani) spontaneous generation.
- Louis Pasteur is credited with conclusively disproving the theory of spontaneous generation with his famous swan-neck flask experiment. He subsequently proposed that “life only comes from life.”

Footnotes

1. 1 K. Zwier. “Aristotle on Spontaneous Generation.” www.sju.edu/int/academics/cas...R.%20Zwier.pdf
2. 2 E. Capanna. “Lazzaro Spallanzani: At the Roots of Modern Biology.” *Journal of Experimental Zoology* 285 no. 3 (1999):178–196.
3. 3 R. Mancini, M. Nigro, G. Ippolito. “Lazzaro Spallanzani and His Refutation of the Theory of Spontaneous Generation.” *Le Infezioni in Medicina* 15 no. 3 (2007):199–206.
4. 4 R. Vallery-Radot. *The Life of Pasteur*, trans. R.L. Devonshire. New York: McClure, Phillips and Co, 1902, 1:142.

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1.3.2: Foundations of Modern Cell Theory

Learning Objectives

- Explain the key points of cell theory and the individual contributions of Hooke, Schleiden, Schwann, Remak, and Virchow
- Explain the key points of endosymbiotic theory and cite the evidence that supports this concept
- Explain the contributions of Semmelweis, Snow, Pasteur, Lister, and Koch to the development of germ theory

While some scientists were arguing over the theory of spontaneous generation, other scientists were making discoveries leading to a better understanding of what we now call the cell theory. Modern cell theory has two basic tenets:

- All cells only come from other cells (the principle of biogenesis).
- Cells are the fundamental units of organisms.

Today, these tenets are fundamental to our understanding of life on earth. However, modern cell theory grew out of the collective work of many scientists.

The Origins of Cell Theory

The English scientist Robert Hooke first used the term “cells” in 1665 to describe the small chambers within cork that he observed under a microscope of his own design. To Hooke, thin sections of cork resembled “Honey-comb,” or “small Boxes or Bladders of Air.” He noted that each “Cavern, Bubble, or Cell” was distinct from the others (Figure 1.3.2.1). At the time, Hooke was not aware that the cork cells were long dead and, therefore, lacked the internal structures found within living cells.

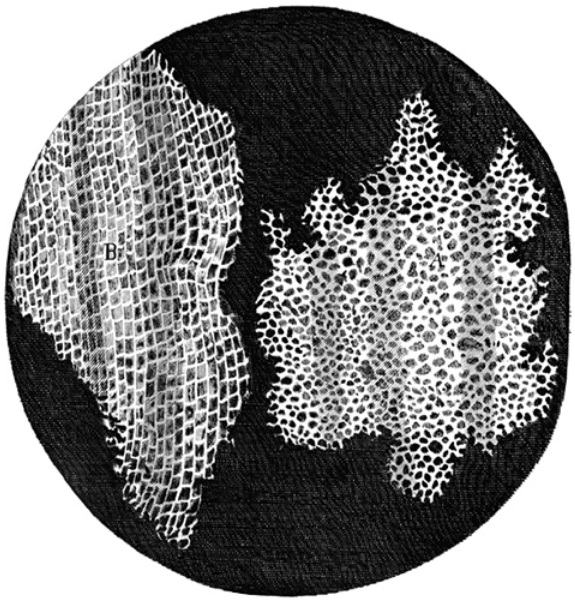


Figure 1.3.2.1: Robert Hooke (1635–1703) was the first to describe cells based upon his microscopic observations of cork. This illustration was published in his work *Micrographia*.

Despite Hooke’s early description of cells, their significance as the fundamental unit of life was not yet recognized. Nearly 200 years later, in 1838, Matthias Schleiden (1804–1881), a German botanist who made extensive microscopic observations of plant tissues, described them as being composed of cells. Visualizing plant cells was relatively easy because plant cells are clearly separated by their thick cell walls. Schleiden believed that cells formed through crystallization, rather than cell division.

Theodor Schwann (1810–1882), a noted German physiologist, made similar microscopic observations of animal tissue. In 1839, after a conversation with Schleiden, Schwann realized that similarities existed between plant and animal tissues. This laid the foundation for the idea that cells are the fundamental components of plants and animals.

In the 1850s, two Polish scientists living in Germany pushed this idea further, culminating in what we recognize today as the modern cell theory. In 1852, Robert Remak (1815–1865), a prominent neurologist and embryologist, published convincing

evidence that cells are derived from other cells as a result of cell division. However, this idea was questioned by many in the scientific community. Three years later, Rudolf Virchow (1821–1902), a well-respected pathologist, published an editorial essay entitled "Cellular Pathology," which popularized the concept of cell theory using the Latin phrase *omnis cellula a cellula* ("all cells arise from cells"), which is essentially the second tenet of modern cell theory.[1]Given the similarity of Virchow's work to Remak's, there is some controversy as to which scientist should receive credit for articulating cell theory. See the following Eye on Ethics feature for more about this controversy.

Science and Plagiarism

Rudolf Virchow, a prominent, Polish-born, German scientist, is often remembered as the "Father of Pathology." Well known for innovative approaches, he was one of the first to determine the causes of various diseases by examining their effects on tissues and organs. He was also among the first to use animals in his research and, as a result of his work, he was the first to name numerous diseases and created many other medical terms. Over the course of his career, he published more than 2,000 papers and headed various important medical facilities, including the Charité – Universitätsmedizin Berlin, a prominent Berlin hospital and medical school. But he is, perhaps, best remembered for his 1855 editorial essay titled "Cellular Pathology," published in *Archiv für Pathologische Anatomie und Physiologie*, a journal that Virchow himself cofounded and still exists today.

Despite his significant scientific legacy, there is some controversy regarding this essay, in which Virchow proposed the central tenet of modern cell theory—that all cells arise from other cells. Robert Remak, a former colleague who worked in the same laboratory as Virchow at the University of Berlin, had published the same idea 3 years before. Though it appears Virchow was familiar with Remak's work, he neglected to credit Remak's ideas in his essay. When Remak wrote a letter to Virchow pointing out similarities between Virchow's ideas and his own, Virchow was dismissive. In 1858, in the preface to one of his books, Virchow wrote that his 1855 publication was just an editorial piece, not a scientific paper, and thus there was no need to cite Remak's work.



(a) (b)

Figure 1.3.2.2: (a) Rudolf Virchow (1821–1902) popularized the cell theory in an 1855 essay entitled "Cellular Pathology." (b) The idea that all cells originate from other cells was first published in 1852 by his contemporary and former colleague Robert Remak (1815–1865).

By today's standards, Virchow's editorial piece would certainly be considered an act of plagiarism, since he presented Remak's ideas as his own. However, in the 19th century, standards for academic integrity were much less clear. Virchow's strong reputation, coupled with the fact that Remak was a Jew in a somewhat anti-Semitic political climate, shielded him from any significant repercussions. Today, the process of peer review and the ease of access to the scientific literature help discourage plagiarism. Although scientists are still motivated to publish original ideas that advance scientific knowledge, those who would consider plagiarizing are well aware of the serious consequences.

In academia, plagiarism represents the theft of both individual thought and research—an offense that can destroy reputations and end careers.[2 3 4 5]

? Exercise 1.3.2.1

1. What are the key points of the cell theory?
2. What contributions did Rudolf Virchow and Robert Remak make to the development of the cell theory?

Endosymbiotic Theory

As scientists were making progress toward understanding the role of cells in plant and animal tissues, others were examining the structures within the cells themselves. In 1831, Scottish botanist Robert Brown (1773–1858) was the first to describe observations of nuclei, which he observed in plant cells. Then, in the early 1880s, German botanist Andreas Schimper (1856–1901) was the first to describe the chloroplasts of plant cells, identifying their role in starch formation during photosynthesis and noting that they divided independent of the nucleus.

Based upon the chloroplasts' ability to reproduce independently, Russian botanist Konstantin Mereschkowski (1855–1921) suggested in 1905 that chloroplasts may have originated from ancestral photosynthetic bacteria living symbiotically inside a eukaryotic cell. He proposed a similar origin for the nucleus of plant cells. This was the first articulation of the endosymbiotic hypothesis, and would explain how eukaryotic cells evolved from ancestral bacteria.

Mereschkowski's endosymbiotic hypothesis was furthered by American anatomist Ivan Wallin (1883–1969), who began to experimentally examine the similarities between mitochondria, chloroplasts, and bacteria—in other words, to put the endosymbiotic hypothesis to the test using objective investigation. Wallin published a series of papers in the 1920s supporting the endosymbiotic hypothesis, including a 1926 publication co-authored with Mereschkowski. Wallin claimed he could culture mitochondria outside of their eukaryotic host cells. Many scientists dismissed his cultures of mitochondria as resulting from bacterial contamination. Modern genome sequencing work supports the dissenting scientists by showing that much of the genome of mitochondria had been transferred to the host cell's nucleus, preventing the mitochondria from being able to live on their own.[6] [7]

Wallin's ideas regarding the endosymbiotic hypothesis were largely ignored for the next 50 years because scientists were unaware that these organelles contained their own DNA. However, with the discovery of mitochondrial and chloroplast DNA in the 1960s, the endosymbiotic hypothesis was resurrected. Lynn Margulis (1938–2011), an American geneticist, published her ideas regarding the endosymbiotic hypothesis of the origins of mitochondria and chloroplasts in 1967.[8] In the decade leading up to her publication, advances in microscopy had allowed scientists to differentiate prokaryotic cells from eukaryotic cells. In her publication, Margulis reviewed the literature and argued that the eukaryotic organelles such as mitochondria and chloroplasts are of prokaryotic origin. She presented a growing body of microscopic, genetic, molecular biology, fossil, and geological data to support her claims.

Again, this hypothesis was not initially popular, but mounting genetic evidence due to the advent of DNA sequencing supported the endosymbiotic theory, which is now defined as the theory that mitochondria and chloroplasts arose as a result of prokaryotic cells establishing a symbiotic relationship within a eukaryotic host (Figure 1.3.2.3). With Margulis' initial endosymbiotic theory gaining wide acceptance, she expanded on the theory in her 1981 book *Symbiosis in Cell Evolution*. In it, she explains how endosymbiosis is a major driving factor in the evolution of organisms. More recent genetic sequencing and phylogenetic analysis show that mitochondrial DNA and chloroplast DNA are highly related to their bacterial counterparts, both in DNA sequence and chromosome structure. However, mitochondrial DNA and chloroplast DNA are reduced compared with nuclear DNA because many of the genes have moved from the organelles into the host cell's nucleus. Additionally, mitochondrial and chloroplast ribosomes are structurally similar to bacterial ribosomes, rather than to the eukaryotic ribosomes of their hosts. Last, the binary fission of these organelles strongly resembles the binary fission of bacteria, as compared with mitosis performed by eukaryotic cells. Since Margulis' original proposal, scientists have observed several examples of bacterial endosymbionts in modern-day eukaryotic cells. Examples include the endosymbiotic bacteria found within the guts of certain insects, such as cockroaches,[9] and photosynthetic bacteria-like organelles found in protists.[10]

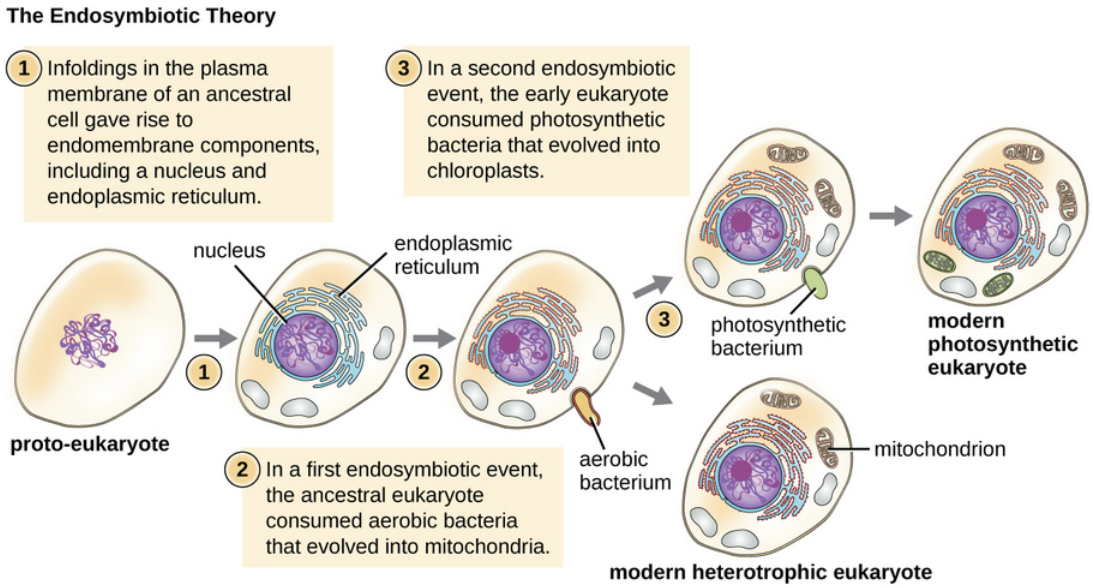


Figure 1.3.2.3: According to the endosymbiotic theory, mitochondria and chloroplasts are each derived from the uptake of bacteria. These bacteria established a symbiotic relationship with their host cell that eventually led to the bacteria evolving into mitochondria and chloroplasts.

? Exercise 1.3.2.2

1. What does the modern endosymbiotic theory state?
2. What evidence supports the endosymbiotic theory?

The Germ Theory of Disease

Prior to the discovery of microbes during the 17th century, other theories circulated about the origins of disease. For example, the ancient Greeks proposed the miasma theory, which held that disease originated from particles emanating from decomposing matter, such as that in sewage or cesspits. Such particles infected humans in close proximity to the rotting material. Diseases including the Black Death, which ravaged Europe's population during the Middle Ages, were thought to have originated in this way.

In 1546, Italian physician Girolamo Fracastoro proposed, in his essay *De Contagione et Contagiosis Morbis*, that seed-like spores may be transferred between individuals through direct contact, exposure to contaminated clothing, or through the air. We now recognize Fracastoro as an early proponent of the germ theory of disease, which states that diseases may result from microbial infection. However, in the 16th century, Fracastoro's ideas were not widely accepted and would be largely forgotten until the 19th century.

In 1847, Hungarian obstetrician Ignaz Semmelweis (Figure 1.3.2.4) observed that mothers who gave birth in hospital wards staffed by physicians and medical students were more likely to suffer and die from puerperal fever after childbirth (10%–20% mortality rate) than were mothers in wards staffed by midwives (1% mortality rate). Semmelweis observed medical students performing autopsies and then subsequently carrying out vaginal examinations on living patients without washing their hands in between. He suspected that the students carried disease from the autopsies to the patients they examined. His suspicions were supported by the untimely death of a friend, a physician who contracted a fatal wound infection after a postmortem examination of a woman who had died of a puerperal infection. The dead physician's wound had been caused by a scalpel used during the examination, and his subsequent illness and death closely paralleled that of the dead patient.

Although Semmelweis did not know the true cause of puerperal fever, he proposed that physicians were somehow transferring the causative agent to their patients. He suggested that the number of puerperal fever cases could be reduced if physicians and medical students simply washed their hands with chlorinated lime water before and after examining every patient. When this practice was implemented, the maternal mortality rate in mothers cared for by physicians dropped to the same 1% mortality rate observed among mothers cared for by midwives. This demonstrated that handwashing was a very effective method for preventing disease transmission. Despite this great success, many discounted Semmelweis's work at the time, and physicians were slow to adopt the

simple procedure of handwashing to prevent infections in their patients because it contradicted established norms for that time period.

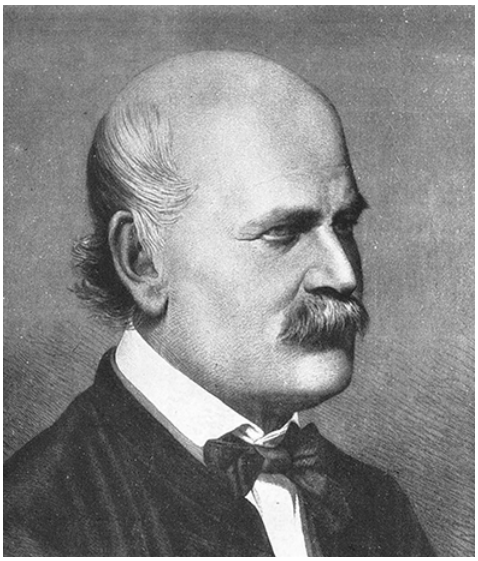


Figure 1.3.2.4: Ignaz Semmelweis (1818–1865) was a proponent of the importance of handwashing to prevent transfer of disease between patients by physicians.

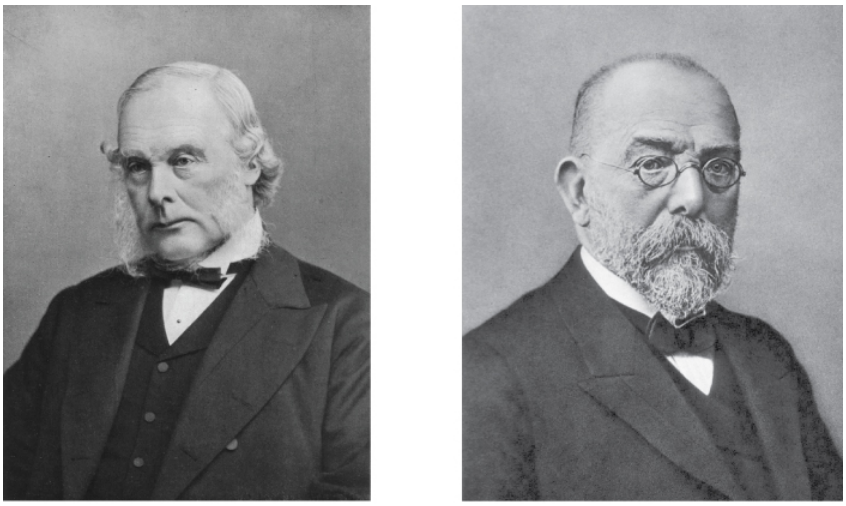
Around the same time Semmelweis was promoting handwashing, in 1848, British physician John Snow conducted studies to track the source of cholera outbreaks in London. By tracing the outbreaks to two specific water sources, both of which were contaminated by sewage, Snow ultimately demonstrated that cholera bacteria were transmitted via drinking water. Snow's work is influential in that it represents the first known epidemiological study, and it resulted in the first known public health response to an epidemic. The work of both Semmelweis and Snow clearly refuted the prevailing miasma theory of the day, showing that disease is not only transmitted through the air but also through contaminated items.

Although the work of Semmelweis and Snow successfully showed the role of sanitation in preventing infectious disease, the cause of disease was not fully understood. The subsequent work of Louis Pasteur, Robert Koch, and Joseph Listerwould further substantiate the germ theory of disease.

While studying the causes of beer and wine spoilage in 1856, Pasteur discovered properties of fermentation by microorganisms. He had demonstrated with his swan-neck flask experiments (link) that airborne microbes, not spontaneous generation, were the cause of food spoilage, and he suggested that if microbes were responsible for food spoilage and fermentation, they could also be responsible for causing infection. This was the foundation for the germ theory of disease.

Meanwhile, British surgeon Joseph Lister (Figure 1.3.2.5) was trying to determine the causes of postsurgical infections. Many physicians did not give credence to the idea that microbes on their hands, on their clothes, or in the air could infect patients' surgical wounds, despite the fact that 50% of surgical patients, on average, were dying of postsurgical infections.[11] Lister, however, was familiar with the work of Semmelweis and Pasteur; therefore, he insisted on handwashing and extreme cleanliness during surgery. In 1867, to further decrease the incidence of postsurgical wound infections, Lister began using carbolic acid (phenol) spray disinfectant/antiseptic during surgery. His extremely successful efforts to reduce postsurgical infection caused his techniques to become a standard medical practice.

A few years later, Robert Koch (Figure 1.3.2.5) proposed a series of postulates (Koch's postulates) based on the idea that the cause of a specific disease could be attributed to a specific microbe. Using these postulates, Koch and his colleagues were able to definitively identify the causative pathogens of specific diseases, including anthrax, tuberculosis, and cholera. Koch's "one microbe, one disease" concept was the culmination of the 19th century's paradigm shift away from miasma theory and toward the germ theory of disease. Koch's postulates are discussed more thoroughly in How Pathogens Cause Disease.



(a) (b)

Figure 1.3.2.5: (a) Joseph Lister developed procedures for the proper care of surgical wounds and the sterilization of surgical equipment. (b) Robert Koch established a protocol to determine the cause of infectious disease. Both scientists contributed significantly to the acceptance of the germ theory of disease.

? Exercise 1.3.2.3

1. Compare and contrast the miasma theory of disease with the germ theory of disease.
2. How did Joseph Lister's work contribute to the debate between the miasma theory and germ theory and how did this increase the success of medical procedures?

Clinical Focus: Part 2

After suffering a fever, congestion, cough, and increasing aches and pains for several days, Barbara suspects that she has a case of the flu. She decides to visit the health center at her university. The PA tells Barbara that her symptoms could be due to a range of diseases, such as influenza, bronchitis, pneumonia, or tuberculosis.

During her physical examination, the PA notes that Barbara's heart rate is slightly elevated. Using a pulse oximeter, a small device that clips on her finger, he finds that Barbara has hypoxemia—a lower-than-normal level of oxygen in the blood. Using a stethoscope, the PA listens for abnormal sounds made by Barbara's heart, lungs, and digestive system. As Barbara breathes, the PA hears a crackling sound and notes a slight shortness of breath. He collects a sputum sample, noting the greenish color of the mucus, and orders a chest radiograph, which shows a "shadow" in the left lung. All of these signs are suggestive of pneumonia, a condition in which the lungs fill with mucus (Figure 1.3.2.6).

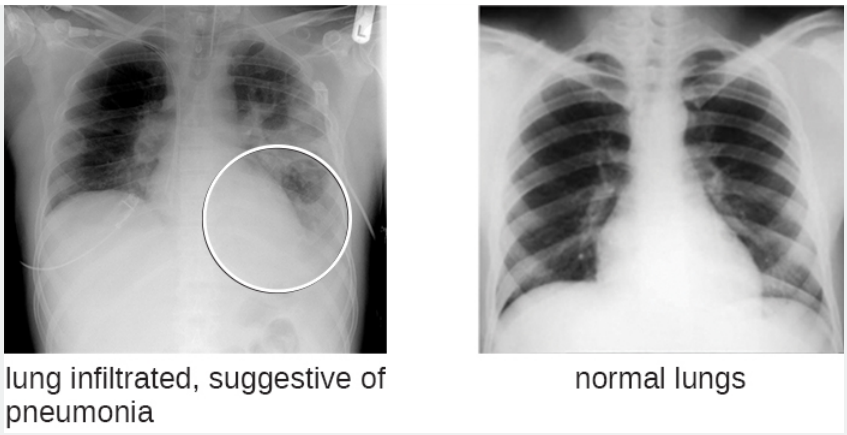


Figure 1.3.2.6: This is a chest radiograph typical of pneumonia. Because X-ray images are negative images, a “shadow” is seen as a white area within the lung that should otherwise be black. In this case, the left lung shows a shadow as a result of pockets in the lung that have become filled with fluid. (credit left: modification of work by “Christaras A”/Wikimedia Commons)

Exercise 1.3.2.4

What kinds of infectious agents are known to cause pneumonia?

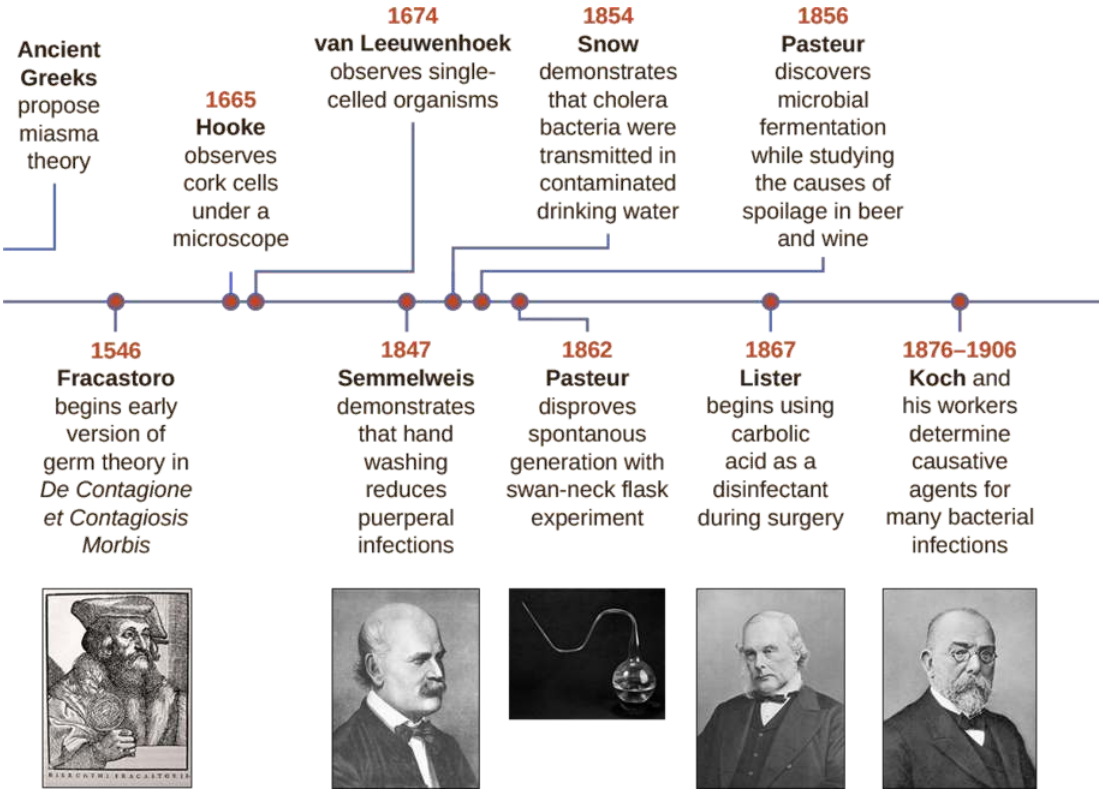


Figure 1.3.2.7: (credit “swan-neck flask”: modification of work by Wellcome Images)

Key Concepts and Summary

- Although cells were first observed in the 1660s by Robert Hooke, **cell theory** was not well accepted for another 200 years. The work of scientists such as Schleiden, Schwann, Remak, and Virchow contributed to its acceptance.
- **Endosymbiotic theory** states that mitochondria and chloroplasts, organelles found in many types of organisms, have their origins in bacteria. Significant structural and genetic information support this theory.
- The **miasma theory of disease** was widely accepted until the 19th century, when it was replaced by the **germ theory of disease** thanks to the work of Semmelweis, Snow, Pasteur, Lister, and Koch, and others.

Footnotes

1. 1 M. Schultz. “Rudolph Virchow.” *Emerging Infectious Diseases* 14 no. 9 (2008):1480–1481.
2. 2 B. Kisch. “Forgotten Leaders in Modern Medicine, Valentin, Gouby, Remak, Auerbach.” *Transactions of the American Philosophical Society* 44 (1954):139–317.
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5. 5 C. Zuchora-Walske. *Key Discoveries in Life Science*. Minneapolis, MN: Lerner Publishing, 2015:12–13.
6. 6 T. Embley, W. Martin. “Eukaryotic Evolution, Changes, and Challenges.” *Nature* Vol. 440 (2006):623–630.
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9. 9 A.E. Douglas. “The Microbial Dimension in Insect Nutritional Ecology.” *Functional Ecology* 23 (2009):38–47.
10. 10 J.M. Jaynes, L.P. Vernon. “The Cyanelle of *Cyanophora paradoxa*: Almost a Cyanobacterial Chloroplast.” *Trends in Biochemical Sciences* 7 no. 1 (1982):22–24.
11. 11 Alexander, J. Wesley. “The Contributions of Infection Control to a Century of Progress” *Annals of Surgery* 201:423-428, 1985.

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1.3.E: The Cell (Exercises)

3.1: Spontaneous Generation

The theory of spontaneous generation states that life arose from nonliving matter. It was a long-held belief dating back to Aristotle and the ancient Greeks. Experimentation by Francesco Redi in the 17th century presented the first significant evidence refuting spontaneous generation by showing that flies must have access to meat for maggots to develop on the meat. Louis Pasteur is credited with conclusively disproving the theory and proposed that “life only comes from life.”

Multiple Choice

Which of the following individuals argued in favor of the theory of spontaneous generation?

A. Francesco Redi
B. Louis Pasteur
C. John Needham
D. Lazzaro Spallanzani

Answer

C

Which of the following individuals is credited for definitively refuting the theory of spontaneous generation using broth in swan-neck flask?

A. Aristotle
B. Jan Baptista van Helmont
C. John Needham
D. Louis Pasteur

Answer

D

Which of the following experimented with raw meat, maggots, and flies in an attempt to disprove the theory of spontaneous generation.

A. Aristotle
B. Lazzaro Spallanzani
C. Antonie van Leeuwenhoek
D. Francesco Redi

Answer

D

Fill in the Blank

The assertion that “life only comes from life” was stated by Louis Pasteur in regard to his experiments that definitively refuted the theory of _____.

Answer

spontaneous generation

True/False

Exposure to air is necessary for microbial growth.

Answer

False

Short Answer

Explain in your own words Pasteur's swan-neck flask experiment.

Explain why the experiments of Needham and Spallanzani yielded in different results even though they used similar methodologies.

Critical Thinking

What would the results of Pasteur's swan-neck flask experiment have looked like if they supported the theory of spontaneous generation?

3.2: Foundations of Modern Cell Theory

Although cells were first observed in the 1660s by Robert Hooke, cell theory was not well accepted for another 200 years. The work of scientists such as Schleiden, Schwann, Remak, and Virchow contributed to its acceptance. Endosymbiotic theory states that mitochondria and chloroplasts, organelles found in many types of organisms, have their origins in bacteria. Significant structural and genetic information support this theory. The miasma theory was widely accepted until the 19th century.

Multiple Choice

Which of the following individuals did not contribute to the establishment of cell theory?

A. Girolamo Fracastoro
B. Matthias Schleiden
C. Robert Remak
D. Robert Hooke

Answer

A

Whose proposal of the endosymbiotic theory of mitochondrial and chloroplast origin was ultimately accepted by the greater scientific community?

A. Rudolf Virchow
B. Ignaz Semmelweis
C. Lynn Margulis
D. Theodor Schwann

Answer

C

Which of the following developed a set of postulates for determining whether a particular disease is caused by a particular pathogen?

A. John Snow
B. Robert Koch
C. Joseph Lister
D. Louis Pasteur

Answer

B

Fill in the Blank

John Snow is known as the Father of _____.

Answer

epidemiology

The _____ theory states that disease may originate from proximity to decomposing matter and is not due to person-to-person contact.

Answer

miasma

The scientist who first described cells was _____.

Answer

Robert Hooke

Short Answer

How did the explanation of Virchow and Remak for the origin of cells differ from that of Schleiden and Schwann?

What evidence exists that supports the endosymbiotic theory?

What were the differences in mortality rates due to puerperal fever that Ignaz Semmelweis observed? How did he propose to reduce the occurrence of puerperal fever? Did it work?

Critical Thinking

Why are mitochondria and chloroplasts unable to multiply outside of a host cell?

Why was the work of Snow so important in supporting the germ theory?

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SECTION OVERVIEW

1.4: Cell Structure

Your body has many kinds of cells, each specialized for a specific purpose. Just as a home is made from a variety of building materials, the human body is constructed from many cell types. For example, epithelial cells protect the surface of the body and cover the organs and body cavities within. Bone cells help to support and protect the body. Cells of the immune system fight invading bacteria. Additionally, blood and blood cells carry nutrients and oxygen throughout the body while removing carbon dioxide. Each of these cell types plays a vital role during the growth, development, and day-to-day maintenance of the body. In spite of their enormous variety, however, cells from all organisms—even ones as diverse as bacteria, onion, and human—share certain fundamental characteristics.

1.4.1: Prelude to Cell Structure

1.4.2: Studying Cells

1.4.3: Prokaryotic Cells

1.4.4: Eukaryotic Cells

1.4.5: The Endomembrane System and Proteins

1.4.6: The Cytoskeleton

1.4.7: Connections between Cells and Cellular Activities

1.4.8: Cell Structure (Exercises)

Thumbnail: The generalized structure of a prokaryotic cell. (CC BY 4.0; OpenStax).

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1.4.1: Prelude to Cell Structure

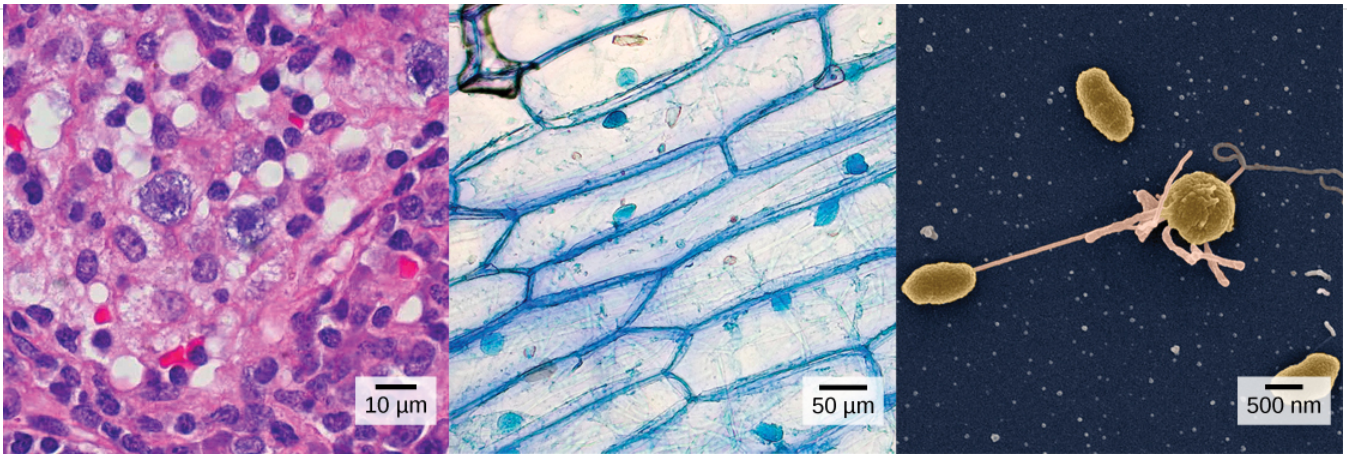


Figure 1.4.1.1: (a) Nasal sinus cells (viewed with a light microscope), (b) onion cells (viewed with a light microscope), and (c) *Vibrio tasmaniensis* bacterial cells (seen through a scanning electron microscope) are from very different organisms, yet all share certain characteristics of basic cell structure. (credit a: modification of work by Ed Uthman, MD; credit b: modification of work by Umberto Salvagnin; credit c: modification of work by Anthony D'Onofrio, William H. Fowle, Eric J. Stewart, and Kim Lewis of the Lewis Lab at Northeastern University; scale-bar data from Matt Russell)

Close your eyes and picture a brick wall. What is the basic building block of that wall? A single brick, of course. Like a brick wall, your body is composed of basic building blocks, and the building blocks of your body are cells.

Your body has many kinds of cells, each specialized for a specific purpose. Just as a home is made from a variety of building materials, the human body is constructed from many cell types. For example, epithelial cells protect the surface of the body and cover the organs and body cavities within. Bone cells help to support and protect the body. Cells of the immune system fight invading bacteria. Additionally, blood and blood cells carry nutrients and oxygen throughout the body while removing carbon dioxide. Each of these cell types plays a vital role during the growth, development, and day-to-day maintenance of the body. In spite of their enormous variety, however, cells from all organisms—even ones as diverse as bacteria, onion, and human—share certain fundamental characteristics.

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1.4.2: Studying Cells

Skills to Develop

- Describe the role of cells in organisms
- Compare and contrast light microscopy and electron microscopy
- Summarize cell theory

A cell is the smallest unit of a living thing. A living thing, whether made of one cell (like bacteria) or many cells (like a human), is called an organism. Thus, cells are the basic building blocks of all organisms.

Several cells of one kind that interconnect with each other and perform a shared function form tissues, several tissues combine to form an organ (your stomach, heart, or brain), and several organs make up an organ system (such as the digestive system, circulatory system, or nervous system). Several systems that function together form an organism (like a human being). Here, we will examine the structure and function of cells.

There are many types of cells, all grouped into one of two broad categories: prokaryotic and eukaryotic. For example, both animal and plant cells are classified as eukaryotic cells, whereas bacterial cells are classified as prokaryotic. Before discussing the criteria for determining whether a cell is prokaryotic or eukaryotic, let's first examine how biologists study cells.

Microscopy

Cells vary in size. With few exceptions, individual cells cannot be seen with the naked eye, so scientists use microscopes (micro- = "small"; -scope = "to look at") to study them. A microscope is an instrument that magnifies an object. Most photographs of cells are taken with a microscope, and these images can also be called micrographs.

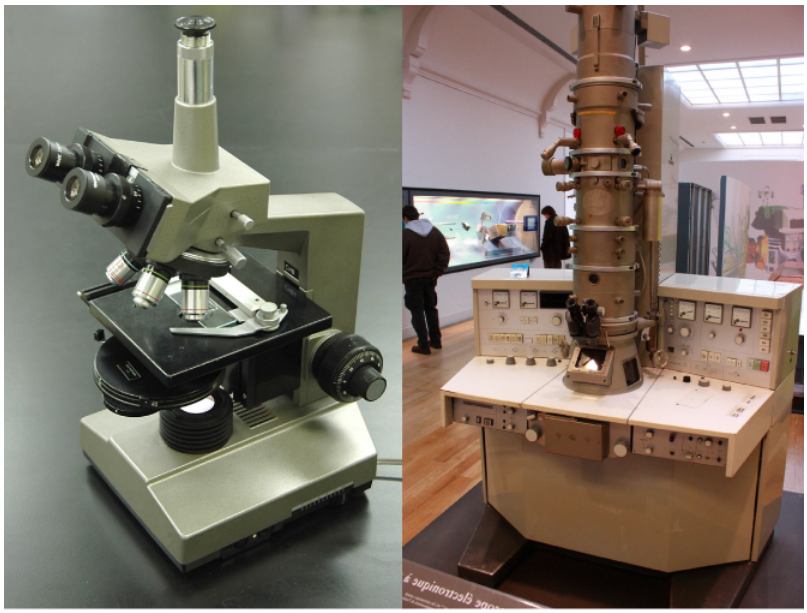
The optics of a microscope's lenses change the orientation of the image that the user sees. A specimen that is right-side up and facing right on the microscope slide will appear upside-down and facing left when viewed through a microscope, and vice versa. Similarly, if the slide is moved left while looking through the microscope, it will appear to move right, and if moved down, it will seem to move up. This occurs because microscopes use two sets of lenses to magnify the image. Because of the manner by which light travels through the lenses, this system of two lenses produces an inverted image (binocular, or dissecting microscopes, work in a similar manner, but include an additional magnification system that makes the final image appear to be upright).

Light Microscopes

To give you a sense of cell size, a typical human red blood cell is about eight millionths of a meter or eight micrometers (abbreviated as eight µm) in diameter; the head of a pin of is about two thousandths of a meter (two mm) in diameter. That means about 250 red blood cells could fit on the head of a pin.

Most student microscopes are classified as light microscopes (Figure 1.4.2.1a). Visible light passes and is bent through the lens system to enable the user to see the specimen. Light microscopes are advantageous for viewing living organisms, but since individual cells are generally transparent, their components are not distinguishable unless they are colored with special stains. Staining, however, usually kills the cells.

Light microscopes commonly used in the undergraduate college laboratory magnify up to approximately 400 times. Two parameters that are important in microscopy are magnification and resolving power. Magnification is the process of enlarging an object in appearance. Resolving power is the ability of a microscope to distinguish two adjacent structures as separate: the higher the resolution, the better the clarity and detail of the image. When oil immersion lenses are used for the study of small objects, magnification is usually increased to 1,000 times. In order to gain a better understanding of cellular structure and function, scientists typically use electron microscopes.



(a) (b)

Figure 1.4.2.1: (a) Most light microscopes used in a college biology lab can magnify cells up to approximately 400 times and have a resolution of about 200 nanometers. (b) Electron microscopes provide a much higher magnification, 100,000x, and a have a resolution of 50 picometers. (credit a: modification of work by "GcG"/Wikimedia Commons; credit b: modification of work by Evan Bench)

Electron Microscopes

In contrast to light microscopes, electron microscopes (Figure 1.4.2.1b) use a beam of electrons instead of a beam of light. Not only does this allow for higher magnification and, thus, more detail (Figure 1.4.2.2), it also provides higher resolving power. The method used to prepare the specimen for viewing with an electron microscope kills the specimen. Electrons have short wavelengths (shorter than photons) that move best in a vacuum, so living cells cannot be viewed with an electron microscope.

In a scanning electron microscope, a beam of electrons moves back and forth across a cell's surface, creating details of cell surface characteristics. In a transmission electron microscope, the electron beam penetrates the cell and provides details of a cell's internal structures. As you might imagine, electron microscopes are significantly more bulky and expensive than light microscopes.



(a) (b)

Figure 1.4.2.2: (a) These *Salmonella* bacteria appear as tiny purple dots when viewed with a light microscope. (b) This scanning electron microscope micrograph shows *Salmonella* bacteria (in red) invading human cells (yellow). Even though subfigure (b) shows a different *Salmonella* specimen than subfigure (a), you can still observe the comparative increase in magnification and detail. (credit a: modification of work by CDC/Armed Forces Institute of Pathology, Charles N. Farmer, Rocky Mountain Laboratories; credit b: modification of work by NIAID, NIH; scale-bar data from Matt Russell)

Link to Learning

For another perspective on cell size, try the HowBig interactive at this site.

Cell Theory

The microscopes we use today are far more complex than those used in the 1600s by Antony van Leeuwenhoek, a Dutch shopkeeper who had great skill in crafting lenses. Despite the limitations of his now-ancient lenses, van Leeuwenhoek observed the movements of protista (a type of single-celled organism) and sperm, which he collectively termed “animalcules.”

In a 1665 publication called *Micrographia*, experimental scientist Robert Hooke coined the term “cell” for the box-like structures he observed when viewing cork tissue through a lens. In the 1670s, van Leeuwenhoek discovered bacteria and protozoa. Later advances in lenses, microscope construction, and staining techniques enabled other scientists to see some components inside cells.

By the late 1830s, botanist Matthias Schleiden and zoologist Theodor Schwann were studying tissues and proposed the unified cell theory, which states that all living things are composed of one or more cells, the cell is the basic unit of life, and new cells arise from existing cells. Rudolf Virchow later made important contributions to this theory.

Career Connection: Cytotechnologist

Have you ever heard of a medical test called a Pap smear (Figure 1.4.2.3)? In this test, a doctor takes a small sample of cells from the uterine cervix of a patient and sends it to a medical lab where a cytotechnologist stains the cells and examines them for any changes that could indicate cervical cancer or a microbial infection.

Cytotechnologists (cyto- = “cell”) are professionals who study cells via microscopic examinations and other laboratory tests. They are trained to determine which cellular changes are within normal limits and which are abnormal. Their focus is not limited to cervical cells; they study cellular specimens that come from all organs. When they notice abnormalities, they consult a pathologist, who is a medical doctor who can make a clinical diagnosis.

Cytotechnologists play a vital role in saving people’s lives. When abnormalities are discovered early, a patient’s treatment can begin sooner, which usually increases the chances of a successful outcome.

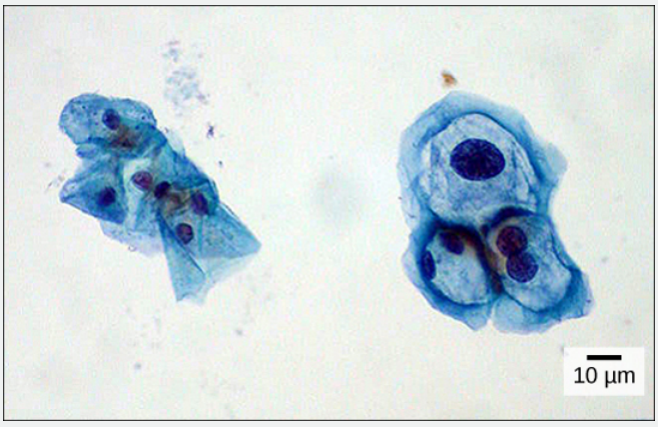


Figure 1.4.2.3: These uterine cervix cells, viewed through a light microscope, were obtained from a Pap smear. Normal cells are on the left. The cells on the right are infected with human papillomavirus (HPV). Notice that the infected cells are larger; also, two of these cells each have two nuclei instead of one, the normal number. (credit: modification of work by Ed Uthman, MD; scale-bar data from Matt Russell)

Summary

A cell is the smallest unit of life. Most cells are so tiny that they cannot be seen with the naked eye. Therefore, scientists use microscopes to study cells. Electron microscopes provide higher magnification, higher resolution, and more detail than light microscopes. The unified cell theory states that all organisms are composed of one or more cells, the cell is the basic unit of life, and new cells arise from existing cells.

Glossary

cell theory
see unified cell theory

electron microscope
an instrument that magnifies an object using a beam of electrons passed and bent through a lens system to visualize a specimen

light microscope
an instrument that magnifies an object using a beam visible light passed and bent through a lens system to visualize a specimen

microscope
an instrument that magnifies an object

unified cell theory
a biological concept that states that all organisms are composed of one or more cells; the cell is the basic unit of life; and new cells arise from existing cells

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1.4.3: Prokaryotic Cells

Skills to Develop

- Name examples of prokaryotic and eukaryotic organisms
- Compare and contrast prokaryotic cells and eukaryotic cells
- Describe the relative sizes of different kinds of cells
- Explain why cells must be small

Cells fall into one of two broad categories: prokaryotic and eukaryotic. Only the predominantly single-celled organisms of the domains Bacteria and Archaea are classified as prokaryotes (pro- = “before”; -kary- = “nucleus”). Cells of animals, plants, fungi, and protists are all eukaryotes (eu- = “true”) and are made up of eukaryotic cells.

Components of Prokaryotic Cells

All cells share four common components: 1) a plasma membrane, an outer covering that separates the cell’s interior from its surrounding environment; 2) cytoplasm, consisting of a jelly-like cytosol within the cell in which other cellular components are found; 3) DNA, the genetic material of the cell; and 4) ribosomes, which synthesize proteins. However, prokaryotes differ from eukaryotic cells in several ways.

A prokaryote is a simple, mostly single-celled (unicellular) organism that lacks a nucleus, or any other membrane-bound organelle. We will shortly come to see that this is significantly different in eukaryotes. Prokaryotic DNA is found in a central part of the cell: the nucleoid (Figure 1.4.3.1).

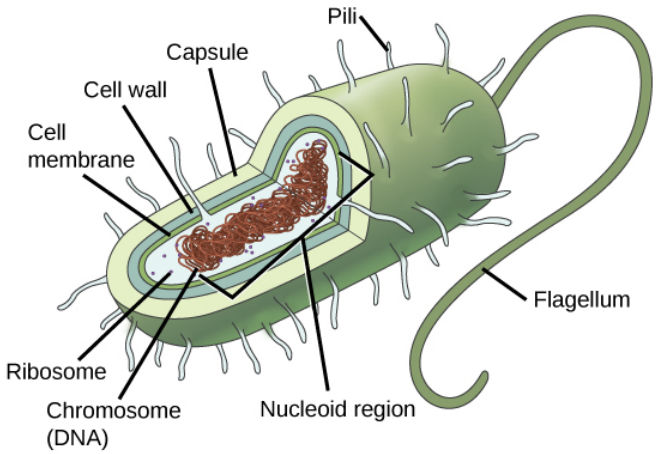


Figure 1.4.3.1: This figure shows the generalized structure of a prokaryotic cell. All prokaryotes have chromosomal DNA localized in a nucleoid, ribosomes, a cell membrane, and a cell wall. The other structures shown are present in some, but not all, bacteria.

Most prokaryotes have a peptidoglycan cell wall and many have a polysaccharide capsule (Figure 1.4.3.1). The cell wall acts as an extra layer of protection, helps the cell maintain its shape, and prevents dehydration. The capsule enables the cell to attach to surfaces in its environment. Some prokaryotes have flagella, pili, or fimbriae. Flagella are used for locomotion. Pili are used to exchange genetic material during a type of reproduction called conjugation. Fimbriae are used by bacteria to attach to a host cell.

Career Connection: Microbiologist

The most effective action anyone can take to prevent the spread of contagious illnesses is to wash his or her hands. Why? Because microbes (organisms so tiny that they can only be seen with microscopes) are ubiquitous. They live on doorknobs, money, your hands, and many other surfaces. If someone sneezes into his hand and touches a doorknob, and afterwards you touch that same doorknob, the microbes from the sneezer’s mucus are now on your hands. If you touch your hands to your mouth, nose, or eyes, those microbes can enter your body and could make you sick.

However, not all microbes (also called microorganisms) cause disease; most are actually beneficial. You have microbes in your gut that make vitamin K. Other microorganisms are used to ferment beer and wine.

Microbiologists are scientists who study microbes. Microbiologists can pursue a number of careers. Not only do they work in the food industry, they are also employed in the veterinary and medical fields. They can work in the pharmaceutical sector, serving key roles in research and development by identifying new sources of antibiotics that could be used to treat bacterial infections.

Environmental microbiologists may look for new ways to use specially selected or genetically engineered microbes for the removal of pollutants from soil or groundwater, as well as hazardous elements from contaminated sites. These uses of microbes are called bioremediation technologies. Microbiologists can also work in the field of bioinformatics, providing specialized knowledge and insight for the design, development, and specificity of computer models of, for example, bacterial epidemics.

Cell Size

At 0.1 to 5.0 µm in diameter, prokaryotic cells are significantly smaller than eukaryotic cells, which have diameters ranging from 10 to 100 µm (Figure 1.4.3.2). The small size of prokaryotes allows ions and organic molecules that enter them to quickly diffuse to other parts of the cell. Similarly, any wastes produced within a prokaryotic cell can quickly diffuse out. This is not the case in eukaryotic cells, which have developed different structural adaptations to enhance intracellular transport.

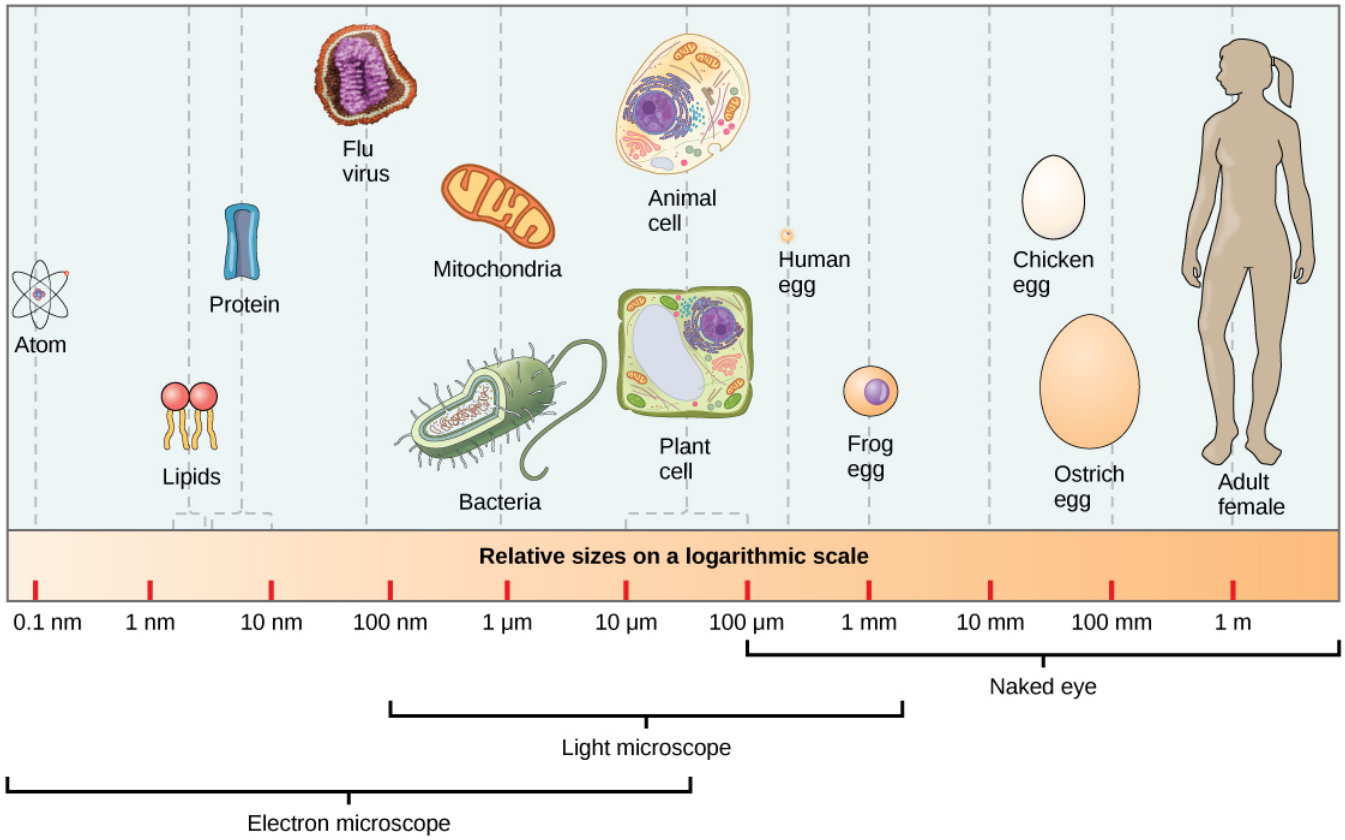


Figure 1.4.3.2: This figure shows relative sizes of microbes on a logarithmic scale (recall that each unit of increase in a logarithmic scale represents a 10-fold increase in the quantity being measured).

Small size, in general, is necessary for all cells, whether prokaryotic or eukaryotic. Let's examine why that is so. First, we'll consider the area and volume of a typical cell. Not all cells are spherical in shape, but most tend to approximate a sphere. You may remember from your high school geometry course that the formula for the surface area of a sphere is $4\pi r^2$, while the formula for its volume is $4\pi r^2/3$. Thus, as the radius of a cell increases, its surface area increases as the square of its radius, but its volume increases as the cube of its radius (much more rapidly). Therefore, as a cell increases in size, its surface area-to-volume ratio decreases. This same principle would apply if the cell had the shape of a cube (Figure 1.4.3.3). If the cell grows too large, the plasma membrane will not have sufficient surface area to support the rate of diffusion required for the increased volume. In other words, as a cell grows, it becomes less efficient. One way to become more efficient is to divide; another way is to develop

organelles that perform specific tasks. These adaptations lead to the development of more sophisticated cells called eukaryotic cells.

Art Connection

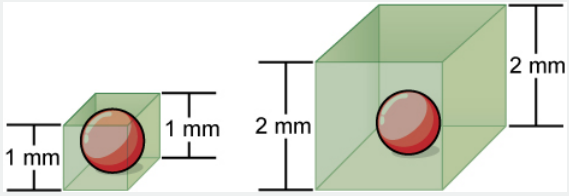


Figure 1.4.3.3: Notice that as a cell increases in size, its surface area-to-volume ratio decreases. When there is insufficient surface area to support a cell's increasing volume, a cell will either divide or die. The cell on the left has a volume of $1\ \text{mm}^3$ and a surface area of $6\ \text{mm}^2$, with a surface area-to-volume ratio of 6 to 1, whereas the cell on the right has a volume of $8\ \text{mm}^3$ and a surface area of $24\ \text{mm}^2$, with a surface area-to-volume ratio of 3 to 1.

Prokaryotic cells are much smaller than eukaryotic cells. What advantages might small cell size confer on a cell? What advantages might large cell size have?

Summary

Prokaryotes are predominantly single-celled organisms of the domains Bacteria and Archaea. All prokaryotes have plasma membranes, cytoplasm, ribosomes, and DNA that is not membrane-bound. Most have peptidoglycan cell walls and many have polysaccharide capsules. Prokaryotic cells range in diameter from 0.1 to 5.0 µm.

As a cell increases in size, its surface area-to-volume ratio decreases. If the cell grows too large, the plasma membrane will not have sufficient surface area to support the rate of diffusion required for the increased volume.

Art Connections

Figure 1.4.3.3: Prokaryotic cells are much smaller than eukaryotic cells. What advantages might small cell size confer on a cell? What advantages might large cell size have?

Answer

Substances can diffuse more quickly through small cells. Small cells have no need for organelles and therefore do not need to expend energy getting substances across organelle membranes. Large cells have organelles that can separate cellular processes, enabling them to build molecules that are more complex.

Glossary

nucleoid

central part of a prokaryotic cell in which the chromosome is found

prokaryote

unicellular organism that lacks a nucleus or any other membrane-bound organelle

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1.4.4: Eukaryotic Cells

Skills to Develop

- Describe the structure of eukaryotic cells
- Compare animal cells with plant cells
- State the role of the plasma membrane
- Summarize the functions of the major cell organelles

Have you ever heard the phrase “form follows function?” It’s a philosophy practiced in many industries. In architecture, this means that buildings should be constructed to support the activities that will be carried out inside them. For example, a skyscraper should be built with several elevator banks; a hospital should be built so that its emergency room is easily accessible.

Our natural world also utilizes the principle of form following function, especially in cell biology, and this will become clear as we explore eukaryotic cells (Figure 1.4.4.1). Unlike prokaryotic cells, eukaryotic cells have: 1) a membrane-bound nucleus; 2) numerous membrane-bound organelles such as the endoplasmic reticulum, Golgi apparatus, chloroplasts, mitochondria, and others; and 3) several, rod-shaped chromosomes. Because a eukaryotic cell’s nucleus is surrounded by a membrane, it is often said to have a “true nucleus.” The word “organelle” means “little organ,” and, as already mentioned, organelles have specialized cellular functions, just as the organs of your body have specialized functions.

At this point, it should be clear to you that eukaryotic cells have a more complex structure than prokaryotic cells. Organelles allow different functions to be compartmentalized in different areas of the cell. Before turning to organelles, let’s first examine two important components of the cell: the plasma membrane and the cytoplasm.

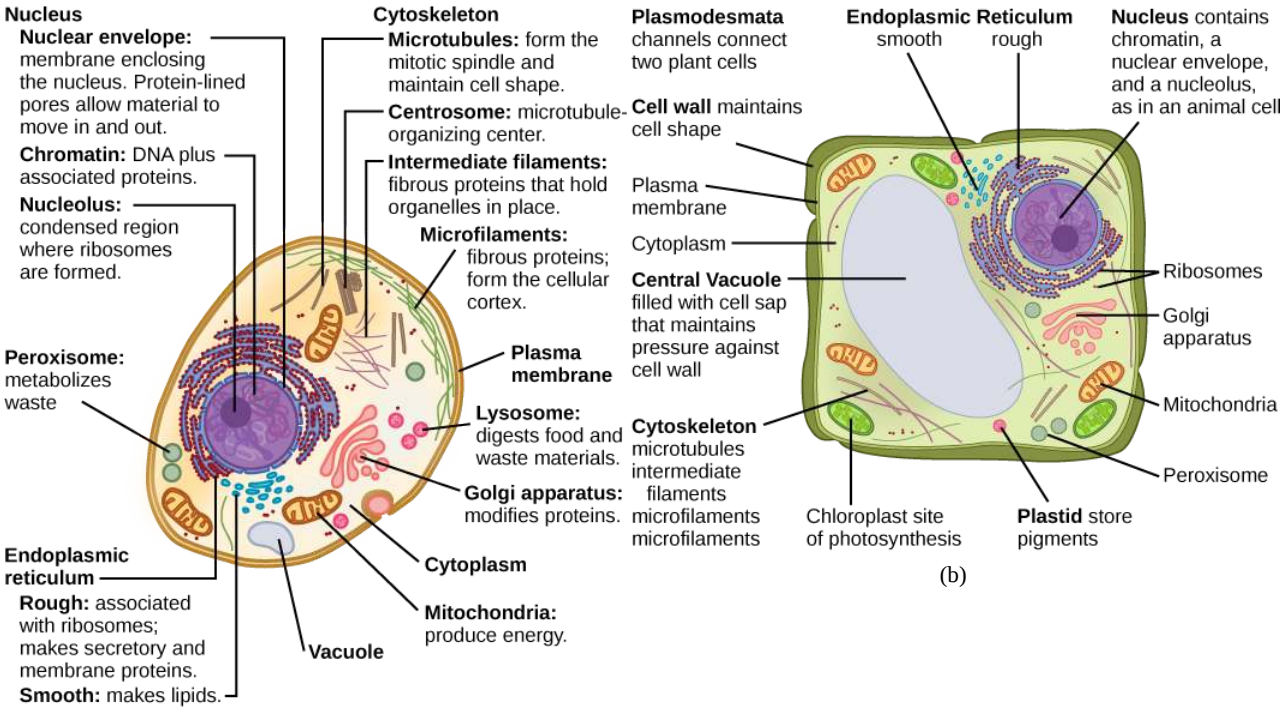


Figure 1.4.4.1: These figures show the major organelles and other cell components of (a) a typical animal cell and (b) a typical eukaryotic plant cell. The plant cell has a cell wall, chloroplasts, plastids, and a central vacuole—structures not found in animal cells. Plant cells do not have lysosomes or centrosomes.

Exercise 1.4.4.1

If the nucleolus were not able to carry out its function, what other cellular organelles would be affected?

The Plasma Membrane

Like prokaryotes, eukaryotic cells have a plasma membrane (Figure 1.4.4.2), a phospholipid bilayer with embedded proteins that separates the internal contents of the cell from its surrounding environment. A phospholipid is a lipid molecule with two fatty acid chains and a phosphate-containing group. The plasma membrane controls the passage of organic molecules, ions, water, and oxygen into and out of the cell. Wastes (such as carbon dioxide and ammonia) also leave the cell by passing through the plasma membrane.

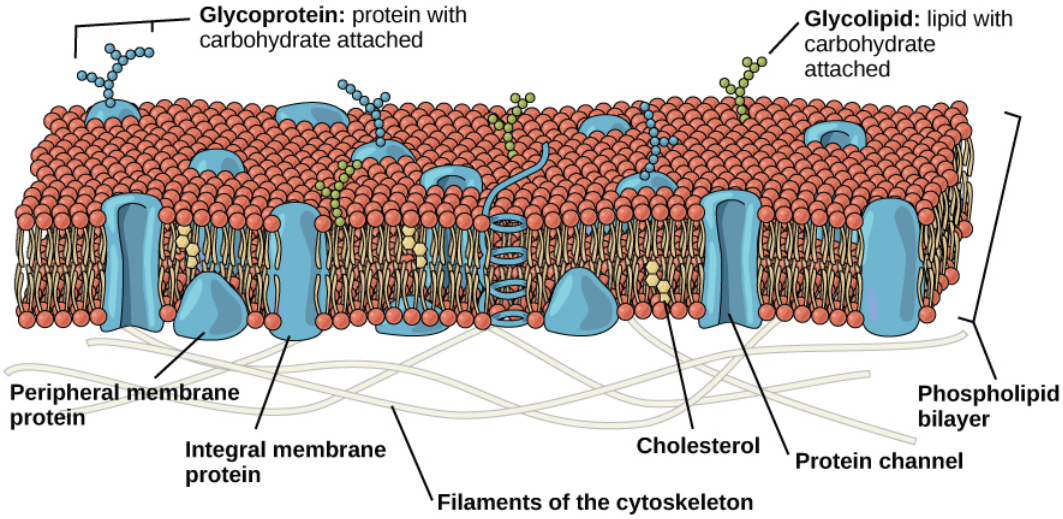


Figure 1.4.4.2: The eukaryotic plasma membrane is a phospholipid bilayer with proteins and cholesterol embedded in it.

The plasma membranes of cells that specialize in absorption are folded into fingerlike projections called microvilli (singular = microvillus); (Figure 1.4.4.3). Such cells are typically found lining the small intestine, the organ that absorbs nutrients from digested food. This is an excellent example of form following function. People with celiac disease have an immune response to gluten, which is a protein found in wheat, barley, and rye. The immune response damages microvilli, and thus, afflicted individuals cannot absorb nutrients. This leads to malnutrition, cramping, and diarrhea. Patients suffering from celiac disease must follow a gluten-free diet.

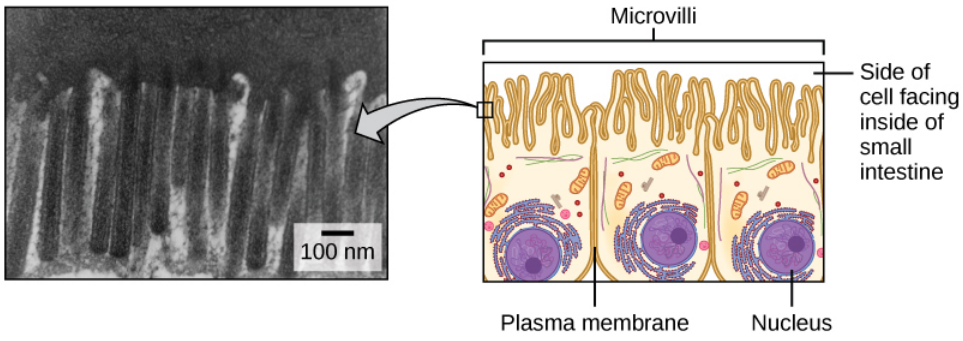


Figure 1.4.4.3: Microvilli, shown here as they appear on cells lining the small intestine, increase the surface area available for absorption. These microvilli are only found on the area of the plasma membrane that faces the cavity from which substances will be absorbed. (credit "micrograph": modification of work by Louisa Howard)

The Cytoplasm

The cytoplasm is the entire region of a cell between the plasma membrane and the nuclear envelope (a structure to be discussed shortly). It is made up of organelles suspended in the gel-like cytosol, the cytoskeleton, and various chemicals (Figure 1.4.4.1). Even though the cytoplasm consists of 70 to 80 percent water, it has a semi-solid consistency, which comes from the proteins

within it. However, proteins are not the only organic molecules found in the cytoplasm. Glucose and other simple sugars, polysaccharides, amino acids, nucleic acids, fatty acids, and derivatives of glycerol are found there, too. Ions of sodium, potassium, calcium, and many other elements are also dissolved in the cytoplasm. Many metabolic reactions, including protein synthesis, take place in the cytoplasm.

The Nucleus

Typically, the nucleus is the most prominent organelle in a cell (Figure 1.4.4.1). The nucleus (plural = nuclei) houses the cell's DNA and directs the synthesis of ribosomes and proteins. Let's look at it in more detail (Figure 1.4.4.4).

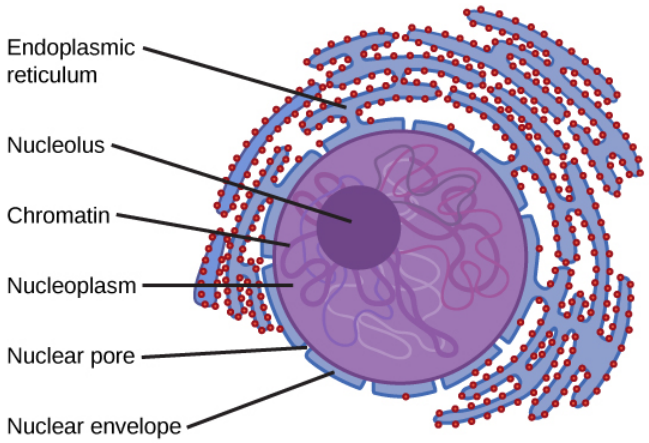


Figure 1.4.4.4: The nucleus stores chromatin (DNA plus proteins) in a gel-like substance called the nucleoplasm. The nucleolus is a condensed region of chromatin where ribosome synthesis occurs. The boundary of the nucleus is called the nuclear envelope. It consists of two phospholipid bilayers: an outer membrane and an inner membrane. The nuclear membrane is continuous with the endoplasmic reticulum. Nuclear pores allow substances to enter and exit the nucleus.

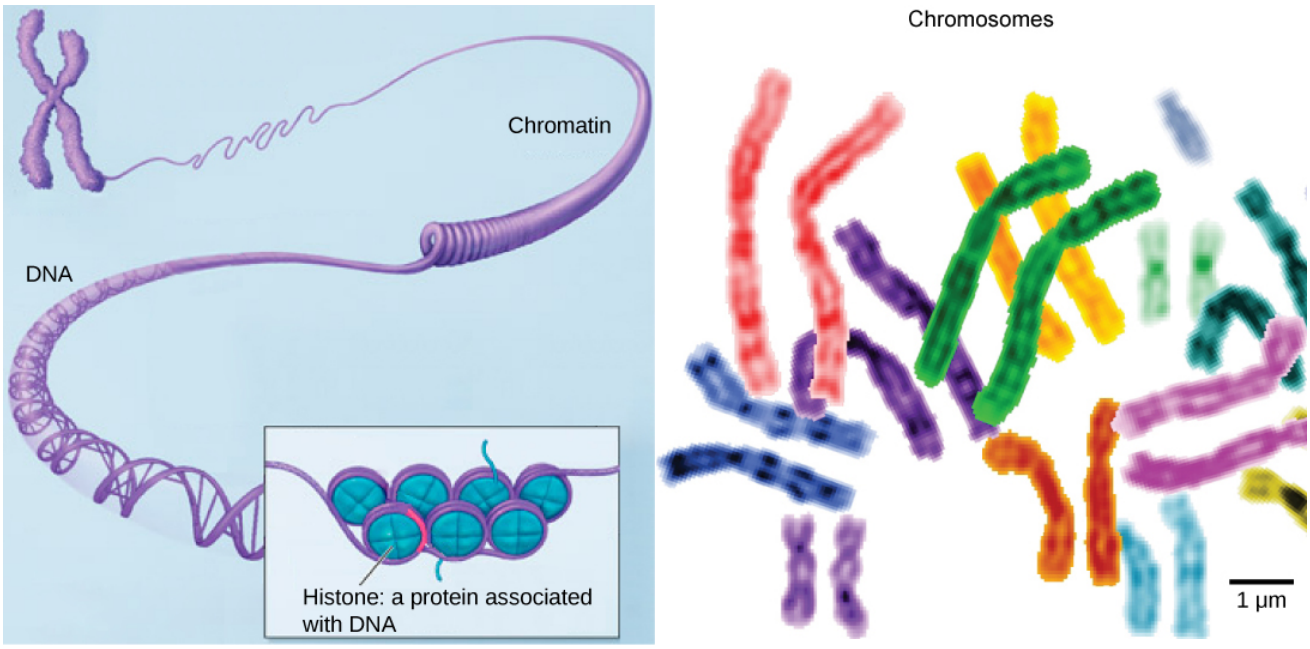
The Nuclear Envelope

The nuclear envelope is a double-membrane structure that constitutes the outermost portion of the nucleus (Figure 1.4.4.4). Both the inner and outer membranes of the nuclear envelope are phospholipid bilayers.

The nuclear envelope is punctuated with pores that control the passage of ions, molecules, and RNA between the nucleoplasm and cytoplasm. The nucleoplasm is the semi-solid fluid inside the nucleus, where we find the chromatin and the nucleolus.

Chromatin and Chromosomes

To understand chromatin, it is helpful to first consider chromosomes. Chromosomes are structures within the nucleus that are made up of DNA, the hereditary material. You may remember that in prokaryotes, DNA is organized into a single circular chromosome. In eukaryotes, chromosomes are linear structures. Every eukaryotic species has a specific number of chromosomes in the nuclei of its body's cells. For example, in humans, the chromosome number is 46, while in fruit flies, it is eight. Chromosomes are only visible and distinguishable from one another when the cell is getting ready to divide. When the cell is in the growth and maintenance phases of its life cycle, proteins are attached to chromosomes, and they resemble an unwound, jumbled bunch of threads. These unwound protein-chromosome complexes are called chromatin (Figure 1.4.4.5); chromatin describes the material that makes up the chromosomes both when condensed and decondensed.



(a) (b)

Figure 1.4.4.5: (a) This image shows various levels of the organization of chromatin (DNA and protein). (b) This image shows paired chromosomes. (credit b: modification of work by NIH; scale-bar data from Matt Russell)

The Nucleolus

We already know that the nucleus directs the synthesis of ribosomes, but how does it do this? Some chromosomes have sections of DNA that encode ribosomal RNA. A darkly staining area within the nucleus called the nucleolus (plural = nucleoli) aggregates the ribosomal RNA with associated proteins to assemble the ribosomal subunits that are then transported out through the pores in the nuclear envelope to the cytoplasm.

Ribosomes

Ribosomes are the cellular structures responsible for protein synthesis. When viewed through an electron microscope, ribosomes appear either as clusters (polyribosomes) or single, tiny dots that float freely in the cytoplasm. They may be attached to the cytoplasmic side of the plasma membrane or the cytoplasmic side of the endoplasmic reticulum and the outer membrane of the nuclear envelope (Figure 1.4.4.1). Electron microscopy has shown us that ribosomes, which are large complexes of protein and RNA, consist of two subunits, aptly called large and small (Figure 1.4.4.6). Ribosomes receive their “orders” for protein synthesis from the nucleus where the DNA is transcribed into messenger RNA (mRNA). The mRNA travels to the ribosomes, which translate the code provided by the sequence of the nitrogenous bases in the mRNA into a specific order of amino acids in a protein. Amino acids are the building blocks of proteins.

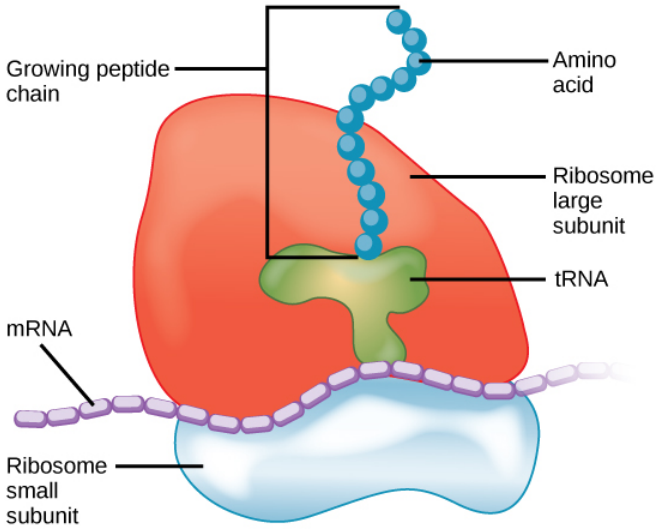


Figure 1.4.4.6: Ribosomes are made up of a large subunit (top) and a small subunit (bottom). During protein synthesis, ribosomes assemble amino acids into proteins.

Because proteins synthesis is an essential function of all cells (including enzymes, hormones, antibodies, pigments, structural components, and surface receptors), ribosomes are found in practically every cell. Ribosomes are particularly abundant in cells that synthesize large amounts of protein. For example, the pancreas is responsible for creating several digestive enzymes and the cells that produce these enzymes contain many ribosomes. Thus, we see another example of form following function.

Mitochondria

Mitochondria (singular = mitochondrion) are often called the “powerhouses” or “energy factories” of a cell because they are responsible for making adenosine triphosphate (ATP), the cell’s main energy-carrying molecule. ATP represents the short-term stored energy of the cell. Cellular respiration is the process of making ATP using the chemical energy found in glucose and other nutrients. In mitochondria, this process uses oxygen and produces carbon dioxide as a waste product. In fact, the carbon dioxide that you exhale with every breath comes from the cellular reactions that produce carbon dioxide as a byproduct.

In keeping with our theme of form following function, it is important to point out that muscle cells have a very high concentration of mitochondria that produce ATP. Your muscle cells need a lot of energy to keep your body moving. When your cells don’t get enough oxygen, they do not make a lot of ATP. Instead, the small amount of ATP they make in the absence of oxygen is accompanied by the production of lactic acid.

Mitochondria are oval-shaped, double membrane organelles (Figure 1.4.4.7) that have their own ribosomes and DNA. Each membrane is a phospholipid bilayer embedded with proteins. The inner layer has folds called cristae. The area surrounded by the folds is called the mitochondrial matrix. The cristae and the matrix have different roles in cellular respiration.

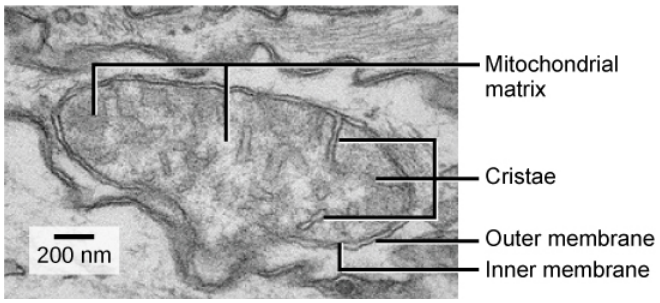


Figure 1.4.4.7: This electron micrograph shows a mitochondrion as viewed with a transmission electron microscope. This organelle has an outer membrane and an inner membrane. The inner membrane contains folds, called cristae, which increase its surface area. The space between the two membranes is called the intermembrane space, and the space inside the inner membrane is called the mitochondrial matrix. ATP synthesis takes place on the inner membrane. (credit: modification of work by Matthew Britton; scale-bar data from Matt Russell)

Peroxisomes

Peroxisomes are small, round organelles enclosed by single membranes. They carry out oxidation reactions that break down fatty acids and amino acids. They also detoxify many poisons that may enter the body. (Many of these oxidation reactions release hydrogen peroxide, H_2O_2, which would be damaging to cells; however, when these reactions are confined to peroxisomes, enzymes safely break down the H_2O_2 into oxygen and water.) For example, alcohol is detoxified by peroxisomes in liver cells. Glyoxysomes, which are specialized peroxisomes in plants, are responsible for converting stored fats into sugars.

Vesicles and Vacuoles

Vesicles and vacuoles are membrane-bound sacs that function in storage and transport. Other than the fact that vacuoles are somewhat larger than vesicles, there is a very subtle distinction between them: The membranes of vesicles can fuse with either the plasma membrane or other membrane systems within the cell. Additionally, some agents such as enzymes within plant vacuoles break down macromolecules. The membrane of a vacuole does not fuse with the membranes of other cellular components.

Animal Cells versus Plant Cells

At this point, you know that each eukaryotic cell has a plasma membrane, cytoplasm, a nucleus, ribosomes, mitochondria, peroxisomes, and in some, vacuoles, but there are some striking differences between animal and plant cells. While both animal and plant cells have microtubule organizing centers (MTOCs), animal cells also have centrioles associated with the MTOC: a complex called the centrosome. Animal cells each have a centrosome and lysosomes, whereas plant cells do not. Plant cells have a cell wall, chloroplasts and other specialized plastids, and a large central vacuole, whereas animal cells do not.

The Centrosome

The centrosome is a microtubule-organizing center found near the nuclei of animal cells. It contains a pair of centrioles, two structures that lie perpendicular to each other (Figure 1.4.4.8). Each centriole is a cylinder of nine triplets of microtubules.

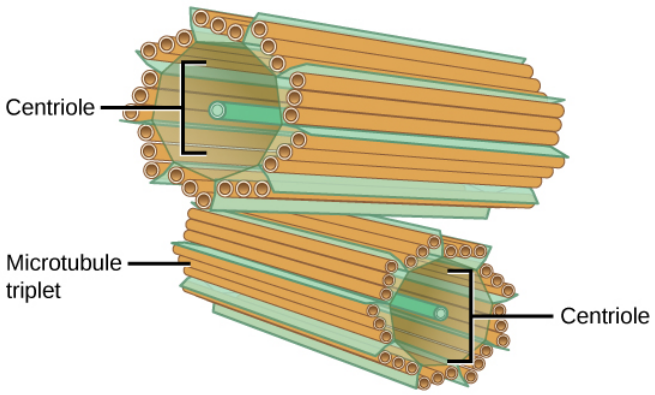


Figure 1.4.4.8: The centrosome consists of two centrioles that lie at right angles to each other. Each centriole is a cylinder made up of nine triplets of microtubules. Nontubulin proteins (indicated by the green lines) hold the microtubule triplets together.

The centrosome (the organelle where all microtubules originate) replicates itself before a cell divides, and the centrioles appear to have some role in pulling the duplicated chromosomes to opposite ends of the dividing cell. However, the exact function of the centrioles in cell division isn't clear, because cells that have had the centrosome removed can still divide, and plant cells, which lack centrosomes, are capable of cell division.

Lysosomes

Animal cells have another set of organelles not found in plant cells: lysosomes. The lysosomes are the cell's "garbage disposal." In plant cells, the digestive processes take place in vacuoles. Enzymes within the lysosomes aid the breakdown of proteins, polysaccharides, lipids, nucleic acids, and even worn-out organelles. These enzymes are active at a much lower pH than that of the cytoplasm. Therefore, the pH within lysosomes is more acidic than the pH of the cytoplasm. Many reactions that take place in the cytoplasm could not occur at a low pH, so again, the advantage of compartmentalizing the eukaryotic cell into organelles is apparent.

The Cell Wall

If you examine Figure 1.4.4.1b, the diagram of a plant cell, you will see a structure external to the plasma membrane called the cell wall. The cell wall is a rigid covering that protects the cell, provides structural support, and gives shape to the cell. Fungal and protistan cells also have cell walls. While the chief component of prokaryotic cell walls is peptidoglycan, the major organic molecule in the plant cell wall is cellulose (Figure 1.4.4.9), a polysaccharide made up of glucose units. Have you ever noticed that when you bite into a raw vegetable, like celery, it crunches? That's because you are tearing the rigid cell walls of the celery cells with your teeth.

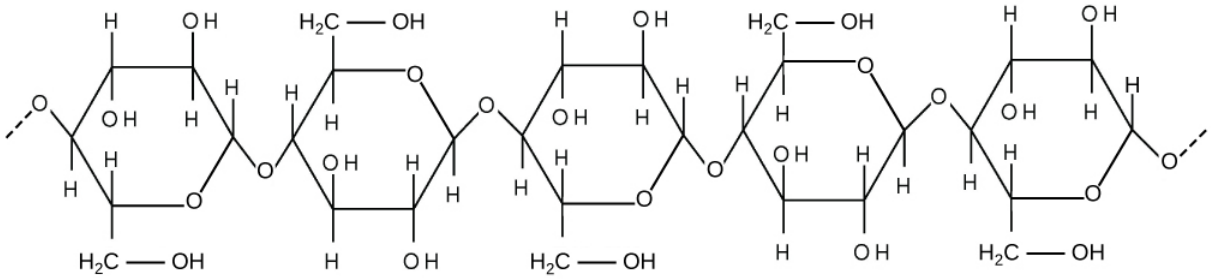


Figure 1.4.4.9: Cellulose is a long chain of β-glucose molecules connected by a 1-4 linkage. The dashed lines at each end of the figure indicate a series of many more glucose units. The size of the page makes it impossible to portray an entire cellulose molecule.

Chloroplasts

Like the mitochondria, chloroplasts have their own DNA and ribosomes, but chloroplasts have an entirely different function. Chloroplasts are plant cell organelles that carry out photosynthesis. Photosynthesis is the series of reactions that use carbon dioxide, water, and light energy to make glucose and oxygen. This is a major difference between plants and animals; plants (autotrophs) are able to make their own food, like sugars, while animals (heterotrophs) must ingest their food.

Like mitochondria, chloroplasts have outer and inner membranes, but within the space enclosed by a chloroplast's inner membrane is a set of interconnected and stacked fluid-filled membrane sacs called thylakoids (Figure 1.4.4.10). Each stack of thylakoids is called a granum (plural = grana). The fluid enclosed by the inner membrane that surrounds the grana is called the stroma.

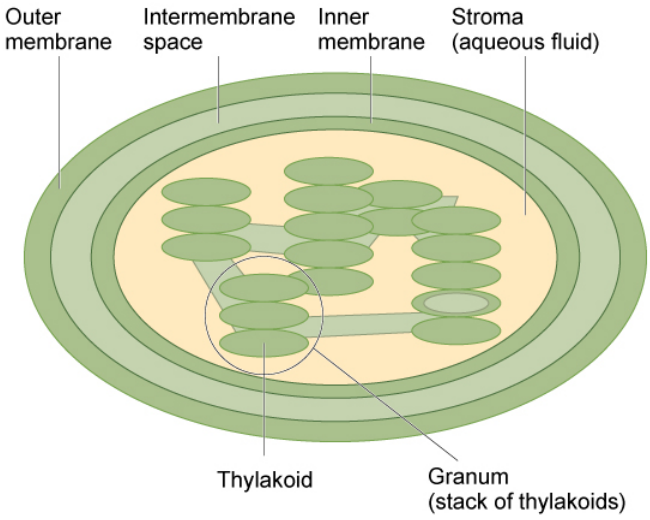


Figure 1.4.4.10: The chloroplast has an outer membrane, an inner membrane, and membrane structures called thylakoids that are stacked into grana. The space inside the thylakoid membranes is called the thylakoid space. The light harvesting reactions take place in the thylakoid membranes, and the synthesis of sugar takes place in the fluid inside the inner membrane, which is called the stroma. Chloroplasts also have their own genome, which is contained on a single circular chromosome.

The chloroplasts contain a green pigment called chlorophyll, which captures the light energy that drives the reactions of photosynthesis. Like plant cells, photosynthetic protists also have chloroplasts. Some bacteria perform photosynthesis, but their chlorophyll is not relegated to an organelle.

Evolution Connection: Endosymbiosis

We have mentioned that both mitochondria and chloroplasts contain DNA and ribosomes. Have you wondered why? Strong evidence points to endosymbiosis as the explanation.

Symbiosis is a relationship in which organisms from two separate species depend on each other for their survival. Endosymbiosis (endo- = "within") is a mutually beneficial relationship in which one organism lives inside the other. Endosymbiotic relationships abound in nature. We have already mentioned that microbes that produce vitamin K live inside the human gut. This relationship is beneficial for us because we are unable to synthesize vitamin K. It is also beneficial for the microbes because they are protected from other organisms and from drying out, and they receive abundant food from the environment of the large intestine.

Scientists have long noticed that bacteria, mitochondria, and chloroplasts are similar in size. We also know that bacteria have DNA and ribosomes, just as mitochondria and chloroplasts do. Scientists believe that host cells and bacteria formed an endosymbiotic relationship when the host cells ingested both aerobic and autotrophic bacteria (cyanobacteria) but did not destroy them. Through many millions of years of evolution, these ingested bacteria became more specialized in their functions, with the aerobic bacteria becoming mitochondria and the autotrophic bacteria becoming chloroplasts.

The Central Vacuole

Previously, we mentioned vacuoles as essential components of plant cells. If you look at Figure 1.4.4.1b, you will see that plant cells each have a large central vacuole that occupies most of the area of the cell. The central vacuole plays a key role in regulating the cell's concentration of water in changing environmental conditions. Have you ever noticed that if you forget to water a plant for a few days, it wilts? That's because as the water concentration in the soil becomes lower than the water concentration in the plant, water moves out of the central vacuoles and cytoplasm. As the central vacuole shrinks, it leaves the cell wall unsupported. This loss of support to the cell walls of plant cells results in the wilted appearance of the plant.

The central vacuole also supports the expansion of the cell. When the central vacuole holds more water, the cell gets larger without having to invest a lot of energy in synthesizing new cytoplasm.

Summary

Like a prokaryotic cell, a eukaryotic cell has a plasma membrane, cytoplasm, and ribosomes, but a eukaryotic cell is typically larger than a prokaryotic cell, has a true nucleus (meaning its DNA is surrounded by a membrane), and has other membrane-bound organelles that allow for compartmentalization of functions. The plasma membrane is a phospholipid bilayer embedded with proteins. The nucleus's nucleolus is the site of ribosome assembly. Ribosomes are either found in the cytoplasm or attached to the cytoplasmic side of the plasma membrane or endoplasmic reticulum. They perform protein synthesis. Mitochondria participate in cellular respiration; they are responsible for the majority of ATP produced in the cell. Peroxisomes hydrolyze fatty acids, amino acids, and some toxins. Vesicles and vacuoles are storage and transport compartments. In plant cells, vacuoles also help break down macromolecules.

Animal cells also have a centrosome and lysosomes. The centrosome has two bodies perpendicular to each other, the centrioles, and has an unknown purpose in cell division. Lysosomes are the digestive organelles of animal cells.

Plant cells and plant-like cells each have a cell wall, chloroplasts, and a central vacuole. The plant cell wall, whose primary component is cellulose, protects the cell, provides structural support, and gives shape to the cell. Photosynthesis takes place in chloroplasts. The central vacuole can expand without having to produce more cytoplasm.

Art Connections

Figure 1.4.4.1: If the nucleolus were not able to carry out its function, what other cellular organelles would be affected?

Answer

Free ribosomes and rough endoplasmic reticulum (which contains ribosomes) would not be able to form.

cell wall
rigid cell covering made of cellulose that protects the cell, provides structural support, and gives shape to the cell

central vacuole
large plant cell organelle that regulates the cell's storage compartment, holds water, and plays a significant role in cell growth as the site of macromolecule degradation

centrosome
region in animal cells made of two centrioles

chlorophyll
green pigment that captures the light energy that drives the light reactions of photosynthesis

chloroplast
plant cell organelle that carries out photosynthesis

chromatin
protein-DNA complex that serves as the building material of chromosomes

chromosome
structure within the nucleus that is made up of chromatin that contains DNA, the hereditary material

cytoplasm
entire region between the plasma membrane and the nuclear envelope, consisting of organelles suspended in the gel-like cytosol, the cytoskeleton, and various chemicals

cytosol
gel-like material of the cytoplasm in which cell structures are suspended

eukaryotic cell
cell that has a membrane-bound nucleus and several other membrane-bound compartments or sacs

lysosome
organelle in an animal cell that functions as the cell's digestive component; it breaks down proteins, polysaccharides, lipids, nucleic acids, and even worn-out organelles

mitochondria
(singular = mitochondrion) cellular organelles responsible for carrying out cellular respiration, resulting in the production of ATP, the cell's main energy-carrying molecule

nuclear envelope
double-membrane structure that constitutes the outermost portion of the nucleus

nucleolus
darkly staining body within the nucleus that is responsible for assembling the subunits of the ribosomes

nucleoplasm
semi-solid fluid inside the nucleus that contains the chromatin and nucleolus

nucleus

cell organelle that houses the cell’s DNA and directs the synthesis of ribosomes and proteins

organelle
compartment or sac within a cell

peroxisome
small, round organelle that contains hydrogen peroxide, oxidizes fatty acids and amino acids, and detoxifies many poisons

plasma membrane
phospholipid bilayer with embedded (integral) or attached (peripheral) proteins, and separates the internal content of the cell from its surrounding environment

ribosome
cellular structure that carries out protein synthesis

vacuole
membrane-bound sac, somewhat larger than a vesicle, which functions in cellular storage and transport

vesicle
small, membrane-bound sac that functions in cellular storage and transport; its membrane is capable of fusing with the plasma membrane and the membranes of the endoplasmic reticulum and Golgi apparatus

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1.4.5: The Endomembrane System and Proteins

Skills to Develop

- List the components of the endomembrane system
- Recognize the relationship between the endomembrane system and its functions

The endomembrane system (endo = “within”) is a group of membranes and organelles (Figure 1.4.5.1) in eukaryotic cells that works together to modify, package, and transport lipids and proteins. It includes the nuclear envelope, lysosomes, and vesicles, which we’ve already mentioned, and the endoplasmic reticulum and Golgi apparatus, which we will cover shortly. Although not technically *within* the cell, the plasma membrane is included in the endomembrane system because, as you will see, it interacts with the other endomembranous organelles. The endomembrane system does not include the membranes of either mitochondria or chloroplasts.

Art Connection

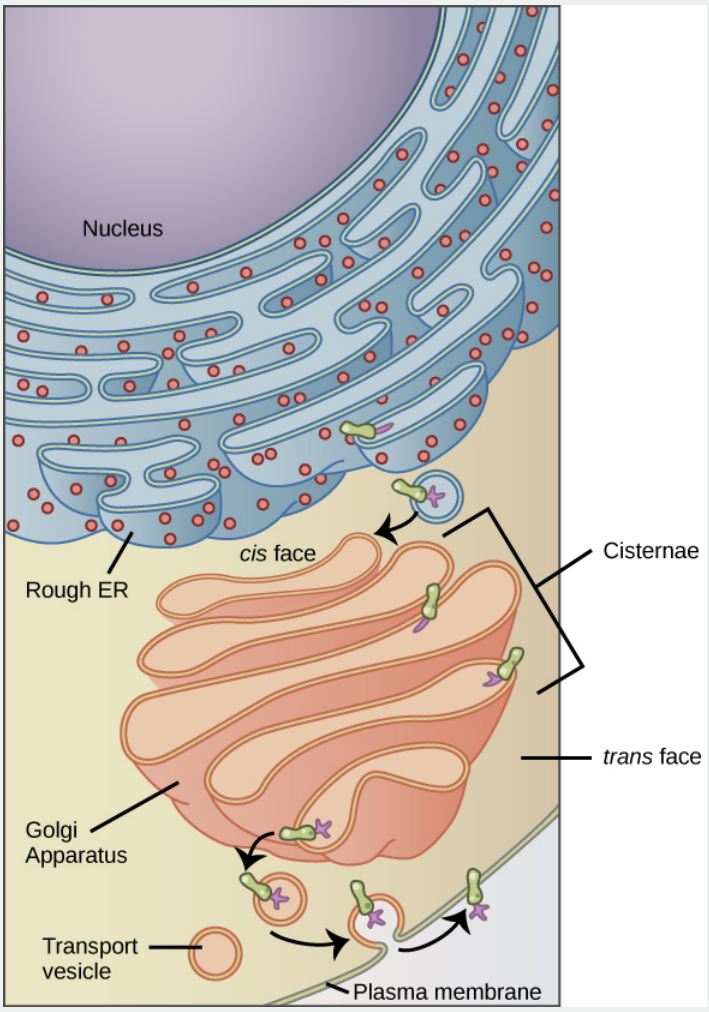


Figure 1.4.5.1: Membrane and secretory proteins are synthesized in the rough endoplasmic reticulum (RER). The RER also sometimes modifies proteins. In this illustration, a (green) integral membrane protein in the ER is modified by attachment of a (purple) carbohydrate. Vesicles with the integral protein bud from the ER and fuse with the cis face of the Golgi apparatus. As the protein passes along the Golgi’s cisternae, it is further modified by the addition of more carbohydrates. After its synthesis is complete, it exits as integral membrane protein of the vesicle that bud from the Golgi’s trans face and when the vesicle fuses with the cell membrane the protein becomes integral portion of that cell membrane. (credit: modification of work by Magnus Manske)

If a peripheral membrane protein were synthesized in the lumen (inside) of the ER, would it end up on the inside or outside of the plasma membrane?

The Endoplasmic Reticulum

The endoplasmic reticulum (ER) (Figure 1.4.5.1) is a series of interconnected membranous sacs and tubules that collectively modifies proteins and synthesizes lipids. However, these two functions are performed in separate areas of the ER: the rough ER and the smooth ER, respectively.

The hollow portion of the ER tubules is called the lumen or cisternal space. The membrane of the ER, which is a phospholipid bilayer embedded with proteins, is continuous with the nuclear envelope.

Rough ER

The rough endoplasmic reticulum (RER) is so named because the ribosomes attached to its cytoplasmic surface give it a studded appearance when viewed through an electron microscope (Figure 1.4.5.2).

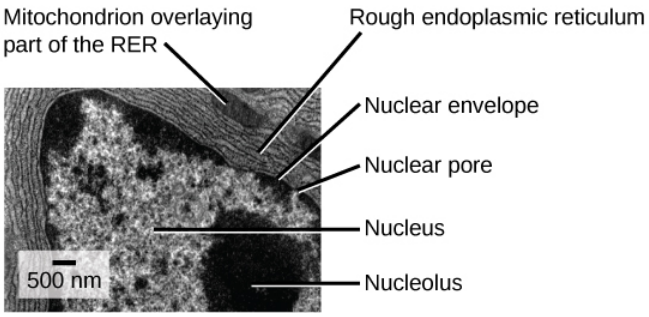


Figure 1.4.5.2: This transmission electron micrograph shows the rough endoplasmic reticulum and other organelles in a pancreatic cell. (credit: modification of work by Louisa Howard)

Ribosomes transfer their newly synthesized proteins into the lumen of the RER where they undergo structural modifications, such as folding or the acquisition of side chains. These modified proteins will be incorporated into cellular membranes—the membrane of the ER or those of other organelles—or secreted from the cell (such as protein hormones, enzymes). The RER also makes phospholipids for cellular membranes.

If the phospholipids or modified proteins are not destined to stay in the RER, they will reach their destinations via transport vesicles that bud from the RER's membrane (Figure 1.4.5.1).

Since the RER is engaged in modifying proteins (such as enzymes, for example) that will be secreted from the cell, you would be correct in assuming that the RER is abundant in cells that secrete proteins. This is the case with cells of the liver, for example.

Smooth ER

The smooth endoplasmic reticulum (SER) is continuous with the RER but has few or no ribosomes on its cytoplasmic surface (Figure 1.4.5.1). Functions of the SER include synthesis of carbohydrates, lipids, and steroid hormones; detoxification of medications and poisons; and storage of calcium ions.

In muscle cells, a specialized SER called the sarcoplasmic reticulum is responsible for storage of the calcium ions that are needed to trigger the coordinated contractions of the muscle cells.

Link to Learning



Video 1.4.5.1: You can watch an excellent animation of the endomembrane system here.

Career Connection: Cardiologist

Heart disease is the leading cause of death in the United States. This is primarily due to our sedentary lifestyle and our high trans-fat diets.

Heart failure is just one of many disabling heart conditions. Heart failure does not mean that the heart has stopped working. Rather, it means that the heart can't pump with sufficient force to transport oxygenated blood to all the vital organs. Left untreated, heart failure can lead to kidney failure and failure of other organs.

The wall of the heart is composed of cardiac muscle tissue. Heart failure occurs when the endoplasmic reticula of cardiac muscle cells do not function properly. As a result, an insufficient number of calcium ions are available to trigger a sufficient contractile force.

Cardiologists (cardi- = "heart"; -ologist = "one who studies") are doctors who specialize in treating heart diseases, including heart failure. Cardiologists can make a diagnosis of heart failure via physical examination, results from an electrocardiogram (ECG, a test that measures the electrical activity of the heart), a chest X-ray to see whether the heart is enlarged, and other tests. If heart failure is diagnosed, the cardiologist will typically prescribe appropriate medications and recommend a reduction in table salt intake and a supervised exercise program.

The Golgi Apparatus

We have already mentioned that vesicles can bud from the ER and transport their contents elsewhere, but where do the vesicles go? Before reaching their final destination, the lipids or proteins within the transport vesicles still need to be sorted, packaged, and tagged so that they wind up in the right place. Sorting, tagging, packaging, and distribution of lipids and proteins takes place in the Golgi apparatus (also called the Golgi body), a series of flattened membranes (Figure 1.4.5.3).

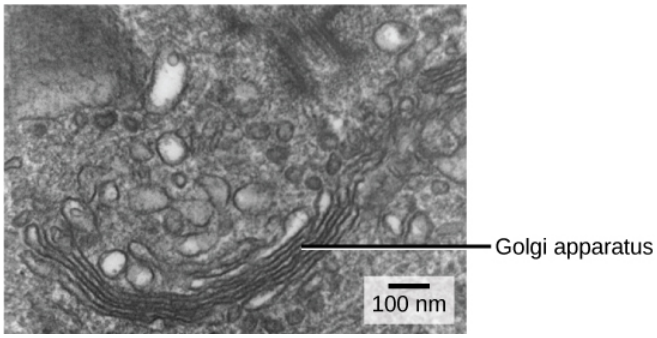


Figure 1.4.5.3: The Golgi apparatus in this white blood cell is visible as a stack of semicircular, flattened rings in the lower portion of the image. Several vesicles can be seen near the Golgi apparatus. (credit: modification of work by Louisa Howard)

The receiving side of the Golgi apparatus is called the *cis* face. The opposite side is called the *trans* face. The transport vesicles that formed from the ER travel to the *cis* face, fuse with it, and empty their contents into the lumen of the Golgi apparatus. As the proteins and lipids travel through the Golgi, they undergo further modifications that allow them to be sorted. The most frequent modification is the addition of short chains of sugar molecules. These newly modified proteins and lipids are then tagged with phosphate groups or other small molecules so that they can be routed to their proper destinations.

Finally, the modified and tagged proteins are packaged into secretory vesicles that bud from the *trans* face of the Golgi. While some of these vesicles deposit their contents into other parts of the cell where they will be used, other secretory vesicles fuse with the plasma membrane and release their contents outside the cell.

In another example of form following function, cells that engage in a great deal of secretory activity (such as cells of the salivary glands that secrete digestive enzymes or cells of the immune system that secrete antibodies) have an abundance of Golgi.

In plant cells, the Golgi apparatus has the additional role of synthesizing polysaccharides, some of which are incorporated into the cell wall and some of which are used in other parts of the cell.

Career Connection: Geneticist

Many diseases arise from genetic mutations that prevent the synthesis of critical proteins. One such disease is Lowe disease (also called oculocerebrorenal syndrome, because it affects the eyes, brain, and kidneys). In Lowe disease, there is a deficiency in an enzyme localized to the Golgi apparatus. Children with Lowe disease are born with cataracts, typically develop kidney disease after the first year of life, and may have impaired mental abilities.

Lowe disease is a genetic disease caused by a mutation on the X chromosome. The X chromosome is one of the two human sex chromosome, as these chromosomes determine a person's sex. Females possess two X chromosomes while males possess one X and one Y chromosome. In females, the genes on only one of the two X chromosomes are expressed. Therefore, females who carry the Lowe disease gene on one of their X chromosomes have a 50/50 chance of having the disease. However, males only have one X chromosome and the genes on this chromosome are always expressed. Therefore, males will always have Lowe disease if their X chromosome carries the Lowe disease gene. The location of the mutated gene, as well as the locations of many other mutations that cause genetic diseases, has now been identified. Through prenatal testing, a woman can find out if the fetus she is carrying may be afflicted with one of several genetic diseases.

Geneticists analyze the results of prenatal genetic tests and may counsel pregnant women on available options. They may also conduct genetic research that leads to new drugs or foods, or perform DNA analyses that are used in forensic investigations.

Lysosomes

In addition to their role as the digestive component and organelle-recycling facility of animal cells, lysosomes are considered to be parts of the endomembrane system. Lysosomes also use their hydrolytic enzymes to destroy pathogens (disease-causing organisms) that might enter the cell. A good example of this occurs in a group of white blood cells called macrophages, which are part of your body’s immune system. In a process known as phagocytosis or endocytosis, a section of the plasma membrane of the macrophage invaginates (folds in) and engulfs a pathogen. The invaginated section, with the pathogen inside, then pinches itself off from the plasma membrane and becomes a vesicle. The vesicle fuses with a lysosome. The lysosome’s hydrolytic enzymes then destroy the pathogen (Figure 1.4.5.4).

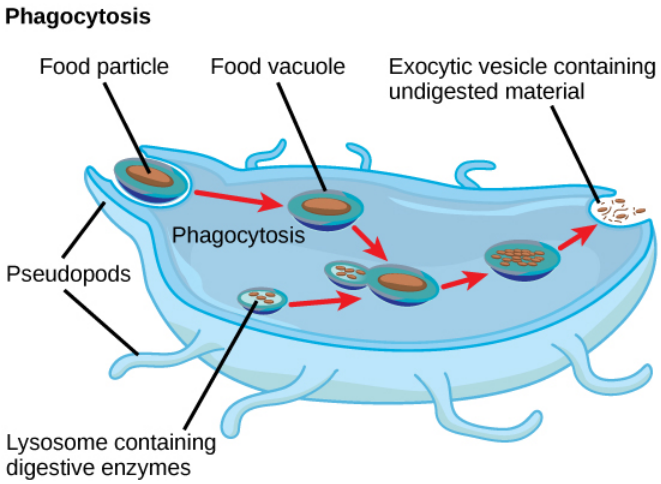


Figure 1.4.5.4: A macrophage has engulfed (phagocytized) a potentially pathogenic bacterium and then fuses with a lysosomes within the cell to destroy the pathogen. Other organelles are present in the cell but for simplicity are not shown.

Summary

The endomembrane system includes the nuclear envelope, lysosomes, vesicles, the ER, and Golgi apparatus, as well as the plasma membrane. These cellular components work together to modify, package, tag, and transport proteins and lipids that form the membranes.

The RER modifies proteins and synthesizes phospholipids used in cell membranes. The SER synthesizes carbohydrates, lipids, and steroid hormones; engages in the detoxification of medications and poisons; and stores calcium ions. Sorting, tagging, packaging, and distribution of lipids and proteins take place in the Golgi apparatus. Lysosomes are created by the budding of the membranes of the RER and Golgi. Lysosomes digest macromolecules, recycle worn-out organelles, and destroy pathogens.

Art Connections

Figure 1.4.5.1: If a peripheral membrane protein were synthesized in the lumen (inside) of the ER, would it end up on the inside or outside of the plasma membrane?

Answer

It would end up on the outside. After the vesicle passes through the Golgi apparatus and fuses with the plasma membrane, it turns inside out.

Glossary

endomembrane system

group of organelles and membranes in eukaryotic cells that work together modifying, packaging, and transporting lipids and proteins

endoplasmic reticulum (ER)

series of interconnected membranous structures within eukaryotic cells that collectively modify proteins and synthesize lipids

Golgi apparatus

eukaryotic organelle made up of a series of stacked membranes that sorts, tags, and packages lipids and proteins for distribution

rough endoplasmic reticulum (RER)

region of the endoplasmic reticulum that is studded with ribosomes and engages in protein modification and phospholipid synthesis

smooth endoplasmic reticulum (SER)

region of the endoplasmic reticulum that has few or no ribosomes on its cytoplasmic surface and synthesizes carbohydrates, lipids, and steroid hormones; detoxifies certain chemicals (like pesticides, preservatives, medications, and environmental pollutants), and stores calcium ions

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1.4.6: The Cytoskeleton

Skills to Develop

- Describe the cytoskeleton
- Compare the roles of microfilaments, intermediate filaments, and microtubules
- Compare and contrast cilia and flagella
- Summarize the differences among the components of prokaryotic cells, animal cells, and plant cells

If you were to remove all the organelles from a cell, would the plasma membrane and the cytoplasm be the only components left? No. Within the cytoplasm, there would still be ions and organic molecules, plus a network of protein fibers that help maintain the shape of the cell, secure some organelles in specific positions, allow cytoplasm and vesicles to move within the cell, and enable cells within multicellular organisms to move. Collectively, this network of protein fibers is known as the cytoskeleton. There are three types of fibers within the cytoskeleton: microfilaments, intermediate filaments, and microtubules (Figure 1.4.6.1). Here, we will examine each.

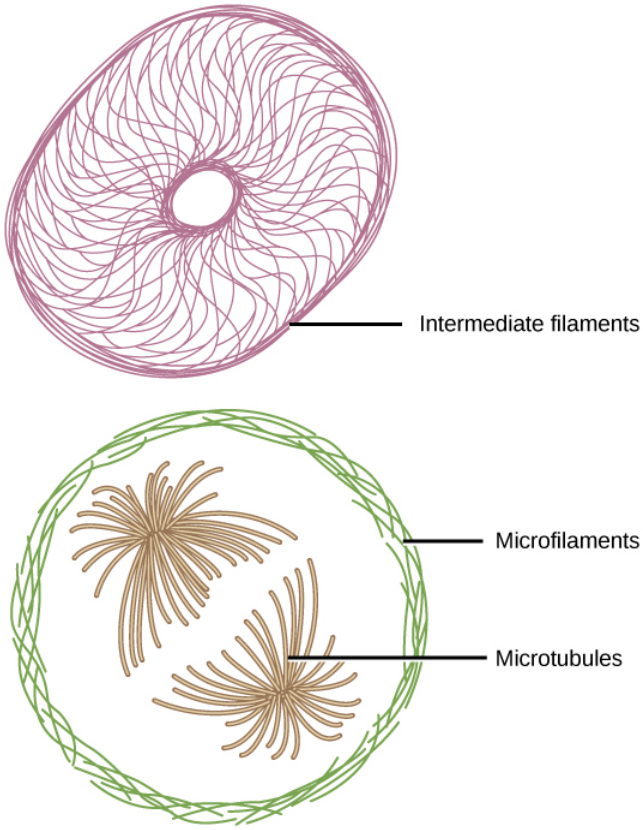


Figure 1.4.6.1: Microfilaments thicken the cortex around the inner edge of a cell; like rubber bands, they resist tension. Microtubules are found in the interior of the cell where they maintain cell shape by resisting compressive forces. Intermediate filaments are found throughout the cell and hold organelles in place.

Microfilaments

Of the three types of protein fibers in the cytoskeleton, microfilaments are the narrowest. They function in cellular movement, have a diameter of about 7 nm, and are made of two intertwined strands of a globular protein called actin (Figure 1.4.6.2). For this reason, microfilaments are also known as actin filaments.

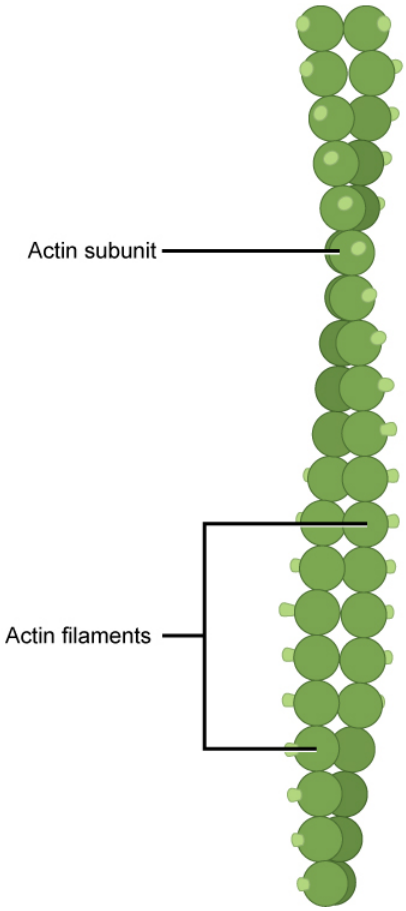


Figure 1.4.6.2: Microfilaments are made of two intertwined strands of actin.

Actin is powered by ATP to assemble its filamentous form, which serves as a track for the movement of a motor protein called myosin. This enables actin to engage in cellular events requiring motion, such as cell division in animal cells and cytoplasmic streaming, which is the circular movement of the cell cytoplasm in plant cells. Actin and myosin are plentiful in muscle cells. When your actin and myosin filaments slide past each other, your muscles contract.

Microfilaments also provide some rigidity and shape to the cell. They can depolymerize (disassemble) and reform quickly, thus enabling a cell to change its shape and move. White blood cells (your body's infection-fighting cells) make good use of this ability. They can move to the site of an infection and phagocytize the pathogen.

Link to Learning



Video 1.4.6.1: To see an example of a white blood cell in action, watch a short time-lapse video of the cell capturing two bacteria. It engulfs one and then moves on to the other.

Intermediate Filaments

Intermediate filaments are made of several strands of fibrous proteins that are wound together (Figure 1.4.6.3). These elements of the cytoskeleton get their name from the fact that their diameter, 8 to 10 nm, is between those of microfilaments and microtubules.



Figure 1.4.6.3: Intermediate filaments consist of several intertwined strands of fibrous proteins.

Intermediate filaments have no role in cell movement. Their function is purely structural. They bear tension, thus maintaining the shape of the cell, and anchor the nucleus and other organelles in place. Figure 1.4.6.1 shows how intermediate filaments create a supportive scaffolding inside the cell.

The intermediate filaments are the most diverse group of cytoskeletal elements. Several types of fibrous proteins are found in the intermediate filaments. You are probably most familiar with keratin, the fibrous protein that strengthens your hair, nails, and the epidermis of the skin.

Microtubules

As their name implies, microtubules are small hollow tubes. The walls of the microtubule are made of polymerized dimers of α-tubulin and β-tubulin, two globular proteins (Figure 1.4.6.4). With a diameter of about 25 nm, microtubules are the widest components of the cytoskeleton. They help the cell resist compression, provide a track along which vesicles move through the cell, and pull replicated chromosomes to opposite ends of a dividing cell. Like microfilaments, microtubules can dissolve and reform quickly.

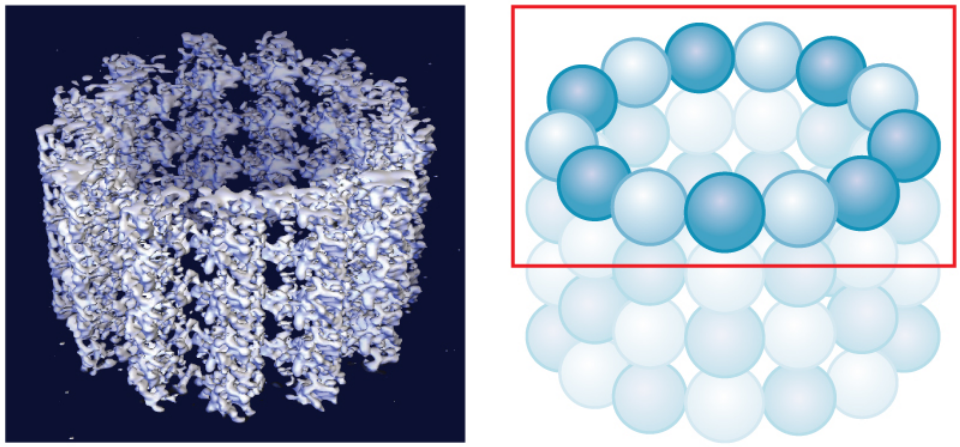


Figure 1.4.6.4: Microtubules are hollow. Their walls consist of 13 polymerized dimers of α-tubulin and β-tubulin (right image). The left image shows the molecular structure of the tube.

Microtubules are also the structural elements of flagella, cilia, and centrioles (the latter are the two perpendicular bodies of the centrosome). In fact, in animal cells, the centrosome is the microtubule-organizing center. In eukaryotic cells, flagella and cilia are quite different structurally from their counterparts in prokaryotes, as discussed below.

Flagella and Cilia

To refresh your memory, flagella (singular = flagellum) are long, hair-like structures that extend from the plasma membrane and are used to move an entire cell (for example, sperm, *Euglena*). When present, the cell has just one flagellum or a few flagella. When cilia (singular = cilium) are present, however, many of them extend along the entire surface of the plasma membrane. They are

short, hair-like structures that are used to move entire cells (such as paramecia) or substances along the outer surface of the cell (for example, the cilia of cells lining the Fallopian tubes that move the ovum toward the uterus, or cilia lining the cells of the respiratory tract that trap particulate matter and move it toward your nostrils.)

Despite their differences in length and number, flagella and cilia share a common structural arrangement of microtubules called a "9 + 2 array." This is an appropriate name because a single flagellum or cilium is made of a ring of nine microtubule doublets, surrounding a single microtubule doublet in the center (Figure 1.4.6.5).

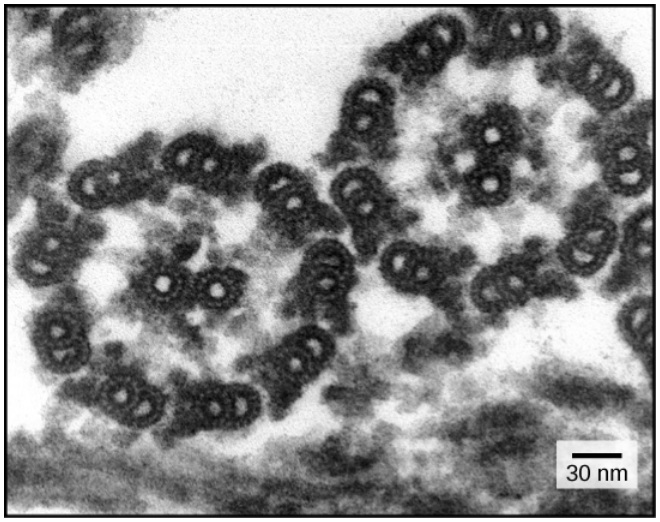


Figure 1.4.6.5: This transmission electron micrograph of two flagella shows the 9 + 2 array of microtubules: nine microtubule doublets surround a single microtubule doublet. (credit: modification of work by Dartmouth Electron Microscope Facility, Dartmouth College; scale-bar data from Matt Russell)

You have now completed a broad survey of the components of prokaryotic and eukaryotic cells. For a summary of cellular components in prokaryotic and eukaryotic cells, see Table 1.4.6.1.

Table 1.4.6.1: Cellular components in prokaryotic and eukaryotic cells.

Cell Component	Function	Present in Prokaryotes?	Present in Animal Cells?	Present in Plant Cells?
Plasma membrane	Separates cell from external environment; controls passage of organic molecules, ions, water, oxygen, and wastes into and out of cell	Yes	Yes	Yes
Cytoplasm	Provides turgor pressure to plant cells as fluid inside the central vacuole; site of many metabolic reactions; medium in which organelles are found	Yes	Yes	Yes
Nucleolus	Darkened area within the nucleus where ribosomal subunits are synthesized.	No	Yes	Yes
Nucleus	Cell organelle that houses DNA and directs synthesis of ribosomes and proteins	No	Yes	Yes
Ribosomes	Protein synthesis	Yes	Yes	Yes
Mitochondria	ATP production/cellular respiration	No	Yes	Yes
Peroxisomes	Oxidizes and thus breaks down fatty acids and amino acids, and detoxifies poisons	No	Yes	Yes
Vesicles and vacuoles	Storage and transport; digestive function in plant cells	No	Yes	Yes
Centrosome	Unspecified role in cell division in animal cells; source of microtubules in animal cells	No	Yes	No
Lysosomes	Digestion of macromolecules; recycling of worn-out organelles	No	Yes	No
Cell wall	Protection, structural support and maintenance of cell shape	Yes, primarily peptidoglycan	No	Yes, primarily cellulose
Chloroplasts	Photosynthesis	No	No	Yes
Endoplasmic reticulum	Modifies proteins and	No	Yes	Yes

Cell Component	Function	Present in Prokaryotes?	Present in Animal Cells?	Present in Plant Cells?
	synthesizes lipids			
Golgi apparatus	Modifies, sorts, tags, packages, and distributes lipids and proteins	No	Yes	Yes
Cytoskeleton	Maintains cell's shape, secures organelles in specific positions, allows cytoplasm and vesicles to move within cell, and enables unicellular organisms to move independently	Yes	Yes	Yes
Flagella	Cellular locomotion	Some	Some	No, except for some plant sperm cells.
Cilia	Cellular locomotion, movement of particles along extracellular surface of plasma membrane, and filtration	Some	Some	No

Summary

The cytoskeleton has three different types of protein elements. From narrowest to widest, they are the microfilaments (actin filaments), intermediate filaments, and microtubules. Microfilaments are often associated with myosin. They provide rigidity and shape to the cell and facilitate cellular movements. Intermediate filaments bear tension and anchor the nucleus and other organelles in place. Microtubules help the cell resist compression, serve as tracks for motor proteins that move vesicles through the cell, and pull replicated chromosomes to opposite ends of a dividing cell. They are also the structural element of centrioles, flagella, and cilia.

Glossary

cilium

(plural = cilia) short, hair-like structure that extends from the plasma membrane in large numbers and is used to move an entire cell or move substances along the outer surface of the cell

cytoskeleton

network of protein fibers that collectively maintain the shape of the cell, secure some organelles in specific positions, allow cytoplasm and vesicles to move within the cell, and enable unicellular organisms to move independently

flagellum

(plural = flagella) long, hair-like structure that extends from the plasma membrane and is used to move the cell

intermediate filament

cytoskeletal component, composed of several intertwined strands of fibrous protein, that bears tension, supports cell-cell junctions, and anchors cells to extracellular structures

microfilament

narrowest element of the cytoskeleton system; it provides rigidity and shape to the cell and enables cellular movements

microtubule

widest element of the cytoskeleton system; it helps the cell resist compression, provides a track along which vesicles move through the cell, pulls replicated chromosomes to opposite ends of a dividing cell, and is the structural element of centrioles, flagella, and cilia

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1.4.7: Connections between Cells and Cellular Activities

Skills to Develop

- Describe the extracellular matrix
- List examples of the ways that plant cells and animal cells communicate with adjacent cells
- Summarize the roles of tight junctions, desmosomes, gap junctions, and plasmodesmata

You already know that a group of similar cells working together is called a tissue. As you might expect, if cells are to work together, they must communicate with each other, just as you need to communicate with others if you work on a group project. Let's take a look at how cells communicate with each other.

Extracellular Matrix of Animal Cells

Most animal cells release materials into the extracellular space. The primary components of these materials are proteins, and the most abundant protein is collagen. Collagen fibers are interwoven with carbohydrate-containing protein molecules called proteoglycans. Collectively, these materials are called the extracellular matrix (Figure 1.4.7.1). Not only does the extracellular matrix hold the cells together to form a tissue, but it also allows the cells within the tissue to communicate with each other. How can this happen?

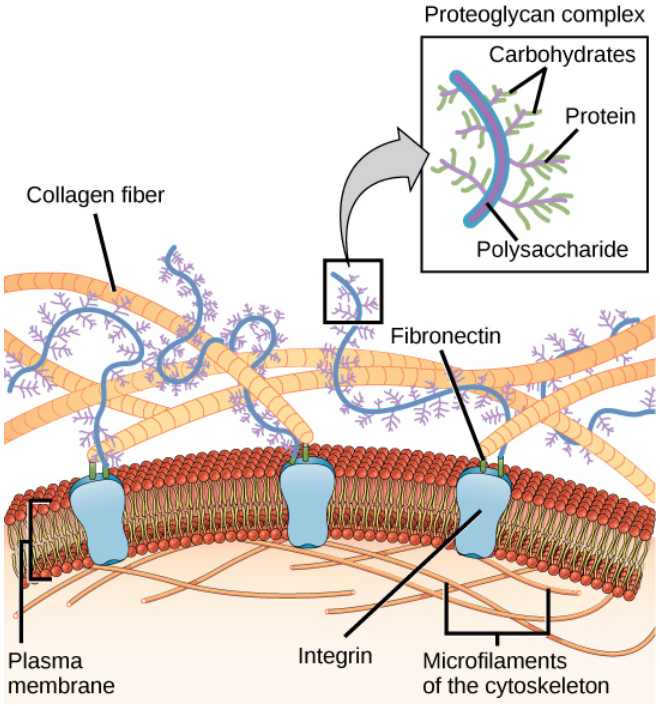


Figure 1.4.7.1: The extracellular matrix consists of a network of proteins and carbohydrates.

Cells have protein receptors on the extracellular surfaces of their plasma membranes. When a molecule within the matrix binds to the receptor, it changes the molecular structure of the receptor. The receptor, in turn, changes the conformation of the microfilaments positioned just inside the plasma membrane. These conformational changes induce chemical signals inside the cell that reach the nucleus and turn "on" or "off" the transcription of specific sections of DNA, which affects the production of associated proteins, thus changing the activities within the cell.

Blood clotting provides an example of the role of the extracellular matrix in cell communication. When the cells lining a blood vessel are damaged, they display a protein receptor called tissue factor. When tissue factor binds with another factor in the extracellular matrix, it causes platelets to adhere to the wall of the damaged blood vessel, stimulates the adjacent smooth muscle cells in the blood vessel to contract (thus constricting the blood vessel), and initiates a series of steps that stimulate the platelets to produce clotting factors.

Intercellular Junctions

Cells can also communicate with each other via direct contact, referred to as intercellular junctions. There are some differences in the ways that plant and animal cells do this. Plasmodesmata are junctions between plant cells, whereas animal cell contacts include tight junctions, gap junctions, and desmosomes.

Plasmodesmata

In general, long stretches of the plasma membranes of neighboring plant cells cannot touch one another because they are separated by the cell wall that surrounds each cell. How then, can a plant transfer water and other soil nutrients from its roots, through its stems, and to its leaves? Such transport uses the vascular tissues (xylem and phloem) primarily. There also exist structural modifications called plasmodesmata (singular = plasmodesma), numerous channels that pass between cell walls of adjacent plant cells, connect their cytoplasm, and enable materials to be transported from cell to cell, and thus throughout the plant (Figure 1.4.7.2).

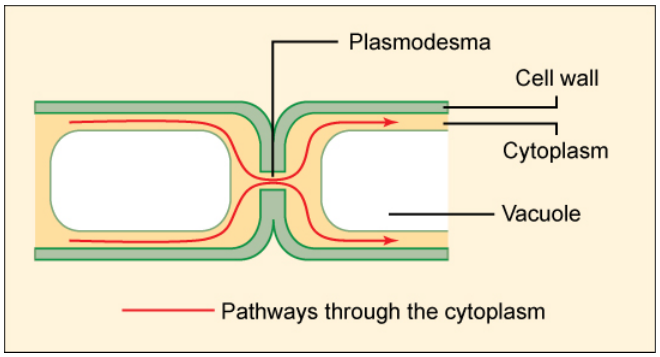


Figure 1.4.7.2: A plasmodesma is a channel between the cell walls of two adjacent plant cells. Plasmodesmata allow materials to pass from the cytoplasm of one plant cell to the cytoplasm of an adjacent cell.

Tight Junctions

A tight junction is a watertight seal between two adjacent animal cells (Figure 1.4.7.3). The cells are held tightly against each other by proteins (predominantly two proteins called claudins and occludins).

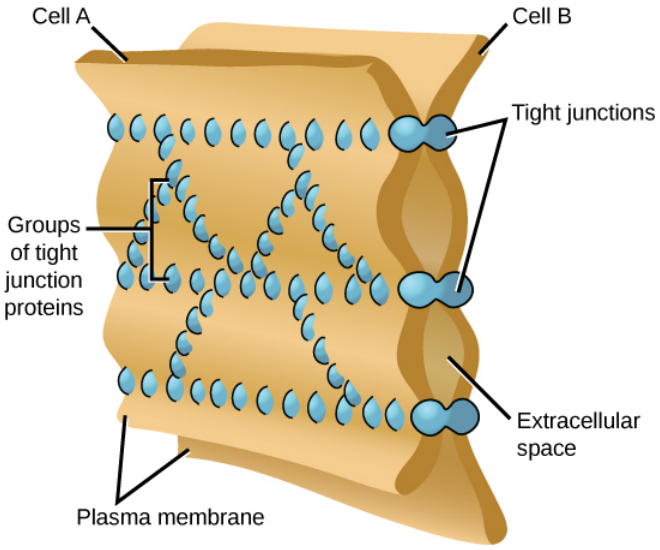


Figure 1.4.7.3: Tight junctions form watertight connections between adjacent animal cells. Proteins create tight junction adherence. (credit: modification of work by Mariana Ruiz Villareal)

This tight adherence prevents materials from leaking between the cells; tight junctions are typically found in epithelial tissues that line internal organs and cavities, and comprise most of the skin. For example, the tight junctions of the epithelial cells lining your urinary bladder prevent urine from leaking out into the extracellular space.

Desmosomes

Also found only in animal cells are desmosomes, which act like spot welds between adjacent epithelial cells (Figure 1.4.7.4). Short proteins called cadherins in the plasma membrane connect to intermediate filaments to create desmosomes. The cadherins join two adjacent cells together and maintain the cells in a sheet-like formation in organs and tissues that stretch, like the skin, heart, and muscles.

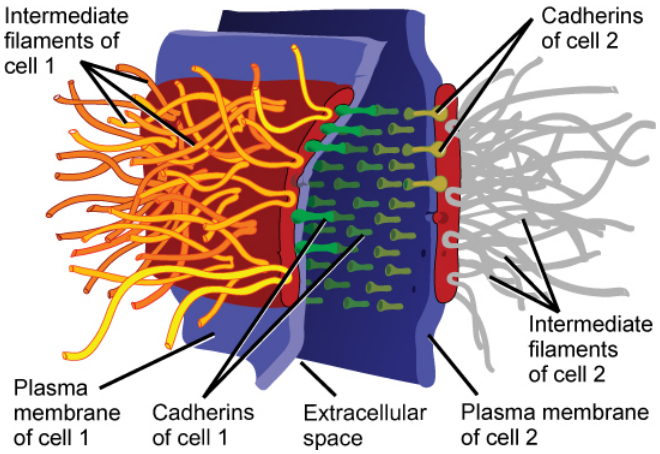


Figure 1.4.7.4: A desmosome forms a very strong spot weld between cells. It is created by the linkage of cadherins and intermediate filaments. (credit: modification of work by Mariana Ruiz Villareal)

Gap Junctions

Gap junctions in animal cells are like plasmodesmata in plant cells in that they are channels between adjacent cells that allow for the transport of ions, nutrients, and other substances that enable cells to communicate (Figure 1.4.7.5). Structurally, however, gap junctions and plasmodesmata differ.

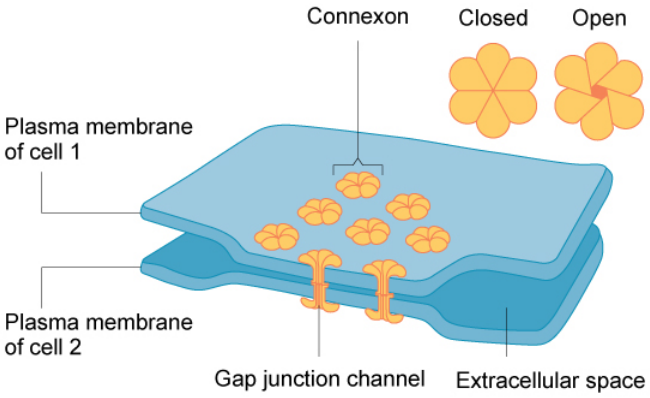


Figure 1.4.7.5: A gap junction is a protein-lined pore that allows water and small molecules to pass between adjacent animal cells. (credit: modification of work by Mariana Ruiz Villareal)

Gap junctions develop when a set of six proteins (called connexins) in the plasma membrane arrange themselves in an elongated donut-like configuration called a connexon. When the pores (“doughnut holes”) of connexons in adjacent animal cells align, a channel between the two cells forms. Gap junctions are particularly important in cardiac muscle: The electrical signal for the muscle to contract is passed efficiently through gap junctions, allowing the heart muscle cells to contract in tandem.

Summary

Animal cells communicate via their extracellular matrices and are connected to each other via tight junctions, desmosomes, and gap junctions. Plant cells are connected and communicate with each other via plasmodesmata.

When protein receptors on the surface of the plasma membrane of an animal cell bind to a substance in the extracellular matrix, a chain of reactions begins that changes activities taking place within the cell. Plasmodesmata are channels between adjacent plant cells, while gap junctions are channels between adjacent animal cells. However, their structures are quite different. A tight junction is a watertight seal between two adjacent cells, while a desmosome acts like a spot weld.

Glossary

desmosome
: linkages between adjacent epithelial cells that form when cadherins in the plasma membrane attach to intermediate filaments

extracellular matrix
: material (primarily collagen, glycoproteins, and proteoglycans) secreted from animal cells that provides mechanical protection and anchoring for the cells in the tissue

gap junction
: channel between two adjacent animal cells that allows ions, nutrients, and low molecular weight substances to pass between cells, enabling the cells to communicate

plasmodesma
: (plural = plasmodesmata) channel that passes between the cell walls of adjacent plant cells, connects their cytoplasm, and allows materials to be transported from cell to cell

tight junction
: firm seal between two adjacent animal cells created by protein adherence

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1.4.8: Cell Structure (Exercises)

4.1: Studying Cells

A cell is the smallest unit of a living thing. A living thing, whether made of one cell (like bacteria) or many cells (like a human), is called an organism. Thus, cells are the basic building blocks of all organisms. There are many types of cells, all grouped into one of two broad categories: prokaryotic and eukaryotic. For example, both animal and plant cells are classified as eukaryotic cells, whereas bacterial cells are classified as prokaryotic.

Review Questions

When viewing a specimen through a light microscope, scientists use _____ to distinguish the individual components of cells.

A. a beam of electrons
B. radioactive isotopes
C. special stains
D. high temperatures

Answer

C

The _____ is the basic unit of life.

A. organism
B. cell
C. tissue
D. organ

Answer

B

Free Response

In your everyday life, you have probably noticed that certain instruments are ideal for certain situations. For example, you would use a spoon rather than a fork to eat soup because a spoon is shaped for scooping, while soup would slip between the tines of a fork. The use of ideal instruments also applies in science. In what situation(s) would the use of a light microscope be ideal, and why?

Answer

A light microscope would be ideal when viewing a small living organism, especially when the cell has been stained to reveal details.

In what situation(s) would the use of a scanning electron microscope be ideal, and why?

Answer

A scanning electron microscope would be ideal when you want to view the minute details of a cell's surface, because its beam of electrons moves back and forth over the surface to convey the image.

In what situation(s) would a transmission electron microscope be ideal, and why?

Answer

A transmission electron microscope would be ideal for viewing the cell's internal structures, because many of the internal structures have membranes that are not visible by the light microscope.

What are the advantages and disadvantages of each of these types of microscopes?

Answer

The advantages of light microscopes are that they are easily obtained, and the light beam does not kill the cells. However, typical light microscopes are somewhat limited in the amount of detail they can reveal. Electron microscopes are ideal because you can view intricate details, but they are bulky and costly, and preparation for the microscopic examination kills the specimen.

4.2: Prokaryotic Cells

Cells fall into one of two broad categories: prokaryotic and eukaryotic. Only the predominantly single-celled organisms of the domains Bacteria and Archaea are classified as prokaryotes (pro- = "before"; -kary- = "nucleus"). Cells of animals, plants, fungi, and protists are all eukaryotes (ceu- = "true") and are made up of eukaryotic cells.

Review Questions

Prokaryotes depend on _____ to obtain some materials and to get rid of wastes.

A. ribosomes
B. flagella
C. cell division
D. diffusion

Answer

D

Bacteria that lack fimbriae are less likely to _____.

A. adhere to cell surfaces
B. swim through bodily fluids
C. synthesize proteins
D. retain the ability to divide

Answer

A

Free Response

Antibiotics are medicines that are used to fight bacterial infections. These medicines kill prokaryotic cells without harming human cells. What part or parts of the bacterial cell do you think antibiotics target? Why?

Answer

The cell wall would be targeted by antibiotics as well as the bacteria's ability to replicate. This would inhibit the bacteria's ability to reproduce, and it would compromise its defense mechanisms.

Explain why not all microbes are harmful.

Answer

Some microbes are beneficial. For instance, *E. coli* bacteria populate the human gut and help break down fiber in the diet. Some foods such as yogurt are formed by bacteria.

4.3: Eukaryotic Cells

Our natural world also utilizes the principle of form following function, especially in cell biology, and this will become clear as we explore eukaryotic cells. Unlike prokaryotic cells, eukaryotic cells have: 1) a membrane-bound nucleus; 2) numerous membrane-bound organelles such as the endoplasmic reticulum, Golgi apparatus, chloroplasts, mitochondria, and others; and 3) several, rod-shaped chromosomes. Because a eukaryotic cell's nucleus is surrounded by a membrane, it is has "true nucleus."

Review Questions

Which of the following is surrounded by two phospholipid bilayers?

A. the ribosomes
B. the vesicles
C. the cytoplasm
D. the nucleoplasm

Answer

D

Peroxisomes got their name because hydrogen peroxide is:

A. used in their detoxification reactions
B. produced during their oxidation reactions
C. incorporated into their membranes
D. a cofactor for the organelles' enzymes

Answer

B

In plant cells, the function of the lysosomes is carried out by _____.

A. vacuoles
B. peroxisomes
C. ribosomes
D. nuclei

Answer

A

Which of the following is found both in eukaryotic and prokaryotic cells?

A. nucleus
B. mitochondrion
C. vacuole
D. ribosomes

Answer

D

Free Response

You already know that ribosomes are abundant in red blood cells. In what other cells of the body would you find them in great abundance? Why?

Answer

Ribosomes are abundant in muscle cells as well because muscle cells are constructed of the proteins made by the ribosomes.

What are the structural and functional similarities and differences between mitochondria and chloroplasts?

Answer

Both are similar in that they are enveloped in a double membrane, both have an intermembrane space, and both make ATP. Both mitochondria and chloroplasts have DNA, and mitochondria have inner folds called cristae and a matrix, while chloroplasts have chlorophyll and accessory pigments in the thylakoids that form stacks (grana) and a stroma.

4.4: The Endomembrane System and Proteins

The endomembrane system is a group of membranes and organelles in eukaryotic cells that works together to modify, package, and transport lipids and proteins. It includes the nuclear envelope, lysosomes, and vesicles, which we've already mentioned, and the endoplasmic reticulum and Golgi apparatus. Although not technically within the cell, the plasma membrane is included in the endomembrane system because, as you will see, it interacts with the other endomembranous organelles.

Review Questions

Which of the following is not a component of the endomembrane system?

A. mitochondrion
B. Golgi apparatus
C. endoplasmic reticulum
D. lysosome

Answer

A

The process by which a cell engulfs a foreign particle is known as:

A. endosymbiosis
B. phagocytosis
C. hydrolysis
D. membrane synthesis

Answer

B

Which of the following is most likely to have the greatest concentration of smooth endoplasmic reticulum?

A. a cell that secretes enzymes
B. a cell that destroys pathogens
C. a cell that makes steroid hormones
D. a cell that engages in photosynthesis

Answer

C

Which of the following sequences correctly lists in order the steps involved in the incorporation of a proteinaceous molecule within a cell?

A. synthesis of the protein on the ribosome; modification in the Golgi apparatus; packaging in the endoplasmic reticulum; tagging in the vesicle
B. synthesis of the protein on the lysosome; tagging in the Golgi; packaging in the vesicle; distribution in the endoplasmic reticulum
C. synthesis of the protein on the ribosome; modification in the endoplasmic reticulum; tagging in the Golgi; distribution via the vesicle
D. synthesis of the protein on the lysosome; packaging in the vesicle; distribution via the Golgi; tagging in the endoplasmic reticulum

Answer

C

Free Response

In the context of cell biology, what do we mean by form follows function? What are at least two examples of this concept?

Answer

"Form follows function" refers to the idea that the function of a body part dictates the form of that body part. As an example, compare your arm to a bat's wing. While the bones of the two correspond, the parts serve different functions in each organism and their forms have adapted to follow that function.

In your opinion, is the nuclear membrane part of the endomembrane system? Why or why not? Defend your answer.

Answer

Since the external surface of the nuclear membrane is continuous with the rough endoplasmic reticulum, which is part of the endomembrane system, then it is correct to say that it is part of the system.

4.5: The Cytoskeleton

Within the cytoplasm, there are ions and organic molecules, plus a network of protein fibers that help maintain the shape of the cell, secure some organelles in specific positions, allow cytoplasm and vesicles to move within the cell, and enable cells within multicellular organisms to move. Collectively, this network of protein fibers is known as the cytoskeleton. There are three types of fibers within the cytoskeleton: microfilaments, intermediate filaments, and microtubules.

Review Questions

Which of the following have the ability to disassemble and reform quickly?

A. microfilaments and intermediate filaments
B. microfilaments and microtubules
C. intermediate filaments and microtubules
D. only intermediate filaments

Answer

B

Which of the following do not play a role in intracellular movement?

A. microfilaments and intermediate filaments
B. microfilaments and microtubules
C. intermediate filaments and microtubules
D. only intermediate filaments

Answer

D

Free Response

What are the similarities and differences between the structures of centrioles and flagella?

Answer

Centrioles and flagella are alike in that they are made up of microtubules. In centrioles, two rings of nine microtubule "triplets" are arranged at right angles to one another. This arrangement does not occur in flagella.

How do cilia and flagella differ?

Answer

Cilia and flagella are alike in that they are made up of microtubules. Cilia are short, hair-like structures that exist in large numbers and usually cover the entire surface of the plasma membrane. Flagella, in contrast, are long, hair-like structures; when flagella are present, a cell has just one or two.

4.6: Connections between Cells and Cellular Activities

You already know that a group of similar cells working together is called a tissue. As you might expect, if cells are to work together, they must communicate with each other, just as you need to communicate with others if you work on a group project. Let's take a look at how cells communicate with each other.

Review Questions

Which of the following are found only in plant cells?

A. gap junctions
B. desmosomes
C. plasmodesmata
D. tight junctions

Answer

C

The key components of desmosomes are cadherins and _____.

A. actin
B. microfilaments
C. intermediate filaments
D. microtubules

Answer

C

Free Response

How does the structure of a plasmodesma differ from that of a gap junction?

Answer

They differ because plant cell walls are rigid. Plasmodesmata, which a plant cell needs for transportation and communication, are able to allow movement of really large molecules. Gap junctions are necessary in animal cells for transportation and communication.

Explain how the extracellular matrix functions.

Answer

The extracellular matrix functions in support and attachment for animal tissues. It also functions in the healing and growth of the tissue.

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CHAPTER OVERVIEW

2: Bacteria, Archaea and Eukaryotic Microorganisms

Topic hierarchy

2.1: Prokaryotic Diversity
- 2.1.1: Prokaryote Habitats, Relationships, and Microbiomes
- 2.1.2: Proteobacteria
- 2.1.3: Nonproteobacteria Gram-negative Bacteria and Phototrophic Bacteria
- 2.1.4: Gram-positive Bacteria
- 2.1.5: Deeply Branching Bacteria
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2.2: The Eukaryotes of Microbiology
- 2.2.1: Unicellular Eukaryotic Microorganisms
- 2.2.2: Parasitic Helminths
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2.3: Cell Membranes
- 2.3.1: Why It Matters- Cell Membranes
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SECTION OVERVIEW

2.1: Prokaryotic Diversity

Scientists have studied prokaryotes for centuries, but it wasn't until 1966 that scientist Thomas Brock (1926–) discovered that certain bacteria can live in boiling water. This led many to wonder whether prokaryotes may also live in other extreme environments, such as at the bottom of the ocean, at high altitudes, or inside volcanoes, or even on other planets.

Prokaryotes have an important role in changing, shaping, and sustaining the entire biosphere. They can produce proteins and other substances used by molecular biologists in basic research and in medicine and industry. For example, the bacterium *Shewanella* lives in the deep sea, where oxygen is scarce. It grows long appendages, which have special sensors used to seek the limited oxygen in its environment. It can also digest toxic waste and generate electricity. Other species of prokaryotes can produce more oxygen than the entire Amazon rainforest, while still others supply plants, animals, and humans with usable forms of nitrogen; and inhabit our body, protecting us from harmful microorganisms and producing some vitally important substances. This chapter will examine the diversity, structure, and function of prokaryotes.

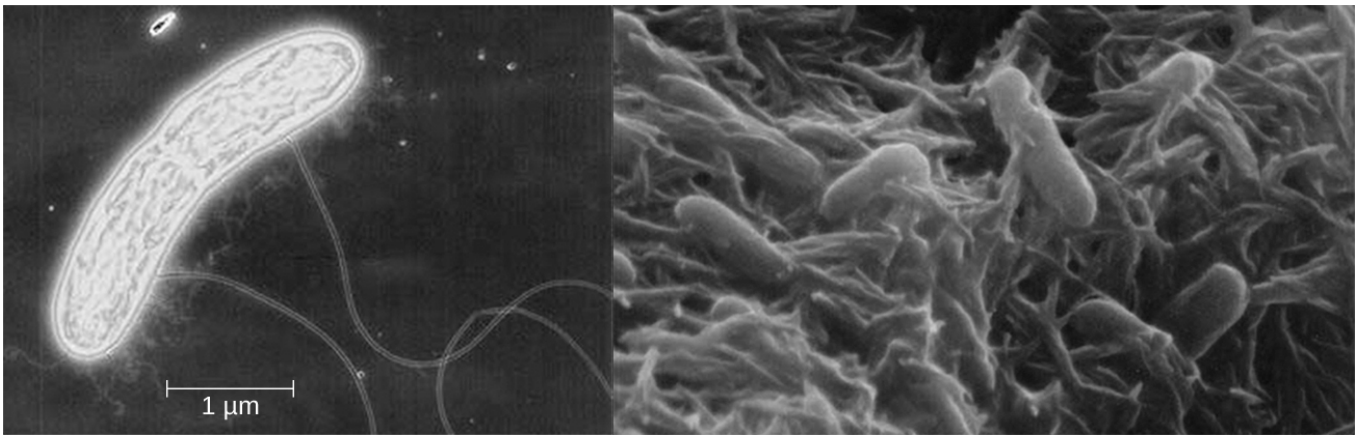


Figure 2.1.1: The bacterium *Shewanella* lives in the deep sea, where there is little oxygen diffused in the water. It is able to survive in this harsh environment by attaching to the sea floor and using long appendages, called "nanocables," to sense oxygen. (credit a: modification of work by NASA; credit b: modification of work by Liza Gross)

2.1.1: Prokaryote Habitats, Relationships, and Microbiomes

2.1.2: Proteobacteria

2.1.3: Nonproteobacteria Gram-negative Bacteria and Phototrophic Bacteria

2.1.4: Gram-positive Bacteria

2.1.5: Deeply Branching Bacteria

2.1.6: Archaea

2.1.E: Prokaryotic Diversity (Exercises)

Thumbnail: A cladogram linking all major groups of living organisms to the LUCA (the black trunk at the bottom), based on ribosomal RNA sequence data.

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2.1.1: Prokaryote Habitats, Relationships, and Microbiomes

Learning Objectives

- Identify and describe unique examples of prokaryotes in various habitats on earth
- Identify and describe symbiotic relationships
- Compare normal/commensal/resident microbiota to transient microbiota
- Explain how prokaryotes are classified

Clinical Focus: Part 1

Marsha, a 20-year-old university student, recently returned to the United States from a trip to Nigeria, where she had interned as a medical assistant for an organization working to improve access to laboratory services for tuberculosis testing. When she returned, Marsha began to feel fatigue, which she initially attributed to jet lag. However, the fatigue persisted, and Marsha soon began to experience other bothersome symptoms, such as occasional coughing, night sweats, loss of appetite, and a low-grade fever of 37.4 °C (99.3 °F).

Marsha expected her symptoms would subside in a few days, but instead, they gradually became more severe. About two weeks after returning home, she coughed up some sputum and noticed that it contained blood and small whitish clumps resembling cottage cheese. Her fever spiked to 38.2 °C (100.8 °F), and she began feeling sharp pains in her chest when breathing deeply. Concerned that she seemed to be getting worse, Marsha scheduled an appointment with her physician.

Exercise 2.1.1.1

Could Marsha's symptoms be related to her overseas travel, even several weeks after returning home?

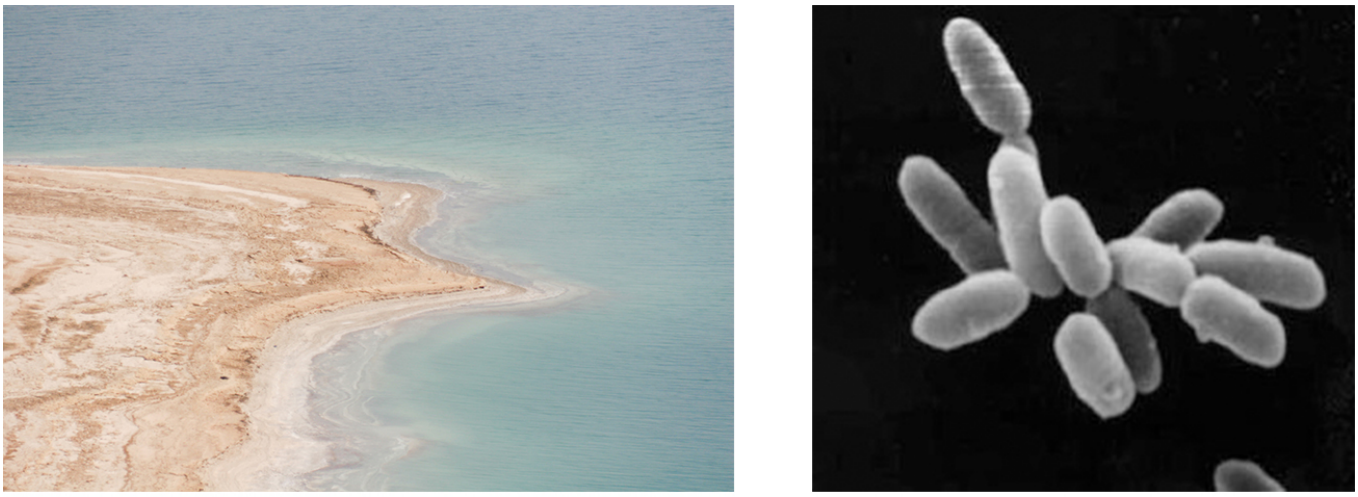
All living organisms are classified into three domains of life: Archaea, Bacteria, and Eukarya. In this chapter, we will focus on the domains Archaea and Bacteria. Archaea and bacteria are unicellular prokaryotic organisms. Unlike eukaryotes, they have no nuclei or any other membrane-bound organelles.

Prokaryote Habitats and Functions

Prokaryotes are ubiquitous. They can be found everywhere on our planet, even in hot springs, in the Antarctic ice shield, and under extreme pressure two miles under water. One bacterium, *Paracoccus denitrificans*, has even been shown to survive when scientists removed it from its native environment (soil) and used a centrifuge to subject it to forces of gravity as strong as those found on the surface of Jupiter.

Prokaryotes also are abundant on and within the human body. According to a report by National Institutes of Health, prokaryotes, especially bacteria, outnumber human cells 10:1.[1] More recent studies suggest the ratio could be closer to 1:1, but even that ratio means that there are a great number of bacteria within the human body.[2] Bacteria thrive in the human mouth, nasal cavity, throat, ears, gastrointestinal tract, and vagina. Large colonies of bacteria can be found on healthy human skin, especially in moist areas (armpits, navel, and areas behind ears). However, even drier areas of the skin are not free from bacteria.

The existence of prokaryotes is very important for the stability and thriving of ecosystems. For example, they are a necessary part of soil formation and stabilization processes through the breakdown of organic matter and development of biofilms. One gram of soil contains up to 10 billion microorganisms (most of them prokaryotic) belonging to about 1,000 species. Many species of bacteria use substances released from plant roots, such as acids and carbohydrates, as nutrients. The bacteria metabolize these plant substances and release the products of bacterial metabolism back to the soil, forming humus and thus increasing the soil's fertility. In salty lakes such as the Dead Sea (Figure 2.1.1.1), salt-loving halobacteria decompose dead brine shrimp and nourish young brine shrimp and flies with the products of bacterial metabolism.



(a) (b)

Figure 2.1.1.1: (a) Some prokaryotes, called halophiles, can thrive in extremely salty environments such as the Dead Sea, pictured here. (b) The archaeon *Halobacterium salinarum*, shown here in an electron micrograph, is a halophile that lives in the Dead Sea. (credit a: modification of work by Jullen Menichini; credit b: modification of work by NASA)

In addition to living in the ground and the water, prokaryotic microorganisms are abundant in the air, even high in the atmosphere. There may be up to 2,000 different kinds of bacteria in the air, similar to their diversity in the soil.

Prokaryotes can be found everywhere on earth because they are extremely resilient and adaptable. They are often metabolically flexible, which means that they might easily switch from one energy source to another, depending on the availability of the sources, or from one metabolic pathway to another. For example, certain prokaryotic cyanobacteria can switch from a conventional type of lipid metabolism, which includes production of fatty aldehydes, to a different type of lipid metabolism that generates biofuel, such as fatty acids and wax esters. Groundwater bacteria store complex high-energy carbohydrates when grown in pure groundwater, but they metabolize these molecules when the groundwater is enriched with phosphates. Some bacteria get their energy by reducing sulfates into sulfides, but can switch to a different metabolic pathway when necessary, producing acids and free hydrogen ions.

Prokaryotes perform functions vital to life on earth by capturing (or “fixing”) and recycling elements like carbon and nitrogen. Organisms such as animals require organic carbon to grow, but, unlike prokaryotes, they are unable to use inorganic carbon sources like carbon dioxide. Thus, animals rely on prokaryotes to convert carbon dioxide into organic carbon products that they can use. This process of converting carbon dioxide to organic carbon products is called carbon fixation.

Plants and animals also rely heavily on prokaryotes for nitrogen fixation, the conversion of atmospheric nitrogen into ammonia, a compound that some plants can use to form many different biomolecules necessary to their survival. Bacteria in the genus *Rhizobium*, for example, are nitrogen-fixing bacteria; they live in the roots of legume plants such as clover, alfalfa, and peas (Figure 2.1.1.2). Ammonia produced by *Rhizobium* helps these plants to survive by enabling them to make building blocks of nucleic acids. In turn, these plants may be eaten by animals—sustaining their growth and survival—or they may die, in which case the products of nitrogen fixation will enrich the soil and be used by other plants.

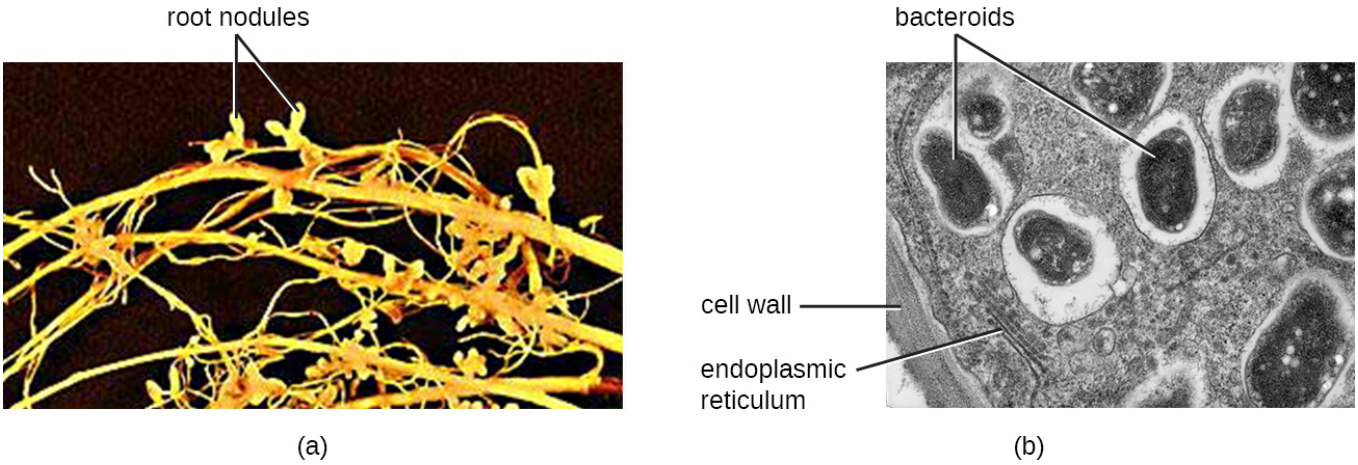


Figure 2.1.1.2: (a) Nitrogen-fixing bacteria such as *Rhizobium* live in the root nodules of legumes such as clover. (b) This micrograph of the root nodule shows bacteroids (bacterium-like cells or modified bacterial cells) within the plant cells. The bacteroids are visible as darker ovals within the larger plant cell. (credit a: modification of work by USDA)

Another positive function of prokaryotes is in cleaning up the environment. Recently, some researchers focused on the diversity and functions of prokaryotes in manmade environments. They found that some bacteria play a unique role in degrading toxic chemicals that pollute water and soil.[3]

Despite all of the positive and helpful roles prokaryotes play, some are human pathogens that may cause illness or infection when they enter the body. In addition, some bacteria can contaminate food, causing spoilage or foodborne illness, which makes them subjects of concern in food preparation and safety. Less than 1% of prokaryotes (all of them bacteria) are thought to be human pathogens, but collectively these species are responsible for a large number of the diseases that afflict humans.

Besides pathogens, which have a direct impact on human health, prokaryotes also affect humans in many indirect ways. For example, prokaryotes are now thought to be key players in the processes of climate change. In recent years, as temperatures in the earth's polar regions have risen, soil that was formerly frozen year-round (permafrost) has begun to thaw. Carbon trapped in the permafrost is gradually released and metabolized by prokaryotes. This produces massive amounts of carbon dioxide and methane, greenhouse gases that escape into the atmosphere and contribute to the greenhouse effect.

? Exercise 2.1.1.2

1. In what types of environments can prokaryotes be found?
2. Name some ways that plants and animals rely on prokaryotes.

Symbiotic Relationships

As we have learned, prokaryotic microorganisms can associate with plants and animals. Often, this association results in unique relationships between organisms. For example, bacteria living on the roots or leaves of a plant get nutrients from the plant and, in return, produce substances that protect the plant from pathogens. On the other hand, some bacteria are plant pathogens that use mechanisms of infection similar to bacterial pathogens of animals and humans.

Prokaryotes live in a community, or a group of interacting populations of organisms. A population is a group of individual organisms belonging to the same biological species and limited to a certain geographic area. Populations can have cooperative interactions, which benefit the populations, or competitive interactions, in which one population competes with another for resources. The study of these interactions between populations is called microbial ecology.

Any interaction between different species within a community is called symbiosis. Such interactions fall along a continuum between opposition and cooperation. Interactions in a symbiotic relationship may be beneficial or harmful, or have no effect on one or both of the species involved. Table 2.1.1.1 summarizes the main types of symbiotic interactions among prokaryotes.

Table 2.1.1.1: Types of Symbiotic Relationships

Type	Population A	Population B
Mutualism	Benefitted	Benefitted
Amensalism	Harmed	Unaffected
Commensalism	Benefitted	Unaffected
Neutralism	Unaffected	Unaffected
Parasitism	Benefitted	Harmed

When two species benefit from each other, the symbiosis is called mutualism (or syntropy, or crossfeeding). For example, humans have a mutualistic relationship with the bacterium *Bacteroides thetaiotetraiotamicron*, which lives in the intestinal tract. *B. thetaiotetraiotamicron* digests complex polysaccharide plant materials that human digestive enzymes cannot break down, converting them into monosaccharides that can be absorbed by human cells. Humans also have a mutualistic relationship with certain strains of *Escherichia coli*, another bacterium found in the gut. *E. coli* relies on intestinal contents for nutrients, and humans derive certain vitamins from *E. coli*, particularly vitamin K, which is required for the formation of blood clotting factors. (This is only true for some strains of *E. coli*, however. Other strains are pathogenic and do not have a mutualistic relationship with humans.)

A type of symbiosis in which one population harms another but remains unaffected itself is called amensalism. In the case of bacteria, some amensalist species produce bactericidal substances that kill other species of bacteria. For example, the bacterium *Lucilia sericata* produces a protein that destroys *Staphylococcus aureus*, a bacterium commonly found on the surface of the human skin. Too much handwashing can affect this relationship and lead to *S. aureus* diseases and transmission.

In another type of symbiosis, called commensalism, one organism benefits while the other is unaffected. This occurs when the bacterium *Staphylococcus epidermidis* uses the dead cells of the human skin as nutrients. Billions of these bacteria live on our skin, but in most cases (especially when our immune system is healthy), we do not react to them in any way.

If neither of the symbiotic organisms is affected in any way, we call this type of symbiosis neutralism. An example of neutralism is the coexistence of metabolically active (vegetating) bacteria and endospores (dormant, metabolically passive bacteria). For example, the bacterium *Bacillus anthracis* typically forms endospores in soil when conditions are unfavorable. If the soil is warmed and enriched with nutrients, some endospores germinate and remain in symbiosis with other endospores that have not germinated.

A type of symbiosis in which one organism benefits while harming the other is called parasitism. The relationship between humans and many pathogenic prokaryotes can be characterized as parasitic because these organisms invade the body, producing toxic substances or infectious diseases that cause harm. Diseases such as tetanus, diphtheria, pertussis, tuberculosis, and leprosy all arise from interactions between bacteria and humans.

Scientists have coined the term microbiome to refer to all prokaryotic and eukaryotic microorganisms that are associated with a certain organism. Within the human microbiome, there are resident microbiota and transient microbiota. The resident microbiota consists of microorganisms that constantly live in or on our bodies. The term transient microbiota refers to microorganisms that are only temporarily found in the human body, and these may include pathogenic microorganisms. Hygiene and diet can alter both the resident and transient microbiota.

The resident microbiota is amazingly diverse, not only in terms of the variety of species but also in terms of the preference of different microorganisms for different areas of the human body. For example, in the human mouth, there are thousands of commensal or mutualistic species of bacteria. Some of these bacteria prefer to inhabit the surface of the tongue, whereas others prefer the internal surface of the cheeks, and yet others prefer the front or back teeth or gums. The inner surface of the cheek has the least diverse microbiota because of its exposure to oxygen. By contrast, the crypts of the tongue and the spaces between teeth are two sites with limited oxygen exposure, so these sites have more diverse microbiota, including bacteria living in the absence of oxygen (e.g., *Bacteroides*, *Fusobacterium*). Differences in the oral microbiota between randomly chosen human individuals are also significant. Studies have shown, for example, that the prevalence of such bacteria as *Streptococcus*, *Haemophilus*, *Neisseria*, and others was dramatically different when compared between individuals.[4]

There are also significant differences between the microbiota of different sites of the same human body. The inner surface of the cheek has a predominance of *Streptococcus*, whereas in the throat, the palatine tonsil, and saliva, there are two to three times fewer *Streptococcus*, and several times more *Fusobacterium*. In the plaque removed from gums, the predominant bacteria belong to the genus *Fusobacterium*. However, in the intestine, both *Streptococcus* and *Fusobacterium* disappear, and the genus *Bacteroides* becomes predominant.

Not only can the microbiota vary from one body site to another, the microbiome can also change over time within the same individual. Humans acquire their first inoculations of normal flora during natural birth and shortly after birth. Before birth, there is a rapid increase in the population of *Lactobacillus* spp. in the vagina, and this population serves as the first colonization of microbiota during natural birth. After birth, additional microbes are acquired from health-care providers, parents, other relatives, and individuals who come in contact with the baby. This process establishes a microbiome that will continue to evolve over the course of the individual's life as new microbes colonize and are eliminated from the body. For example, it is estimated that within a 9-hour period, the microbiota of the small intestine can change so that half of the microbial inhabitants will be different.[5] The importance of the initial *Lactobacillus* colonization during vaginal child birth is highlighted by studies demonstrating a higher incidence of diseases in individuals born by cesarean section, compared to those born vaginally. Studies have shown that babies born vaginally are predominantly colonized by vaginal lactobacillus, whereas babies born by cesarean section are more frequently colonized by microbes of the normal skin microbiota, including common hospital-acquired pathogens.

Throughout the body, resident microbiotas are important for human health because they occupy niches that might be otherwise taken by pathogenic microorganisms. For instance, *Lactobacillus* spp. are the dominant bacterial species of the normal vaginal microbiota for most women. lactobacillus produce lactic acid, contributing to the acidity of the vagina and inhibiting the growth of pathogenic yeasts. However, when the population of the resident microbiota is decreased for some reason (e.g., because of taking antibiotics), the pH of the vagina increases, making it a more favorable environment for the growth of yeasts such as *Candida albicans*. Antibiotic therapy can also disrupt the microbiota of the intestinal tract and respiratory tract, increasing the risk for secondary infections and/or promoting the long-term carriage and shedding of pathogens.

? Exercise 2.1.1.3

1. Explain the difference between cooperative and competitive interactions in microbial communities.
2. List the types of symbiosis and explain how each population is affected.

Taxonomy and Systematics

Assigning prokaryotes to a certain species is challenging. They do not reproduce sexually, so it is not possible to classify them according to the presence or absence of interbreeding. Also, they do not have many morphological features. Traditionally, the classification of prokaryotes was based on their shape, staining patterns, and biochemical or physiological differences. More recently, as technology has improved, the nucleotide sequences in genes have become an important criterion of microbial classification.

In 1923, American microbiologist David Hendricks Bergey (1860–1937) published *A Manual in Determinative Bacteriology.* With this manual, he attempted to summarize the information about the kinds of bacteria known at that time, using Latin binomial classification. Bergey also included the morphological, physiological, and biochemical properties of these organisms. His manual has been updated multiple times to include newer bacteria and their properties. It is a great aid in bacterial taxonomy and methods of characterization of bacteria. A more recent sister publication, the five-volume *Bergey's Manual of Systematic Bacteriology*, expands on Bergey's original manual. It includes a large number of additional species, along with up-to-date descriptions of the taxonomy and biological properties of all named prokaryotic taxa. This publication incorporates the approved names of bacteria as determined by the List of Prokaryotic Names with Standing in Nomenclature (LPSN).

Classification by Staining Patterns

According to their staining patterns, which depend on the properties of their cell walls, bacteria have traditionally been classified into gram-positive, gram-negative, and "atypical," meaning neither gram-positive nor gram-negative. As explained in Staining Microscopic Specimens, gram-positive bacteria possess a thick peptidoglycan cell wall that retains the primary stain (crystal violet) during the decolorizing step; they remain purple after the gram-stain procedure because the crystal violet dominates the light

red/pink color of the secondary counterstain, safranin. In contrast, gram-negative bacteria possess a thin peptidoglycan cell wall that does not prevent the crystal violet from washing away during the decolorizing step; therefore, they appear light red/pink after staining with the safranin. Bacteria that cannot be stained by the standard Gram stain procedure are called atypical bacteria. Included in the atypical category are species of *Mycoplasma* and *Chlamydia*, which lack a cell wall and therefore cannot retain the gram-stain reagents. *Rickettsia*are also considered atypical because they are too small to be evaluated by the Gram stain.

More recently, scientists have begun to further classify gram-negative and gram-positive bacteria. They have added a special group of deeply branching bacteria based on a combination of physiological, biochemical, and genetic features. They also now further classify gram-negative bacteria into Proteobacteria, *Cytophaga-Flavobacterium-Bacteroides* (CFB), and spirochetes.

The deeply branching bacteria are thought to be a very early evolutionary form of bacteria (see Deeply Branching Bacteria). They live in hot, acidic, ultraviolet-light-exposed, and anaerobic (deprived of oxygen) conditions. Proteobacteria is a phylum of very diverse groups of gram-negative bacteria; it includes some important human pathogens (e.g., *E. coli* and *Bordetella pertussis*). The CFB group of bacteria includes components of the normal human gut microbiota, like *Bacteroides*. The spirochetes are spiral-shaped bacteria and include the pathogen *Treponema pallidum*, which causes syphilis. We will characterize these groups of bacteria in more detail later in the chapter.

Based on their prevalence of guanine and cytosine nucleotides, gram-positive bacteria are also classified into low G+C and high G+C gram-positive bacteria. The low G+C gram-positive bacteria have less than 50% of guanine and cytosine nucleotides in their DNA. They include human pathogens, such as those that cause anthrax (*Bacillus anthracis*), tetanus (*Clostridium tetani*), and listeriosis (*Listeria monocytogenes*). High G+C gram-positive bacteria, which have more than 50% guanine and cytosine nucleotides in their DNA, include the bacteria that cause diphtheria (*Corynebacterium diphtheriae*), tuberculosis (*Mycobacterium tuberculosis*), and other diseases.

The classifications of prokaryotes are constantly changing as new species are being discovered. We will describe them in more detail, along with the diseases they cause, in later sections and chapters.

? Exercise 2.1.1.4

How do scientists classify prokaryotes?

Human Microbiome Project

The Human Microbiome Project was launched by the National Institutes of Health (NIH) in 2008. One main goal of the project is to create a large repository of the gene sequences of important microbes found in humans, helping biologists and clinicians understand the dynamics of the human microbiome and the relationship between the human microbiota and diseases. A network of labs working together has been compiling the data from swabs of several areas of the skin, gut, and mouth from hundreds of individuals.

One of the challenges in understanding the human microbiome has been the difficulty of culturing many of the microbes that inhabit the human body. It has been estimated that we are only able to culture 1% of the bacteria in nature and that we are unable to grow the remaining 99%. To address this challenge, researchers have used metagenomic analysis, which studies genetic material harvested directly from microbial communities, as opposed to that of individual species grown in a culture. This allows researchers to study the genetic material of all microbes in the microbiome, rather than just those that can be cultured.[6]

One important achievement of the Human Microbiome Project is establishing the first reference database on microorganisms living in and on the human body. Many of the microbes in the microbiome are beneficial, but some are not. It was found, somewhat unexpectedly, that all of us have some serious microbial pathogens in our microbiota. For example, the conjunctiva of the human eye contains 24 genera of bacteria and numerous pathogenic species.[7] A healthy human mouth contains a number of species of the genus *Streptococcus*, including pathogenic species *S. pyogenes* and *S. pneumoniae*.[8] This raises the question of why certain prokaryotic organisms exist commensally in certain individuals but act as deadly pathogens in others. Also unexpected was the number of organisms that had never been cultured. For example, in one metagenomic study of the human gut microbiota, 174 new species of bacteria were identified.[9]

> Another goal for the near future is to characterize the human microbiota in patients with different diseases and to find out whether there are any relationships between the contents of an individual's microbiota and risk for or susceptibility to specific diseases. Analyzing the microbiome in a person with a specific disease may reveal new ways to fight diseases.

Summary

- Prokaryotes are unicellular microorganisms whose cells have no nucleus.
- Prokaryotes can be found everywhere on our planet, even in the most extreme environments.
- Prokaryotes are very flexible metabolically, so they are able to adjust their feeding to the available natural resources.
- Prokaryotes live in **communities** that interact among themselves and with large organisms that they use as hosts (including humans).
- The totality of forms of prokaryotes (particularly bacteria) living on the human body is called the human microbiome, which varies between regions of the body and individuals, and changes over time.
- The totality of forms of prokaryotes (particularly bacteria) living in a certain region of the human body (e.g., mouth, throat, gut, eye, vagina) is called the **microbiota** of this region.
- Prokaryotes are classified into domains Archaea and Bacteria.
- In recent years, the traditional approaches to classification of prokaryotes have been supplemented by approaches based on molecular genetics.

Footnotes

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2.1.2: Proteobacteria

Learning Objectives

- Describe the unique features of each class within the phylum Proteobacteria: Alphaproteobacteria, Betaproteobacteria, Gammaproteobacteria, Deltaproteobacteria, and Epsilonproteobacteria
- Give an example of a bacterium in each class of Proteobacteria

In 1987, the American microbiologist Carl Woese (1928–2012) suggested that a large and diverse group of bacteria that he called "purple bacteria and their relatives" should be defined as a separate phylum within the domain Bacteria based on the similarity of the nucleotide sequences in their genome.[1] This phylum of gram-negative bacteria subsequently received the name Proteobacteria. It includes many bacteria that are part of the normal human microbiota as well as many pathogens. The Proteobacteria are further divided into five classes: Alphaproteobacteria, Betaproteobacteria, Gammaproteobacteria, Deltaproteobacteria, and Epsilonproteobacteria.

Alphaproteobacteria

The first class of Proteobacteria is the Alphaproteobacteria. The unifying characteristic of this class is that they are oligotrophs, organisms capable of living in low-nutrient environments such as deep oceanic sediments, glacial ice, or deep undersurface soil.

Among the Alphaproteobacteria are two taxa, chlamydias and rickettsias, that are obligate intracellular pathogens, meaning that part of their life cycle must occur inside other cells called host cells. When not growing inside a host cell, *Chlamydia* and *Rickettsia* are metabolically inactive outside of the host cell. They cannot synthesize their own adenosine triphosphate (ATP), and, therefore, rely on cells for their energy needs.

Rickettsia spp. include a number of serious human pathogens. For example, *R. rickettsii* causes Rocky Mountain spotted fever, a life-threatening form of meningoencephalitis (inflammation of the membranes that wrap the brain). *R. rickettsii* infects ticks and can be transmitted to humans via a bite from an infected tick (Figure 2.1.2.1).

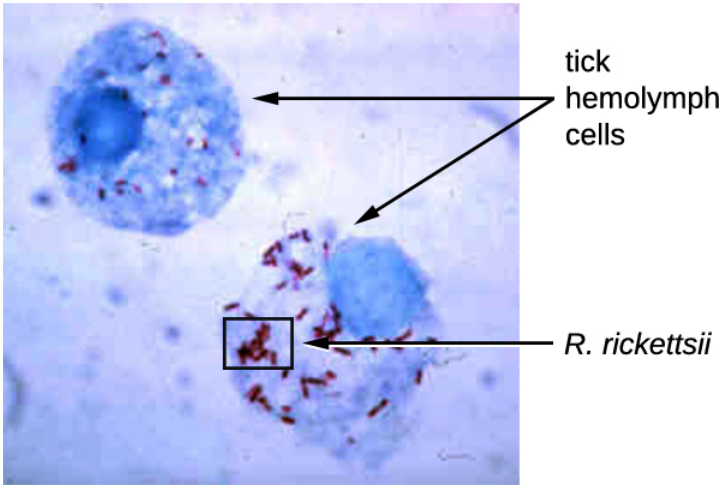


Figure 2.1.2.1: Rickettsias require special staining methods to see them under a microscope. Here, *R. rickettsii*, which causes Rocky Mountain spotted fever, is shown infecting the cells of a tick. (credit: modification of work by Centers for Disease Control and Prevention)

Another species of *Rickettsia*, *R. prowazekii*, is spread by lice. It causes epidemic typhus, a severe infectious disease common during warfare and mass migrations of people. *R. prowazekii* infects human endothelium cells, causing inflammation of the inner lining of blood vessels, high fever, abdominal pain, and sometimes delirium. A relative, *R. typhi*, causes a less severe disease known as murine or endemic typhus, which is still observed in the southwestern United States during warm seasons.

Chlamydia is another taxon of the Alphaproteobacteria. Members of this genus are extremely resistant to the cellular defenses, giving them the ability to spread from host to host rapidly via elementary bodies. The metabolically and reproductively inactive

elementary bodies are the endospore-like form of intracellular bacteria that enter an epithelial cell, where they become active. Figure 2.1.2.2 illustrates the life cycle of *Chlamydia*.

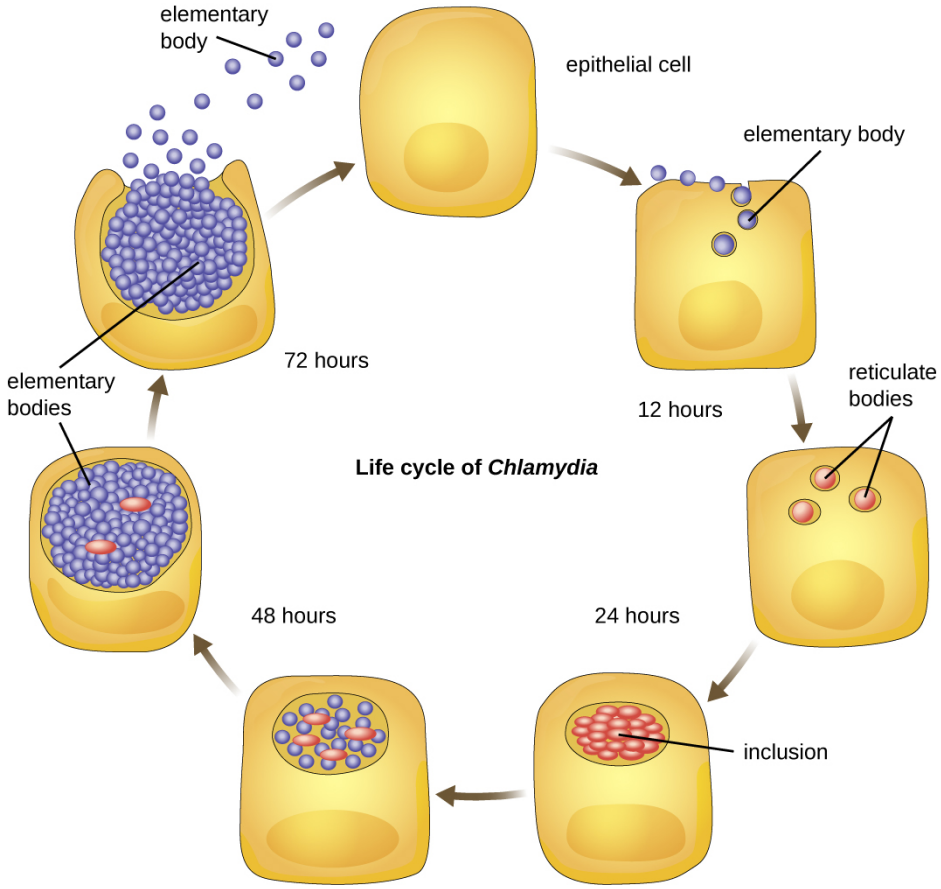


Figure 2.1.2.2: Chlamydia begins infection of a host when the metabolically inactive elementary bodies enter an epithelial cell. Once inside the host cell, the elementary bodies turn into active reticulate bodies. The reticulate bodies multiply and release more elementary bodies when the cell dies after the *Chlamydia* uses all of the host cell's ATP. (credit: modification of work by Centers for Disease Control and Prevention)

C. trachomatis is a human pathogen that causes trachoma, a disease of the eyes, often leading to blindness. *C. trachomatis* also causes the sexually transmitted disease lymphogranuloma venereum (LGV). This disease is often mildly symptomatic, manifesting as regional lymph node swelling, or it may be asymptomatic, but it is extremely contagious and is common on college campuses. Table 2.1.2.1 summarizes the characteristics of important genera of Alphaproteobacteria.

Table 2.1.2.1: Class Alphaproteobacteria

Genus	Microscopic Morphology	Unique Characteristics
Agrobacterium	Gram-negative bacillus	Plant pathogen; one species, *A. tumefaciens*, causes tumors in plants
Bartonella	Gram-negative, pleomorphic, flagellated coccobacillus	Facultative intracellular bacteria, transmitted by lice and fleas, cause trench fever and cat scratch disease in humans
Brucella	Gram-negative, small, flagellated coccobacillus	Facultative intracellular bacteria, transmitted by contaminated milk from infected cows, cause brucellosis in cattle and humans
Caulobacter	Gram-negative bacillus	Used in studies on cellular adaptation and differentiation because of its peculiar life cycle (during cell division, forms “swarm” cells and “stalked” cells)
Chlamydia	Gram-negative, coccoid or ovoid bacterium	Obligatory intracellular bacteria; some cause chlamydia, trachoma, and pneumonia
Coxiella	Small, gram-negative bacillus	Obligatory intracellular bacteria; cause Q fever; potential for use as biological weapon
Ehrlichia	Very small, gram-negative, coccoid or ovoid bacteria	Obligatory intracellular bacteria; can be transported from cell to cell; transmitted by ticks; cause ehrlichiosis (destruction of white blood cells and inflammation) in humans and dogs
Hyphomicrobium	Gram-negative bacilli; grows from a stalk	Similar to *Caulobacter*
Methylocystis	Gram-negative, coccoid or short bacilli	Nitrogen-fixing aerobic bacteria
Rhizobium	Gram-negative, rectangular bacilli with rounded ends forming clusters	Nitrogen-fixing bacteria that live in soil and form symbiotic relationship with roots of legumes (e.g., clover, alfalfa, and beans)
Rickettsia	Gram-negative, highly pleomorphic bacteria (may be cocci, rods, or threads)	Obligate intracellular bacteria; transmitted by ticks; may cause Rocky Mountain spotted fever and typhus

? Exercise 2.1.2.1

What characteristic do all Alphaproteobacteria share?

Betaproteobacteria

Unlike Alphaproteobacteria, which survive on a minimal amount of nutrients, the class Betaproteobacteria are eutrophs (or copiotrophs), meaning that they require a copious amount of organic nutrients. Betaproteobacteria often grow between aerobic and anaerobic areas (e.g., in mammalian intestines). Some genera include species that are human pathogens, able to cause severe, sometimes life-threatening disease. The genus *Neisseria*, for example, includes the bacteria *N. gonorrhoeae*, the causative agent of the STI gonorrhea, and *N. meningitides*, the causative agent of bacterial meningitis.

Neisseria are cocci that live on mucosal surfaces of the human body. They are fastidious, or difficult to culture, and they require high levels of moisture, nutrient supplements, and carbon dioxide. Also, *Neisseria* are microaerophilic, meaning that they require

low levels of oxygen. For optimal growth and for the purposes of identification, *Neisseria* spp. are grown on chocolate agar (i.e., agar supplemented by partially hemolyzed red blood cells). Their characteristic pattern of growth in culture is diplococcal: pairs of cells resembling coffee beans (Figure 2.1.2.3).

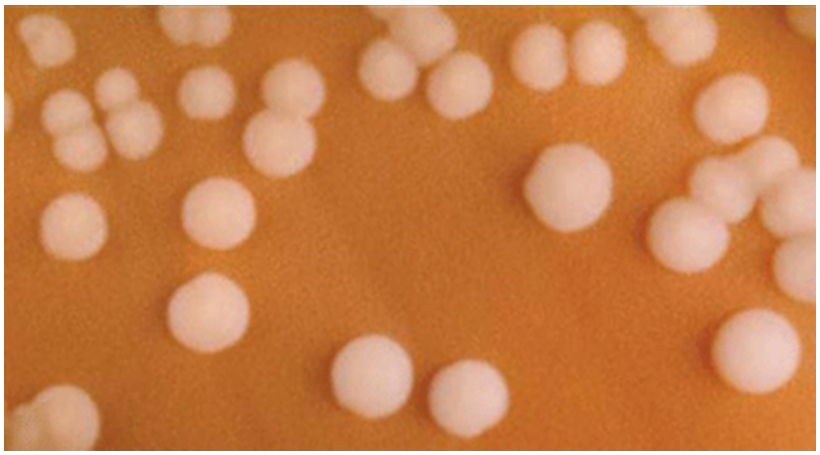


Figure 2.1.2.3: Neisseria meningitidis growing in colonies on a chocolate agar plate. (credit: Centers for Disease Control and Prevention)

The pathogen responsible for pertussis (whooping cough) is also a member of Betaproteobacteria. The bacterium *Bordetella pertussis*, from the order Burkholderiales, produces several toxins that paralyze the movement of cilia in the human respiratory tract and directly damage cells of the respiratory tract, causing a severe cough. Table 2.1.2.2 summarizes the characteristics of important genera of Betaproteobacteria.

Table 2.1.2.2: Class Betaproteobacteria

Example Genus	Microscopic Morphology	Unique Characteristics
Bordetella	A small, gram-negative coccobacillus	Aerobic, very fastidious; *B. pertussis* causes pertussis (whooping cough)
Burkholderia	Gram-negative bacillus	Aerobic, aquatic, cause diseases in horses and humans (especially patients with cystic fibrosis); agents of nosocomial infections
Leptothrix	Gram-negative, sheathed, filamentous bacillus	Aquatic; oxidize iron and manganese; can live in wastewater treatment plants and clog pipes
Neisseria	Gram-negative, coffee bean-shaped coccus forming pairs	Require moisture and high concentration of carbon dioxide; oxidase positive, grow on chocolate agar; pathogenic species cause gonorrhea and meningitis
Thiobacillus	Gram-negative bacillus	Thermophilic, acidophilic, strictly aerobic bacteria; oxidize iron and sulfur

? Exercise 2.1.2.2

What characteristic do all Betaproteobacteria share?

Clinical Focus: Part 2

When Marsha finally went to the doctor's office, the physician listened to her breathing through a stethoscope. He heard some crepitation (a crackling sound) in her lungs, so he ordered a chest radiograph and asked the nurse to collect a sputum sample

for microbiological evaluation and cytology. The radiologic evaluation found cavities, opacities, and a particular pattern of distribution of abnormal material (Figure 2.1.2.4).

Exercise 2.1.2.3

What are some possible diseases that could be responsible for Marsha's radiograph results?

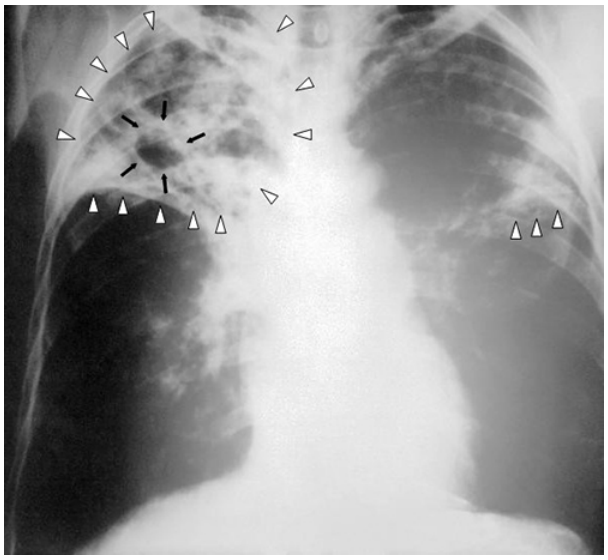


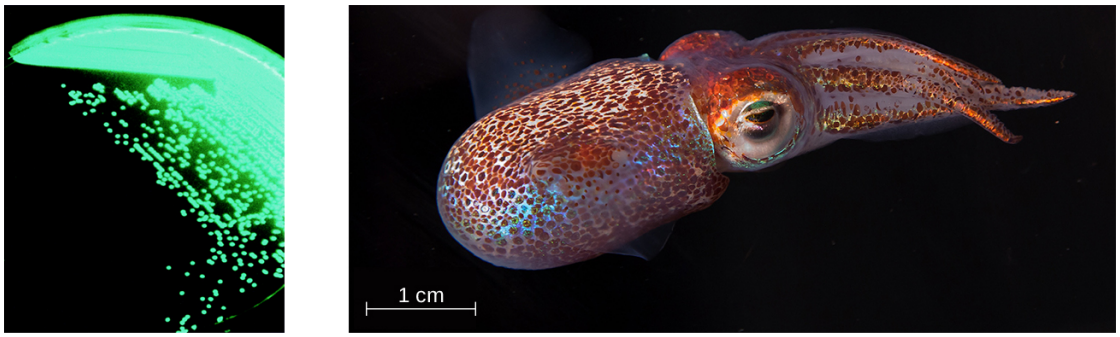
Figure 2.1.2.4: This anteroposterior radiograph shows the presence of bilateral pulmonary infiltrate (white triangles) and "caving formation" (black arrows) present in the right apical region. (credit: Centers for Disease Control and Prevention)

Gammaproteobacteria

The most diverse class of gram-negative bacteria is Gammaproteobacteria, and it includes a number of human pathogens. For example, a large and diverse family, *Pseudomonaceae*, includes the genus *Pseudomonas*. Within this genus is the species *P. aeruginosa*, a pathogen responsible for diverse infections in various regions of the body. *P. aeruginosa* is a strictly aerobic, nonfermenting, highly motile bacterium. It often infects wounds and burns, can be the cause of chronic urinary tract infections, and can be an important cause of respiratory infections in patients with cystic fibrosis or patients on mechanical ventilators. Infections by *P. aeruginosa* are often difficult to treat because the bacterium is resistant to many antibiotics and has a remarkable ability to form biofilms. Other representatives of *Pseudomonas* include the fluorescent (glowing) bacterium *P. fluorescens* and the soil bacteria *P. putida*, which is known for its ability to degrade xenobiotics (substances not naturally produced or found in living organisms).

The *Pasteurellaceae* also includes several clinically relevant genera and species. This family includes several bacteria that are human and/or animal pathogens. For example, *Pasteurella haemolytica* causes severe pneumonia in sheep and goats. *P. multocida* is a species that can be transmitted from animals to humans through bites, causing infections of the skin and deeper tissues. The genus *Haemophilus* contains two human pathogens, *H. influenzae* and *H. ducreyi*. Despite its name, *H. influenzae* does not cause influenza (which is a viral disease). *H. influenzae* can cause both upper and lower respiratory tract infections, including sinusitis, bronchitis, ear infections, and pneumonia. Before the development of effective vaccination, strains of *H. influenzae* were a leading cause of more invasive diseases, like meningitis in children. *H. ducreyi* causes the STI known as chancroid.

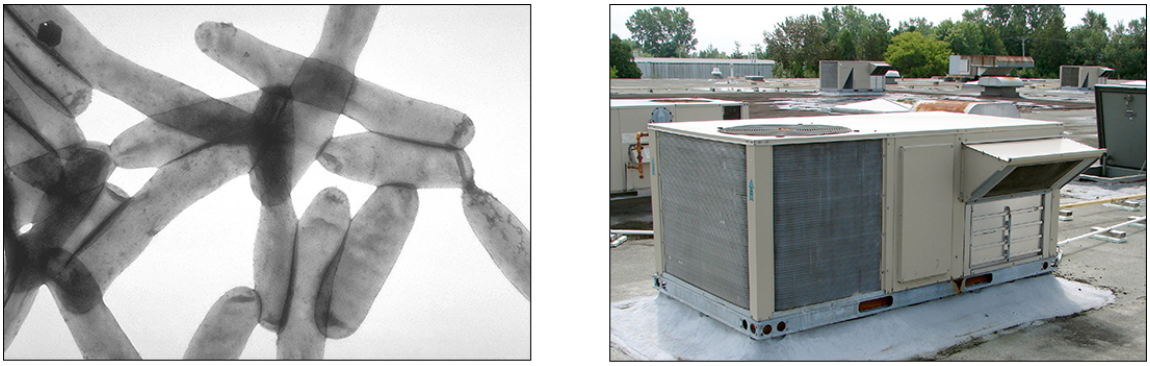
The order Vibrionales includes the human pathogen *Vibrio cholerae*. This comma-shaped aquatic bacterium thrives in highly alkaline environments like shallow lagoons and sea ports. A toxin produced by *V. cholerae* causes hypersecretion of electrolytes and water in the large intestine, leading to profuse watery diarrhea and dehydration. *V. parahaemolyticus* is also a cause of gastrointestinal disease in humans, whereas *V. vulnificus* causes serious and potentially life-threatening cellulitis (infection of the skin and deeper tissues) and blood-borne infections. Another representative of Vibrionales, *Aliivibrio fischeri*, engages in a symbiotic relationship with squid. The squid provides nutrients for the bacteria to grow and the bacteria produce bioluminescence that protects the squid from predators (Figure 2.1.2.5).



(a) (b)

Figure 2.1.2.5: (a) *Aliivibrio fischeri* is a bioluminescent bacterium. (b) *A. fischeri* colonizes and lives in a mutualistic relationship with the Hawaiian bobtail squid (*Euprymna scolopes*). (credit a: modification of work by American Society for Microbiology; credit b: modification of work by Margaret McFall-Ngai)

The genus *Legionella* also belongs to the Gammaproteobacteria. *L. pneumophila*, the pathogen responsible for Legionnaires disease, is an aquatic bacterium that tends to inhabit pools of warm water, such as those found in the tanks of air conditioning units in large buildings (Figure 2.1.2.6). Because the bacteria can spread in aerosols, outbreaks of Legionnaires disease often affect residents of a building in which the water has become contaminated with *Legionella*. In fact, these bacteria derive their name from the first known outbreak of Legionnaires disease, which occurred in a hotel hosting an American Legion veterans' association convention in Philadelphia in 1976.



(a) (b)

Figure 2.1.2.6: (a) *Legionella pneumophila*, the causative agent of Legionnaires disease, thrives in warm water. (b) Outbreaks of Legionnaires disease often originate in the air conditioning units of large buildings when water in or near the system becomes contaminated with *L. pneumophila*. (credit a: modification of work by Centers for Disease Control and Prevention)

Enterobacteriaceae is a large family of enteric (intestinal) bacteria belonging to the Gammaproteobacteria. They are facultative anaerobes and are able to ferment carbohydrates. Within this family, microbiologists recognize two distinct categories. The first category is called the coliforms, after its prototypical bacterium species, *Escherichia coli*. Coliforms are able to ferment lactose completely (i.e., with the production of acid and gas). The second category, noncoliforms, either cannot ferment lactose or can only ferment it incompletely (producing either acid or gas, but not both). The noncoliforms include some notable human pathogens, such as *Salmonella* spp., *Shigella* spp., and *Yersinia pestis*.

E. coli has been perhaps the most studied bacterium since it was first described in 1886 by Theodor Escherich (1857–1911). Many strains of *E. coli* are in mutualistic relationships with humans. However, some strains produce a potentially deadly toxin called Shiga toxin, which perforates cellular membranes in the large intestine, causing bloody diarrhea and peritonitis (inflammation of the inner linings of the abdominal cavity). Other *E. coli* strains may cause traveler's diarrhea, a less severe but very widespread disease.

The genus *Salmonella*, which belongs to the noncoliform group of *Enterobacteriaceae*, is interesting in that there is still no consensus about how many species it includes. Scientists have reclassified many of the groups they once thought to be species as serotypes (also called serovars), which are strains or variations of the same species of bacteria. Their classification is based on patterns of reactivity by animal antisera against molecules on the surface of the bacterial cells. A number of serotypes of

Salmonella can cause salmonellosis, characterized by inflammation of the small and the large intestine, accompanied by fever, vomiting, and diarrhea. The species *S. enterobacterica* (serovar *typhi*) causes typhoid fever, with symptoms including fever, abdominal pain, and skin rashes (Figure 2.1.2.7). Table 2.1.2.3 summarizes the characteristics of important genera of Gammaproteobacteria.

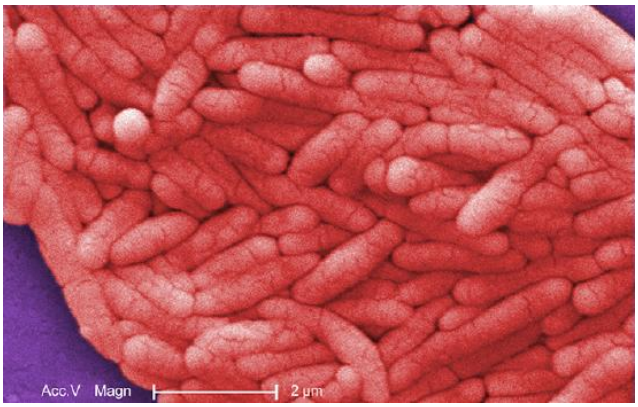


Figure 2.1.2.7: Salmonella typhi is the causative agent of typhoid fever. (credit: Centers for Disease Control and Prevention)

Table 2.1.2.3: Class Gammaproteobacteria

Example Genus	Microscopic Morphology	Unique Characteristics
Beggiatoa	Gram-negative bacteria; disc-shaped or cylindrical	Aquatic, live in water with high content of hydrogen disulfide; can cause problems for sewage treatment
Enterobacter	Gram-negative bacillus	Facultative anaerobe; cause urinary and respiratory tract infections in hospitalized patients; implicated in the pathogenesis of obesity
Erwinia	Gram-negative bacillus	Plant pathogen causing leaf spots and discoloration; may digest cellulose; prefer relatively low temperatures (25–30 °C)
Escherichia	Gram-negative bacillus	Facultative anaerobe; inhabit the gastrointestinal tract of warm-blooded animals; some strains are mutualists, producing vitamin K; others, like serotype *E. coli* O157:H7, are pathogens; *E. coli* has been a model organism for many studies in genetics and molecular biology
Hemophilus	Gram-negative bacillus	Pleomorphic, may appear as coccobacillus, aerobe, or facultative anaerobe; grow on blood agar; pathogenic species can cause respiratory infections, chancroid, and other diseases
Klebsiella	Gram-negative bacillus; appears rounder and thicker than other members of *Enterobacteriaceae*	Facultative anaerobe, encapsulated, nonmotile; pathogenic species may cause pneumonia, especially in people with alcoholism
Legionella	Gram-negative bacillus	Fastidious, grow on charcoal-buffered yeast extract; *L. pneumophila* causes Legionnaires disease
Methylomonas	Gram-negative bacillus	Use methane as source of carbon and energy
Proteus	Gram-negative bacillus (pleomorphic)	Common inhabitants of the human gastrointestinal tract; motile; produce urease; opportunistic pathogens; may cause urinary tract infections and sepsis
Pseudomonas	Gram-negative bacillus	Aerobic; versatile; produce yellow and blue pigments, making them appear green in culture; opportunistic, antibiotic-resistant pathogens may cause wound infections, hospital-acquired infections, and secondary infections in patients with cystic fibrosis
Serratia	Gram-negative bacillus	Motile; may produce red pigment; opportunistic pathogens responsible for a large number of hospital-acquired infections
Shigella	Gram-negative bacillus	Nonmotile; dangerously pathogenic;

Example Genus	Microscopic Morphology	Unique Characteristics
		produce Shiga toxin, which can destroy cells of the gastrointestinal tract; can cause dysentery
Vibrio	Gram-negative, comma- or curved rod-shaped bacteria	Inhabit seawater; flagellated, motile; may produce toxin that causes hypersecretion of water and electrolytes in the gastrointestinal tract; some species may cause serious wound infections
Yersinia	Gram-negative bacillus	Carried by rodents; human pathogens; *Y. pestis* causes bubonic plague and pneumonic plague; *Y. enterocolitica* can be a pathogen causing diarrhea in humans

? Exercise 2.1.2.4

List two families of Gammaproteobacteria.

Deltaproteobacteria

The Deltaproteobacteria is a small class of gram-negative Proteobacteria that includes sulfate-reducing bacteria(SRBs), so named because they use sulfate as the final electron acceptor in the electron transport chain. Few SRBs are pathogenic. However, the SRB *Desulfovibrio orale* is associated with periodontal disease (disease of the gums).

Deltaproteobacteria also includes the genus *Bdellovibrio*, species of which are parasites of other gram-negative bacteria. *Bdellovibrio* invades the cells of the host bacterium, positioning itself in the periplasm, the space between the plasma membrane and the cell wall, feeding on the host's proteins and polysaccharides. The infection is lethal for the host cells.

Another type of Deltaproteobacteria, myxobacteria, lives in the soil, scavenging inorganic compounds. Motile and highly social, they interact with other bacteria within and outside their own group. They can form multicellular, macroscopic "fruiting bodies" (Figure 2.1.2.8), structures that are still being studied by biologists and bacterial ecologists.[2]These bacteria can also form metabolically inactive myxospores. Table 2.1.2.4 summarizes the characteristics of several important genera of Deltaproteobacteria.

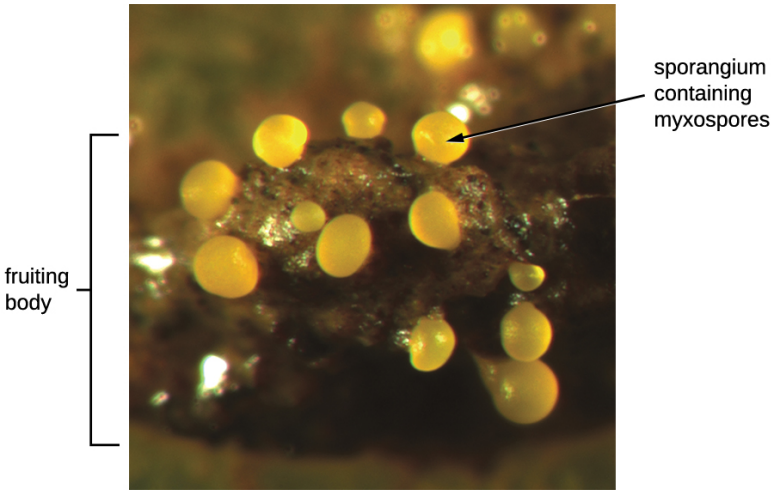


Figure 2.1.2.8: Myxobacteria form fruiting bodies. (credit: modification of work by Michiel Vos)

Table 2.1.2.4: Class Deltaproteobacteria

Genus	Microscopic Morphology	Unique characteristics
Bdellovibrio	Gram-negative, comma-shaped rod	Obligate aerobes; motile; parasitic (infecting other bacteria)
Desulfovibrio(formerly *Desufuromonas*)	Gram-negative, comma-shaped rod	Reduce sulfur; can be used for removal of toxic and radioactive waste
Myxobacterium	Gram-negative, coccoid bacteria forming colonies (swarms)	Live in soil; can move by gliding; used as a model organism for studies of intercellular communication (signaling)

? Exercise 2.1.2.5

What type of Deltaproteobacteria forms fruiting bodies?

Epsilonproteobacteria

The smallest class of Proteobacteria is Epsilonproteobacteria, which are gram-negative microaerophilic bacteria (meaning they only require small amounts of oxygen in their environment). Two clinically relevant genera of Epsilonproteobacteria are *Campylobacter* and *Helicobacter*, both of which include human pathogens. *Campylobacter* can cause food poisoning that manifests as severe enteritis (inflammation in the small intestine). This condition, caused by the species *C. jejuni*, is rather common in developed countries, usually because of eating contaminated poultry products. Chickens often harbor *C. jejuni* in their gastrointestinal tract and feces, and their meat can become contaminated during processing.

Within the genus *Helicobacter,* the helical, flagellated bacterium *H. pylori* has been identified as a beneficial member of the stomach microbiota, but it is also the most common cause of chronic gastritis and ulcers of the stomach and duodenum (Figure 2.1.2.9). Studies have also shown that *H. pylori* is linked to stomach cancer.[3] *H. pylori* is somewhat unusual in its ability to survive in the highly acidic environment of the stomach. It produces urease and other enzymes that modify its environment to make it less acidic. Table 2.1.2.5 summarizes the characteristics of the most clinically relevant genera of Epsilonproteobacteria.



Figure 2.1.2.9: Helicobacter pylori can cause chronic gastritis, which can lead to ulcers and stomach cancer.

Table 2.1.2.5: Class Epsilonproteobacteria

Example Genus	Microscopic Morphology	Unique Characteristics
Campylobacter	Gram-negative, spiral-shaped rod	Aerobic (microaerophilic); often infects chickens; may infect humans via undercooked meat, causing severe enteritis
Helicobacter	Gram-negative, spiral-shaped rod	Aerobic (microaerophilic) bacterium; can damage the inner lining of the stomach, causing chronic gastritis, peptic ulcers, and stomach cancer

? Exercise 2.1.2.1

Name two Epsilonproteobacteria that cause gastrointestinal disorders.

Summary

- **Proteobacteria** is a phylum of gram-negative bacteria discovered by Carl Woese in the 1980s based on nucleotide sequence homology.
- Proteobacteria are further classified into the classes alpha-, beta-, gamma-, delta- and epsilonproteobacteria, each class having separate orders, families, genera, and species.
- **Alphaproteobacteria** are **oligotrophs**. The taxa chlamydias and rickettsias are **obligate intracellular pathogens,** feeding on cells of host organisms; they are metabolically inactive outside of the host cell. Some Alphaproteobacteria can convert atmospheric nitrogen to nitrites, making nitrogen usable by other forms of life.
- **Betaproteobacteria** are **eutrophs**. They include human pathogens of the genus *Neisseria* and the species *Bordetella pertussis*.
- **Gammaproteobacteria** are the largest and the most diverse group of Proteobacteria. Many are human pathogens that are aerobes or facultative anaerobes. Some Gammaproteobacteria are **enteric** bacteria that may be coliform or noncoliform. *Escherichia coli*, a member of Gammaproteobacteria, is perhaps the most studied bacterium.
- **Deltaproteobacteria** make up a small group able to reduce sulfate or elemental sulfur. Some are scavengers and form myxospores, with multicellular fruiting bodies.
- **Epsilonproteobacteria** make up the smallest group of Proteobacteria. The genera *Campylobacter* and *Helicobacter* are human pathogens.

Footnotes

1. C.R. Woese. “Bacterial Evolution.” *Microbiological Review* 51 no. 2 (1987):221–271.
2. H. Reichenbach. “Myxobacteria, Producers of Novel Bioactive Substances.” *Journal of Industrial Microbiology & Biotechnology* 27 no. 3 (2001):149–156.
3. S. Suerbaum, P. Michetti. “*Helicobacter pylori* infection.” *New England Journal of Medicine* 347 no. 15 (2002):1175–1186.

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2.1.3: Nonproteobacteria Gram-negative Bacteria and Phototrophic Bacteria

Learning Objectives

- Describe the unique features of nonproteobacteria gram-negative bacteria
- Give an example of a nonproteobacteria bacterium in each category
- Describe the unique features of phototrophic bacteria
- Identify phototrophic bacteria

The majority of the gram-negative bacteria belong to the phylum Proteobacteria, discussed in the previous section. Those that do not are called the nonproteobacteria. In this section, we will describe three classes of gram-negative nonproteobacteria: the spirochetes, the CFB group, and the Planctomycetes. A diverse group of phototrophic bacteria that includes Proteobacteria and nonproteobacteria will be discussed at the end of this section.

Spirochetes

Spirochetes are characterized by their long (up to 250 µm), spiral-shaped bodies. Most spirochetes are also very thin, which makes it difficult to examine gram-stained preparations under a conventional brightfield microscope. Darkfield fluorescent microscopy is typically used instead. Spirochetes are also difficult or even impossible to culture. They are highly motile, using their axial filament to propel themselves. The axial filament is similar to a flagellum, but it wraps around the cell and runs inside the cell body of a spirochete in the periplasmic space between the outer membrane and the plasma membrane (Figure 2.1.3.1).

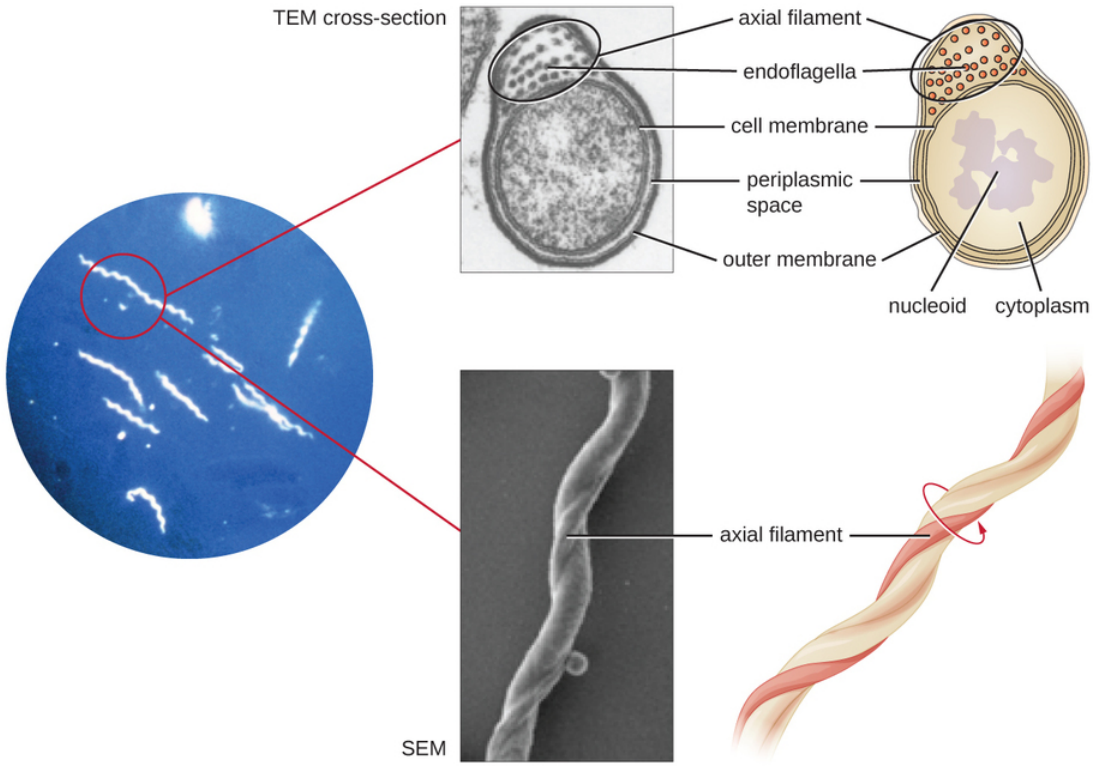


Figure 2.1.3.1: Spirochetes are typically observed using darkfield microscopy (left). However, electron microscopy (top center, bottom center) provides a more detailed view of their cellular morphology. The flagella found between the inner and outer membranes of spirochetes wrap around the bacterium, causing a twisting motion used for locomotion. (credit "spirochetes" micrograph: modification of work by Centers for Disease Control and Prevention; credit "SEM/TEM": modification of work by Guyard C, Raffel SJ, Schrumpf ME, Dahlstrom E, Sturdevant D, Ricklefs SM, Martens C, Hayes SF, Fischer ER, Hansen BT, Porcella SF, Schwan TG)

Several genera of spirochetes include human pathogens. For example, the genus *Treponema* includes a species *T. pallidum*, which is further classified into four subspecies: *T. pallidum pallidum*, *T. pallidum pertenue*, *T. pallidum carateum*, and *T. pallidum endemicum*. The subspecies *T. pallidum pallidum* causes the sexually transmitted infection known as syphilis, the third most

prevalent sexually transmitted bacterial infection in the United States, after chlamydia and gonorrhea. The other subspecies of *T. pallidum* cause tropical infectious diseases of the skin, bones, and joints.

Another genus of spirochete, *Borrelia*, contains a number of pathogenic species. *B. burgdorferi* causes Lyme disease, which is transmitted by several genera of ticks (notably *Ixodes* and *Amblyomma*) and often produces a "bull's eye" rash, fever, fatigue, and, sometimes, debilitating arthritis. *B. recurrens* causes a condition known as relapsing fever.

? Exercise 2.1.3.1

Why do scientists typically use darkfield fluorescent microscopy to visualize spirochetes?

Cytophaga, Fusobacterium, and Bacteroides

The gram-negative nonproteobacteria of the genera *Cytophaga*, *Fusobacterium*, and *Bacteroides* are classified together as a phylum and called the CFB group. Although they are phylogenetically diverse, bacteria of the CFB group share some similarities in the sequence of nucleotides in their DNA. They are rod-shaped bacteria adapted to anaerobic environments, such as the tissue of the gums, gut, and rumen of ruminating animals. CFB bacteria are avid fermenters, able to process cellulose in rumen, thus enabling ruminant animals to obtain carbon and energy from grazing.

Cytophaga are motile aquatic bacteria that glide. *Fusobacteria* inhabit the human mouth and may cause severe infectious diseases. The largest genus of the CFB group is *Bacteroides*, which includes dozens of species that are prevalent inhabitants of the human large intestine, making up about 30% of the entire gut microbiome (Figure 2.1.3.2). One gram of human feces contains up to 100 billion *Bacteroides* cells. Most *Bacteroides* are mutualistic. They benefit from nutrients they find in the gut, and humans benefit from their ability to prevent pathogens from colonizing the large intestine. Indeed, when populations of *Bacteroides* are reduced in the gut—as often occurs when a patient takes antibiotics—the gut becomes a more favorable environment for pathogenic bacteria and fungi, which can cause secondary infections.

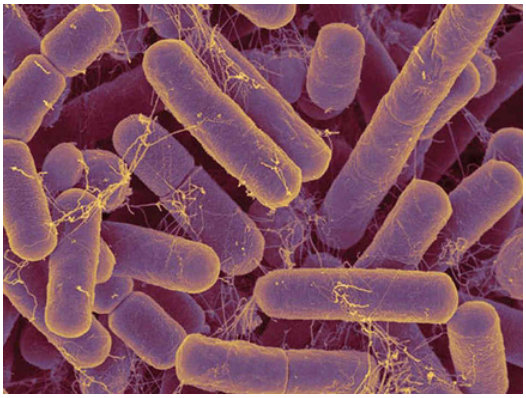


Figure 2.1.3.2: Bacteroides comprise up to 30% of the normal microbiota in the human gut. (credit: NOAA)

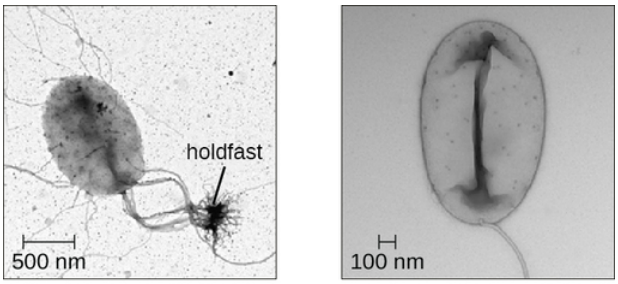
Only a few species of *Bacteroides* are pathogenic. *B. melaninogenicus*, for example, can cause wound infections in patients with weakened immune systems.

? Exercise 2.1.3.2

Why are *Cytophaga*, *Fusobacterium*, and *Bacteroides* classified together as the CFB group?

Planctomycetes

The Planctomycetes are found in aquatic environments, inhabiting freshwater, saltwater, and brackish water. Planctomycetes are unusual in that they reproduce by budding, meaning that instead of one maternal cell splitting into two equal daughter cells in the process of binary fission, the mother cell forms a bud that detaches from the mother cell and lives as an independent cell. These so-called swarmer cells are motile and not attached to a surface. However, they will soon differentiate into sessile (immobile) cells with an appendage called a holdfast that allows them to attach to surfaces in the water (Figure 2.1.3.3). Only the sessile cells are able to reproduce.



(a) (b)

Figure 2.1.3.3: (a) Sessile Planctomycetes have a holdfast that allows them to adhere to surfaces in aquatic environments. (b) Swarmers are motile and lack a holdfast. (credit: modification of work by American Society for Microbiology)

Table 2.1.3.1 summarizes the characteristics of some of the most clinically relevant genera of nonproteobacteria.

Table 2.1.3.1: Nonproteobacteria

Example Genus	Microscopic Morphology	Unique Characteristics
Bacteroides	Gram-negative bacillus	Obligate anaerobic bacteria; abundant in the human gastrointestinal tract; usually mutualistic, although some species are opportunistic pathogens
Cytophaga	Gram-negative bacillus	Motile by gliding; live in soil or water; decompose cellulose; may cause disease in fish
Fusobacterium	Gram-negative bacillus with pointed ends	Anaerobic; form; biofilms; some species cause disease in humans (periodontitis, ulcers)
Leptospira	Spiral-shaped bacterium (spirochetes); gram negative-like (better viewed by darkfield microscopy); very thin	Aerobic, abundant in shallow water reservoirs; infect rodents and domestic animals; can be transmitted to humans by infected animals' urine; may cause severe disease
Sphingobacterium	Gram-negative bacillus	Oxidase positive; nonmotile; contain high amounts of sphingophospholipids; rarely cause disease in humans
Treponema	Gram-negative-like spirochete; very thin; better viewed by darkfield microscopy	Motile; do not grow in culture; *T. pallidum* (subspecies *T. pallidum pallidum*) causes syphilis

? Exercise 2.1.3.3

How do Planctomycetes reproduce?

Phototrophic Bacteria

The phototrophic bacteria are a large and diverse category of bacteria that do not represent a taxon but, rather, a group of bacteria that use sunlight as their primary source of energy. This group contains both Proteobacteria and nonproteobacteria. They use solar energy to synthesize ATP through photosynthesis. When they produce oxygen, they perform oxygenic photosynthesis. When they do not produce oxygen, they perform anoxygenic photosynthesis. With the exception of some cyanobacteria, the majority of phototrophic bacteria perform anoxygenic photosynthesis.

One large group of phototrophic bacteria includes the purple or green bacteria that perform photosynthesis with the help of bacteriochlorophylls, which are green, purple, or blue pigments similar to chlorophyll in plants. Some of these bacteria have a varying amount of red or orange pigments called carotenoids. Their color varies from orange to red to purple to green (Figure 2.1.3.4), and they are able to absorb light of various wavelengths. Traditionally, these bacteria are classified into sulfur and nonsulfur bacteria; they are further differentiated by color.

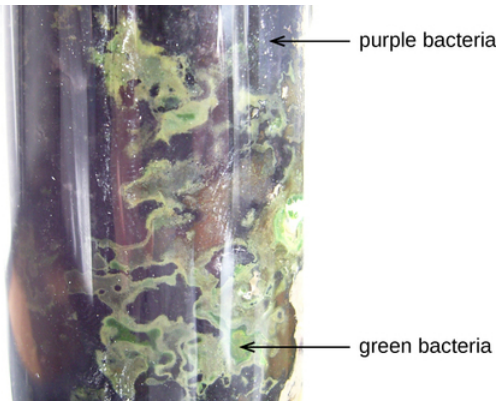


Figure 2.1.3.4: Purple and green sulfur bacteria use bacteriochlorophylls to perform photosynthesis.

The sulfur bacteria perform anoxygenic photosynthesis, using sulfites as electron donors and releasing free elemental sulfur. Nonsulfur bacteria use organic substrates, such as succinate and malate, as donors of electrons.

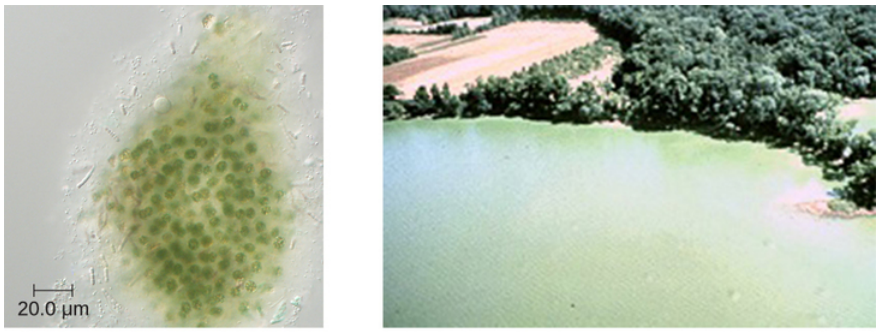
The purple sulfur bacteria oxidize hydrogen sulfide into elemental sulfur and sulfuric acid and get their purple color from the pigments bacteriochlorophylls and carotenoids. Bacteria of the genus *Chromatium* are purple sulfur Gammaproteobacteria. These microorganisms are strict anaerobes and live in water. They use carbon dioxide as their only source of carbon, but their survival and growth are possible only in the presence of sulfites, which they use as electron donors. *Chromatium* has been used as a model for studies of bacterial photosynthesis since the 1950s.[1]

The green sulfur bacteria use sulfide for oxidation and produce large amounts of green bacteriochlorophyll. The genus *Chlorobium* is a green sulfur bacterium that is implicated in climate change because it produces methane, a greenhouse gas. These bacteria use at least four types of chlorophyll for photosynthesis. The most prevalent of these, bacteriochlorophyll, is stored in special vesicle-like organelles called chlorosomes.

Purple nonsulfur bacteria are similar to purple sulfur bacteria, except that they use hydrogen rather than hydrogen sulfide for oxidation. Among the purple nonsulfur bacteria is the genus *Rhodospirillum*. These microorganisms are facultative anaerobes, which are actually pink rather than purple, and can metabolize (“fix”) nitrogen. They may be valuable in the field of biotechnology because of their potential ability to produce biological plastic and hydrogen fuel.[2]

The green nonsulfur bacteria are similar to green sulfur bacteria but they use substrates other than sulfides for oxidation. *Chloroflexus* is an example of a green nonsulfur bacterium. It often has an orange color when it grows in the dark, but it becomes green when it grows in sunlight. It stores bacteriochlorophyll in chlorosomes, similar to *Chlorobium*, and performs anoxygenic photosynthesis, using organic sulfites (low concentrations) or molecular hydrogen as electron donors, so it can survive in the dark if oxygen is available. *Chloroflexus* does not have flagella but can glide, like *Cytophaga*. It grows at a wide range of temperatures, from 35 °C to 70 °C, thus can be thermophilic.

Another large, diverse group of phototrophic bacteria compose the phylum Cyanobacteria; they get their blue-green color from the chlorophyll contained in their cells (Figure 2.1.3.5). Species of this group perform oxygenic photosynthesis, producing megatons of gaseous oxygen. Scientists hypothesize that cyanobacteria played a critical role in the change of our planet’s anoxic atmosphere 1–2 billion years ago to the oxygen-rich environment we have today.[3]



(a) (b)

Figure 2.1.3.5: (a) *Microcystis aeruginosa* is a type of cyanobacteria commonly found in freshwater environments. (b) In warm temperatures, *M. aeruginosa* and other cyanobacteria can multiply rapidly and produce neurotoxins, resulting in blooms that are harmful to fish and other aquatic animals. (credit a: modification of work by Dr. Barry H. Rosen/U.S. Geological Survey; credit b: modification of work by NOAA)

Cyanobacteria have other remarkable properties. Amazingly adaptable, they thrive in many habitats, including marine and freshwater environments, soil, and even rocks. They can live at a wide range of temperatures, even in the extreme temperatures of the Antarctic. They can live as unicellular organisms or in colonies, and they can be filamentous, forming sheaths or biofilms. Many of them fix nitrogen, converting molecular nitrogen into nitrites and nitrates that other bacteria, plants, and animals can use. The reactions of nitrogen fixation occur in specialized cells called heterocysts.

Photosynthesis in Cyanobacteria is oxygenic, using the same type of chlorophyll a found in plants and algae as the primary photosynthetic pigment. Cyanobacteria also use phycocyanin and cyanophycin, two secondary photosynthetic pigments that give them their characteristic blue color. They are located in special organelles called phycobilisomes and in folds of the cellular membrane called thylakoids, which are remarkably similar to the photosynthetic apparatus of plants. Scientists hypothesize that plants originated from endosymbiosis of ancestral eukaryotic cells and ancestral photosynthetic bacteria.[4] Cyanobacteria are also an interesting object of research in biochemistry,[5] with studies investigating their potential as biosorbents[6] and products of human nutrition.[7]

Unfortunately, cyanobacteria can sometimes have a negative impact on human health. Genera such as *Microcystis* can form harmful cyanobacterial blooms, forming dense mats on bodies of water and producing large quantities of toxins that can harm wildlife and humans. These toxins have been implicated in tumors of the liver and diseases of the nervous system in animals and humans.[8]

Table 2.1.3.2 summarizes the characteristics of important phototrophic bacteria.

Table 2.1.3.2: Phototrophic Bacteria

Phylum	Class	Example Genus or Species	Common Name	Oxygenic or Anoxygenic	Sulfur Deposition
Cyanobacteria	Cyanophyceae	*Microcystisaeruginosa*	Blue-green bacteria	Oxygenic	None
Chlorobi	Chlorobia	*Chlorobium*	Green sulfur bacteria	Anoxygenic	Outside the cell
Chloroflexi(Division)	Chloroflexi	*Chloroflexus*	Green nonsulfur bacteria	Anoxygenic	None
Proteobacteria	Alphaproteobacteria	*Rhodospirillum*	Purple nonsulfur bacteria	Anoxygenic	None
	Betaproteobacteria	*Rhodocyclus*	Purple nonsulfur bacteria	Anoxygenic	None
	Gammaproteobacteria	*Chromatium*	Purple sulfur bacteria	Anoxygenic	Inside the cell

? Exercise 2.1.3.4

What characteristic makes phototrophic bacteria different from other prokaryotes?

Summary

- Gram-negative nonproteobacteria include the taxa **spirochetes**; the *Cytophaga*, *Fusobacterium*, *Bacteroides* group; Planctomycetes; and many representatives of **phototrophic bacteria.**
- Spirochetes are motile, spiral bacteria with a long, narrow body; they are difficult or impossible to culture.
- Several genera of spirochetes contain human pathogens that cause such diseases as syphilis and Lyme disease.
- *Cytophaga*, *Fusobacterium*, and *Bacteroides* are classified together as a phylum called the **CFB group**. They are rod-shaped anaerobic organoheterotrophs and avid fermenters. *Cytophaga* are aquatic bacteria with the gliding motility. *Fusobacteria* inhabit the human mouth and may cause severe infectious diseases. *Bacteroides* are present in vast numbers in the human gut, most of them being mutualistic but some are pathogenic.
- Planctomycetes are aquatic bacteria that reproduce by budding; they may form large colonies, and develop a holdfast.
- Phototrophic bacteria are not a taxon but, rather, a group categorized by their ability to use the energy of sunlight. They include Proteobacteria and nonproteobacteria, as well as sulfur and nonsulfur bacteria colored purple or green.
- Sulfur bacteria perform anoxygenic photosynthesis, using sulfur compounds as donors of electrons, whereas nonsulfur bacteria use organic compounds (succinate, malate) as donors of electrons.
- Some phototrophic bacteria are able to fix nitrogen, providing the usable forms of nitrogen to other organisms.
- **Cyanobacteria** are oxygen-producing bacteria thought to have played a critical role in the forming of the earth's atmosphere.

Footnotes

1. 1 R.C. Fuller et al. "Carbon Metabolism in *Chromatium*." *Journal of Biological Chemistry* 236 (1961):2140–2149.
2. 2 T.T. Selao et al. "Comparative Proteomic Studies in *Rhodospirillum rubrum* Grown Under Different Nitrogen Conditions." *Journal of Proteome Research* 7 no. 8 (2008):3267–3275.
3. 3 A. De los Rios et al. "Ultrastructural and Genetic Characteristics of Endolithic Cyanobacterial Biofilms Colonizing Antarctic Granite Rocks." *FEMS Microbiology Ecology* 59 no. 2 (2007):386–395.
4. 4 T. Cavalier-Smith. "Membrane Heredity and Early Chloroplast Evolution." *Trends in Plant Science* 5 no. 4 (2000):174–182.
5. 5 S. Zhang, D.A. Bryant. "The Tricarboxylic Acid Cycle in Cyanobacteria." *Science* 334 no. 6062 (2011):1551–1553.
6. 6 A. Cain et al. "Cyanobacteria as a Biosorbent for Mercuric Ion." Bioresource Technology 99 no. 14 (2008):6578–6586.
7. 7 C.S. Ku et al. "Edible Blue-Green Algae Reduce the Production of Pro-Inflammatory Cytokines by Inhibiting NF-κB Pathway in Macrophages and Splenocytes." *Biochimica et Biophysica Acta* 1830 no. 4 (2013):2981–2988.
8. 8 I. Stewart et al. Cyanobacterial Poisoning in Livestock, Wild Mammals and Birds – an Overview. *Advances in Experimental Medicine and Biology* 619 (2008):613–637.

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2.1.4: Gram-positive Bacteria

Learning Objectives

- Describe the unique features of each category of high G+C and low G+C gram-positive bacteria
- Identify similarities and differences between high G+C and low G+C bacterial groups
- Give an example of a bacterium of high G+C and low G+C group commonly associated with each category

Prokaryotes are identified as gram-positive if they have a multiple layer matrix of peptidoglycan forming the cell wall. Crystal violet, the primary stain of the Gram stain procedure, is readily retained and stabilized within this matrix, causing gram-positive prokaryotes to appear purple under a brightfield microscope after Gram staining. For many years, the retention of Gram stain was one of the main criteria used to classify prokaryotes, even though some prokaryotes did not readily stain with either the primary or secondary stains used in the Gram stain procedure.

Advances in nucleic acid biochemistry have revealed additional characteristics that can be used to classify gram-positive prokaryotes, namely the guanine to cytosine ratios (G+C) in DNA and the composition of 16S rRNA subunits. Microbiologists currently recognize two distinct groups of gram-positive, or weakly staining gram-positive, prokaryotes. The class Actinobacteria comprises the high G+C gram-positive bacteria, which have more than 50% guanine and cytosine nucleotides in their DNA. The class Bacilli comprises low G+C gram-positive bacteria, which have less than 50% of guanine and cytosine nucleotides in their DNA.

Actinobacteria: High G+C Gram-Positive Bacteria

The name Actinobacteria comes from the Greek words for *rays* and *small rod*, but Actinobacteria are very diverse. Their microscopic appearance can range from thin filamentous branching rods to coccobacilli. Some Actinobacteria are very large and complex, whereas others are among the smallest independently living organisms. Most Actinobacteria live in the soil, but some are aquatic. The vast majority are aerobic. One distinctive feature of this group is the presence of several different peptidoglycans in the cell wall.

The genus *Actinomyces* is a much studied representative of Actinobacteria. *Actinomyces* spp. play an important role in soil ecology, and some species are human pathogens. A number of *Actinomyces* spp. inhabit the human mouth and are opportunistic pathogens, causing infectious diseases like periodontitis (inflammation of the gums) and oral abscesses. The species *A. israelii* is an anaerobe notorious for causing endocarditis (inflammation of the inner lining of the heart) (Figure 2.1.4.1).



Figure 2.1.4.1: (a) *Actinomyces israelii* (false-color scanning electron micrograph [SEM]) has a branched structure. (b) *Corynebacterium diphtheria* causes the deadly disease diphtheria. Note the distinctive palisades. (c) The gram-variable bacterium *Gardnerella vaginalis* causes bacterial vaginosis in women. This micrograph shows a Pap smear from a woman with vaginosis. (credit a: modification of work by "GrahamColm"/Wikimedia Commons; credit b: modification of work by Centers for Disease Control and Prevention; credit c: modification of work by Mwakigonja AR, Torres LM, Mwakyoma HA, Kaaya EE)

The genus *Mycobacterium* is represented by bacilli covered with a mycolic acid coat. This waxy coat protects the bacteria from some antibiotics, prevents them from drying out, and blocks penetration by Gram stain reagents (see Staining Microscopic Specimens). Because of this, a special acid-fast staining procedure is used to visualize these bacteria. The genus *Mycobacterium* is

an important cause of a diverse group of infectious diseases. *M. tuberculosis* is the causative agent of tuberculosis, a disease that primarily impacts the lungs but can infect other parts of the body as well. It has been estimated that one-third of the world's population has been infected with *M. tuberculosis* and millions of new infections occur each year. Treatment of *M. tuberculosis* is challenging and requires patients to take a combination of drugs for an extended time. Complicating treatment even further is the development and spread of multidrug-resistant strains of this pathogen.

Another pathogenic species, *M. leprae*, is the cause of Hansen's disease (leprosy), a chronic disease that impacts peripheral nerves and the integrity of the skin and mucosal surface of the respiratory tract. Loss of pain sensation and the presence of skin lesions increase susceptibility to secondary injuries and infections with other pathogens.

Bacteria in the genus *Corynebacterium* contain diaminopimelic acid in their cell walls, and microscopically often form *palisades*, or pairs of rod-shaped cells resembling the letter V. Cells may contain metachromatic granules, intracellular storage of inorganic phosphates that are useful for identification of *Corynebacterium*. The vast majority of *Corynebacterium* spp. are nonpathogenic; however, *C. diphtheria* is the causative agent of diphtheria, a disease that can be fatal, especially in children (Figure 2.1.4.1). *C. diphtheria* produces a toxin that forms a pseudomembrane in the patient's throat, causing swelling, difficulty breathing, and other symptoms that can become serious if untreated.

The genus *Bifidobacterium* consists of filamentous anaerobes, many of which are commonly found in the gastrointestinal tract, vagina, and mouth. In fact, *Bifidobacterium* spp. constitute a substantial part of the human gut microbiota and are frequently used as probiotics and in yogurt production.

The genus *Gardnerella*, contains only one species, *G. vaginalis*. This species is defined as "gram-variable" because its small coccobacilli do not show consistent results when Gram stained (Figure 2.1.4.1). Based on its genome, it is placed into the high G+C gram-positive group. *G. vaginalis* can cause bacterial vaginosis in women; symptoms are typically mild or even undetectable, but can lead to complications during pregnancy.

Table 2.1.4.1 summarizes the characteristics of some important genera of Actinobacteria.

Table 2.1.4.1: Actinobacteria: High G+C Gram-Positive

Example Genus	Microscopic Morphology	Unique Characteristics
Actinomyces	Gram-positive bacillus; in colonies, shows fungus-like threads (hyphae)	Facultative anaerobes; in soil, decompose organic matter; in the human mouth, may cause gum disease
Arthrobacter	Gram-positive bacillus (at the exponential stage of growth) or coccus (in stationary phase)	Obligate aerobes; divide by "snapping," forming V-like pairs of daughter cells; degrade phenol, can be used in bioremediation
Bifidobacterium	Gram-positive, filamentous actinobacterium	Anaerobes commonly found in human gut microbiota
Corynebacterium	Gram-positive bacillus	Aerobes or facultative anaerobes; form palisades; grow slowly; require enriched media in culture; *C. diphtheriae* causes diphtheria
Frankia	Gram-positive, fungus-like (filamentous) bacillus	Nitrogen-fixing bacteria; live in symbiosis with legumes
Gardnerella	Gram-variable coccobacillus	Colonize the human vagina, may alter the microbial ecology, thus leading to vaginosis
Micrococcus	Gram-positive coccus, form microscopic clusters	Ubiquitous in the environment and on the human skin; oxidase-positive (as opposed to morphologically similar *S. aureus*); some are opportunistic pathogens
Mycobacterium	Gram-positive, acid-fast bacillus	Slow growing, aerobic, resistant to drying and phagocytosis; covered with a waxy coat made of mycolic acid; *M. tuberculosis* causes tuberculosis; *M. leprae* causes leprosy
Nocardia	Weakly gram-positive bacillus; forms acid-fast branches	May colonize the human gingiva; may cause severe pneumonia and inflammation of the skin
Propionibacterium	Gram-positive bacillus	Aerotolerant anaerobe; slow-growing; *P. acnes* reproduces in the human sebaceous glands and may cause or contribute to acne
Rhodococcus	Gram-positive bacillus	Strict aerobe; used in industry for biodegradation of pollutants; *R. fascians* is a plant pathogen, and *R. equi* causes pneumonia in foals
Streptomyces	Gram-positive, fungus-like (filamentous) bacillus	Very diverse genus (>500 species); aerobic, spore-forming bacteria; scavengers, decomposers found in soil (give the soil its "earthy" odor); used in pharmaceutical industry as antibiotic producers (more than two-thirds of clinically useful antibiotics)

Exercise 2.1.4.1

What is one distinctive feature of Actinobacteria?

Low G+C Gram-positive Bacteria

The low G+C gram-positive bacteria have less than 50% guanine and cytosine in their DNA, and this group of bacteria includes a number of genera of bacteria that are pathogenic.

Clinical Focus: Part 3

Based on her symptoms, Marsha's doctor suspected that she had a case of tuberculosis. Although less common in the United States, tuberculosis is still extremely common in many parts of the world, including Nigeria. Marsha's work there in a medical lab likely exposed her to *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis.

Marsha's doctor ordered her to stay at home, wear a respiratory mask, and confine herself to one room as much as possible. He also said that Marsha had to take one semester off school. He prescribed isoniazid and rifampin, antibiotics used in a drug cocktail to treat tuberculosis, which Marsha was to take three times a day for at least three months.

Exercise 2.1.4.2

Why did the doctor order Marsha to stay home for three months?

Clostridia

One large and diverse class of low G+C gram-positive bacteria is Clostridia. The best studied genus of this class is *Clostridium*. These rod-shaped bacteria are generally obligate anaerobes that produce endospores and can be found in anaerobic habitats like soil and aquatic sediments rich in organic nutrients. The endospores may survive for many years.

Clostridium spp. produce more kinds of protein toxins than any other bacterial genus, and several species are human pathogens. *C. perfringens* is the third most common cause of food poisoning in the United States and is the causative agent of an even more serious disease called gas gangrene. Gas gangrene occurs when *C. perfringens* endospores enter a wound and germinate, becoming viable bacterial cells and producing a toxin that can cause the necrosis (death) of tissue. *C. tetani*, which causes tetanus, produces a neurotoxin that is able to enter neurons, travel to regions of the central nervous system where it blocks the inhibition of nerve impulses involved in muscle contractions, and cause a life-threatening spastic paralysis. *C. botulinum* produces botulinum neurotoxin, the most lethal biological toxin known. Botulinum toxin is responsible for rare but frequently fatal cases of botulism. The toxin blocks the release of acetylcholine in neuromuscular junctions, causing flaccid paralysis. In very small concentrations, botulinum toxin has been used to treat muscle pathologies in humans and in a cosmetic procedure to eliminate wrinkles. *C. difficile* is a common source of hospital-acquired infections (Figure 2.1.4.2) that can result in serious and even fatal cases of colitis (inflammation of the large intestine). Infections often occur in patients who are immunosuppressed or undergoing antibiotic therapy that alters the normal microbiota of the gastrointestinal tract.

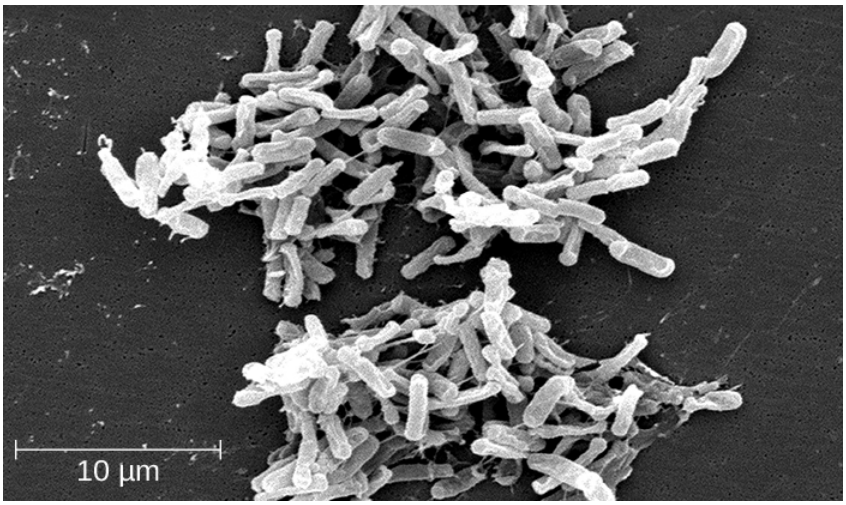


Figure 2.1.4.2: Clostridium difficile, a gram-positive, rod-shaped bacterium, causes severe colitis and diarrhea, often after the normal gut microbiota is eradicated by antibiotics. (credit: modification of work by Centers for Disease Control and Prevention)

Lactobacillales

The order Lactobacillales comprises low G+C gram-positive bacteria that include both bacilli and cocci in the genera *Lactobacillus*, *Leuconostoc*, *Enterococcus*, and *Streptococcus*. Bacteria of the latter three genera typically are spherical or ovoid and often form chains.

Streptococcus, the name of which comes from the Greek word for *twisted chain*, is responsible for many types of infectious diseases in humans. Species from this genus, often referred to as streptococci, are usually classified by serotypes called Lancefield groups, and by their ability to lyse red blood cells when grown on blood agar.

S. pyogenes belongs to the Lancefield group A, β-hemolytic *Streptococcus*. This species is considered a pyogenic pathogen because of the associated pus production observed with infections it causes (Figure 2.1.4.3). *S. pyogenes* is the most common cause of bacterial pharyngitis (strep throat); it is also an important cause of various skin infections that can be relatively mild (e.g., impetigo) or life threatening (e.g., necrotizing fasciitis, also known as flesh eating disease), life threatening.

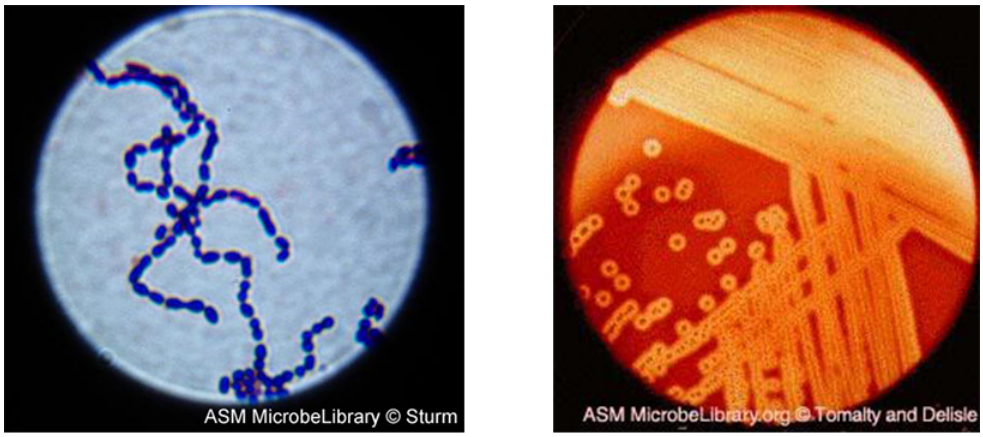


Figure 2.1.4.3: (a) A gram-stained specimen of *Streptococcus pyogenes* shows the chains of cocci characteristic of this organism's morphology. (b) *S. pyogenes* on blood agar shows characteristic lysis of red blood cells, indicated by the halo of clearing around colonies. (credit a, b: modification of work by American Society for Microbiology)

The nonpyogenic (i.e., not associated with pus production) streptococci are a group of streptococcal species that are not a taxon but are grouped together because they inhabit the human mouth. The nonpyogenic streptococci do not belong to any of the Lancefield groups. Most are commensals, but a few, such as *S. mutans*, are implicated in the development of dental caries.

S. pneumoniae (commonly referred to as pneumococcus), is a *Streptococcus* species that also does not belong to any Lancefield group. *S. pneumoniae* cells appear microscopically as diplococci, pairs of cells, rather than the long chains typical of most streptococci. Scientists have known since the 19th century that *S. pneumoniae* causes pneumonia and other respiratory infections. However, this bacterium can also cause a wide range of other diseases, including meningitis, septicemia, osteomyelitis, and endocarditis, especially in newborns, the elderly, and patients with immunodeficiency.

Bacilli

The name of the class Bacilli suggests that it is made up of bacteria that are bacillus in shape, but it is a morphologically diverse class that includes bacillus-shaped and cocccus-shaped genera. Among the many genera in this class are two that are very important clinically: *Bacillus* and *Staphylococcus*.

Bacteria in the genus *Bacillus* are bacillus in shape and can produce endospores. They include aerobes or facultative anaerobes. A number of *Bacillus* spp. are used in various industries, including the production of antibiotics (e.g., barnase), enzymes (e.g., alpha-amylase, BamH1 restriction endonuclease), and detergents (e.g., subtilisin).

Two notable pathogens belong to the genus *Bacillus*. *B. anthracis* is the pathogen that causes anthrax, a severe disease that affects wild and domesticated animals and can spread from infected animals to humans. Anthrax manifests in humans as charcoal-black ulcers on the skin, severe enterocolitis, pneumonia, and brain damage due to swelling. If untreated, anthrax is lethal. *B. cereus*, a closely related species, is a pathogen that may cause food poisoning. It is a rod-shaped species that forms chains. Colonies appear milky white with irregular shapes when cultured on blood agar (Figure 2.1.4.4). One other important species is *B. thuringiensis*. This bacterium produces a number of substances used as insecticides because they are toxic for insects.

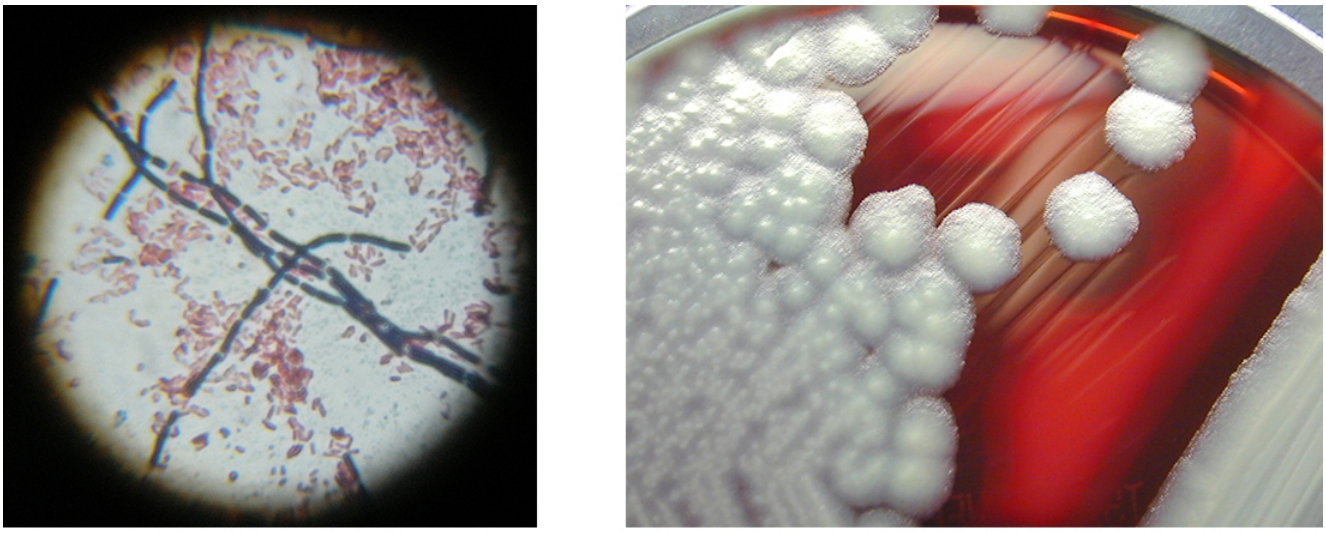


Figure 2.1.4.4: (a) In this gram-stained specimen, the violet rod-shaped cells forming chains are the gram-positive bacteria *Bacillus cereus*. The small, pink cells are the gram-negative bacteria *Escherichia coli*. (b) In this culture, white colonies of *B. cereus* have been grown on sheep blood agar. (credit a: modification of work by "Bibliomaniac 15"/Wikimedia Commons; credit b: modification of work by Centers for Disease Control and Prevention)

The genus *Staphylococcus* also belongs to the class Bacilli, even though its shape is coccus rather than a bacillus. The name *Staphylococcus* comes from a Greek word for *bunches of grapes*, which describes their microscopic appearance in culture (Figure 2.1.4.5). *Staphylococcus* spp. are facultative anaerobic, halophilic, and nonmotile. The two best-studied species of this genus are *S. epidermidis* and *S. aureus*.

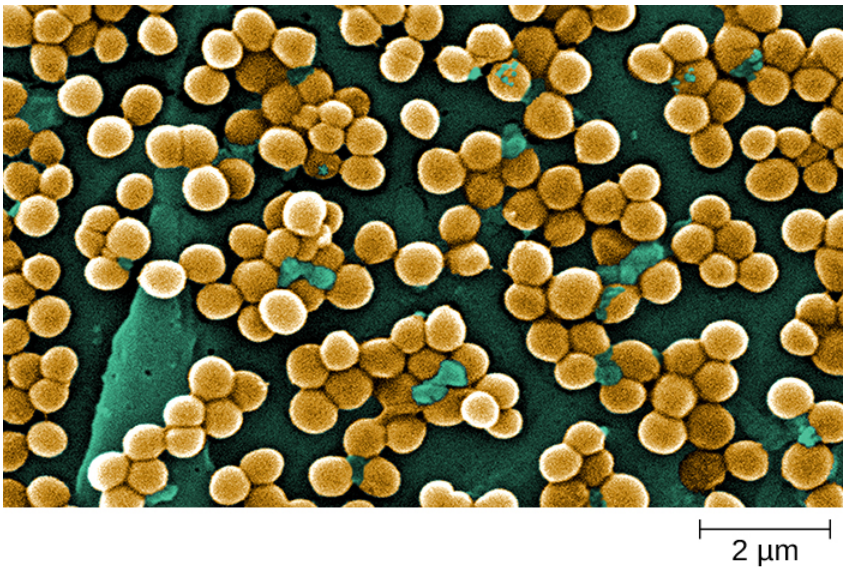


Figure 2.1.4.5: This SEM of *Staphylococcus aureus* illustrates the typical "grape-like" clustering of cells. (credit: modification of work by Centers for Disease Control and Prevention)

S. epidermidis, whose main habitat is the human skin, is thought to be nonpathogenic for humans with healthy immune systems, but in patients with immunodeficiency, it may cause infections in skin wounds and prostheses (e.g., artificial joints, heart valves). *S. epidermidis* is also an important cause of infections associated with intravenous catheters. This makes it a dangerous pathogen in hospital settings, where many patients may be immunocompromised.

Strains of *S. aureus* cause a wide variety of infections in humans, including skin infections that produce boils, carbuncles, cellulitis, or impetigo. Certain strains of *S. aureus* produce a substance called enterotoxin, which can cause severe enteritis, often called staph food poisoning. Some strains of *S. aureus* produce the toxin responsible for toxic shock syndrome, which can result in cardiovascular collapse and death.

Many strains of *S. aureus* have developed resistance to antibiotics. Some antibiotic-resistant strains are designated as methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *S. aureus* (VRSA). These strains are some of the most difficult to treat because they exhibit resistance to nearly all available antibiotics, not just methicillin and vancomycin. Because they are difficult to treat with antibiotics, infections can be lethal. MRSA and VRSA are also contagious, posing a serious threat in hospitals, nursing homes, dialysis facilities, and other places where there are large populations of elderly, bedridden, and/or immunocompromised patients.

Mycoplasmas

Although *Mycoplasma* spp. do not possess a cell wall and, therefore, are not stained by Gram-stain reagents, this genus is still included with the low G+C gram-positive bacteria. The genus *Mycoplasma* includes more than 100 species, which share several unique characteristics. They are very small cells, some with a diameter of about 0.2 µm, which is smaller than some large viruses. They have no cell walls and, therefore, are pleomorphic, meaning that they may take on a variety of shapes and can even resemble very small animal cells. Because they lack a characteristic shape, they can be difficult to identify. One species, *M. pneumoniae*, causes the mild form of pneumonia known as "walking pneumonia" or "atypical pneumonia." This form of pneumonia is typically less severe than forms caused by other bacteria or viruses.

Table 2.1.4.2 summarizes the characteristics of notable genera low G+C Gram-positive bacteria.

Table 2.1.4.2: Bacilli - Low G+C Gram-Positive Bacteria

Example Genus	Microscopic Morphology	Unique Characteristics
Bacillus	Large, gram-positive bacillus	Aerobes or facultative anaerobes; form endospores; *B. anthracis* causes anthrax in cattle and humans, *B. cereus* may cause food poisoning
Clostridium	Gram-positive bacillus	Strict anaerobes; form endospores; all known species are pathogenic, causing tetanus, gas gangrene, botulism, and colitis
Enterococcus	Gram-positive coccus; forms microscopic pairs in culture (resembling *Streptococcus pneumoniae*)	Anaerobic aerotolerant bacteria, abundant in the human gut, may cause urinary tract and other infections in the nosocomial environment
Lactobacillus	Gram-positive bacillus	Facultative anaerobes; ferment sugars into lactic acid; part of the vaginal microbiota; used as probiotics
Leuconostoc	Gram-positive coccus; may form microscopic chains in culture	Fermenter, used in food industry to produce sauerkraut and kefir
Mycoplasma	The smallest bacteria; appear pleomorphic under electron microscope	Have no cell wall; classified as low G+C Gram-positive bacteria because of their genome; *M. pneumoniae* causes “walking” pneumonia
Staphylococcus	Gram-positive coccus; forms microscopic clusters in culture that resemble bunches of grapes	Tolerate high salt concentration; facultative anaerobes; produce catalase; *S. aureus* can also produce coagulase and toxins responsible for local (skin) and generalized infections
Streptococcus	Gram-positive coccus; forms chains or pairs in culture	Diverse genus; classified into groups based on sharing certain antigens; some species cause hemolysis and may produce toxins responsible for human local (throat) and generalized disease
Ureaplasma	Similar to *Mycoplasma*	Part of the human vaginal and lower urinary tract microbiota; may cause inflammation, sometimes leading to internal scarring and infertility

Exercise 2.1.4.3

1. Name some ways in which streptococci are classified.
2. Name one pathogenic low G+C gram-positive bacterium and a disease it causes.

Clinical Focus: Resolution

Marsha’s sputum sample was sent to the microbiology lab to confirm the identity of the microorganism causing her infection. The lab also performed antimicrobial susceptibility testing (AST) on the sample to confirm that the physician has prescribed the correct antimicrobial drugs.

Direct microscopic examination of the sputum revealed acid-fast bacteria (AFB) present in Marsha's sputum. When placed in culture, there were no signs of growth for the first 8 days, suggesting that microorganism was either dead or growing very slowly. Slow growth is a distinctive characteristic of *M. tuberculosis*.

After four weeks, the lab microbiologist observed distinctive colorless granulated colonies (Figure 2.1.4.6). The colonies contained AFB showing the same microscopic characteristics as those revealed during the direct microscopic examination of Marsha's sputum. To confirm the identification of the AFB, samples of the colonies were analyzed using nucleic acid hybridization, or direct nucleic acid amplification (NAA) testing. When a bacterium is acid-fast, it is classified in the family *Mycobacteriaceae*. DNA sequencing of variable genomic regions of the DNA extracted from these bacteria revealed that it was high G+C. This fact served to finalize Marsha's diagnosis as infection with *M. tuberculosis*. After nine months of treatment with the drugs prescribed by her doctor, Marsha made a full recovery.

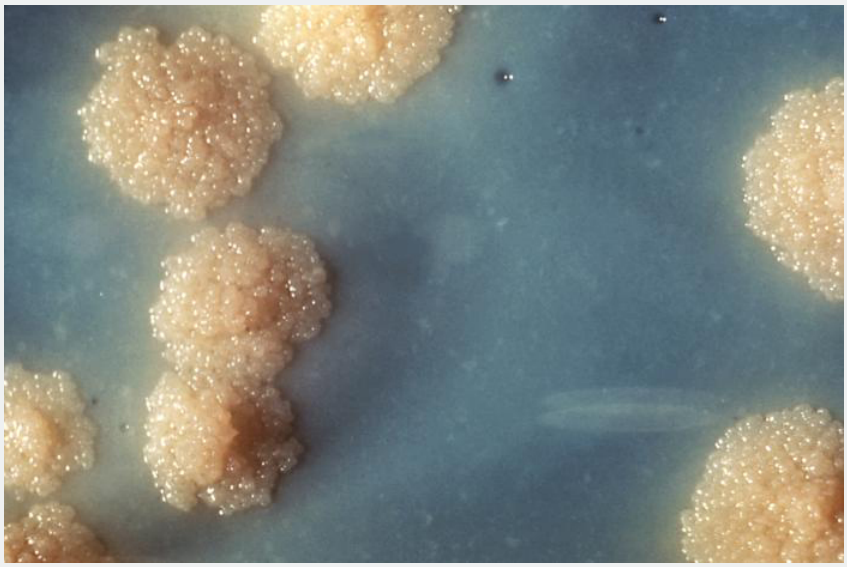


Figure 2.1.4.6: M. tuberculosis grows on Löwenstein-Jensen (LJ) agar in distinct colonies. (credit: Centers for Disease Control and Prevention)

Biopiracy and Bioprospecting

In 1969, an employee of a Swiss pharmaceutical company was vacationing in Norway and decided to collect some soil samples. He took them back to his lab, and the Swiss company subsequently used the fungus *Tolypocladium inflatum* in those samples to develop cyclosporine A, a drug widely used in patients who undergo tissue or organ transplantation. The Swiss company earns more than $1 billion a year for production of cyclosporine A, yet Norway receives nothing in return—no payment to the government or benefit for the Norwegian people. Despite the fact the cyclosporine A saves numerous lives, many consider the means by which the soil samples were obtained to be an act of "biopiracy," essentially a form of theft. Do the ends justify the means in a case like this?

Nature is full of as-yet-undiscovered bacteria and other microorganisms that could one day be used to develop new life-saving drugs or treatments.[1] Pharmaceutical and biotechnology companies stand to reap huge profits from such discoveries, but ethical questions remain. To whom do biological resources belong? Should companies who invest (and risk) millions of dollars in research and development be required to share revenue or royalties for the right to access biological resources?

Compensation is not the only issue when it comes to bioprospecting. Some communities and cultures are philosophically opposed to bioprospecting, fearing unforeseen consequences of collecting genetic or biological material. Native Hawaiians, for example, are very protective of their unique biological resources.

For many years, it was unclear what rights government agencies, private corporations, and citizens had when it came to collecting samples of microorganisms from public land. Then, in 1993, the Convention on Biological Diversity granted each nation the rights to any genetic and biological material found on their own land. Scientists can no longer collect samples

without a prior arrangement with the land owner for compensation. This convention now ensures that companies act ethically in obtaining the samples they use to create their products.

Summary

- Gram-positive bacteria are a very large and diverse group of microorganisms. Understanding their taxonomy and knowing their unique features is important for diagnostics and treatment of infectious diseases.
- Gram-positive bacteria are classified into **high G+C gram-positive** and **low G+C gram-positive** bacteria, based on the prevalence of guanine and cytosine nucleotides in their genome
- Actinobacteria is the taxonomic name of the class of high G+C gram-positive bacteria. This class includes the genera *Actinomyces*, *Arthrobacter*, *Corynebacterium*, *Frankia*, *Gardnerella*, *Micrococcus*, *Mycobacterium*, *Nocardia*, *Propionibacterium*, *Rhodococcus*, and *Streptomyces*. Some representatives of these genera are used in industry; others are human or animal pathogens.
- Examples of high G+C gram-positive bacteria that are human pathogens include *Mycobacterium tuberculosis*, which causes tuberculosis; *M. leprae*, which causes leprosy (Hansen's disease); and *Corynebacteriumdiphtheriae*, which causes diphtheria.
- *Clostridia* spp. are low G+C gram-positive bacteria that are generally obligate anaerobes and can form endospores. Pathogens in this genus include *C. perfringens* (gas gangrene), *C. tetani* (tetanus), and *C. botulinum* (botulism).
- Lactobacillales include the genera *Enterococcus*, *Lactobacillus*, *Leuconostoc*, and *Streptococcus. Streptococcus* is responsible for many human diseases, including pharyngitis (strep throat), scarlet fever, rheumatic fever, glomerulonephritis, pneumonia, and other respiratory infections.
- Bacilli is a taxonomic class of low G+C gram-positive bacteria that include rod-shaped and coccus-shaped species, including the genera *Bacillus* and *Staphylococcus*. *B. anthracis* causes anthrax, *B. cereus* may cause opportunistic infections of the gastrointestinal tract, and *S. aureus* strains can cause a wide range of infections and diseases, many of which are highly resistant to antibiotics.
- *Mycoplasma* spp. are very small, **pleomorphic** low G+C gram-positive bacteria that lack cell walls. *M. pneumoniae* causes atypical pneumonia.

Footnotes

1. 1 J. Andre. *Bioethics as Practice*. Chapel Hill, NC: University of North Carolina Press, 2002.

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2.1.5: Deeply Branching Bacteria

Learning Objectives

- Describe the unique features of deeply branching bacteria
- Give examples of significant deeply branching bacteria

On a phylogenetic tree (see A Systematic Approach), the trunk or root of the tree represents a common ancient evolutionary ancestor, often called the last universal common ancestor (LUCA), and the branches are its evolutionary descendants. Scientists consider the deeply branching bacteria, such as the genus *Acetothermus*, to be the first of these non-LUCA forms of life produced by evolution some 3.5 billion years ago. When placed on the phylogenetic tree, they stem from the common root of life, deep and close to the LUCA root—hence the name "deeply branching" (Figure 2.1.5.1).

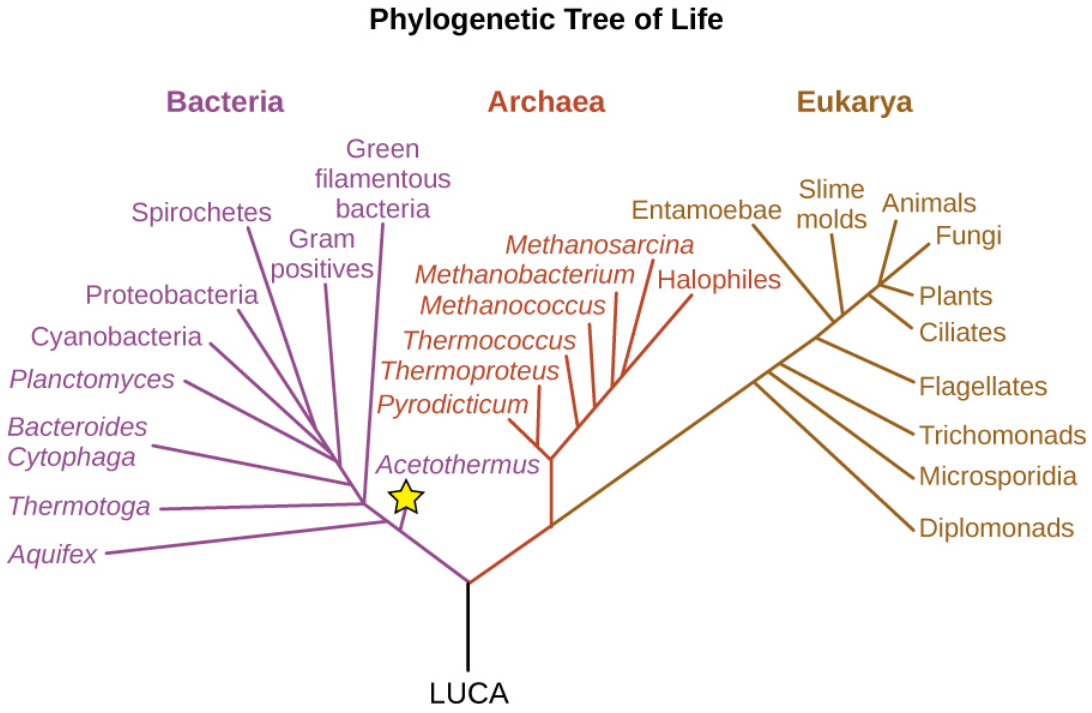


Figure 2.1.5.1: The star on this phylogenetic tree of life shows the position of the deeply branching bacteria Acetothermus. (credit: modification of work by Eric Gaba)

The deeply branching bacteria may provide clues regarding the structure and function of ancient and now extinct forms of life. We can hypothesize that ancient bacteria, like the deeply branching bacteria that still exist, were thermophiles or hyperthermophiles, meaning that they thrived at very high temperatures. *Acetothermus paucivorans*, a gram-negative anaerobic bacterium discovered in 1988 in sewage sludge, is a thermophile growing at an optimal temperature of 58 °C.[1] Scientists have determined it to be the deepest branching bacterium, or the closest evolutionary relative of the LUCA (Figure 2.1.5.1).

The class Aquificae includes deeply branching bacteria that are adapted to the harshest conditions on our planet, resembling the conditions thought to dominate the earth when life first appeared. Bacteria from the genus *Aquifex* are hyperthermophiles, living in hot springs at a temperature higher than 90 °C. The species *A. pyrophilus* thrives near underwater volcanoes and thermal ocean vents, where the temperature of water (under high pressure) can reach 138 °C. *Aquifex* bacteria use inorganic substances as nutrients. For example, *A. pyrophilus* can reduce oxygen, and it is able to reduce nitrogen in anaerobic conditions. They also show a remarkable resistance to ultraviolet light and ionizing radiation. Taken together, these observations support the hypothesis that the ancient ancestors of deeply branching bacteria began evolving more than 3 billion years ago, when the earth was hot and lacked an atmosphere, exposing the bacteria to nonionizing and ionizing radiation.

The class Thermotogae is represented mostly by hyperthermophilic, as well as some mesophilic (preferring moderate temperatures), anaerobic gram-negative bacteria whose cells are wrapped in a peculiar sheath-like outer membrane called a toga.

The thin layer of peptidoglycan in their cell wall has an unusual structure; it contains diaminopimelic acid and D-lysine. These bacteria are able to use a variety of organic substrates and produce molecular hydrogen, which can be used in industry. The class contains several genera, of which the best known is the genus *Thermotoga*. One species of this genus, *T. maritima*, lives near the thermal ocean vents and thrives in temperatures of 90 °C; another species, *T. subterranea*, lives in underground oil reservoirs.

Finally, the deeply branching bacterium *Deinococcus radiodurans* belongs to a genus whose name is derived from a Greek word meaning *terrible berry*. Nicknamed "Conan the Bacterium," *D. radiodurans* is considered a polyextremophile because of its ability to survive under the many different kinds of extreme conditions—extreme heat, drought, vacuum, acidity, and radiation. It owes its name to its ability to withstand doses of ionizing radiation that kill all other known bacteria; this special ability is attributed to some unique mechanisms of DNA repair.

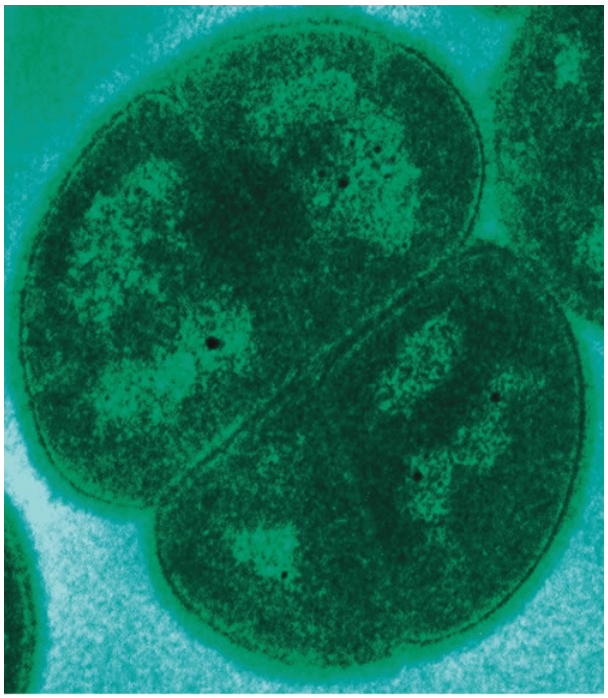


Figure 2.1.5.1: Deinococcus radiodurans, or "Conan the Bacterium," survives in the harshest conditions on earth.

Summary

- **Deeply branching bacteria** are phylogenetically the most ancient forms of life, being the closest to the last universal common ancestor.
- Deeply branching bacteria include many species that thrive in extreme environments that are thought to resemble conditions on earth billions of years ago
- Deeply branching bacteria are important for our understanding of evolution; some of them are used in industry

Footnotes

1. 1 G. Dietrich et al. "*Acetothermus paucivorans*, gen. nov., sp. Nov., a Strictly Anaerobic, Thermophilic Bacterium From Sewage Sludge, Fermenting Hexoses to Acetate, CO_2, and H_2." *Systematic and Applied Microbiology* 10 no. 2 (1988):174–179.

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2.1.6: Archaea

Learning Objectives

- Describe the unique features of each category of Archaea
- Explain why archaea might not be associated with human microbiomes or pathology
- Give common examples of archaea commonly associated with unique environmental habitats

Like organisms in the domain Bacteria, organisms of the domain Archaea are all unicellular organisms. However, archaea differ structurally from bacteria in several significant ways, as discussed in Unique Characteristics of Prokaryotic Cells. To summarize:

- The archaeal cell membrane is composed of ether linkages with branched isoprene chains (as opposed to the bacterial cell membrane, which has ester linkages with unbranched fatty acids).
- Archaeal cell walls lack peptidoglycan, but some contain a structurally similar substance called pseudopeptidoglycan or pseudomurein.
- The genomes of Archaea are larger and more complex than those of bacteria.

Domain Archaea is as diverse as domain Bacteria, and its representatives can be found in any habitat. Some archaea are mesophiles, and many are extremophiles, preferring extreme hot or cold, extreme salinity, or other conditions that are hostile to most other forms of life on earth. Their metabolism is adapted to the harsh environments, and they can perform methanogenesis, for example, which bacteria and eukaryotes cannot.

The size and complexity of the archaeal genome makes it difficult to classify. Most taxonomists agree that within the Archaea, there are currently five major phyla: Crenarchaeota, Euryarchaeota, Korarchaeota, Nanoarchaeota, and Thaumarchaeota. There are likely many other archaeal groups that have not yet been systematically studied and classified.

With few exceptions, archaea are not present in the human microbiota, and none are currently known to be associated with infectious diseases in humans, animals, plants, or microorganisms. However, many play important roles in the environment and may thus have an indirect impact on human health.

Crenarchaeota

Crenarchaeota is a class of Archaea that is extremely diverse, containing genera and species that differ vastly in their morphology and requirements for growth. All Crenarchaeota are aquatic organisms, and they are thought to be the most abundant microorganisms in the oceans. Most, but not all, Crenarchaeota are hyperthermophiles; some of them (notably, the genus *Pyrolobus*) are able to grow at temperatures up to 113 °C.[1]

Archaea of the genus *Sulfolobus* (Figure 2.1.6.1) are thermophiles that prefer temperatures around 70–80°C and acidophiles that prefer a pH of 2–3.[2] *Sulfolobus* can live in aerobic or anaerobic environments. In the presence of oxygen, *Sulfolobus* spp. use metabolic processes similar to those of heterotrophs. In anaerobic environments, they oxidize sulfur to produce sulfuric acid, which is stored in granules. *Sulfolobus* spp. are used in biotechnology for the production of thermostable and acid-resistant proteins called affitins.[3] Affitins can bind and neutralize various antigens (molecules found in toxins or infectious agents that provoke an immune response from the body).

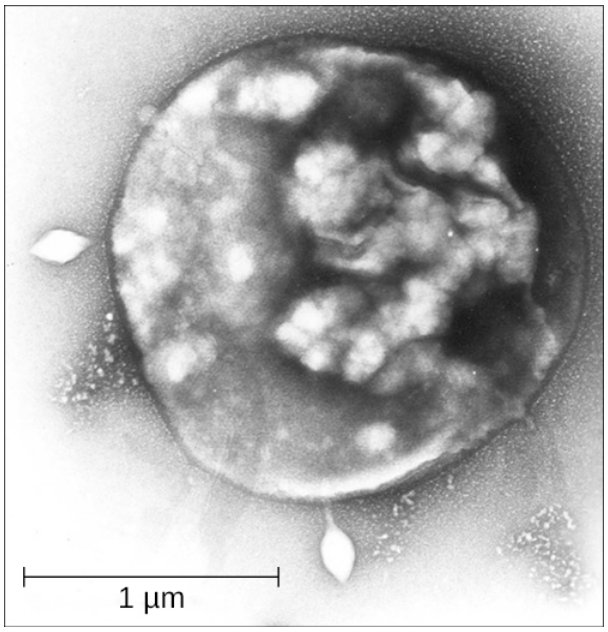


Figure 2.1.6.1: Sulfolobus, an archaeon of the class Crenarchaeota, oxidizes sulfur and stores sulfuric acid in its granules.

Another genus, *Thermoproteus*, is represented by strictly anaerobic organisms with an optimal growth temperature of 85 °C. They have flagella and, therefore, are motile. *Thermoproteus* has a cellular membrane in which lipids form a monolayer rather than a bilayer, which is typical for archaea. Its metabolism is autotrophic. To synthesize ATP, *Thermoproteus* spp. reduce sulfur or molecular hydrogen and use carbon dioxide or carbon monoxide as a source of carbon. *Thermoproteus* is thought to be the deepest-branching genus of Archaea, and thus is a living example of some of our planet's earliest forms of life.

? Exercise 2.1.6.1

What types of environments do Crenarchaeota prefer?

Euryarchaeota

The phylum Euryarchaeota includes several distinct classes. Species in the classes Methanobacteria, Methanococci, and Methanomicrobia represent Archaea that can be generally described as methanogens. Methanogens are unique in that they can reduce carbon dioxide in the presence of hydrogen, producing methane. They can live in the most extreme environments and can reproduce at temperatures varying from below freezing to boiling. Methanogens have been found in hot springs as well as deep under ice in Greenland. Some scientists have even hypothesized that methanogens may inhabit the planet Mars because the mixture of gases produced by methanogens resembles the makeup of the Martian atmosphere.[4]

Methanogens are thought to contribute to the formation of anoxic sediments by producing hydrogen sulfide, making "marsh gas." They also produce gases in ruminants and humans. Some genera of methanogens, notably *Methanosarcina*, can grow and produce methane in the presence of oxygen, although the vast majority are strict anaerobes.

The class Halobacteria (which was named before scientists recognized the distinction between Archaea and Bacteria) includes halophilic ("salt-loving") archaea. Halobacteria require a very high concentrations of sodium chloride in their aquatic environment. The required concentration is close to saturation, at 36%; such environments include the Dead Sea as well as some salty lakes in Antarctica and south-central Asia. One remarkable feature of these organisms is that they perform photosynthesis using the protein bacteriorhodopsin, which gives them, and the bodies of water they inhabit, a beautiful purple color (Figure 2.1.6.2).



Figure 2.1.6.1: Halobacteria growing in these salt ponds gives them a distinct purple color. (credit: modification of work by Tony Hisgett)

Notable species of Halobacteria include *Halobacterium salinarum*, which may be the oldest living organism on earth; scientists have isolated its DNA from fossils that are 250 million years old.[5] Another species, *Haloferax volcanii*, shows a very sophisticated system of ion exchange, which enables it to balance the concentration of salts at high temperatures

? Exercise 2.1.6.2

Where do Halobacteria live?

Finding a Link Between Archaea and Disease

Archaea are not known to cause any disease in humans, animals, plants, bacteria, or in other archaea. Although this makes sense for the extremophiles, not all archaea live in extreme environments. Many genera and species of Archaea are mesophiles, so they can live in human and animal microbiomes, although they rarely do. As we have learned, some methanogens exist in the human gastrointestinal tract. Yet we have no reliable evidence pointing to any archaean as the causative agent of any human disease.

Still, scientists have attempted to find links between human disease and archaea. For example, in 2004, Lepp et al. presented evidence that an archaean called *Methanobrevibacter oralis* inhabits the gums of patients with periodontal disease. The authors suggested that the activity of these methanogens causes the disease.[6] However, it was subsequently shown that there was no causal relationship between *M. oralis* and periodontitis. It seems more likely that periodontal disease causes an enlargement of anaerobic regions in the mouth that are subsequently populated by *M. oralis*.[7]

There remains no good answer as to why archaea do not seem to be pathogenic, but scientists continue to speculate and hope to find the answer.

Summary

- **Archaea** are unicellular, prokaryotic microorganisms that differ from bacteria in their genetics, biochemistry, and ecology.
- Some archaea are extremophiles, living in environments with extremely high or low temperatures, or extreme salinity.
- Only archaea are known to produce methane. Methane-producing archaea are called **methanogens**.
- Halophilic archaea prefer a concentration of salt close to saturation and perform photosynthesis using bacteriorhodopsin.
- Some archaea, based on fossil evidence, are among the oldest organisms on earth.
- Archaea do not live in great numbers in human microbiomes and are not known to cause disease.

Footnotes

1. E. Blochl et al.“*Pyrolobus fumani*, gen. and sp. nov., represents a novel group of Archaea, extending the upper temperature limit for life to 113°C.” *Extremophiles* 1 (1997):14–21.
2. T.D. Brock et al. “*Sulfolobus*: A New Genus of Sulfur-Oxidizing Bacteria Living at Low pH and High Temperature.” *Archiv für Mikrobiologie* 84 no. 1 (1972):54–68.
3. S. Pacheco et al. “Affinity Transfer to the Archaeal Extremophilic Sac7d Protein by Insertion of a CDR.” *Protein Engineering Design and Selection* 27 no. 10 (2014):431-438.
4. R.R. Britt “Crater Critters: Where Mars Microbes Might Lurk.” www.space.com/1880-crater-cri...obes-lurk.html. Accessed April 7, 2015.
5. H. Vreeland et al. “Fatty acid and DA Analyses of Permian Bacterium Isolated From Ancient Salt Crystals Reveal Differences With Their Modern Relatives.” *Extremophiles* 10 (2006):71–78.
6. P.W. Lepp et al. “Methanogenic Archaea and Human Gum Disease.” *Proceedings of the National Academies of Science of the United States of America* 101 no. 16 (2004):6176–6181.
7. R.I. Aminov. “Role of Archaea in Human Disease.” *Frontiers in Cellular and Infection Microbiology* 3 (2013):42.

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2.1.E: Prokaryotic Diversity (Exercises)

4.1: Prokaryote Habitats, Relationships, and Microbiomes

Prokaryotes are unicellular microorganisms whose cells have no nucleus. Prokaryotes can be found everywhere on our planet, even in the most extreme environments. Prokaryotes are very flexible metabolically, so they are able to adjust their feeding to the available natural resources. Prokaryotes live in communities that interact among themselves and with large organisms that they use as hosts (including humans).

Multiple Choice

The term prokaryotes refers to which of the following?

A. very small organisms
B. unicellular organisms that have no nucleus
C. multicellular organisms
D. cells that resemble animal cells more than plant cells

Answer

B

The term microbiota refers to which of the following?

A. all microorganisms of the same species
B. all of the microorganisms involved in a symbiotic relationship
C. all microorganisms in a certain region of the human body
D. all microorganisms in a certain geographic region

Answer

C

Which of the following refers to the type of interaction between two prokaryotic populations in which one population benefits and the other is not affected?

A. mutualism
B. commensalism
C. parasitism
D. neutralism

Answer

B

True/False

Among prokaryotes, there are some that can live in every environment on earth.

Answer

True

Fill in the Blank

When prokaryotes live as interacting communities in which one population benefits to the harm of the other, the type of symbiosis is called _____.

Answer

parasitism

The domain _____ does not include prokaryotes.

Answer

Eukarya

Pathogenic bacteria that are part of the transient microbiota can sometimes be eliminated by _____ therapy.

Answer

antibiotic

Nitrogen-fixing bacteria provide other organisms with usable nitrogen in the form of _____.

Answer

ammonia

Short Answer

Compare commensalism and amensalism.

Give an example of the changes of human microbiota that result from medical intervention.

4.2: Proteobacteria

Proteobacteria is a phylum of gram-negative bacteria and are classified into the classes alpha-, beta-, gamma-, delta- and epsilonproteobacteria, each class having separate orders, families, genera, and species. Alphaproteobacteria are oligotrophs. The taxa chlamydias and rickettsias are obligate intracellular pathogens, feeding on cells of host organisms; they are metabolically inactive outside of the host cell. Some Alphaproteobacteria can convert atmospheric nitrogen to nitrites.

Multiple Choice

Which of the following describes Proteobacteria in domain Bacteria?

A. phylum
B. class
C. species
D. genus

Answer

A

All Alphaproteobacteria are which of the following?

A. oligotrophs
B. intracellular
C. pathogenic
D. all of the above
E. none of the above

Answer

A

Class Betaproteobacteria includes all but which of the following genera?

A. *Neisseria*.
B. *Bordetella*.
C. *Leptothrix*.
D. *Campylobacter*.

Answer

D

Haemophilus influenzae is a common cause of which of the following?

A. influenza
B. dysentery
C. upper respiratory tract infections
D. hemophilia

Answer

C

Fill in the Blank

Rickettsias are _____ intracellular bacteria.

Answer

obligate

The species _____, which belongs to Epsilonproteobacteria, causes peptic ulcers of the stomach and duodenum.

Answer

Helicobacter pylori

The genus *Salmonella* belongs to the class _____ and includes pathogens that cause salmonellosis and typhoid fever.

Answer

Gammaproteobacteria

Short Answer

What is the metabolic difference between coliforms and noncoliforms? Which category contains several species of intestinal pathogens?

Why are *Mycoplasma* and *Chlamydia* classified as obligate intracellular pathogens?

Critical Thinking

The cell shown is found in the human stomach and is now known to cause peptic ulcers. What is the name of this bacterium?



(credit: American Society for Microbiology)

4.3: Nonproteobacteria Gram-negative Bacteria and Phototrophic Bacteria

Gram-negative nonproteobacteria include the taxa spirochetes; the Cytophaga, Fusobacterium, Bacteroides group; Planctomycetes; and many representatives of phototrophic bacteria. Spirochetes are motile, spiral bacteria with a long, narrow body; they are difficult or impossible to culture. Several genera of spirochetes contain human pathogens that cause such diseases as syphilis and Lyme disease. Cytophaga, Fusobacterium, and Bacteroides are classified together as a phylum called the CFB group.

Multiple Choice

Which of the following is the organelle that spirochetes use to propel themselves?

A. plasma membrane
B. axial filament
C. pilum
D. fimbria

Answer

B

Which of the following bacteria are the most prevalent in the human gut?

A. cyanobacteria
B. staphylococci
C. *Borrelia*
D. *Bacteroides*

Answer

D

Which of the following refers to photosynthesis performed by bacteria with the use of water as the donor of electrons?

A. oxygenic
B. anoxygenic
C. heterotrophic
D. phototrophic

Answer

A

Fill in the Blank

The bacterium that causes syphilis is called _____.

Answer

Treponema pallidum pallidum

Bacteria in the genus *Rhodospirillum* that use hydrogen for oxidation and fix nitrogen are _____ bacteria.

Answer

purple nonsulfur

Short Answer

Explain the term CFB group and name the genera that this group includes.

Name and briefly describe the bacterium that causes Lyme disease.

Characterize the phylum Cyanobacteria.

4.4: Gram-positive Bacteria

Gram-positive bacteria are a very large and diverse group of microorganisms. Understanding their taxonomy and knowing their unique features is important for diagnostics and treatment of infectious diseases. Gram-positive bacteria are classified into high G+C gram-positive and low G+C gram-positive bacteria, based on the prevalence of guanine and cytosine nucleotides in their genome.

Multiple Choice

Which of the following bacterial species is classified as high G+C gram-positive?

A. *Corynebacterium diphtheriae*
B. *Staphylococcus aureus*
C. *Bacillus anthracis*
D. *Streptococcus pneumonia*

Answer

A

Fill in the Blank

Streptococcus is the _____ of bacteria that is responsible for many human diseases.

Answer

genus

One species of *Streptococcus*, *S. pyogenes*, is a classified as a _____ pathogen due to the characteristic production of pus in infections it causes.

Answer

pyogenic

Propionibacterium belongs to _____ G+C gram-positive bacteria. One of its species is used in the food industry and another causes acne.

Answer

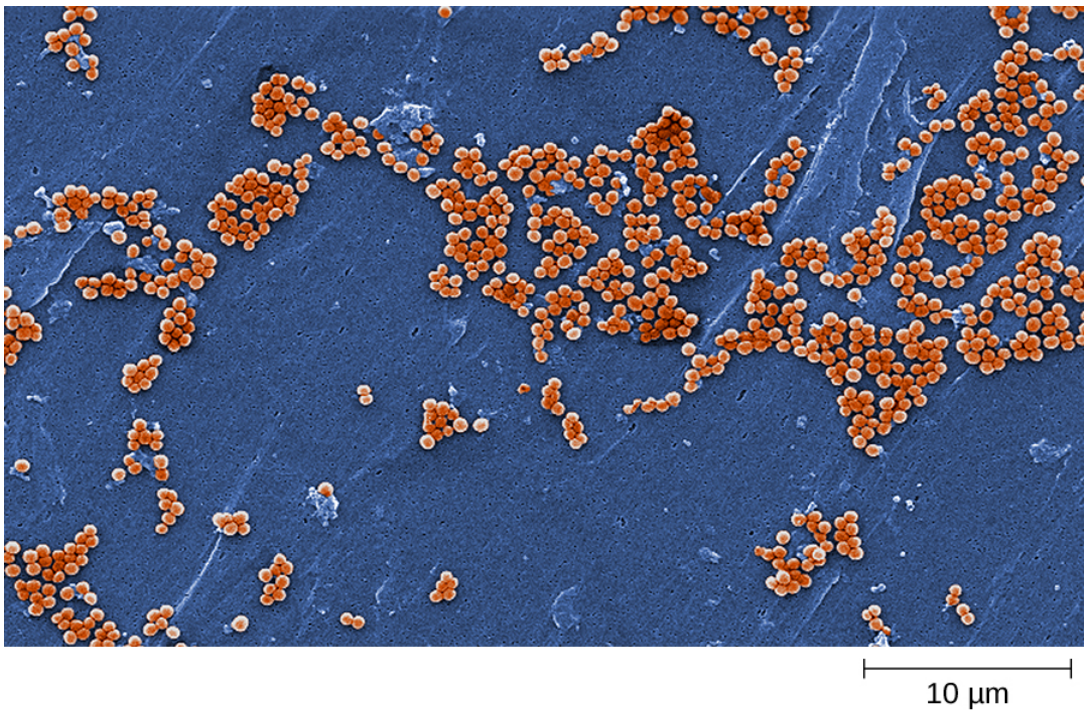
high

Short Answer

Name and describe two types of *S. aureus* that show multiple antibiotic resistance.

Critical Thinking

The microscopic growth pattern shown is characteristic of which genus of bacteria?



(credit: modification of work by Janice Haney Carr/Centers for Disease Control and Prevention)

4.5: Deeply Branching Bacteria

Deeply branching bacteria are phylogenetically the most ancient forms of life, being the closest to the last universal common ancestor. Deeply branching bacteria include many species that thrive in extreme environments that are thought to resemble conditions on earth billions of years ago. Deeply branching bacteria are important for our understanding of evolution; some of them are used in industry.

Multiple Choice

The term “deeply branching” refers to which of the following?

A. the cellular shape of deeply branching bacteria
B. the position in the evolutionary tree of deeply branching bacteria
C. the ability of deeply branching bacteria to live in deep ocean waters
D. the pattern of growth in culture of deeply branching bacteria

Answer

B

Which of these deeply branching bacteria is considered a polyextremophile?

A. *Aquifex pyrophilus*
B. *Deinococcus radiodurans*

C. *Staphylococcus aureus*
D. *Mycobacterium tuberculosis*

Answer

B

Fill in the Blank

The length of the branches of the evolutionary tree characterizes the evolutionary _____ between organisms.

Answer

distance

The deeply branching bacteria are thought to be the form of life closest to the last universal _____ _____.

Answer

common ancestor

Many of the deeply branching bacteria are aquatic and hyperthermophilic, found near underwater volcanoes and thermal ocean _____.

Answer

vents

The deeply branching bacterium *Deinococcus radiodurans* is able to survive exposure to high doses of _____.

Answer

ionizing radiation

Short Answer

Briefly describe the significance of deeply branching bacteria for basic science and for industry.

What is thought to account for the unique radiation resistance of *D. radiodurans*?

4.6: Archaea

Archaea are unicellular, prokaryotic microorganisms that differ from bacteria in their genetics, biochemistry, and ecology. Some archaea are extremophiles, living in environments with extremely high or low temperatures, or extreme salinity. Only archaea are known to produce methane. Methane-producing archaea are called methanogens. Halophilic archaea prefer a concentration of salt close to saturation and perform photosynthesis using bacteriorhodopsin.

Multiple Choice

Archaea and Bacteria are most similar in terms of their _____.

A. genetics
B. cell wall structure
C. ecology
D. unicellular structure

Answer

D

Which of the following is true of archaea that produce methane?

A. They reduce carbon dioxide in the presence of nitrogen.
B. They live in the most extreme environments.

C. They are always anaerobes.
D. They have been discovered on Mars.

Answer

B

Fill in the Blank

_____ is a genus of Archaea. Its optimal environmental temperature ranges from 70 °C to 80 °C, and its optimal pH is 2–3. It oxidizes sulfur and produces sulfuric acid.

Answer

Sulfolobus

_____ was once thought to be the cause of periodontal disease, but, more recently, the causal relationship between this archaean and the disease was not confirmed.

Answer

Methanobrevibacter oralis

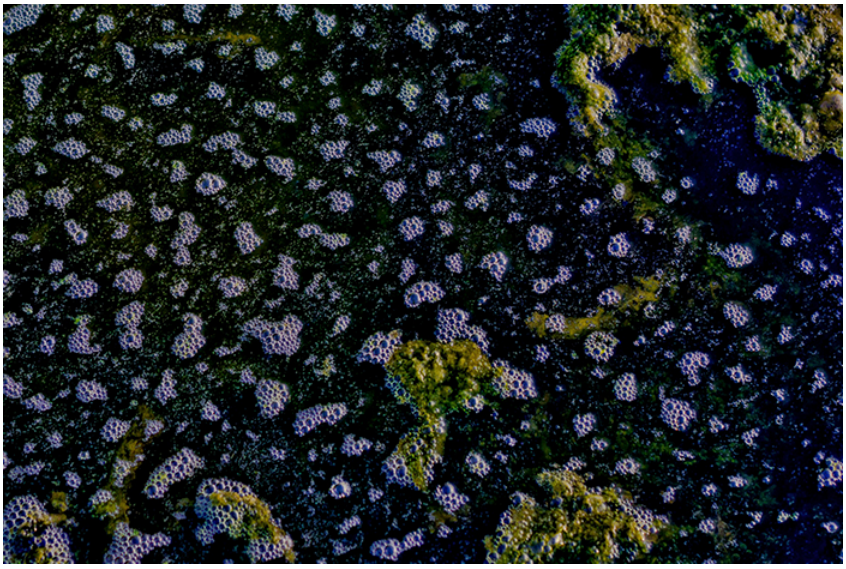
Short Answer

What accounts for the purple color in salt ponds inhabited by halophilic archaea?

What evidence supports the hypothesis that some archaea live on Mars?

Critical Thinking

What is the connection between this methane bog and archaea?



(credit: Chad Skeers)

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SECTION OVERVIEW

2.2: The Eukaryotes of Microbiology

Although bacteria and viruses account for a large number of the infectious diseases that afflict humans, many serious illnesses are caused by eukaryotic organisms. One example is malaria, which is caused by *Plasmodium*, a eukaryotic organism transmitted through mosquito bites. Malaria is a major cause of morbidity (illness) and mortality (death) that threatens 3.4 billion people worldwide.[1] In severe cases, organ failure and blood or metabolic abnormalities contribute to medical emergencies and sometimes death. Even after initial recovery, relapses may occur years later. In countries where malaria is endemic, the disease represents a major public health challenge that can place a tremendous strain on developing economies.

Worldwide, major efforts are underway to reduce malaria infections. Efforts include the distribution of insecticide-treated bed nets and the spraying of pesticides. Researchers are also making progress in their efforts to develop effective vaccines.[2] The President's Malaria Initiative, started in 2005, supports prevention and treatment. The Bill and Melinda Gates Foundation has a large initiative to eliminate malaria. Despite these efforts, malaria continues to cause long-term morbidity (such as intellectual disabilities in children) and mortality (especially in children younger than 5 years), so we still have far to go.

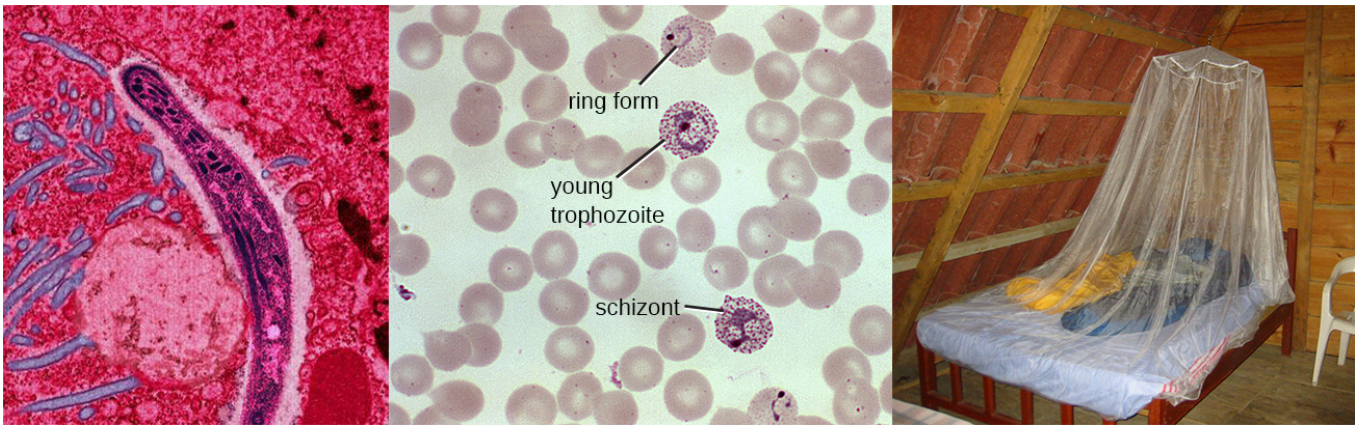


Figure 2.2.1: Malaria is a disease caused by a eukaryotic parasite transmitted to humans by mosquitos. Micrographs (left and center) show a sporozoite life stage, trophozoites, and a schizont in a blood smear. On the right is depicted a primary defense against mosquito-borne illnesses like malaria—mosquito netting. (credit left: modification of work by Ute Frevert; credit middle: modification of work by Centers for Disease Control and Prevention; credit right: modification of work by Tjeerd Wiersma)

2.2.1: Unicellular Eukaryotic Microorganisms

2.2.2: Parasitic Helminths

2.2.3: Fungi

2.2.4: Algae

2.2.5: Lichens

2.2.E: The Eukaryotes of Microbiology (Exercises)

Footnotes

1. 1 Centers for Disease Control and Prevention. "Impact of Malaria." September 22, 2015. http://www.cdc.gov/malaria/malaria_w...de/impact.html. Accessed January 18, 2016.
2. 2 RTS, S Clinical Trials Partnership. "Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial." The Lancet 23 April 2015. DOI: http://dx.doi.org/10.1016/S0140-6736(15)60721-8.

Thumbnail: Mold growing on a clementine. (CC SA-BY 3.0; NotFromUtrecht).

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2.2.1: Unicellular Eukaryotic Microorganisms

Learning Objectives

- Summarize the general characteristics of unicellular eukaryotic parasites
- Describe the general life cycles and modes of reproduction in unicellular eukaryotic parasites
- Identify challenges associated with classifying unicellular eukaryotes
- Explain the taxonomic scheme used for unicellular eukaryotes
- Give examples of infections caused by unicellular eukaryotes

Clinical Focus: Part 1

Upon arriving home from school, 7-year-old Sarah complains that a large spot on her arm will not stop itching. She keeps scratching at it, drawing the attention of her parents. Looking more closely, they see that it is a red circular spot with a raised red edge (Figure 2.2.1.1). The next day, Sarah's parents take her to their doctor, who examines the spot using a Wood's lamp. A Wood's lamp produces ultraviolet light that causes the spot on Sarah's arm to fluoresce, which confirms what the doctor already suspected: Sarah has a case of ringworm.

Sarah's mother is mortified to hear that her daughter has a "worm." How could this happen?

Exercise 2.2.1.1

What are some likely ways that Sarah might have contracted ringworm?



Figure 2.2.1.1: Ringworm presents as a raised, red ring on the skin. (credit: Centers for Disease Control and Prevention)

Eukaryotic microbes are an extraordinarily diverse group, including species with a wide range of life cycles, morphological specializations, and nutritional needs. Although more diseases are caused by viruses and bacteria than by microscopic eukaryotes, these eukaryotes are responsible for some diseases of great public health importance. For example, the protozoal disease malaria was responsible for 584,000 deaths worldwide (primarily children in Africa) in 2013, according to the World Health Organization (WHO). The protist parasite *Giardia* causes a diarrheal illness (giardiasis) that is easily transmitted through contaminated water supplies. In the United States, *Giardia* is the most common human intestinal parasite (Figure 2.2.1.2). Although it may seem surprising, parasitic worms are included within the study of microbiology because identification depends on observation of microscopic adult worms or eggs. Even in developed countries, these worms are important parasites of humans and of domestic animals. There are fewer fungal pathogens, but these are important causes of illness, as well. On the other hand, fungi have been important in producing antimicrobial substances such as penicillin. In this chapter, we will examine characteristics of protists, worms, and fungi while considering their roles in causing disease.

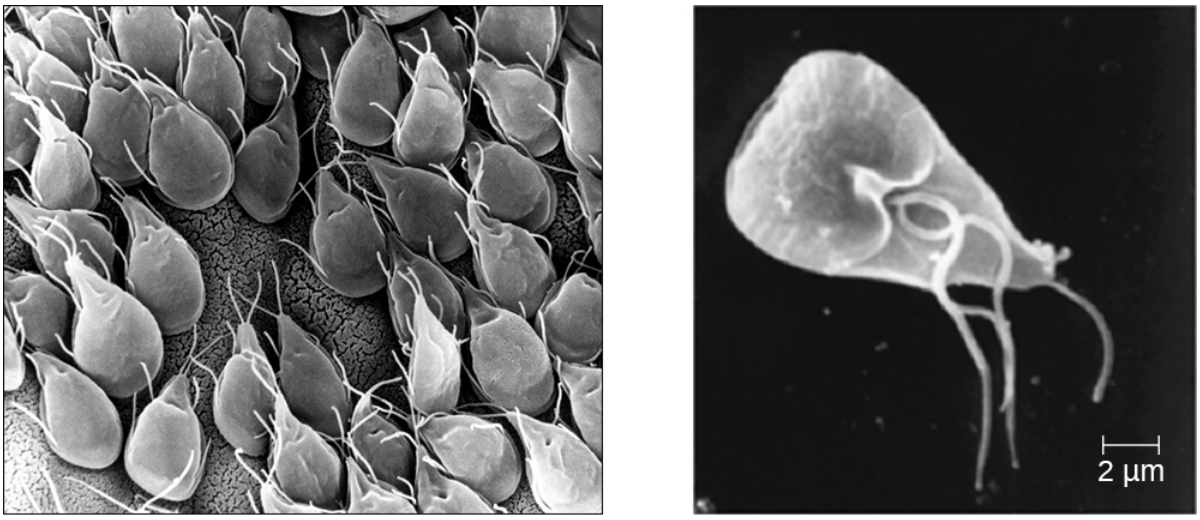


Figure 2.2.1.2: (a) A scanning electron micrograph shows many *Giardia* parasites in the trophozoite, or feeding stage, in a gerbil intestine. (b) An individual trophozoite of *G. lamblia*, visualized here in a scanning electron micrograph. This waterborne protist causes severe diarrhea when ingested. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Characteristics of Protists

The word *protist* is a historical term that is now used informally to refer to a diverse group of microscopic eukaryotic organisms. It is not considered a formal taxonomic term because the organisms it describes do not have a shared evolutionary origin. Historically, the protists were informally grouped into the "animal-like" protozoans, the "plant-like" algae, and the "fungus-like" protists such as water molds. These three groups of protists differ greatly in terms of their basic characteristics. For example, algae are photosynthetic organisms that can be unicellular or multicellular. Protozoa, on the other hand, are nonphotosynthetic, motile organisms that are always unicellular. Other informal terms may also be used to describe various groups of protists. For example, microorganisms that drift or float in water, moved by currents, are referred to as plankton. Types of plankton include zooplankton, which are motile and nonphotosynthetic, and phytoplankton, which are photosynthetic.

Protozoans inhabit a wide variety of habitats, both aquatic and terrestrial. Many are free-living, while others are parasitic, carrying out a life cycle within a host or hosts and potentially causing illness. There are also beneficial symbionts that provide metabolic services to their hosts. During the feeding and growth part of their life cycle, they are called trophozoites; these feed on small particulate food sources such as bacteria. While some types of protozoa exist exclusively in the trophozoite form, others can develop from trophozoite to an encapsulated cyst stage when environmental conditions are too harsh for the trophozoite. A cyst is a cell with a protective wall, and the process by which a trophozoite becomes a cyst is called encystment. When conditions become more favorable, these cysts are triggered by environmental cues to become active again through excystment.

One protozoan genus capable of encystment is *Eimeria*, which includes some human and animal pathogens. Figure 2.2.1.3 illustrates the life cycle of *Eimeria*.

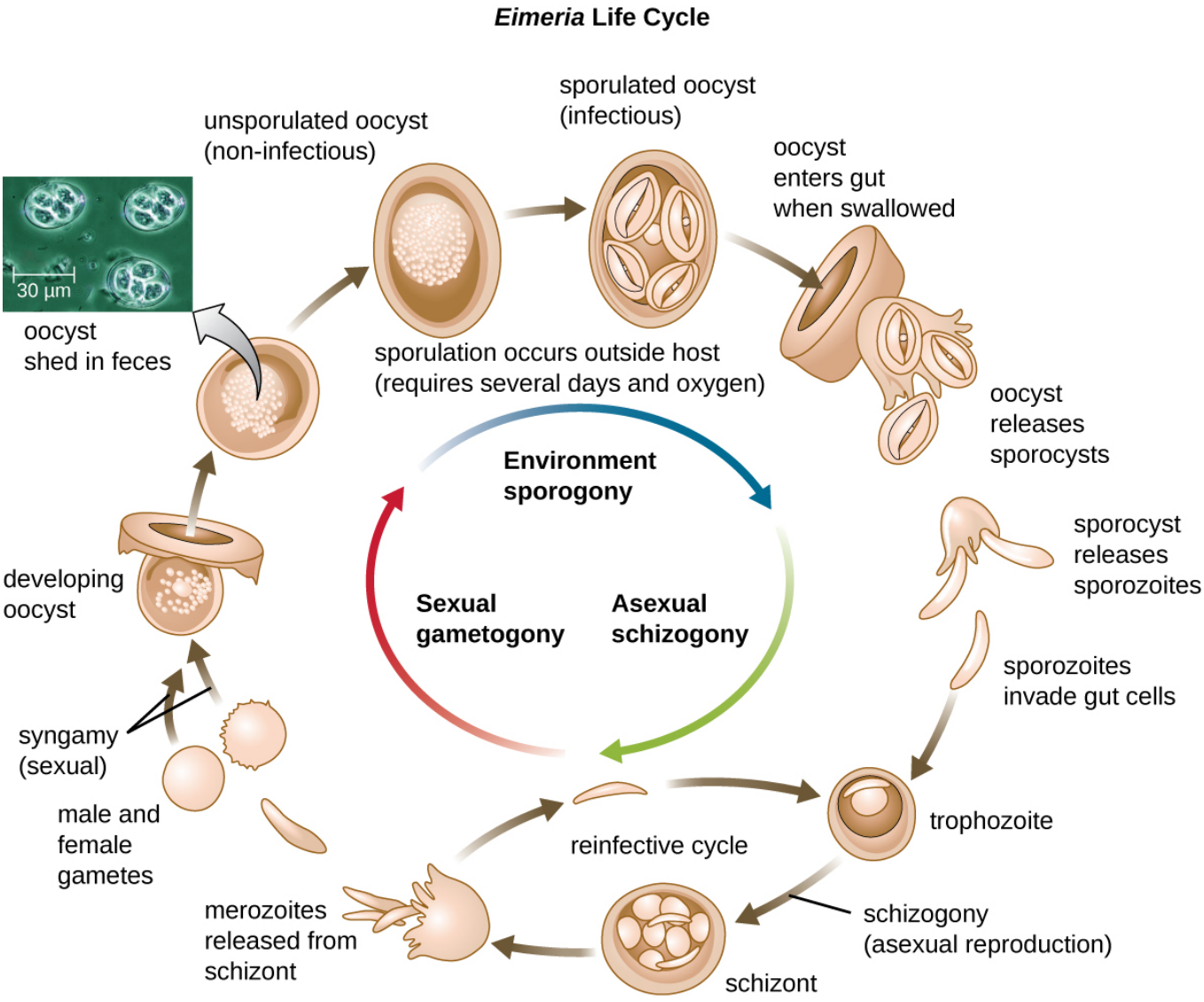


Figure 2.2.1.3: In the sexual/asexual life cycle of Eimeria, oocysts (inset) are shed in feces and may cause disease when ingested by a new host. (credit "life cycle," "micrograph": modification of work by USDA)

Protozoans have a variety of reproductive mechanisms. Some protozoans reproduce asexually and others reproduce sexually; still others are capable of both sexual and asexual reproduction. In protozoans, asexual reproduction occurs by binary fission, budding, or schizogony. In schizogony, the nucleus of a cell divides multiple times before the cell divides into many smaller cells. The products of schizogony are called merozoites and they are stored in structures known as schizonts. Protozoans may also reproduce sexually, which increases genetic diversity and can lead to complex life cycles. Protozoans can produce haploid gametes that fuse through syngamy. However, they can also exchange genetic material by joining to exchange DNA in a process called conjugation. This is a different process than the conjugation that occurs in bacteria. The term protist conjugation refers to a true form of eukaryotic sexual reproduction between two cells of different mating types. It is found in ciliates, a group of protozoans, and is described later in this subsection.

All protozoans have a plasma membrane, or plasmalemma, and some have bands of protein just inside the membrane that add rigidity, forming a structure called the pellicle. Some protists, including protozoans, have distinct layers of cytoplasm under the membrane. In these protists, the outer gel layer (with microfilaments of actin) is called the ectoplasm. Inside this layer is a sol (fluid) region of cytoplasm called the endoplasm. These structures contribute to complex cell shapes in some protozoans, whereas others (such as amoebas) have more flexible shapes (Figure 2.2.1.4).

Different groups of protozoans have specialized feeding structures. They may have a specialized structure for taking in food through phagocytosis, called a cytostome, and a specialized structure for the exocytosis of wastes called a cytoproct. Oral grooves

leading to cytostomes are lined with hair-like cilia to sweep in food particles. Protozoans are heterotrophic. Protozoans that are holozoic ingest whole food particles through phagocytosis. Forms that are saprozoic ingest small, soluble food molecules.

Many protists have whip-like flagella or hair-like cilia made of microtubules that can be used for locomotion (Figure 2.2.1.4). Other protists use cytoplasmic extensions known as pseudopodia ("false feet") to attach the cell to a surface; they then allow cytoplasm to flow into the extension, thus moving themselves forward.

Protozoans have a variety of unique organelles and sometimes lack organelles found in other cells. Some have contractile vacuoles, organelles that can be used to move water out of the cell for osmotic regulation (salt and water balance) (Figure 2.2.1.4). Mitochondria may be absent in parasites or altered to kinetoplastids (modified mitochondria) or hydrogenosomes (see Unique Characteristics of Eukaryotic Cells for more discussion of these structures).

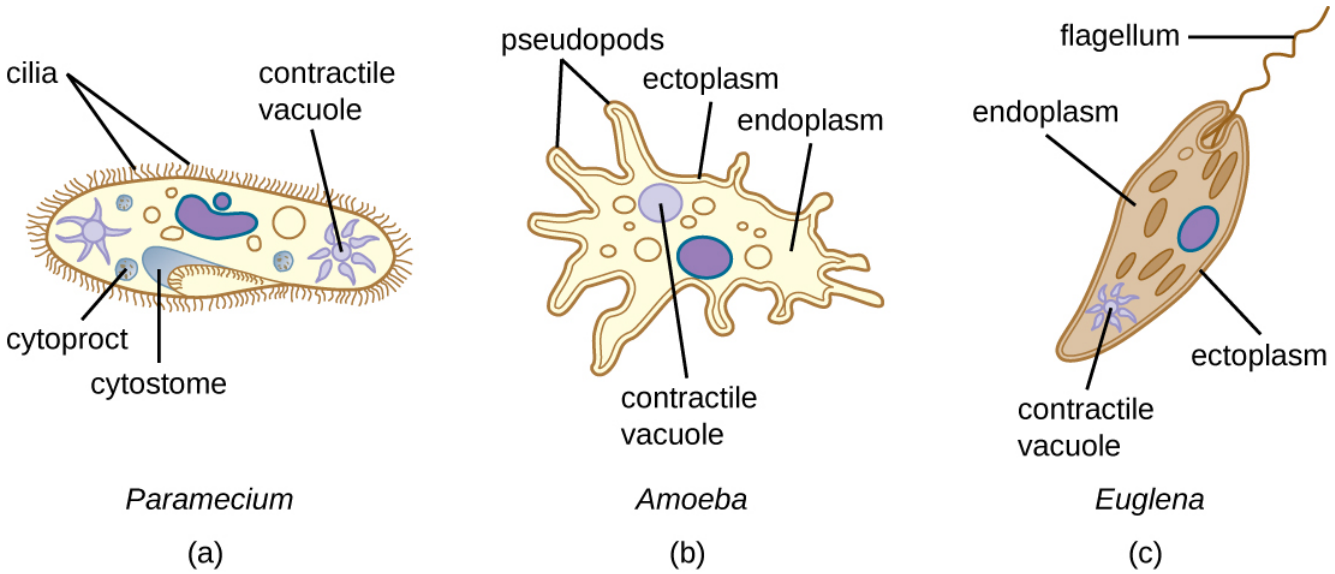


Figure 2.2.1.4: (a) *Paramecium* spp. have hair-like appendages called cilia for locomotion. (b) *Amoeba* spp. use lobe-like pseudopodia to anchor the cell to a solid surface and pull forward. (c) *Euglena* spp. use a whip-like structure called a flagellum to propel the cell.

? Exercise 2.2.1.2

What is the sequence of events in reproduction by schizogony and what are the cells produced called?

Taxonomy of Protists

The protists are a polyphyletic group, meaning they lack a shared evolutionary origin. Since the current taxonomy is based on evolutionary history (as determined by biochemistry, morphology, and genetics), protists are scattered across many different taxonomic groups within the domain Eukarya. Eukarya is currently divided into six supergroups that are further divided into subgroups, as illustrated in (Figure 2.2.1.5). In this section, we will primarily be concerned with the supergroups Amoebozoa, Excavata, and Chromalveolata; these supergroups include many protozoans of clinical significance. The supergroups Opisthokonta and Rhizaria also include some protozoans, but few of clinical significance. In addition to protozoans, Opisthokonta also includes animals and fungi, some of which we will discuss in Parasitic Helminths and Fungi. Some examples of the Archaeplastida will be discussed in Algae. Figure 2.2.1.6 and Figure 2.2.1.7 summarize the characteristics of each supergroup and subgroup and list representatives of each.

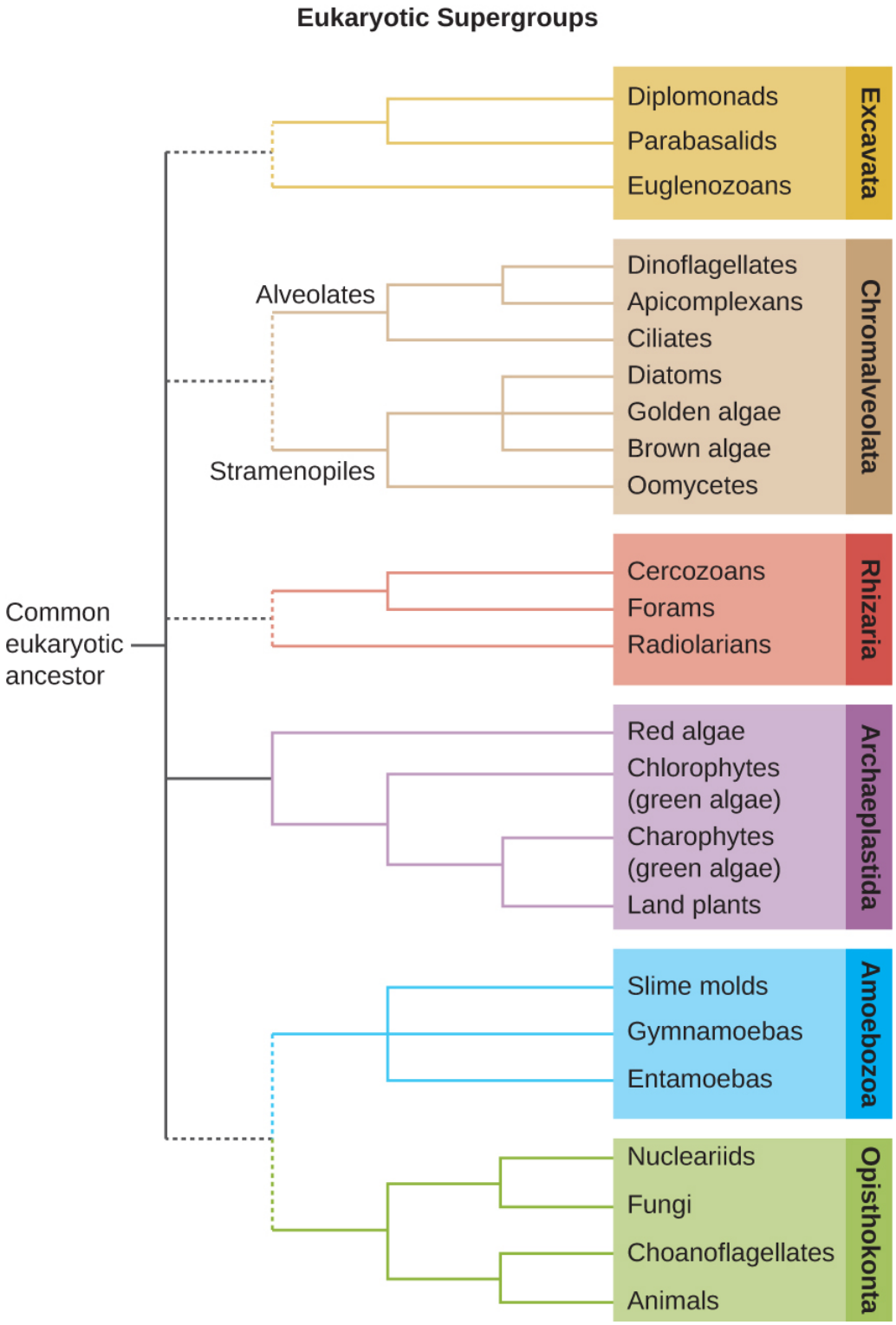


Figure 2.2.1.5: This tree shows a proposed classification of the domain Eukarya based on evolutionary relationships. Currently, the domain Eukarya is divided into six supergroups. Within each supergroup are multiple kingdoms. Dotted lines indicate suggested evolutionary relationships that remain under debate.

The Eukaryote Supergroups and Some Examples				
Supergroup	**Subgroups**	**Distinguishing Features**	**Examples**	**Clinical Notes**
Excavata	Fornicata	Form cysts Pair of equal nuclei No mitochondria Often parasitic Four free flagella	*Giardia lamblia*	Giardiasis
	Parabasalids	No mitochondria Four free flagella One attached flagellum No cysts Parasitic or symbiotic Basal bodies Kinetoplastids	*Trichomonas*	Trichomoniasis
	Euglenozoans	Photosynthetic or heterotrophic Flagella	*Euglena*	N/a
			Trypanosoma	African sleeping sickness, Chagas disease
			Leishmania	Leishmaniasis
Chromalveolata	Dinoflagellates	Cellulose theca Two dissimilar flagella	*Gonyaulax*	Red tides
			Alexandrium	Paralytic shellfish poisoning
			Pfiesteria	Harmful algal blooms
	Apicomplexans	Intracellular parasite Apical organelles	*Plasmodium*	Malaria
			Cryptosporidium	Cryptosporidiosis
			Theileria (Babesia)	Babesiosis
			Toxoplasma	Toxoplasmosis
	Ciliates	Cilia	*Balantidium*	Balantidiasis
			Paramecium	N/a
			Stentor	N/a
	Öomycetes/ peronosporomy-cetes	“Water molds” Generally diploid Cellulose cell walls	*Phytophthora*	Diseases in crops

Figure 2.2.1.6

The Eukaryote Supergroups and Some Examples (continued)				
Supergroup	**Subgroups**	**Distinguishing Features**	**Examples**	**Clinical Notes**
Rhizaria	Foraminifera	Amoeboid Threadlike pseudopodia Calcium carbonate shells	*Astrolonche*	N/a
	Radiolaria	Amoeboid Threadlike pseudopodia Silica shells	*Actinomma*	N/a
	Cercozoa	Amoeboid Threadlike pseudopodia Complex shells Parasitic forms	*Spongospora subterranea*	Powdery scab (potato disease)
			Plasmodiophora brassicae	Cabbage clubroot
Archaeplastida	Red algae	Chlorophyll *a* Phycoerythrin Phycocyanin Floridean starch Agar in cell walls	*Gelidium*	Source of agar
			Gracilaria	Source of agar
	Chlorophytes	Chlorophyll *a* Chlorophyll *b* Cellulose cell walls Starch storage	*Acetabularia*	N/a
			Ulva	N/a
Amoebozoa	Slime molds	Plasmodial and cellular forms	*Dictyostelium*	N/a
	Entamoebas	Trophozoites Form cysts	*Entamoeba*	Amoebiasis
			Naegleria	Primary amoebic meningoencephalitis
			Acanthamoeba	Keratitis, granulomatous amoebic encephalitis
Opisthokonta	Fungi	Chitin cell walls Unicellular or multicellular Often hyphae	Zygomycetes	Zygomycosis
			Ascomycetes	Candidiasis
			Basidiomycetes	Cryptococcosis
			Microsporidia	Microsporidiosis
	Animals	Multicellular heterotrophs No cell walls	Nematoda	Trichinosis; hookworm and pinworm infections
			Trematoda	Schistosomiasis
			Cestoda	Tapeworm infections

Figure 2.2.1.7

? Exercise 2.2.1.3

Which supergroups contain the clinically significant protists?

Amoebozoa

The supergroup Amoebozoa includes protozoans that use amoeboid movement. Actin microfilaments produce pseudopodia, into which the remainder of the protoplasm flows, thereby moving the organism. The genus *Entamoeba*includes commensal or parasitic

species, including the medically important *E. histolytica*, which is transmitted by cysts in feces and is the primary cause of amoebic dysentery. The notorious “brain-eating amoeba,” *Naegleria fowleri*, is also classified within the Amoebozoa. This deadly parasite is found in warm, fresh water and causes primary amoebic meningoencephalitis (PAM). Another member of this group is *Acanthamoeba*, which can cause keratitis (corneal inflammation) and blindness.

The Eumycetozoa are an unusual group of organisms called slime molds, which have previously been classified as animals, fungi, and plants (Figure 2.2.1.8). Slime molds can be divided into two types: cellular slime molds and plasmodial slime molds. The cellular slime molds exist as individual amoeboid cells that periodically aggregate into a mobile slug. The aggregate then forms a fruiting body that produces haploid spores. Plasmodial slime molds exist as large, multinucleate amoeboid cells that form reproductive stalks to produce spores that divide into gametes. One cellular slime mold, *Dictyostelium discoideum*, has been an important study organism for understanding cell differentiation, because it has both single-celled and multicelled life stages, with the cells showing some degree of differentiation in the multicelled form. Figure 2.2.1.9and Figure 2.2.1.10 illustrate the life cycles of cellular and plasmodial slime molds, respectively.



(a) (b)

Figure 2.2.1.8: (a) The cellular slime mold *Dictyostelium discoideum* can be grown on agar in a Petri dish. In this image, individual amoeboid cells (visible as small spheres) are streaming together to form an aggregation that is beginning to rise in the upper right corner of the image. The primitively multicellular aggregation consists of individual cells that each have their own nucleus. (b) *Fuligo septica* is a plasmodial slime mold. This brightly colored organism consists of a large cell with many nuclei.

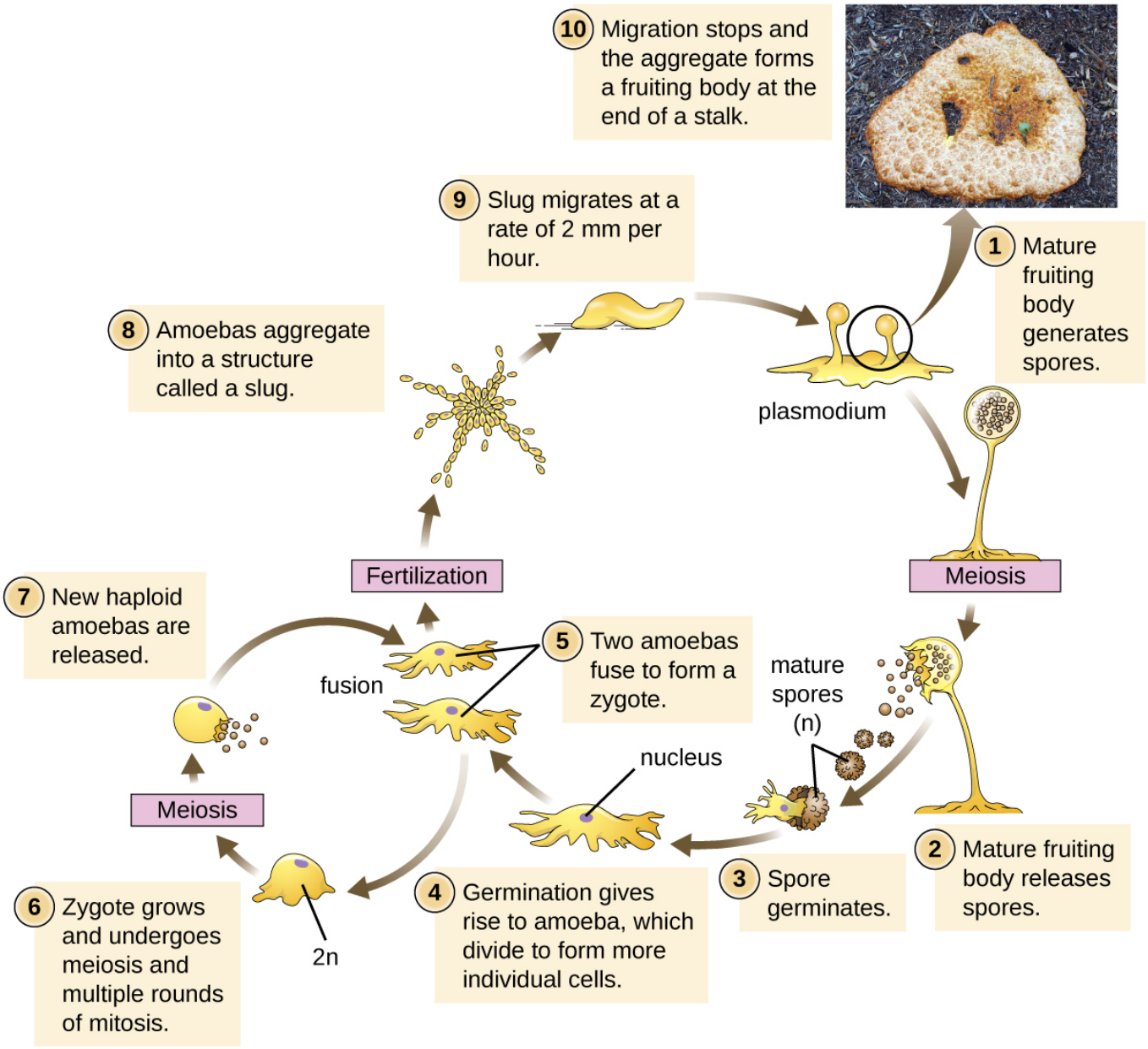


Figure 2.2.1.9: The life cycle of the cellular slime mold *Dictyostelium discoideum* primarily involves individual amoebas but includes the formation of a multinucleate plasmodium formed from a uninucleate zygote (the result of the fusion of two individual amoeboid cells). The plasmodium is able to move and forms a fruiting body that generates haploid spores. (credit "photo": modification of work by "thatredhead4"/Flickr)

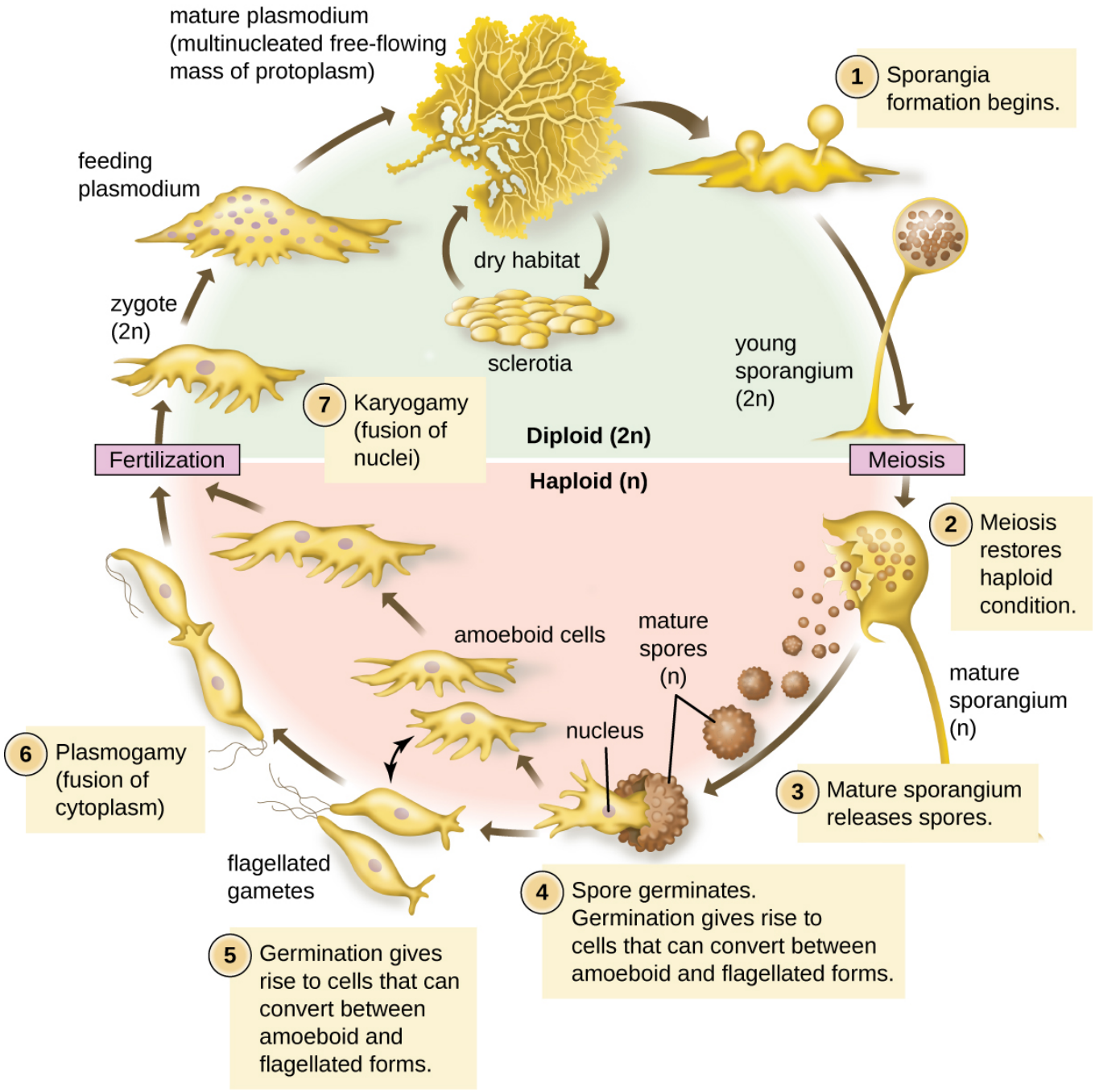


Figure 2.2.1.1: Plasmodial slime molds exist as large multinucleate amoeboid cells that form reproductive stalks to produce spores that divide into gametes.

Chromalveolata

The supergroup Chromalveolata is united by similar origins of its members' plastids and includes the apicomplexans, ciliates, diatoms, and dinoflagellates, among other groups (we will cover the diatoms and dinoflagellates in Algae). The apicomplexans are intra- or extracellular parasites that have an apical complex at one end of the cell. The apical complex is a concentration of organelles, vacuoles, and microtubules that allows the parasite to enter host cells (Figure 2.2.1.11). Apicomplexans have complex life cycles that include an infective sporozoite that undergoes schizogony to make many merozoites (see the example in Figure 2.2.1.3). Many are capable of infecting a variety of animal cells, from insects to livestock to humans, and their life cycles often depend on transmission between multiple hosts. The genus *Plasmodium* is an example of this group.

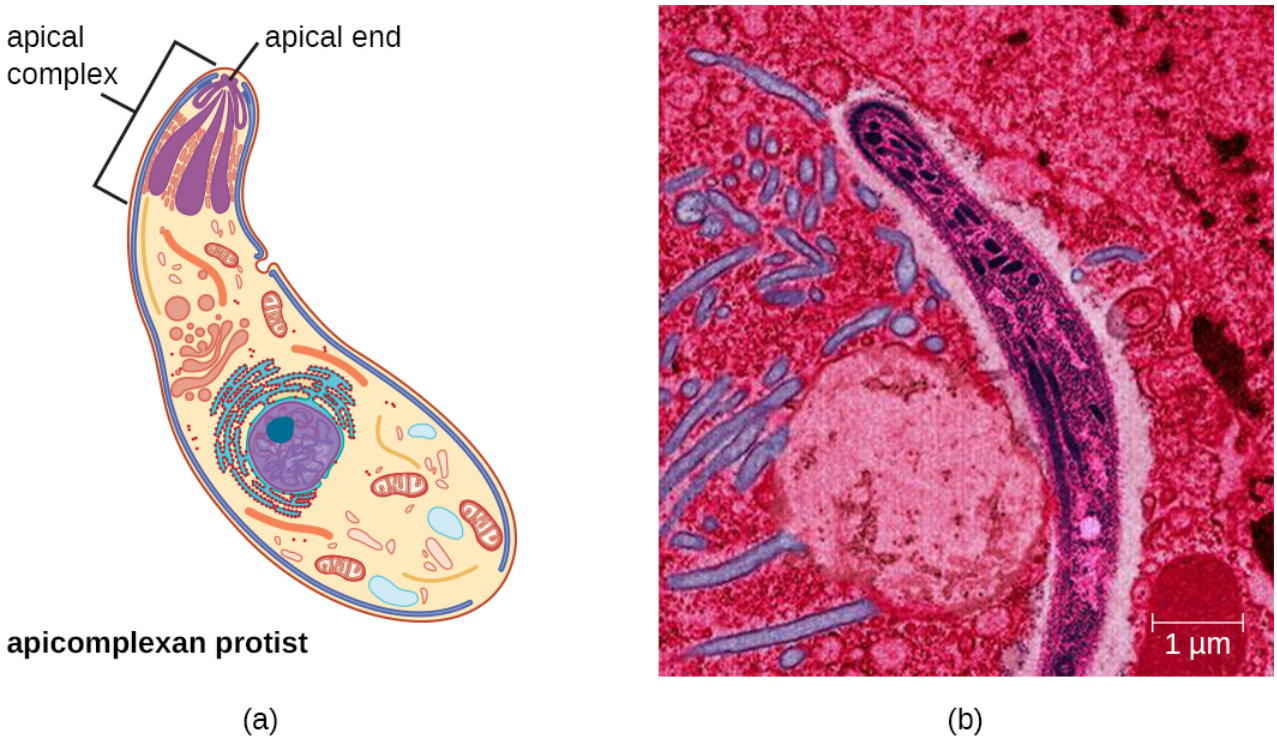


Figure 2.2.1.11: (a) Apicomplexans are parasitic protists. They have a characteristic apical complex that enables them to infect host cells. (b) A colorized electron microscope image of a *Plasmodium* sporozoite. (credit b: modification of work by Ute Frevert)

Other apicomplexans are also medically important. *Cryptosporidium parvum* causes intestinal symptoms and can cause epidemic diarrhea when the cysts contaminate drinking water. *Theileria (Babesia) microti*, transmitted by the tick *Ixodes scapularis*, causes recurring fever that can be fatal and is becoming a common transfusion-transmitted pathogen in the United States (*Theileria* and *Babesia* are closely related genera and there is some debate about the best classification). Finally, *Toxoplasma gondii* causes toxoplasmosis and can be transmitted from cat feces, unwashed fruit and vegetables, or from undercooked meat. Because toxoplasmosis can be associated with serious birth defects, pregnant women need to be aware of this risk and use caution if they are exposed to the feces of potentially infected cats. A national survey found the frequency of individuals with antibodies for toxoplasmosis (and thus who presumably have a current latent infection) in the United States to be 11%. Rates are much higher in other countries, including some developed countries.[1] There is also evidence and a good deal of theorizing that the parasite may be responsible for altering infected humans' behavior and personality traits.[2]

The ciliates (Ciliaphora), also within the Chromalveolata, are a large, very diverse group characterized by the presence of cilia on their cell surface. Although the cilia may be used for locomotion, they are often used for feeding, as well, and some forms are nonmotile. *Balantidium coli* (Figure 2.2.1.12) is the only parasitic ciliate that affects humans by causing intestinal illness, although it rarely causes serious medical issues except in the immunocompromised (those having a weakened immune system). Perhaps the most familiar ciliate is *Paramecium*, a motile organism with a clearly visible cytostomeand cytoproct that is often studied in biology laboratories (Figure 2.2.1.13). Another ciliate, *Stentor*, is sessile and uses its cilia for feeding (Figure 2.2.1.14). Generally, these organisms have a micronucleus that is diploid, somatic, and used for sexual reproduction by conjugation. They also have a macronucleus that is derived from the micronucleus; the macronucleus becomes polyploid (multiple sets of duplicate chromosomes), and has a reduced set of metabolic genes.

Ciliates are able to reproduce through conjugation, in which two cells attach to each other. In each cell, the diploid micronuclei undergo meiosis, producing eight haploid nuclei each. Then, all but one of the haploid micronuclei and the macronucleus disintegrate; the remaining (haploid) micronucleus undergoes mitosis. The two cells then exchange one micronucleus each, which fuses with the remaining micronucleus present to form a new, genetically different, diploid micronucleus. The diploid micronucleus undergoes two mitotic divisions, so each cell has four micronuclei, and two of the four combine to form a new macronucleus. The chromosomes in the macronucleus then replicate repeatedly, the macronucleus reaches its polyploid state, and the two cells separate. The two cells are now genetically different from each other and from their previous versions.



Figure 2.2.1.12: This specimen of the ciliate *Balantidium coli* is a trophozoite form isolated from the gut of a primate. *B. coli* is the only ciliate capable of parasitizing humans. (credit: modification of work by Kouassi RYW, McGraw SW, Yao PK, Abou-Bacar A, Brunet J, Pesson B, Bonfoh B, N'goran EK & Candolfi E)

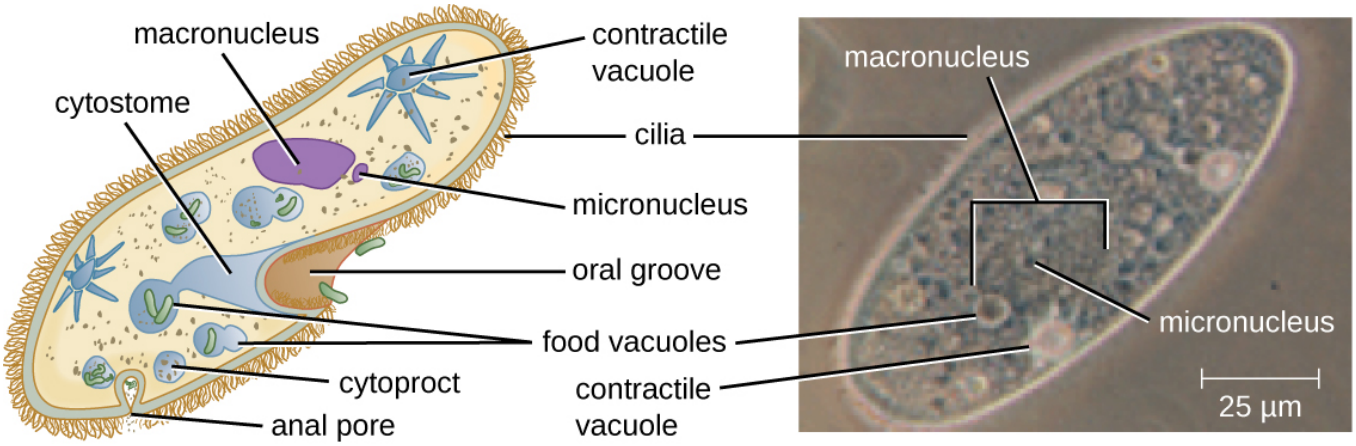


Figure 2.2.1.13: Paramecium has a primitive mouth (called an oral groove) to ingest food, and an anal pore to excrete it. Contractile vacuoles allow the organism to excrete excess water. Cilia enable the organism to move.

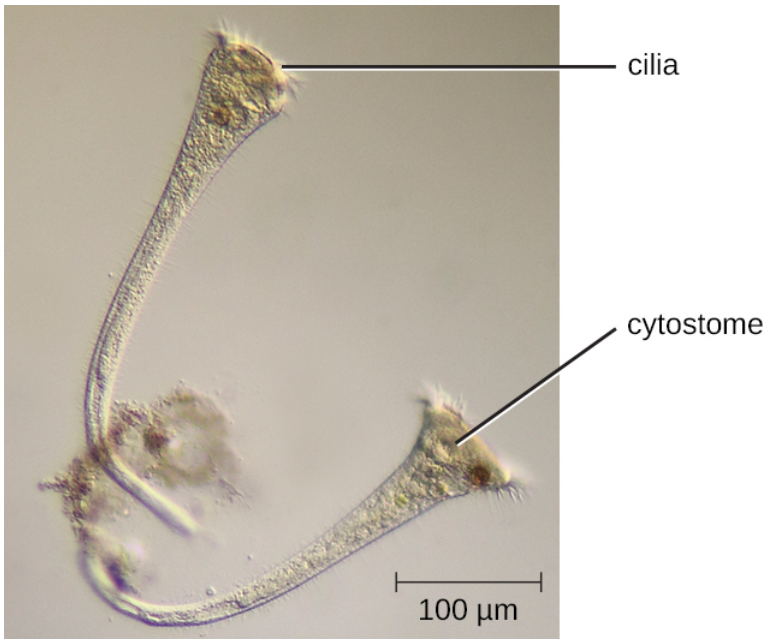


Figure 2.2.1.14: This differential interference contrast micrograph (magnification: ×65) of *Stentor roeselie* shows cilia present on the margins of the structure surrounding the cytostome; the cilia move food particles. (credit: modification of work by "picturepest"/Flickr)

Öomycetes have similarities to fungi and were once classified with them. They are also called water molds. However, they differ from fungi in several important ways. Öomycetes have cell walls of cellulose (unlike the chitinous cell walls of fungi) and they are generally diploid, whereas the dominant life forms of fungi are typically haploid. *Phytophthora*, the plant pathogen found in the soil that caused the Irish potato famine, is classified within this group (Figure 2.2.1.15).



Figure 2.2.1.15: A saprobic oomycete, or water mold, engulfs a dead insect. (credit: modification of work by Thomas Bresson)

Link to Learning

This video shows the feeding of *Stentor*.

Excavata

The third and final supergroup to be considered in this section is the Excavata, which includes primitive eukaryotes and many parasites with limited metabolic abilities. These organisms have complex cell shapes and structures, often including a depression on the surface of the cell called an excavate. The group Excavata includes the subgroups Fornicata, Parabasalia, and Euglenozoa. The Fornicata lack mitochondria but have flagella. This group includes *Giardia lamblia* (also known as *G. intestinalis* or *G. duodenalis)*, a widespread pathogen that causes diarrheal illness and can be spread through cysts from feces that contaminate water supplies (Figure 2.2.1.2). Parabasalia are frequent animal endosymbionts; they live in the guts of animals like termites and cockroaches. They have basal bodies and modified mitochondria (kinetoplastids). They also have a large, complex cell structure with an undulating membrane and often have many flagella. The trichomonads (a subgroup of the Parabasalia) include pathogens such as *Trichomonas vaginalis*, which causes the human sexually transmitted disease trichomoniasis. Trichomoniasis often does not cause symptoms in men, but men are able to transmit the infection. In women, it causes vaginal discomfort and discharge and may cause complications in pregnancy if left untreated.

The Euglenozoa are common in the environment and include photosynthetic and nonphotosynthetic species. Members of the genus *Euglena* are typically not pathogenic. Their cells have two flagella, a pellicle, a stigma (eyespot) to sense light, and chloroplasts for photosynthesis (Figure 2.2.1.16). The pellicle of *Euglena* is made of a series of protein bands surrounding the cell; it supports the cell membrane and gives the cell shape.

The Euglenozoa also include the trypanosomes, which are parasitic pathogens. The genus *Trypanosoma* includes *T. brucei*, which causes African trypanosomiasis (African sleeping sickness and *T. cruzi*, which causes American trypanosomiasis (Chagas disease). These tropical diseases are spread by insect bites. In African sleeping sickness, *T. brucei* colonizes the blood and the brain after being transmitted via the bite of a tsetse fly (*Glossina* spp.) (Figure 2.2.1.17). The early symptoms include confusion, difficulty sleeping, and lack of coordination. Left untreated, it is fatal.

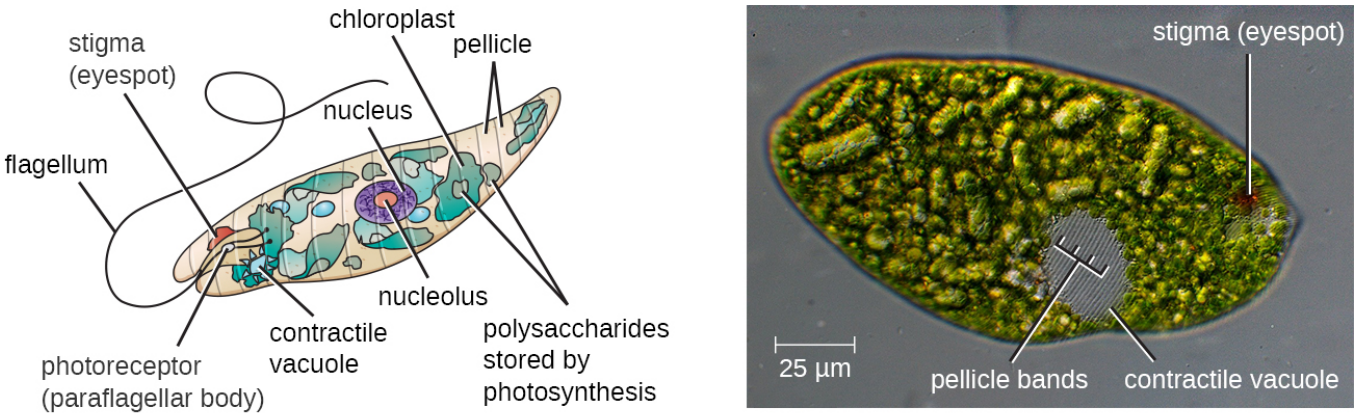


Figure 2.2.1.16: (a) This illustration of a *Euglena* shows the characteristic structures, such as the stigma and flagellum. (b) The pellicle, under the cell membrane, gives the cell its distinctive shape and is visible in this image as delicate parallel striations over the surface of the entire cell (especially visible over the grey contractile vacuole). (credit a: modification of work by Claudio Miklos; credit b: modification of work by David Shykind)

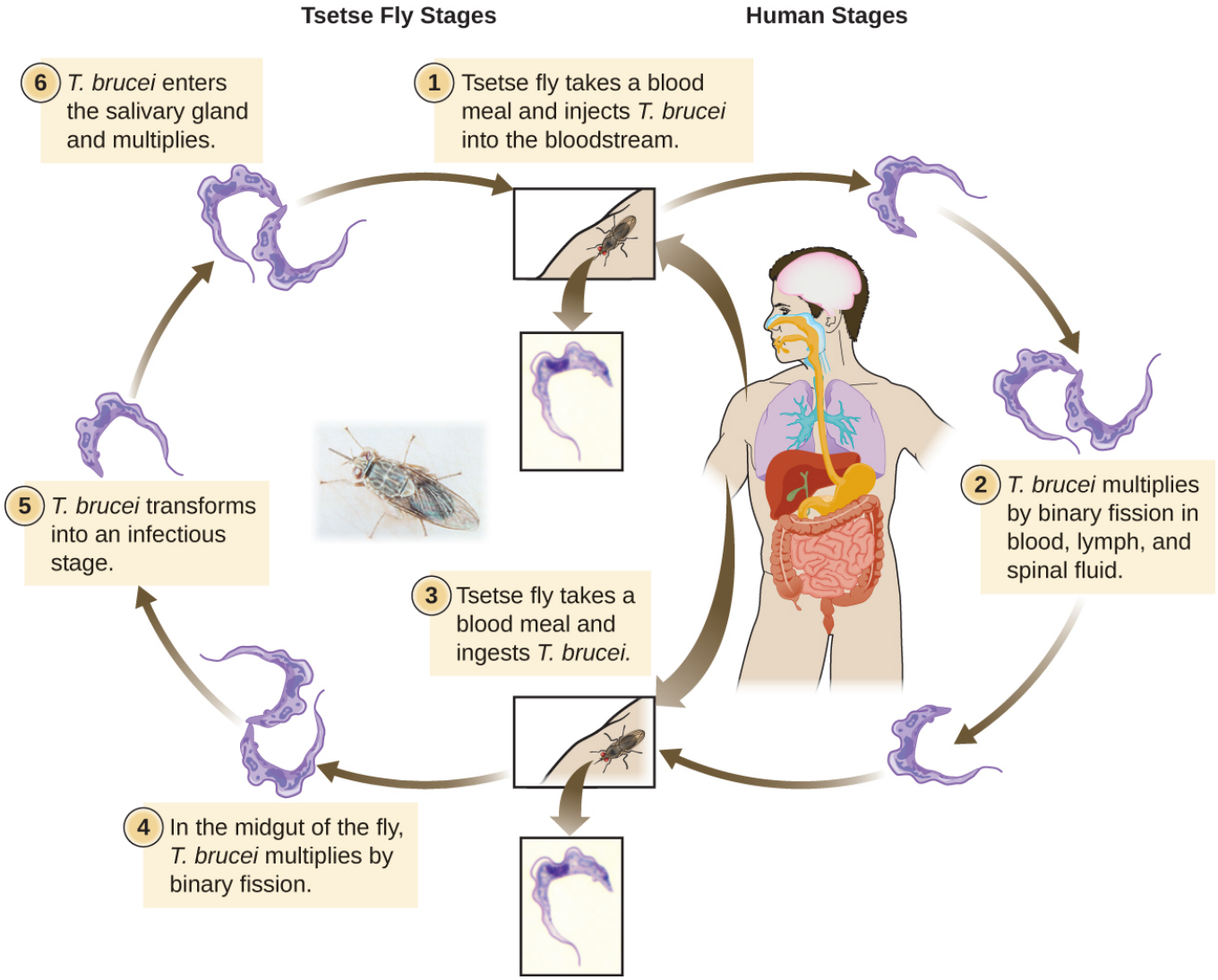


Figure 2.2.1.17: Trypanosoma brucei, the causative agent of African trypanosomiasis, spends part of its life cycle in the tsetse fly and part in humans. (credit "illustration": modification of work by Centers for Disease Control and Prevention; credit "photo": DPDx/Centers for Disease Control and Prevention)

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Chagas' disease originated and is most common in Latin America. The disease is transmitted by *Triatoma* spp., insects often called "kissing bugs," and affects either the heart tissue or tissues of the digestive system. Untreated cases can eventually lead to heart failure or significant digestive or neurological disorders.

The genus *Leishmania* includes trypanosomes that cause disfiguring skin disease and sometimes systemic illness as well.

Neglected Parasites

The Centers for Disease Control and Prevention (CDC) is responsible for identifying public health priorities in the United States and developing strategies to address areas of concern. As part of this mandate, the CDC has officially identified five parasitic diseases it considers to have been neglected (i.e., not adequately studied). These neglected parasitic infections (NPIs) include toxoplasmosis, Chagas disease, toxocariasis (a nematode infection transmitted primarily by infected dogs), cysticercosis (a disease caused by a tissue infection of the tapeworm *Taenia solium*), and trichomoniasis (a sexually transmitted disease caused by the parabasalid *Trichomonas vaginalis*).

The decision to name these specific diseases as NPIs means that the CDC will devote resources toward improving awareness and developing better diagnostic testing and treatment through studies of available data. The CDC may also advise on treatment of these diseases and assist in the distribution of medications that might otherwise be difficult to obtain.3

Of course, the CDC does not have unlimited resources, so by prioritizing these five diseases, it is effectively deprioritizing others. Given that many Americans have never heard of many of these NPIs, it is fair to ask what criteria the CDC used in prioritizing diseases. According to the CDC, the factors considered were the number of people infected, the severity of the illness, and whether the illness can be treated or prevented. Although several of these NPIs may seem to be more common outside the United States, the CDC argues that many cases in the United States likely go undiagnosed and untreated because so little is known about these diseases.4

What criteria should be considered when prioritizing diseases for purposes of funding or research? Are those identified by the CDC reasonable? What other factors could be considered? Should government agencies like the CDC have the same criteria as private pharmaceutical research labs? What are the ethical implications of deprioritizing other potentially neglected parasitic diseases such as leishmaniasis?

Key Concepts and Summary

- **Protists** are a diverse, **polyphyletic** group of eukaryotic organisms.
- Protists may be unicellular or multicellular. They vary in how they get their nutrition, morphology, method of locomotion, and mode of reproduction.
- Important structures of protists include **contractile vacuoles**, cilia, flagella, **pellicles**, and pseudopodia; some lack organelles such as mitochondria.
- Taxonomy of protists is changing rapidly as relationships are reassessed using newer techniques.
- The protists include important pathogens and parasites.

Footnotes

1. 1 J. Flegr et al. "Toxoplasmosis—A Global Threat. Correlation of Latent Toxoplasmosis With Specific Disease Burden in a Set of 88 Countries." *PloS ONE* 9 no. 3 (2014):e90203.
2. 2 J. Flegr. "Effects of Toxoplasma on Human Behavior." *Schizophrenia Bull* 33, no. 3 (2007):757–760.
3. 3 Centers for Disease Control and Prevention. "Neglected Parasitic Infections (NPIs) in the United States." http://www.cdc.gov/parasites/npi/. Last updated July 10, 2014.
4. 4 Centers for Disease Control and Prevention. "Fact Sheet: Neglected Parasitic Infections in the United States." www.cdc.gov/parasites/resourc..._factsheet.pdf

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2.2.2: Parasitic Helminths

Learning Objectives

- Explain why we include the study of parasitic worms within the discipline of microbiology
- Compare the basic morphology of the major groups of parasitic helminthes
- Describe the characteristics of parasitic nematodes, and give an example of infective eggs and infective larvae
- Describe the characteristics of parasitic trematodes and cestodes, and give examples of each
- Identify examples of the primary causes of infections due to nematodes, trematodes, and cestodes
- Classify parasitic worms according to major groups

Parasitic helminths are animals that are often included within the study of microbiology because many species of these worms are identified by their microscopic eggs and larvae. There are two major groups of parasitic helminths: the roundworms (Nematoda) and flatworms (Platyhelminthes). Of the many species that exist in these groups, about half are parasitic and some are important human pathogens. As animals, they are multicellular and have organ systems. However, the parasitic species often have limited digestive tracts, nervous systems, and locomotor abilities. Parasitic forms may have complex reproductive cycles with several different life stages and more than one type of host. Some are monoecious, having both male and female reproductive organs in a single individual, while others are dioecious, each having either male or female reproductive organs.

Nematoda (Roundworms)

Phylum Nematoda (the roundworms) is a diverse group containing more than 15,000 species, of which several are important human parasites (Figure 2.2.2.1). These unsegmented worms have a full digestive system even when parasitic. Some are common intestinal parasites, and their eggs can sometimes be identified in feces or around the anus of infected individuals. *Ascaris lumbricoides* is the largest nematode intestinal parasite found in humans; females may reach lengths greater than 1 meter. *A. lumbricoides* is also very widespread, even in developed nations, although it is now a relatively uncommon problem in the United States. It may cause symptoms ranging from relatively mild (such as a cough and mild abdominal pain) to severe (such as intestinal blockage and impaired growth).

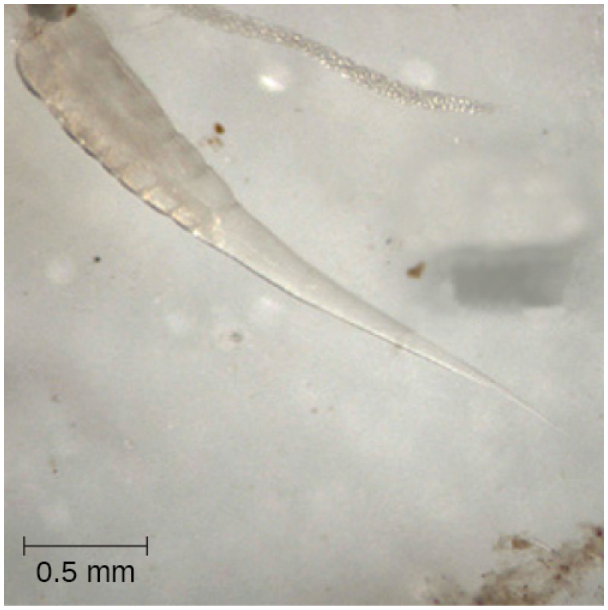


Figure 2.2.2.1: A micrograph of the nematode *Enterobius vermicularis*, also known as the pinworm. (credit: modification of work by Centers for Disease Control and Prevention)

Of all nematode infections in the United States, pinworm (caused by *Enterobius vermicularis*) is the most common. Pinworm causes sleeplessness and itching around the anus, where the female worms lay their eggs during the night. *Toxocara canis* and *T. cati* are nematodes found in dogs and cats, respectively, that can be transmitted to humans, causing toxocariasis. Antibodies to these parasites have been found in approximately 13.9% of the U.S. population, suggesting that exposure is common.[1] Infection can

cause larval migrans, which can result in vision loss and eye inflammation, or fever, fatigue, coughing, and abdominal pain, depending on whether the organism infects the eye or the viscera. Another common nematode infection is hookworm, which is caused by *Necator americanus* (the New World or North American hookworm) and *Ancylostoma duodenale* (the Old World hookworm). Symptoms of hookworm infection can include abdominal pain, diarrhea, loss of appetite, weight loss, fatigue, and anemia.

Trichinellosis, also called trichinosis, caused by *Trichinella spiralis*, is contracted by consuming undercooked meat, which releases the larvae and allows them to encyst in muscles. Infection can cause fever, muscle pains, and digestive system problems; severe infections can lead to lack of coordination, breathing and heart problems, and even death. Finally, heartworm in dogs and other animals is caused by the nematode *Dirofilaria immitis*, which is transmitted by mosquitoes. Symptoms include fatigue and cough; when left untreated, death may result.

Clinical Focus: Part 2

The physician explains to Sarah's mother that ringworm can be transferred between people through touch. "It's common in school children, because they often come in close contact with each other, but anyone can become infected," he adds. "Because you can transfer it through objects, locker rooms and public pools are also a potential source of infection. It's very common among wrestlers and athletes in other contact sports."

Looking very uncomfortable, Sarah says to her mother "I want this worm out of me."

The doctor laughs and says, "Sarah, you're in luck because ringworm is just a name; it is not an actual worm. You have nothing wriggling around under your skin."

"Then what is it?" asks Sarah.

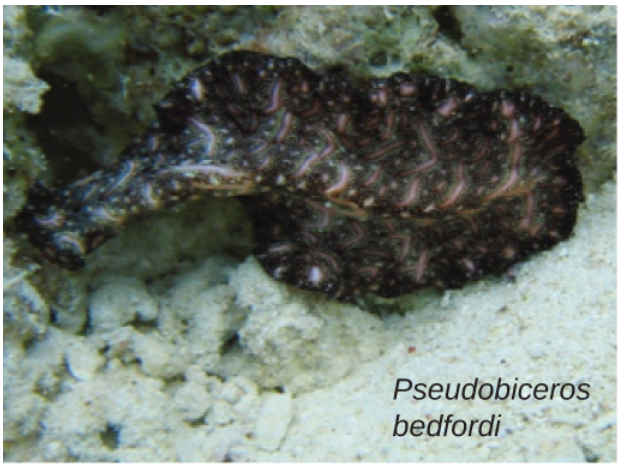
Exercise 2.2.2.1

1. What type of pathogen causes ringworm?
2. What is the most common nematode infection in the United States?

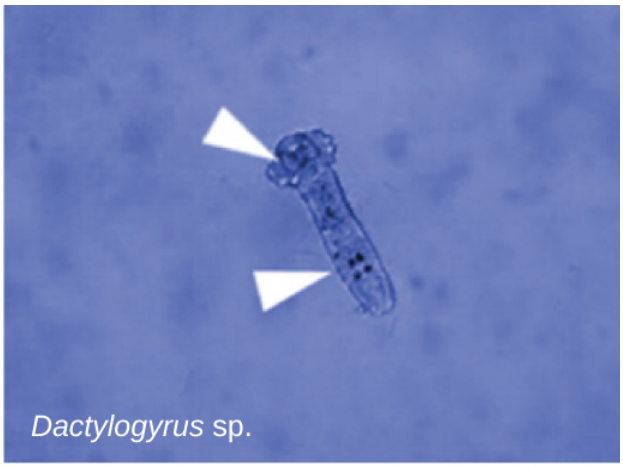
Platyhelminths (Flatworms)

Phylum Platyhelminthes (the platyhelminths) are flatworms. This group includes the flukes, tapeworms, and the turbellarians, which include planarians. The flukes and tapeworms are medically important parasites (Figure 2.2.2.2).

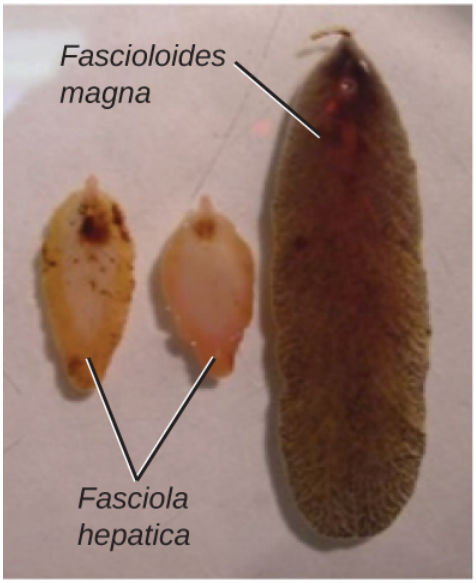
The flukes (trematodes) are nonsegmented flatworms that have an oral sucker (Figure 2.2.2.3) (and sometimes a second ventral sucker) and attach to the inner walls of intestines, lungs, large blood vessels, or the liver. Trematodes have complex life cycles, often with multiple hosts. Several important examples are the liver flukes (*Clonorchis* and *Opisthorchis*), the intestinal fluke (*Fasciolopsis buski*), and the oriental lung fluke (*Paragonimus westermani*). Schistosomiasis is a serious parasitic disease, considered second in the scale of its impact on human populations only to malaria. The parasites *Schistosoma mansoni*, *S. haematobium*, and *S. japonicum*, which are found in freshwater snails, are responsible for schistosomiasis (Figure 2.2.2.4). Immature forms burrow through the skin into the blood. They migrate to the lungs, then to the liver and, later, other organs. Symptoms include anemia, malnutrition, fever, abdominal pain, fluid buildup, and sometimes death.



(a) Class Turbellaria



(b) Class Monogenea



(c) Class Trematoda



(d) Class Cestoda

Figure 2.2.2.2: Phylum Platyhelminthes is divided into four classes. (a) Class Turbellaria includes the Bedford's flatworm (*Pseudobiceros bedfordi*), which is about 8–10 cm long. (b) The parasitic class Monogenea includes *Dactylogyrus* spp. Worms in this genus are commonly called gill flukes. The specimen pictured here is about 0.2 mm long and has two anchors, indicated by arrows, that it uses to latch onto the gills of host fish. (c) The Trematoda class includes the common liver fluke *Fasciola hepatica* and the giant liver fluke *Fascioloides magna* (right). The *F. magna* specimen shown here is about 7 cm long. (d) Class Cestoda includes tapeworms such as *Taenia saginata*, which infects both cattle and humans and can reach lengths of 4–10 meters; the specimen shown here is about 4 meters long. (credit c: modification of work by "Flukeman"/Wikimedia Commons)

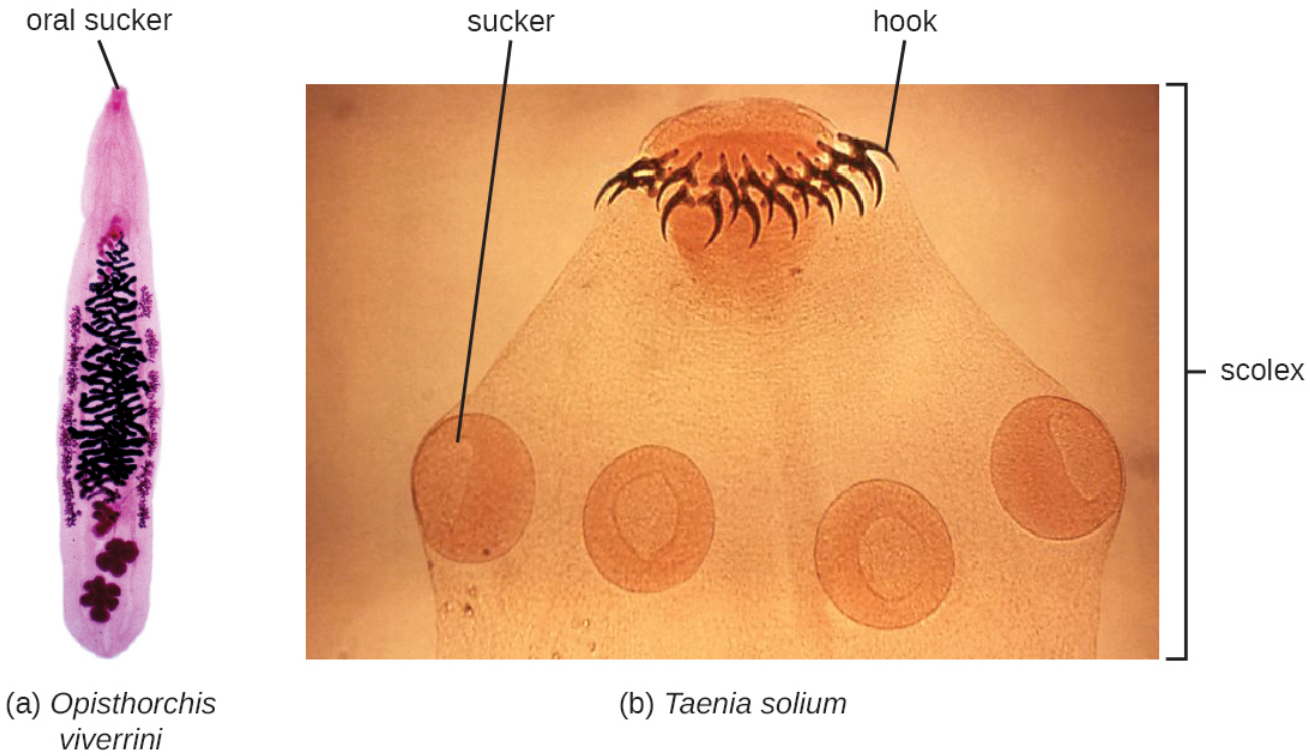


Figure 2.2.2.3: (a) The oral sucker is visible on the anterior end of this liver fluke, *Opisthorchis viverrini*. (b) This micrograph shows the scolex of the cestode *Taenia solium*, also known as the pork tapeworm. The visible suckers and hooks allow the worm to attach itself to the inner wall of the intestine. (credit a: modification of work by Sripa B, Kaewkes S, Sithithaworn P, Mairiang E, Laha T, and Smout M; credit b: modification of work by Centers for Disease Control and Prevention)

The other medically important group of platyhelminths are commonly known as tapeworms (cestodes) and are segmented flatworms that may have suckers or hooks at the scolex (head region) (Figure 2.2.2.3). Tapeworms use these suckers or hooks to attach to the wall of the small intestine. The body of the worm is made up of segments called proglottids that contain reproductive structures; these detach when the gametes are fertilized, releasing gravid proglottids with eggs. Tapeworms often have an intermediate host that consumes the eggs, which then hatch into a larval form called an oncosphere. The oncosphere migrates to a particular tissue or organ in the intermediate host, where it forms cysticerci. After being eaten by the definitive host, the cysticerci develop into adult tapeworms in the host's digestive system (Figure 2.2.2.5). *Taenia saginata* (the beef tapeworm) and *T. solium* (the pork tapeworm) enter humans through ingestion of undercooked, contaminated meat. The adult worms develop and reside in the intestine, but the larval stage may migrate and be found in other body locations such as skeletal and smooth muscle. The beef tapeworm is relatively benign, although it can cause digestive problems and, occasionally, allergic reactions. The pork tapeworm can cause more serious problems when the larvae leave the intestine and colonize other tissues, including those of the central nervous system. *Diphylobothrium latum* is the largest human tapeworm and can be ingested in undercooked fish. It can grow to a length of 15 meters. *Echinococcus granulosus*, the dog tapeworm, can parasitize humans and uses dogs as an important host.

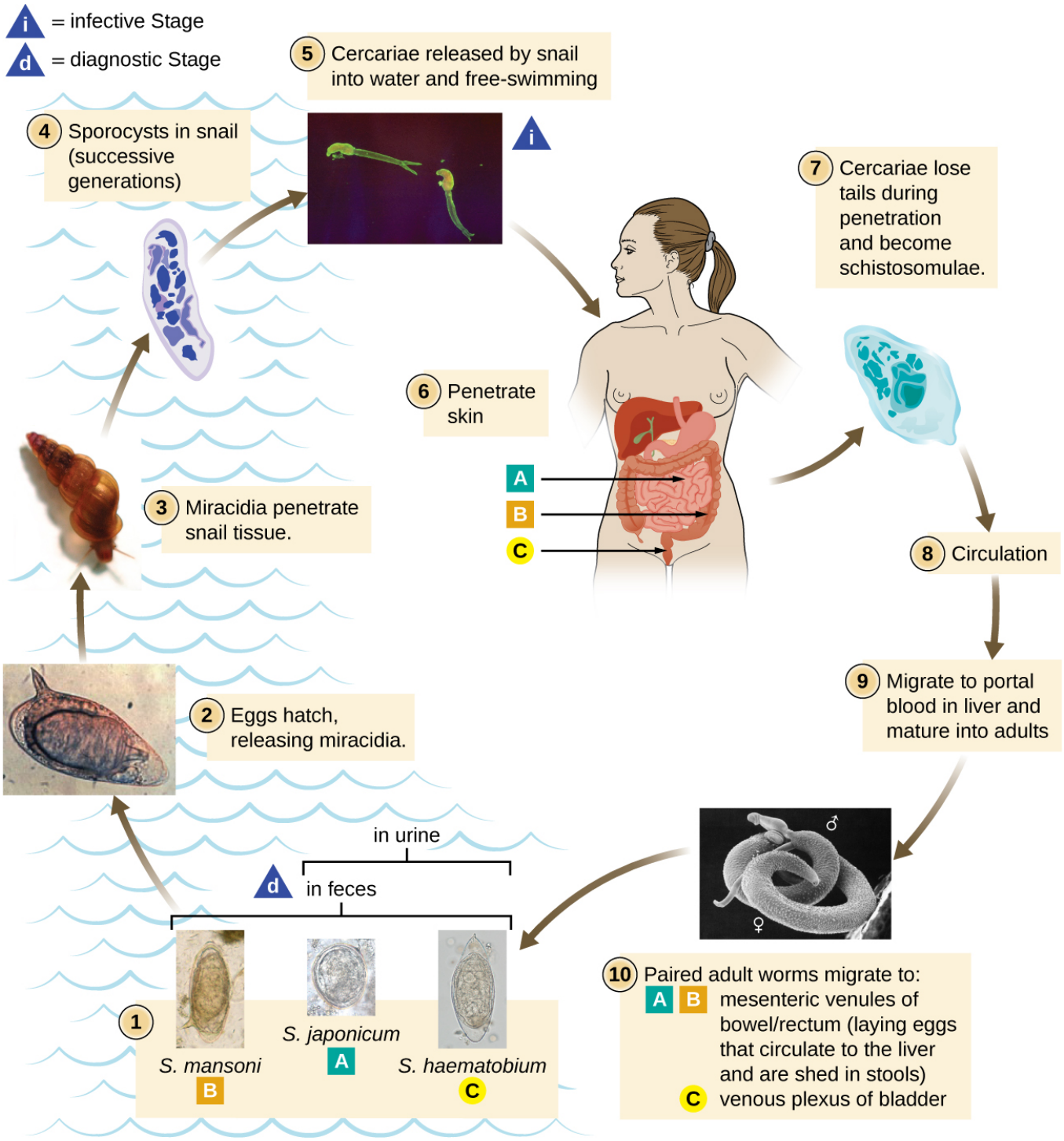


Figure 2.2.2.4: The life cycle of *Schistosoma* spp. includes several species of water snails, which serve as secondary hosts. The parasite is transmitted to humans through contact with contaminated water and takes up residence in the veins of the digestive system. Eggs escape the host in the urine or feces and infect a snail to complete the life cycle. (credit "illustration": modification of work by Centers for Disease Control and Prevention; credit "step 3 photo": modification of work by Fred A. Lewis, Yung-san Liang, Nithya Raghavan & Matty Knight)

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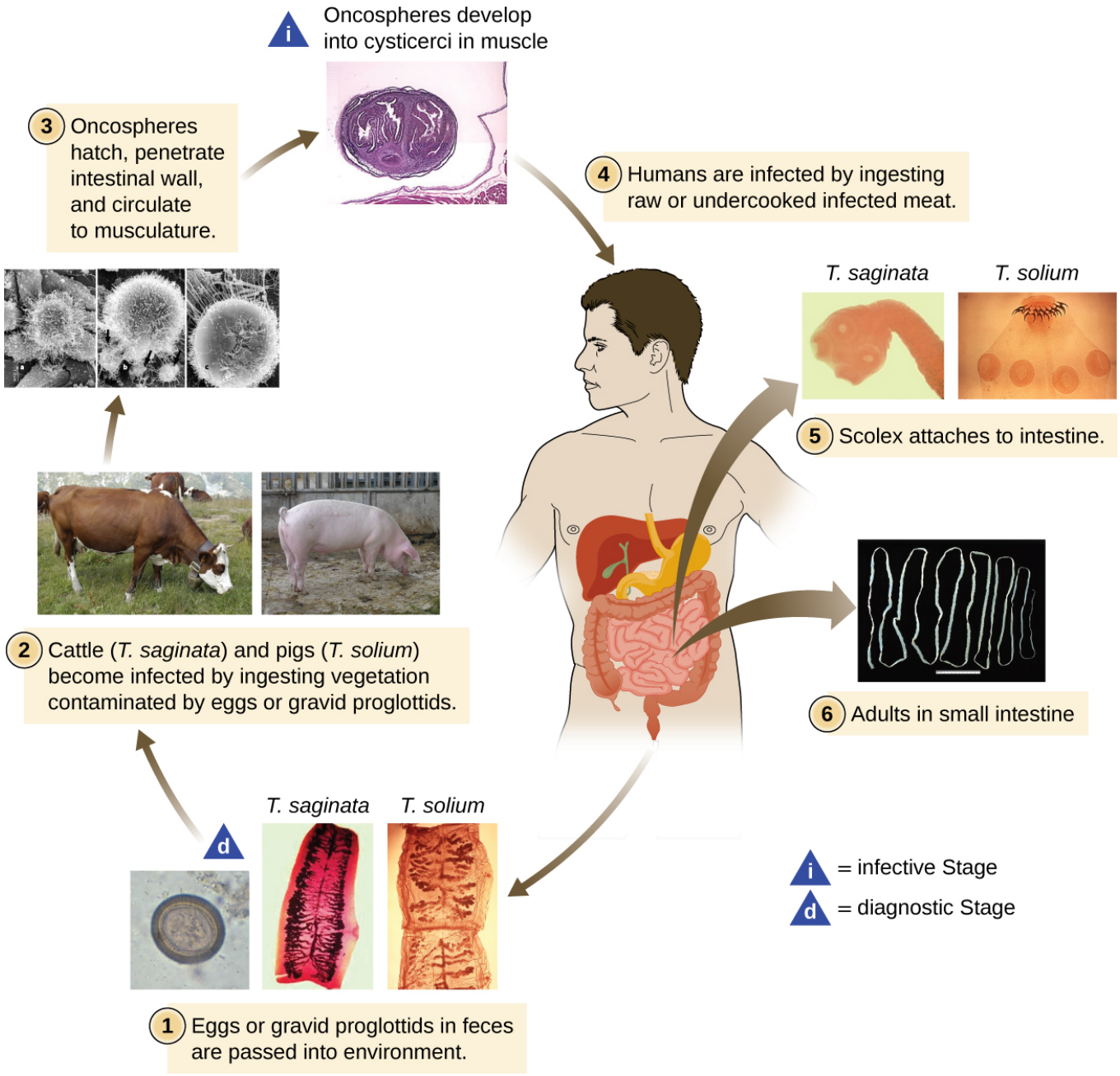


Figure 2.2.2.5: Life cycle of a tapeworm. (credit "illustration": modification of work by Centers for Disease Control and Prevention; credit "step 3 micrographs": modification of work by American Society for Microbiology)

? Exercise 2.2.2.2

What group of medically important flatworms is segmented and what group is unsegmented?

Food for Worms?

For residents of temperate, developed countries, it may be difficult to imagine just how common helminth infections are in the human population. In fact, they are quite common and even occur frequently in the United States. Worldwide, approximately 807–1,221 million people are infected with *Ascaris lumbricoides* (perhaps one-sixth of the human population) and far more are infected if all nematode species are considered.[2] Rates of infection are relatively high even in industrialized nations. Approximately 604–795 million people are infected with whipworm (*Trichuris*) worldwide (*Trichuris* can also

infect dogs), and 576–740 million people are infected with hookworm (*Necator americanus* and *Ancylostoma duodenale*).[3] *Toxocara,* a nematode parasite of dogs and cats, is also able to infect humans. It is widespread in the United States, with about 10,000 symptomatic cases annually. However, one study found 14% of the population (more than 40 million Americans) was seropositive, meaning they had been exposed to the parasite at one time. More than 200 million people have schistosomiasis worldwide. Most of the World Health Organization (WHO) neglected tropical diseases are helminths. In some cases, helminths may cause subclinical illnesses, meaning the symptoms are so mild that that they go unnoticed. In other cases, the effects may be more severe or chronic, leading to fluid accumulation and organ damage. With so many people affected, these parasites constitute a major global public health concern.

Eradicating the Guinea Worm

Dracunculiasis, or Guinea worm disease, is caused by a nematode called *Dracunculus medinensis*. When people consume contaminated water, water fleas (small crustaceans) containing the nematode larvae may be ingested. These larvae migrate out of the intestine, mate, and move through the body until females eventually emerge (generally through the feet). While Guinea worm disease is rarely fatal, it is extremely painful and can be accompanied by secondary infections and edema (Figure 2.2.2.6).



Figure 2.2.2.6: The Guinea worm can be removed from a leg vein of an infected person by gradually winding it around a stick, like this matchstick. (credit: Centers for Disease Control and Prevention)

An eradication campaign led by WHO, the CDC, the United Nations Children's Fund (UNICEF), and the Carter Center (founded by former U.S. president Jimmy Carter) has been extremely successful in reducing cases of dracunculiasis. This has been possible because diagnosis is straightforward, there is an inexpensive method of control, there is no animal reservoir, the water fleas are not airborne (they are restricted to still water), the disease is geographically limited, and there has been a commitment from the governments involved. Additionally, no vaccines or medication are required for treatment and prevention. In 1986, 3.5 million people were estimated to be affected. After the eradication campaign, which included helping people in affected areas learn to filter water with cloth, only four countries continue to report the disease (Chad, Mali, South Sudan, and Ethiopia) with a total of 126 cases reported to WHO in 2014.

Key Concepts and Summary

- Helminth parasites are included within the study of microbiology because they are often identified by looking for microscopic eggs and larvae.
- The two major groups of helminth parasites are the roundworms (Nematoda) and the flatworms (Platyhelminthes).
- Nematodes are common intestinal parasites often transmitted through undercooked foods, although they are also found in other environments.
- Platyhelminths include **tapeworms** and **flukes**, which are often transmitted through undercooked meat.

Footnotes

1. 1 Won K, Kruszon-Moran D, Schantz P, Jones J. "National seroprevalence and risk factors for zoonotic Toxocara spp. infection." In: Abstracts of the 56th American Society of Tropical Medicine and Hygiene; Philadelphia, Pennsylvania; 2007

Nov 4-8.
2. 2 Fenwick, A. “The global burden of neglected tropical diseases.” *Public health* 126 no.3 (Mar 2012): 233–6.
3. 3 de Silva, N., et. al. (2003). “Soil-transmitted helminth infections: updating the global picture”. *Trends in Parasitology* 19 (December 2003): 547–51.
4. 4 World Health Organization. “South Sudan Reports Zero Cases of Guinea-Worm Disease for Seventh Consecutive Month.” 2016. http://www.who.int/dracunculiasis/no...ive_months/en/. Accessed May 2, 2016.

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2.2.3: Fungi

Learning Objectives

- Explain why the study of fungi such as yeast and molds is within the discipline of microbiology
- Describe the unique characteristics of fungi
- Describe examples of asexual and sexual reproduction of fungi
- Compare the major groups of fungi in this chapter, and give examples of each
- Identify examples of the primary causes of infections due to yeasts and molds
- Identify examples of toxin-producing fungi
- Classify fungal organisms according to major groups

The fungi comprise a diverse group of organisms that are heterotrophic and typically saprozoic. In addition to the well-known macroscopic fungi (such as mushrooms and molds), many unicellular yeasts and spores of macroscopic fungi are microscopic. For this reason, fungi are included within the field of microbiology.

Fungi are important to humans in a variety of ways. Both microscopic and macroscopic fungi have medical relevance, with some pathogenic species that can cause mycoses (illnesses caused by fungi). Some pathogenic fungi are opportunistic, meaning that they mainly cause infections when the host's immune defenses are compromised and do not normally cause illness in healthy individuals. Fungi are important in other ways. They act as decomposers in the environment, and they are critical for the production of certain foods such as cheeses. Fungi are also major sources of antibiotics, such as penicillin from the fungus *Penicillium*.

Characteristics of Fungi

Fungi have well-defined characteristics that set them apart from other organisms. Most multicellular fungal bodies, commonly called molds, are made up of filaments called hyphae. Hyphae can form a tangled network called a mycelium and form the thallus (body) of fleshy fungi. Hyphae that have walls between the cells are called septate hyphae; hyphae that lack walls and cell membranes between the cells are called nonseptate or coenocytic hyphae). (Figure 2.2.3.1).

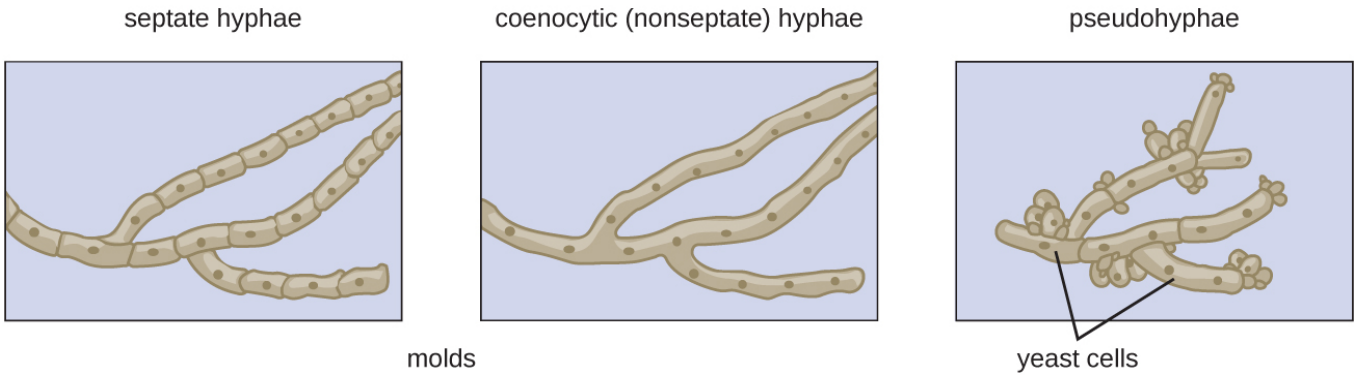


Figure 2.2.3.1: Multicellular fungi (molds) form hyphae, which may be septate or nonseptate. Unicellular fungi (yeasts) cells form pseudohyphae from individual yeast cells.

In contrast to molds, yeasts are unicellular fungi. The budding yeasts reproduce asexually by budding off a smaller daughter cell; the resulting cells may sometimes stick together as a short chain or pseudohypha (Figure 2.2.3.1). *Candida albicans* is a common yeast that forms pseudohyphae; it is associated with various infections in humans, including vaginal yeast infections, oral thrush, and candidiasis of the skin.

Some fungi are dimorphic, having more than one appearance during their life cycle. These dimorphic fungi may be able to appear as yeasts or molds, which can be important for infectivity. They are capable of changing their appearance in response to environmental changes such as nutrient availability or fluctuations in temperature, growing as a mold, for example, at 25 °C (77 °F), and as yeast cells at 37 °C (98.6 °F). This ability helps dimorphic fungi to survive in diverse environments. *Histoplasma capsulatum*, the pathogen that causes histoplasmosis, a lung infection, is an example of a dimorphic fungus (Figure 2.2.3.2).

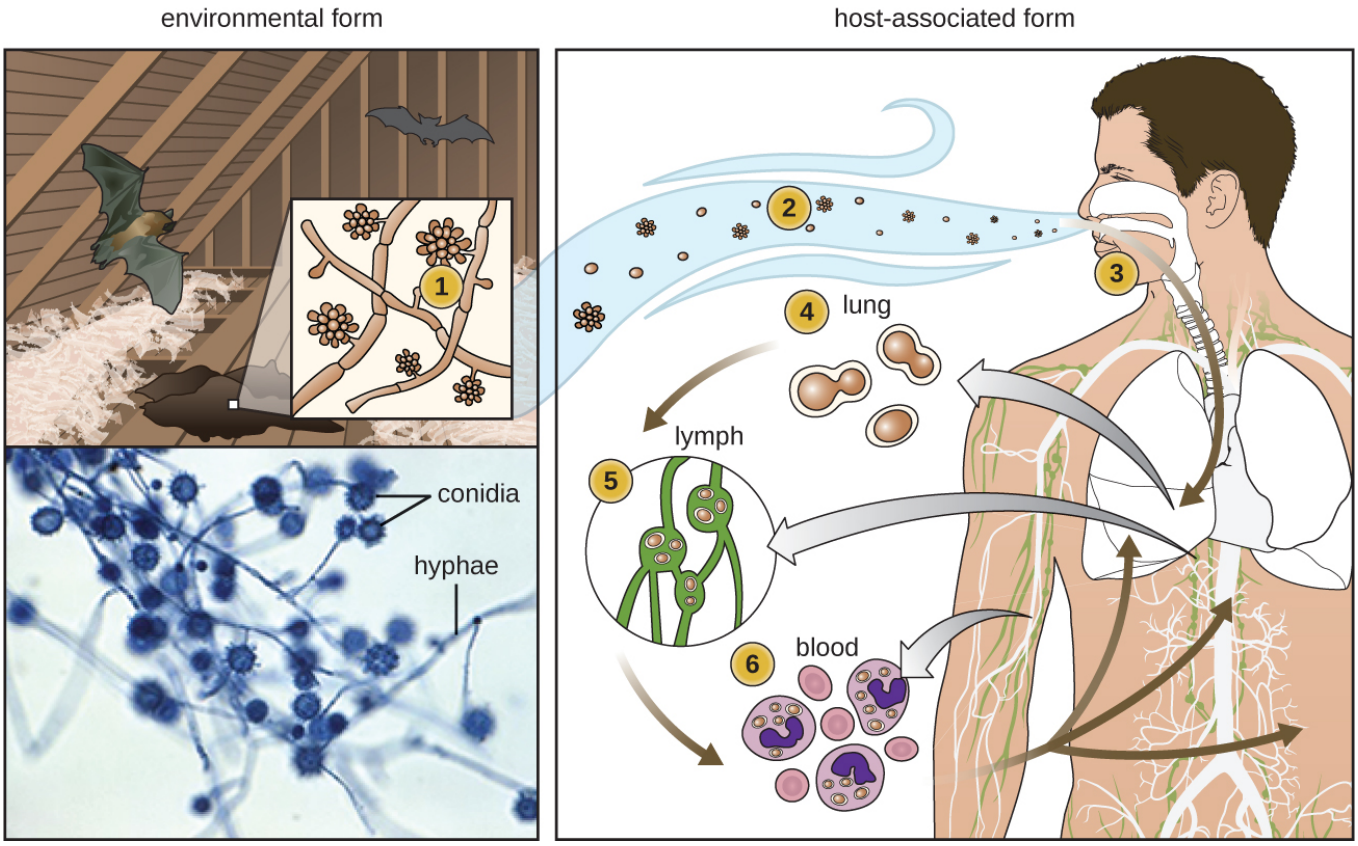


Figure 2.2.3.2: Histoplasma capsulatum is a dimorphic fungus that grows in soil exposed to bird feces or bat feces (guano) (top left). It can change forms to survive at different temperatures. In the outdoors, it typically grows as a mycelium (as shown in the micrograph, bottom left), but when the spores are inhaled (right), it responds to the high internal temperature of the body (37 °C [98.6 °F]) by turning into a yeast that can multiply in the lungs, causing the chronic lung disease histoplasmosis. (credit: modification of work by Centers for Disease Control and Prevention)

There are notable unique features in fungal cell walls and membranes. Fungal cell walls contain chitin, as opposed to the cellulose found in the cell walls of plants and many protists. Additionally, whereas animals have cholesterol in their cell membranes, fungal cell membranes have different sterols called ergosterols. Ergosterols are often exploited as targets for antifungal drugs.

Fungal life cycles are unique and complex. Fungi reproduce sexually either through cross- or self-fertilization. Haploid fungi form hyphae that have gametes at the tips. Two different mating types (represented as "+ type" and "– type") are involved. The cytoplasms of the + and – type gametes fuse (in an event called plasmogamy), producing a cell with two distinct nuclei (a dikaryotic cell). Later, the nuclei fuse (in an event called karyogamy) to create a diploid zygote. The zygote undergoes meiosis to form spores that germinate to start the haploid stage, which eventually creates more haploid mycelia (Figure 2.2.3.3). Depending on the taxonomic group, these sexually produced spores are known as zygospores (in Zygomycota), ascospores (in Ascomycota), or basidiospores (in Basidiomycota) (Figure 2.2.3.4).

Fungi may also exhibit asexual reproduction by mitosis, mitosis with budding, fragmentation of hyphae, and formation of asexual spores by mitosis. These spores are specialized cells that, depending on the organism, may have unique characteristics for survival, reproduction, and dispersal. Fungi exhibit several types of asexual spores and these can be important in classification.

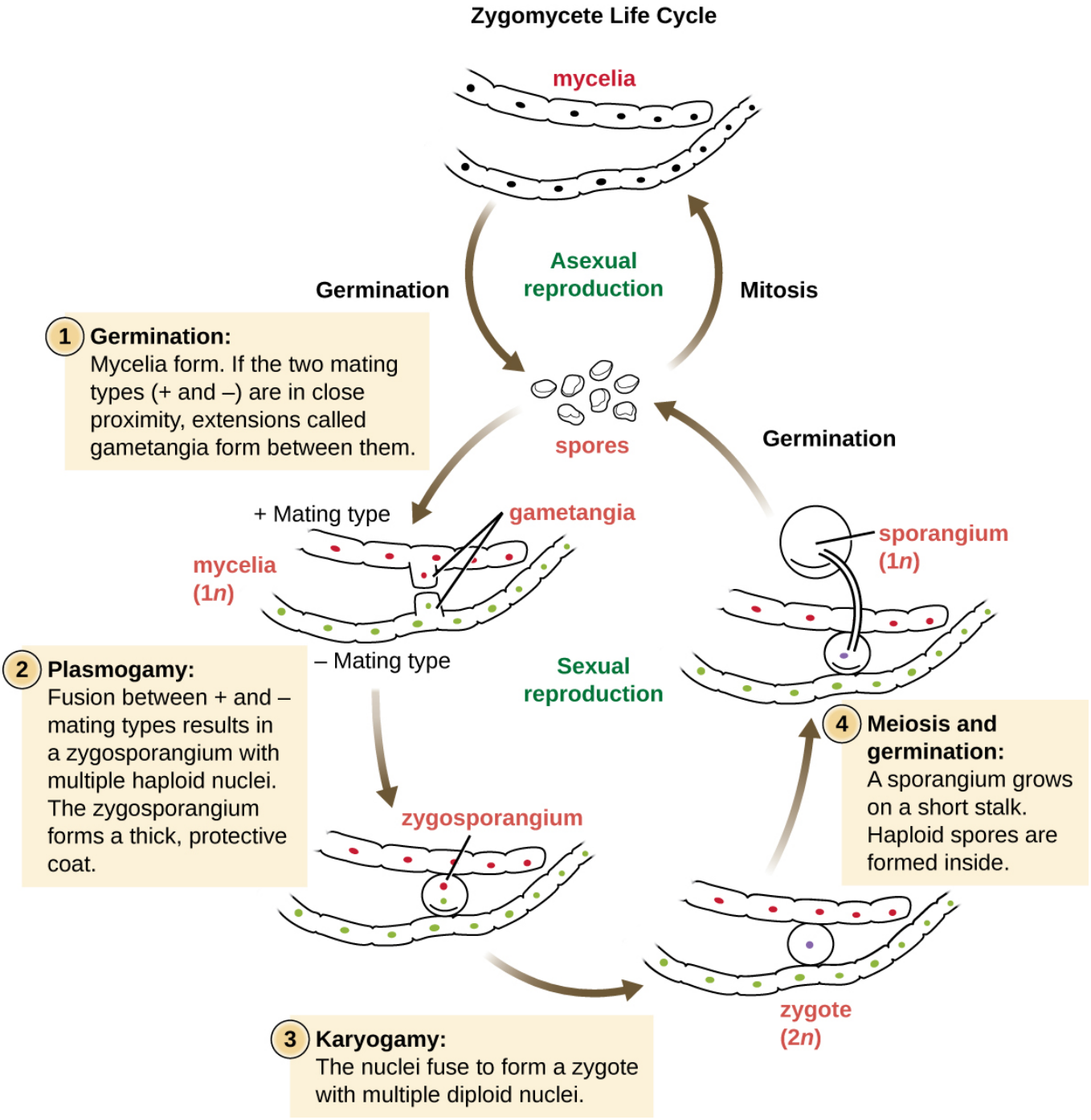


Figure 2.2.3.3: Zygomycetes have sexual and asexual life cycles. In the sexual life cycle, + and – mating types conjugate to form a zygosporangium.



Figure 2.2.3.4: These images show asexually produced spores. (a) This brightfield micrograph shows the release of spores from a sporangium at the end of a hypha called a sporangiophore. The organism is a *Mucor* sp. fungus, a mold often found indoors. (b) Sporangia grow at the ends of stalks, which appear as the white fuzz seen on this bread mold, *Rhizopus stolonifer*. The tips of bread mold are the dark, spore-containing sporangia. (credit a: modification of work by Centers for Disease Control and Prevention; credit b right: modification of work by "Andrew"/Flickr)

? Exercise 2.2.3.1

Is a dimorphic fungus a yeast or a mold? Explain.

Fungal Diversity

The fungi are very diverse, comprising seven major groups. Not all of the seven groups contain pathogens. Some of these groups are generally associated with plants and include plant pathogens. For example, Urediniomycetes and Ustilagomycetes include the plant rusts and smuts, respectively. These form reddish or dark masses, respectively, on plants as rusts (red) or smuts (dark). Some species have substantial economic impact because of their ability to reduce crop yields. Glomeromycota includes the mycorrhizal fungi, important symbionts with plant roots that can promote plant growth by acting like an extended root system. The Glomeromycota are obligate symbionts, meaning that they can only survive when associated with plant roots; the fungi receive carbohydrates from the plant and the plant benefits from the increased ability to take up nutrients and minerals from the soil. The Chytridiomycetes (chytrids) are small fungi, but are extremely ecologically important. Chytrids are generally aquatic and have flagellated, motile gametes; specific types are implicated in amphibian declines around the world. Because of their medical importance, we will focus on Zygomycota, Ascomycota, Basidiomycota, and Microsporidia. Figure 2.2.3.9 summarizes the characteristics of these medically important groups of fungi.

The Zygomycota (zygomycetes) are mainly saprophytes with coenocytic hyphae and haploid nuclei. They use sporangiospores for asexual reproduction. The group name comes from the zygospores that they use for sexual reproduction (Figure 2.2.3.3), which have hard walls formed from the fusion of reproductive cells from two individuals. Zygomycetes are important for food science and as crop pathogens. One example is *Rhizopus stolonifer* (Figure 2.2.3.4), an important bread mold that also causes rice seedling blight. *Mucor* is a genus of fungi that can potentially cause necrotizing infections in humans, although most species are intolerant of temperatures found in mammalian bodies (Figure 2.2.3.4).

The Ascomycota include fungi that are used as food (edible mushrooms, morels, and truffles), others that are common causes of food spoilage (bread molds and plant pathogens), and still others that are human pathogens. Ascomycota may have septate hyphae and cup-shaped fruiting bodies called ascocarps. Some genera of Ascomycota use sexually produced ascospores as well as asexual spores called conidia, but sexual phases have not been discovered or described for others. Some produce an ascus containing ascospores within an ascocarp (Figure 2.2.3.5).

Examples of the Ascomycota include several bread molds and minor pathogens, as well as species capable of causing more serious mycoses. Species in the genus *Aspergillus* are important causes of allergy and infection, and are useful in research and in the production of certain fermented alcoholic beverages such as Japanese *sake*. The fungus *Aspergillus flavus*, a contaminant of nuts and stored grains, produces an aflatoxin that is both a toxin and the most potent known natural carcinogen. *Neurospora crassa* is of particular use in genetics research because the spores produced by meiosis are kept inside the ascus in a row that reflects the cell

divisions that produced them, giving a direct view of segregation and assortment of genes (Figure 2.2.3.6). *Penicillium* produces the antibiotic penicillin (Figure 2.2.3.5).

Many species of ascomycetes are medically important. A large number of species in the genera *Trichophyton*, *Microsporum*, and *Epidermophyton* are dermatophytes, pathogenic fungi capable of causing skin infections such as athlete's foot, jock itch, and ringworm. *Blastomyces dermatitidis* is a dimorphic fungus that can cause blastomycosis, a respiratory infection that, if left untreated, can become disseminated to other body sites, sometimes leading to death. Another important respiratory pathogen is the dimorphic fungus *Histoplasma capsulatum* (Figure 2.2.3.2), which is associated with birds and bats in the Ohio and Mississippi river valleys. *Coccidioides immitis* causes the serious lung disease Valley fever. *Candida albicans*, the most common cause of vaginal and other yeast infections, is also an ascomycete fungus; it is a part of the normal microbiota of the skin, intestine, genital tract, and ear (Figure 2.2.3.5). Ascomycetes also cause plant diseases, including ergot infections, Dutch elm disease, and powdery mildews.

Saccharomyces yeasts, including the baker's yeast *S. cerevisiae*, are unicellular ascomycetes with haploid and diploid stages (Figure 2.2.3.7). This and other *Saccharomyces* species are used for brewing beer.

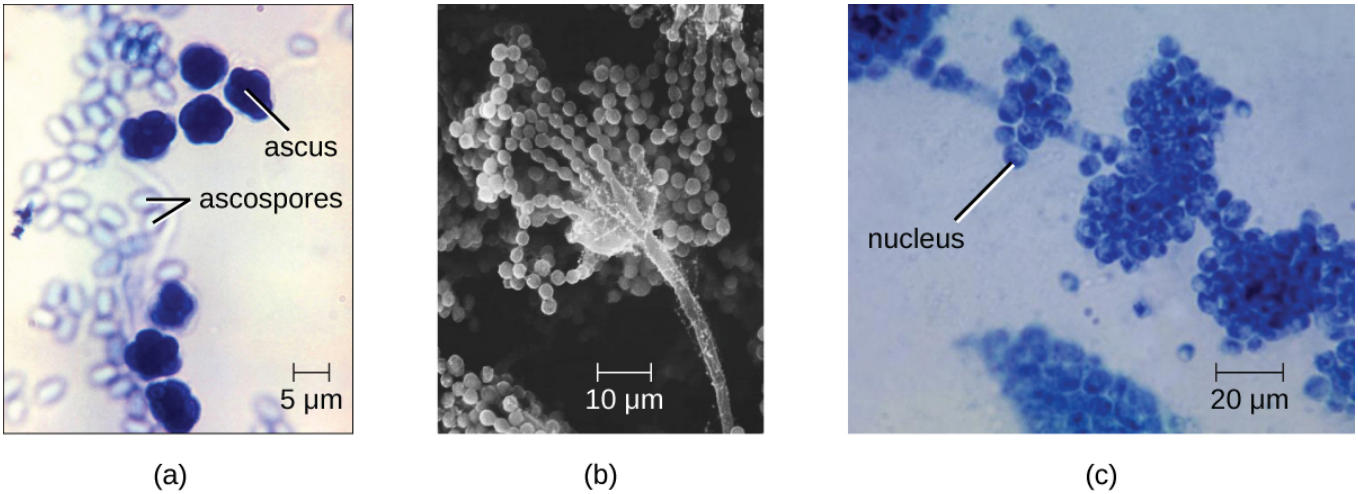


Figure 2.2.3.5: (a) This brightfield micrograph shows ascospores being released from asci in the fungus *Talaromyces flavus* var. *flavus*. (b) This electron micrograph shows the conidia (spores) borne on the conidiophore of *Aspergillus*, a type of toxic fungus found mostly in soil and plants. (c) This brightfield micrograph shows the yeast *Candida albicans*, the causative agent of candidiasis and thrush. (credit a, b, c: modification of work by Centers for Disease Control and Prevention)

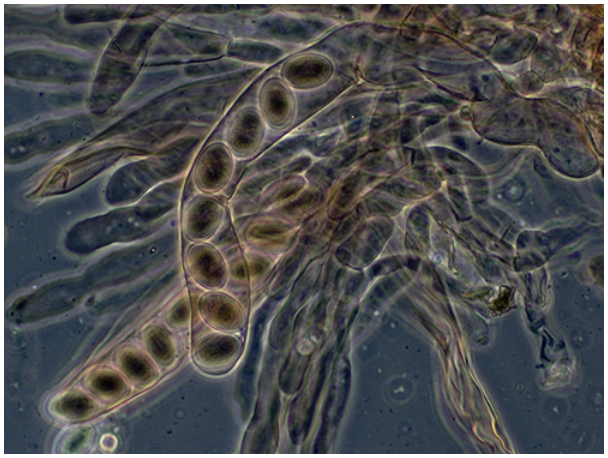


Figure 2.2.3.6: These ascospores, lined up within an ascus, are produced sexually. (credit: Peter G. Werner)

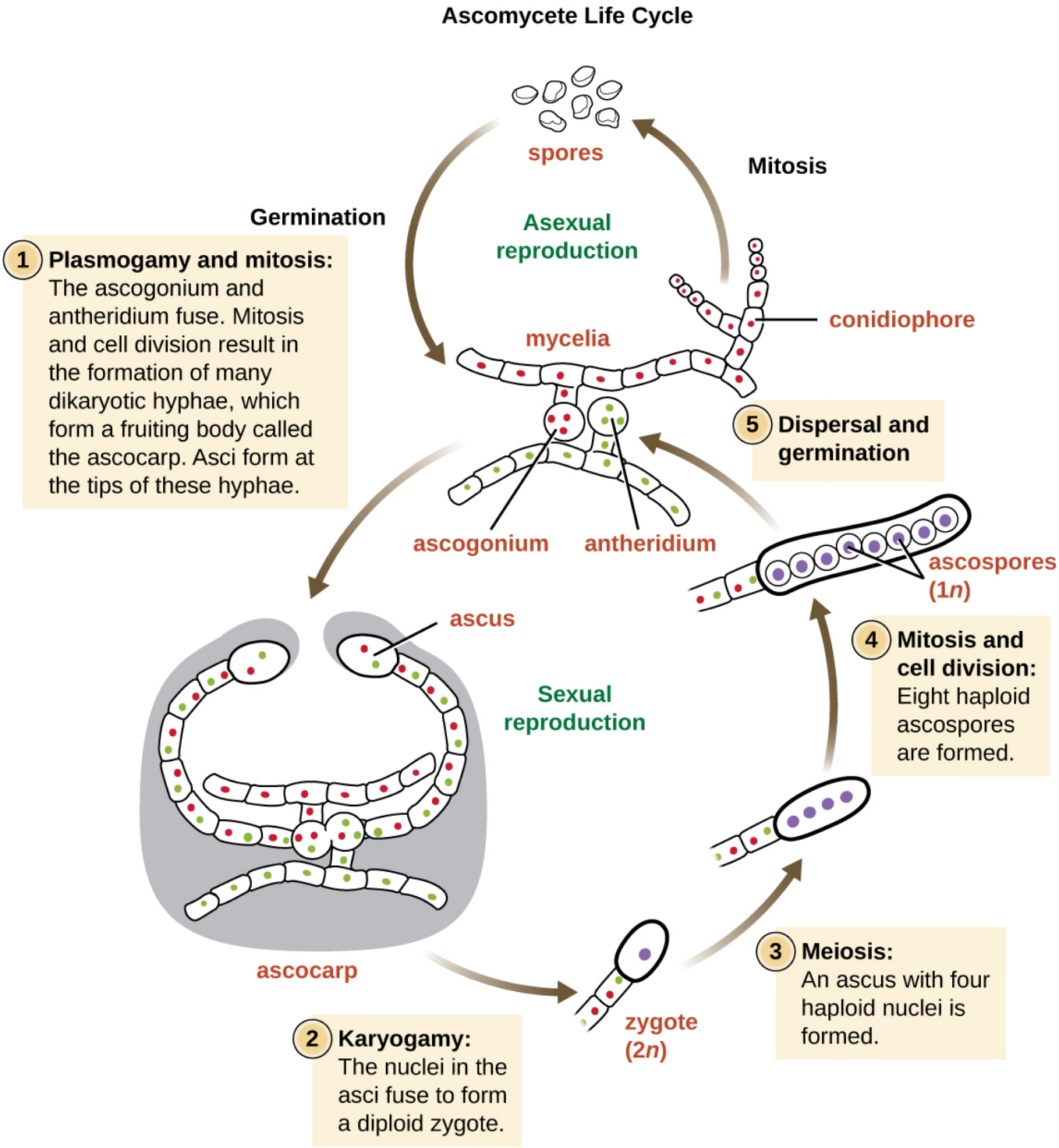


Figure 2.2.3.7: The life cycle of an ascomycete is characterized by the production of asci during the sexual phase. The haploid phase is the predominant phase of the life cycle.

The Basidiomycota (basidiomycetes) are fungi that have basidia (club-shaped structures) that produce basidiospores(spores produced through budding) within fruiting bodies called basidiocarps (Figure 2.2.3.8). They are important as decomposers and as food. This group includes rusts, stinkhorns, puffballs, and mushrooms. Several species are of particular importance. *Cryptococcus neoformans*, a fungus commonly found as a yeast in the environment, can cause serious lung infections when inhaled by individuals with weakened immune systems. The edible meadow mushroom, *Agricus campestris*, is a basidiomycete, as is the poisonous mushroom *Amanita phalloides*, known as the death cap. The deadly toxins produced by *A. phalloides* have been used to study transcription.

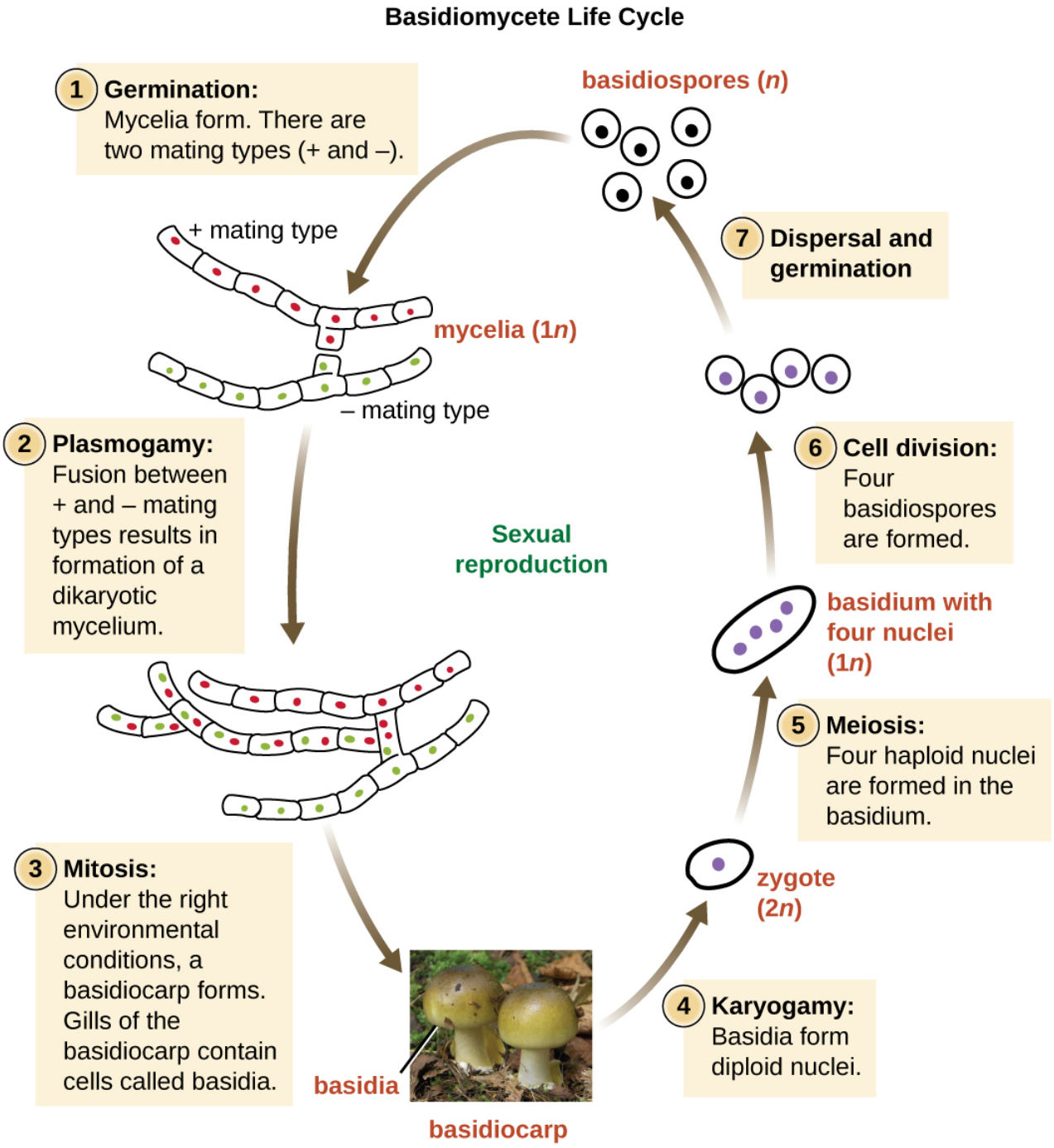
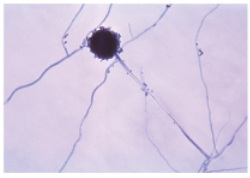
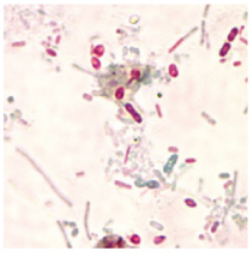
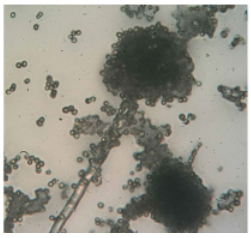


Figure 2.2.3.8: The life cycle of a basidiomycete alternates a haploid generation with a prolonged stage in which two nuclei (dikaryon) are present in the hyphae.

Finally, the Microsporidia are unicellular fungi that are obligate intracellular parasites. They lack mitochondria, peroxisomes, and centrioles, but their spores release a unique polar tubule that pierces the host cell membrane to allow the fungus to gain entry into the cell. A number of microsporidia are human pathogens, and infections with microsporidia are called microsporidiosis. One pathogenic species is *Enterocystozoan bieneusi*, which can cause symptoms such as diarrhea, cholecystitis (inflammation of the gall bladder), and in rare cases, respiratory illness.

Select Groups of Fungi				
Group	**Characteristics**	**Examples**	**Medically Important Species**	**Image**
Ascomycota	Septate hyphae Ascus with ascospores in ascocarp Conidiospores	Cup fungi Edible mushrooms Morels Truffles *Neurospora* *Penicillium*	*Aspergillus* spp. *Trichophyton* spp. *Microsporum* spp. *Epidermophyton* spp. *Blastomyces dermititidis* *Histoplasma capsulatum*	 *Aspergillus niger*
Basidiomycota	Basidia produce basidiospores in a basidiocarp	Club fungi Rusts Stinkhorns Puffballs Mushrooms *Cryptococcus neoformans* *Amanita phalloides*	*Crytococcus neoformans*	 *Amanita phalloides*
Microsporidia	Lack mitochondria, perioxisomes, centrioles Spores produce a polar tube	*Entero-cystozoan bieneusi*	*Enterocystozoan bieneusi*	 Microsporidia (unidentified)
Zygomycota	Mainly saprophytes Coenocytic hyphae Haploid nuclei Zygospores	*Rhizopus stolonifera*	*Mucor* spp.	

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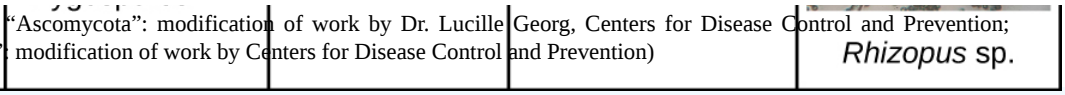


Figure 2.2.3.9: (credit "Ascomycota": modification of work by Dr. Lucille Georg, Centers for Disease Control and Prevention; credit "Microsporidia": modification of work by Centers for Disease Control and Prevention)

? Exercise 2.2.3.2

Which group of fungi appears to be associated with the greatest number of human diseases?

Eukaryotic Pathogens in Eukaryotic Hosts

When we think about antimicrobial medications, antibiotics such as penicillin often come to mind. Penicillin and related antibiotics interfere with the synthesis of peptidoglycan cell walls, which effectively targets bacterial cells. These antibiotics are useful because humans (like all eukaryotes) do not have peptidoglycan cell walls.

Developing medications that are effective against eukaryotic cells but not harmful to human cells is more difficult. Despite huge morphological differences, the cells of humans, fungi, and protists are similar in terms of their ribosomes, cytoskeletons, and cell membranes. As a result, it is more challenging to develop medications that target protozoans and fungi in the same way that antibiotics target prokaryotes.

Fungicides have relatively limited modes of action. Because fungi have ergosterols(instead of cholesterol) in their cell membranes, the different enzymes involved in sterol production can be a target of some medications. The azole and morpholine fungicidesinterfere with the synthesis of membrane sterols. These are used widely in agriculture (fenpropimorph) and clinically (e.g., miconazole). Some antifungal medications target the chitin cell walls of fungi. Despite the success of these compounds in targeting fungi, antifungal medications for systemic infections still tend to have more toxic side effects than antibiotics for bacteria.

Clinical Focus: Part 3

Sarah is relieved the ringworm is not an actual worm, but wants to know what it really is. The physician explains that ringworm is a fungus. He tells her that she will not see mushrooms popping out of her skin, because this fungus is more like the invisible part of a mushroom that hides in the soil. He reassures her that they are going to get the fungus out of her too.

The doctor cleans and then carefully scrapes the lesion to place a specimen on a slide. By looking at it under a microscope, the physician is able to confirm that a fungal infection is responsible for Sarah's lesion. In Figure 2.2.3.10, it is possible to see macro- and microconidia in *Trichophyton rubrum*. Cell walls are also visible. Even if the pathogen resembled a helminth under the microscope, the presence of cell walls would rule out the possibility because animal cells lack cell walls.

The doctor prescribes an antifungal cream for Sarah's mother to apply to the ringworm. Sarah's mother asks, "What should we do if it doesn't go away?"

? Exercise 2.2.3.3

Can all forms of ringworm be treated with the same antifungal medication?

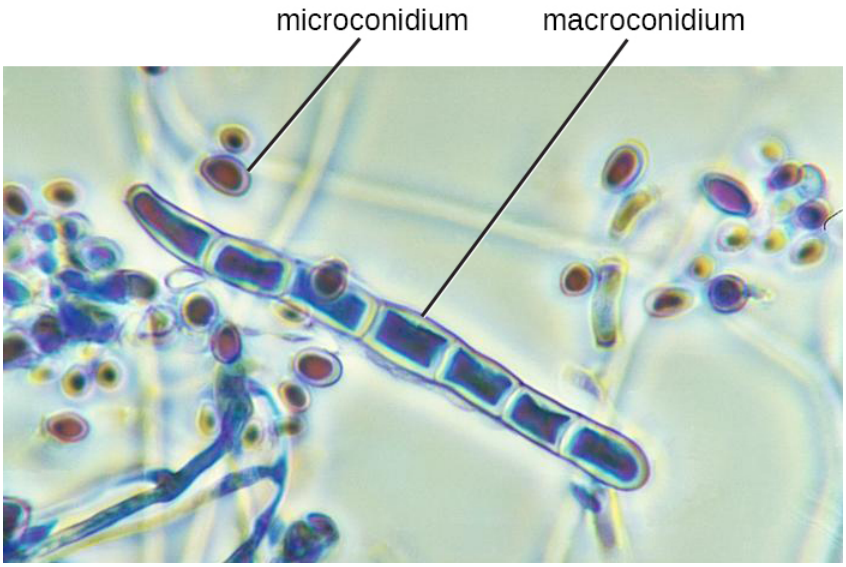


Figure 2.2.3.10: This micrograph shows hyphae (macroconidium) and microconidia of *Trichophyton rubrum*, a dermatophyte responsible for fungal infections of the skin. (credit: modification of work by Centers for Disease Control and Prevention)

Key Concepts and Summary

- The fungi include diverse saprotrophic eukaryotic organisms with chitin cell walls
- Fungi can be unicellular or multicellular; some (like yeast) and fungal spores are microscopic, whereas some are large and conspicuous
- Reproductive types are important in distinguishing fungal groups
- Medically important species exist in the four fungal groups Zygomycota, Ascomycota, Basidiomycota, and Microsporidia
- Members of Zygomycota, Ascomycota, and Basidiomycota produce deadly toxins
- Important differences in fungal cells, such as ergosterols in fungal membranes, can be targets for antifungal medications, but similarities between human and fungal cells make it difficult to find targets for medications and these medications often have toxic adverse effects

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2.2.4: Algae

Learning Objectives

- Explain why algae are included within the discipline of microbiology
- Describe the unique characteristics of algae
- Identify examples of toxin-producing algae
- Compare the major groups of algae in this chapter, and give examples of each
- Classify algal organisms according to major groups

The algae are autotrophic protists that can be unicellular or multicellular. These organisms are found in the supergroups Chromalveolata (dinoflagellates, diatoms, golden algae, and brown algae) and Archaeplastida (red algae and green algae). They are important ecologically and environmentally because they are responsible for the production of approximately 70% of the oxygen and organic matter in aquatic environments. Some types of algae, even those that are microscopic, are regularly eaten by humans and other animals. Additionally, algae are the source for agar, agarose, and carrageenan, solidifying agents used in laboratories and in food production. Although algae are typically not pathogenic, some produce toxins. Harmful algal blooms, which occur when algae grow quickly and produce dense populations, can produce high concentrations of toxins that impair liver and nervous-system function in aquatic animals and humans.

Like protozoans, algae often have complex cell structures. For instance, algal cells can have one or more chloroplasts that contain structures called pyrenoids to synthesize and store starch. The chloroplasts themselves differ in their number of membranes, indicative of secondary or rare tertiary endosymbiotic events. Primary chloroplasts have two membranes—one from the original cyanobacteria that the ancestral eukaryotic cell engulfed, and one from the plasma membrane of the engulfing cell. Chloroplasts in some lineages appear to have resulted from secondary endosymbiosis, in which another cell engulfed a green or red algal cell that already had a primary chloroplast within it. The engulfing cell destroyed everything except the chloroplast and possibly the cell membrane of its original cell, leaving three or four membranes around the chloroplast. Different algal groups have different pigments, which are reflected in common names such as red algae, brown algae, and green algae.

Some algae, the seaweeds, are macroscopic and may be confused with plants. Seaweeds can be red, brown, or green, depending on their photosynthetic pigments. Green algae, in particular, share some important similarities with land plants; however, there are also important distinctions. For example, seaweeds do not have true tissues or organs like plants do. Additionally, seaweeds do not have a waxy cuticle to prevent desiccation. Algae can also be confused with cyanobacteria, photosynthetic bacteria that bear a resemblance to algae; however, cyanobacteria are prokaryotes (see Nonproteobacteria Gram-negative Bacteria and Phototrophic Bacteria).

Algae have a variety of life cycles. Reproduction may be asexual by mitosis or sexual using gametes.

Algal Diversity

Although the algae and protozoa were formerly separated taxonomically, they are now mixed into supergroups. The algae are classified within the Chromalveolata and the Archaeplastida. Although the Euglenozoa (within the supergroup Excavata) include photosynthetic organisms, these are not considered algae because they feed and are motile.

The dinoflagellates and stramenopiles fall within the Chromalveolata. The dinoflagellates are mostly marine organisms and are an important component of plankton. They have a variety of nutritional types and may be phototrophic, heterotrophic, or mixotrophic. Those that are photosynthetic use chlorophyll *a*, chlorophyll c_2, and other photosynthetic pigments (Figure 2.2.4.1). They generally have two flagella, causing them to whirl (in fact, the name dinoflagellate comes from the Greek word for “whirl”: *dini*). Some have cellulose plates forming a hard outer covering, or theca, as armor. Additionally, some dinoflagellates produce neurotoxins that can cause paralysis in humans or fish. Exposure can occur through contact with water containing the dinoflagellate toxins or by feeding on organisms that have eaten dinoflagellates.

When a population of dinoflagellates becomes particularly dense, a red tide (a type of harmful algal bloom) can occur. Red tides cause harm to marine life and to humans who consume contaminated marine life. Major toxin producers include *Gonyaulax* and *Alexandrium*, both of which cause paralytic shellfish poisoning. Another species, *Pfiesteria piscicida*, is known as a fish killer

because, at certain parts of its life cycle, it can produce toxins harmful to fish and it appears to be responsible for a suite of symptoms, including memory loss and confusion, in humans exposed to water containing the species.

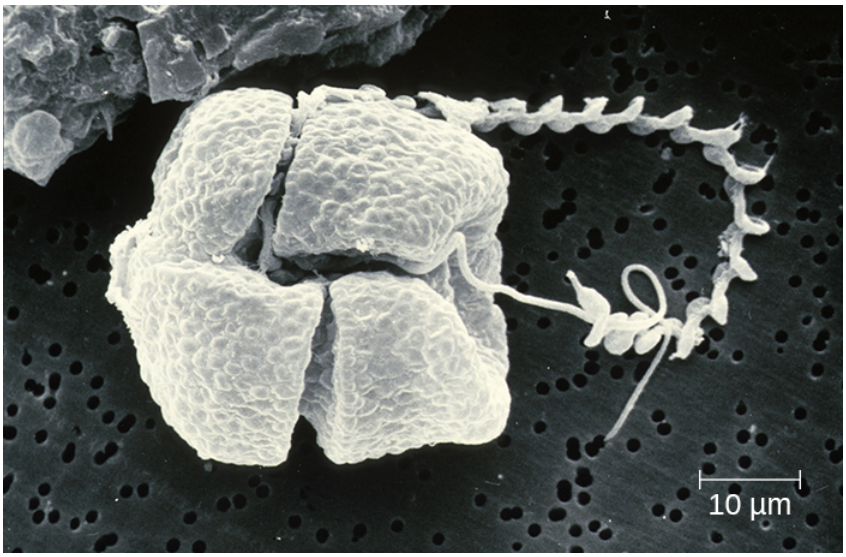


Figure 2.2.4.1: The dinoflagellates exhibit great diversity in shape. Many are encased in cellulose armor and have two flagella that fit in grooves between the plates. Movement of these two perpendicular flagella causes a spinning motion. (credit: modification of work by CSIRO)

The stramenopiles include the golden algae (Chrysophyta), the brown algae (Phaeophyta), and the diatoms(Bacillariophyta). Stramenopiles have chlorophyll *a*, chlorophyll c_1/c_2, and fucoxanthin as photosynthetic pigments. Their storage carbohydrate is chrysolaminarin. While some lack cell walls, others have scales. Diatoms have flagella and frustules, which are outer cell walls of crystallized silica; their fossilized remains are used to produce diatomaceous earth, which has a range of uses such as filtration and insulation. Additionally, diatoms can reproduce sexually or asexually. One diatom genus, *Pseudo-nitzschia*, is known to be associated with harmful algal blooms.

Brown algae (Phaeophyta) are multicellular marine seaweeds. Some can be extremely large, such as the giant kelp (*Laminaria*). They have leaf-like blades, stalks, and structures called holdfasts that are used to attach to substrate. However, these are not true leaves, stems, or roots (Figure 2.2.4.2). Their photosynthetic pigments are chlorophyll *a*, chlorophyll *c*, *β*-carotene, and fucoxanthine. They use laminarin as a storage carbohydrate.

The Archaeplastids include the green algae (Chlorophyta), the red algae (Rhodophyta), another group of green algae (Charophyta), and the land plants. The Charaphyta are the most similar to land plants because they share a mechanism of cell division and an important biochemical pathway, among other traits that the other groups do not have. Like land plants, the Charophyta and Chlorophyta have chlorophyll *a* and chlorophyll *b* as photosynthetic pigments, cellulose cell walls, and starch as a carbohydrate storage molecule. *Chlamydomonas* is a green alga that has a single large chloroplast, two flagella, and a stigma (eyespot); it is important in molecular biology research (Figure 2.2.4.3).

Chlorella is a nonmotile, large, unicellular alga, and *Acetabularia* is an even larger unicellular green alga. The size of these organisms challenges the idea that all cells are small, and they have been used in genetics research since Joachim Hämmerling (1901–1980) began to work with them in 1943. *Volvox* is a colonial, unicellular alga (Figure 2.2.4.3). A larger, multicellular green alga is *Ulva*, also known as the sea lettuce because of its large, edible, green blades. The range of life forms within the Chlorophyta —from unicellular to various levels of coloniality to multicellular forms—has been a useful research model for understanding the evolution of multicellularity. The red algae are mainly multicellular but include some unicellular forms. They have rigid cell walls containing agar or carrageenan, which are useful as food solidifying agents and as a solidifier added to growth media for microbes.

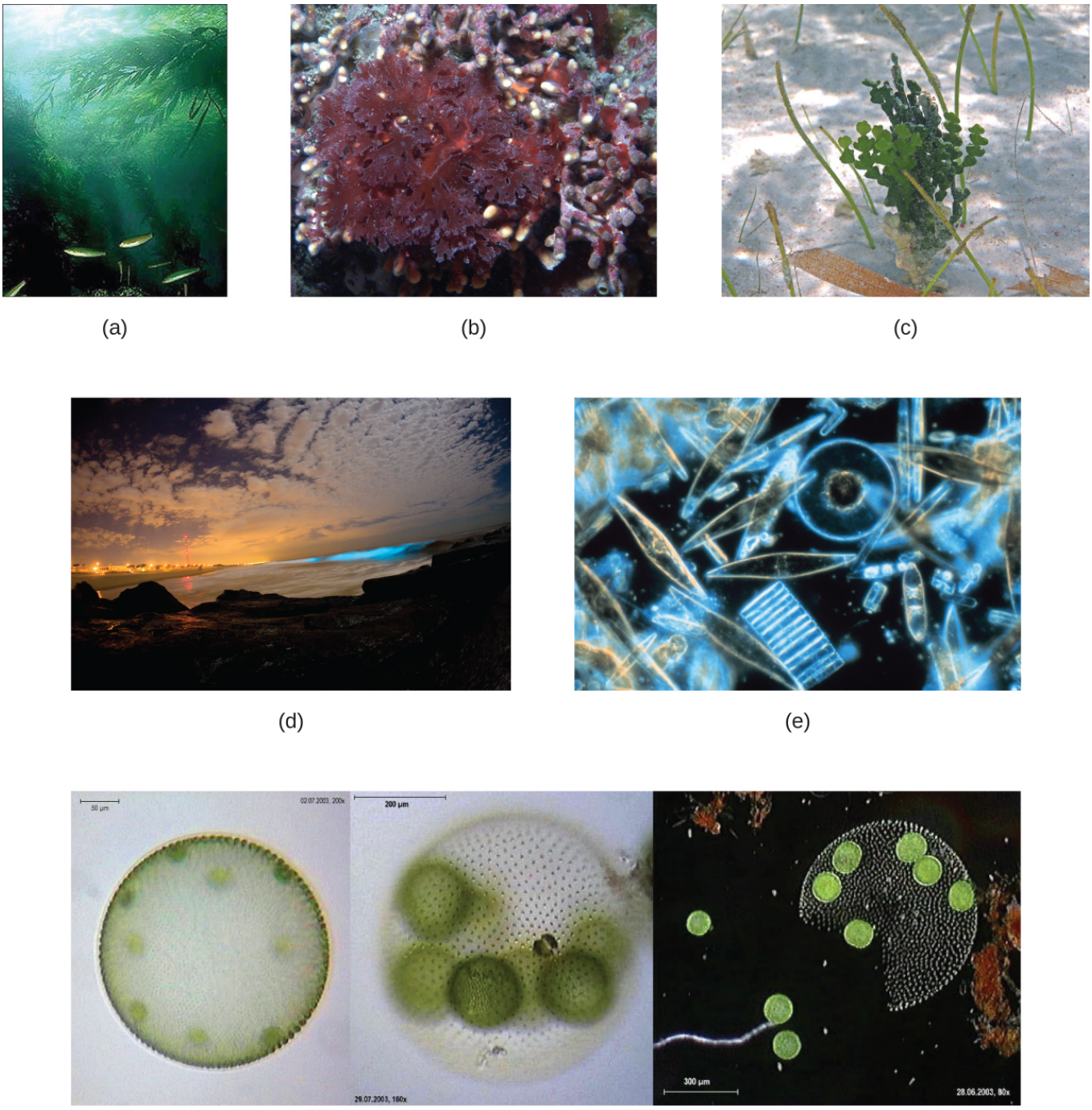


Figure 2.2.4.2: (a) These large multicellular kelps are members of the brown algae. Note the “leaves” and “stems” that make them appear similar to green plants. (b) This is a species of red algae that is also multicellular. (c) The green alga *Halimeda incrassata*, shown here growing on the sea floor in shallow water, appears to have plant-like structures, but is not a true plant. (d) Bioluminesence, visible in the cresting wave in this picture, is a phenomenon of certain dinoflagellates. (e) Diatoms (pictured in this micrograph) produce silicaceous tests (skeletons) that form diatomaceous earths. (f) Colonial green algae, like volvox in these three micrographs, exhibit simple cooperative associations of cells. (credit a, e: modification of work by NOAA; credit b: modification of work by Ed Bierman; credit c: modification of work by James St. John; credit d: modification of work by “catalano82”/Flickr; credit f: modification of work by Dr. Ralf Wagner)

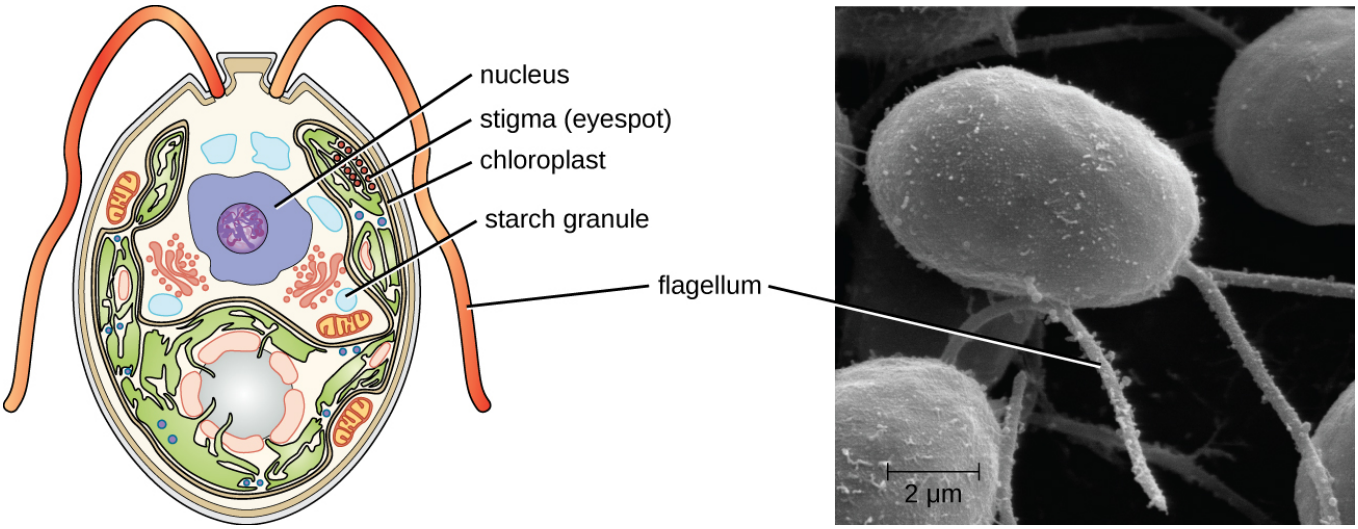


Figure 2.2.4.3: Chlamydomonas is a unicellular green alga.

? Exercise 2.2.4.1

Which groups of algae are associated with harmful algal blooms?

Key Concepts and Summary

- Algae are a diverse group of photosynthetic eukaryotic protists.
- Algae may be unicellular or multicellular.
- Large, multicellular algae are called seaweeds but are not plants and lack plant-like tissues and organs.
- Although algae have little pathogenicity, they may be associated with toxic **algal blooms** that can harm aquatic wildlife and contaminate seafood with toxins that cause paralysis.
- Algae are important for producing **agar**, which is used as a solidifying agent in microbiological media, and **carrageenan**, which is used as a solidifying agent.

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2.2.5: Lichens

Learning Objectives

- Explain why lichens are included in the study of microbiology
- Describe the unique characteristics of a lichen and the role of each partner in the symbiotic relationship of a lichen
- Describe ways in which lichens are beneficial to the environment

No one has to worry about getting sick from a lichen infection, but lichens are interesting from a microbiological perspective and they are an important component of most terrestrial ecosystems. Lichens provide opportunities for study of close relationships between unrelated microorganisms. Lichens contribute to soil production by breaking down rock, and they are early colonizers in soilless environments such as lava flows. The cyanobacteria in some lichens can fix nitrogen and act as a nitrogen source in some environments. Lichens are also important soil stabilizers in some desert environments and they are an important winter food source for caribou and reindeer. Finally, lichens produce compounds that have antibacterial effects, and further research may discover compounds that are medically useful to humans.

Characteristics

A lichen is a combination of two organisms, a green alga or cyanobacterium and an ascomycete fungus, living in a symbiotic relationship. Whereas algae normally grow only in aquatic or extremely moist environments, lichens can potentially be found on almost any surface (especially rocks) or as epiphytes (meaning that they grow on other plants).

In some ways, the symbiotic relationship between lichens and algae seems like a mutualism (a relationship in which both organisms benefit). The fungus can obtain photosynthates from the algae or cyanobacterium and the algae or cyanobacterium can grow in a drier environment than it could otherwise tolerate. However, most scientists consider this symbiotic relationship to be a controlled parasitism (a relationship in which one organism benefits and the other is harmed) because the photosynthetic organism grows less well than it would without the fungus. It is important to note that such symbiotic interactions fall along a continuum between conflict and cooperation.

Lichens are slow growing and can live for centuries. They have been used in foods and to extract chemicals as dyes or antimicrobial substances. Some are very sensitive to pollution and have been used as environmental indicators.

Lichens have a body called a thallus, an outer, tightly packed fungal layer called a cortex, and an inner, loosely packed fungal layer called a medulla (Figure 2.2.5.1). Lichens use hyphal bundles called rhizines to attach to the substrate.

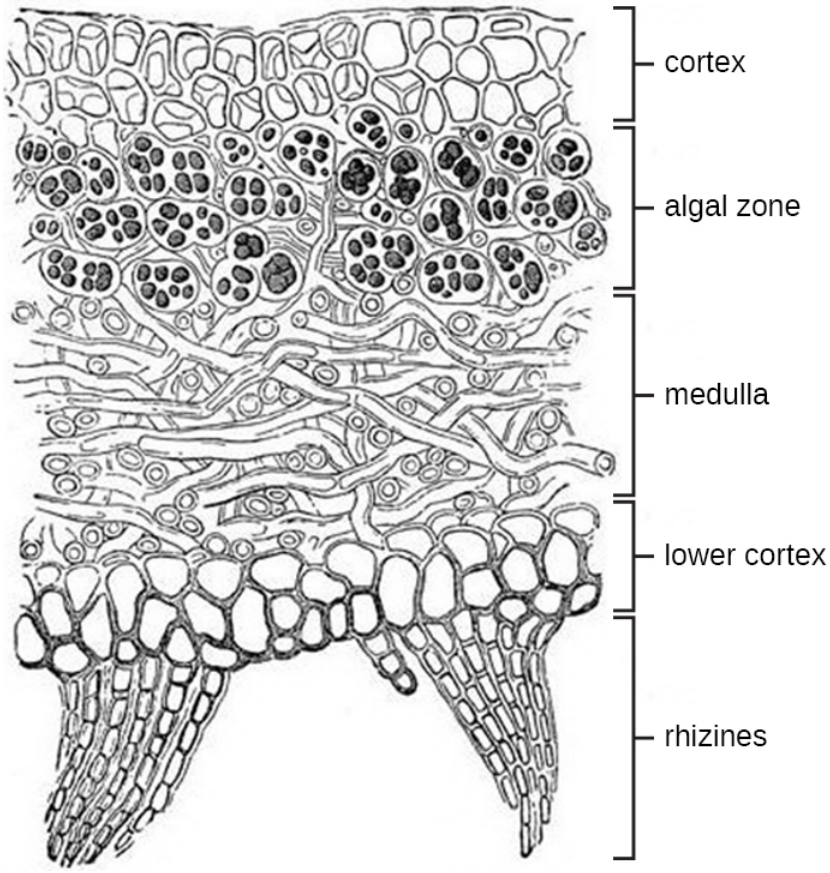


Figure 2.2.5.1: This cross-section of a lichen thallus shows its various components. The upper cortex of fungal hyphae provides protection. Photosynthesis occurs in the algal zone. The medulla consists of fungal hyphae. The lower cortex also provides protection. The rhizines anchor the thallus to the substrate.

Lichen Diversity

Lichens are classified as fungi and the fungal partners belong to the Ascomycota and Basidiomycota. Lichens can also be grouped into types based on their morphology. There are three major types of lichens, although other types exist as well. Lichens that are tightly attached to the substrate, giving them a crusty appearance, are called crustose lichens. Those that have leaf-like lobes are foliose lichens; they may only be attached at one point in the growth form, and they also have a second cortex below the medulla. Finally, fruticose lichens have rounded structures and an overall branched appearance. Figure 2.2.5.2 shows an example of each of the forms of lichens.



(a) (b) (c)

Figure 2.2.5.2: Examples of the three types of lichens are shown here. (a) This is a crustose lichen found mostly on marine rocks, *Caloplaca marina*. (b) This is a foliose lichen, *Flavoparmelia caperata*. (c) This is a fruticose lichen, *Letharia vulpina*, which is sufficiently poisonous that it was once used to make arrowheads. (credit b, c: modification of work by Jason Hollinger)

? Exercise 2.2.5.1

1. What types of organisms are found in lichens?
2. What are the three growth forms of lichens?

Clinical Focus: Resolution

Sarah's mother asks the doctor what she should do if the cream prescribed for Sarah's ringworm does not work. The doctor explains that ringworm is a general term for a condition caused by multiple species. The first step is to take a scraping for examination under the microscope, which the doctor has already done. He explains that he has identified the infection as a fungus, and that the antifungal cream works against the most common fungi associated with ringworm. However, the cream may not work against some species of fungus. If the cream is not working after a couple of weeks, Sarah should come in for another visit, at which time the doctor will take steps to identify the species of the fungus.

Positive identification of dermatophytes requires culturing. For this purpose, Sabouraud's agar may be used. In the case of Sarah's infection, which cleared up within 2 weeks of treatment, the culture would have a granular texture and would appear pale pink on top and red underneath. These features suggest that the fungus is *Trichophyton rubrum*, a common cause of ringworm.

Key Concepts and Summary

- **Lichens** are a symbiotic association between a fungus and an algae or a cyanobacterium
- The symbiotic association found in lichens is currently considered to be a controlled **parasitism**, in which the fungus benefits and the algae or cyanobacterium is harmed
- Lichens are slow growing and can live for centuries in a variety of habitats
- Lichens are environmentally important, helping to create soil, providing food, and acting as indicators of air pollution

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2.2.E: The Eukaryotes of Microbiology (Exercises)

5.1: Unicellular Eukaryotic Microorganisms

Protists are a diverse, polyphyletic group of eukaryotic organisms. Protists may be unicellular or multicellular. They vary in how they get their nutrition, morphology, method of locomotion, and mode of reproduction. Important structures of protists include contractile vacuoles, cilia, flagella, pellicles, and pseudopodia; some lack organelles such as mitochondria. Taxonomy of protists is changing rapidly as relationships are reassessed using newer techniques.

Multiple Choice

Which genus includes the causative agent for malaria?

A. *Euglena*
B. *Paramecium*
C. *Plasmodium*
D. *Trypanosoma*

Answer

C

Which protist is a concern because of its ability to contaminate water supplies and cause diarrheal illness?

A. *Plasmodium vivax*
B. *Toxoplasma gondii*
C. *Giardia lamblia*
D. *Trichomonas vaginalis*

Answer

C

Fill in the Blank

The plasma membrane of a protist is called the _____.

Answer

plasmalemma

Animals belong to the same supergroup as the kingdom _____.

Answer

Fungi

Short Answer

What are kinetoplastids?

Aside from a risk of birth defects, what other effect might a toxoplasmosis infection have?

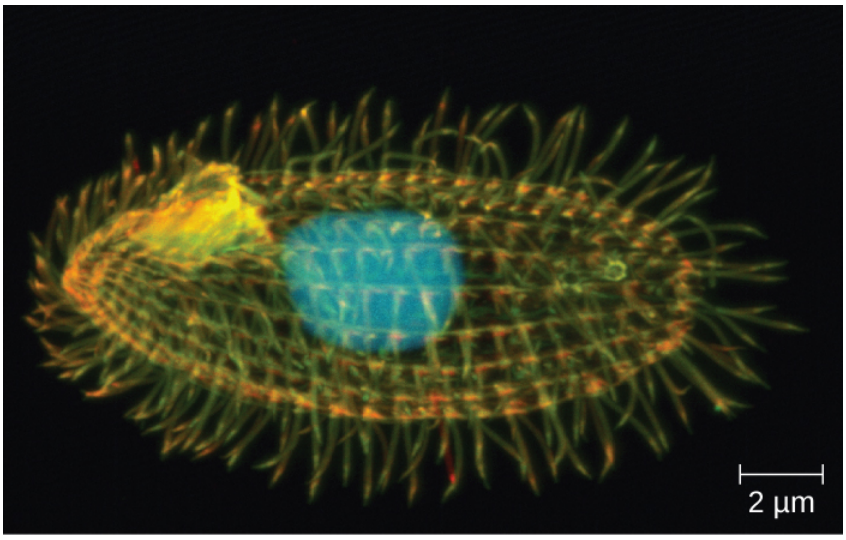
What is the function of the ciliate macronucleus?

Critical Thinking

The protist shown has which of the following?

A. pseudopodia
B. flagella
C. a shell

D. cilia



(credit: modification of work by Richard Robinson)

Protist taxonomy has changed greatly in recent years as relationships have been re-examined using newer approaches. How do newer approaches differ from older approaches?

What characteristics might make you think a protist could be pathogenic? Are certain nutritional characteristics, methods of locomotion, or morphological differences likely to be associated with the ability to cause disease?

5.2: Parasitic Helminths

Helminth parasites are included within the study of microbiology because they are often identified by looking for microscopic eggs and larvae. The two major groups of helminth parasites are the roundworms (Nematoda) and the flatworms (Platyhelminthes). Nematodes are common intestinal parasites often transmitted through undercooked foods, although they are also found in other environments. Platyhelminths include tapeworms and flukes, which are often transmitted through undercooked meat.

Multiple Choice

A fluke is classified within which of the following?

A. Nematoda
B. Rotifera
C. Platyhelminthes
D. Annelida

Answer

C

A nonsegmented worm is found during a routine colonoscopy of an individual who reported having abdominal cramps, nausea, and vomiting. This worm is likely which of the following?

A. nematode
B. fluke
C. trematode
D. annelid

Answer

A

A segmented worm has male and female reproductive organs in each segment. Some use hooks to attach to the intestinal wall. Which type of worm is this?

A. fluke
B. nematode
C. cestode
D. annelid

Answer

C

Fill in the Blank

Flukes are in class _____.

Answer

Trematoda

A species of worm in which there are distinct male and female individuals is described as _____.

Answer

dioecious

Short Answer

What is the best defense against tapeworm infection?

Critical Thinking

Given the life cycle of the *Schistosoma* parasite, suggest a method of prevention of the disease.

5.3: Fungi

The fungi include diverse saprotrophic eukaryotic organisms with chitin cell walls. Fungi can be unicellular or multicellular; some (like yeast) and fungal spores are microscopic, whereas some are large and conspicuous. Reproductive types are important in distinguishing fungal groups. Medically important species exist in the four fungal groups Zygomycota, Ascomycota, Basidiomycota, and Microsporidia.

Multiple Choice

Mushrooms are a type of which of the following?

A. conidia
B. ascus
C. polar tubule
D. basidiocarp

Answer

D

Which of the following is the most common cause of human yeast infections?

A. *Candida albicans*
B. *Blastomyces dermatitidis*
C. *Cryptococcus neoformans*
D. *Aspergillus fumigatus*

Answer

A

Which of the following is an ascomycete fungus associated with bat droppings that can cause a respiratory infection if inhaled?

A. *Candida albicans*
B. *Histoplasma capsulatum*
C. *Rhizopus stolonifera*
D. *Trichophyton rubrum*

Answer

B

Fill in the Blank

Nonseptate hyphae are also called _____.

Answer

coenocytic

Unicellular fungi are called _____.

Answer

yeasts

Some fungi have proven medically useful because they can be used to produce _____.

Answer

antibiotics

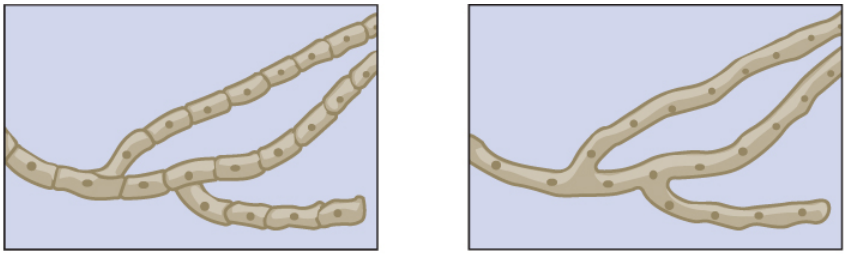
Short Answer

Which genera of fungi are common dermatophytes (fungi that cause skin infections)?

What is a dikaryotic cell?

Critical Thinking

Which of the drawings shows septate hyphae?



A B

Explain the benefit of research into the pathways involved in the synthesis of chitin in fungi.

5.4: Algae

Algae are a diverse group of photosynthetic eukaryotic protists. Algae may be unicellular or multicellular. Large, multicellular algae are called seaweeds but are not plants and lack plant-like tissues and organs. Although algae have little pathogenicity, they may be associated with toxic algal blooms that can harm aquatic wildlife and contaminate seafood with toxins that cause paralysis.

Multiple Choice

Which polysaccharide found in red algal cell walls is a useful solidifying agent?

A. chitin
B. cellulose
C. phycoerythrin
D. agar

Answer

D

Which is the term for the hard outer covering of some dinoflagellates?

A. theca
B. thallus
C. mycelium
D. shell

Answer

A

Which protists are associated with red tides?

A. red algae
B. brown algae
C. dinoflagellates
D. green algae

Answer

C

Fill in the Blank

Structures in chloroplasts used to synthesize and store starch are called _____.

Answer

pyrenoids

Algae with chloroplasts with three or four membranes are a result of _____ _____.

Answer

secondary endosymbiosis

Short Answer

What is a distinctive feature of diatoms?

Why are algae not considered parasitic?

Which groups contain the multicellular algae?

5.5: Lichens

Lichens are a symbiotic association between a fungus and an algae or a cyanobacterium. The symbiotic association found in lichens is currently considered to be a controlled parasitism, in which the fungus benefits and the algae or cyanobacterium is harmed. Lichens are slow growing and can live for centuries in a variety of habitats. Lichens are environmentally important, helping to create soil, providing food, and acting as indicators of air pollution.

Multiple Choice

You encounter a lichen with leafy structures. Which term describes this lichen?

A. crustose
B. foliose
C. fruticose
D. agarose

Answer

B

Which of the following is the term for the outer layer of a lichen?

A. the cortex
B. the medulla
C. the thallus
D. the theca

Answer

A

The fungus in a lichen is which of the following?

A. a basidiomycete
B. an ascomycete
C. a zygomycete
D. an apicomplexan

Answer

B

Short Answer

What are three ways that lichens are environmentally valuable?

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SECTION OVERVIEW

2.3: Cell Membranes

2.3.1: Why It Matters- Cell Membranes

2.3.2: Structure of the Membrane

2.3.3: Kinds of Transport

2.3.4: Endocytosis and Exocytosis

2.3.5: Putting It Together- Cell Membranes

2.3.6: Assignment- Membranes Alive!

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2.3.1: Why It Matters- Cell Membranes

Why learn about cell membranes?

Cystic fibrosis (CF) is a genetic disorder that primarily affects the lungs, as well as the pancreas, liver, and intestine. CF is characterized by abnormal transport of chloride and sodium across body tissues, leading to thick, viscous secretions. The hallmark symptoms of cystic fibrosis are salty tasting skin, poor growth, poor weight gain despite a normal food intake, accumulation of thick, sticky mucus, frequent chest infections, and coughing or shortness of breath. Symptoms often appear in infancy and childhood, such as bowel obstruction in newborn babies.

The most serious symptoms of CF are difficulty breathing and frequent lung infections. Often, lung transplantation is ultimately necessary as CF worsens. Other symptoms, including sinus infections, poor growth, and infertility affect other parts of the body.

Cystic fibrosis results from the malfunctioning of a single membrane transporter. How could this error in membrane transport result in such a disease?

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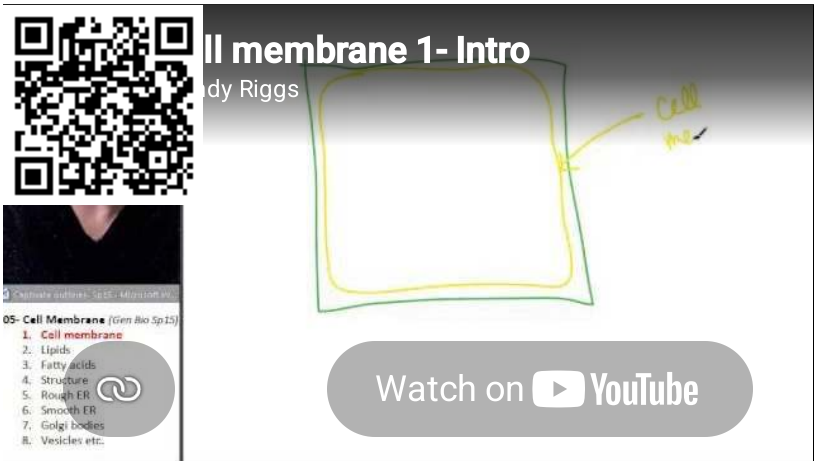
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2.3.2: Structure of the Membrane

What you'll learn to do: Describe the structure and function of membranes, especially the phospholipid bilayer

In this outcome, we'll learn about the structure of membranes:



Learning Objectives

- Describe the structure of cell membranes
- Identify components of the cell membrane, including phospholipids, cholesterol, proteins, and carbohydrates

Cell Membranes are Fluid

A cell's plasma membrane defines the boundary of the cell and determines the nature of its contact with the environment. Cells exclude some substances, take in others, and excrete still others, all in controlled quantities. Plasma membranes enclose the borders of cells, but rather than being a static bag, they are dynamic and constantly in flux. The plasma membrane must be sufficiently flexible to allow certain cells, such as red blood cells and white blood cells, to change shape as they pass through narrow capillaries. These are the more obvious functions of a plasma membrane. In addition, the surface of the plasma membrane carries markers that allow cells to recognize one another, which is vital as tissues and organs form during early development, and which later plays a role in the "self" versus "non-self" distinction of the immune response.

The plasma membrane also carries receptors, which are attachment sites for specific substances that interact with the cell. Each receptor is structured to bind with a specific substance. For example, surface receptors of the membrane create changes in the interior, such as changes in enzymes of metabolic pathways. These metabolic pathways might be vital for providing the cell with energy, making specific substances for the cell, or breaking down cellular waste or toxins for disposal. Receptors on the plasma membrane's exterior surface interact with hormones or neurotransmitters, and allow their messages to be transmitted into the cell. Some recognition sites are used by viruses as attachment points. Although they are highly specific, pathogens like viruses may evolve to exploit receptors to gain entry to a cell by mimicking the specific substance that the receptor is meant to bind. This specificity helps to explain why human immunodeficiency virus (HIV) or any of the five types of hepatitis viruses invade only specific cells.

Cell Membranes are Mosaics

In 1972, S. J. Singer and Garth L. Nicolson proposed a new model of the plasma membrane that, compared to earlier understanding, better explained both microscopic observations and the function of the plasma membrane. This was called the **fluid mosaic model**. The model has evolved somewhat over time, but still best accounts for the structure and functions of the plasma membrane as we now understand them. The fluid mosaic model describes the structure of the plasma membrane as a mosaic of components—including phospholipids, cholesterol, proteins, and carbohydrates—in which the components are able to flow and change position, while maintaining the basic integrity of the membrane. Both phospholipid molecules and embedded proteins are

able to diffuse rapidly and laterally in the membrane. The fluidity of the plasma membrane is necessary for the activities of certain enzymes and transport molecules within the membrane. Plasma membranes range from 5–10 nm thick. As a comparison, human red blood cells, visible via light microscopy, are approximately 8 µm thick, or approximately 1,000 times thicker than a plasma membrane. (Figure 1)

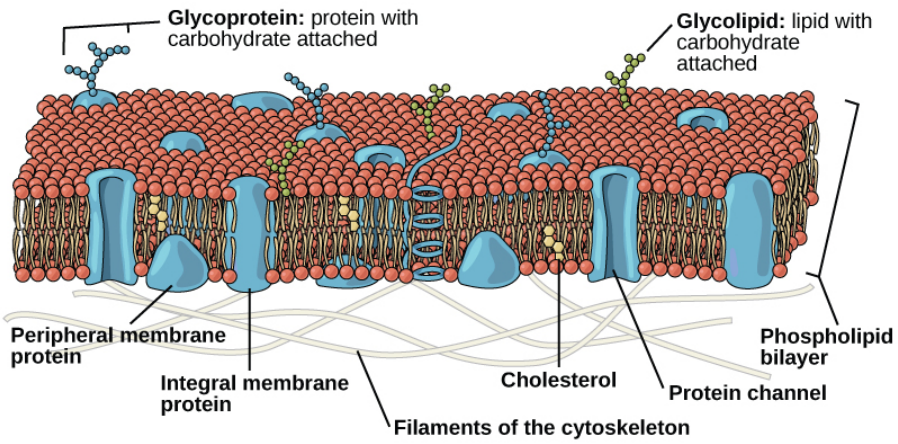


Figure 1. The fluid mosaic model of the plasma membrane structure describes the plasma membrane as a fluid combination of phospholipids, cholesterol, proteins, and carbohydrates.

The plasma membrane is made up primarily of a bilayer of phospholipids with embedded proteins, carbohydrates, glycolipids, and glycoproteins, and, in animal cells, cholesterol. The amount of cholesterol in animal plasma membranes regulates the fluidity of the membrane and changes based on the temperature of the cell's environment. In other words, cholesterol acts as antifreeze in the cell membrane and is more abundant in animals that live in cold climates.

The main fabric of the membrane is composed of two layers of phospholipid molecules, and the polar ends of these molecules (which look like a collection of balls in an artist's rendition of the model) (Figure 1) are in contact with aqueous fluid both inside and outside the cell. Thus, both surfaces of the plasma membrane are hydrophilic. In contrast, the interior of the membrane, between its two surfaces, is a hydrophobic or nonpolar region because of the fatty acid tails. This region has no attraction for water or other polar molecules.

Proteins make up the second major chemical component of plasma membranes. Integral proteins are embedded in the plasma membrane and may span all or part of the membrane. Integral proteins may serve as channels or pumps to move materials into or out of the cell. Peripheral proteins are found on the exterior or interior surfaces of membranes, attached either to integral proteins or to phospholipid molecules. Both integral and peripheral proteins may serve as enzymes, as structural attachments for the fibers of the cytoskeleton, or as part of the cell's recognition sites.

Carbohydrates are the third major component of plasma membranes. They are always found on the exterior surface of cells and are bound either to proteins (forming glycoproteins) or to lipids (forming glycolipids). These carbohydrate chains may consist of 2–60 monosaccharide units and may be either straight or branched. Along with peripheral proteins, carbohydrates form specialized sites on the cell surface that allow cells to recognize each other.

Try It

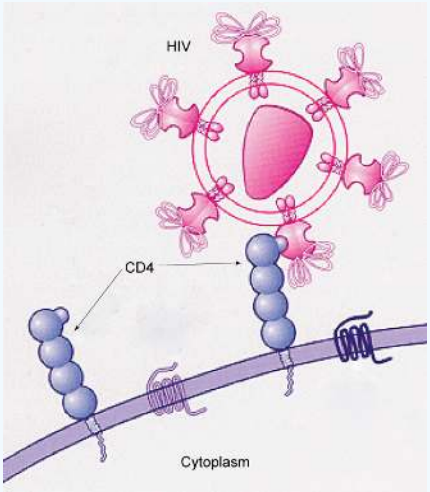


Figure 2. HIV docks at and binds to the CD4 receptor, a glycoprotein on the surface of T cells, before entering, or infecting, the cell. (credit: modification of work by US National Institutes of Health/National Institute of Allergy and Infectious Diseases)

Specific glycoprotein molecules exposed on the surface of the cell membranes of host cells are exploited by many viruses to infect specific organs. For example, HIV is able to penetrate the plasma membranes of specific kinds of white blood cells called T-helper cells and monocytes, as well as some cells of the central nervous system. The hepatitis virus attacks only liver cells.

These viruses are able to invade these cells, because the cells have binding sites on their surfaces that the viruses have exploited with equally specific glycoproteins in their coats. (Figure 2). The cell is tricked by the mimicry of the virus coat molecules, and the virus is able to enter the cell. Other recognition sites on the virus's surface interact with the human immune system, prompting the body to produce antibodies. Antibodies are made in response to the antigens (or proteins associated with invasive pathogens). These same sites serve as places for antibodies to attach, and either destroy or inhibit the activity of the virus. Unfortunately, these sites on HIV are encoded by genes that change quickly, making the production of an effective vaccine against the virus very difficult. The virus population within an infected individual quickly evolves through mutation into different populations, or variants, distinguished by differences in these recognition sites. This rapid change of viral surface markers decreases the effectiveness of the person's immune system in attacking the virus, because the antibodies will not recognize the new variations of the surface patterns.

Learning Objectives

The modern understanding of the plasma membrane is referred to as the fluid mosaic model. The plasma membrane is composed of a bilayer of phospholipids, with their hydrophobic, fatty acid tails in contact with each other. The landscape of the membrane is studded with proteins, some of which span the membrane. Some of these proteins serve to transport materials into or out of the cell. Carbohydrates are attached to some of the proteins and lipids on the outward-facing surface of the membrane. These form complexes that function to identify the cell to other cells. The fluid nature of the membrane owes itself to the configuration of the fatty acid tails, the presence of cholesterol embedded in the membrane (in animal cells), and the mosaic nature of the proteins and protein-carbohydrate complexes, which are not firmly fixed in place. Plasma membranes enclose the borders of cells, but rather than being a static bag, they are dynamic and constantly in flux.

Check Your Understanding

Answer the question(s) below to see how well you understand the topics covered in the previous section. This short quiz does **not** count toward your grade in the class, and you can retake it an unlimited number of times.

Use this quiz to check your understanding and decide whether to (1) study the previous section further or (2) move on to the next section.

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2.3.3: Kinds of Transport

What you'll learn to do: Explain how substances are directly transported across a membrane

Plasma membranes must allow certain substances to enter and leave a cell, and prevent some harmful materials from entering and some essential materials from leaving. In other words, plasma membranes are **selectively permeable**—they allow some substances to pass through, but not others. If they were to lose this selectivity, the cell would no longer be able to sustain itself, and it would be destroyed. Some cells require larger amounts of specific substances than do other cells; they must have a way of obtaining these materials from extracellular fluids. This may happen passively, as certain materials move back and forth, or the cell may have special mechanisms that facilitate transport. Some materials are so important to a cell that it spends some of its energy, hydrolyzing adenosine triphosphate (ATP), to obtain these materials. For example, red blood cells use some of their energy doing just that. All cells spend the majority of their energy to maintain an imbalance of sodium and potassium ions between the interior and exterior of the cell.

Learning Objectives

- Define and describe passive transport
- Define and describe active transport

Passive Transport

The most direct forms of membrane transport are passive. **Passive transport** is a naturally occurring phenomenon and does not require the cell to exert any of its energy to accomplish the movement. In passive transport, substances move from an area of higher concentration to an area of lower concentration. A physical space in which there is a range of concentrations of a single substance is said to have a **concentration gradient**.

Selective Permeability

Plasma membranes are asymmetric: the interior of the membrane is not identical to the exterior of the membrane. In fact, there is a considerable difference between the array of phospholipids and proteins between the two leaflets that form a membrane. On the interior of the membrane, some proteins serve to anchor the membrane to fibers of the cytoskeleton. There are peripheral proteins on the exterior of the membrane that bind elements of the extracellular matrix. Carbohydrates, attached to lipids or proteins, are also found on the exterior surface of the plasma membrane. These carbohydrate complexes help the cell bind substances that the cell needs in the extracellular fluid. This adds considerably to the selective nature of plasma membranes (Figure 1).

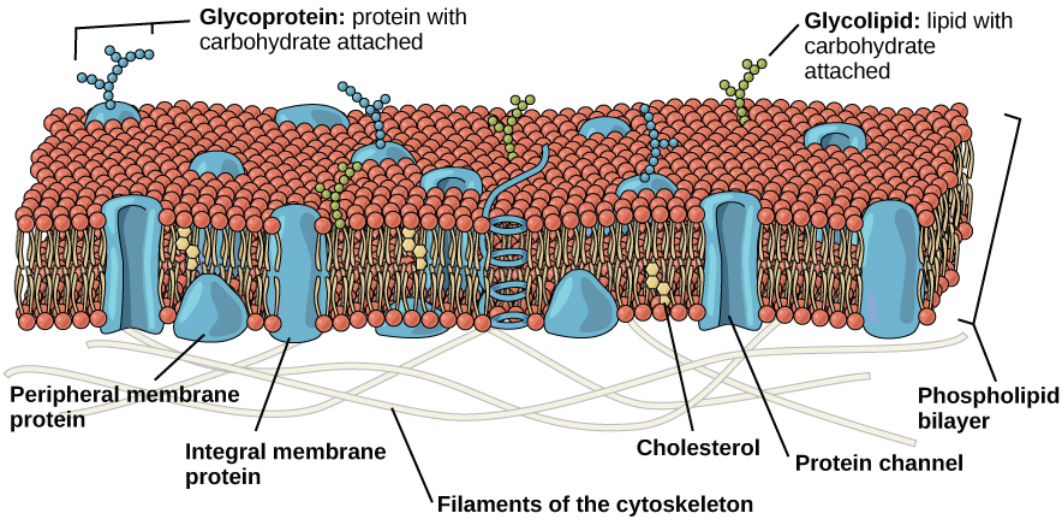


Figure 1. The eukaryotic plasma membrane is a phospholipid bilayer with proteins and cholesterol embedded in it.

Recall that plasma membranes are amphiphilic: they have hydrophilic and hydrophobic regions. This characteristic helps the movement of some materials through the membrane and hinders the movement of others. Lipid-soluble material with a low

molecular weight can easily slip through the hydrophobic lipid core of the membrane. Substances such as the fat-soluble vitamins A, D, E, and K readily pass through the plasma membranes in the digestive tract and other tissues. Fat-soluble drugs and hormones also gain easy entry into cells and are readily transported into the body's tissues and organs. Molecules of oxygen and carbon dioxide have no charge and so pass through membranes by simple diffusion.

Polar substances present problems for the membrane. While some polar molecules connect easily with the outside of a cell, they cannot readily pass through the lipid core of the plasma membrane. Additionally, while small ions could easily slip through the spaces in the mosaic of the membrane, their charge prevents them from doing so. Ions such as sodium, potassium, calcium, and chloride must have special means of penetrating plasma membranes. Simple sugars and amino acids also need help with transport across plasma membranes, achieved by various transmembrane proteins (channels).

Diffusion



Figure 2. Dispersion

Diffusion is a passive process of transport (see Figure 2). A single substance tends to move from an area of high concentration to an area of low concentration until the concentration is equal across a space. You are familiar with diffusion of substances through the air.

For example, think about someone opening a bottle of ammonia in a room filled with people. The ammonia gas is at its highest concentration in the bottle; its lowest concentration is at the edges of the room. The ammonia vapor will diffuse, or spread away, from the bottle, and gradually, more and more people will smell the ammonia as it spreads. Materials move within the cell's cytosol by diffusion, and certain materials move through the plasma membrane by diffusion (Figure 3). Diffusion expends no energy. On the contrary, concentration gradients are a form of potential energy, dissipated as the gradient is eliminated.

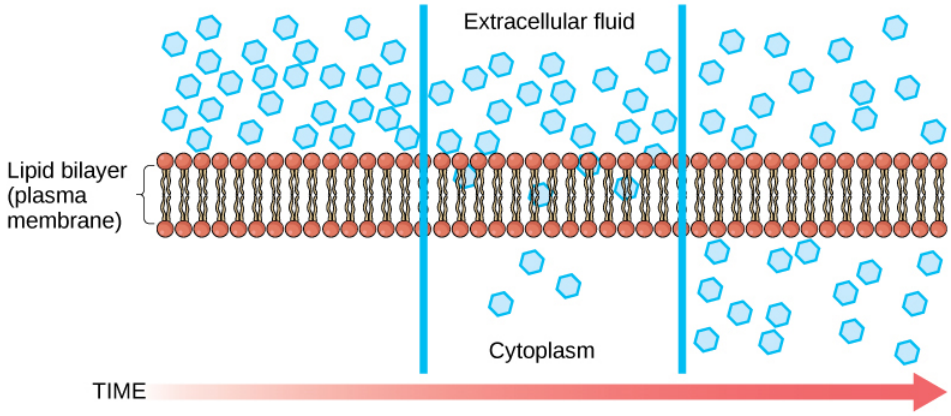


Figure 3. Diffusion through a permeable membrane moves a substance from an area of high concentration (extracellular fluid, in this case) down its concentration gradient (into the cytoplasm). (credit: modification of work by Mariana Ruiz Villareal)

Each separate substance in a medium, such as the extracellular fluid, has its own concentration gradient, independent of the concentration gradients of other materials. In addition, each substance will diffuse according to that gradient. Within a system, there will be different rates of diffusion of the different substances in the medium.

Facilitated Transport

In facilitated transport, also called facilitated diffusion, materials diffuse across the plasma membrane with the help of membrane proteins. A concentration gradient exists that would allow these materials to diffuse into the cell without expending cellular energy. However, these materials are ions or polar molecules that are repelled by the hydrophobic parts of the cell membrane. Facilitated transport proteins shield these materials from the repulsive force of the membrane, allowing them to diffuse into the cell.

The material being transported is first attached to protein or glycoprotein receptors on the exterior surface of the plasma membrane. This allows the material that is needed by the cell to be removed from the extracellular fluid. The substances are then passed to specific integral proteins that facilitate their passage. Some of these integral proteins are collections of beta pleated sheets that form a pore or channel through the phospholipid bilayer. Others are carrier proteins which bind with the substance and aid its diffusion through the membrane.

Channels

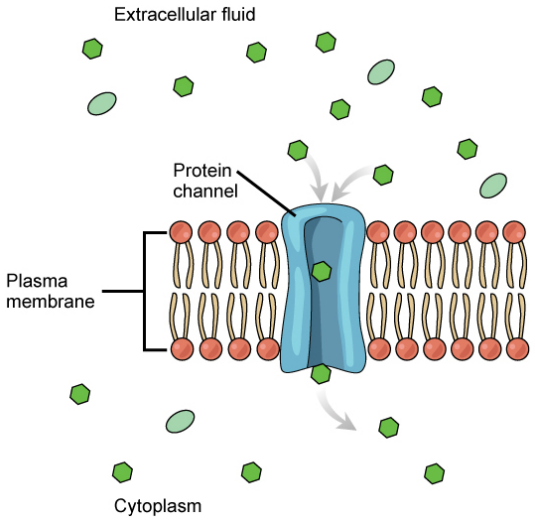


Figure 4. Facilitated transport moves substances down their concentration gradients. They may cross the plasma membrane with the aid of channel proteins. (credit: modification of work by Mariana Ruiz Villareal)

The integral proteins involved in facilitated transport are collectively referred to as **transport proteins**, and they function as either channels for the material or carriers. In both cases, they are transmembrane proteins. Channels are specific for the substance that is being transported. **Channel proteins** have hydrophilic domains exposed to the intracellular and extracellular fluids; they additionally have a hydrophilic channel through their core that provides a hydrated opening through the membrane layers (Figure 4). Passage through the channel allows polar compounds to avoid the nonpolar central layer of the plasma membrane that would otherwise slow or prevent their entry into the cell. **Aquaporins** are channel proteins that allow water to pass through the membrane at a very high rate.

Channel proteins are either open at all times or they are “gated,” which controls the opening of the channel. The attachment of a particular ion to the channel protein may control the opening, or other mechanisms or substances may be involved. In some tissues, sodium and chloride ions pass freely through open channels, whereas in other tissues a gate must be opened to allow passage. An example of this occurs in the kidney, where both forms of channels are found in different parts of the renal tubules. Cells involved in the transmission of electrical impulses, such as nerve and muscle cells, have gated channels for sodium, potassium, and calcium in their membranes. Opening and closing of these channels changes the relative concentrations on opposing sides of the membrane of these ions, resulting in the facilitation of electrical transmission along membranes (in the case of nerve cells) or in muscle contraction (in the case of muscle cells).

Carrier Proteins

Another type of protein embedded in the plasma membrane is a **carrier protein**. This aptly named protein binds a substance and, in doing so, triggers a change of its own shape, moving the bound molecule from the outside of the cell to its interior (Figure 5); depending on the gradient, the material may move in the opposite direction. Carrier proteins are typically specific for a single substance. This selectivity adds to the overall selectivity of the plasma membrane. The exact mechanism for the change of shape is

poorly understood. Proteins can change shape when their hydrogen bonds are affected, but this may not fully explain this mechanism. Each carrier protein is specific to one substance, and there are a finite number of these proteins in any membrane. This can cause problems in transporting enough of the material for the cell to function properly. When all of the proteins are bound to their ligands, they are saturated and the rate of transport is at its maximum. Increasing the concentration gradient at this point will not result in an increased rate of transport.

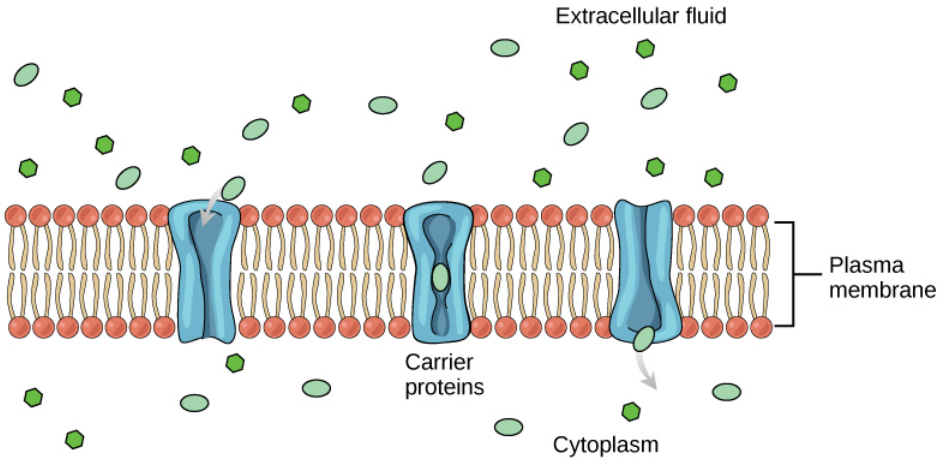


Figure 5. Some substances are able to move down their concentration gradient across the plasma membrane with the aid of carrier proteins. Carrier proteins change shape as they move molecules across the membrane. (credit: modification of work by Mariana Ruiz Villareal)

An example of this process occurs in the kidney. Glucose, water, salts, ions, and amino acids needed by the body are filtered in one part of the kidney. This filtrate, which includes glucose, is then reabsorbed in another part of the kidney. Because there are only a finite number of carrier proteins for glucose, if more glucose is present than the proteins can handle, the excess is not transported and it is excreted from the body in the urine. In a diabetic individual, this is described as “spilling glucose into the urine.” A different group of carrier proteins called glucose transport proteins, or GLUTs, are involved in transporting glucose and other hexose sugars through plasma membranes within the body.

Channel and carrier proteins transport material at different rates. Channel proteins transport much more quickly than do carrier proteins. Channel proteins facilitate diffusion at a rate of tens of millions of molecules per second, whereas carrier proteins work at a rate of a thousand to a million molecules per second.

Osmosis

Osmosis is the movement of water through a semipermeable membrane according to the concentration gradient of water across the membrane, which is inversely proportional to the concentration of solutes. While diffusion transports material across membranes and within cells, osmosis transports *only water* across a membrane and the membrane limits the diffusion of solutes in the water. Not surprisingly, the aquaporins that facilitate water movement play a large role in osmosis, most prominently in red blood cells and the membranes of kidney tubules.

Mechanism

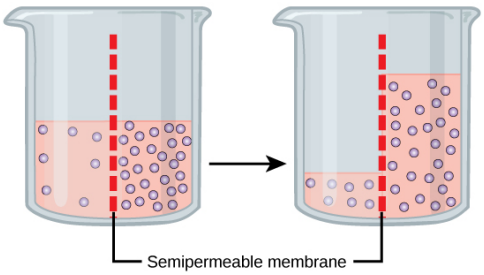


Figure 6. In osmosis, water always moves from an area of higher water concentration to one of lower concentration. In the diagram shown, the solute cannot pass through the selectively permeable membrane, but the water can.

Osmosis is a special case of diffusion. Water, like other substances, moves from an area of high concentration to one of low concentration. An obvious question is what makes water move at all? Imagine a beaker with a semipermeable membrane separating the two sides or halves (Figure 6). On both sides of the membrane the water level is the same, but there are different concentrations of a dissolved substance, or **solute**, that cannot cross the membrane (otherwise the concentrations on each side would be balanced by the solute crossing the membrane). If the volume of the solution on both sides of the membrane is the same, but the concentrations of solute are different, then there are different amounts of water, the solvent, on either side of the membrane.

To illustrate this, imagine two full glasses of water. One has a single teaspoon of sugar in it, whereas the second one contains one-quarter cup of sugar. If the total volume of the solutions in both cups is the same, which cup contains more water? Because the large amount of sugar in the second cup takes up much more space than the teaspoon of sugar in the first cup, the first cup has more water in it.

Returning to the beaker example, recall that it has a mixture of solutes on either side of the membrane. A principle of diffusion is that the molecules move around and will spread evenly throughout the medium if they can. However, only the material capable of getting through the membrane will diffuse through it. In this example, the solute cannot diffuse through the membrane, but the water can. Water has a concentration gradient in this system. Thus, water will diffuse down its concentration gradient, crossing the membrane to the side where it is less concentrated. This diffusion of water through the membrane—osmosis—will continue until the concentration gradient of water goes to zero or until the hydrostatic pressure of the water balances the osmotic pressure. Osmosis proceeds constantly in living systems.

Tonicity

Tonicity describes how an extracellular solution can change the volume of a cell by affecting osmosis. A solution's tonicity often directly correlates with the osmolarity of the solution. **Osmolarity** describes the total solute concentration of the solution. A solution with low osmolarity has a greater number of water molecules relative to the number of solute particles; a solution with high osmolarity has fewer water molecules with respect to solute particles. In a situation in which solutions of two different osmolarities are separated by a membrane permeable to water, though not to the solute, water will move from the side of the membrane with lower osmolarity (and more water) to the side with higher osmolarity (and less water). This effect makes sense if you remember that the solute cannot move across the membrane, and thus the only component in the system that can move—the water—moves along its own concentration gradient. An important distinction that concerns living systems is that osmolarity measures the number of particles (which may be molecules) in a solution. Therefore, a solution that is cloudy with cells may have a lower osmolarity than a solution that is clear, if the second solution contains more dissolved molecules than there are cells.

Hypotonic Solutions

Three terms—hypotonic, isotonic, and hypertonic—are used to relate the osmolarity of a cell to the osmolarity of the extracellular fluid that contains the cells. In a hypotonic situation, the extracellular fluid has lower osmolarity than the fluid inside the cell, and water enters the cell. (In living systems, the point of reference is always the cytoplasm, so the prefix *hypo–* means that the extracellular fluid has a lower concentration of solutes, or a lower osmolarity, than the cell cytoplasm.) It also means that the extracellular fluid has a higher concentration of water in the solution than does the cell. In this situation, water will follow its concentration gradient and enter the cell.

Hypertonic Solutions

As for a hypertonic solution, the prefix *hyper–* refers to the extracellular fluid having a higher osmolarity than the cell's cytoplasm; therefore, the fluid contains less water than the cell does. Because the cell has a relatively higher concentration of water, water will leave the cell.

Isotonic Solutions

In an isotonic solution, the extracellular fluid has the same osmolarity as the cell. If the osmolarity of the cell matches that of the extracellular fluid, there will be no net movement of water into or out of the cell, although water will still move in and out. Blood cells and plant cells (Figure 7) in hypertonic, isotonic, and hypotonic solutions take on characteristic appearances.

Practice Question

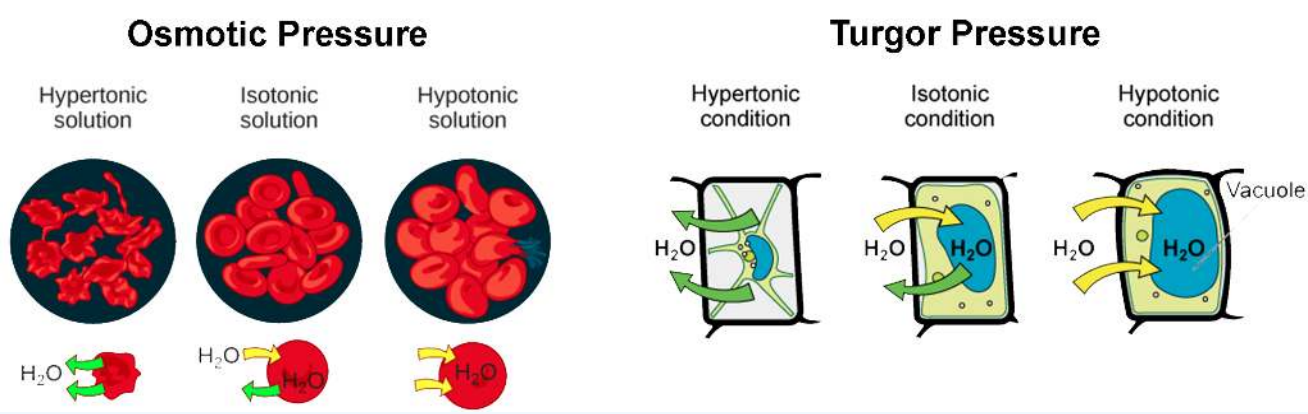


Figure 7. Osmotic pressure changes the shape of red blood cells in hypertonic, isotonic, and hypotonic solutions. The turgor pressure within a plant cell depends on the tonicity of the solution that it is bathed in. (credit: modification of work by Mariana Ruiz Villareal)

A doctor injects a patient with what the doctor thinks is an isotonic saline solution. The patient dies, and an autopsy reveals that many red blood cells have been destroyed. Do you think the solution the doctor injected was really isotonic?

Show Answer

No, it must have been hypotonic as a hypotonic solution would cause water to enter the cells, thereby making them burst.

Video Review

Watch this review of osmosis and diffusion.



In Summary: Passive Transport

No energy is required. The “driving force” is a difference in the concentration of a substance on one side of the membrane compared that on the other side.

- Simple diffusion (O_2, CO_2, H_20. Water and nonpolar molecules).
  - Osmosis is a special kind of simple diffusion for water only.
- Familiarize yourself with the terms *hypotonic*, *isotonic*, and *hypertonic*, and be able to indicate what either a plant or an animal cell will look like if placed in a particular kind of solution.
  - Example: a plant cell has a cell wall and is full and happy when placed in water (a hypotonic solution). An animal cell does not have a cell wall and will swell and burst if placed in water. This is why a patient should never receive an IV injection of water: it will cause their red blood cells to burst.
- Facilitated diffusion (sugars, ions, amino acids, etc. Charged or polar molecules).

- Carrier proteins
- Channel proteins (such as ion channels or aquaporin)

Active Transport

Active transport mechanisms require the use of the cell's energy, usually in the form of adenosine triphosphate (ATP). If a substance must move into the cell against its concentration gradient—that is, if the concentration of the substance inside the cell is greater than its concentration in the extracellular fluid (and vice versa)—the cell must use energy to move the substance. Some active transport mechanisms move small-molecular weight materials, such as ions, through the membrane. Other mechanisms transport much larger molecules.

Electrochemical Gradient

We have discussed simple concentration gradients—differential concentrations of a substance across a space or a membrane—but in living systems, gradients are more complex. Because ions move into and out of cells and because cells contain proteins that do not move across the membrane and are mostly negatively charged, there is also an electrical gradient, a difference of charge, across the plasma membrane. The interior of living cells is electrically negative with respect to the extracellular fluid in which they are bathed, and at the same time, cells have higher concentrations of potassium (K^+) and lower concentrations of sodium (Na^+) than does the extracellular fluid. So in a living cell, the concentration gradient of Na^+ tends to drive it into the cell, and the electrical gradient of Na^+ (a positive ion) also tends to drive it inward to the negatively charged interior. The situation is more complex, however, for other elements such as potassium. The electrical gradient of K^+, a positive ion, also tends to drive it into the cell, but the concentration gradient of K^+ tends to drive K^+ *out* of the cell (Figure 8). The combined gradient of concentration and electrical charge that affects an ion is called its **electrochemical gradient**.

? Practice Question

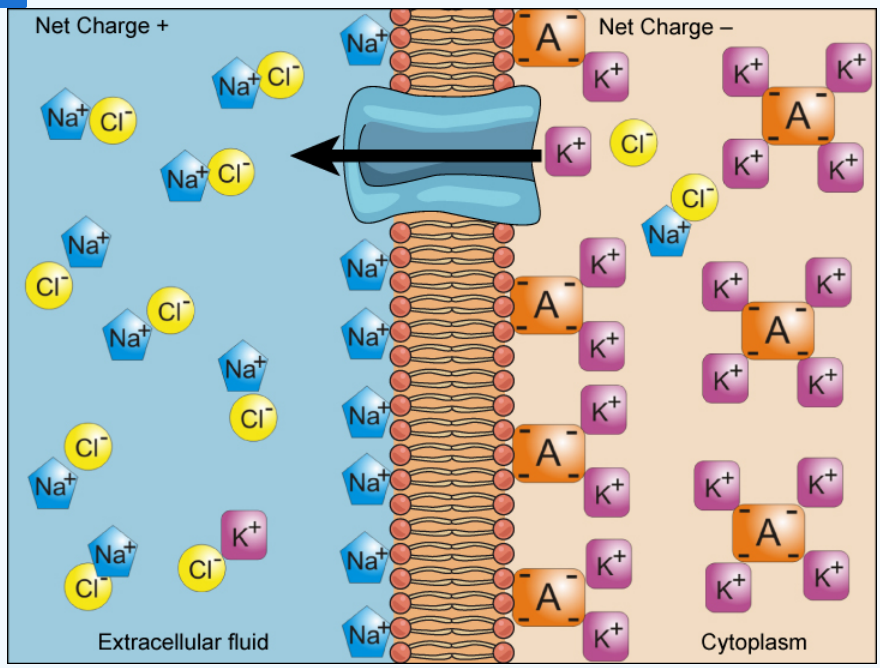


Figure 8. Electrochemical gradients arise from the combined effects of concentration gradients and electrical gradients. (credit: "Synaptitude"/Wikimedia Commons)

Injection of a potassium solution into a person's blood is lethal; this is used in capital punishment and euthanasia. Why do you think a potassium solution injection is lethal?

Show Answer

Cells typically have a high concentration of potassium in the cytoplasm and are bathed in a high concentration of sodium. Injection of potassium dissipates this electrochemical gradient. In heart muscle, the sodium/potassium potential is

responsible for transmitting the signal that causes the muscle to contract. When this potential is dissipated, the signal can't be transmitted, and the heart stops beating. Potassium injections are also used to stop the heart from beating during surgery.

Moving Against a Gradient

To move substances against a concentration or electrochemical gradient, the cell must use energy. This energy is harvested from ATP generated through the cell's metabolism. Active transport mechanisms, collectively called **pumps**, work against electrochemical gradients. Small substances constantly pass through plasma membranes. Active transport maintains concentrations of ions and other substances needed by living cells in the face of these passive movements. Much of a cell's supply of metabolic energy may be spent maintaining these processes. (Most of a red blood cell's metabolic energy is used to maintain the imbalance between exterior and interior sodium and potassium levels required by the cell.) Because active transport mechanisms depend on a cell's metabolism for energy, they are sensitive to many metabolic poisons that interfere with the supply of ATP.

Two mechanisms exist for the transport of small-molecular weight material and small molecules. **Primary active transport** moves ions across a membrane and creates a difference in charge across that membrane, which is directly dependent on ATP. **Secondary active transport** describes the movement of material that is due to the electrochemical gradient established by primary active transport that does not directly require ATP.

Carrier Proteins for Active Transport

An important membrane adaption for active transport is the presence of specific carrier proteins or pumps to facilitate movement: there are three types of these proteins or **transporters** (Figure 9). A **uniporter** carries one specific ion or molecule. A **symporter** carries two different ions or molecules, both in the same direction. An **antiporter** also carries two different ions or molecules, but in different directions. All of these transporters can also transport small, uncharged organic molecules like glucose. These three types of carrier proteins are also found in facilitated diffusion, but they do not require ATP to work in that process. Some examples of pumps for active transport are Na^{+}–K^{+} ATPase, which carries sodium and potassium ions, and H^{+}–K^{+} ATPase, which carries hydrogen and potassium ions. Both of these are antiporter carrier proteins. Two other carrier proteins are Ca^{2+} ATPase and H^{+} ATPase, which carry only calcium and only hydrogen ions, respectively. Both are pumps.

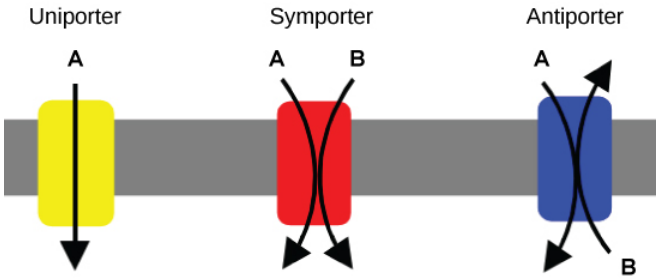


Figure 9. A uniporter carries one molecule or ion. A symporter carries two different molecules or ions, both in the same direction. An antiporter also carries two different molecules or ions, but in different directions. (credit: modification of work by "Lupask"/Wikimedia Commons)

Primary Active Transport

The primary active transport that functions with the active transport of sodium and potassium allows secondary active transport to occur. The second transport method is still considered active because it depends on the use of energy as does primary transport (Figure 10).

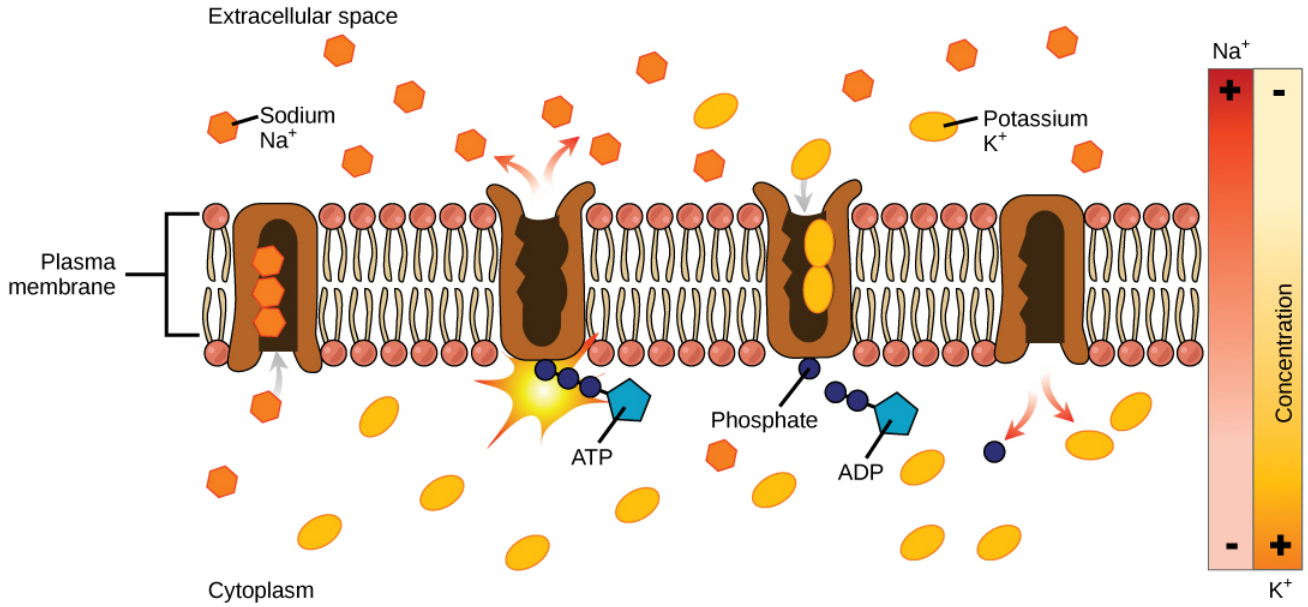


Figure 10. Primary active transport moves ions across a membrane, creating an electrochemical gradient (electrogenic transport). (credit: modification of work by Mariana Ruiz Villareal)

One of the most important pumps in animals cells is the sodium-potassium pump (Na^+-K^+ ATPase), which maintains the electrochemical gradient (and the correct concentrations of Na^+ and K^+) in living cells. The sodium-potassium pump moves K^+ into the cell while moving Na+ out at the same time, at a ratio of three Na^+ for every two K^+ ions moved in. Several things have happened as a result of this process. At this point, there are more sodium ions outside of the cell than inside and more potassium ions inside than out. For every three ions of sodium that move out, two ions of potassium move in. This results in the interior being slightly more negative relative to the exterior. This difference in charge is important in creating the conditions necessary for the secondary process. The sodium-potassium pump is, therefore, an electrogenic pump (a pump that creates a charge imbalance), creating an electrical imbalance across the membrane and contributing to the membrane potential.

Secondary Active Transport (Co-transport)

Secondary active transport brings sodium ions, and possibly other compounds, into the cell. As sodium ion concentrations build outside of the plasma membrane because of the action of the primary active transport process, an electrochemical gradient is created. If a channel protein exists and is open, the sodium ions will be pulled through the membrane. This movement is used to transport other substances that can attach themselves to the transport protein through the membrane (Figure 11). Many amino acids, as well as glucose, enter a cell this way. This secondary process is also used to store high-energy hydrogen ions in the mitochondria of plant and animal cells for the production of ATP. The potential energy that accumulates in the stored hydrogen ions is translated into kinetic energy as the ions surge through the channel protein ATP synthase, and that energy is used to convert ADP into ATP.

? Practice Question

An electrochemical gradient, created by primary active transport, can move other substances against their concentration gradients, a process called co-transport or secondary active transport.

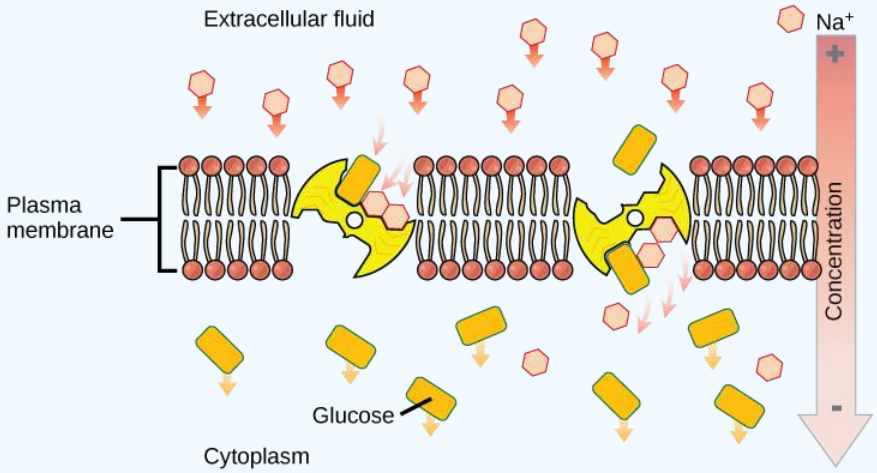


Figure 11. (credit: modification of work by Mariana Ruiz Villareal)

If the pH outside the cell decreases, would you expect the amount of amino acids transported into the cell to increase or decrease?

Show Answer

A decrease in pH means an increase in positively charged H^+ ions, and an increase in the electrical gradient across the membrane. The transport of amino acids into the cell will increase.

In Summary: Active Transport

Energy is required.

- Primary active transport (ATP is the “driving force”).
- Secondary active transport (the energy is provided by an electrochemical gradient).

Membranes and Transport

Now that we’ve learned about active and passive transport separately, let’s review both topics together. In addition to reviewing the ways transport works across membranes, this video will discuss the reasons cells must be selectively permeable.



Check Your Understanding

Answer the question(s) below to see how well you understand the topics covered in the previous section. This short quiz does **not** count toward your grade in the class, and you can retake it an unlimited number of times.

Use this quiz to check your understanding and decide whether to (1) study the previous section further or (2) move on to the next section.

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2.3.4: Endocytosis and Exocytosis

What you'll learn to do: Describe the primary mechanisms by which cells import and export macromolecules

In addition to moving small ions and molecules through the membrane, cells also need to remove and take in larger molecules and particles. Some cells are even capable of engulfing entire unicellular microorganisms. You might have correctly hypothesized that the uptake and release of large particles by the cell requires energy. A large particle, however, cannot pass through the membrane, even with energy supplied by the cell. Instead, cells use one of two primary mechanisms that transport these large particles: endocytosis and exocytosis.

Learning Objectives

- Describe endocytosis and identify different varieties of import, including phagocytosis, pinocytosis, and receptor-mediated endocytosis
- Identify the steps of exocytosis

Endocytosis

Endocytosis is a type of active transport that moves particles, such as large molecules, parts of cells, and even whole cells, into a cell. There are different variations of endocytosis, but all share a common characteristic: the plasma membrane of the cell invaginates, forming a pocket around the target particle. The pocket pinches off, resulting in the particle being contained in a newly created intracellular vesicle formed from the plasma membrane.

Phagocytosis

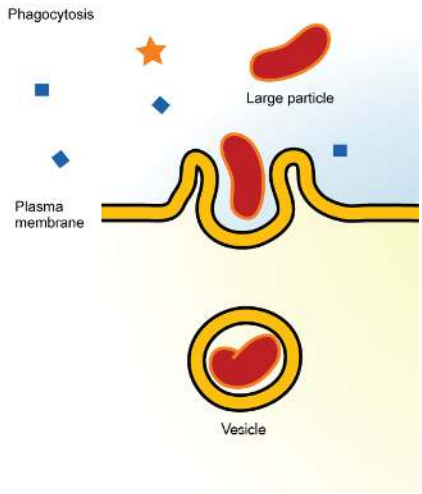


Figure 1. In phagocytosis, the cell membrane surrounds the particle and engulfs it. (credit: Mariana Ruiz Villareal)

Phagocytosis (the condition of "cell eating") is the process by which large particles, such as cells or relatively large particles, are taken in by a cell. For example, when microorganisms invade the human body, a type of white blood cell called a neutrophil will remove the invaders through this process, surrounding and engulfing the microorganism, which is then destroyed by the neutrophil (Figure 1).

In preparation for phagocytosis, a portion of the inward-facing surface of the plasma membrane becomes coated with a protein called *clathrin*, which stabilizes this section of the membrane. The coated portion of the membrane then extends from the body of the cell and surrounds the particle, eventually enclosing it. Once the vesicle containing the particle is enclosed within the cell, the clathrin disengages from the membrane and the vesicle merges with a lysosome for the breakdown of the material in the newly formed compartment (endosome). When accessible nutrients from the degradation of the vesicular contents have been extracted, the newly formed endosome merges with the plasma membrane and releases its contents into the extracellular fluid. The endosomal membrane again becomes part of the plasma membrane.

Pinocytosis

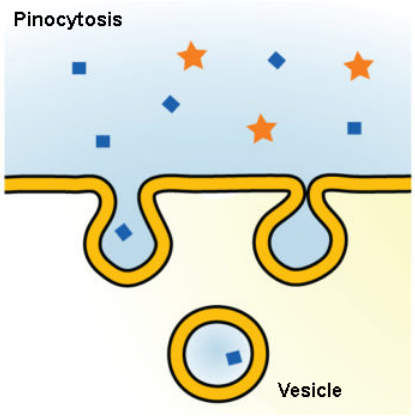


Figure 2. In pinocytosis, the cell membrane invaginates, surrounds a small volume of fluid, and pinches off. (credit: Mariana Ruiz Villareal)

A variation of endocytosis is called pinocytosis. This literally means “cell drinking” and was named at a time when the assumption was that the cell was purposefully taking in extracellular fluid. In reality, this is a process that takes in molecules, including water, which the cell needs from the extracellular fluid. Pinocytosis results in a much smaller vesicle than does phagocytosis, and the vesicle does not need to merge with a lysosome (Figure 2).

A variation of pinocytosis is called potocytosis. This process uses a coating protein, called caveolin, on the cytoplasmic side of the plasma membrane, which performs a similar function to clathrin. The cavities in the plasma membrane that form the vacuoles have membrane receptors and lipid rafts in addition to caveolin.

The vacuoles or vesicles formed in caveolae (singular caveola) are smaller than those in pinocytosis. Potocytosis is used to bring small molecules into the cell and to transport these molecules through the cell for their release on the other side of the cell, a process called transcytosis.

Receptor-Mediated Endocytosis

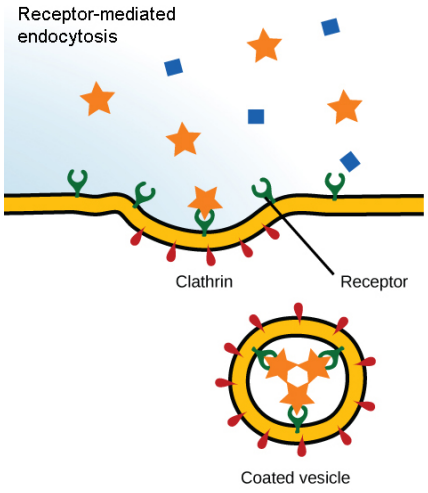


Figure 3. In receptor-mediated endocytosis, uptake of substances by the cell is targeted to a single type of substance that binds to the receptor on the external surface of the cell membrane. (credit: modification of work by Mariana Ruiz Villareal)

A targeted variation of endocytosis employs receptor proteins in the plasma membrane that have a specific binding affinity for certain substances (Figure 3).

In receptor-mediated endocytosis, as in phagocytosis, clathrin is attached to the cytoplasmic side of the plasma membrane. If uptake of a compound is dependent on receptor-mediated endocytosis and the process is ineffective, the material will not be removed from the tissue fluids or blood. Instead, it will stay in those fluids and increase in concentration.

Some human diseases are caused by the failure of receptor-mediated endocytosis. For example, the form of cholesterol termed low-density lipoprotein or LDL (also referred to as “bad” cholesterol) is removed from the blood by receptor-mediated endocytosis. In the human genetic disease familial hypercholesterolemia, the LDL receptors are defective or missing entirely. People with this condition have life-threatening levels of cholesterol in their blood, because their cells cannot clear LDL particles from their blood.

Although receptor-mediated endocytosis is designed to bring specific substances that are normally found in the extracellular fluid into the cell, other substances may gain entry into the cell at the same site. Flu viruses, diphtheria, and cholera toxin all have sites that cross-react with normal receptor-binding sites and gain entry into cells.

Learning Objectives

Cells perform three main types of endocytosis. Phagocytosis is the process by which cells ingest large particles, including other cells, by enclosing the particles in an extension of the cell membrane and budding off a new vesicle. During pinocytosis, cells take in molecules such as water from the extracellular fluid. Finally, receptor-mediated endocytosis is a targeted version of endocytosis where receptor proteins in the plasma membrane ensure only specific, targeted substances are brought into the cell.

Exocytosis

The reverse process of moving material into a cell is the process of exocytosis. Exocytosis is the opposite of the processes discussed in the last section in that its purpose is to expel material from the cell into the extracellular fluid. Waste material is enveloped in a membrane and fuses with the interior of the plasma membrane. This fusion opens the membranous envelope on the exterior of the cell, and the waste material is expelled into the extracellular space (Figure 4). Other examples of cells releasing molecules via exocytosis include the secretion of proteins of the extracellular matrix and secretion of neurotransmitters into the synaptic cleft by synaptic vesicles.

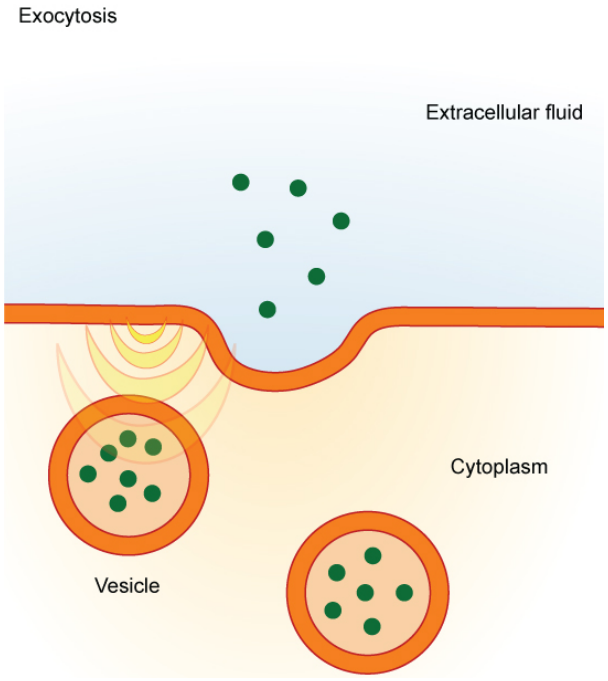


Figure 4. In exocytosis, vesicles containing substances fuse with the plasma membrane. The contents are then released to the exterior of the cell. (credit: modification of work by Mariana Ruiz Villareal)

A summary of the cellular transport methods discussed is contained in Table 1, which also includes the energy requirements and materials transported by each.

Table 1. Methods of Transport, Energy Requirements, and Types of Material Transported		
Transport Method	Active/Passive	Material Transported
Diffusion	Passive	Small-molecular weight material
Osmosis	Passive	Water
Facilitated transport/diffusion	Passive	Sodium, potassium, calcium, glucose
Primary active transport	Active	Sodium, potassium, calcium
Secondary active transport	Active	Amino acids, lactose
Phagocytosis	Active	Large macromolecules, whole cells, or cellular structures
Pinocytosis	Active	Small molecules (liquids/water)
Receptor-mediated endocytosis	Active	Large quantities of macromolecules
Exocytosis	Active	Waste materials, proteins for the extracellular matrix, neurotransmitters

Learning Objectives

Exocytosis in many ways is the reverse process from endocytosis. Here cells expel material through the fusion of vesicles with the plasma membrane and subsequent dumping of their content into the extracellular fluid.

Check Your Understanding

Answer the question(s) below to see how well you understand the topics covered in the previous section. This short quiz does **not** count toward your grade in the class, and you can retake it an unlimited number of times.

Use this quiz to check your understanding and decide whether to (1) study the previous section further or (2) move on to the next section.

https://assessments.lumenlearning.co...sessments/6873

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2.3.5: Putting It Together- Cell Membranes

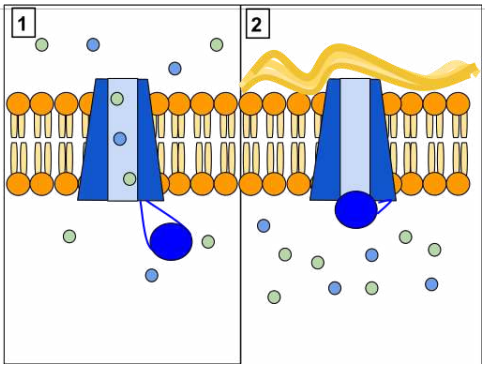


Figure 1. Panel 1 shows a properly working CFTR protein. Panel 2 shows a malfunctioning CFTR protein.

Let's return to our discussion of cystic fibrosis. Cystic fibrosis (CF) is caused by a defect in a single transmembrane protein: cystic fibrosis transmembrane conductance regulator (CFTR), as seen in Figure 1.

This regulator is a chloride ion channel that crosses through the plasma membrane. This channel is specifically active in epithelial tissues where it normally helps produce thin mucus via the movement of water. When mutated, the channel does not work properly and mucus becomes thick and viscous. This in turn leads directly to many of the symptoms of CF: thick, sticky mucus, frequent chest infections, and coughing or shortness of breath.

Treatment

Cystic fibrosis is a difficult disease to treat. As we mentioned at the beginning of the chapter, patients with CF often suffer lung infections and sometimes require lung transplants. In addition to this, many CF patients are on one or more antibiotics at all times —even when healthy—to suppress infection. Several mechanical techniques are used to dislodge sputum and encourage its expectoration. In the hospital setting, chest physiotherapy is utilized. As lung disease worsens, mechanical breathing support may become necessary. Bi-lateral lung transplantation often becomes necessary for individuals with cystic fibrosis as lung function and exercise tolerance declines.

Gene therapy has been explored as a potential cure for cystic fibrosis. Ideally, gene therapy attempts to place a normal copy of the CFTR gene into affected cells. Transferring the normal CFTR gene into the affected epithelium cells would result in the production of functional CFTR in all target cells, without adverse reactions or an inflammation response. Studies have shown that to prevent the lung manifestations of cystic fibrosis, only 5–10 percent the normal amount of CFTR gene expression is needed.

Finally, a number of small molecules that aim at compensating various mutations of the CFTR gene are under development. About 10 percent of CF cases result from a premature stop codon in the DNA, leading to early termination of protein synthesis and truncated proteins. One approach to combating a faulty receptor is to develop drugs that get the ribosome to overcome this premature stop codon and synthesize a full-length CFTR protein.

? Try It

- Cystic Fibrosis Foundation
- Cystic Fibrosis on the Mayo Clinic

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2.3.6: Assignment- Membranes Alive!

For this assessment you will conduct a kitchen science experiment in which you study the movement of materials into and out of cells. Individual cells are generally too small to see; however, a chicken egg is actually a single cell. Please note that on the whole this lab will take you 3 days to complete. However, there is less than 1 hour of 'hands-on' work on the first and last days.

Use the Membrane Lab procedure for your experimental set up.

When complete, write a lab report in MLA format that includes the following sections.

- Introduction
- Hypotheses
- Materials and Methods
- Results
- Discussion
- Conclusion
- References

Use this example to give you an idea of how your experiment may look in progress, and to help with completing your lab report.

Basic Requirements (the assignment will not be accepted or assessed unless the follow criteria have been met):

- Assignment has been proofread and does not contain any major spelling or grammatical errors
- Assignment includes appropriate references
- Assignment is formatted throughout using the MLA style.
- Assignment includes all the identified components of a lab report (hypothesis, materials and methods, results, discussion, conclusion). Images and tables are included where required and as appropriate.

Rubric

Membranes Alive!
Outcome: Describe and explain the structure and function of membranes

Membranes Alive!				
Criteria	Ratings			Pts
Introduction and conclusion sections discuss how a membrane is selectively permeable and how the experimental results demonstrate that.	Introduction and conclusion sections address selectively permeable nature of membranes and experimental results in detail. 5.0 pts	Introduction and conclusion sections address selectively permeable nature of membranes and experimental results. 4.0 pts	Introduction and/or conclusion sections lack sufficient detail or do not connect to the experiment and results. 0.0 pts	5 pts
Discussion and conclusion section address the movement of the tested substances across the membrane.	Movement of tested substances addressed correctly and in detail in both discussion and conclusion sections. Illustrations may be included. 5.0 pts	Movement of tested substances addressed correctly in both discussion and conclusion sections. 4.0 pts	Movement of tested substances not addressed correctly in both discussion and conclusion sections. 0.0 pts	5 pts
Proper terminology is used to demonstrate an understanding of transport mechanisms and how substances move across membranes in different types of solutions. Both direction and relative speed of transport is discussed.	Terminology is used accurately and speed/direction are discussed correctly and in detail. Illustrations may be included. 5.0 pts	Terminology is used accurately and speed/direction are discussed correctly. Illustrations may be included. 4.0 pts	Terminology is used incorrectly; direction and/or speed are not correctly discussed. 0.0 pts	5 pts
				Total points: 15

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CHAPTER OVERVIEW

3: Viruses and Viral Infections

Topic hierarchy

3.1: Viruses

3.1.1: Prelude to Viruses

3.1.2: Viral Evolution, Morphology, and Classification

3.1.3: Virus Infections and Hosts

3.1.4: Prevention and Treatment of Viral Infections

3.1.5: Other Acellular Entities - Prions and Viroids

3.1.E: Viruses (Exercises)

3.2: The Viruses

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SECTION OVERVIEW

3.1: Viruses

Viruses are acellular, parasitic entities that are not classified within any kingdom. Viruses are not cells and cannot divide. They infect a host cell and use the host's replication processes to produce identical progeny virus particles. Viruses infect organisms as diverse as bacteria, plants, and animals and exist in a netherworld between a living organism and a nonliving entity. Living things grow, metabolize, and reproduce. Viruses replicate, but to do so, they are entirely dependent on their host cells.

3.1.1: Prelude to Viruses

3.1.2: Viral Evolution, Morphology, and Classification

3.1.3: Virus Infections and Hosts

3.1.4: Prevention and Treatment of Viral Infections

3.1.5: Other Acellular Entities - Prions and Viroids

3.1.E: Viruses (Exercises)

Thumbnail: Ebola virus. (Public Domain; CDC).

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3.1.1: Prelude to Viruses

No one knows exactly when viruses emerged or from where they came, since viruses do not leave historical footprints such as fossils. Modern viruses are thought to be a mosaic of bits and pieces of nucleic acids picked up from various sources along their respective evolutionary paths. Viruses are acellular, parasitic entities that are not classified within any kingdom. Unlike most living organisms, viruses are not cells and cannot divide. Instead, they infect a host cell and use the host's replication processes to produce identical progeny virus particles. Viruses infect organisms as diverse as bacteria, plants, and animals. They exist in a netherworld between a living organism and a nonliving entity. Living things grow, metabolize, and reproduce. Viruses replicate, but to do so, they are entirely dependent on their host cells. They do not metabolize or grow, but are assembled in their mature form.

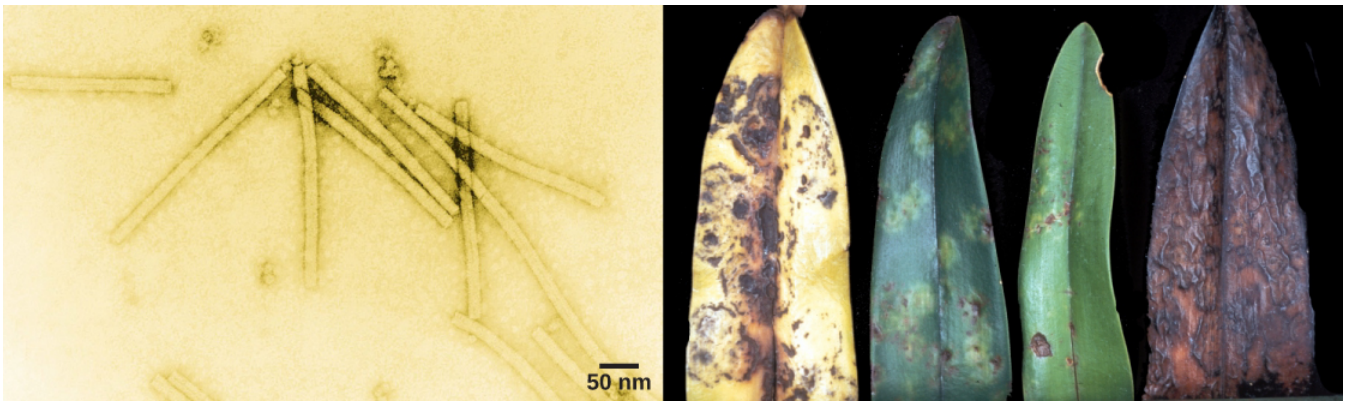


Figure 3.1.1.1: The tobacco mosaic virus (left), seen here by transmission electron microscopy, was the first virus to be discovered. The virus causes disease in tobacco and other plants, such as the orchid (right). (credit a: USDA ARS; credit b: modification of work by USDA Forest Service, Department of Plant Pathology Archive North Carolina State University; scale-bar data from Matt Russell)

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3.1.2: Viral Evolution, Morphology, and Classification

Skills to Develop

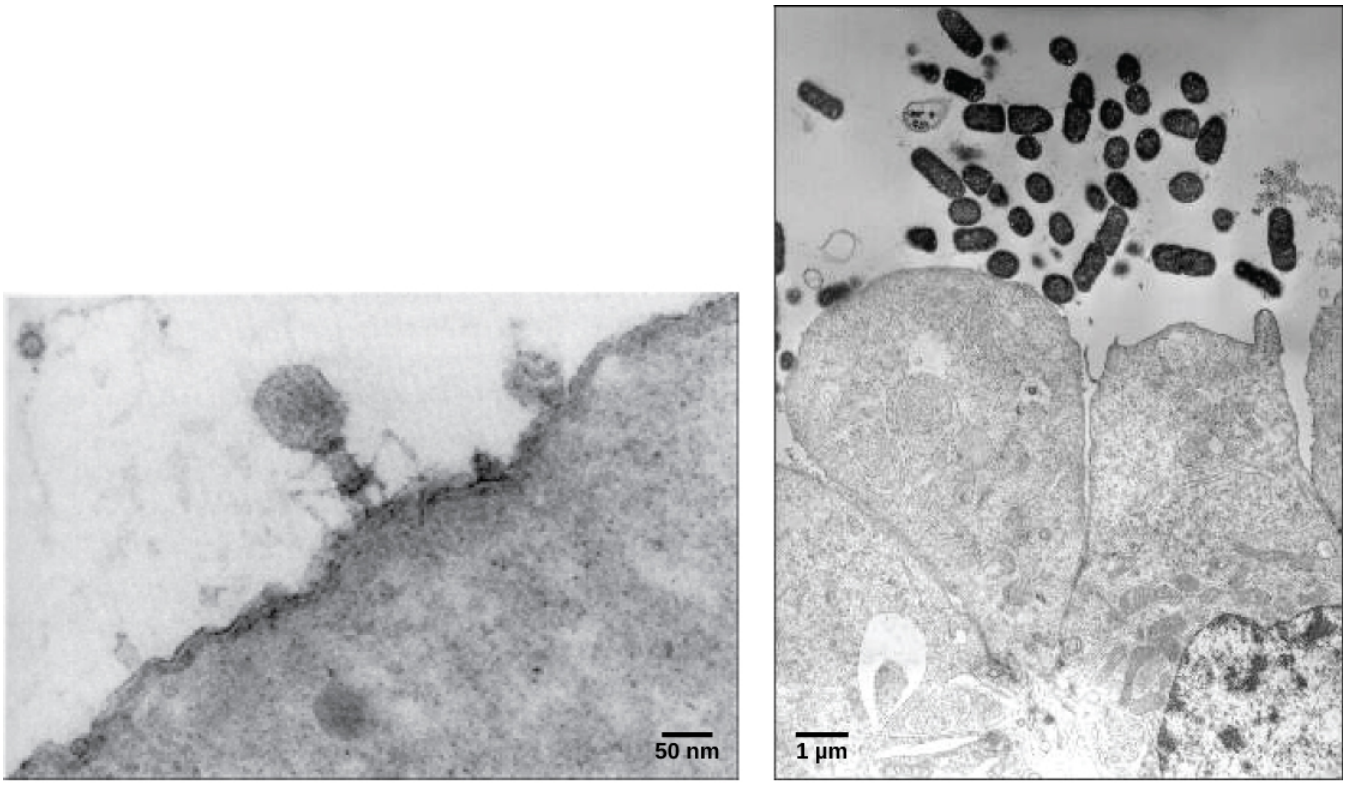
- Describe how viruses were first discovered and how they are detected
- Discuss three hypotheses about how viruses evolved
- Recognize the basic shapes of viruses
- Understand past and emerging classification systems for viruses

Viruses are diverse entities. They vary in their structure, their replication methods, and in their target hosts. Nearly all forms of life—from bacteria and archaea to eukaryotes such as plants, animals, and fungi—have viruses that infect them. While most biological diversity can be understood through evolutionary history, such as how species have adapted to conditions and environments, much about virus origins and evolution remains unknown.

Discovery and Detection

Viruses were first discovered after the development of a porcelain filter, called the Chamberland-Pasteur filter, which could remove all bacteria visible in the microscope from any liquid sample. In 1886, Adolph Meyer demonstrated that a disease of tobacco plants, tobacco mosaic disease, could be transferred from a diseased plant to a healthy one via liquid plant extracts. In 1892, Dmitri Ivanowski showed that this disease could be transmitted in this way even after the Chamberland-Pasteur filter had removed all viable bacteria from the extract. Still, it was many years before it was proven that these "filterable" infectious agents were not simply very small bacteria but were a new type of very small, disease-causing particle.

Virions, single virus particles, are very small, about 20–250 nanometers in diameter. These individual virus particles are the infectious form of a virus outside the host cell. Unlike bacteria (which are about 100-times larger), we cannot see viruses with a light microscope, with the exception of some large virions of the poxvirus family. It was not until the development of the electron microscope in the late 1930s that scientists got their first good view of the structure of the tobacco mosaic virus (TMV) (Figure 3.1.2.1) and other viruses (Figure 3.1.2.1). The surface structure of virions can be observed by both scanning and transmission electron microscopy, whereas the internal structures of the virus can only be observed in images from a transmission electron microscope. The use of these technologies has allowed for the discovery of many viruses of all types of living organisms. They were initially grouped by shared morphology. Later, groups of viruses were classified by the type of nucleic acid they contained, DNA or RNA, and whether their nucleic acid was single- or double-stranded. More recently, molecular analysis of viral replicative cycles has further refined their classification.



(a) (b)

Figure 3.1.2.1: In these transmission electron micrographs, (a) a virus is dwarfed by the bacterial cell it infects, while (b) these *E. coli* cells are dwarfed by cultured colon cells. (credit a: modification of work by U.S. Dept. of Energy, Office of Science, LBL, PBD; credit b: modification of work by J.P. Nataro and S. Sears, unpub. data, CDC; scale-bar data from Matt Russell)

Evolution of Viruses

Although biologists have accumulated a significant amount of knowledge about how present-day viruses evolve, much less is known about how viruses originated in the first place. When exploring the evolutionary history of most organisms, scientists can look at fossil records and similar historic evidence. However, viruses do not fossilize, so researchers must conjecture by investigating how today's viruses evolve and by using biochemical and genetic information to create speculative virus histories.

While most findings agree that viruses don't have a single common ancestor, scholars have yet to find a single hypothesis about virus origins that is fully accepted in the field. One such hypothesis, called devolution or the regressive hypothesis, proposes to explain the origin of viruses by suggesting that viruses evolved from free-living cells. However, many components of how this process might have occurred are a mystery. A second hypothesis (called escapist or the progressive hypothesis) accounts for viruses having either an RNA or a DNA genome and suggests that viruses originated from RNA and DNA molecules that escaped from a host cell. A third hypothesis posits a system of self-replication similar to that of other self-replicating molecules, likely evolving alongside the cells they rely on as hosts; studies of some plant pathogens support this hypothesis.

As technology advances, scientists may develop and refine further hypotheses to explain the origin of viruses. The emerging field called virus molecular systematics attempts to do just that through comparisons of sequenced genetic material. These researchers hope to one day better understand the origin of viruses, a discovery that could lead to advances in the treatments for the ailments they produce.

Viral Morphology

Viruses are acellular, meaning they are biological entities that do not have a cellular structure. They therefore lack most of the components of cells, such as organelles, ribosomes, and the plasma membrane. A virion consists of a nucleic acid core, an outer protein coating or capsid, and sometimes an outer envelope made of protein and phospholipid membranes derived from the host cell. Viruses may also contain additional proteins, such as enzymes. The most obvious difference between members of viral

families is their morphology, which is quite diverse. An interesting feature of viral complexity is that the complexity of the host does not correlate with the complexity of the virion. Some of the most complex virion structures are observed in bacteriophages, viruses that infect the simplest living organisms, bacteria.

Morphology

Viruses come in many shapes and sizes, but these are consistent and distinct for each viral family. All virions have a nucleic acid genome covered by a protective layer of proteins, called a capsid. The capsid is made up of protein subunits called capsomeres. Some viral capsids are simple polyhedral “spheres,” whereas others are quite complex in structure.

In general, the shapes of viruses are classified into four groups: filamentous, isometric (or icosahedral), enveloped, and head and tail. Filamentous viruses are long and cylindrical. Many plant viruses are filamentous, including TMV. Isometric viruses have shapes that are roughly spherical, such as poliovirus or herpesviruses. Enveloped viruses have membranes surrounding capsids. Animal viruses, such as HIV, are frequently enveloped. Head and tail viruses infect bacteria and have a head that is similar to icosahedral viruses and a tail shape like filamentous viruses.

Many viruses use some sort of glycoprotein to attach to their host cells via molecules on the cell called viral receptors (Figure 3.1.2.2). For these viruses, attachment is a requirement for later penetration of the cell membrane, so they can complete their replication inside the cell. The receptors that viruses use are molecules that are normally found on cell surfaces and have their own physiological functions. Viruses have simply evolved to make use of these molecules for their own replication. For example, HIV uses the CD4 molecule on T lymphocytes as one of its receptors. CD4 is a type of molecule called a cell adhesion molecule, which functions to keep different types of immune cells in close proximity to each other during the generation of a T lymphocyte immune response.

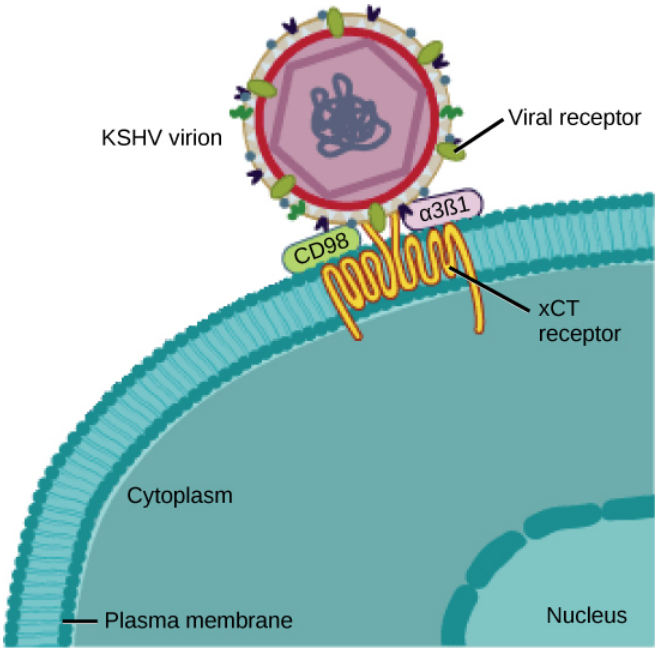


Figure 3.1.2.2: The KSHV virus binds the xCT receptor on the surface of human cells. xCT receptors protect cells against stress. Stressed cells express more xCT receptors than non-stressed cells. The KSHV virion causes cells to become stressed, thereby increasing expression of the receptor to which it binds. (credit: modification of work by NIAID, NIH)

Among the most complex virions known, the T4 bacteriophage, which infects the *Escherichia coli* bacterium, has a tail structure that the virus uses to attach to host cells and a head structure that houses its DNA.

Adenovirus, a non-enveloped animal virus that causes respiratory illnesses in humans, uses glycoprotein spikes protruding from its capsomeres to attach to host cells. Non-enveloped viruses also include those that cause polio (poliovirus), plantar warts (papillomavirus), and hepatitis A (hepatitis A virus).

Enveloped virions like HIV, the causative agent in AIDS, consist of nucleic acid (RNA in the case of HIV) and capsid proteins surrounded by a phospholipid bilayer envelope and its associated proteins. Glycoproteins embedded in the viral envelope are used

to attach to host cells. Other envelope proteins are the matrix proteins that stabilize the envelope and often play a role in the assembly of progeny virions. Chicken pox, influenza, and mumps are examples of diseases caused by viruses with envelopes. Because of the fragility of the envelope, non-enveloped viruses are more resistant to changes in temperature, pH, and some disinfectants than enveloped viruses.

Overall, the shape of the virion and the presence or absence of an envelope tell us little about what disease the virus may cause or what species it might infect, but they are still useful means to begin viral classification (Figure 3.1.2.3).

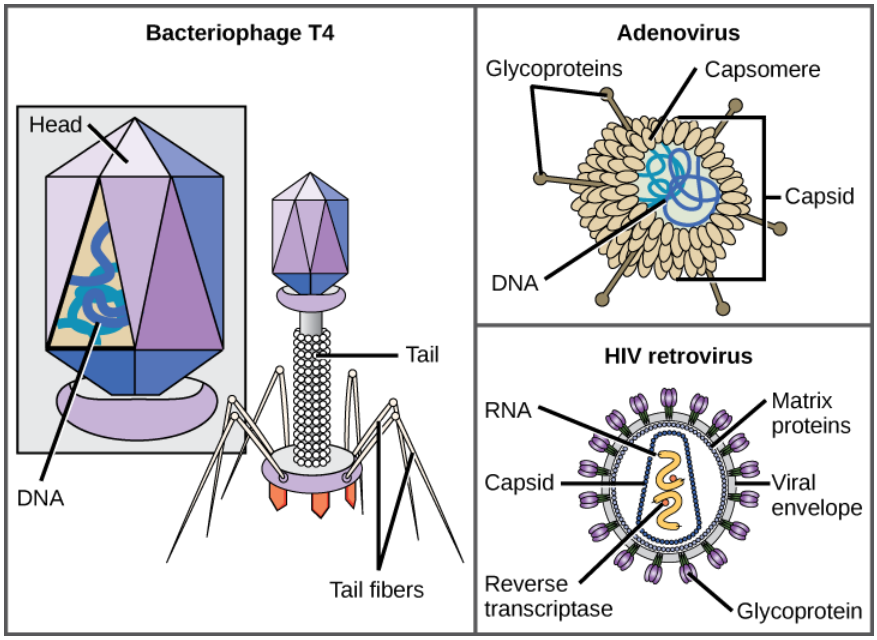


Figure 3.1.2.3: Viruses can be either complex in shape or relatively simple. This figure shows three relatively complex virions: the bacteriophage T4, with its DNA-containing head group and tail fibers that attach to host cells; adenovirus, which uses spikes from its capsid to bind to host cells; and HIV, which uses glycoproteins embedded in its envelope to bind to host cells. Notice that HIV has proteins called matrix proteins, internal to the envelope, which help stabilize virion shape. (credit "bacteriophage, adenovirus": modification of work by NCBI, NIH; credit "HIV retrovirus": modification of work by NIAID, NIH)

Exercise 3.1.2.1

Which of the following statements about virus structure is true?

A. All viruses are encased in a viral membrane.
B. The capsomere is made up of small protein subunits called capsids.
C. DNA is the genetic material in all viruses.
D. Glycoproteins help the virus attach to the host cell.

Answer

D

Types of Nucleic Acid

Unlike nearly all living organisms that use DNA as their genetic material, viruses may use either DNA or RNA as theirs. The virus core contains the genome or total genetic content of the virus. Viral genomes tend to be small, containing only those genes that encode proteins that the virus cannot get from the host cell. This genetic material may be single- or double-stranded. It may also be linear or circular. While most viruses contain a single nucleic acid, others have genomes that have several, which are called segments.

In DNA viruses, the viral DNA directs the host cell's replication proteins to synthesize new copies of the viral genome and to transcribe and translate that genome into viral proteins. DNA viruses cause human diseases, such as chickenpox, hepatitis B, and some venereal diseases, like herpes and genital warts.

RNA viruses contain only RNA as their genetic material. To replicate their genomes in the host cell, the RNA viruses encode enzymes that can replicate RNA into DNA, which cannot be done by the host cell. These RNA polymerase enzymes are more likely to make copying errors than DNA polymerases, and therefore often make mistakes during transcription. For this reason, mutations in RNA viruses occur more frequently than in DNA viruses. This causes them to change and adapt more rapidly to their host. Human diseases caused by RNA viruses include hepatitis C, measles, and rabies.

Virus Classification

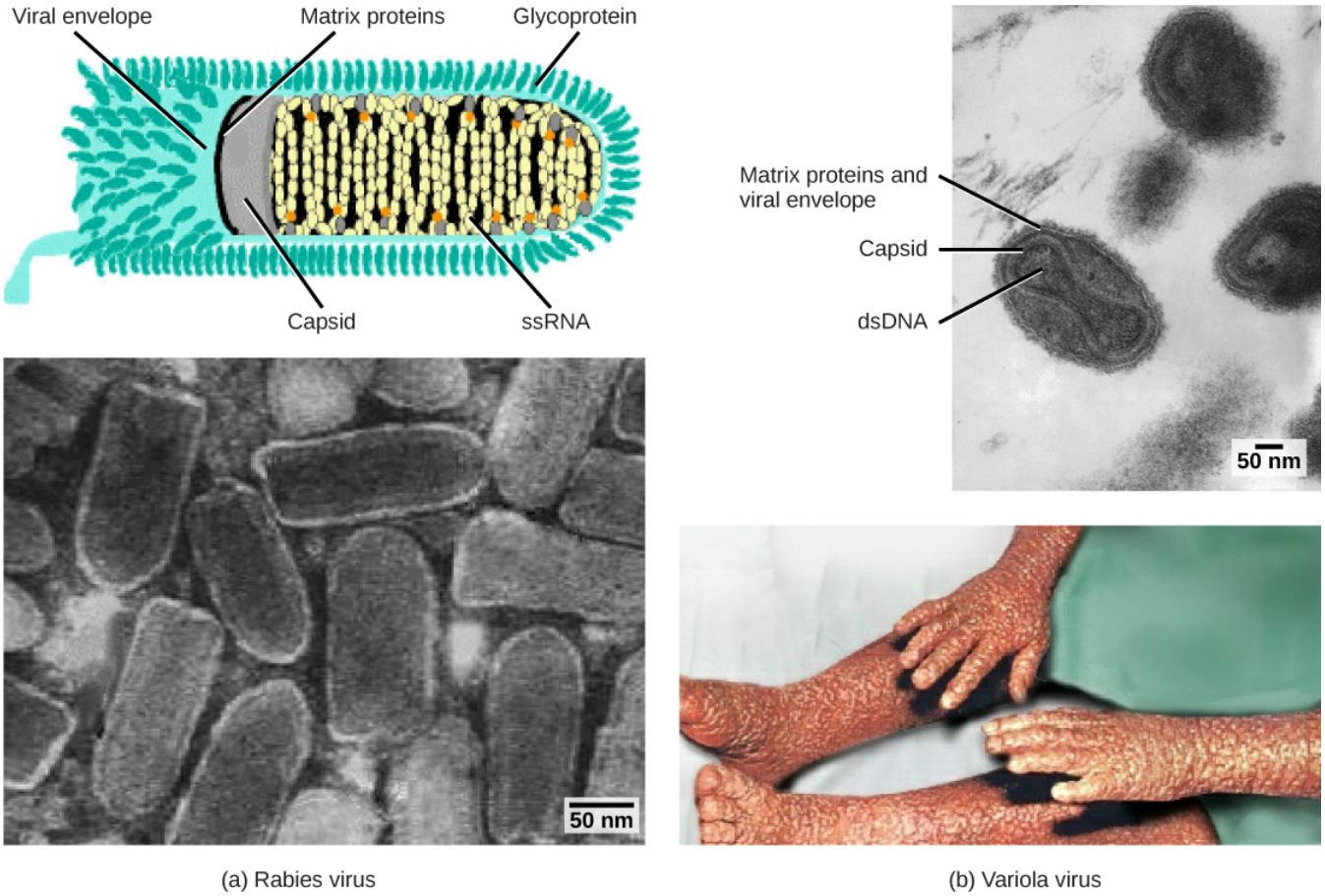
To understand the features shared among different groups of viruses, a classification scheme is necessary. As most viruses are not thought to have evolved from a common ancestor, however, the methods that scientists use to classify living things are not very useful. Biologists have used several classification systems in the past, based on the morphology and genetics of the different viruses. However, these earlier classification methods grouped viruses differently, based on which features of the virus they were using to classify them. The most commonly used classification method today is called the Baltimore classification scheme and is based on how messenger RNA (mRNA) is generated in each particular type of virus.

Past Systems of Classification

Viruses are classified in several ways: by factors such as their core content (Table 3.1.2.1 and Figure 3.1.2.2), the structure of their capsids, and whether they have an outer envelope. The type of genetic material (DNA or RNA) and its structure (single- or double-stranded, linear or circular, and segmented or non-segmented) are used to classify the virus core structures.

Table 3.1.2.1: Virus Classification by Genome Structure and Core

Core Classifications	Examples
• RNA • DNA	• Rabies virus, retroviruses • Herpesviruses, smallpox virus
• Single-stranded • Double-stranded	• Rabies virus, retroviruses • Herpesviruses, smallpox virus
• Linear • Circular	• Rabies virus, retroviruses, herpesviruses, smallpox virus • Papillomaviruses, many bacteriophages
• Non-segmented: genome consists of a single segment of genetic material • Segmented: genome is divided into multiple segments	• Parainfluenza viruses • Influenza viruses



(a) Rabies virus

(b) Variola virus

Figure 3.1.2.4: Viruses are classified based on their core genetic material and capsid design. (a) Rabies virus has a single-stranded RNA (ssRNA) core and an enveloped helical capsid, whereas (b) variola virus, the causative agent of smallpox, has a double-stranded DNA (dsDNA) core and a complex capsid. Rabies transmission occurs when saliva from an infected mammal enters a wound. The virus travels through neurons in the peripheral nervous system to the central nervous system where it impairs brain function, and then travels to other tissues. The virus can infect any mammal, and most die within weeks of infection. Smallpox is a human virus transmitted by inhalation of the variola virus, localized in the skin, mouth, and throat, which causes a characteristic rash. Before its eradication in 1979, infection resulted in a 30–35 percent mortality rate. (credit "rabies diagram": modification of work by CDC; "rabies micrograph": modification of work by Dr. Fred Murphy, CDC; credit "small pox micrograph": modification of work by Dr. Fred Murphy, Sylvia Whitfield, CDC; credit "smallpox photo": modification of work by CDC; scale-bar data from Matt Russell)

Viruses can also be classified by the design of their capsids (Figure 3.1.2.3 and Figure 3.1.2.4). Capsids are classified as naked icosahedral, enveloped icosahedral, enveloped helical, naked helical, and complex (Figure 3.1.2.5 and Figure 3.1.2.6). The type of genetic material (DNA or RNA) and its structure (single- or double-stranded, linear or circular, and segmented or non-segmented) are used to classify the virus core structures (Table 3.1.2.2).

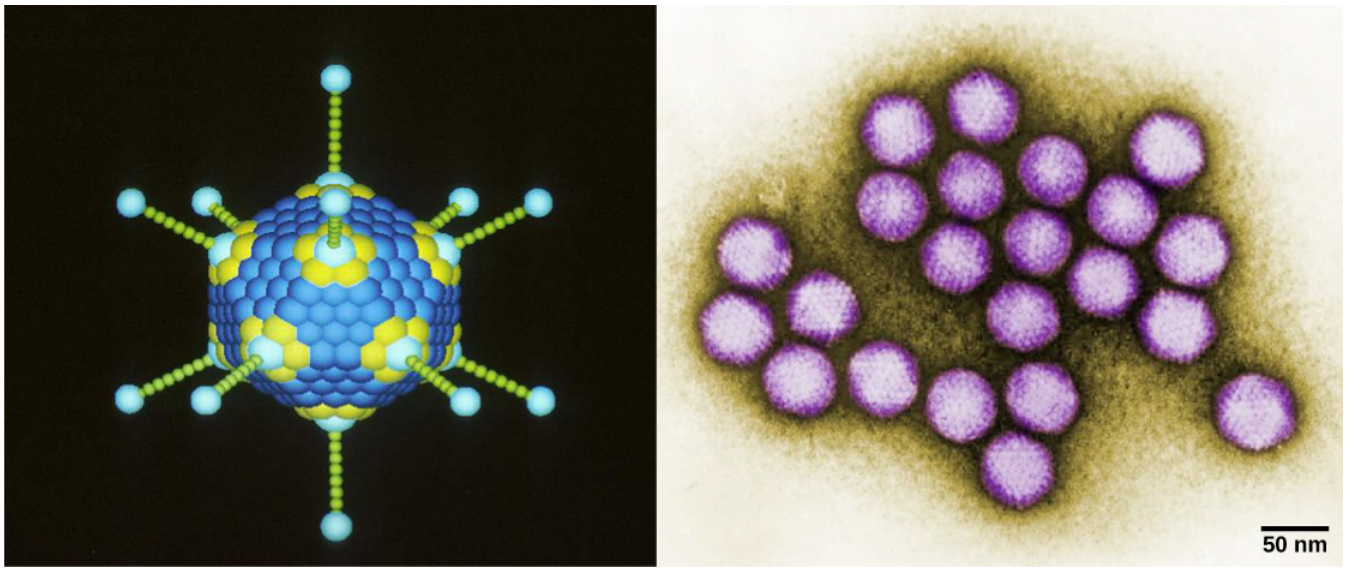


Figure 3.1.2.5: Adenovirus (left) is depicted with a double-stranded DNA genome enclosed in an icosahedral capsid that is 90–100 nm across. The virus, shown clustered in the micrograph (right), is transmitted orally and causes a variety of illnesses in vertebrates, including human eye and respiratory infections. (credit “adenovirus”: modification of work by Dr. Richard Feldmann, National Cancer Institute; credit “micrograph”: modification of work by Dr. G. William Gary, Jr., CDC; scale-bar data from Matt Russell)

Table 3.1.2.2: Virus Classification by Capsid Structure

Capsid Classification	Examples
Naked icosahedral	Hepatitis A virus, polioviruses
Enveloped icosahedral	Epstein-Barr virus, herpes simplex virus, rubella virus, yellow fever virus, HIV-1
Enveloped helical	Influenza viruses, mumps virus, measles virus, rabies virus
Naked helical	Tobacco mosaic virus
Complex with many proteins; some have combinations of icosahedral and helical capsid structures	Herpesviruses, smallpox virus, hepatitis B virus, T4 bacteriophage

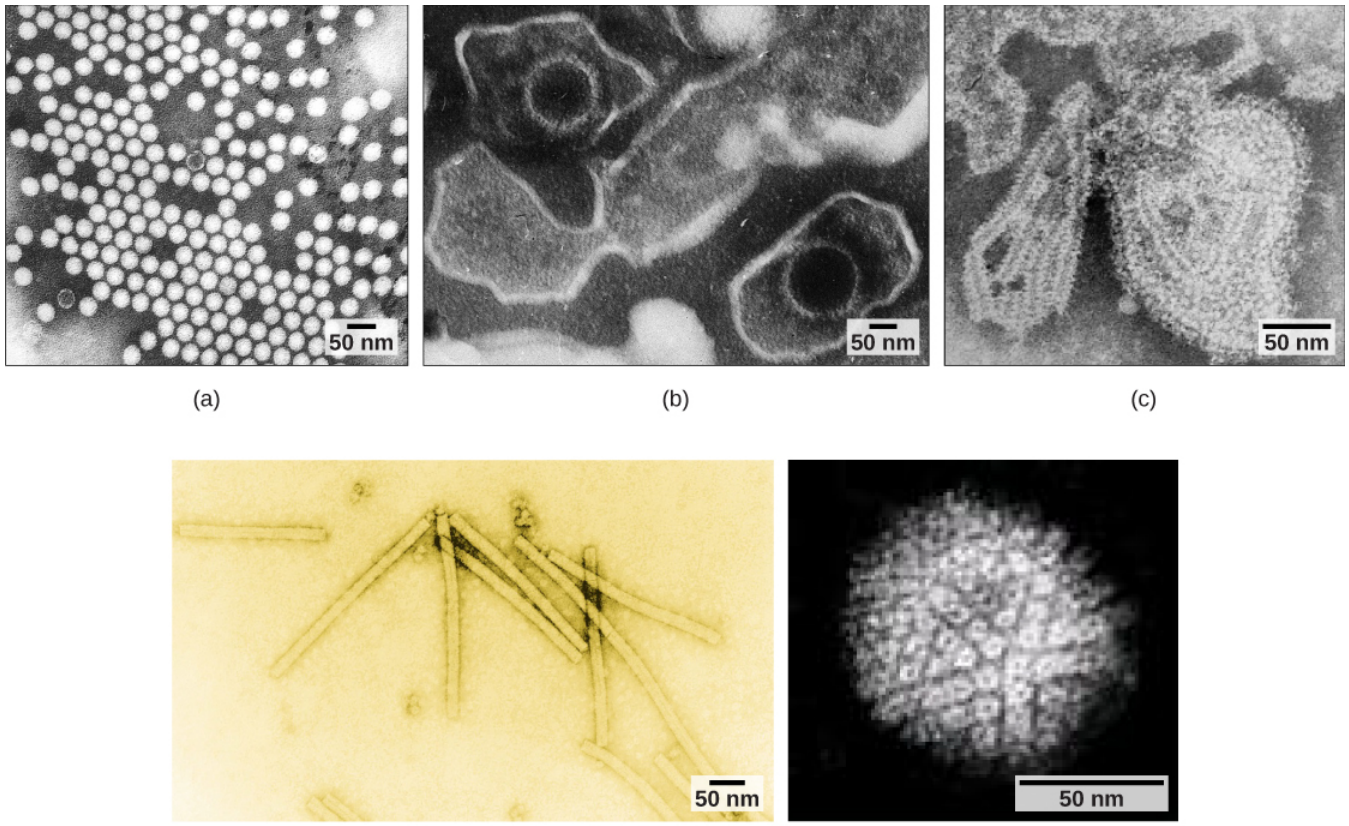


Figure 3.1.2.6: Transmission electron micrographs of various viruses show their structures. The capsid of the (a) polio virus is naked icosahedral; (b) the Epstein-Barr virus capsid is enveloped icosahedral; (c) the mumps virus capsid is an enveloped helix; (d) the tobacco mosaic virus capsid is naked helical; and (e) the herpesvirus capsid is complex. (credit a: modification of work by Dr. Fred Murphy, Sylvia Whitfield; credit b: modification of work by Liza Gross; credit c: modification of work by Dr. F. A. Murphy, CDC; credit d: modification of work by USDA ARS; credit e: modification of work by Linda Stannard, Department of Medical Microbiology, University of Cape Town, South Africa, NASA; scale-bar data from Matt Russell)

Baltimore Classification

The most commonly used system of virus classification was developed by Nobel Prize-winning biologist David Baltimore in the early 1970s. In addition to the differences in morphology and genetics mentioned above, the Baltimore classification scheme groups viruses according to how the mRNA is produced during the replicative cycle of the virus.

Group I viruses contain double-stranded DNA (dsDNA) as their genome. Their mRNA is produced by transcription in much the same way as with cellular DNA. Group II viruses have single-stranded DNA (ssDNA) as their genome. They convert their single-stranded genomes into a dsDNA intermediate before transcription to mRNA can occur. Group III viruses use dsRNA as their genome. The strands separate, and one of them is used as a template for the generation of mRNA using the RNA-dependent RNA polymerase encoded by the virus. Group IV viruses have ssRNA as their genome with a positive polarity. Positive polarity means that the genomic RNA can serve directly as mRNA. Intermediates of dsRNA, called replicative intermediates, are made in the process of copying the genomic RNA. Multiple, full-length RNA strands of negative polarity (complimentary to the positive-stranded genomic RNA) are formed from these intermediates, which may then serve as templates for the production of RNA with positive polarity, including both full-length genomic RNA and shorter viral mRNAs. Group V viruses contain ssRNA genomes with a negative polarity, meaning that their sequence is complementary to the mRNA. As with Group IV viruses, dsRNA intermediates are used to make copies of the genome and produce mRNA. In this case, the negative-stranded genome can be converted directly to mRNA. Additionally, full-length positive RNA strands are made to serve as templates for the production of the negative-stranded genome. Group VI viruses have diploid (two copies) ssRNA genomes that must be converted, using the enzyme reverse transcriptase, to dsDNA; the dsDNA is then transported to the nucleus of the host cell and inserted into the host genome. Then, mRNA can be produced by transcription of the viral DNA that was integrated into the host genome. Group VII viruses have partial dsDNA genomes and make ssRNA intermediates that act as mRNA, but are also converted back into dsDNA genomes by reverse

transcriptase, necessary for genome replication. The characteristics of each group in the Baltimore classification are summarized in the Table 3.1.2.3 with examples of each group.

Table 3.1.2.3: Baltimore Classification

Group	Characteristics	Mode of mRNA Production	Example
I	Double-stranded DNA	mRNA is transcribed directly from the DNA template	Herpes simplex (herpesvirus)
II	Single-stranded DNA	DNA is converted to double-stranded form before RNA is transcribed	Canine parvovirus (parvovirus)
III	Double-stranded RNA	mRNA is transcribed from the RNA genome	Childhood gastroenteritis (rotavirus)
IV	Single stranded RNA (+)	Genome functions as mRNA	Common cold (pircornavirus)
V	Single stranded RNA (-)	mRNA is transcribed from the RNA genome	Rabies (rhabdovirus)
VI	Single stranded RNA viruses with reverse transcriptase	Reverse transcriptase makes DNA from the RNA genome; DNA is then incorporated in the host genome; mRNA is transcribed from the incorporated DNA	Human immunodeficiency virus (HIV)
VII	Double stranded DNA viruses with reverse transcriptase	The viral genome is double-stranded DNA, but viral DNA is replicated through an RNA intermediate; the RNA may serve directly as mRNA or as a template to make mRNA	Hepatitis B virus (hepadnavirus)

Summary

Viruses are tiny, acellular entities that can usually only be seen with an electron microscope. Their genomes contain either DNA or RNA—never both—and they replicate using the replication proteins of a host cell. Viruses are diverse, infecting archaea, bacteria, fungi, plants, and animals. Viruses consist of a nucleic acid core surrounded by a protein capsid with or without an outer lipid envelope. The capsid shape, presence of an envelope, and core composition dictate some elements of the classification of viruses. The most commonly used classification method, the Baltimore classification, categorizes viruses based on how they produce their mRNA.

Glossary

acellular
lacking cells

capsid
protein coating of the viral core

capsomere
protein subunit that makes up the capsid

envelope
lipid bilayer that envelopes some viruses

group I virus
virus with a dsDNA genome

group II virus
virus with a ssDNA genome

group III virus
virus with a dsRNA genome

group IV virus
virus with a ssRNA genome with positive polarity

group V virus
virus with a ssRNA genome with negative polarity

group VI virus
virus with a ssRNA genomes converted into dsDNA by reverse transcriptase

group VII virus
virus with a single-stranded mRNA converted into dsDNA for genome replication

matrix protein
envelope protein that stabilizes the envelope and often plays a role in the assembly of progeny virions

negative polarity
ssRNA viruses with genomes complimentary to their mRNA

positive polarity
ssRNA virus with a genome that contains the same base sequences and codons found in their mRNA

replicative intermediate
dsRNA intermediate made in the process of copying genomic RNA

reverse transcriptase
enzyme found in Baltimore groups VI and VII that converts single-stranded RNA into double-stranded DNA

viral receptor
glycoprotein used to attach a virus to host cells via molecules on the cell

virion
individual virus particle outside a host cell

virus core
contains the virus genome

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3.1.3: Virus Infections and Hosts

Skills to Develop

- List the steps of replication and explain what occurs at each step
- Describe the lytic and lysogenic cycles of virus replication
- Explain the transmission and diseases of animal and plant viruses
- Discuss the economic impact of animal and plant viruses

Viruses can be seen as obligate, intracellular parasites. A virus must attach to a living cell, be taken inside, manufacture its proteins and copy its genome, and find a way to escape the cell so that the virus can infect other cells. Viruses can infect only certain species of hosts and only certain cells within that host. Cells that a virus may use to replicate are called permissive. For most viruses, the molecular basis for this specificity is that a particular surface molecule known as the viral receptor must be found on the host cell surface for the virus to attach. Also, metabolic and host cell immune response differences seen in different cell types based on differential gene expression are a likely factor in which cells a virus may target for replication. The permissive cell must make the substances that the virus needs or the virus will not be able to replicate there.

Steps of Virus Infections

A virus must use cell processes to replicate. The viral replication cycle can produce dramatic biochemical and structural changes in the host cell, which may cause cell damage. These changes, called cytopathic (causing cell damage) effects, can change cell functions or even destroy the cell. Some infected cells, such as those infected by the common cold virus known as rhinovirus, die through lysis (bursting) or apoptosis (programmed cell death or “cell suicide”), releasing all progeny virions at once. The symptoms of viral diseases result from the immune response to the virus, which attempts to control and eliminate the virus from the body, and from cell damage caused by the virus. Many animal viruses, such as HIV (human immunodeficiency virus), leave the infected cells of the immune system by a process known as budding, where virions leave the cell individually. During the budding process, the cell does not undergo lysis and is not immediately killed. However, the damage to the cells that the virus infects may make it impossible for the cells to function normally, even though the cells remain alive for a period of time. Most productive viral infections follow similar steps in the virus replication cycle: attachment, penetration, uncoating, replication, assembly, and release (Figure 3.1.3.1).

Attachment

A virus attaches to a specific receptor site on the host cell membrane through attachment proteins in the capsid or via glycoproteins embedded in the viral envelope. The specificity of this interaction determines the host—and the cells within the host—that can be infected by a particular virus. This can be illustrated by thinking of several keys and several locks, where each key will fit only one specific lock.

Entry

The nucleic acid of bacteriophages enters the host cell naked, leaving the capsid outside the cell. Plant and animal viruses can enter through endocytosis, in which the cell membrane surrounds and engulfs the entire virus. Some enveloped viruses enter the cell when the viral envelope fuses directly with the cell membrane. Once inside the cell, the viral capsid is degraded, and the viral nucleic acid is released, which then becomes available for replication and transcription.

Replication and Assembly

The replication mechanism depends on the viral genome. DNA viruses usually use host cell proteins and enzymes to make additional DNA that is transcribed to messenger RNA (mRNA), which is then used to direct protein synthesis. RNA viruses usually use the RNA core as a template for synthesis of viral genomic RNA and mRNA. The viral mRNA directs the host cell to synthesize viral enzymes and capsid proteins, and assemble new virions. Of course, there are exceptions to this pattern. If a host cell does not provide the enzymes necessary for viral replication, viral genes supply the information to direct synthesis of the missing proteins. Retroviruses, such as HIV, have an RNA genome that must be reverse transcribed into DNA, which then is incorporated into the host cell genome. They are within group VI of the Baltimore classification scheme. To convert RNA into DNA, retroviruses must

contain genes that encode the virus-specific enzyme reverse transcriptase that transcribes an RNA template to DNA. Reverse transcription never occurs in uninfected host cells—the needed enzyme reverse transcriptase is only derived from the expression of viral genes within the infected host cells. The fact that HIV produces some of its own enzymes not found in the host has allowed researchers to develop drugs that inhibit these enzymes. These drugs, including the reverse transcriptase inhibitor AZT, inhibit HIV replication by reducing the activity of the enzyme without affecting the host's metabolism. This approach has led to the development of a variety of drugs used to treat HIV and has been effective at reducing the number of infectious virions (copies of viral RNA) in the blood to non-detectable levels in many HIV-infected individuals.

Egress

The last stage of viral replication is the release of the new virions produced in the host organism, where they are able to infect adjacent cells and repeat the replication cycle. As you've learned, some viruses are released when the host cell dies, and other viruses can leave infected cells by budding through the membrane without directly killing the cell.

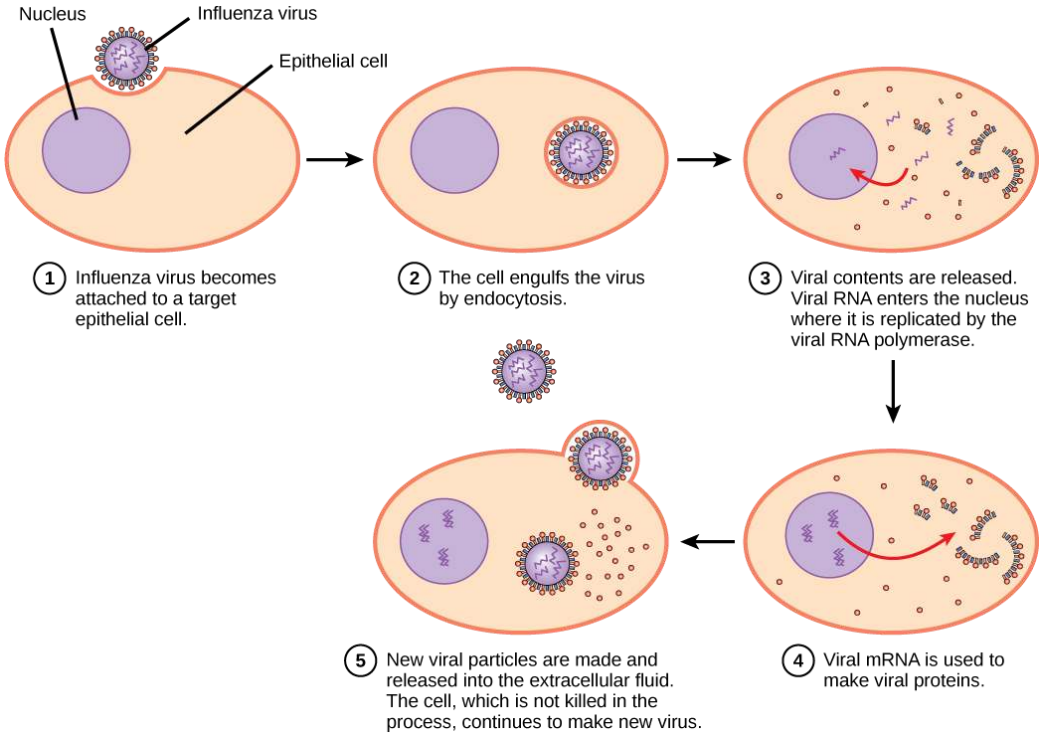


Figure 3.1.3.1: In influenza virus infection, glycoproteins attach to a host epithelial cell. As a result, the virus is engulfed. RNA and proteins are made and assembled into new virions.

Exercise 3.1.3.1

Influenza virus is packaged in a viral envelope that fuses with the plasma membrane. This way, the virus can exit the host cell without killing it. What advantage does the virus gain by keeping the host cell alive?

Answer

The host cell can continue to make new virus particles.

Link to Learning



Watch a video on viruses, identifying structures, modes of transmission, replication, and more.

Different Hosts and Their Viruses

As you've learned, viruses are often very specific as to which hosts and which cells within the host they will infect. This feature of a virus makes it specific to one or a few species of life on Earth. On the other hand, so many different types of viruses exist on Earth that nearly every living organism has its own set of viruses that tries to infect its cells. Even the smallest and simplest of cells, prokaryotic bacteria, may be attacked by specific types of viruses.

Bacteriophages

Bacteriophages are viruses that infect bacteria (Figure 3.1.3.2). When infection of a cell by a bacteriophage results in the production of new virions, the infection is said to be productive. If the virions are released by bursting the cell, the virus replicates by means of a lytic cycle (Figure 3.1.3.3).

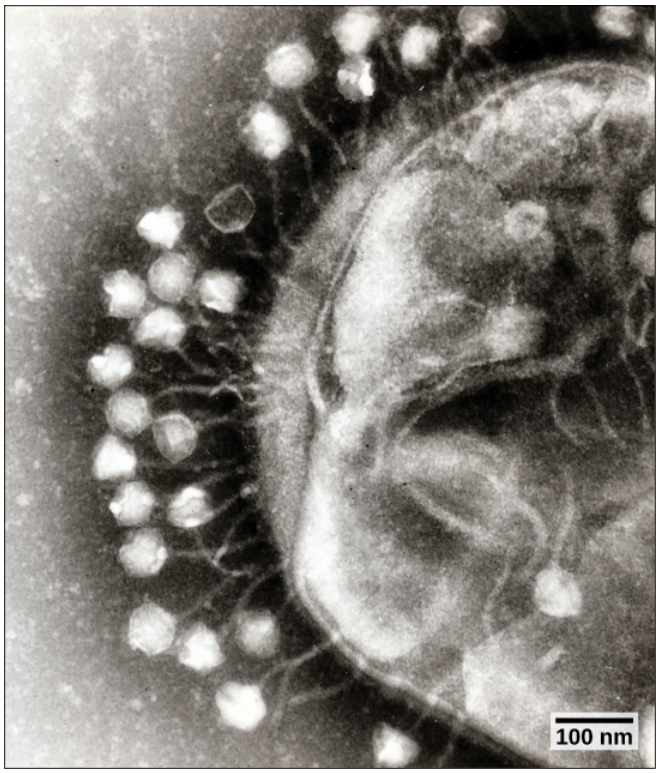


Figure 3.1.3.2: This transmission electron micrograph shows bacteriophages attached to a bacterial cell. (credit: modification of work by Dr. Graham Beards; scale-bar data from Matt Russell)

An example of a lytic bacteriophage is T4, which infects *Escherichia coli* found in the human intestinal tract. Sometimes, however, a virus can remain within the cell without being released. For example, when a temperate bacteriophage infects a bacterial cell, it replicates by means of a lysogenic cycle (Figure 3.1.3.3), and the viral genome is incorporated into the genome of the host cell. When the phage DNA is incorporated into the host cell genome, it is called a prophage. An example of a lysogenic bacteriophage is the λ (lambda) virus, which also infects the *E. coli* bacterium. Viruses that infect plant or animal cells may also undergo infections where they are not producing virions for long periods. An example is the animal herpesviruses, including herpes simplex viruses, the cause of oral and genital herpes in humans. In a process called latency, these viruses can exist in nervous tissue for long periods of time without producing new virions, only to leave latency periodically and cause lesions in the skin where the virus replicates. Even though there are similarities between lysogeny and latency, the term lysogenic cycle is usually reserved to describe bacteriophages. Latency will be described in more detail below.

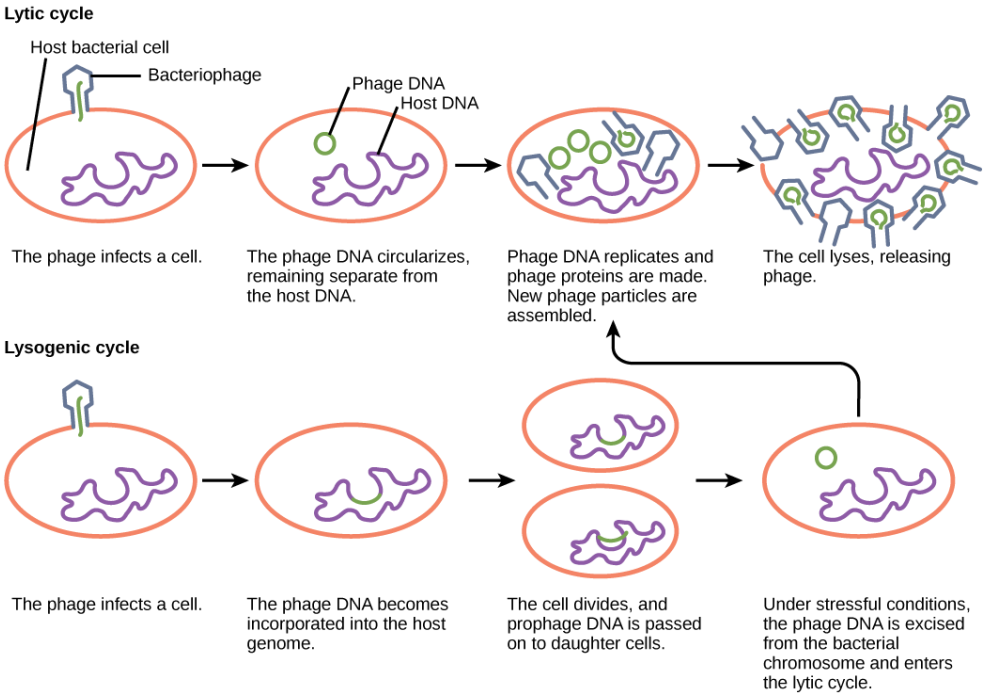


Figure 3.1.3.3: A temperate bacteriophage has both lytic and lysogenic cycles. In the lytic cycle, the phage replicates and lyses the host cell. In the lysogenic cycle, phage DNA is incorporated into the host genome, where it is passed on to subsequent generations. Environmental stressors such as starvation or exposure to toxic chemicals may cause the prophage to excise and enter the lytic cycle.

Exercise 3.1.3.2

Which of the following statements is false?

A. In the lytic cycle, new phage are produced and released into the environment.
B. In the lysogenic cycle, phage DNA is incorporated into the host genome.
C. An environmental stressor can cause the phage to initiate the lysogenic cycle.
D. Cell lysis only occurs in the lytic cycle.

Answer

C

Animal Viruses

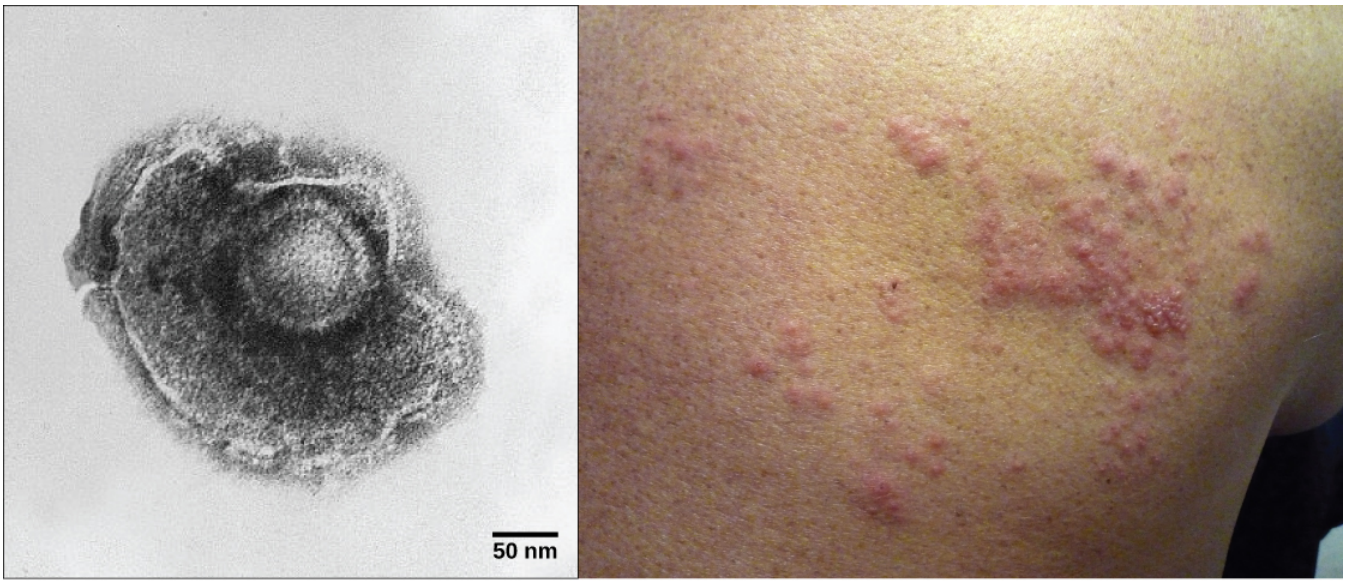
Animal viruses, unlike the viruses of plants and bacteria, do not have to penetrate a cell wall to gain access to the host cell. Non-enveloped or “naked” animal viruses may enter cells in two different ways. As a protein in the viral capsid binds to its receptor on the host cell, the virus may be taken inside the cell via a vesicle during the normal cell process of receptor-mediated endocytosis. An alternative method of cell penetration used by non-enveloped viruses is for capsid proteins to undergo shape changes after binding to the receptor, creating channels in the host cell membrane. The viral genome is then “injected” into the host cell through these channels in a manner analogous to that used by many bacteriophages. Enveloped viruses also have two ways of entering cells after binding to their receptors: receptor-mediated endocytosis, or fusion. Many enveloped viruses enter the cell by receptor-mediated endocytosis in a fashion similar to some non-enveloped viruses. On the other hand, fusion only occurs with enveloped virions. These viruses, which include HIV among others, use special fusion proteins in their envelopes to cause the envelope to fuse with the plasma membrane of the cell, thus releasing the genome and capsid of the virus into the cell cytoplasm.

After making their proteins and copying their genomes, animal viruses complete the assembly of new virions and exit the cell. As we have already discussed using the example of HIV, enveloped animal viruses may bud from the cell membrane as they assemble themselves, taking a piece of the cell’s plasma membrane in the process. On the other hand, non-enveloped viral progeny, such as rhinoviruses, accumulate in infected cells until there is a signal for lysis or apoptosis, and all virions are released together.

As you will learn in the next module, animal viruses are associated with a variety of human diseases. Some of them follow the classic pattern of acute disease, where symptoms get increasingly worse for a short period followed by the elimination of the virus from the body by the immune system and eventual recovery from the infection. Examples of acute viral diseases are the common cold and influenza. Other viruses cause long-term chronic infections, such as the virus causing hepatitis C, whereas others, like herpes simplex virus, only cause intermittent symptoms. Still other viruses, such as human herpesviruses 6 and 7, which in some cases can cause the minor childhood disease roseola, often successfully cause productive infections without causing any symptoms at all in the host, and thus we say these patients have an asymptomatic infection.

In hepatitis C infections, the virus grows and reproduces in liver cells, causing low levels of liver damage. The damage is so low that infected individuals are often unaware that they are infected, and many infections are detected only by routine blood work on patients with risk factors such as intravenous drug use. On the other hand, since many of the symptoms of viral diseases are caused by immune responses, a lack of symptoms is an indication of a weak immune response to the virus. This allows for the virus to escape elimination by the immune system and persist in individuals for years, all the while producing low levels of progeny virions in what is known as a chronic viral disease. Chronic infection of the liver by this virus leads to a much greater chance of developing liver cancer, sometimes as much as 30 years after the initial infection.

As already discussed, herpes simplex virus can remain in a state of latency in nervous tissue for months, even years. As the virus “hides” in the tissue and makes few if any viral proteins, there is nothing for the immune response to act against, and immunity to the virus slowly declines. Under certain conditions, including various types of physical and psychological stress, the latent herpes simplex virus may be reactivated and undergo a lytic replication cycle in the skin, causing the lesions associated with the disease. Once virions are produced in the skin and viral proteins are synthesized, the immune response is again stimulated and resolves the skin lesions in a few days by destroying viruses in the skin. As a result of this type of replicative cycle, appearances of cold sores and genital herpes outbreaks only occur intermittently, even though the viruses remain in the nervous tissue for life. Latent infections are common with other herpesviruses as well, including the varicella-zoster virus that causes chickenpox. After having a chickenpox infection in childhood, the varicella-zoster virus can remain latent for many years and reactivate in adults to cause the painful condition known as “shingles” (Figure 3.1.3.4).



(a) (b)

Figure 3.1.3.4: (a) Varicella-zoster, the virus that causes chickenpox, has an enveloped icosahedral capsid visible in this transmission electron micrograph. Its double-stranded DNA genome becomes incorporated in the host DNA and can reactivate after latency in the form of (b) shingles, often exhibiting a rash. (credit a: modification of work by Dr. Erskine Palmer, B. G. Martin, CDC; credit b: modification of work by "rosmary"/Flickr; scale-bar data from Matt Russell)

Some animal-infecting viruses, including the hepatitis C virus discussed above, are known as oncogenic viruses: They have the ability to cause cancer. These viruses interfere with the normal regulation of the host cell cycle either by either introducing genes that stimulate unregulated cell growth (oncogenes) or by interfering with the expression of genes that inhibit cell growth. Oncogenic viruses can be either DNA or RNA viruses. Cancers known to be associated with viral infections include cervical cancer caused by human papillomavirus (HPV) (Figure 3.1.3.5), liver cancer caused by hepatitis B virus, T-cell leukemia, and several types of lymphoma.

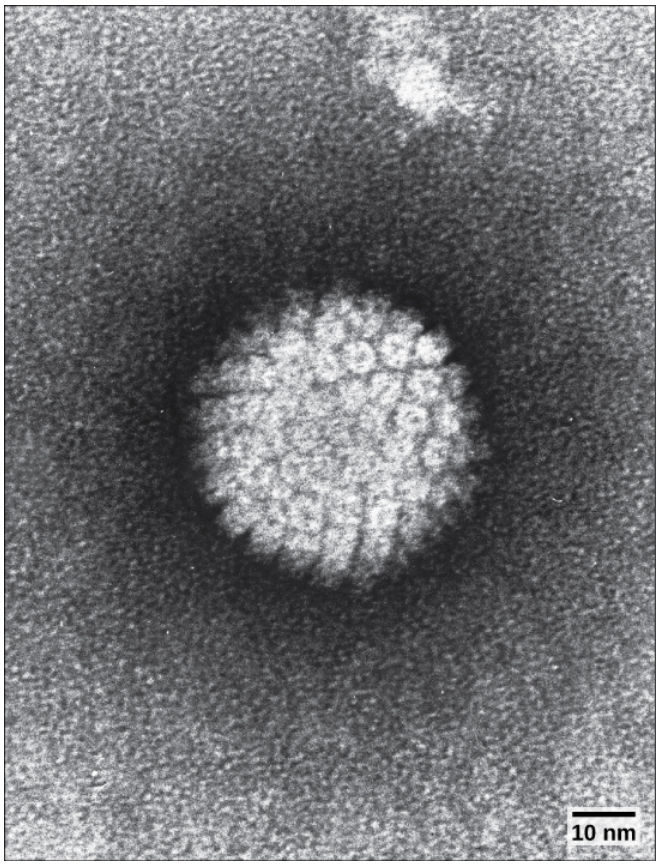
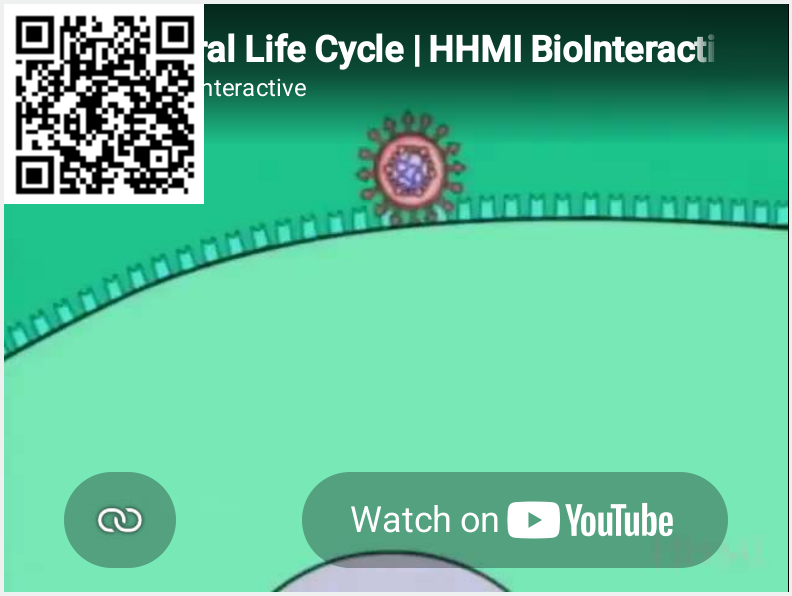


Figure 3.1.3.5: HPV, or human papillomavirus, has a naked icosahedral capsid visible in this transmission electron micrograph and a double-stranded DNA genome that is incorporated into the host DNA. The virus, which is sexually transmitted, is oncogenic and can lead to cervical cancer. (credit: modification of work by NCI, NIH; scale-bar data from Matt Russell)

Link to Learning



Visit the interactive animations showing the various stages of the replicative cycles of animal viruses and click on the flash animation links.

Plant Viruses

Plant viruses, like other viruses, contain a core of either DNA or RNA. You have already learned about one of these, the tobacco mosaic virus. As plant viruses have a cell wall to protect their cells, these viruses do not use receptor-mediated endocytosis to enter host cells as is seen with animal viruses. For many plant viruses to be transferred from plant to plant, damage to some of the plants' cells must occur to allow the virus to enter a new host. This damage is often caused by weather, insects, animals, fire, or human activities like farming or landscaping. Additionally, plant offspring may inherit viral diseases from parent plants. Plant viruses can be transmitted by a variety of vectors, through contact with an infected plant's sap, by living organisms such as insects and nematodes, and through pollen. When plants viruses are transferred between different plants, this is known as horizontal transmission, and when they are inherited from a parent, this is called vertical transmission.

Symptoms of viral diseases vary according to the virus and its host (Table 3.1.3.1). One common symptom is hyperplasia, the abnormal proliferation of cells that causes the appearance of plant tumors known as galls. Other viruses induce hypoplasia, or decreased cell growth, in the leaves of plants, causing thin, yellow areas to appear. Still other viruses affect the plant by directly killing plant cells, a process known as cell necrosis. Other symptoms of plant viruses include malformed leaves, black streaks on the stems of the plants, altered growth of stems, leaves, or fruits, and ring spots, which are circular or linear areas of discoloration found in a leaf.

Table 3.1.3.1: Some Common Symptoms of Plant Viral Diseases

Symptom	Appears as
Hyperplasia	Galls (tumors)
Hypoplasia	Thinned, yellow splotches on leaves
Cell necrosis	Dead, blackened stems, leaves, or fruit
Abnormal growth patterns	Malformed stems, leaves, or fruit
Discoloration	Yellow, red, or black lines, or rings in stems, leaves, or fruit

Plant viruses can seriously disrupt crop growth and development, significantly affecting our food supply. They are responsible for poor crop quality and quantity globally, and can bring about huge economic losses annually. Others viruses may damage plants used in landscaping. Some viruses that infect agricultural food plants include the name of the plant they infect, such as tomato spotted wilt virus, bean common mosaic virus, and cucumber mosaic virus. In plants used for landscaping, two of the most common viruses are peony ring spot and rose mosaic virus. There are far too many plant viruses to discuss each in detail, but symptoms of bean common mosaic virus result in lowered bean production and stunted, unproductive plants. In the ornamental rose, the rose mosaic disease causes wavy yellow lines and colored splotches on the leaves of the plant.

Summary

Viral replication within a living cell always produces changes in the cell, sometimes resulting in cell death and sometimes slowly killing the infected cells. There are six basic stages in the virus replication cycle: attachment, penetration, uncoating, replication, assembly, and release. A viral infection may be productive, resulting in new virions, or nonproductive, which means that the virus remains inside the cell without producing new virions. Bacteriophages are viruses that infect bacteria. They have two different modes of replication: the lytic cycle, where the virus replicates and bursts out of the bacteria, and the lysogenic cycle, which involves the incorporation of the viral genome into the bacterial host genome. Animal viruses cause a variety of infections, with some causing chronic symptoms (hepatitis C), some intermittent symptoms (latent viruses such a herpes simplex virus 1), and others that cause very few symptoms, if any (human herpesviruses 6 and 7). Oncogenic viruses in animals have the ability to cause cancer by interfering with the regulation of the host cell cycle. Viruses of plants are responsible for significant economic damage in both agriculture and plants used for ornamentation.

Glossary

acute disease

disease where the symptoms rise and fall within a short period of time

asymptomatic disease
disease where there are no symptoms and the individual is unaware of being infected unless lab tests are performed

AZT
anti-HIV drug that inhibits the viral enzyme reverse transcriptase

bacteriophage
virus that infects bacteria

budding
method of exit from the cell used in certain animal viruses, where virions leave the cell individually by capturing a piece of the host plasma membrane

cell necrosis
cell death

chronic infection
describes when the virus persists in the body for a long period of time

cytopathic
causing cell damage

fusion
method of entry by some enveloped viruses, where the viral envelope fuses with the plasma membrane of the host cell

gall
appearance of a plant tumor

horizontal transmission
transmission of a disease from parent to offspring

hyperplasia
abnormally high cell growth and division

hypoplasia
abnormally low cell growth and division

intermittent symptom
symptom that occurs periodically

latency
virus that remains in the body for a long period of time but only causes intermittent symptoms

lysis
bursting of a cell

lytic cycle
type of virus replication in which virions are released through lysis, or bursting, of the cell

lysogenic cycle
type of virus replication in which the viral genome is incorporated into the genome of the host cell

oncogenic virus
virus that has the ability to cause cancer

permissive
cell type that is able to support productive replication of a virus

productive
viral infection that leads to the production of new virions

prophage
phage DNA that is incorporated into the host cell genome

vertical transmission
transmission of disease between unrelated individuals

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3.1.4: Prevention and Treatment of Viral Infections

Skills to Develop

- Identify major viral illnesses that affect humans
- Compare vaccinations and anti-viral drugs as medical approaches to viruses

Viruses cause a variety of diseases in animals, including humans, ranging from the common cold to potentially fatal illnesses like meningitis (Figure 3.1.4.1). These diseases can be treated by antiviral drugs or by vaccines, but some viruses, such as HIV, are capable of both avoiding the immune response and mutating to become resistant to antiviral drugs.

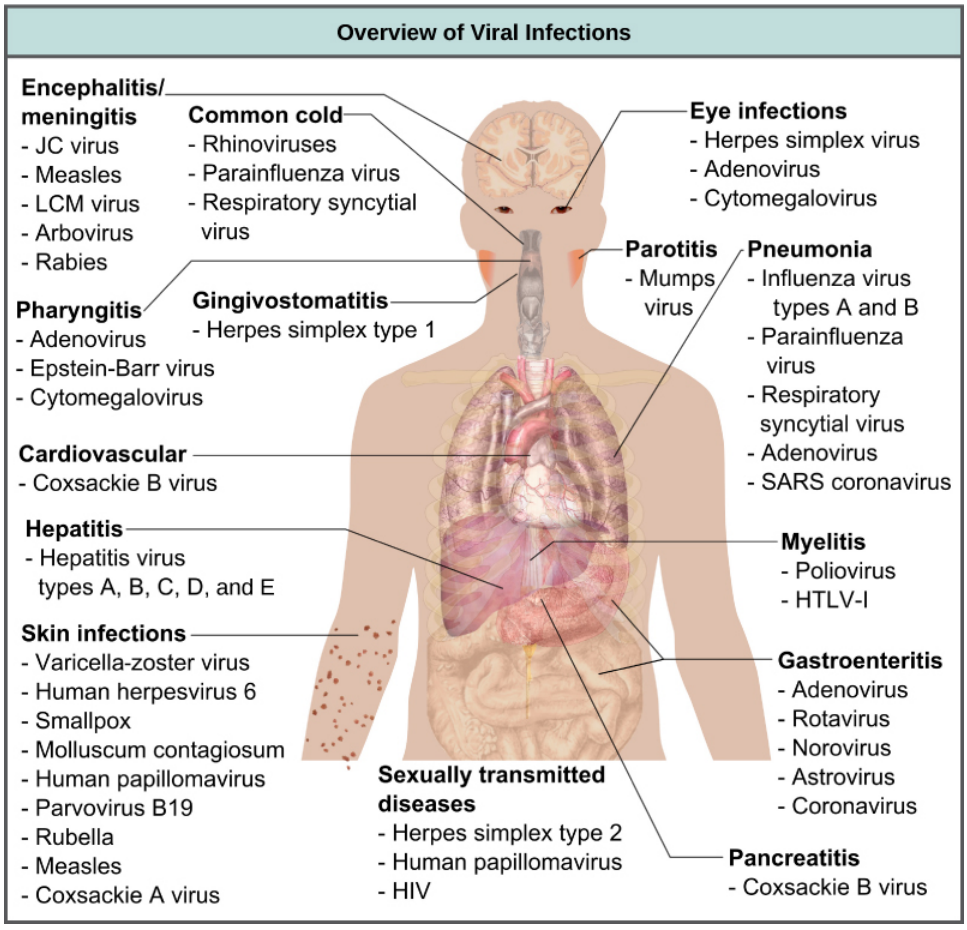


Figure 3.1.4.1: Viruses can cause dozens of ailments in humans, ranging from mild illnesses to serious diseases. (credit: modification of work by Mikael Häggström)

Vaccines for Prevention

While we do have limited numbers of effective antiviral drugs, such as those used to treat HIV and influenza, the primary method of controlling viral disease is by vaccination, which is intended to prevent outbreaks by building immunity to a virus or virus family (Figure3.1.4.1). Vaccines may be prepared using live viruses, killed viruses, or molecular subunits of the virus. The killed viral vaccines and subunit viruses are both incapable of causing disease.

Live viral vaccines are designed in the laboratory to cause few symptoms in recipients while giving them protective immunity against future infections. Polio was one disease that represented a milestone in the use of vaccines. Mass immunization campaigns in the 1950s (killed vaccine) and 1960s (live vaccine) significantly reduced the incidence of the disease, which caused muscle paralysis in children and generated a great amount of fear in the general population when regional epidemics occurred. The success of the polio vaccine paved the way for the routine dispensation of childhood vaccines against measles, mumps, rubella, chickenpox, and other diseases.

The danger of using live vaccines, which are usually more effective than killed vaccines, is the low but significant danger that these viruses will revert to their disease-causing form by back mutations. Live vaccines are usually made by attenuating (weakening) the "wild-type" (disease-causing) virus by growing it in the laboratory in tissues or at temperatures different from what the virus is accustomed to in the host. Adaptations to these new cells or temperatures induce mutations in the genomes of the virus, allowing it to grow better in the laboratory while inhibiting its ability to cause disease when reintroduced into conditions found in the host. These attenuated viruses thus still cause infection, but they do not grow very well, allowing the immune response to develop in time to prevent major disease. Back mutations occur when the vaccine undergoes mutations in the host such that it readapts to the host and can again cause disease, which can then be spread to other humans in an epidemic. This type of scenario happened as recently as 2007 in Nigeria where mutations in a polio vaccine led to an epidemic of polio in that country.

Some vaccines are in continuous development because certain viruses, such as influenza and HIV, have a high mutation rate compared to other viruses and normal host cells. With influenza, mutations in the surface molecules of the virus help the organism evade the protective immunity that may have been obtained in a previous influenza season, making it necessary for individuals to get vaccinated every year. Other viruses, such as those that cause the childhood diseases measles, mumps, and rubella, mutate so infrequently that the same vaccine is used year after year.



Figure 3.1.4.2: Vaccinations are designed to boost immunity to a virus to prevent infection. (credit: USACE Europe District)

Link to Learning



Watch this NOVA video to learn how microbiologists are attempting to replicate the deadly 1918 Spanish influenza virus so they can understand more about virology.

Vaccines and Anti-viral Drugs for Treatment

In some cases, vaccines can be used to treat an active viral infection. The concept behind this is that by giving the vaccine, immunity is boosted without adding more disease-causing virus. In the case of rabies, a fatal neurological disease transmitted via the saliva of rabies virus-infected animals, the progression of the disease from the time of the animal bite to the time it enters the central nervous system may be 2 weeks or longer. This is enough time to vaccinate an individual who suspects that they have been bitten by a rabid animal, and their boosted immune response is sufficient to prevent the virus from entering nervous tissue. Thus, the potentially fatal neurological consequences of the disease are averted, and the individual only has to recover from the infected bite. This approach is also being used for the treatment of Ebola, one of the fastest and most deadly viruses on earth. Transmitted by bats and great apes, this disease can cause death in 70–90 percent of infected humans within 2 weeks. Using newly developed vaccines that boost the immune response in this way, there is hope that affected individuals will be better able to control the virus, potentially saving a greater percentage of infected persons from a rapid and very painful death.

Another way of treating viral infections is the use of antiviral drugs. These drugs often have limited success in curing viral disease, but in many cases, they have been used to control and reduce symptoms for a wide variety of viral diseases. For most viruses, these drugs can inhibit the virus by blocking the actions of one or more of its proteins. It is important that the targeted proteins be encoded by viral genes and that these molecules are not present in a healthy host cell. In this way, viral growth is inhibited without damaging the host. There are large numbers of antiviral drugs available to treat infections, some specific for a particular virus and others that can affect multiple viruses.

Antivirals have been developed to treat genital herpes (herpes simplex II) and influenza. For genital herpes, drugs such as acyclovir can reduce the number and duration of episodes of active viral disease, during which patients develop viral lesions in their skin cells. As the virus remains latent in nervous tissue of the body for life, this drug is not curative but can make the symptoms of the disease more manageable. For influenza, drugs like Tamiflu (oseltamivir) (Figure 3.1.4.3) can reduce the duration of “flu” symptoms by 1 or 2 days, but the drug does not prevent symptoms entirely. Tamiflu works by inhibiting an enzyme (viral neuraminidase) that allows new virions to leave their infected cells. Thus, Tamiflu inhibits the spread of virus from infected to uninfected cells. Other antiviral drugs, such as Ribavirin, have been used to treat a variety of viral infections, although its mechanism of action against certain viruses remains unclear.

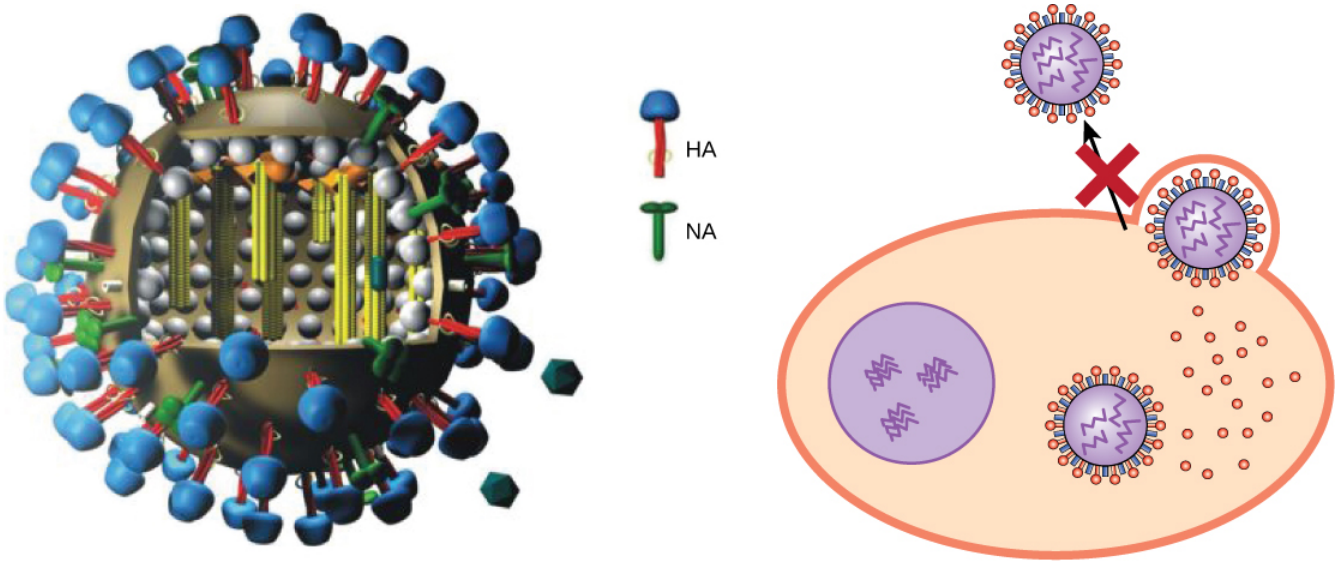


Figure 3.1.4.3: (a) Tamiflu inhibits a viral enzyme called neuraminidase (NA) found in the influenza viral envelope. (b) Neuraminidase cleaves the connection between viral hemagglutinin (HA), also found in the viral envelope, and glycoproteins on the host cell surface. Inhibition of neuraminidase prevents the virus from detaching from the host cell, thereby blocking further infection. (credit a: modification of work by M. Eickmann)

By far, the most successful use of antivirals has been in the treatment of the retrovirus HIV, which causes a disease that, if untreated, is usually fatal within 10–12 years after infection. Anti-HIV drugs have been able to control viral replication to the point that individuals receiving these drugs survive for a significantly longer time than the untreated.

Anti-HIV drugs inhibit viral replication at many different phases of the HIV replicative cycle (Figure 3.1.4.4). Drugs have been developed that inhibit the fusion of the HIV viral envelope with the plasma membrane of the host cell (fusion inhibitors), the conversion of its RNA genome into double-stranded DNA (reverse transcriptase inhibitors), the integration of the viral DNA into the host genome (integrase inhibitors), and the processing of viral proteins (protease inhibitors).

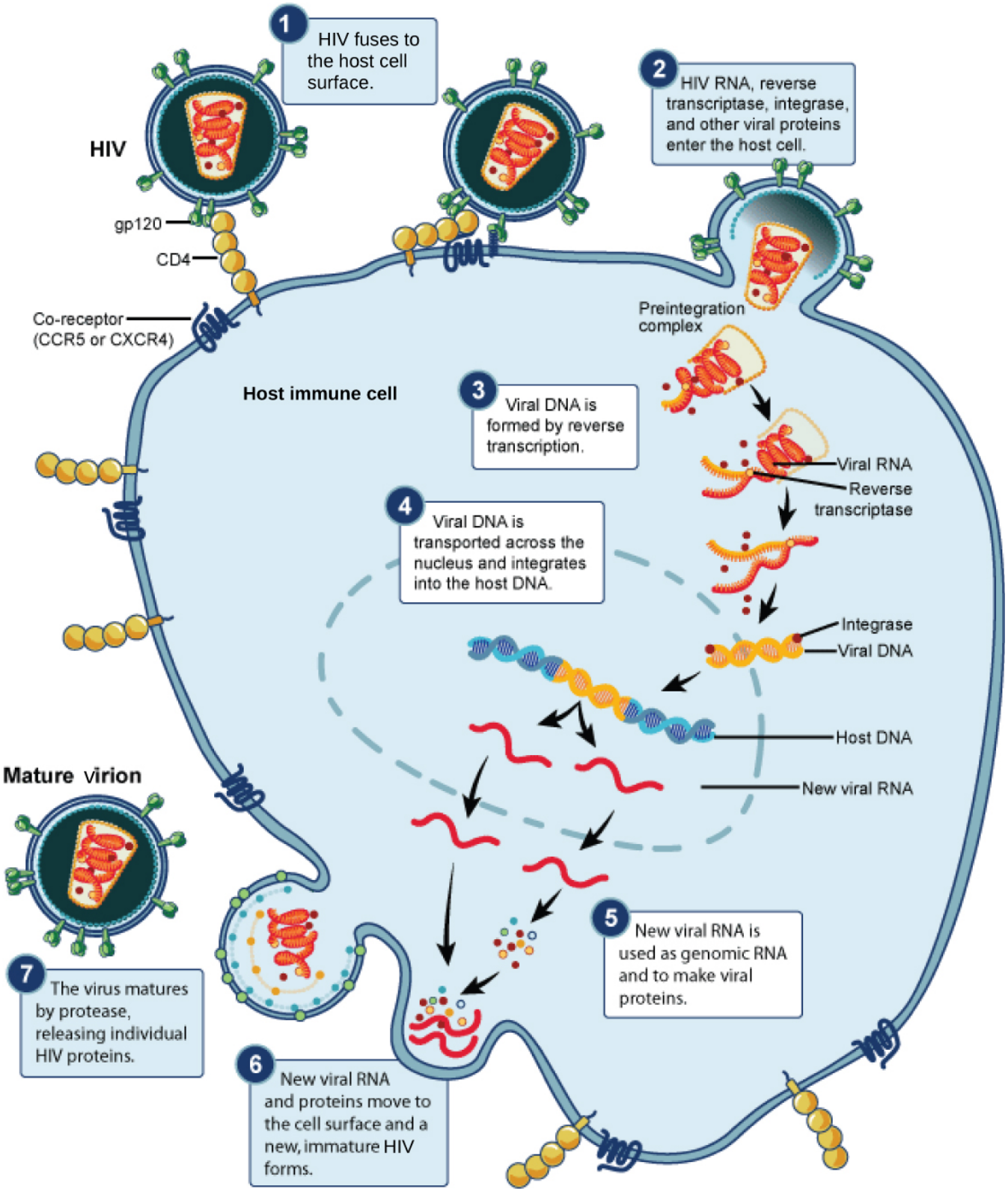


Figure 3.1.4.4: HIV, an enveloped, icosahedral virus, attaches to the CD4 receptor of an immune cell and fuses with the cell membrane. Viral contents are released into the cell, where viral enzymes convert the single-stranded RNA genome into DNA and incorporate it into the host genome. (credit: NIAID, NIH)

When any of these drugs are used individually, the high mutation rate of the virus allows it to easily and rapidly develop resistance to the drug, limiting the drug's effectiveness. The breakthrough in the treatment of HIV was the development of HAART, highly active anti-retroviral therapy, which involves a mixture of different drugs, sometimes called a drug "cocktail." By attacking the

virus at different stages of its replicative cycle, it is much more difficult for the virus to develop resistance to multiple drugs at the same time. Still, even with the use of combination HAART therapy, there is concern that, over time, the virus will develop resistance to this therapy. Thus, new anti-HIV drugs are constantly being developed with the hope of continuing the battle against this highly fatal virus.

Everyday Connection: Applied Virology

The study of viruses has led to the development of a variety of new ways to treat non-viral diseases. Viruses have been used in gene therapy. Gene therapy is used to treat genetic diseases such as severe combined immunodeficiency (SCID), a heritable, recessive disease in which children are born with severely compromised immune systems. One common type of SCID is due to the lack of an enzyme, adenosine deaminase (ADA), which breaks down purine bases. To treat this disease by gene therapy, bone marrow cells are taken from a SCID patient and the ADA gene is inserted. This is where viruses come in, and their use relies on their ability to penetrate living cells and bring genes in with them. Viruses such as adenovirus, an upper respiratory human virus, are modified by the addition of the ADA gene, and the virus then transports this gene into the cell. The modified cells, now capable of making ADA, are then given back to the patients in the hope of curing them. Gene therapy using viruses as carrier of genes (viral vectors), although still experimental, holds promise for the treatment of many genetic diseases. Still, many technological problems need to be solved for this approach to be a viable method for treating genetic disease.

Another medical use for viruses relies on their specificity and ability to kill the cells they infect. Oncolytic viruses are engineered in the laboratory specifically to attack and kill cancer cells. A genetically modified adenovirus known as H101 has been used since 2005 in clinical trials in China to treat head and neck cancers. The results have been promising, with a greater short-term response rate to the combination of chemotherapy and viral therapy than to chemotherapy treatment alone. This ongoing research may herald the beginning of a new age of cancer therapy, where viruses are engineered to find and specifically kill cancer cells, regardless of where in the body they may have spread.

A third use of viruses in medicine relies on their specificity and involves using bacteriophages in the treatment of bacterial infections. Bacterial diseases have been treated with antibiotics since the 1940s. However, over time, many bacteria have developed resistance to antibiotics. A good example is methicillin-resistant *Staphylococcus aureus* (MRSA, pronounced “mersa”), an infection commonly acquired in hospitals. This bacterium is resistant to a variety of antibiotics, making it difficult to treat. The use of bacteriophages specific for such bacteria would bypass their resistance to antibiotics and specifically kill them. Although phage therapy is in use in the Republic of Georgia to treat antibiotic-resistant bacteria, its use to treat human diseases has not been approved in most countries. However, the safety of the treatment was confirmed in the United States when the U.S. Food and Drug Administration approved spraying meats with bacteriophages to destroy the food pathogen *Listeria*. As more and more antibiotic-resistant strains of bacteria evolve, the use of bacteriophages might be a potential solution to the problem, and the development of phage therapy is of much interest to researchers worldwide.

Summary

Viruses cause a variety of diseases in humans. Many of these diseases can be prevented by the use of viral vaccines, which stimulate protective immunity against the virus without causing major disease. Viral vaccines may also be used in active viral infections, boosting the ability of the immune system to control or destroy the virus. A series of antiviral drugs that target enzymes and other protein products of viral genes have been developed and used with mixed success. Combinations of anti-HIV drugs have been used to effectively control the virus, extending the lifespans of infected individuals. Viruses have many uses in medicines, such as in the treatment of genetic disorders, cancer, and bacterial infections.

Glossary

attenuation

weakening of a virus during vaccine development

back mutation

when a live virus vaccine reverts back to it disease-causing phenotype

gene therapy
treatment of genetic disease by adding genes, using viruses to carry the new genes inside the cell

oncolytic virus
virus engineered to specifically infect and kill cancer cells

phage therapy
treatment of bacterial diseases using bacteriophages specific to a particular bacterium

vaccine
weakened solution of virus components, viruses, or other agents that produce an immune response

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3.1.5: Other Acellular Entities - Prions and Viroids

Skills to Develop

- Describe prions and their basic properties
- Define viroids and their targets of infection

Prions and viroids are pathogens (agents with the ability to cause disease) that have simpler structures than viruses but, in the case of prions, still can produce deadly diseases.

Prions

Prions, so-called because they are proteinaceous, are infectious particles—smaller than viruses—that contain no nucleic acids (neither DNA nor RNA). Historically, the idea of an infectious agent that did not use nucleic acids was considered impossible, but pioneering work by Nobel Prize-winning biologist Stanley Prusiner has convinced the majority of biologists that such agents do indeed exist.

Fatal neurodegenerative diseases, such as kuru in humans and bovine spongiform encephalopathy (BSE) in cattle (commonly known as “mad cow disease”) were shown to be transmitted by prions. The disease was spread by the consumption of meat, nervous tissue, or internal organs between members of the same species. Kuru, native to humans in Papua New Guinea, was spread from human to human via ritualistic cannibalism. BSE, originally detected in the United Kingdom, was spread between cattle by the practice of including cattle nervous tissue in feed for other cattle. Individuals with kuru and BSE show symptoms of loss of motor control and unusual behaviors, such as uncontrolled bursts of laughter with kuru, followed by death. Kuru was controlled by inducing the population to abandon its ritualistic cannibalism.

On the other hand, BSE was initially thought to only affect cattle. Cattle dying of the disease were shown to have developed lesions or “holes” in the brain, causing the brain tissue to resemble a sponge. Later on in the outbreak, however, it was shown that a similar encephalopathy in humans known as variant Creutzfeldt-Jakob disease (CJD) could be acquired from eating beef from animals with BSE, sparking bans by various countries on the importation of British beef and causing considerable economic damage to the British beef industry (Figure 3.1.5.1). BSE still exists in various areas, and although a rare disease, individuals that acquire CJD are difficult to treat. The disease can be spread from human to human by blood, so many countries have banned blood donation from regions associated with BSE.

The cause of spongiform encephalopathies, such as kuru and BSE, is an infectious structural variant of a normal cellular protein called PrP (prion protein). It is this variant that constitutes the prion particle. PrP exists in two forms, PrP^{c}, the normal form of the protein, and PrP^{sc}, the infectious form. Once introduced into the body, the PrP^{sc} contained within the prion binds to PrP^{c} and converts it to PrP^{sc}. This leads to an exponential increase of the PrP^{sc} protein, which aggregates. PrP^{sc} is folded abnormally, and the resulting conformation (shape) is directly responsible for the lesions seen in the brains of infected cattle. Thus, although not without some detractors among scientists, the prion seems likely to be an entirely new form of infectious agent, the first one found whose transmission is not reliant upon genes made of DNA or RNA.

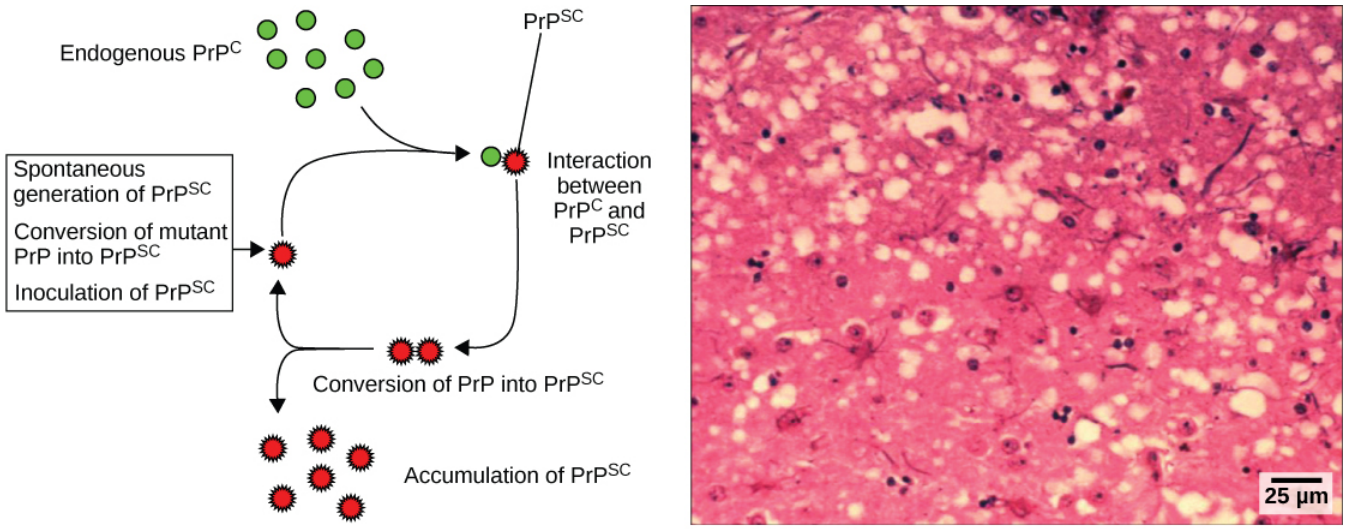


Figure 3.1.5.1: (a) Endogenous normal prion protein (PrP^C) is converted into the disease-causing form (PrP^{sc}) when it encounters this variant form of the protein. PrP^{sc} may arise spontaneously in brain tissue, especially if a mutant form of the protein is present, or it may occur via the spread of misfolded prions consumed in food into brain tissue. (b) This prion-infected brain tissue, visualized using light microscopy, shows the vacuoles that give it a spongy texture, typical of transmissible spongiform encephalopathies. (credit b: modification of work by Dr. Al Jenny, USDA APHIS; scale-bar data from Matt Russell)

Viroids

Viroids are plant pathogens: small, single-stranded, circular RNA particles that are much simpler than a virus. They do not have a capsid or outer envelope, but like viruses can reproduce only within a host cell. Viroids do not, however, manufacture any proteins, and they only produce a single, specific RNA molecule. Human diseases caused by viroids have yet to be identified.

Viroids are known to infect plants (Figure 3.1.5.2) and are responsible for crop failures and the loss of millions of dollars in agricultural revenue each year. Some of the plants they infect include potatoes, cucumbers, tomatoes, chrysanthemums, avocados, and coconut palms.



Figure 3.1.5.2: These potatoes have been infected by the potato spindle tuber viroid (PSTV), which is typically spread when infected knives are used to cut healthy potatoes, which are then planted. (credit: Pamela Roberts, University of Florida Institute of Food and Agricultural Sciences, USDA ARS)

Career Connection: Virologist

Virology is the study of viruses, and a virologist is an individual trained in this discipline. Training in virology can lead to many different career paths. Virologists are actively involved in academic research and teaching in colleges and medical schools. Some virologists treat patients or are involved in the generation and production of vaccines. They might participate in epidemiologic studies (Figure 3.1.5.3) or become science writers, to name just a few possible careers.



Figure 3.1.5.3: This virologist is engaged in fieldwork, sampling eggs from this nest for avian influenza. (credit: Don Becker, USGS EROS, U.S. Fish and Wildlife Service)

If you think you may be interested in a career in virology, find a mentor in the field. Many large medical centers have departments of virology, and smaller hospitals usually have virology labs within their microbiology departments. Volunteer in a virology lab for a semester or work in one over the summer. Discussing the profession and getting a first-hand look at the work will help you decide whether a career in virology is right for you. The American Society of Virology's website is a good resource for information regarding training and careers in virology.

Summary

Prions are infectious agents that consist of protein, but no DNA or RNA, and seem to produce their deadly effects by duplicating their shapes and accumulating in tissues. They are thought to contribute to several progressive brain disorders, including mad cow disease and Creutzfeldt-Jakob disease. Viroids are single-stranded RNA pathogens that infect plants. Their presence can have a severe impact on the agriculture industry.

Glossary

pathogen
: agent with the ability to cause disease

prion
: infectious particle that consists of proteins that replicate without DNA or RNA

PrP^{c}
: normal prion protein

PrP^{sc}
: infectious form of a prion protein

viroid

plant pathogen that produces only a single, specific RNA

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3.1.E: Viruses (Exercises)

21.1: Viral Evolution, Morphology, and Classification

Viruses are diverse entities. They vary in their structure, their replication methods, and in their target hosts. Nearly all forms of life—from bacteria and archaea to eukaryotes such as plants, animals, and fungi—have viruses that infect them. While most biological diversity can be understood through evolutionary history, such as how species have adapted to conditions and environments, much about virus origins and evolution remains unknown.

Review Questions

Which statement is true?

A. A virion contains DNA and RNA.
B. Viruses are acellular.
C. Viruses replicate outside of the cell.
D. Most viruses are easily visualized with a light microscope.

Answer

B

The viral _____ plays a role in attaching a virion to the host cell.

A. core
B. capsid
C. envelope
D. both b and c

Answer

D

Viruses_____.

A. all have a round shape
B. cannot have a long shape
C. do not maintain any shape
D. vary in shape

Answer

D

Free Response

The first electron micrograph of a virus (tobacco mosaic virus) was produced in 1939. Before that time, how did scientists know that viruses existed if they could not see them? (Hint: Early scientists called viruses “filterable agents.”)

Answer

Viruses pass through filters that eliminated all bacteria that were visible in the light microscopes at the time. As the bacteria-free filtrate could still cause infections when given to a healthy organism, this observation demonstrated the existence of very small infectious agents. These agents were later shown to be unrelated to bacteria and were classified as viruses.

21.2: Virus Infections and Hosts

Viruses can be seen as obligate, intracellular parasites. A virus must attach to a living cell, be taken inside, manufacture its proteins and copy its genome, and find a way to escape the cell so that the virus can infect other cells. Viruses can infect only certain species of hosts and only certain cells within that host. Cells that a virus may use to replicate are called permissive.

Review Questions

Which statement is *not* true of viral replication?

A. A lysogenic cycle kills the host cell.
B. There are six basic steps in the viral replication cycle.
C. Viral replication does not affect host cell function.
D. Newly released virions can infect adjacent cells.

Answer

D

Which statement is true of viral replication?

A. In the process of apoptosis, the cell survives.
B. During attachment, the virus attaches at specific sites on the cell surface.
C. The viral capsid helps the host cell produce more copies of the viral genome.
D. mRNA works outside of the host cell to produce enzymes and proteins.

Answer

B

Which statement is true of reverse transcriptase?

A. It is a nucleic acid.
B. It infects cells.
C. It transcribes RNA to make DNA.
D. It is a lipid.

Answer

C

Oncogenic virus cores can be_____.

A. RNA
B. DNA
C. neither RNA nor DNA
D. either RNA or DNA

Answer

D

Which is true of DNA viruses?

A. They use the host cell’s machinery to produce new copies of their genome.
B. They all have envelopes.
C. They are the only kind of viruses that can cause cancer.

D. They are not important plant pathogens.

Answer

A

A bacteriophage can infect _____.

A. the lungs
B. viruses
C. prions
D. bacteria

Answer

D

Free Response

Why can’t dogs catch the measles?

Answer

The virus can’t attach to dog cells, because dog cells do not express the receptors for the virus and/or there is no cell within the dog that is permissive for viral replication.

One of the first and most important targets for drugs to fight infection with HIV (a retrovirus) is the reverse transcriptase enzyme. Why?

Answer

Reverse transcriptase is needed to make more HIV-1 viruses, so targeting the reverse transcriptase enzyme may be a way to inhibit the replication of the virus. Importantly, by targeting reverse transcriptase, we do little harm to the host cell, since host cells do not make reverse transcriptase. Thus, we can specifically attack the virus and not the host cell when we use reverse transcriptase inhibitors.

In this section, you were introduced to different types of viruses and viral diseases. Briefly discuss the most interesting or surprising thing you learned about viruses.

Answer

Answer is open and will vary.

Although plant viruses cannot infect humans, what are some of the ways in which they affect humans?

Answer

Plant viruses infect crops, causing crop damage and failure, and considerable economic losses.

21.3: Prevention and Treatment of Viral Infections

Viruses cause a variety of diseases in animals, including humans, ranging from the common cold to potentially fatal illnesses like meningitis . These diseases can be treated by antiviral drugs or by vaccines, but some viruses, such as HIV, are capable of both avoiding the immune response and mutating to become resistant to antiviral drugs.

Review Questions

Which of the following is NOT used to treat active viral disease?

A. vaccines
B. antiviral drugs
C. antibiotics
D. phage therapy

Answer

C

Vaccines_____.

A. are similar to viroids
B. are only needed once
C. kill viruses
D. stimulate an immune response

Answer

D

Free Response

Why is immunization after being bitten by a rabid animal so effective and why aren't people vaccinated for rabies like dogs and cats are?

Answer

Rabies vaccine works after a bite because it takes week for the virus to travel from the site of the bite to the central nervous system, where the most severe symptoms of the disease occur. Adults are not routinely vaccinated for rabies for two reasons: first, because the routine vaccination of domestic animals makes it unlikely that humans will contract rabies from an animal bite; second, if one is bitten by a wild animal or a domestic animal that one cannot confirm has been immunized, there is still time to give the vaccine and avoid the often fatal consequences of the disease.

21.4: Other Acellular Entities - Prions and Viroids

Prions and viroids are pathogens (agents with the ability to cause disease) that have simpler structures than viruses but, in the case of prions, still can produce deadly diseases.

Review Questions

Which of the following is not associated with prions?

A. replicating shapes
B. mad cow disease
C. DNA
D. toxic proteins

Answer

C

Which statement is true of viroids?

A. They are single-stranded RNA particles.

B. They reproduce only outside of the cell.
C. They produce proteins.
D. They affect both plants and animals.

Answer

A

Free Response

Prions are responsible for variant Creutzfeldt-Jakob Disease, which has resulted in over 100 human deaths in Great Britain during the last 10 years. How do humans obtain this disease?

Answer

This prion-based disease is transmitted through human consumption of infected meat.

How are viroids like viruses?

Answer

They both replicate in a cell, and they both contain nucleic acid.

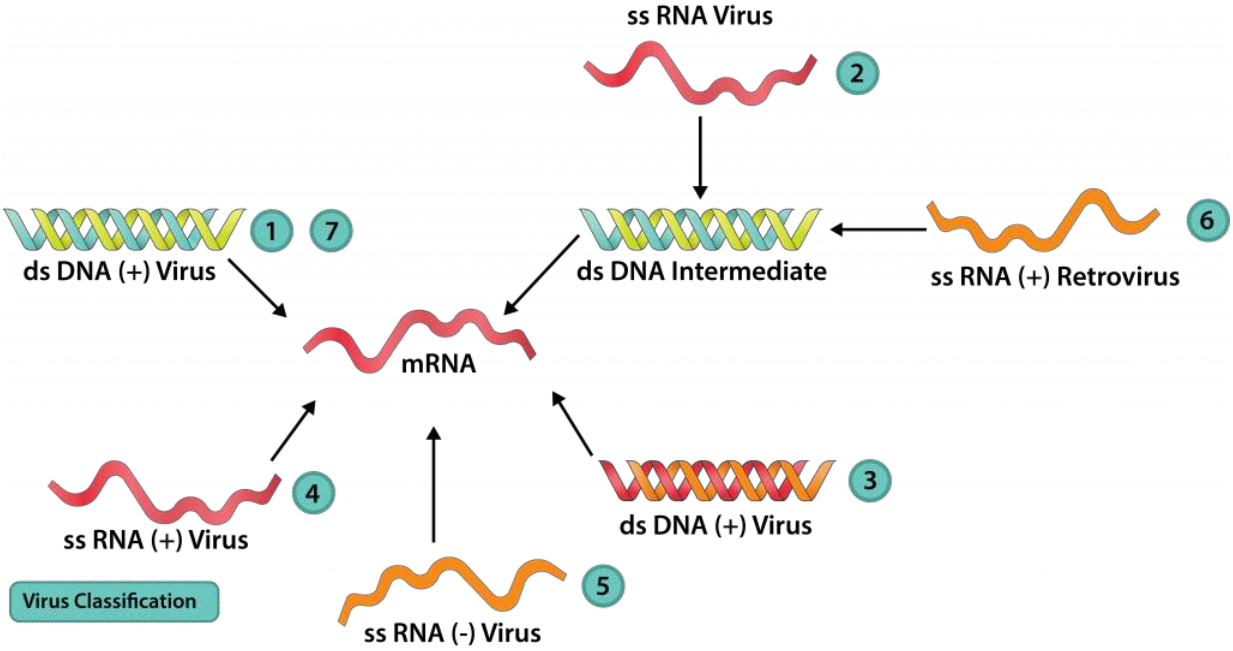
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3.2: The Viruses

Viral Classification

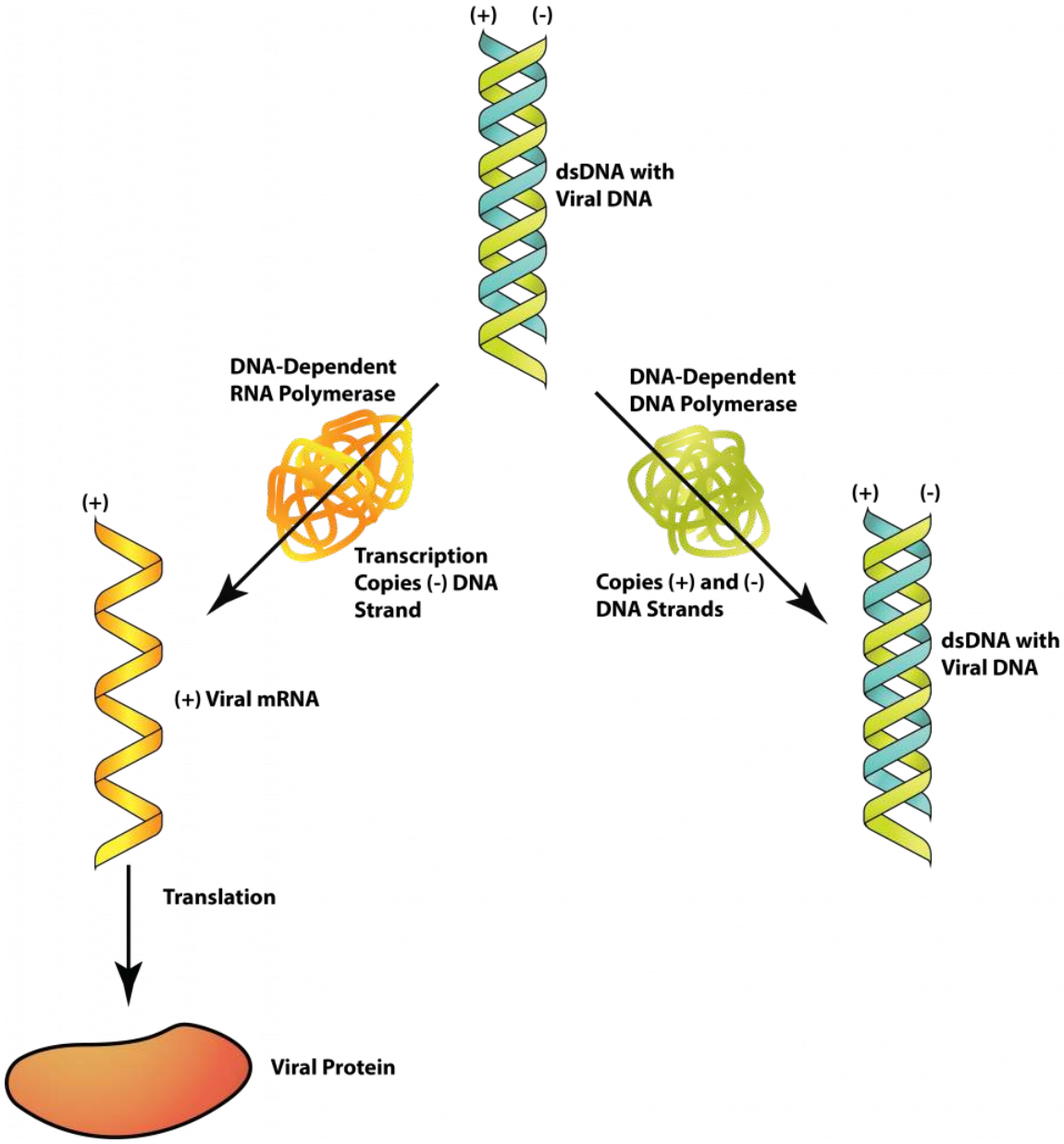
Since viruses lack ribosomes (and thus rRNA), they cannot be classified within the Three Domain Classification scheme with cellular organisms. Alternatively, Dr. David Baltimore derived a viral classification scheme, one that focuses on the relationship between a viral genome to how it produces its mRNA. The **Baltimore Scheme** recognizes seven classes of viruses.



DNA viruses

Class I: dsDNA

DNA viruses with a dsDNA genome, like bacteriophages T4 and lambda, have a genome exactly the same as the host cell that they are infecting. For this reason, many host enzymes can be utilized for replication and/or protein production. The flow of information follows a conventional pathway: dsDNA → mRNA → protein, with a **DNA-dependent RNA-polymerase** producing the mRNA and the host ribosome producing the protein. The genome replication, dsDNA → dsDNA, requires a **DNA-dependent DNA-polymerase** from either the virus or the host cell.



dsDNA.

The virus often employs strategies for control of gene expression, to insure that particular viral products are made at specific times in the virus replication. In the case of T4, the host RNA polymerase binds to the viral DNA and begins transcribing early genes immediately after the DNA is injected into the cell. One of the early viral proteins modifies the host RNA polymerase so that it will no longer recognize host promoters at all, in addition to moving on to transcribe genes for middle-stage viral proteins. A further modification (catalyzed by middle-stage viral proteins) further modified the RNA polymerase so it will recognize viral genes coding for late-stage proteins. This insures an orderly production of viral proteins.

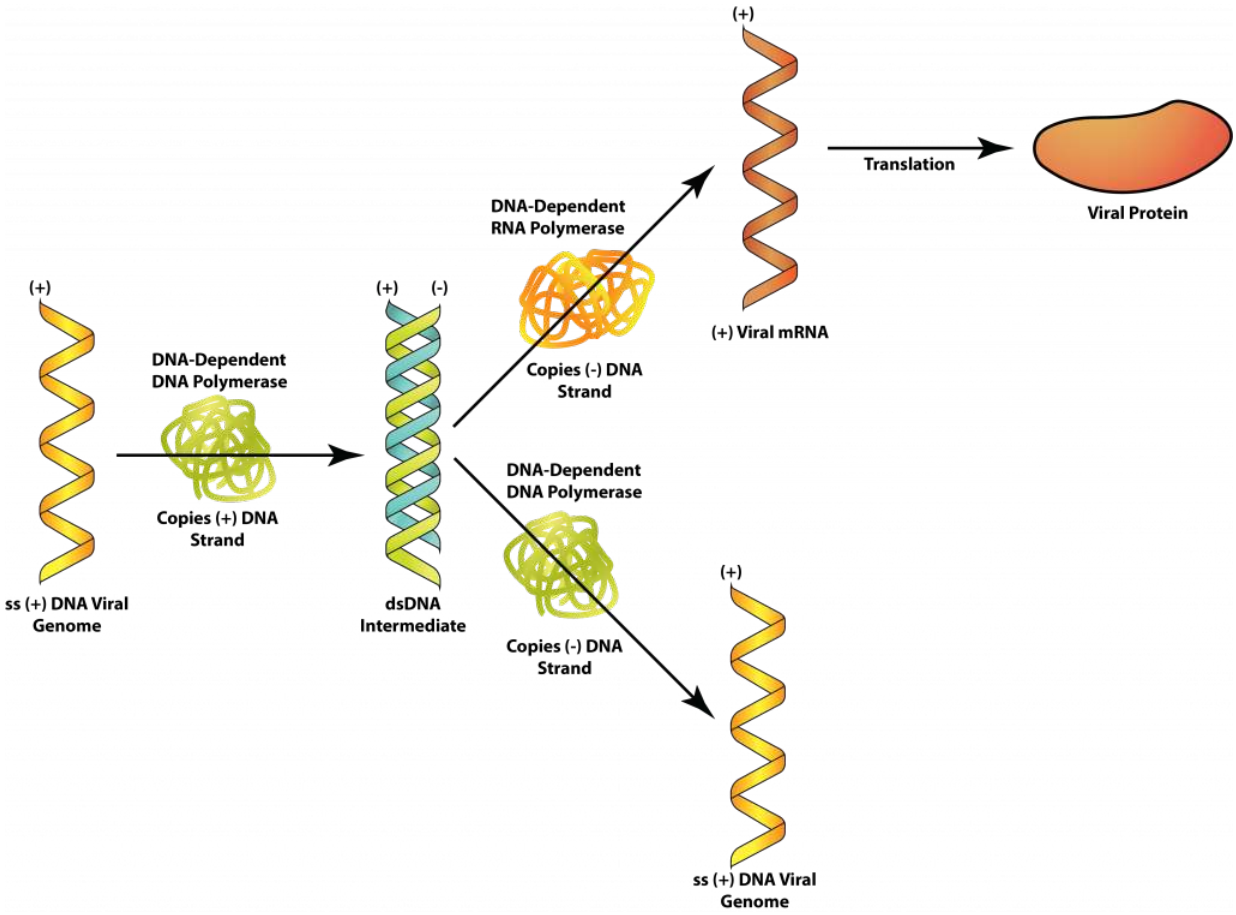
The replication of several dsDNA viruses results in the production of **concatemers**, where several viral genomes are linked together due to short single-stranded regions with terminal repeats. As the genome is packaged into the capsid a viral endonuclease cuts the concatemer to an appropriate length.

There are several animal viruses with dsDNA genomes, such as the pox viruses and the adenoviruses. The herpesviruses have several notable features, such as the link of several members with cancer and the ability of the viruses to remain in a latent form within their host. A **productive infection** results in an explosive viral population, cell death, and development of disease signs,

during which neurons are infected. A **latent infection** develops in the neurons, allowing the virus to remain undetected in the host. If the viral genome is reactivated, a productive infection results, leading to viral replication and disease signs again.

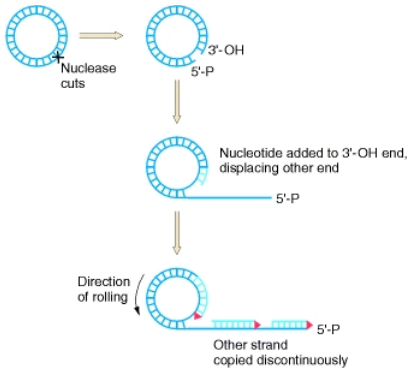
Class II: ssDNA

The flow of information for ssDNA viruses, such as the parvoviruses, will still follow the conventional pathway, to a certain extent: DNA → mRNA → protein. But the viral genome can either have the same base sequence as the mRNA (**plus-strand DNA**) or be complementary to the mRNA (**minus-strand DNA**). In the former case, a DNA strand that is complementary to the viral genome must be manufactured first, forming a double-stranded **replicative form (RF)**. This can be used to both manufacture viral proteins and as a template for viral genome copies. For the minus-strand DNA viruses, the genome can be used directly to produce mRNA but a complementary copy will still need to be made, to serve as a template for viral genome copies.



ssDNA.

The replicative form can be used for **rolling-circle replication**, where one strand is nicked and replication enzymes are used to extend the free 3' end. As a complementary strand is synthesized around the circular DNA, the 5' end is peeled off, leading to a displaced strand that continues to grow in length.



Rolling-Circle Replication.

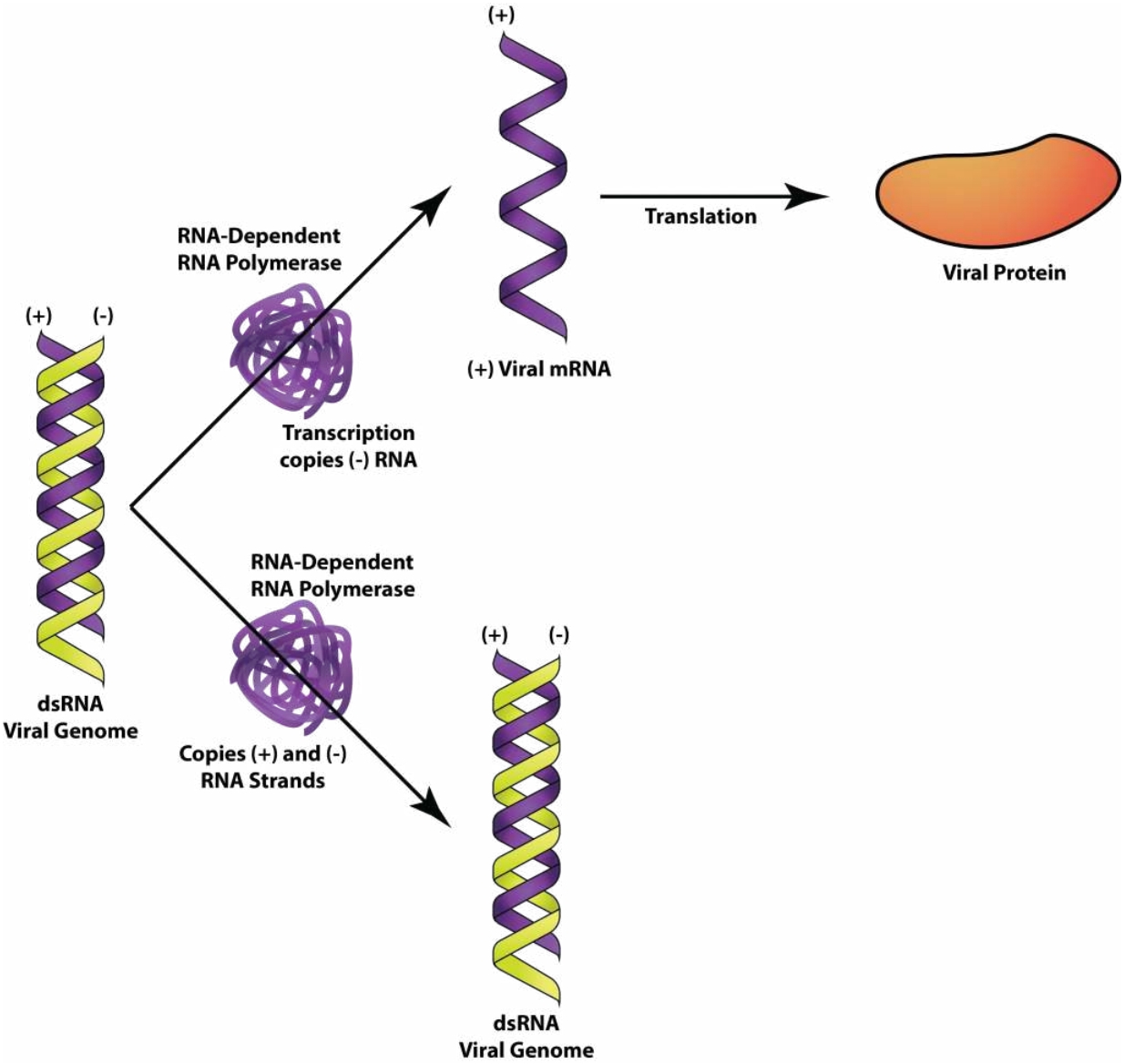
Class VII: DNA viruses that use reverse transcriptase

The hepadnaviruses contain a DNA genome that is partially double-stranded, but contains a single-stranded region. After gaining entrance into the cell's nucleus, host cell enzymes are used to fill in the gap with complementary bases to form a dsDNA closed loop. Gene transcription yields a plus-strand RNA known as the **pregenome**, as well as the viral enzyme **reverse transcriptase**, an **RNA-dependent DNA-polymerase.** The pregenome is used as a template for the reverse transcriptase to produced minus-strand DNA genomes, with a small piece of pregenome used as a primer to produce the double-stranded region of the genomes.

RNA viruses

Class III: dsRNA

Double-stranded RNA viruses infect bacteria, fungi, plants, and animals, such as the rotavirus that causes diarrheal illness in humans. But cells do not utilize dsRNA in any of their processes and have systems in place to destroy any dsRNA found in the cell. Thus the viral genome, in its dsRNA form, must be hidden or protected from the cell enzymes. Cells also lack **RNA-dependent RNA-polymerases**, necessary for replication of the viral genome so the virus must provide this enzyme itself. The viral RNA-dependent RNA polymerase acts as both a **transcriptase** to transcribe mRNA, as well as a **replicase** to replicate the RNA genome.

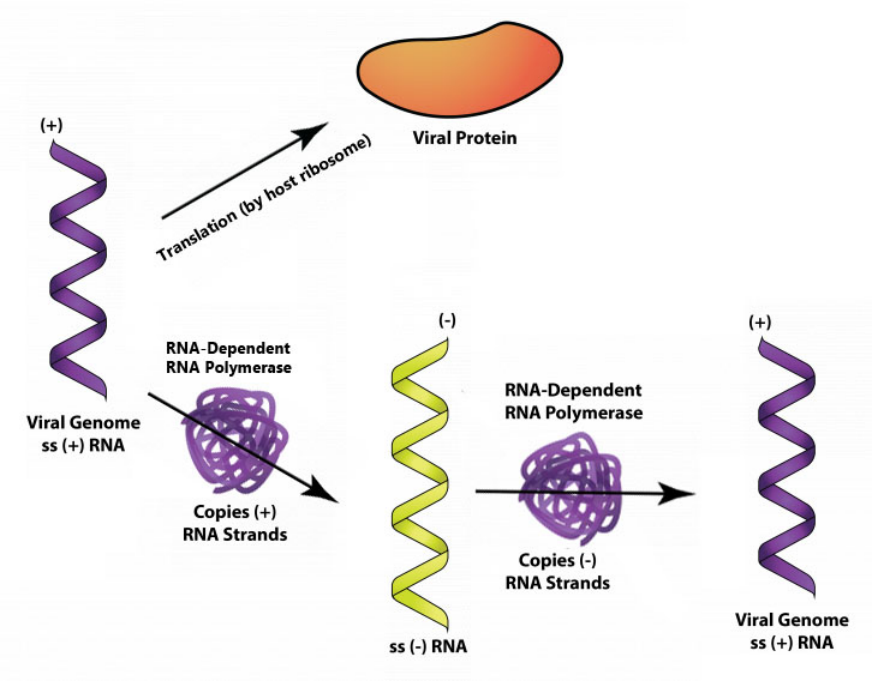


dsRNA.

For the rotavirus, the viral nucleocapsid remains intact in the cytoplasm with replication events occurring inside, allowing the dsRNA to remain protected. Messenger RNA is transcribed from the minus-strand of the RNA genome and then translated by the host ribosome in the cytoplasm. Viral proteins aggregate to form new nucleocapsids around RNA replicase and plus-strand RNA. The minus-strand RNA is then synthesized by the RNA replicase within the nucleocapsid, once again insuring protection of the dsRNA genome.

Class IV: +ssRNA

Viruses with plus-strand RNA, such as poliovirus, can use their genome directly as mRNA with translation by the host ribosome occurring as soon as the unsegmented viral genome gains entry into the cell. One of the viral genes expressed yields an RNA-dependent RNA-polymerase (or RNA replicase), which creates minus-strand RNA from the plus-strand genome. The minus-strand RNA can be used as a template for more plus-strand RNA, which can be used as mRNA or as genomes for the newly forming viruses.



+ssRNA.

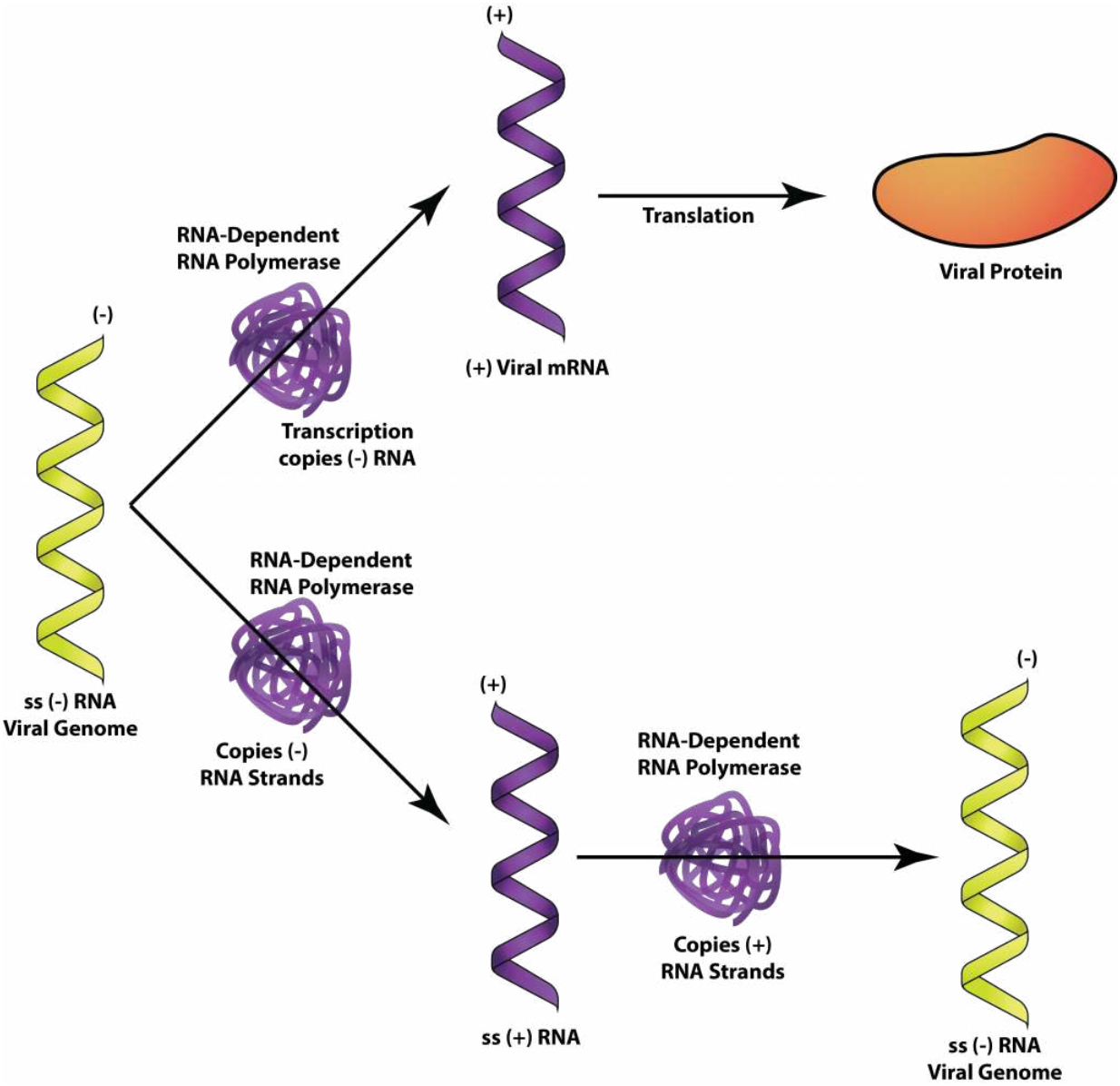
Translation of the poliovirus genome yields a **polyprotein**, a large protein with protease activity that cleaves itself into three smaller proteins. Additional cleavage activity eventually yields all the proteins needed for capsid formation, as well as an RNA-dependent RNA-polymerase.

The formation of a polyprotein that is cut into several smaller proteins illustrates one possible strategy to an issue faced by many +ssRNA viruses – how to generate multiple proteins from an unsegmented +ssRNA genome? Other possibilities include:

- **subgenomic mRNA –** during translation, portions of the viral RNA may be skipped, resulting in different proteins than what is made from the viral RNA in its entirety.
- **ribosomal frame-shifting –** the ribosome "reads" the mRNA in groups of three nucleotides or codon, which translate to one amino acid. If the ribosome starts with nucleotide #1, that is one **open reading frame** (**ORF**), resulting in one set of amino acids. If the ribosome were to move forward where nucleotide 2 is the starting nucleotide that would be ORF #2, resulting in a completely different set of amino acids. If the ribosome were to move forward again where nucleotide 3 is the starting nucleotide that would be ORF#3, resulting in an entirely different set of amino acids. Some viruses have viral genes that deliberately overlap within different ORFs, leading to the production of different proteins from a single mRNA.
- **readthrough mechanism –** a viral genome can have stop codons embedded throughout the sequence. When the ribosome comes to a **stop codon** it can either stop, ending the amino acid sequence, or it can ignore the stop codon, continuing on to make a longer string of amino acids. For viruses with the readthrough mechanism, they acquire a variety of proteins by having stop codons that are periodically ignored. Sometimes this function is combined with the ribosomal frame-shifting to produce an even greater variety of viral proteins.

Class V: -ssRNA

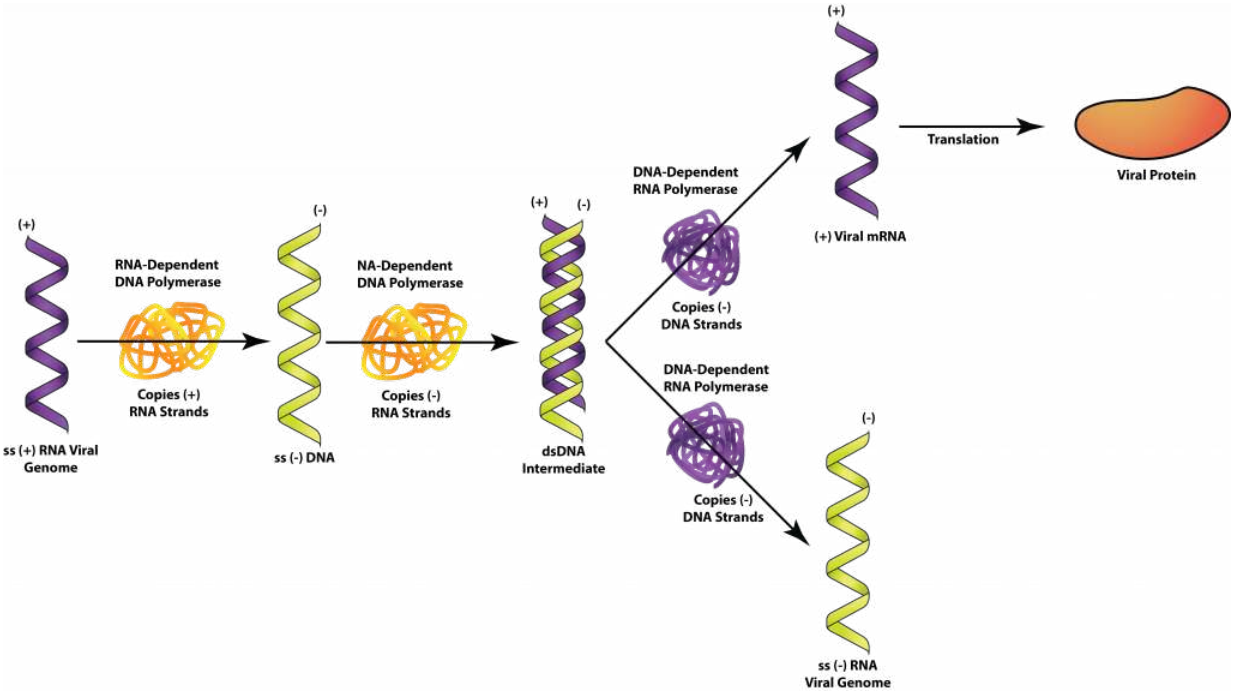
Minus-strand RNA viruses include many members notable for humans, such as influenza virus, rabies virus, and Ebola virus. Since the genome of minus-strand RNA viruses cannot be used directly as mRNA, the virus must carry an RNA-dependent RNA-polymerase within its capsid. Upon entrance into the host cell, the plus-strand RNAs generated by the polymerase are used as mRNA for protein production. When viral genomes are needed the plus-strand RNAs are used as templates to make minus-strand RNA.



-ssRNA.

Class VI: +ssRNA, retroviruses

Despite the fact that the retroviral genome is composed of +ssRNA, it is not used as mRNA. Instead, the virus uses its reverse transcriptase to synthesize a piece of ssDNA complementary to the viral genome. The reverse transcriptase also possesses **ribonuclease** activity, which is used to degrade the RNA strand of the RNA-DNA hybrid. Lastly, the reverse transcriptase is used as a DNA polymerase to make a complementary copy to the ssDNA, yielding a dsDNA molecule. This allows the virus to insert its genome, in a dsDNA form, into the host chromosome, forming a **provirus**. Unlike a prophage, a provirus can remain latent indefinitely or cause the expression of viral genes, leading to the production of new viruses. Excision of the provirus does not occur for gene expression.



+ssRNA, retroviruses.

Other Infectious Agents

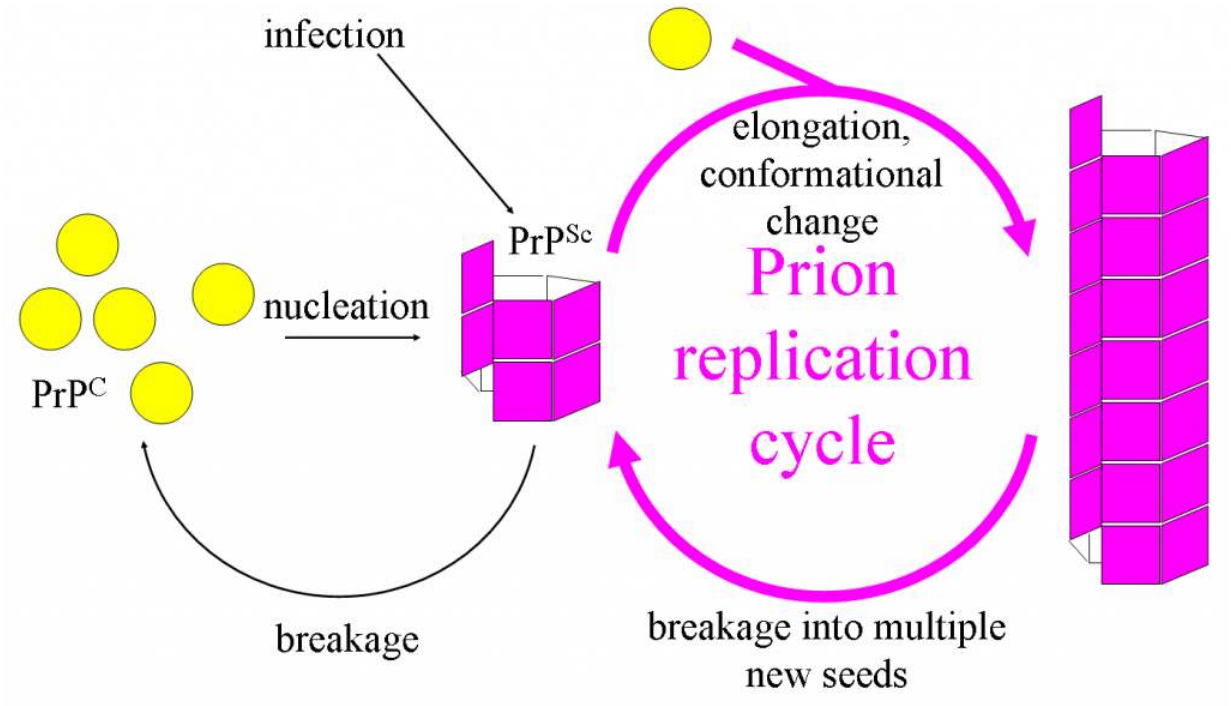
Viroids

Viroids are small, circular ssRNA molecules that lack protein. These infectious molecules are associated with a number of plant diseases. Since ssRNA is highly susceptible to enzymatic degradation, the viroid RNA has extensive complementary base pairing, causing the viroid to take on a hairpin configuration that is resistant to enzymes. For replication viroids rely on a plant RNA polymerase with RNA replicase activity.

Prions

Prions are infectious agents that completely lack nucleic acid of any kind, being made entirely of protein. They are associated with a variety of diseases, primarily in animals, although a prion has been found that infects yeast (!). Diseases include bovine spongiform encephalopathy (BSE or “mad cow disease”), Creutzfeld-Jakob disease in humans, and scrapie in sheep.

The prion protein is found in the neurons of healthy animals (**PrPC or Prion Protein Cellular**), with a particular secondary structure. The pathogenic form (**PrPSC or Prion Protein Scrapie**) has a different secondary structure and is capable of converting the PrPC into the pathogenic form. Accumulation of the pathogenic form causes destruction of brain and nervous tissue, leading to disease symptoms such as memory loss, lack of coordination, and eventually death.



Prions. Joannamasel at English Wikipedia [CC BY-SA 3.0], via Wikimedia Commons

Key Words

Baltimore Scheme, Class I, Class II, Class III, Class IV, Class V, Class VI, Class VII, DNA-dependent RNA polymerase, DNA-dependent DNA-polymerase, concatemer, productive infection, latent infection, plus-strand DNA/+DNA, minus-strand DNA/-DNA, dsDNA, ssDNA, replicative form (RF), rolling-circle replication, pregenome, reverse transcriptase, RNA-dependent DNA-polymerase, dsRNA, RNA-dependent RNA-polymerase, transcriptase, replicase, plus-strand RNA/+ssRNA, minus-strand RNA/-ssRNA, polyprotein, subgenomic mRNA, ribosomal frame-shifting, open reading frame (ORF), readthrough mechanism, stop codon, retrovirus, ribonuclease, provirus, viroid, prion, PrPC/Prion Protein Cellular, PrPSC/Prion Protein Scrapie.

Essential Questions/Objectives

1. What is the Baltimore system of classification? What viral characteristics does it use?How does each viral group make proteins and replicate their genome? Where do the necessary components come from? (virus or host cell) What modifications are necessary, for viruses with a genome different from the host cell?
2. What strategy do dsDNA viruses use for control of gene expression? What are concatemers? What are productive and latent infections?
3. What is a replicative form? What is rolling circle replication? What is the advantage of these viral mechanisms?
4. What is a pregenome? What is reverse transcriptase? What role does it play for the Class VII viruses?
5. What issues do dsRNA viruses face? How do they overcome these issues? What is a transcriptase? What is a replicase?
6. How is the genome used by Class IV +ssRNA viruses? What are the strategies used by these viruses to generate multiple proteins from an unsegmented genome?
7. What steps are necessary for the –ssRNA viruses?
8. How do the retroviruses, as +ssRNA viruses, differ from the Class IV viruses? What is a ribonuclease? What is a provirus?
9. What is a viroid? What is a prion? How do these agents cause disease? How do they replicate?

Exploratory Questions (OPTIONAL)

1. Why were scientists initially so resistant to the idea of prions lacking any type of nucleic acid?

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CHAPTER OVERVIEW

4: Microbial Growth and Metabolism

Topic hierarchy

- 4.1: Microbial Growth
  - 4.1.1: How Microbes Grow
  - 4.1.2: Oxygen Requirements for Microbial Growth
  - 4.1.3: The Effects of pH on Microbial Growth
  - 4.1.4: Temperature and Microbial Growth
  - 4.1.5: Other Environmental Conditions that Affect Growth
  - 4.1.6: Media Used for Bacterial Growth
  - 4.1.E: Microbial Growth (Exercises)
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SECTION OVERVIEW

4.1: Microbial Growth

We are all familiar with the slimy layer on a pond surface or that makes rocks slippery. These are examples of biofilms—microorganisms embedded in thin layers of matrix material (Figure 4.1.1). Biofilms were long considered random assemblages of cells and had little attention from researchers. Recently, progress in visualization and biochemical methods has revealed that biofilms are an organized ecosystem within which many cells, usually of different species of bacteria, fungi, and algae, interact through cell signaling and coordinated responses. The biofilm provides a protected environment in harsh conditions and aids colonization by microorganisms. Biofilms also have clinical importance. They form on medical devices, resist routine cleaning and sterilization, and cause health-acquired infections. Within the body, biofilms form on the teeth as plaque, in the lungs of patients with cystic fibrosis, and on the cardiac tissue of patients with endocarditis. The slime layer helps protect the cells from host immune defenses and antibiotic treatments.

Studying biofilms requires new approaches. Because of the cells' adhesion properties, many of the methods for culturing and counting cells that are explored in this chapter are not easily applied to biofilms. This is the beginning of a new era of challenges and rewarding insight into the ways that microorganisms grow and thrive in nature.

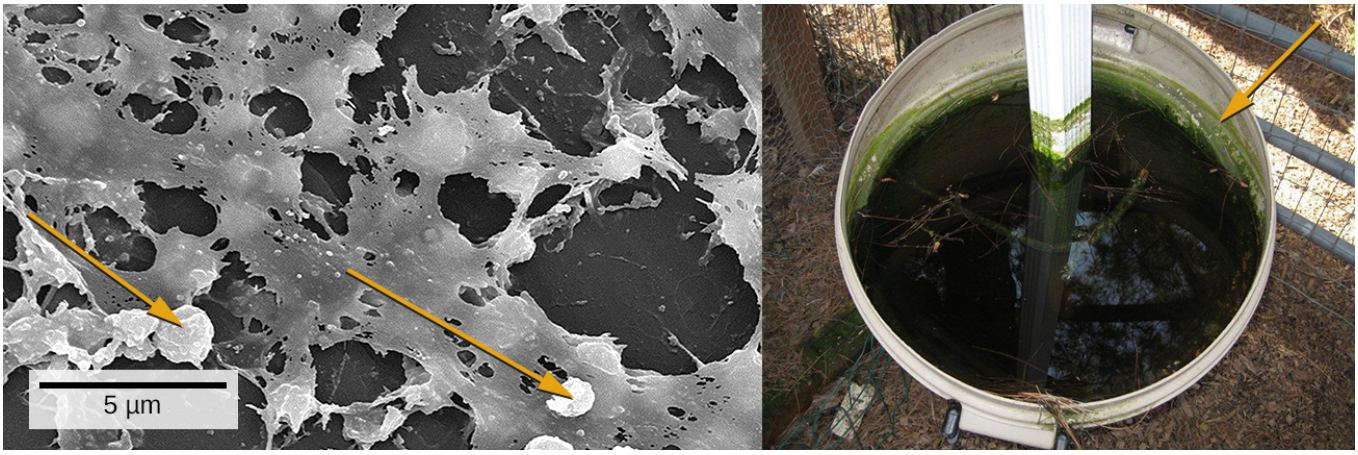


Figure 4.1.1: Medical devices that are inserted into a patient's body often become contaminated with a thin biofilm of microorganisms enmeshed in the sticky material they secrete. The electron micrograph (left) shows the inside walls of an indwelling catheter. Arrows point to the round cells of *Staphylococcus aureus* bacteria attached to the layers of extracellular substrate. The garbage can (right) served as a rain collector. The arrow points to a green biofilm on the sides of the container. (credit left: modification of work by Centers for Disease Control and Prevention; credit right: modification of work by NASA)

4.1.1: How Microbes Grow

4.1.2: Oxygen Requirements for Microbial Growth

4.1.3: The Effects of pH on Microbial Growth

4.1.4: Temperature and Microbial Growth

4.1.5: Other Environmental Conditions that Affect Growth

4.1.6: Media Used for Bacterial Growth

4.1.E: Microbial Growth (Exercises)

Thumbnail: Heavy rains cause runoff of fertilizers into Lake Erie, triggering extensive algal blooms, which can be observed along the shoreline. Notice the brown unplanted and green planted agricultural land on the shore. (credit: NASA)

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4.1.1: How Microbes Grow

Learning Objectives

- Define the generation time for growth based on binary fission
- Identify and describe the activities of microorganisms undergoing typical phases of binary fission (simple cell division) in a growth curve
- Explain several laboratory methods used to determine viable and total cell counts in populations undergoing exponential growth
- Describe examples of cell division not involving binary fission, such as budding or fragmentation
- Describe the formation and characteristics of biofilms
- Identify health risks associated with biofilms and how they are addressed
- Describe quorum sensing and its role in cell-to-cell communication and coordination of cellular activities

Clinical Focus: Part 1

Jeni, a 24-year-old pregnant woman in her second trimester, visits a clinic with complaints of high fever, 38.9 °C (102 °F), fatigue, and muscle aches—typical flu-like signs and symptoms. Jeni exercises regularly and follows a nutritious diet with emphasis on organic foods, including raw milk that she purchases from a local farmer's market. All of her immunizations are up to date. However, the health-care provider who sees Jeni is concerned and orders a blood sample to be sent for testing by the microbiology laboratory.

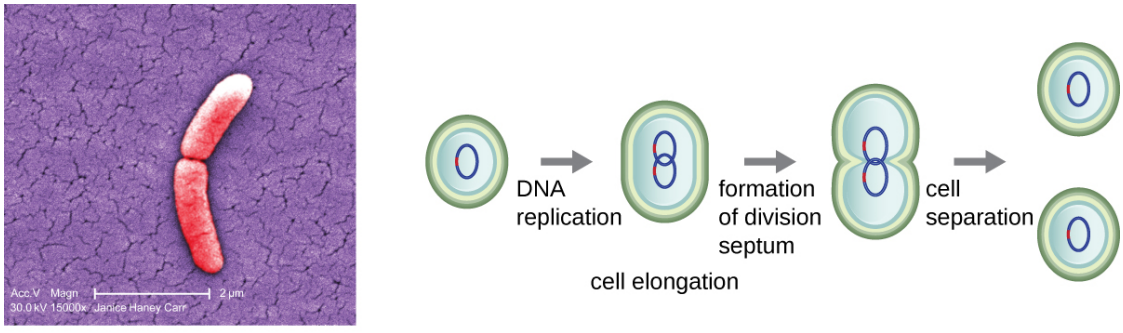
Exercise 4.1.1.1

Why is the health-care provider concerned about Jeni's signs and symptoms?

The bacterial cell cycle involves the formation of new cells through the replication of DNA and partitioning of cellular components into two daughter cells. In prokaryotes, reproduction is always asexual, although extensive genetic recombination in the form of horizontal gene transfer takes place, as will be explored in a different chapter. Most bacteria have a single circular chromosome; however, some exceptions exist. For example, *Borrelia burgdorferi*, the causative agent of Lyme disease, has a linear chromosome.

Binary Fission

The most common mechanism of cell replication in bacteria is a process called binary fission, which is depicted in Figure 4.1.1.1. Before dividing, the cell grows and increases its number of cellular components. Next, the replication of DNA starts at a location on the circular chromosome called the origin of replication, where the chromosome is attached to the inner cell membrane. Replication continues in opposite directions along the chromosome until the terminus is reached.



(a) (b)

Figure 4.1.1.1: (a) The electron micrograph depicts two cells of *Salmonella typhimurium* after a binary fission event. (b) Binary fission in bacteria starts with the replication of DNA as the cell elongates. A division septum forms in the center of the cell. Two daughter cells of similar size form and separate, each receiving a copy of the original chromosome. (credit a: modification of work by Centers for Disease Control and Prevention).

The center of the enlarged cell constricts until two daughter cells are formed, each offspring receiving a complete copy of the parental genome and a division of the cytoplasm (cytokinesis). This process of cytokinesis and cell division is directed by a protein called FtsZ. FtsZ assembles into a Z ring on the cytoplasmic membrane (Figure 4.1.1.2). The Z ring is anchored by FtsZ-binding proteins and defines the division plane between the two daughter cells. Additional proteins required for cell division are added to the Z ring to form a structure called the divisome. The divisome activates to produce a peptidoglycan cell wall and build a septum that divides the two daughter cells. The daughter cells are separated by the division septum, where all of the cells' outer layers (the cell wall and outer membranes, if present) must be remodeled to complete division. For example, we know that specific enzymes break bonds between the monomers in peptidoglycans and allow addition of new subunits along the division septum.

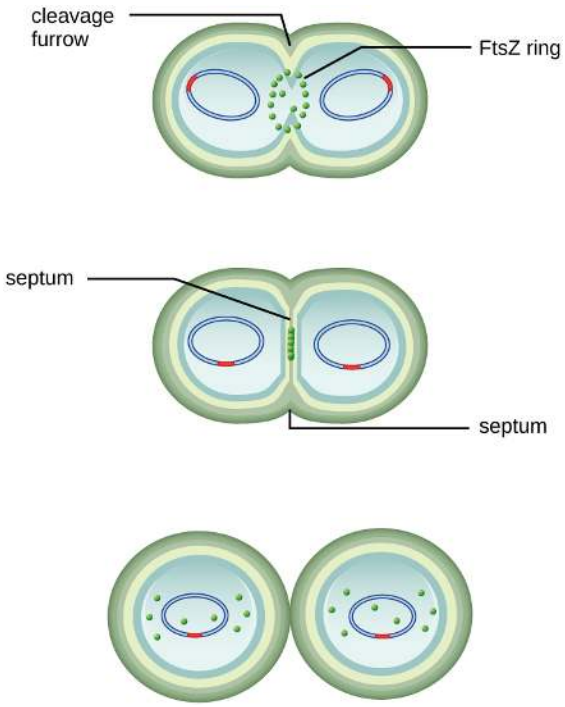


Figure 4.1.1.2: FtsZ proteins assemble to form a Z ring that is anchored to the plasma membrane. The Z ring pinches the cell envelope to separate the cytoplasm of the new cells.

? Exercise 4.1.1.2

What is the name of the protein that assembles into a Z ring to initiate cytokinesis and cell division?

Generation Time

In eukaryotic organisms, the generation time is the time between the same points of the life cycle in two successive generations. For example, the typical generation time for the human population is 25 years. This definition is not practical for bacteria, which may reproduce rapidly or remain dormant for thousands of years. In prokaryotes (Bacteria and Archaea), the generation time is also called the doubling time and is defined as the time it takes for the population to double through one round of binary fission. Bacterial doubling times vary enormously. Whereas *Escherichia coli* can double in as little as 20 minutes under optimal growth conditions in the laboratory, bacteria of the same species may need several days to double in especially harsh environments. Most pathogens grow rapidly, like *E. coli*, but there are exceptions. For example, *Mycobacterium tuberculosis*, the causative agent of tuberculosis, has a generation time of between 15 and 20 hours. On the other hand, *M. leprae*, which causes Hansen's disease (leprosy), grows much more slowly, with a doubling time of 14 days.

Calculating Number of Cells

It is possible to predict the number of cells in a population when they divide by binary fission at a constant rate. As an example, consider what happens if a single cell divides every 30 minutes for 24 hours. The diagram in Figure 4.1.1.3 shows the increase in cell numbers for the first three generations.

The number of cells increases exponentially and can be expressed as 2^n, where n is the number of generations. If cells divide every 30 minutes, after 24 hours, 48 divisions would have taken place. If we apply the formula 2^n, where n is equal to 48, the single cell would give rise to 2^{48} or 281,474,976,710,656 cells at 48 generations (24 hours). When dealing with such huge numbers, it is more practical to use scientific notation. Therefore, we express the number of cells as 2.8×10^{14} cells.

In our example, we used one cell as the initial number of cells. For any number of starting cells, the formula is adapted as follows:

$$N_n = N_0 2^n \tag{4.1.1.1}$$

N_n is the number of cells at any generation n, N_0 is the initial number of cells, and n is the number of generations.

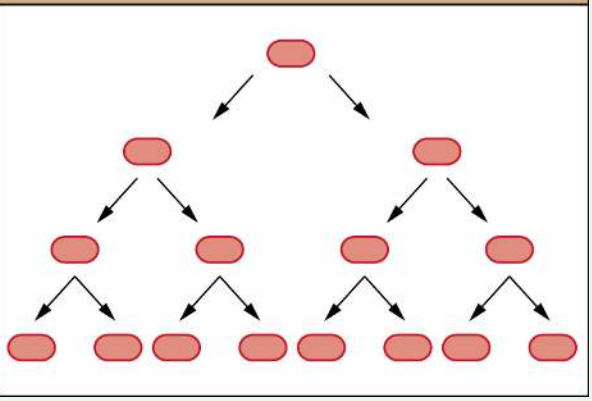
Number of generations (n)	Number of cells	Each division adds two new cells
0	1	
1	2	
2	4	
3	8	

Figure 4.1.1.3: The parental cell divides and gives rise to two daughter cells. Each of the daughter cells, in turn, divides, giving a total of four cells in the second generation and eight cells in the third generation. Each division doubles the number of cells.

? Exercise 4.1.1.3

With a doubling time of 30 minutes and a starting population size of 1×10^5 cells, how many cells will be present after 2 hours, assuming no cell death?

The Growth Curve

Microorganisms grown in closed culture (also known as a batch culture), in which no nutrients are added and most waste is not removed, follow a reproducible growth pattern referred to as the growth curve. An example of a batch culture in nature is a pond in which a small number of cells grow in a closed environment. The culture density is defined as the number of cells per unit volume. In a closed environment, the culture density is also a measure of the number of cells in the population. Infections of the body do not always follow the growth curve, but correlations can exist depending upon the site and type of infection. When the number of live cells is plotted against time, distinct phases can be observed in the curve (Figure 4.1.1.4).

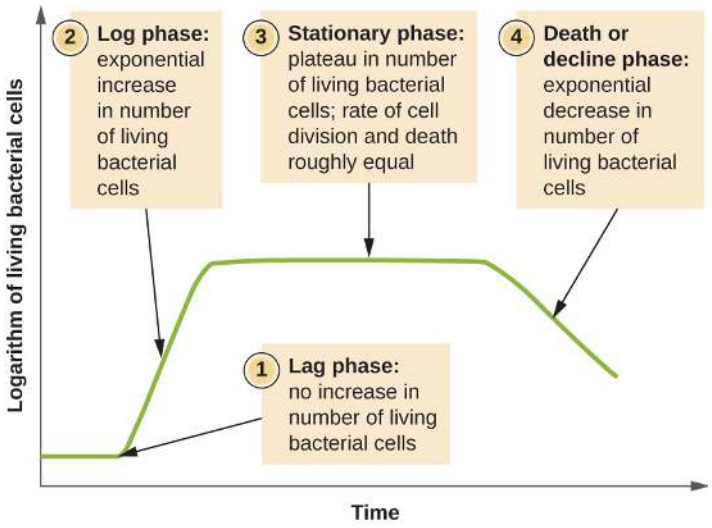


Figure 4.1.1.4: The growth curve of a bacterial culture is represented by the logarithm of the number of live cells plotted as a function of time. The graph can be divided into four phases according to the slope, each of which matches events in the cell. The four phases are lag, log, stationary, and death.

The Lag Phase

The beginning of the growth curve represents a small number of cells, referred to as an inoculum, that are added to a fresh culture medium, a nutritional broth that supports growth. The initial phase of the growth curve is called the lag phase, during which cells are gearing up for the next phase of growth. The number of cells does not change during the lag phase; however, cells grow larger and are metabolically active, synthesizing proteins needed to grow within the medium. If any cells were damaged or shocked during the transfer to the new medium, repair takes place during the lag phase. The duration of the lag phase is determined by many factors, including the species and genetic make-up of the cells, the composition of the medium, and the size of the original inoculum.

The Log Phase

In the logarithmic (log) growth phase, sometimes called exponential growth phase, the cells are actively dividing by binary fission and their number increases exponentially. For any given bacterial species, the generation time under specific growth conditions (nutrients, temperature, pH, and so forth) is genetically determined, and this generation time is called the intrinsic growth rate. During the log phase, the relationship between time and number of cells is not linear but exponential; however, the growth curve is often plotted on a semilogarithmic graph, as shown in Figure 4.1.1.5, which gives the appearance of a linear relationship.

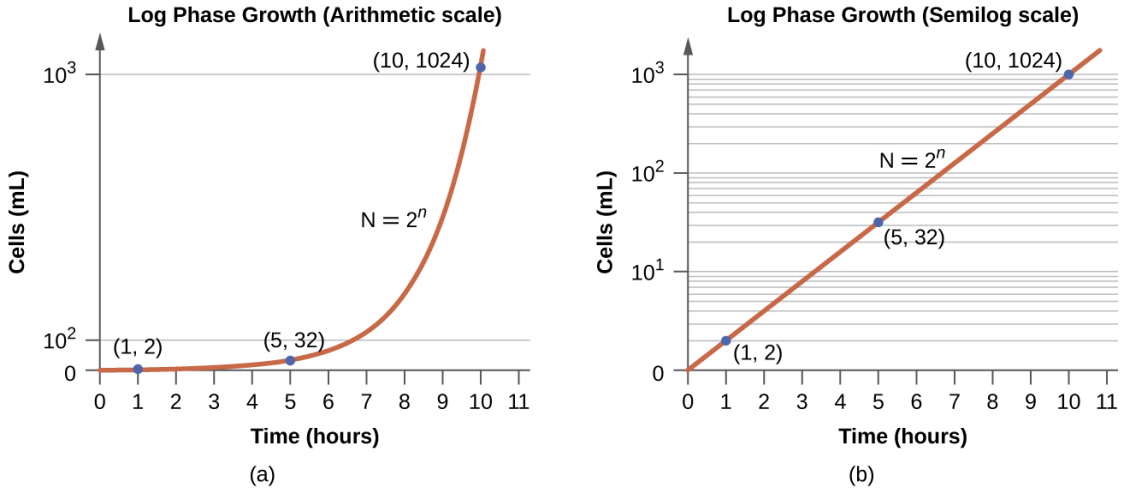


Figure 4.1.1.5: Both graphs illustrate population growth during the log phase for a bacterial sample with an initial population of one cell and a doubling time of 1 hour. (a) When plotted on an arithmetic scale, the growth rate resembles a curve. (b) When plotted on a semilogarithmic scale (meaning the values on the y-axis are logarithmic), the growth rate appears linear.

Cells in the log phase show constant growth rate and uniform metabolic activity. For this reason, cells in the log phase are preferentially used for industrial applications and research work. The log phase is also the stage where bacteria are the most susceptible to the action of disinfectants and common antibiotics that affect protein, DNA, and cell-wall synthesis.

Stationary Phase

As the number of cells increases through the log phase, several factors contribute to a slowing of the growth rate. Waste products accumulate and nutrients are gradually used up. In addition, gradual depletion of oxygen begins to limit aerobic cell growth. This combination of unfavorable conditions slows and finally stalls population growth. The total number of live cells reaches a plateau referred to as the stationary phase (Figure 4.1.1.4). In this phase, the number of new cells created by cell division is now equivalent to the number of cells dying; thus, the total population of living cells is relatively stagnant. The culture density in a stationary culture is constant. The culture's carrying capacity, or maximum culture density, depends on the types of microorganisms in the culture and the specific conditions of the culture; however, carrying capacity is constant for a given organism grown under the same conditions.

During the stationary phase, cells switch to a survival mode of metabolism. As growth slows, so too does the synthesis of peptidoglycans, proteins, and nucleic-acids; thus, stationary cultures are less susceptible to antibiotics that disrupt these processes. In bacteria capable of producing endospores, many cells undergo sporulation during the stationary phase. Secondary metabolites, including antibiotics, are synthesized in the stationary phase. In certain pathogenic bacteria, the stationary phase is also associated with the expression of virulence factors, products that contribute to a microbe's ability to survive, reproduce, and cause disease in a host organism. For example, quorum sensing in *Staphylococcus aureus* initiates the production of enzymes that can break down human tissue and cellular debris, clearing the way for bacteria to spread to new tissue where nutrients are more plentiful.

The Death Phase

As a culture medium accumulates toxic waste and nutrients are exhausted, cells die in greater and greater numbers. Soon, the number of dying cells exceeds the number of dividing cells, leading to an exponential decrease in the number of cells (Figure 4.1.1.4). This is the aptly named death phase, sometimes called the decline phase. Many cells lyse and release nutrients into the medium, allowing surviving cells to maintain viability and form endospores. A few cells, the so-called persisters, are characterized by a slow metabolic rate. Persister cells are medically important because they are associated with certain chronic infections, such as tuberculosis, that do not respond to antibiotic treatment.

Sustaining Microbial Growth

The growth pattern shown in Figure 4.1.1.4 takes place in a closed environment; nutrients are not added and waste and dead cells are not removed. In many cases, though, it is advantageous to maintain cells in the logarithmic phase of growth. One example is in industries that harvest microbial products. A chemostat (Figure 4.1.1.6) is used to maintain a continuous culture in which nutrients are supplied at a steady rate. A controlled amount of air is mixed in for aerobic processes. Bacterial suspension is removed at the same rate as nutrients flow in to maintain an optimal growth environment.

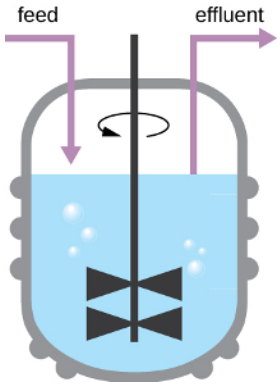


Figure 4.1.1.6: A chemostat is a culture vessel fitted with an opening to add nutrients (feed) and an outlet to remove contents (effluent), effectively diluting toxic wastes and dead cells. The addition and removal of fluids is adjusted to maintain the culture in the logarithmic phase of growth. If aerobic bacteria are grown, suitable oxygen levels are maintained.

? Exercise 4.1.1.4

1. During which phase does growth occur at the fastest rate?
2. Name two factors that limit microbial growth.

Measurement of Bacterial Growth

Estimating the number of bacterial cells in a sample, known as a bacterial count, is a common task performed by microbiologists. The number of bacteria in a clinical sample serves as an indication of the extent of an infection. Quality control of drinking water, food, medication, and even cosmetics relies on estimates of bacterial counts to detect contamination and prevent the spread of disease. Two major approaches are used to measure cell number. The direct methods involve counting cells, whereas the indirect methods depend on the measurement of cell presence or activity without actually counting individual cells. Both direct and indirect methods have advantages and disadvantages for specific applications.

Direct Cell Count

Direct cell count refers to counting the cells in a liquid culture or colonies on a plate. It is a direct way of estimating how many organisms are present in a sample. Let's look first at a simple and fast method that requires only a specialized slide and a compound microscope.

The simplest way to count bacteria is called the direct microscopic cell count, which involves transferring a known volume of a culture to a calibrated slide and counting the cells under a light microscope. The calibrated slide is called a Petroff-Hausser chamber (Figure 4.1.1.7) and is similar to a hemocytometer used to count red blood cells. The central area of the counting chamber is etched into squares of various sizes. A sample of the culture suspension is added to the chamber under a coverslip that is placed at a specific height from the surface of the grid. It is possible to estimate the concentration of cells in the original sample by counting individual cells in a number of squares and determining the volume of the sample observed. The area of the squares and the height at which the coverslip is positioned are specified for the chamber. The concentration must be corrected for dilution if the sample was diluted before enumeration.

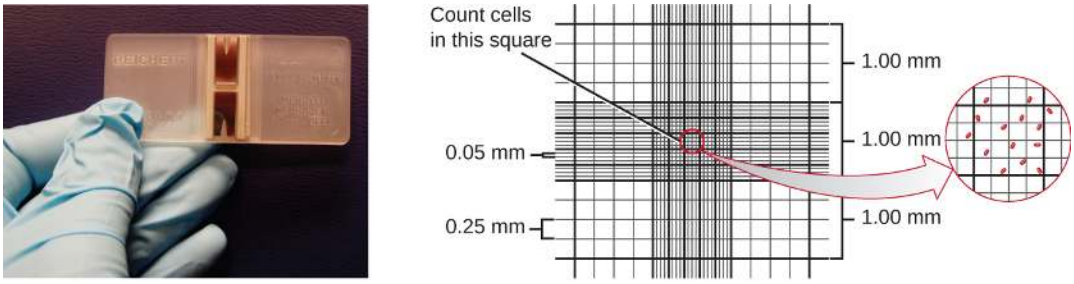


Figure 4.1.1.7: (a) A Petroff-Hausser chamber is a special slide designed for counting the bacterial cells in a measured volume of a sample. A grid is etched on the slide to facilitate precision in counting. (b) This diagram illustrates the grid of a Petroff-Hausser chamber, which is made up of squares of known areas. The enlarged view shows the square within which bacteria (red cells) are counted. If the coverslip is 0.2 mm above the grid and the square has an area of 0.04 mm^2, then the volume is 0.008 mm^3, or 0.000008 mL. Since there are 10 cells inside the square, the density of bacteria is 10 cells/0.000008 mL, which equates to 1,250,000 cells/mL. (credit a: modification of work by Jeffrey M. Vinocur)

Cells in several small squares must be counted and the average taken to obtain a reliable measurement. The advantages of the chamber are that the method is easy to use, relatively fast, and inexpensive. On the downside, the counting chamber does not work well with dilute cultures because there may not be enough cells to count.

Using a counting chamber does not necessarily yield an accurate count of the number of live cells because it is not always possible to distinguish between live cells, dead cells, and debris of the same size under the microscope. However, newly developed fluorescence staining techniques make it possible to distinguish viable and dead bacteria. These viability stains (or live stains) bind to nucleic acids, but the primary and secondary stains differ in their ability to cross the cytoplasmic membrane. The primary stain, which fluoresces green, can penetrate intact cytoplasmic membranes, staining both live and dead cells. The secondary stain, which fluoresces red, can stain a cell only if the cytoplasmic membrane is considerably damaged. Thus, live cells fluoresce green because

they only absorb the green stain, whereas dead cells appear red because the red stain displaces the green stain on their nucleic acids (Figure 4.1.1.8).

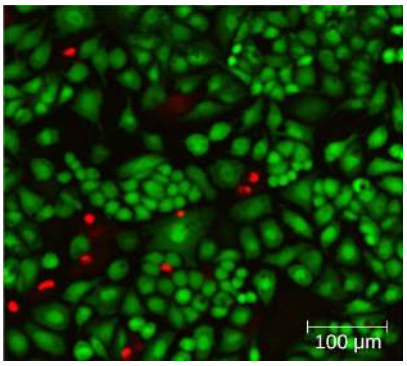
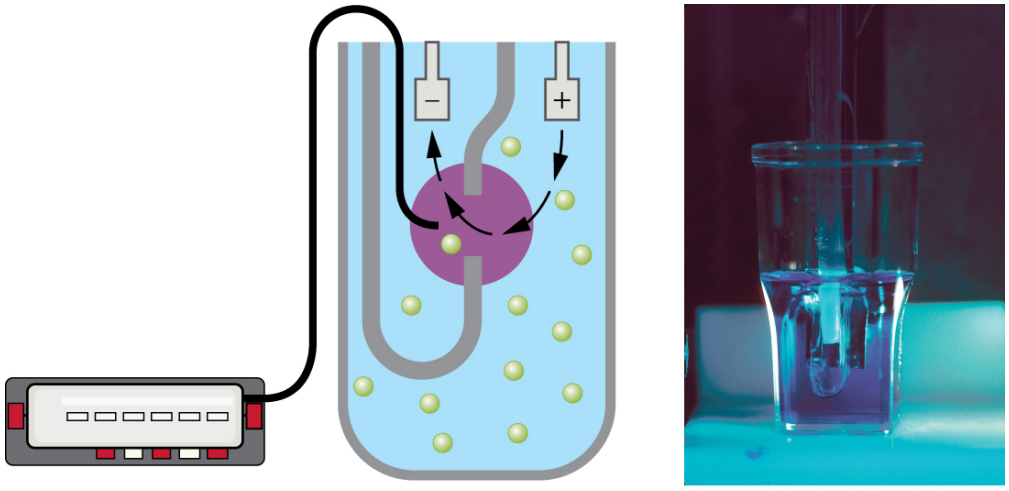


Figure 4.1.1.8: Fluorescence staining can be used to differentiate between viable and dead bacterial cells in a sample for purposes of counting. Viable cells are stained green, whereas dead cells are stained red. (credit: modification of work by Panseri S, Cunha C, D'Alessandro T, Sandri M, Giavaresi G, Maracci M, Hung CT, Tampieri A)

Another technique uses an electronic cell counting device (Coulter counter) to detect and count the changes in electrical resistance in a saline solution. A glass tube with a small opening is immersed in an electrolyte solution. A first electrode is suspended in the glass tube. A second electrode is located outside of the tube. As cells are drawn through the small aperture in the glass tube, they briefly change the resistance measured between the two electrodes and the change is recorded by an electronic sensor (Figure 4.1.1.9); each resistance change represents a cell. The method is rapid and accurate within a range of concentrations; however, if the culture is too concentrated, more than one cell may pass through the aperture at any given time and skew the results. This method also does not differentiate between live and dead cells.

Direct counts provide an estimate of the total number of cells in a sample. However, in many situations, it is important to know the number of live, or viable, cells. Counts of live cells are needed when assessing the extent of an infection, the effectiveness of antimicrobial compounds and medication, or contamination of food and water.



(a) (b)

Figure 4.1.1.9: A Coulter counter is an electronic device that counts cells. It measures the change in resistance in an electrolyte solution that takes place when a cell passes through a small opening in the inside container wall. A detector automatically counts the number of cells passing through the opening. (credit b: modification of work by National Institutes of Health)

? Exercise 4.1.1.5

1. Why would you count the number of cells in more than one square in the Petroff-Hausser chamber to estimate cell numbers?
2. In the viability staining method, why do dead cells appear red?

Plate Count

The viable plate count, or simply plate count, is a count of viable or live cells. It is based on the principle that viable cells replicate and give rise to visible colonies when incubated under suitable conditions for the specimen. The results are usually expressed as colony-forming units per milliliter (CFU/mL) rather than cells per milliliter because more than one cell may have landed on the same spot to give rise to a single colony. Furthermore, samples of bacteria that grow in clusters or chains are difficult to disperse and a single colony may represent several cells. Some cells are described as viable but nonculturable and will not form colonies on solid media. For all these reasons, the viable plate count is considered a low estimate of the actual number of live cells. These limitations do not detract from the usefulness of the method, which provides estimates of live bacterial numbers.

Microbiologists typically count plates with 30–300 colonies. Samples with too few colonies (<30) do not give statistically reliable numbers, and overcrowded plates (>300 colonies) make it difficult to accurately count individual colonies. Also, counts in this range minimize occurrences of more than one bacterial cell forming a single colony. Thus, the calculated CFU is closer to the true number of live bacteria in the population.

There are two common approaches to inoculating plates for viable counts: the pour plate and the spread plate methods. Although the final inoculation procedure differs between these two methods, they both start with a serial dilution of the culture.

Serial Dilution

The serial dilution of a culture is an important first step before proceeding to either the pour plate or spread plate method. The goal of the serial dilution process is to obtain plates with CFUs in the range of 30–300, and the process usually involves several dilutions in multiples of 10 to simplify calculation. The number of serial dilutions is chosen according to a preliminary estimate of the culture density. Figure 4.1.1.10 illustrates the serial dilution method.

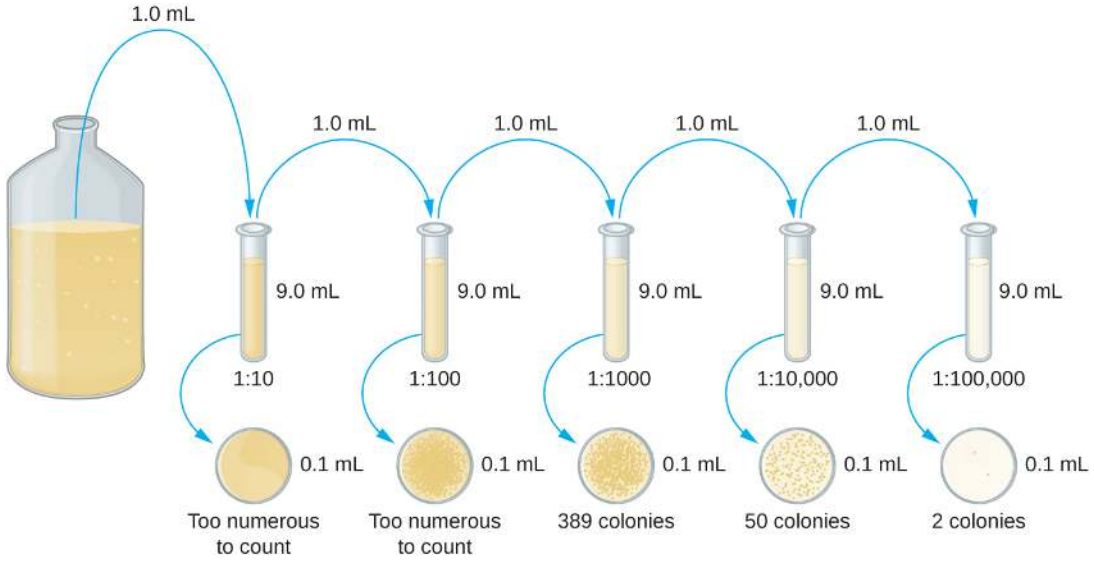


Figure 4.1.1.10: Serial dilution involves diluting a fixed volume of cells mixed with dilution solution using the previous dilution as an inoculum. The result is dilution of the original culture by an exponentially growing factor. (credit: modification of work by "Leberechtc"/Wikimedia Commons)

A fixed volume of the original culture, 1.0 mL, is added to and thoroughly mixed with the first dilution tube solution, which contains 9.0 mL of sterile broth. This step represents a dilution factor of 10, or 1:10, compared with the original culture. From this first dilution, the same volume, 1.0 mL, is withdrawn and mixed with a fresh tube of 9.0 mL of dilution solution. The dilution factor is now 1:100 compared with the original culture. This process continues until a series of dilutions is produced that will bracket the desired cell concentration for accurate counting. From each tube, a sample is plated on solid medium using either the pour plate method (Figure 4.1.1.11) or the spread plate method (Figure 4.1.1.12). The plates are incubated until colonies appear. Two to three plates are usually prepared from each dilution and the numbers of colonies counted on each plate are averaged. In all cases, thorough mixing of samples with the dilution medium (to ensure the cell distribution in the tube is random) is paramount to obtaining reliable results.

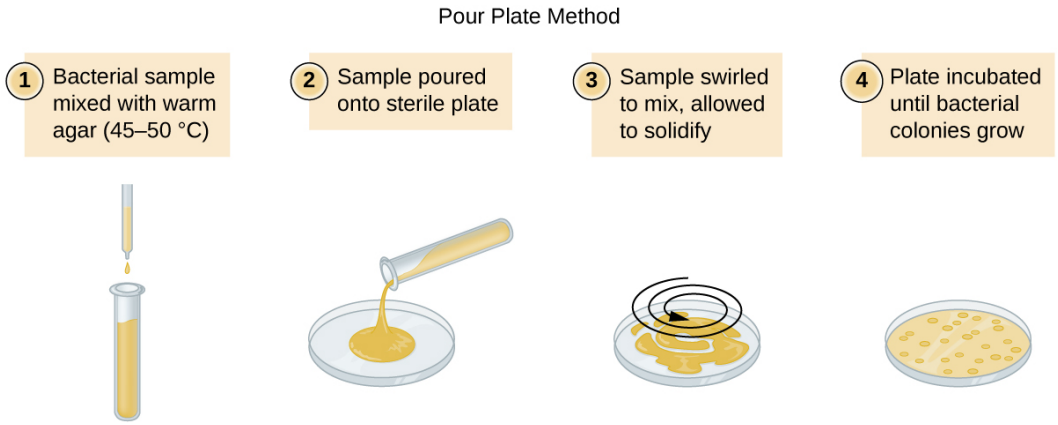


Figure 4.1.1.11: In the pour plate method of cell counting, the sample is mixed in liquid warm agar (45–50 °C) poured into a sterile Petri dish and further mixed by swirling. This process is repeated for each serial dilution prepared. The resulting colonies are counted and provide an estimate of the number of cells in the original volume sampled.

The dilution factor is used to calculate the number of cells in the original cell culture. In our example, an average of 50 colonies was counted on the plates obtained from the 1:10,000 dilution. Because only 0.1 mL of suspension was pipetted on the plate, the multiplier required to reconstitute the original concentration is 10 × 10,000. The number of CFU per mL is equal to 50 × 100 × 10,000 = 5,000,000. The number of bacteria in the culture is estimated as 5 million cells/mL. The colony count obtained from the 1:1000 dilution was 389, well below the expected 500 for a 10-fold difference in dilutions. This highlights the issue of inaccuracy when colony counts are greater than 300 and more than one bacterial cell grows into a single colony.

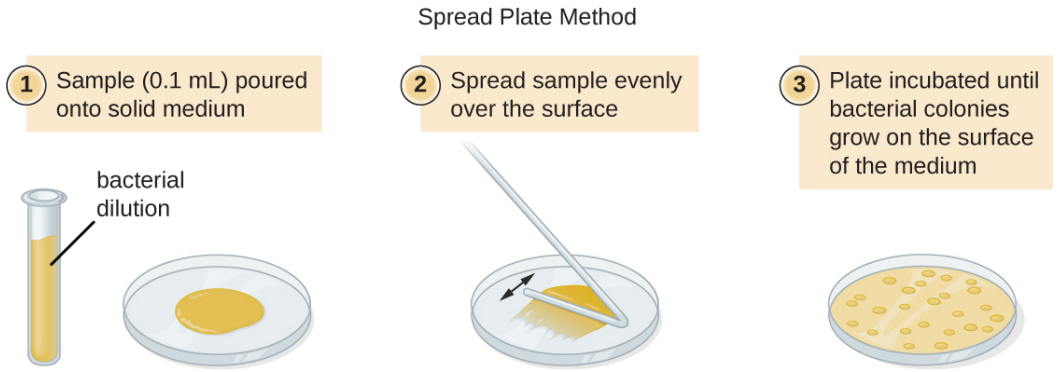


Figure 4.1.1.12: In the spread plate method of cell counting, the sample is poured onto solid agar and then spread using a sterile spreader. This process is repeated for each serial dilution prepared. The resulting colonies are counted and provide an estimate of the number of cells in the original volume samples.

A very dilute sample—drinking water, for example—may not contain enough organisms to use either of the plate count methods described. In such cases, the original sample must be concentrated rather than diluted before plating. This can be accomplished using a modification of the plate count technique called the membrane filtration technique. Known volumes are vacuum-filtered aseptically through a membrane with a pore size small enough to trap microorganisms. The membrane is transferred to a Petri plate containing an appropriate growth medium. Colonies are counted after incubation. Calculation of the cell density is made by dividing the cell count by the volume of filtered liquid.

Link to Learning

Watch this video for demonstrations of serial dilutions and spread plate techniques.

The Most Probable Number

The number of microorganisms in dilute samples is usually too low to be detected by the plate count methods described thus far. For these specimens, microbiologists routinely use the most probable number (MPN) method, a statistical procedure for estimating of the number of viable microorganisms in a sample. Often used for water and food samples, the MPN method evaluates detectable growth by observing changes in turbidity or color due to metabolic activity.

A typical application of MPN method is the estimation of the number of coliforms in a sample of pond water. Coliforms are gram-negative rod bacteria that ferment lactose. The presence of coliforms in water is considered a sign of contamination by fecal matter. For the method illustrated in Figure 4.1.1.13, a series of three dilutions of the water sample is tested by inoculating five lactose broth tubes with 10 mL of sample, five lactose broth tubes with 1 mL of sample, and five lactose broth tubes with 0.1 mL of sample. The lactose broth tubes contain a pH indicator that changes color from red to yellow when the lactose is fermented. After inoculation and incubation, the tubes are examined for an indication of coliform growth by a color change in media from red to yellow. The first set of tubes (10-mL sample) showed growth in all the tubes; the second set of tubes (1 mL) showed growth in two tubes out of five; in the third set of tubes, no growth is observed in any of the tubes (0.1-mL dilution). The numbers 5, 2, and 0 are compared with Figure B1 in Appendix B, which has been constructed using a probability model of the sampling procedure. From our reading of the table, we conclude that 49 is the most probable number of bacteria per 100 mL of pond water.

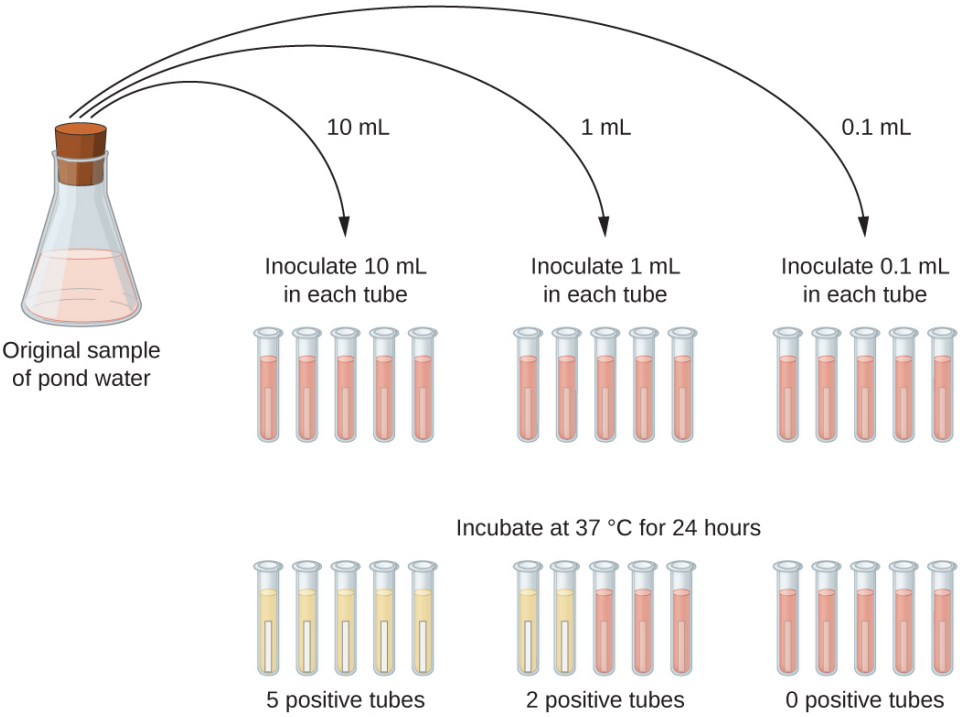


Figure 4.1.1.13: In the most probable number method, sets of five lactose broth tubes are inoculated with three different volumes of pond water: 10 mL, 1 mL, and 0.1mL. Bacterial growth is assessed through a change in the color of the broth from red to yellow as lactose is fermented.

? Exercise 4.1.1.6

1. What is a colony-forming unit?
2. What two methods are frequently used to estimate bacterial numbers in water samples?

Indirect Cell Counts

Besides direct methods of counting cells, other methods, based on an indirect detection of cell density, are commonly used to estimate and compare cell densities in a culture. The foremost approach is to measure the turbidity (cloudiness) of a sample of bacteria in a liquid suspension. The laboratory instrument used to measure turbidity is called a spectrophotometer (Figure 4.1.1.14). In a spectrophotometer, a light beam is transmitted through a bacterial suspension, the light passing through the suspension is measured by a detector, and the amount of light passing through the sample and reaching the detector is converted to either percent transmission or a logarithmic value called absorbance (optical density). As the numbers of bacteria in a suspension increase, the turbidity also increases and causes less light to reach the detector. The decrease in light passing through the sample and reaching the detector is associated with a decrease in percent transmission and increase in absorbance measured by the spectrophotometer.

Measuring turbidity is a fast method to estimate cell density as long as there are enough cells in a sample to produce turbidity. It is possible to correlate turbidity readings to the actual number of cells by performing a viable plate count of samples taken from

cultures having a range of absorbance values. Using these values, a calibration curve is generated by plotting turbidity as a function of cell density. Once the calibration curve has been produced, it can be used to estimate cell counts for all samples obtained or cultured under similar conditions and with densities within the range of values used to construct the curve.

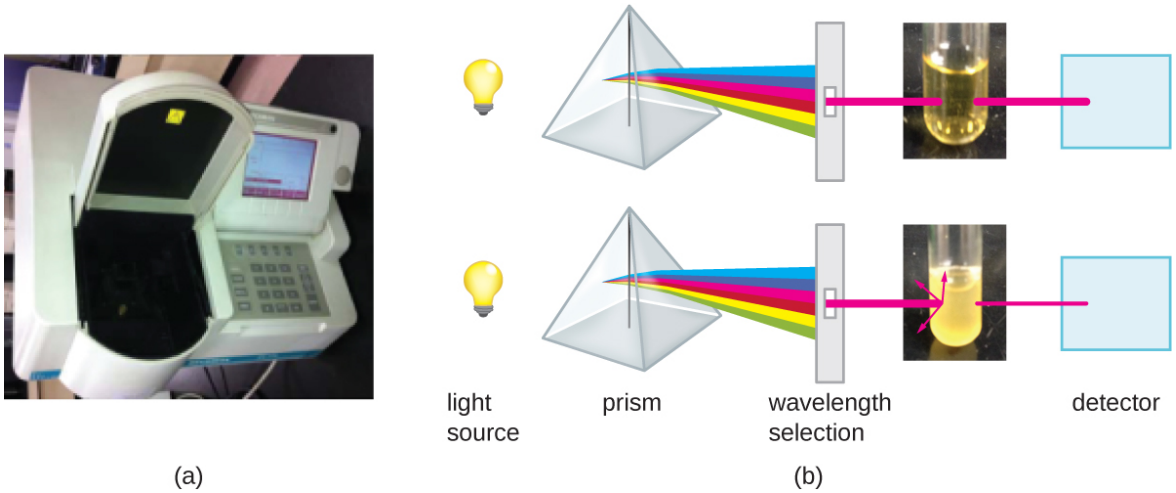


Figure 4.1.1.14: (a) A spectrophotometer is commonly used to measure the turbidity of a bacterial cell suspension as an indirect measure of cell density. (b) A spectrophotometer works by splitting white light from a source into a spectrum. The spectrophotometer allows choice of the wavelength of light to use for the measurement. The optical density (turbidity) of the sample will depend on the wavelength, so once one wavelength is chosen, it must be used consistently. The filtered light passes through the sample (or a control with only medium) and the light intensity is measured by a detector. The light passing into a suspension of bacteria is scattered by the cells in such a way that some fraction of it never reaches the detector. This scattering happens to a far lesser degree in the control tube with only the medium. (credit a: modification of work by Hwang HS, Kim MS; credit b "test tube photos": modification of work by Suzanne Wakim)

Measuring dry weight of a culture sample is another indirect method of evaluating culture density without directly measuring cell counts. The cell suspension used for weighing must be concentrated by filtration or centrifugation, washed, and then dried before the measurements are taken. The degree of drying must be standardized to account for residual water content. This method is especially useful for filamentous microorganisms, which are difficult to enumerate by direct or viable plate count.

As we have seen, methods to estimate viable cell numbers can be labor intensive and take time because cells must be grown. Recently, indirect ways of measuring live cells have been developed that are both fast and easy to implement. These methods measure cell activity by following the production of metabolic products or disappearance of reactants. Adenosine triphosphate (ATP) formation, biosynthesis of proteins and nucleic acids, and consumption of oxygen can all be monitored to estimate the number of cells.

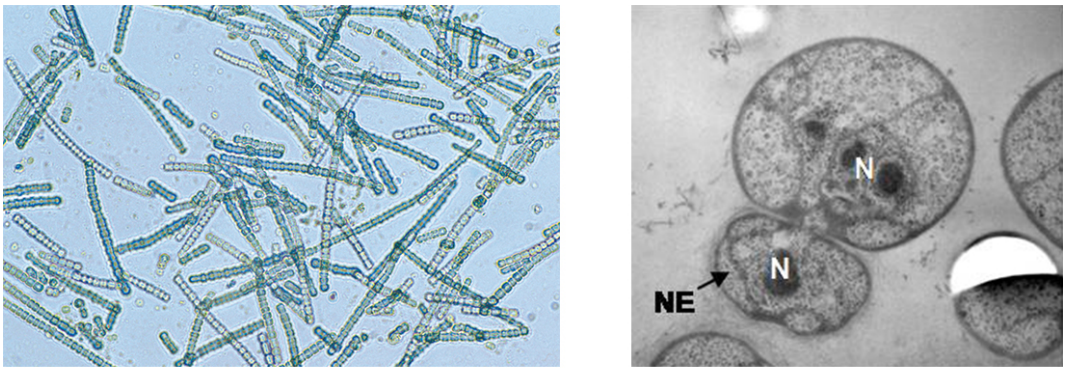
? Exercise 4.1.1.7

1. What is the purpose of a calibration curve when estimating cell count from turbidity measurements?
2. What are the newer indirect methods of counting live cells?

Alternative Patterns of Cell Division

Binary fission is the most common pattern of cell division in prokaryotes, but it is not the only one. Other mechanisms usually involve asymmetrical division (as in budding) or production of spores in aerial filaments.

In some cyanobacteria, many nucleoids may accumulate in an enlarged round cell or along a filament, leading to the generation of many new cells at once. The new cells often split from the parent filament and float away in a process called fragmentation (Figure 4.1.1.15). Fragmentation is commonly observed in the Actinomycetes, a group of gram-positive, anaerobic bacteria commonly found in soil. Another curious example of cell division in prokaryotes, reminiscent of live birth in animals, is exhibited by the giant bacterium *Epulopiscium*. Several daughter cells grow fully in the parent cell, which eventually disintegrates, releasing the new cells to the environment. Other species may form a long narrow extension at one pole in a process called budding. The tip of the extension swells and forms a smaller cell, the bud that eventually detaches from the parent cell. Budding is most common in yeast (Figure 4.1.1.15), but it is also observed in prosthecate bacteria and some cyanobacteria.



(a) (b)

Figure 4.1.1.15: (a) Filamentous cyanobacteria, like those pictured here, replicate by fragmentation. (b) In this electron micrograph, cells of the bacterium *Gemmata obscuriglobus* are budding. The larger cell is the mother cell. Labels indicate the nucleoids (N) and the still-forming nuclear envelope (NE) of the daughter cell. (credit a: modification of work by CSIRO; credit b: modification of work by Kuo-Chang Lee, Rick I Webb and John A Fuerst)

The soil bacteria *Actinomyces* grow in long filaments divided by septa, similar to the mycelia seen in fungi, resulting in long cells with multiple nucleoids. Environmental signals, probably related to low nutrient availability, lead to the formation of aerial filaments. Within these aerial filaments, elongated cells divide simultaneously. The new cells, which contain a single nucleoid, develop into spores that give rise to new colonies.

? Exercise 4.1.1.8

Identify at least one difference between fragmentation and budding.

Biofilms

In nature, microorganisms grow mainly in biofilms, complex and dynamic ecosystems that form on a variety of environmental surfaces, from industrial conduits and water treatment pipelines to rocks in river beds. Biofilms are not restricted to solid surface substrates, however. Almost any surface in a liquid environment containing some minimal nutrients will eventually develop a biofilm. Microbial mats that float on water, for example, are biofilms that contain large populations of photosynthetic microorganisms. Biofilms found in the human mouth may contain hundreds of bacterial species. Regardless of the environment where they occur, biofilms are not random collections of microorganisms; rather, they are highly structured communities that provide a selective advantage to their constituent microorganisms.

Biofilm Structure

Observations using confocal microscopy have shown that environmental conditions influence the overall structure of biofilms. Filamentous biofilms called streamers form in rapidly flowing water, such as freshwater streams, eddies, and specially designed laboratory flow cells that replicate growth conditions in fast-moving fluids. The streamers are anchored to the substrate by a “head” and the “tail” floats downstream in the current. In still or slow-moving water, biofilms mainly assume a mushroom-like shape. The structure of biofilms may also change with other environmental conditions such as nutrient availability.

Detailed observations of biofilms under confocal laser and scanning electron microscopes reveal clusters of microorganisms embedded in a matrix interspersed with open water channels. The extracellular matrix consists of extracellular polymeric substances (EPS) secreted by the organisms in the biofilm. The extracellular matrix represents a large fraction of the biofilm, accounting for 50%–90% of the total dry mass. The properties of the EPS vary according to the resident organisms and environmental conditions.

EPS is a hydrated gel composed primarily of polysaccharides and containing other macromolecules such as proteins, nucleic acids, and lipids. It plays a key role in maintaining the integrity and function of the biofilm. Channels in the EPS allow movement of nutrients, waste, and gases throughout the biofilm. This keeps the cells hydrated, preventing desiccation. EPS also shelters organisms in the biofilm from predation by other microbes or cells (e.g., protozoans, white blood cells in the human body).

Biofilm Formation

Free-floating microbial cells that live in an aquatic environment are called planktonic cells. The formation of a biofilm essentially involves the attachment of planktonic cells to a substrate, where they become sessile (attached to a surface). This occurs in stages, as depicted in Figure 4.1.1.16. The first stage involves the attachment of planktonic cells to a surface coated with a conditioning film of organic material. At this point, attachment to the substrate is reversible, but as cells express new phenotypes that facilitate the formation of EPS, they transition from a planktonic to a sessile lifestyle. The biofilm develops characteristic structures, including an extensive matrix and water channels. Appendages such as fimbriae, pili, and flagella interact with the EPS, and microscopy and genetic analysis suggest that such structures are required for the establishment of a mature biofilm. In the last stage of the biofilm life cycle, cells on the periphery of the biofilm revert to a planktonic lifestyle, sloughing off the mature biofilm to colonize new sites. This stage is referred to as dispersal.

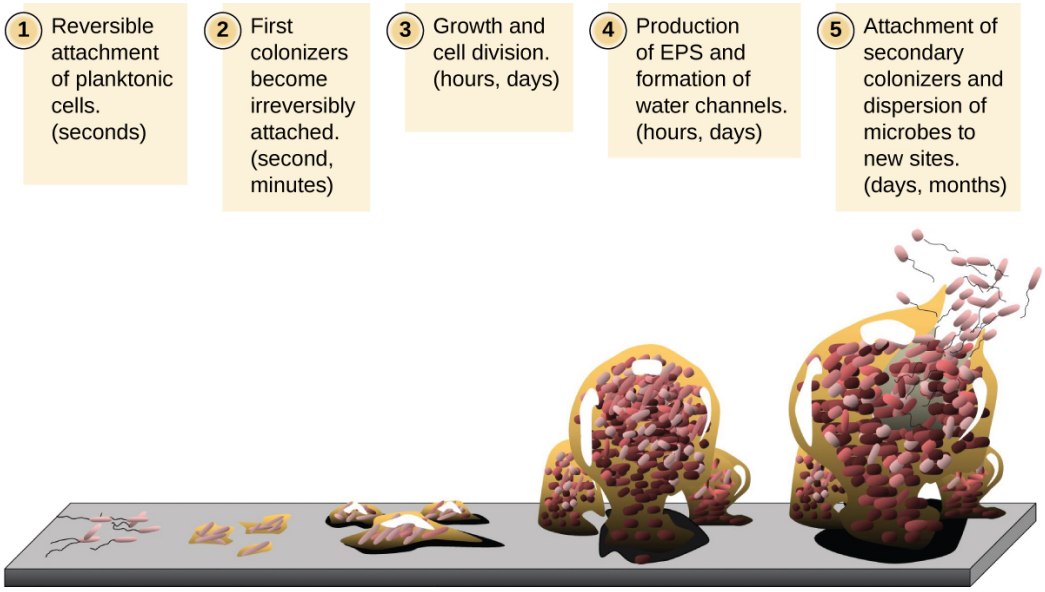


Figure 4.1.1.16: Stages in the formation and life cycle of a biofilm. (credit: modification of work by Public Library of Science and American Society for Microbiology)

Within a biofilm, different species of microorganisms establish metabolic collaborations in which the waste product of one organism becomes the nutrient for another. For example, aerobic microorganisms consume oxygen, creating anaerobic regions that promote the growth of anaerobes. This occurs in many polymicrobial infections that involve both aerobic and anaerobic pathogens.

The mechanism by which cells in a biofilm coordinate their activities in response to environmental stimuli is called quorum sensing. Quorum sensing—which can occur between cells of different species within a biofilm—enables microorganisms to detect their cell density through the release and binding of small, diffusible molecules called autoinducers. When the cell population reaches a critical threshold (a quorum), these autoinducers initiate a cascade of reactions that activate genes associated with cellular functions that are beneficial only when the population reaches a critical density. For example, in some pathogens, synthesis of virulence factors only begins when enough cells are present to overwhelm the immune defenses of the host. Although mostly studied in bacterial populations, quorum sensing takes place between bacteria and eukaryotes and between eukaryotic cells such as the fungus *Candida albicans*, a common member of the human microbiota that can cause infections in immunocompromised individuals.

The signaling molecules in quorum sensing belong to two major classes. Gram-negative bacteria communicate mainly using N-acylated homoserine lactones, whereas gram-positive bacteria mostly use small peptides (Figure 4.1.1.17). In all cases, the first step in quorum sensing consists of the binding of the autoinducer to its specific receptor only when a threshold concentration of signaling molecules is reached. Once binding to the receptor takes place, a cascade of signaling events leads to changes in gene expression. The result is the activation of biological responses linked to quorum sensing, notably an increase in the production of signaling molecules themselves, hence the term autoinducer.

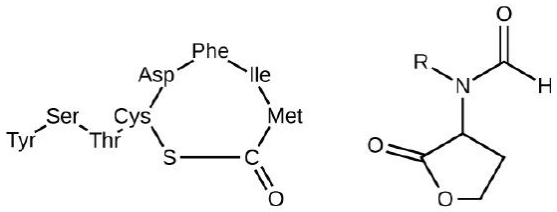


Figure 4.1.1.17: Short peptides in gram-positive bacteria and N-acetylated homoserine lactones in gram-negative bacteria act as autoinducers in quorum sensing and mediate the coordinated response of bacterial cells. The R side chain of the N-acetylated homoserine lactone is specific for the species of gram-negative bacteria. Some secreted homoserine lactones are recognized by more than one species.

Biofilms and Human Health

The human body harbors many types of biofilms, some beneficial and some harmful. For example, the layers of normal microbiota lining the intestinal and respiratory mucosa play a role in warding off infections by pathogens. However, other biofilms in the body can have a detrimental effect on health. For example, the plaque that forms on teeth is a biofilm that can contribute to dental and periodontal disease. Biofilms can also form in wounds, sometimes causing serious infections that can spread. The bacterium *Pseudomonas aeruginosa* often colonizes biofilms in the airways of patients with cystic fibrosis, causing chronic and sometimes fatal infections of the lungs. Biofilms can also form on medical devices used in or on the body, causing infections in patients with in-dwelling catheters, artificial joints, or contact lenses.

Pathogens embedded within biofilms exhibit a higher resistance to antibiotics than their free-floating counterparts. Several hypotheses have been proposed to explain why. Cells in the deep layers of a biofilm are metabolically inactive and may be less susceptible to the action of antibiotics that disrupt metabolic activities. The EPS may also slow the diffusion of antibiotics and antiseptics, preventing them from reaching cells in the deeper layers of the biofilm. Phenotypic changes may also contribute to the increased resistance exhibited by bacterial cells in biofilms. For example, the increased production of efflux pumps, membrane-embedded proteins that actively extrude antibiotics out of bacterial cells, have been shown to be an important mechanism of antibiotic resistance among biofilm-associated bacteria. Finally, biofilms provide an ideal environment for the exchange of extrachromosomal DNA, which often includes genes that confer antibiotic resistance.

? Exercise 4.1.1.9

1. What is the matrix of a biofilm composed of?
2. What is the role of quorum sensing in a biofilm?

Key Concepts and Summary

- Most bacterial cells divide by **binary fission**. **Generation time** in bacterial growth is defined as the **doubling time**of the population.
- Cells in a closed system follow a pattern of growth with four phases: **lag**, **logarithmic (exponential)**, **stationary**, and **death**.
- Cells can be counted by **direct viable cell count**. The **pour plate** and **spread plate** methods are used to plate **serial dilutions** into or onto, respectively, agar to allow counting of viable cells that give rise to **colony-forming units**. **Membrane filtration** is used to count live cells in dilute solutions. The **most probable cell number (MPN)**method allows estimation of cell numbers in cultures without using solid media.
- Indirect methods can be used to estimate **culture density** by measuring **turbidity** of a culture or live cell density by measuring metabolic activity.
- Other patterns of cell division include multiple nucleoid formation in cells; asymmetric division, as in **budding**; and the formation of hyphae and terminal spores.
- **Biofilms** are communities of microorganisms enmeshed in a matrix of **extracellular polymeric substance**. The formation of a biofilm occurs when **planktonic** cells attach to a substrate and become **sessile**. Cells in biofilms coordinate their activity by communicating through **quorum sensing**.

- Biofilms are commonly found on surfaces in nature and in the human body, where they may be beneficial or cause severe infections. Pathogens associated with biofilms are often more resistant to antibiotics and disinfectants.

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4.1.2: Oxygen Requirements for Microbial Growth

Learning Objectives

- Interpret visual data demonstrating minimum, optimum, and maximum oxygen or carbon dioxide requirements for growth
- Identify and describe different categories of microbes with requirements for growth with or without oxygen: obligate aerobe, obligate anaerobe, facultative anaerobe, aerotolerant anaerobe, microaerophile, and capnophile
- Give examples of microorganisms for each category of growth requirements

Ask most people "What are the major requirements for life?" and the answers are likely to include water and oxygen. Few would argue about the need for water, but what about oxygen? Can there be life without oxygen?

The answer is that molecular oxygen (O_2) is not always needed. The earliest signs of life are dated to a period when conditions on earth were highly reducing and free oxygen gas was essentially nonexistent. Only after cyanobacteria started releasing oxygen as a byproduct of photosynthesis and the capacity of iron in the oceans for taking up oxygen was exhausted did oxygen levels increase in the atmosphere. This event, often referred to as the Great Oxygenation Event or the Oxygen Revolution, caused a massive extinction. Most organisms could not survive the powerful oxidative properties of reactive oxygen species (ROS), highly unstable ions and molecules derived from partial reduction of oxygen that can damage virtually any macromolecule or structure with which they come in contact. Singlet oxygen (O_2•), superoxide (O_2^-), peroxides (H_2O_2), hydroxyl radical (OH•), and hypochlorite ion (OCl^-), the active ingredient of household bleach, are all examples of ROS. The organisms that were able to detoxify reactive oxygen species harnessed the high electronegativity of oxygen to produce free energy for their metabolism and thrived in the new environment.

Oxygen Requirements of Microorganisms

Many ecosystems are still free of molecular oxygen. Some are found in extreme locations, such as deep in the ocean or in earth's crust; others are part of our everyday landscape, such as marshes, bogs, and sewers. Within the bodies of humans and other animals, regions with little or no oxygen provide an anaerobic environment for microorganisms. (Figure 4.1.2.1).



(a) (b)

Figure 4.1.2.1: Anaerobic environments are still common on earth. They include environments like (a) a bog where undisturbed dense sediments are virtually devoid of oxygen, and (b) the rumen (the first compartment of a cow's stomach), which provides an oxygen-free incubator for methanogens and other obligate anaerobic bacteria. (credit a: modification of work by National Park Service; credit b: modification of work by US Department of Agriculture)

We can easily observe different requirements for molecular oxygen by growing bacteria in thioglycolate tube cultures. A test-tube culture starts with autoclaved thioglycolate medium containing a low percentage of agar to allow motile bacteria to move throughout the medium. Thioglycolate has strong reducing properties and autoclaving flushes out most of the oxygen. The tubes are inoculated with the bacterial cultures to be tested and incubated at an appropriate temperature. Over time, oxygen slowly diffuses throughout the thioglycolate tube culture from the top. Bacterial density increases in the area where oxygen concentration is best suited for the growth of that particular organism.

The growth of bacteria with varying oxygen requirements in thioglycolate tubes is illustrated in Figure 4.1.2.2. In tube A, all the growth is seen at the top of the tube. The bacteria are obligate (strict) aerobes that cannot grow without an abundant supply of

oxygen. Tube B looks like the opposite of tube A. Bacteria grow at the bottom of tube B. Those are obligate anaerobes, which are killed by oxygen. Tube C shows heavy growth at the top of the tube and growth throughout the tube, a typical result with facultative anaerobes. Facultative anaerobes are organisms that thrive in the presence of oxygen but also grow in its absence by relying on fermentation or anaerobic respiration, if there is a suitable electron acceptor other than oxygen and the organism is able to perform anaerobic respiration. The aerotolerant anaerobes in tube D are indifferent to the presence of oxygen. They do not use oxygen because they usually have a fermentative metabolism, but they are not harmed by the presence of oxygen as obligate anaerobes are. Tube E on the right shows a "Goldilocks" culture. The oxygen level has to be just right for growth, not too much and not too little. These microaerophiles are bacteria that require a minimum level of oxygen for growth, about 1%–10%, well below the 21% found in the atmosphere.

Examples of obligate aerobes are *Mycobacterium tuberculosis*, the causative agent of tuberculosis and *Micrococcus luteus*, a gram-positive bacterium that colonizes the skin. *Neisseria meningitidis*, the causative agent of severe bacterial meningitis, and *N. gonorrheae*, the causative agent of sexually transmitted gonorrhea, are also obligate aerobes.

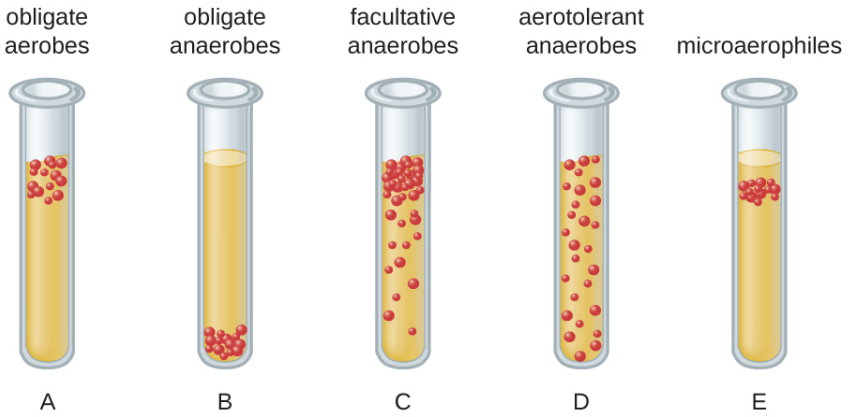
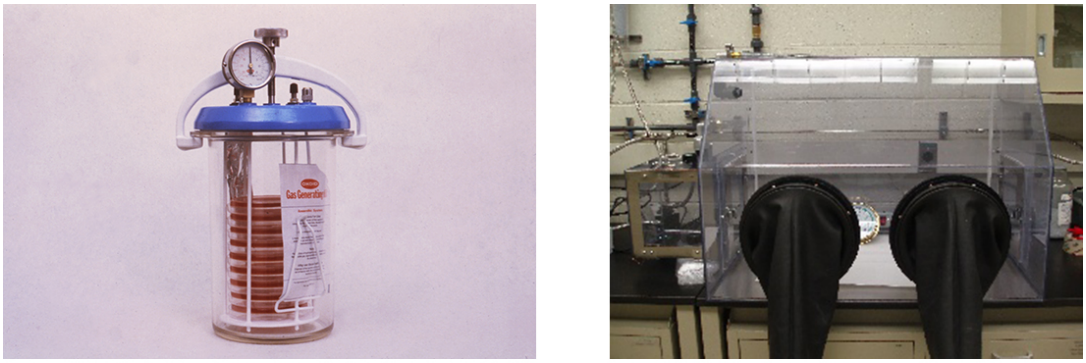


Figure 4.1.2.2: Diagram of bacterial cell distribution in thioglycolate tubes.

Many obligate anaerobes are found in the environment where anaerobic conditions exist, such as in deep sediments of soil, still waters, and at the bottom of the deep ocean where there is no photosynthetic life. Anaerobic conditions also exist naturally in the intestinal tract of animals. Obligate anaerobes, mainly *Bacteroidetes*, represent a large fraction of the microbes in the human gut. Transient anaerobic conditions exist when tissues are not supplied with blood circulation; they die and become an ideal breeding ground for obligate anaerobes. Another type of obligate anaerobe encountered in the human body is the gram-positive, rod-shaped *Clostridium* spp. Their ability to form endospores allows them to survive in the presence of oxygen. One of the major causes of health-acquired infections is *C. difficile*, known as C. diff. Prolonged use of antibiotics for other infections increases the probability of a patient developing a secondary *C. difficile* infection. Antibiotic treatment disrupts the balance of microorganisms in the intestine and allows the colonization of the gut by *C. difficile*, causing a significant inflammation of the colon.

Other clostridia responsible for serious infections include *C. tetani*, the agent of tetanus, and *C. perfringens*, which causes gas gangrene. In both cases, the infection starts in necrotic tissue (dead tissue that is not supplied with oxygen by blood circulation). This is the reason that deep puncture wounds are associated with tetanus. When tissue death is accompanied by lack of circulation, gangrene is always a danger.

The study of obligate anaerobes requires special equipment. Obligate anaerobic bacteria must be grown under conditions devoid of oxygen. The most common approach is culture in an anaerobic jar (Figure 4.1.2.3). Anaerobic jars include chemical packs that remove oxygen and release carbon dioxide (CO_2). An anaerobic chamber is an enclosed box from which all oxygen is removed. Gloves sealed to openings in the box allow handling of the cultures without exposing the culture to air (Figure 4.1.2.3).



(a) (b)

Figure 4.1.2.3: (a) An anaerobic jar is pictured that is holding nine Petri plates supporting cultures. (b) Openings in the side of an anaerobic box are sealed by glove-like sleeves that allow for the handling of cultures inside the box. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by NIST)

Staphylococci and Enterobacteriaceae are examples of facultative anaerobes. Staphylococci are found on the skin and upper respiratory tract. Enterobacteriaceae are found primarily in the gut and upper respiratory tract but can sometimes spread to the urinary tract, where they are capable of causing infections. It is not unusual to see mixed bacterial infections in which the facultative anaerobes use up the oxygen, creating an environment for the obligate anaerobes to flourish.

Examples of aerotolerant anaerobes include lactobacilli and streptococci, both found in the oral microbiota. *Campylobacter jejuni*, which causes gastrointestinal infections, is an example of a microaerophile and is grown under low-oxygen conditions.

The optimum oxygen concentration, as the name implies, is the ideal concentration of oxygen for a particular microorganism. The lowest concentration of oxygen that allows growth is called the minimum permissive oxygen concentration. The highest tolerated concentration of oxygen is the maximum permissive oxygen concentration. The organism will not grow outside the range of oxygen levels found between the minimum and maximum permissive oxygen concentrations.

? Exercise 4.1.2.1

1. Would you expect the oldest bacterial lineages to be aerobic or anaerobic?
2. Which bacteria grow at the top of a thioglycolate tube, and which grow at the bottom of the tube?

An Unwelcome Anaerobe

Charles is a retired bus driver who developed type 2 diabetes over 10 years ago. Since his retirement, his lifestyle has become very sedentary and he has put on a substantial amount of weight. Although he has felt tingling and numbness in his left foot for a while, he has not been worried because he thought his foot was simply “falling asleep.” Recently, a scratch on his foot does not seem to be healing and is becoming increasingly ugly. Because the sore did not bother him much, Charles figured it could not be serious until his daughter noticed a purplish discoloration spreading on the skin and oozing (Figure 4.1.2.4). When he was finally seen by his physician, Charles was rushed to the operating room. His open sore, or ulcer, is the result of a diabetic foot.

The concern here is that gas gangrene may have taken hold in the dead tissue. The most likely agent of gas gangrene is *Clostridium perfringens*, an endospore-forming, gram-positive bacterium. It is an obligate anaerobe that grows in tissue devoid of oxygen. Since dead tissue is no longer supplied with oxygen by the circulatory system, the dead tissue provides pockets of ideal environment for the growth of *C. perfringens*.

A surgeon examines the ulcer and radiographs of Charles’s foot and determines that the bone is not yet infected. The wound will have to be surgically debrided (debridement refers to the removal of dead and infected tissue) and a sample sent for microbiological lab analysis, but Charles will not have to have his foot amputated. Many diabetic patients are not so lucky. In 2008, nearly 70,000 diabetic patients in the United States lost a foot or limb to amputation, according to statistics from the Centers for Disease Control and Prevention.



Figure 4.1.2.4: This clinical photo depicts ulcers on the foot of a diabetic patient. Dead tissue accumulating in ulcers can provide an ideal growth environment for the anaerobe *C. perfringens*, a causative agent of gas gangrene. (credit: Shigeo Kono, Reiko Nakagawachi, Jun Arata, Benjamin A Lipsky)

Exercise 4.1.2.2

Which growth conditions would you recommend for the detection of *C. perfringens*?

Detoxification of Reactive Oxygen Species

Aerobic respiration constantly generates reactive oxygen species (ROS), byproducts that must be detoxified. Even organisms that do not use aerobic respiration need some way to break down some of the ROS that may form from atmospheric oxygen. Three main enzymes break down those toxic byproducts: superoxide dismutase, peroxidase, and catalase. Each one catalyzes a different reaction. Reactions of type seen in Reaction 1 are catalyzed by peroxidases.

$$\mathrm{X} - (2\mathrm{H}^+) + \mathrm{H_2O_2} \rightarrow \text{oxidized-X} + 2\mathrm{H_2O} \tag{4.1.2.1}$$

In these reactions, an electron donor (reduced compound; e.g., reduced nicotinamide adenine dinucleotide [NADH]) oxidizes hydrogen peroxide, or other peroxides, to water. The enzymes play an important role by limiting the damage caused by peroxidation of membrane lipids. Reaction 2 is mediated by the enzyme superoxide dismutase (SOD) and breaks down the powerful superoxide anions generated by aerobic metabolism:

$$2\mathrm{O_2^-} + 2\mathrm{H}^+ \rightarrow \mathrm{H_2O_2} + \mathrm{O_2} \tag{4.1.2.2}$$

The enzyme catalase converts hydrogen peroxide to water and oxygen as shown in Reaction 3.

$$2\mathrm{H_2O_2} \rightarrow 2\mathrm{H_2O} + \mathrm{O_2} \tag{4.1.2.3}$$

Obligate anaerobes usually lack all three enzymes. Aerotolerant anaerobes do have SOD but no catalase. Reaction 3, shown occurring in Figure 4.1.2.5, is the basis of a useful and rapid test to distinguish streptococci, which are aerotolerant and do not possess catalase, from staphylococci, which are facultative anaerobes. A sample of culture rapidly mixed in a drop of 3% hydrogen peroxide will release bubbles if the culture is catalase positive.

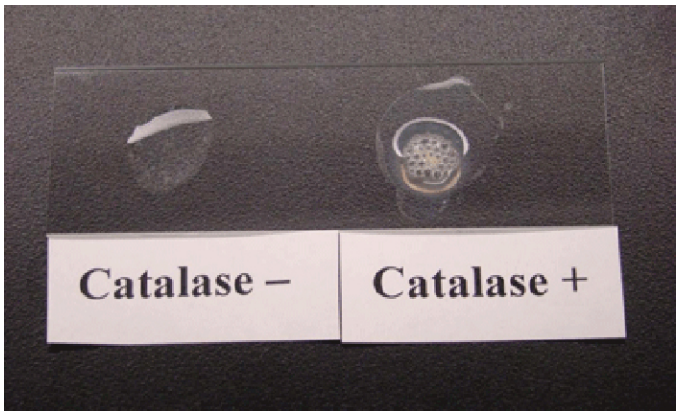


Figure 4.1.2.5: The catalase test detects the presence of the enzyme catalase by noting whether bubbles are released when hydrogen peroxide is added to a culture sample. Compare the positive result (right) with the negative result (left). (credit: Centers for Disease Control and Prevention)

Bacteria that grow best in a higher concentration of CO_2 and a lower concentration of oxygen than present in the atmosphere are called capnophiles. One common approach to grow capnophiles is to use a candle jar. A candle jar consists of a jar with a tight-fitting lid that can accommodate the cultures and a candle. After the cultures are added to the jar, the candle is lit and the lid closed. As the candle burns, it consumes most of the oxygen present and releases CO_2.

? Exercise 4.1.2.3

1. What substance is added to a sample to detect catalase?
2. What is the function of the candle in a candle jar?

Clinical Focus: Part 2

The health-care provider who saw Jeni was concerned primarily because of her pregnancy. Her condition enhances the risk for infections and makes her more vulnerable to those infections. The immune system is downregulated during pregnancy, and pathogens that cross the placenta can be very dangerous for the fetus. A note on the provider's order to the microbiology lab mentions a suspicion of infection by *Listeria monocytogenes*, based on the signs and symptoms exhibited by the patient.

Jeni's blood samples are streaked directly on sheep blood agar, a medium containing tryptic soy agar enriched with 5% sheep blood. (Blood is considered sterile; therefore, competing microorganisms are not expected in the medium.) The inoculated plates are incubated at 37 °C for 24 to 48 hours. Small grayish colonies surrounded by a clear zone emerge. Such colonies are typical of *Listeria* and other pathogens such as streptococci; the clear zone surrounding the colonies indicates complete lysis of blood in the medium, referred to as beta-hemolysis (Figure 4.1.2.6). When tested for the presence of catalase, the colonies give a positive response, eliminating *Streptococcus* as a possible cause. Furthermore, a Gram stain shows short gram-positive bacilli. Cells from a broth culture grown at room temperature displayed the tumbling motility characteristic of *Listeria* (Figure 4.1.2.6). All of these clues lead the lab to positively confirm the presence of *Listeria* in Jeni's blood samples.



Figure 4.1.2.6: (a) A sample blood agar test showing beta-hemolysis. (b) A sample motility test showing both positive and negative results. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by "VeeDunn"/Flickr)

Exercise 4.1.2.4

How serious is Jeni's condition and what is the appropriate treatment?

Key Concepts and Summary

- Aerobic and anaerobic environments can be found in diverse niches throughout nature, including different sites within and on the human body.
- Microorganisms vary in their requirements for molecular oxygen. **Obligate aerobes** depend on aerobic respiration and use oxygen as a terminal electron acceptor. They cannot grow without oxygen.
- **Obligate anaerobes** cannot grow in the presence of oxygen. They depend on fermentation and anaerobic respiration using a final electron acceptor other than oxygen.
- **Facultative anaerobes** show better growth in the presence of oxygen but will also grow without it.
- Although **aerotolerant anaerobes** do not perform aerobic respiration, they can grow in the presence of oxygen. Most aerotolerant anaerobes test negative for the enzyme **catalase**.
- **Microaerophiles** need oxygen to grow, albeit at a lower concentration than 21% oxygen in air.
- **Optimum oxygen concentration** for an organism is the oxygen level that promotes the fastest growth rate. The **minimum permissive oxygen concentration** and the **maximum permissive oxygen concentration** are, respectively, the lowest and the highest oxygen levels that the organism will tolerate.
- **Peroxidase**, **superoxide dismutase**, and **catalase** are the main enzymes involved in the detoxification of the **reactive oxygen species**. Superoxide dismutase is usually present in a cell that can tolerate oxygen. All three enzymes are usually detectable in cells that perform aerobic respiration and produce more ROS.
- A **capnophile** is an organism that requires a higher than atmospheric concentration of CO_2 to grow.

Footnotes

1. 1 Centers for Disease Control and Prevention. "Living With Diabetes: Keep Your Feet Healthy." http://www.cdc.gov/Features/DiabetesFootHealth/

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4.1.3: The Effects of pH on Microbial Growth

Learning Objectives

- Illustrate and briefly describe minimum, optimum, and maximum pH requirements for growth
- Identify and describe the different categories of microbes with pH requirements for growth: acidophiles, neutrophiles, and alkaliphiles
- Give examples of microorganisms for each category of pH requirement

Yogurt, pickles, sauerkraut, and lime-seasoned dishes all owe their tangy taste to a high acid content (Figure 4.1.3.1). Recall that acidity is a function of the concentration of hydrogen ions [H^+] and is measured as pH. Environments with pH values below 7.0 are considered acidic, whereas those with pH values above 7.0 are considered basic. Extreme pH affects the structure of all macromolecules. The hydrogen bonds holding together strands of DNA break up at high pH. Lipids are hydrolyzed by an extremely basic pH. The proton motive force responsible for production of ATP in cellular respiration depends on the concentration gradient of H^+ across the plasma membrane (see Cellular Respiration). If H^+ ions are neutralized by hydroxide ions, the concentration gradient collapses and impairs energy production. But the component most sensitive to pH in the cell is its workhorse, the protein. Moderate changes in pH modify the ionization of amino-acid functional groups and disrupt hydrogen bonding, which, in turn, promotes changes in the folding of the molecule, promoting denaturation and destroying activity.



Figure 4.1.3.1: Lactic acid bacteria that ferment milk into yogurt or transform vegetables in pickles thrive at a pH close to 4.0. Sauerkraut and dishes such as pico de gallo owe their tangy flavor to their acidity. Acidic foods have been a mainstay of the human diet for centuries, partly because most microbes that cause food spoilage grow best at a near neutral pH and do not tolerate acidity well. (credit “yogurt”: modification of work by “nina.jsc”/Flickr; credit “pickles”: modification of work by Noah Sussman; credit “sauerkraut”: modification of work by Jesse LaBuff; credit “pico de gallo”: modification of work by “regan76”/Flickr)

The optimum growth pH is the most favorable pH for the growth of an organism. The lowest pH value that an organism can tolerate is called the minimum growth pH and the highest pH is the maximum growth pH. These values can cover a wide range, which is important for the preservation of food and to microorganisms’ survival in the stomach. For example, the optimum growth pH of *Salmonella* spp. is 7.0–7.5, but the minimum growth pH is closer to 4.2.

Most bacteria are neutrophiles, meaning they grow optimally at a pH within one or two pH units of the neutral pH of 7 (see Figure 4.1.3.2). Most familiar bacteria, like *Escherichia coli*, staphylococci, and *Salmonella* spp. are neutrophiles and do not fare well in the acidic pH of the stomach. However, there are pathogenic strains of *E. coli*, *S. typhi*, and other species of intestinal pathogens that are much more resistant to stomach acid. In comparison, fungi thrive at slightly acidic pH values of 5.0–6.0.

Microorganisms that grow optimally at pH less than 5.55 are called acidophiles. For example, the sulfur-oxidizing *Sulfolobus* spp. isolated from sulfur mud fields and hot springs in Yellowstone National Park are extreme acidophiles. These archaea survive at pH values of 2.5–3.5. Species of the archaean genus *Ferroplasma* live in acid mine drainage at pH values of 0–2.9. *Lactobacillus* bacteria, which are an important part of the normal microbiota of the vagina, can tolerate acidic environments at pH values 3.5–6.8 and also contribute to the acidity of the vagina (pH of 4, except at the onset of menstruation) through their metabolic production of lactic acid. The vagina’s acidity plays an important role in inhibiting other microbes that are less tolerant of acidity. Acidophilic microorganisms display a number of adaptations to survive in strong acidic environments. For example, proteins show increased negative surface charge that stabilizes them at low pH. Pumps actively eject H^+ ions out of the cells. The changes in the composition of membrane phospholipids probably reflect the need to maintain membrane fluidity at low pH.

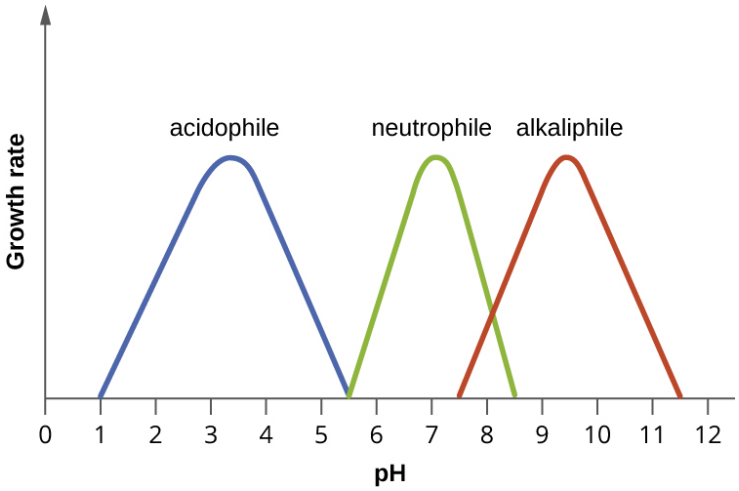


Figure 4.1.3.2: The curves show the approximate pH ranges for the growth of the different classes of pH-specific prokaryotes. Each curve has an optimal pH and extreme pH values at which growth is much reduced. Most bacteria are neutrophiles and grow best at near-neutral pH (center curve). Acidophiles have optimal growth at pH values near 3 and alkaliphiles have optimal growth at pH values above 9.

At the other end of the spectrum are alkaliphiles, microorganisms that grow best at pH between 8.0 and 10.5. *Vibrio cholerae*, the pathogenic agent of cholera, grows best at the slightly basic pH of 8.0; it can survive pH values of 11.0 but is inactivated by the acid of the stomach. When it comes to survival at high pH, the bright pink archaean *Natronobacterium*, found in the soda lakes of the African Rift Valley, may hold the record at a pH of 10.5 (Figure 4.1.3.3). Extreme alkaliphiles have adapted to their harsh environment through evolutionary modification of lipid and protein structure and compensatory mechanisms to maintain the proton motive force in an alkaline environment. For example, the alkaliphile *Bacillus firmus* derives the energy for transport reactions and motility from a Na^+ ion gradient rather than a proton motive force. Many enzymes from alkaliphiles have a higher isoelectric point, due to an increase in the number of basic amino acids, than homologous enzymes from neutrophiles.



Figure 4.1.3.3: View from space of Lake Natron in Tanzania. The pink color is due to the pigmentation of the extreme alkaliphilic and halophilic microbes that colonize the lake. (credit: NASA)

Survival at the Low pH of the Stomach

Peptic ulcers (or stomach ulcers) are painful sores on the stomach lining. Until the 1980s, they were believed to be caused by spicy foods, stress, or a combination of both. Patients were typically advised to eat bland foods, take anti-acid medications, and avoid stress. These remedies were not particularly effective, and the condition often recurred. This all changed dramatically when the real cause of most peptic ulcers was discovered to be a slim, corkscrew-shaped bacterium, *Helicobacter pylori*. This organism was identified and isolated by Barry Marshall and Robin Warren, whose discovery earned them the Nobel Prize in Medicine in 2005.

The ability of *H. pylori* to survive the low pH of the stomach would seem to suggest that it is an extreme acidophile. As it turns out, this is not the case. In fact, *H. pylori* is a neutrophile. So, how does it survive in the stomach? Remarkably, *H. pylori* creates a microenvironment in which the pH is nearly neutral. It achieves this by producing large amounts of the enzyme urease, which breaks down urea to form NH_4^+ and CO_2. The ammonium ion raises the pH of the immediate environment.

This metabolic capability of *H. pylori* is the basis of an accurate, noninvasive test for infection. The patient is given a solution of urea containing radioactively labeled carbon atoms. If *H. pylori* is present in the stomach, it will rapidly break down the urea, producing radioactive CO_2 that can be detected in the patient's breath. Because peptic ulcers may lead to gastric cancer, patients who are determined to have *H. pylori* infections are treated with antibiotics.

? Exercise 4.1.3.1

1. What effect do extremes of pH have on proteins?
2. What pH-adaptive type of bacteria would most human pathogens be?

Key Concepts and Summary

- Bacteria are generally **neutrophiles**. They grow best at neutral pH close to 7.0.
- **Acidophiles** grow optimally at a pH near 3.0. **Alkaliphiles** are organisms that grow optimally between a pH of 8 and 10.5. Extreme acidophiles and alkaliphiles grow slowly or not at all near neutral pH.
- Microorganisms grow best at their **optimum growth pH**. Growth occurs slowly or not at all below the **minimum growth pH** and above the **maximum growth pH**.

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4.1.4: Temperature and Microbial Growth

Learning Objectives

- Illustrate and briefly describe minimum, optimum, and maximum temperature requirements for growth
- Identify and describe different categories of microbes with temperature requirements for growth: psychrophile, psychrotrophs, mesophile, thermophile, hyperthermophile
- Give examples of microorganisms in each category of temperature tolerance

When the exploration of Lake Whillans started in Antarctica, researchers did not expect to find much life. Constant subzero temperatures and lack of obvious sources of nutrients did not seem to be conditions that would support a thriving ecosystem. To their surprise, the samples retrieved from the lake showed abundant microbial life. In a different but equally harsh setting, bacteria grow at the bottom of the ocean in sea vents (Figure 4.1.4.1), where temperatures can reach 340 °C (700 °F).

Microbes can be roughly classified according to the range of temperature at which they can grow. The growth rates are the highest at the optimum growth temperature for the organism. The lowest temperature at which the organism can survive and replicate is its minimum growth temperature. The highest temperature at which growth can occur is its maximum growth temperature. The following ranges of permissive growth temperatures are approximate only and can vary according to other environmental factors.

Organisms categorized as mesophiles (“middle loving”) are adapted to moderate temperatures, with optimal growth temperatures ranging from room temperature (about 20 °C) to about 45 °C. As would be expected from the core temperature of the human body, 37 °C (98.6 °F), normal human microbiota and pathogens (e.g., *E. coli*, *Salmonella* spp., and *Lactobacillus* spp.) are mesophiles.

Organisms called psychrotrophs, also known as psychrotolerant, prefer cooler environments, from a high temperature of 25 °C to refrigeration temperature about 4 °C. They are found in many natural environments in temperate climates. They are also responsible for the spoilage of refrigerated food.

Clinical Focus: Resolution

The presence of *Listeria* in Jeni’s blood suggests that her symptoms are due to listeriosis, an infection caused by *L. monocytogenes*. Listeriosis is a serious infection with a 20% mortality rate and is a particular risk to Jeni’s fetus. A sample from the amniotic fluid cultured for the presence of *Listeria* gave negative results. Because the absence of organisms does not rule out the possibility of infection, a molecular test based on the nucleic acid amplification of the 16S ribosomal RNA of *Listeria* was performed to confirm that no bacteria crossed the placenta. Fortunately, the results from the molecular test were also negative.

Jeni was admitted to the hospital for treatment and recovery. She received a high dose of two antibiotics intravenously for 2 weeks. The preferred drugs for the treatment of listeriosis are ampicillin or penicillin G with an aminoglycoside antibiotic. Resistance to common antibiotics is still rare in *Listeria* and antibiotic treatment is usually successful. She was released to home care after a week and fully recovered from her infection.

L. monocytogenes is a gram-positive short rod found in soil, water, and food. It is classified as a psychrophile and is halotolerant. Its ability to multiply at refrigeration temperatures (4–10 °C) and its tolerance for high concentrations of salt (up to 10% sodium chloride [NaCl]) make it a frequent source of food poisoning. Because *Listeria* can infect animals, it often contaminates food such as meat, fish, or dairy products. Contamination of commercial foods can often be traced to persistent biofilms that form on manufacturing equipment that is not sufficiently cleaned.

Listeria infection is relatively common among pregnant women because the elevated levels of progesterone downregulate the immune system, making them more vulnerable to infection. The pathogen can cross the placenta and infect the fetus, often resulting in miscarriage, stillbirth, or fatal neonatal infection. Pregnant women are thus advised to avoid consumption of soft cheeses, refrigerated cold cuts, smoked seafood, and unpasteurized dairy products. Because *Listeria* bacteria can easily be confused with diphtheroids, another common group of gram-positive rods, it is important to alert the laboratory when listeriosis is suspected.

The organisms retrieved from arctic lakes such as Lake Whillans are considered extreme psychrophiles (cold loving). Psychrophiles are microorganisms that can grow at 0 °C and below, have an optimum growth temperature close to 15 °C, and usually do not survive at temperatures above 20 °C. They are found in permanently cold environments such as the deep waters of the oceans. Because they are active at low temperature, psychrophiles and psychrotrophs are important decomposers in cold climates.

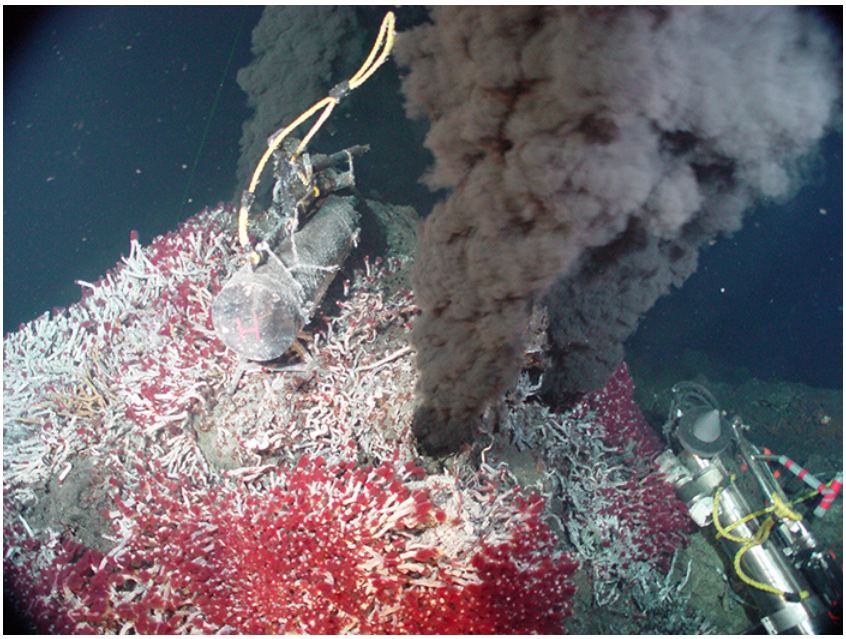


Figure 4.1.4.1: A black smoker at the bottom of the ocean belches hot, chemical-rich water, and heats the surrounding waters. Sea vents provide an extreme environment that is nonetheless teeming with macroscopic life (the red tubeworms) supported by an abundant microbial ecosystem. (credit: NOAA)

Organisms that grow at optimum temperatures of 50 °C to a maximum of 80 °C are called thermophiles (“heat loving”). They do not multiply at room temperature. Thermophiles are widely distributed in hot springs, geothermal soils, and manmade environments such as garden compost piles where the microbes break down kitchen scraps and vegetal material. Examples of thermophiles include *Thermus aquaticus* and *Geobacillus* spp. Higher up on the extreme temperature scale we find the hyperthermophiles, which are characterized by growth ranges from 80 °C to a maximum of 110 °C, with some extreme examples that survive temperatures above 121 °C, the average temperature of an autoclave. The hydrothermal vents at the bottom of the ocean are a prime example of extreme environments, with temperatures reaching an estimated 340 °C (Figure 4.1.4.1). Microbes isolated from the vents achieve optimal growth at temperatures higher than 100 °C. Noteworthy examples are *Pyrobolus* and *Pyrodictium*, archaea that grow at 105 °C and survive autoclaving. Figure 4.1.4.2 shows the typical skewed curves of temperature-dependent growth for the categories of microorganisms we have discussed.

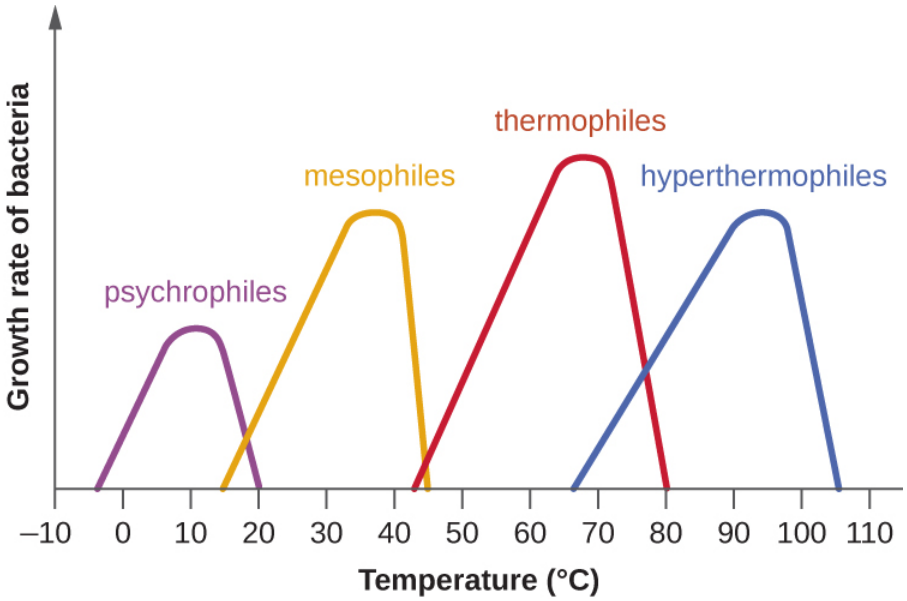


Figure 4.1.4.2: The graph shows growth rate of bacteria as a function of temperature. Notice that the curves are skewed toward the optimum temperature. The skewing of the growth curve is thought to reflect the rapid denaturation of proteins as the temperature rises past the optimum for growth of the microorganism.

Life in extreme environments raises fascinating questions about the adaptation of macromolecules and metabolic processes. Very low temperatures affect cells in many ways. Membranes lose their fluidity and are damaged by ice crystal formation. Chemical reactions and diffusion slow considerably. Proteins become too rigid to catalyze reactions and may undergo denaturation. At the opposite end of the temperature spectrum, heat denatures proteins and nucleic acids. Increased fluidity impairs metabolic processes in membranes. Some of the practical applications of the destructive effects of heat on microbes are sterilization by steam, pasteurization, and incineration of inoculating loops. Proteins in psychrophiles are, in general, rich in hydrophobic residues, display an increase in flexibility, and have a lower number of secondary stabilizing bonds when compared with homologous proteins from mesophiles. Antifreeze proteins and solutes that decrease the freezing temperature of the cytoplasm are common. The lipids in the membranes tend to be unsaturated to increase fluidity. Growth rates are much slower than those encountered at moderate temperatures. Under appropriate conditions, mesophiles and even thermophiles can survive freezing. Liquid cultures of bacteria are mixed with sterile glycerol solutions and frozen to −80 °C for long-term storage as stocks. Cultures can withstand freeze drying (lyophilization) and then be stored as powders in sealed ampules to be reconstituted with broth when needed.

Macromolecules in thermophiles and hyperthermophiles show some notable structural differences from what is observed in the mesophiles. The ratio of saturated to polyunsaturated lipids increases to limit the fluidity of the cell membranes. Their DNA sequences show a higher proportion of guanine–cytosine nitrogenous bases, which are held together by three hydrogen bonds in contrast to adenine and thymine, which are connected in the double helix by two hydrogen bonds. Additional secondary ionic and covalent bonds, as well as the replacement of key amino acids to stabilize folding, contribute to the resistance of proteins to denaturation. The so-called thermoenzymes purified from thermophiles have important practical applications. For example, amplification of nucleic acids in the polymerase chain reaction (PCR) depends on the thermal stability of *Taq* polymerase, an enzyme isolated from *T. aquaticus*. Degradation enzymes from thermophiles are added as ingredients in hot-water detergents, increasing their effectiveness.

? Exercise 4.1.4.1

1. What temperature requirements do most bacterial human pathogens have?
2. What DNA adaptation do thermophiles exhibit?

Feeding the World…and the World's Algae

Artificial fertilizers have become an important tool in food production around the world. They are responsible for many of the gains of the so-called green revolution of the 20th century, which has allowed the planet to feed many of its more than 7 billion people. Artificial fertilizers provide nitrogen and phosphorus, key limiting nutrients, to crop plants, removing the normal barriers that would otherwise limit the rate of growth. Thus, fertilized crops grow much faster, and farms that use fertilizer produce higher crop yields.

However, careless use and overuse of artificial fertilizers have been demonstrated to have significant negative impacts on aquatic ecosystems, both freshwater and marine. Fertilizers that are applied at inappropriate times or in too-large quantities allow nitrogen and phosphorus compounds to escape use by crop plants and enter drainage systems. Inappropriate use of fertilizers in residential settings can also contribute to nutrient loads, which find their way to lakes and coastal marine ecosystems. As water warms and nutrients are plentiful, microscopic algae bloom, often changing the color of the water because of the high cell density.

Most algal blooms are not directly harmful to humans or wildlife; however, they can cause harm indirectly. As the algal population expands and then dies, it provides a large increase in organic matter to the bacteria that live in deep water. With this large supply of nutrients, the population of nonphotosynthetic microorganisms explodes, consuming available oxygen and creating "dead zones" where animal life has virtually disappeared.

Depletion of oxygen in the water is not the only damaging consequence of some algal blooms. The algae that produce red tides in the Gulf of Mexico, *Karenia brevis*, secrete potent toxins that can kill fish and other organisms and also accumulate in shellfish. Consumption of contaminated shellfish can cause severe neurological and gastrointestinal symptoms in humans. Shellfish beds must be regularly monitored for the presence of the toxins, and harvests are often shut down when it is present, incurring economic costs to the fishery. Cyanobacteria, which can form blooms in marine and freshwater ecosystems, produce toxins called microcystins, which can cause allergic reactions and liver damage when ingested in drinking water or during swimming. Recurring cyanobacterial algal blooms in Lake Erie (Figure 4.1.4.3) have forced municipalities to issue drinking water bans for days at a time because of unacceptable toxin levels.

This is just a small sampling of the negative consequences of algal blooms, red tides, and dead zones. Yet the benefits of crop fertilizer—the main cause of such blooms—are difficult to dispute. There is no easy solution to this dilemma, as a ban on fertilizers is not politically or economically feasible. In lieu of this, we must advocate for responsible use and regulation in agricultural and residential contexts, as well as the restoration of wetlands, which can absorb excess fertilizers before they reach lakes and oceans.



Figure 4.1.4.3: Heavy rains cause runoff of fertilizers into Lake Erie, triggering extensive algal blooms, which can be observed along the shoreline. Notice the brown unplanted and green planted agricultural land on the shore. (credit: NASA)

Link to Learning

This video discusses algal blooms and dead zones in more depth.

Key Concepts and Summary

- Microorganisms thrive at a wide range of temperatures; they have colonized different natural environments and have adapted to extreme temperatures. Both extreme cold and hot temperatures require evolutionary adjustments to macromolecules and biological processes.
- **Psychrophiles** grow best in the temperature range of 0–15 °C whereas **psychrotrophs** thrive between 4 °C and 25 °C.
- **Mesophiles** grow best at moderate temperatures in the range of 20 °C to about 45 °C. Pathogens are usually mesophiles.
- **Thermophiles** and **hyperthemophiles** are adapted to life at temperatures above 50 °C.
- Adaptations to cold and hot temperatures require changes in the composition of membrane lipids and proteins.

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4.1.5: Other Environmental Conditions that Affect Growth

Learning Objectives

- Identify and describe different categories of microbes with specific growth requirements other than oxygen, pH, and temperature, such as altered barometric pressure, osmotic pressure, humidity, and light
- Give at least one example microorganism for each category of growth requirement

Microorganisms interact with their environment along more dimensions than pH, temperature, and free oxygen levels, although these factors require significant adaptations. We also find microorganisms adapted to varying levels of salinity, barometric pressure, humidity, and light.

Osmotic and Barometric Pressure

Most natural environments tend to have lower solute concentrations than the cytoplasm of most microorganisms. Rigid cell walls protect the cells from bursting in a dilute environment. Not much protection is available against high osmotic pressure. In this case, water, following its concentration gradient, flows out of the cell. This results in plasmolysis (the shrinking of the protoplasm away from the intact cell wall) and cell death. This fact explains why brines and layering meat and fish in salt are time-honored methods of preserving food. Microorganisms called halophiles ("salt loving") actually require high salt concentrations for growth. These organisms are found in marine environments where salt concentrations hover at 3.5%. Extreme halophilic microorganisms, such as the red alga *Dunaliella salina* and the archaeal species *Halobacterium* in Figure 4.1.5.1, grow in hypersaline lakes such as the Great Salt Lake, which is 3.5–8 times saltier than the ocean, and the Dead Sea, which is 10 times saltier than the ocean.

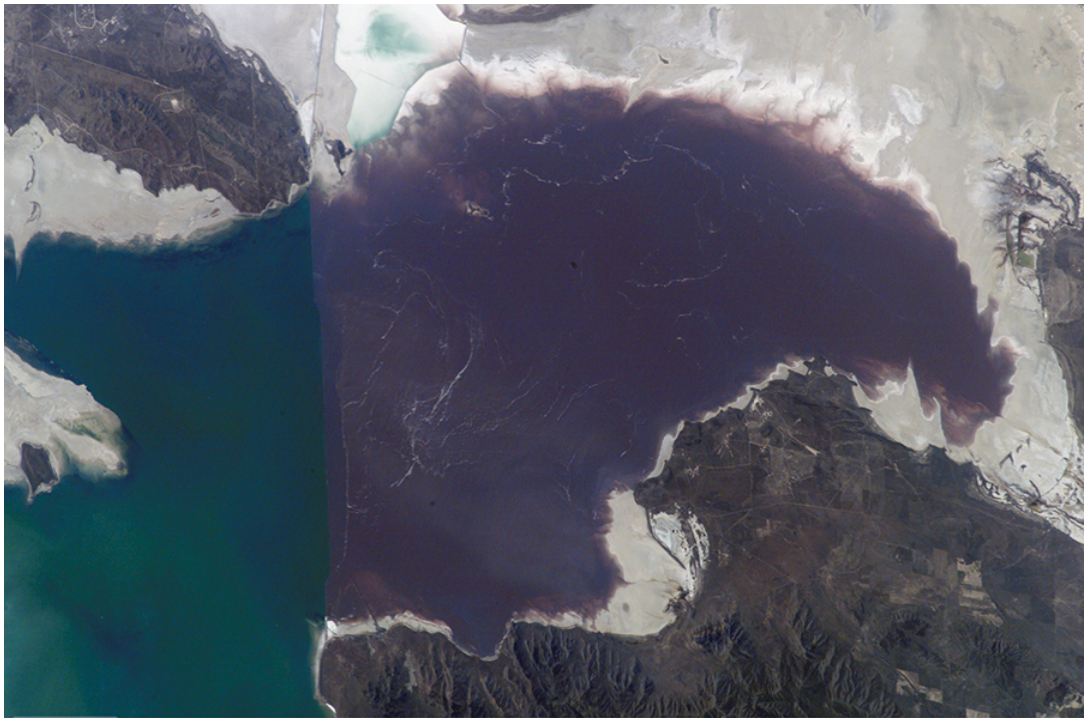


Figure 4.1.5.1: Photograph taken from space of the Great Salt Lake in Utah. The purple color is caused by high density of the alga *Dunaliella* and the archaean *Halobacterium* spp. (credit: NASA)

Dunaliella spp. counters the tremendous osmotic pressure of the environment with a high cytoplasmic concentration of glycerol and by actively pumping out salt ions. *Halobacterium* spp. accumulates large concentrations of K^+ and other ions in its cytoplasm. Its proteins are designed for high salt concentrations and lose activity at salt concentrations below 1–2 M. Although most halotolerant organisms, for example *Halomonas* spp. in salt marshes, do not need high concentrations of salt for growth, they will survive and divide in the presence of high salt. Not surprisingly, the staphylococci, micrococci, and corynebacteria that colonize our skin tolerate salt in their environment. Halotolerant pathogens are an important cause of food-borne illnesses because they

survive and multiply in salty food. For example, the halotolerant bacteria *S. aureus*, *Bacillus cereus*, and *V. cholerae* produce dangerous enterotoxins and are major causes of food poisoning.

Microorganisms depend on available water to grow. Available moisture is measured as water activity (a_w), which is the ratio of the vapor pressure of the medium of interest to the vapor pressure of pure distilled water; therefore, the a_w of water is equal to 1.0. Bacteria require high a_w (0.97–0.99), whereas fungi can tolerate drier environments; for example, the range of a_w for growth of *Aspergillus* spp. is 0.8–0.75. Decreasing the water content of foods by drying, as in jerky, or through freeze-drying or by increasing osmotic pressure, as in brine and jams, are common methods of preventing spoilage.

Microorganisms that require high atmospheric pressure for growth are called barophiles. The bacteria that live at the bottom of the ocean must be able to withstand great pressures. Because it is difficult to retrieve intact specimens and reproduce such growth conditions in the laboratory, the characteristics of these microorganisms are largely unknown.

Light

Photoautotrophs, such as cyanobacteria or green sulfur bacteria, and photoheterotrophs, such as purple nonsulfur bacteria, depend on sufficient light intensity at the wavelengths absorbed by their pigments to grow and multiply. Energy from light is captured by pigments and converted into chemical energy that drives carbon fixation and other metabolic processes. The portion of the electromagnetic spectrum that is absorbed by these organisms is defined as photosynthetically active radiation (PAR). It lies within the visible light spectrum ranging from 400 to 700 nanometers (nm) and extends in the near infrared for some photosynthetic bacteria. A number of accessory pigments, such as fucoxanthin in brown algae and phycobilins in cyanobacteria, widen the useful range of wavelengths for photosynthesis and compensate for the low light levels available at greater depths of water. Other microorganisms, such as the archaea of the class Halobacteria, use light energy to drive their proton and sodium pumps. The light is absorbed by a pigment protein complex called bacteriorhodopsin, which is similar to the eye pigment rhodopsin. Photosynthetic bacteria are present not only in aquatic environments but also in soil and in symbiosis with fungi in lichens. The peculiar watermelon snow is caused by a microalga *Chlamydomonas nivalis*, a green alga rich in a secondary red carotenoid pigment (astaxanthin) which gives the pink hue to the snow where the alga grows.

? Exercise 4.1.5.1

1. Which photosynthetic pigments were described in this section?
2. What is the fundamental stress of a hypersaline environment for a cell?

Key Concepts and Summary

- **Halophiles** require high salt concentration in the medium, whereas **halotolerant** organisms can grow and multiply in the presence of high salt but do not require it for growth.
- Halotolerant pathogens are an important source of foodborne illnesses because they contaminate foods preserved in salt.
- Photosynthetic bacteria depend on visible light for energy.
- Most bacteria, with few exceptions, require high moisture to grow.

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4.1.6: Media Used for Bacterial Growth

Learning Objectives

- Identify and describe culture media for the growth of bacteria, including examples of all-purpose media, enriched, selective, differential, defined, and enrichment media

The study of microorganisms is greatly facilitated if we are able to culture them, that is, to keep reproducing populations alive under laboratory conditions. Culturing many microorganisms is challenging because of highly specific nutritional and environmental requirements and the diversity of these requirements among different species.

Nutritional Requirements

The number of available media to grow bacteria is considerable. Some media are considered general all-purpose media and support growth of a large variety of organisms. A prime example of an all-purpose medium is tryptic soy broth (TSB). Specialized media are used in the identification of bacteria and are supplemented with dyes, pH indicators, or antibiotics. One type, enriched media, contains growth factors, vitamins, and other essential nutrients to promote the growth of fastidious organisms, organisms that cannot make certain nutrients and require them to be added to the medium. When the complete chemical composition of a medium is known, it is called a chemically defined medium. For example, in EZ medium, all individual chemical components are identified and the exact amounts of each is known. In complex media, which contain extracts and digests of yeasts, meat, or plants, the precise chemical composition of the medium is not known. Amounts of individual components are undetermined and variable. Nutrient broth, tryptic soy broth, and brain heart infusion, are all examples of complex media.

Media that inhibit the growth of unwanted microorganisms and support the growth of the organism of interest by supplying nutrients and reducing competition are called selective media. An example of a selective medium is MacConkey agar. It contains bile salts and crystal violet, which interfere with the growth of many gram-positive bacteria and favor the growth of gram-negative bacteria, particularly the Enterobacteriaceae. These species are commonly named enterics, reside in the intestine, and are adapted to the presence of bile salts. The enrichment cultures foster the preferential growth of a desired microorganism that represents a fraction of the organisms present in an inoculum. For example, if we want to isolate bacteria that break down crude oil, hydrocarbonoclastic bacteria, sequential subculturing in a medium that supplies carbon only in the form of crude oil will enrich the cultures with oil-eating bacteria. The differential media make it easy to distinguish colonies of different bacteria by a change in the color of the colonies or the color of the medium. Color changes are the result of end products created by interaction of bacterial enzymes with differential substrates in the medium or, in the case of hemolytic reactions, the lysis of red blood cells in the medium. In Figure 4.1.6.1, the differential fermentation of lactose can be observed on MacConkey agar. The lactose fermenters produce acid, which turns the medium and the colonies of strong fermenters hot pink. The medium is supplemented with the pH indicator neutral red, which turns to hot pink at low pH. Selective and differential media can be combined and play an important role in the identification of bacteria by biochemical methods.



Figure 4.1.6.1: On this MacConkey agar plate, the lactose-fermenter *E. coli* colonies are bright pink. *Serratia marcescens*, which does not ferment lactose, forms a cream-colored streak on the tan medium. (credit: American Society for Microbiology)

? Exercise 4.1.6.1

1. Distinguish complex and chemically defined media.
2. Distinguish selective and enrichment media.

Link to Learning

Compare the compositions of EZ medium and sheep blood agar.

The End-of-Year Picnic

The microbiology department is celebrating the end of the school year in May by holding its traditional picnic on the green. The speeches drag on for a couple of hours, but finally all the faculty and students can dig into the food: chicken salad, tomatoes, onions, salad, and custard pie. By evening, the whole department, except for two vegetarian students who did not eat the chicken salad, is stricken with nausea, vomiting, retching, and abdominal cramping. Several individuals complain of diarrhea. One patient shows signs of shock (low blood pressure). Blood and stool samples are collected from patients, and an analysis of all foods served at the meal is conducted.

Bacteria can cause gastroenteritis (inflammation of the stomach and intestinal tract) either by colonizing and replicating in the host, which is considered an infection, or by secreting toxins, which is considered intoxication. Signs and symptoms of infections are typically delayed, whereas intoxication manifests within hours, as happened after the picnic.

Blood samples from the patients showed no signs of bacterial infection, which further suggests that this was a case of intoxication. Since intoxication is due to secreted toxins, bacteria are not usually detected in blood or stool samples. MacConkey agar and sorbitol-MacConkey agar plates and xylose-lysine-deoxycholate (XLD) plates were inoculated with stool samples and did not reveal any unusually colored colonies, and no black colonies or white colonies were observed on XLD. All lactose fermenters on MacConkey agar also ferment sorbitol. These results ruled out common agents of food-borne illnesses: *E. coli*, *Salmonella* spp., and *Shigella* spp.

Analysis of the chicken salad revealed an abnormal number of gram-positive cocci arranged in clusters (Figure 4.1.6.2). A culture of the gram-positive cocci releases bubbles when mixed with hydrogen peroxide. The culture turned mannitol salt agar yellow after a 24-hour incubation.

All the tests point to *Staphylococcus aureus* as the organism that secreted the toxin. Samples from the salad showed the presence of gram-positive cocci bacteria in clusters. The colonies were positive for catalase. The bacteria grew on mannitol salt agar fermenting mannitol, as shown by the change to yellow of the medium. The pH indicator in mannitol salt agar is phenol red, which turns to yellow when the medium is acidified by the products of fermentation.

The toxin secreted by *S. aureus* is known to cause severe gastroenteritis. The organism was probably introduced into the salad during preparation by the food handler and multiplied while the salad was kept in the warm ambient temperature during the speeches.

Exercise 4.1.6.2

1. What are some other factors that might have contributed to rapid growth of *S. aureus* in the chicken salad?
2. Why would *S. aureus* not be inhibited by the presence of salt in the chicken salad?

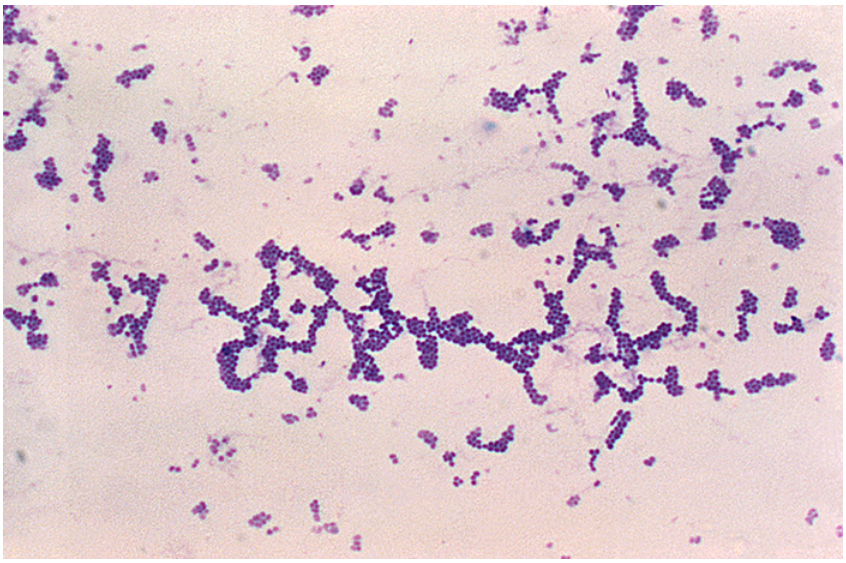


Figure 4.1.6.2: Gram-positive cocci in clusters. (credit: Centers for Disease Control and Prevention)

Key Concepts and Summary

- **Chemically defined media** contain only chemically known components.
- **Selective media** favor the growth of some microorganisms while inhibiting others.
- **Enriched media** contain added essential nutrients a specific organism needs to grow
- **Differential media** help distinguish bacteria by the color of the colonies or the change in the medium.

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4.1.E: Microbial Growth (Exercises)

9.1: How Microbes Grow

The bacterial cell cycle involves the formation of new cells through the replication of DNA and partitioning of cellular components into two daughter cells. In prokaryotes, reproduction is always asexual, although extensive genetic recombination in the form of horizontal gene transfer takes place, as will be explored in a different chapter. Most bacteria have a single circular chromosome; however, some exceptions exist.

Multiple Choice

Which of the following methods would be used to measure the concentration of bacterial contamination in processed peanut butter?

A. turbidity measurement
B. total plate count
C. dry weight measurement
D. direct counting of bacteria on a calibrated slide under the microscope

Answer

B

In which phase would you expect to observe the most endospores in a *Bacillus* cell culture?

A. death phase
B. lag phase
C. log phase
D. log, lag, and death phases would all have roughly the same number of endospores.

Answer

A

During which phase would penicillin, an antibiotic that inhibits cell-wall synthesis, be most effective?

A. death phase
B. lag phase
C. log phase
D. stationary phase

Answer

C

Which of the following is the best definition of generation time in a bacterium?

A. the length of time it takes to reach the log phase
B. the length of time it takes for a population of cells to double
C. the time it takes to reach stationary phase
D. the length of time of the exponential phase

Answer

B

What is the function of the Z ring in binary fission?

A. It controls the replication of DNA.
B. It forms a contractile ring at the septum.
C. It separates the newly synthesized DNA molecules.

D. It mediates the addition of new peptidoglycan subunits.

Answer

B

If a culture starts with 50 cells, how many cells will be present after five generations with no cell death?

A. 200
B. 400
C. 1600
D. 3200

Answer

C

Filamentous cyanobacteria often divide by which of the following?

A. budding
B. mitosis
C. fragmentation
D. formation of endospores

Answer

C

Which is a reason for antimicrobial resistance being higher in a biofilm than in free-floating bacterial cells?

A. The EPS allows faster diffusion of chemicals in the biofilm.
B. Cells are more metabolically active at the base of a biofilm.
C. Cells are metabolically inactive at the base of a biofilm.
D. The structure of a biofilm favors the survival of antibiotic resistant cells.

Answer

C

Quorum sensing is used by bacterial cells to determine which of the following?

A. the size of the population
B. the availability of nutrients
C. the speed of water flow
D. the density of the population

Answer

D

Which of the following statements about autoinducers is incorrect?

A. They bind directly to DNA to activate transcription.
B. They can activate the cell that secreted them.
C. N-acylated homoserine lactones are autoinducers in gram-negative cells.
D. Autoinducers may stimulate the production of virulence factors.

Answer

A

Fill in the Blank

Direct count of total cells can be performed using a _____ or a _____.

Answer

hemocytometer, Petroff-Hausser counting chamber

The _____ method allows direct count of total cells growing on solid medium.

Answer

plate count

A statistical estimate of the number of live cells in a liquid is usually done by _____.

Answer

most probable number

For this indirect method of estimating the growth of a culture, you measure _____ using a spectrophotometer.

Answer

turbidity

Active growth of a culture may be estimated indirectly by measuring the following products of cell metabolism: _____ or _____.

Answer

ATP, acid from fermentation

Matching

Match the definition with the name of the growth phase in the growth curve.

___Number of dying cells is higher than the number of cells dividing	A. Lag phase
___Number of new cells equal to number of dying cells	B. Log phase
___New enzymes to use available nutrients are induced	C. Stationary phase
___Binary fission is occurring at maximum rate	D. Death phase

Answer

D, C, A, B

Short Answer

Why is it important to measure the transmission of light through a control tube with only broth in it when making turbidity measures of bacterial cultures?

In terms of counting cells, what does a plating method accomplish that an electronic cell counting method does not?

Order the following stages of the development of a biofilm from the earliest to the last step.

1. secretion of EPS
2. reversible attachment
3. dispersal
4. formation of water channels
5. irreversible attachment

Infections among hospitalized patients are often related to the presence of a medical device in the patient. Which conditions favor the formation of biofilms on in-dwelling catheters and prostheses?

Critical Thinking

A patient in the hospital has an intravenous catheter inserted to allow for the delivery of medications, fluids, and electrolytes. Four days after the catheter is inserted, the patient develops a fever and an infection in the skin around the catheter. Blood cultures reveal that the patient has a blood-borne infection. Tests in the clinical laboratory identify the blood-borne pathogen as *Staphylococcus epidermidis*, and antibiotic susceptibility tests are performed to provide doctors with essential information for selecting the best drug for treatment of the infection. Antibacterial chemotherapy is initiated and delivered through the intravenous catheter that was originally inserted into the patient. Within 7 days, the skin infection is gone, blood cultures are negative for *S. epidermidis*, and the antibacterial chemotherapy is discontinued. However, 2 days after discontinuing the antibacterial chemotherapy, the patient develops another fever and skin infection and the blood cultures are positive for the same strain of *S. epidermidis* that had been isolated the previous week. This time, doctors remove the intravenous catheter and administer oral antibiotics, which successfully treat both the skin and blood-borne infection caused by *S. epidermidis*. Furthermore, the infection does not return after discontinuing the oral antibacterial chemotherapy. What are some possible reasons why intravenous chemotherapy failed to completely cure the patient despite laboratory tests showing the bacterial strain was susceptible to the prescribed antibiotic? Why might the second round of antibiotic therapy have been more successful? Justify your answers.

Why are autoinducers small molecules?

Refer to Figure B.1 in Appendix B. If the results from a pond water sample were recorded as 3, 2, 1, what would be the MPN of bacteria in 100 mL of pond water?

Refer to Figure 9.1.14. Why does turbidity lose reliability at high cell concentrations when the culture reaches the stationary phase?

9.2: Oxygen Requirements for Microbial Growth

Ask most people “What are the major requirements for life?” and the answers are likely to include water and oxygen. Few would argue about the need for water, but what about oxygen? Can there be life without oxygen? The answer is that molecular oxygen is not always needed. The earliest signs of life are dated to a period when conditions on earth were highly reducing and free oxygen gas was essentially nonexistent.

Multiple Choice

An inoculated thioglycolate medium culture tube shows dense growth at the surface and turbidity throughout the rest of the tube. What is your conclusion?

A. The organisms die in the presence of oxygen
B. The organisms are facultative anaerobes.
C. The organisms should be grown in an anaerobic chamber.
D. The organisms are obligate aerobes.

Answer

B

An inoculated thioglycolate medium culture tube is clear throughout the tube except for dense growth at the bottom of the tube. What is your conclusion?

A. The organisms are obligate anaerobes.
B. The organisms are facultative anaerobes.
C. The organisms are aerotolerant.
D. The organisms are obligate aerobes.

Answer

A

Pseudomonas aeruginosa is a common pathogen that infects the airways of patients with cystic fibrosis. It does not grow in the absence of oxygen. The bacterium is probably which of the following?

A. an aerotolerant anaerobe
B. an obligate aerobe
C. an obligate anaerobe
D. a facultative anaerobe

Answer

B

Streptococcus mutans is a major cause of cavities. It resides in the gum pockets, does not have catalase activity, and can be grown outside of an anaerobic chamber. The bacterium is probably which of the following?

A. a facultative anaerobe
B. an obligate aerobe
C. an obligate anaerobe
D. an aerotolerant anaerobe

Answer

D

Why do the instructions for the growth of *Neisseria gonorrheae* recommend a CO_2-enriched atmosphere?

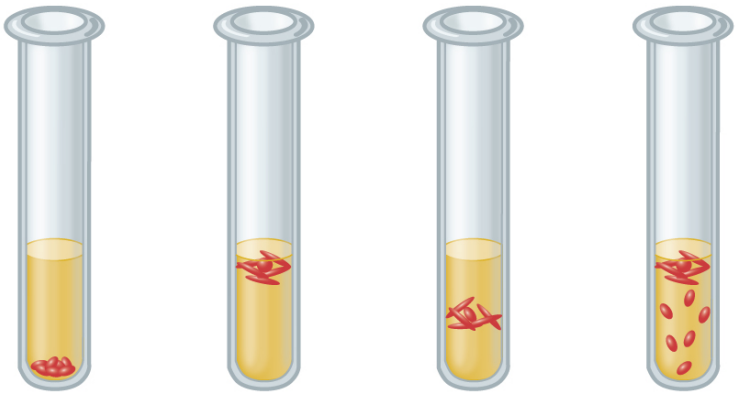
A. It uses CO_2 as a final electron acceptor in respiration.
B. It is an obligate anaerobe.
C. It is a capnophile.
D. It fixes CO_2 through photosynthesis.

Answer

C

Matching

Four tubes are illustrated with cultures grown in a medium that slows oxygen diffusion. Match the culture tube with the correct type of bacteria from the following list: facultative anaerobe, obligate anaerobe, microaerophile, aerotolerant anaerobe, obligate aerobe.



Answer

(a) obligate anaerobe, (b) obligate aerobe, (c) microaerophile, (d) facultative anaerobe

Short Answer

Why are some obligate anaerobes able to grow in tissues (e.g., gum pockets) that are not completely free of oxygen?

Why should *Haemophilus influenzae* be grown in a candle jar?

In terms of oxygen requirements, what type of organism would most likely be responsible for a foodborne illness associated with canned foods?

Critical Thinking

A microbiology instructor prepares cultures for a gram-staining practical laboratory by inoculating growth medium with a gram-positive coccus (nonmotile) and a gram-negative rod (motile). The goal is to demonstrate staining of a mixed culture. The flask is incubated at 35 °C for 24 hours without aeration. A sample is stained and reveals only gram-negative rods. Both cultures are known facultative anaerobes. Give a likely reason for success of the gram-negative rod. Assume that the cultures have comparable intrinsic growth rates.

9.3: The Effects of pH on Microbial Growth

Bacteria are generally neutrophiles. They grow best at neutral pH close to 7.0. Acidophiles grow optimally at a pH near 3.0. Alkaliphiles are organisms that grow optimally between a pH of 8 and 10.5. Extreme acidophiles and alkaliphiles grow slowly or not at all near neutral pH. Microorganisms grow best at their optimum growth pH. Growth occurs slowly or not at all below the minimum growth pH and above the maximum growth pH.

Multiple Choice

Bacteria that grow in mine drainage at pH 1–2 are probably which of the following?

A. alkaliphiles
B. acidophiles
C. neutrophiles
D. obligate anaerobes

Answer

B

Bacteria isolated from Lake Natron, where the water pH is close to 10, are which of the following?

A. alkaliphiles
B. facultative anaerobes
C. neutrophiles
D. obligate anaerobes

Answer

A

In which environment are you most likely to encounter an acidophile?

A. human blood at pH 7.2
B. a hot vent at pH 1.5
C. human intestine at pH 8.5
D. milk at pH 6.5

Answer

B

Fill in the Blank

A bacterium that thrives in a soda lake where the average pH is 10.5 can be classified as a(n) _____.

Answer

alkaliphile

Lactobacillus acidophilus grows best at pH 4.5. It is considered a(n) _____.

Answer

acidophile

Short Answer

Which macromolecule in the cell is most sensitive to changes in pH?

Which metabolic process in the bacterial cell is particularly challenging at high pH?

Critical Thinking

People who use proton pumps inhibitors or antacids are more prone to infections of the gastrointestinal tract. Can you explain the observation in light of what you have learned?

9.4: Temperature and Microbial Growth

Microorganisms thrive at a wide range of temperatures; they have colonized different natural environments and have adapted to extreme temperatures. Both extreme cold and hot temperatures require evolutionary adjustments to macromolecules and biological processes. Psychrophiles grow best in the temperature range of 0–15 °C whereas psychrotrophs thrive between 4 °C and 25 °C. Mesophiles grow best at moderate temperatures in the range of 20 °C to about 45 °C. Pathogens are usually mesophiles.

Multiple Choice

A soup container was forgotten in the refrigerator and shows contamination. The contaminants are probably which of the following?

A. thermophiles
B. acidophiles
C. mesophiles
D. psychrotrophs

Answer

D

Bacteria isolated from a hot tub at 39 °C are probably which of the following?

A. thermophiles
B. psychrotrophs
C. mesophiles
D. hyperthermophiles

Answer

C

In which environment are you most likely to encounter a hyperthermophile?

A. hot tub
B. warm ocean water in Florida
C. hydrothermal vent at the bottom of the ocean
D. human body

Answer

C

Which of the following environments would harbor psychrophiles?

A. mountain lake with a water temperature of 12 °C
B. contaminated plates left in a 35 °C incubator
C. yogurt cultured at room temperature
D. salt pond in the desert with a daytime temperature of 34 °C

Answer

A

Matching

Match the type of bacterium with its environment. Each choice may be used once, more than once, or not at all. Put the appropriate letter beside the environment.

___psychotroph	A. water heater set at 50 °C
___mesophile	B. hydrothermal vent
___thermophile	C. deep ocean waters
___hyperthermophile	D. human pathogen
___psychrophile	E. soil bacteria in temperate forest

Answer

C, D, E, B, A

Short Answer

How are hyperthermophile's proteins adapted to the high temperatures of their environment?

Why would NASA be funding microbiology research in Antarctica?

Critical Thinking

The bacterium that causes Hansen's disease (leprosy), *Mycobacterium leprae*, infects mostly the extremities of the body: hands, feet, and nose. Can you make an educated guess as to its optimum temperature of growth?

Refer to Figure 9.4.2. Some hyperthermophiles can survive autoclaving temperatures. Are they a concern in health care?

9.5: Other Environmental Conditions that Affect Growth

Microorganisms interact with their environment along more dimensions than pH, temperature, and free oxygen levels, although these factors require significant adaptations. We also find microorganisms adapted to varying levels of salinity, barometric pressure, humidity, and light.

Multiple Choice

Which of the following is the reason jams and dried meats often do not require refrigeration to prevent spoilage?

A. low pH
B. toxic alkaline chemicals
C. naturally occurring antibiotics
D. low water activity

Answer

D

Bacteria living in salt marshes are most likely which of the following?

A. acidophiles
B. barophiles
C. halotolerant
D. thermophiles

Answer

C

Fill in the Blank

A bacterium that thrives in the Great Salt Lake but not in fresh water is probably a _____.

Answer

halophile

Bacteria isolated from the bottom of the ocean need high atmospheric pressures to survive. They are _____.

Answer

barophiles

Staphylococcus aureus can be grown on multipurpose growth medium or on mannitol salt agar that contains 7.5% NaCl. The bacterium is _____.

Answer

halotolerant

Short Answer

Fish sauce is a salty condiment produced using fermentation. What type of organism is likely responsible for the fermentation of the fish sauce?

9.6: Media Used for Bacterial Growth

The study of microorganisms is greatly facilitated if we are able to culture them, that is, to keep reproducing populations alive under laboratory conditions. Culturing many microorganisms is challenging because of highly specific nutritional and environmental requirements and the diversity of these requirements among different species.

Multiple Choice

EMB agar is a medium used in the identification and isolation of pathogenic bacteria. It contains digested meat proteins as a source of organic nutrients. Two indicator dyes, eosin and methylene blue, inhibit the growth of gram-positive bacteria and distinguish between lactose fermenting and nonlactose fermenting organisms. Lactose fermenters form metallic green or deep purple colonies, whereas the nonlactose fermenters form completely colorless colonies. EMB agar is an example of which of the following?

A. a selective medium only
B. a differential medium only
C. a selective medium and a chemically defined medium
D. a selective medium, a differential medium, and a complex medium

Answer

D

Haemophilus influenzae must be grown on chocolate agar, which is blood agar treated with heat to release growth factors in the medium. *H. influenzae* is described as _____.

A. an acidophile
B. a thermophile
C. an obligate anaerobe
D. fastidious

Answer

D

Fill in the Blank

Blood agar contains many unspecified nutrients, supports the growth of a large number of bacteria, and allows differentiation of bacteria according to hemolysis (breakdown of blood). The medium is _____ and _____.

Answer

complex, differential

Rogosa agar contains yeast extract. The pH is adjusted to 5.2 and discourages the growth of many microorganisms; however, all the colonies look similar. The medium is _____ and _____.

Answer

complex, selective

Short Answer

What is the major difference between an enrichment culture and a selective culture?

Critical Thinking

Haemophilus, *influenzae* grows best at 35–37 °C with ~5% CO_2 (or in a candle-jar) and requires hemin (X factor) and nicotinamide-adenine-dinucleotide (NAD, also known as V factor) for growth.[1] Using the vocabulary learned in this chapter, describe *H. influenzae*.

Footnotes

1. 1 Centers for Disease Control and Prevention, World Health Organization. "*CDC Laboratory Methods for the Diagnosis of Meningitis Caused by* Neisseria meningitidis, Streptococcus pneumoniae, *and* Haemophilus influenza. WHO Manual, 2nd edition." 2011. http://www.cdc.gov/meningitis/lab-ma...ull-manual.pdf

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4.2: Microbial Nutrition

All microbes have a need for three things: carbon, energy, and electrons. There are specific terms associated with the source of each of these items, to help define organisms.

Let us focus on carbon first. All organisms are carbon-based with macromolecules – proteins, carbohydrates, lipids, nucleic acid – having a fundamental core of carbon. On one hand, organisms can use reduced, preformed organic substances as a carbon source. These are the **heterotrophs** or "other eaters." Alternatively, they can rely on carbon dioxide (CO_2) as a carbon source, reducing or "fixing" it this inorganic form of carbon into an organic molecule. These are the **autotrophs** or "self feeders."

For energy, there are two possibilities as well: light energy or chemical energy. Light energy comes from the sun, while chemical energy can come from either organic or inorganic chemicals. Those organisms that use light energy are called **phototrophs** ("light eaters"), while those that use chemical energy are called **chemotrophs** ("chemical eaters"). Chemical energy can come from inorganic sources or organic sources. An organism that uses inorganic sources is known as a **lithotroph** ("rock eater"), while an organism that uses organic sources is called an **organotroph** ("organic eater").

These terms can all be combined, to derive a single term that gives you an idea of what an organism is using to meet its basic needs for energy, electrons, and carbon.

Nutritional Types of Microorganisms

Energy Source	Electron Source	Carbon Source	Nutritional Type
Light *Photo-*	Organic *-organo-*	Organic *-heterotroph*	Photoorganoheterotroph
		Carbon dioxide *-autotroph*	(no known organisms)
	Inorganic *-litho-*	Organic *-heterotroph*	(no known organisms)
		Carbon dioxide *-autotroph*	Photolithoautotroph
Chemical compounds *Chemo-*	Organic *-organo-*	Organic *-heterotroph*	Chemoorganoheterotroph
		Carbon dioxide *-autotroph*	(no known organisms)
	Inorganic *-litho-*	Organic *-heterotroph*	Chemolithoheterotroph
		Carbon dioxide *-autotroph*	Chemolithoautotroph

Macronutrients

In addition to carbon, hydrogen and oxygen, cells need a few other elements in sufficient quantity. In particular, cells need nitrogen for the formation of proteins, nucleic acids, and a few other cell components. Cells also need phosphorous, which is a crucial component of nucleic acids (think sugar-*phosphate* backbone!), phospholipids, and adenosine tri*phosphate* or ATP. Sulfur is necessary for a few amino acids, as well as several vitamins, while potassium is needed for enzymes, and magnesium is used to stabilize ribosomes and membrane. Collectively these elements (including C, H, and O) are referred to as the **macronutrients**.

Growth Factors

Some microbes can synthesize certain organic molecules that they need from scratch, as long as they are provided with carbon source and inorganic salts. Other microbes require that certain organic compounds exist within their environment. These organic molecules essential for growth are called **growth factors** and fall in three categories: 1) amino acids (building blocks of protein), 2) purines and pyrimidines (building blocks of nucleic acid), and 3) vitamins (enzyme cofactors).

Uptake of Nutrients

In order to support its' activities, a cell must bring in nutrients from the external environment across the cell membrane. In bacteria and archaea, several different transport mechanisms exist.

Passive Diffusion

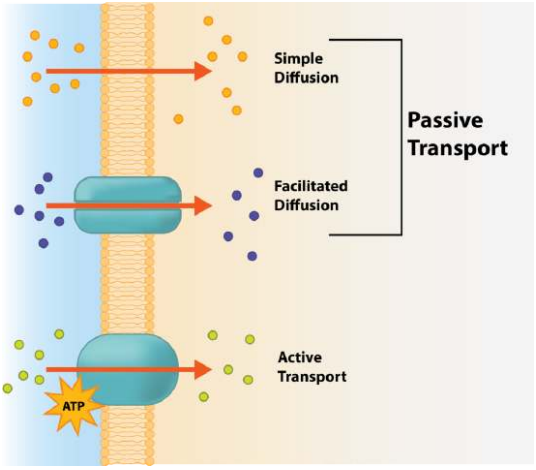
Passive or **simple diffusion** allows for the passage across the cell membrane of simple molecules and gases, such as CO2, O2, and H2O. In this case, a concentration gradient must exist, where there is higher concentration of the substance outside of the cell than there is inside the cell. As more of the substance is transported into the cell the concentration gradient decreases, slowing the rate of diffusion.

Facilitated Diffusion

Facilitated diffusion also involves the use of a concentration gradient, where the concentration of the substance is higher outside the cell, but differs with the use of **carrier proteins** (sometimes called **permeases**). These proteins are embedded within the cell membrane and provide a channel or pore across the membrane barrier, allowing for the passage of larger molecules. If the concentration gradient dissipates, the passage of molecules into the cell stops. Each carrier protein typically exhibits specificity, only transporting in a particular type of molecule or closely related molecules.

Active Transport

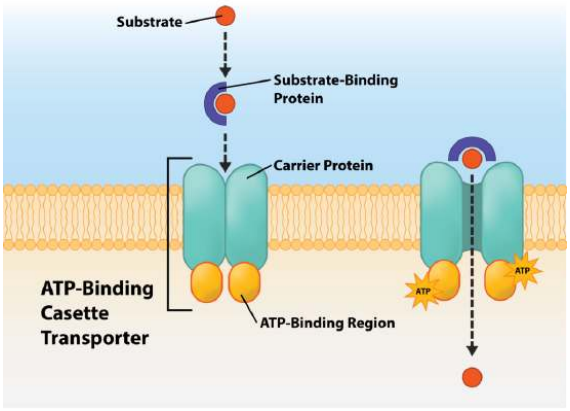
Many types of nutrient uptake require that a cell be able to transport substances against a concentration gradient (i.e. with a higher concentration inside the cell than outside). In order to do this, a cell must utilize metabolic energy for the transport of the substance through carrier proteins embedded in the membrane. This is known as **active transport**. All types of active transport utilize carrier proteins.



Active Transport Versus Facilitated Diffusion.

Primary active transport

Primary active transport involves the use of chemical energy, such as ATP, to drive the transport. One example is the **ABC system**, which utilizes **ATP-Binding Cassette transporters**. Each **ABC transporter** is composed of three different components: 1) membrane-spanning proteins that form a pore across the cell membrane (i.e. carrier protein), 2) an ATP binding region that hydrolyzes ATP, providing the energy for the passage across the membrane, and 3) a substrate-binding protein, a peripheral protein that binds to the appropriate substance to be transporter and ferries it to the membrane-spanning proteins. In gram negative bacteria the substrate-binding protein is located in the cell's periplasm, while in gram positive bacteria the substrate-binding protein is attached to the outside of the cell membrane.

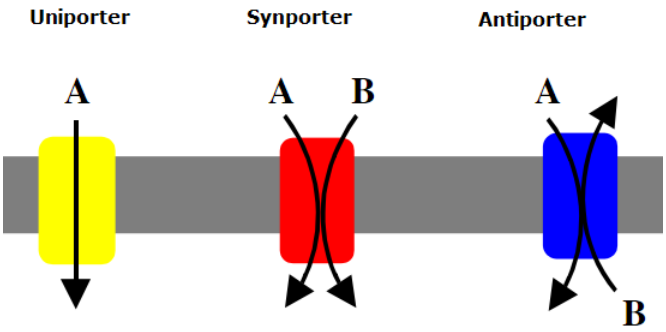


ABC Transporter Structure.

Secondary active transport

Secondary active transport utilizes energy from a **proton motive force (PMF)**. A PMF is an ion gradient that develops when the cell transports electrons during energy-conserving processes. Positively charged protons accumulate along the outside of the negatively charged cell, creating a proton gradient between the outside of the cell and the inside.

There are three different types of transport events for simple transport: **uniport**, **symport**, and **antiport** and each mechanism utilizes a different protein **porter**. **Uniporters** transport a single substance across the membrane, either in or out. **Symporters** transport two substances across the membrane at the same time, typically a proton paired with another molecule. **Antiporters** transport two substances across the membrane as well, but in opposite directions. As one substance enters the cell, the other substance is transported out.

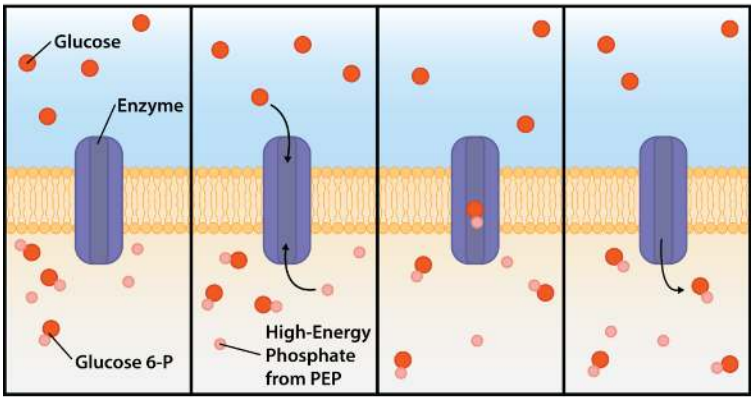


Uniport Synport Antiport. By Lupask (Own work) [Public domain], via Wikimedia Commons

Group Translocation

Group translocation is a distinct type of active transport, using energy from an energy-rich organic compound that is not ATP. Group translocation also differs from both simple transport and ABC transporters in that the substance being transported is chemically modified in the process.

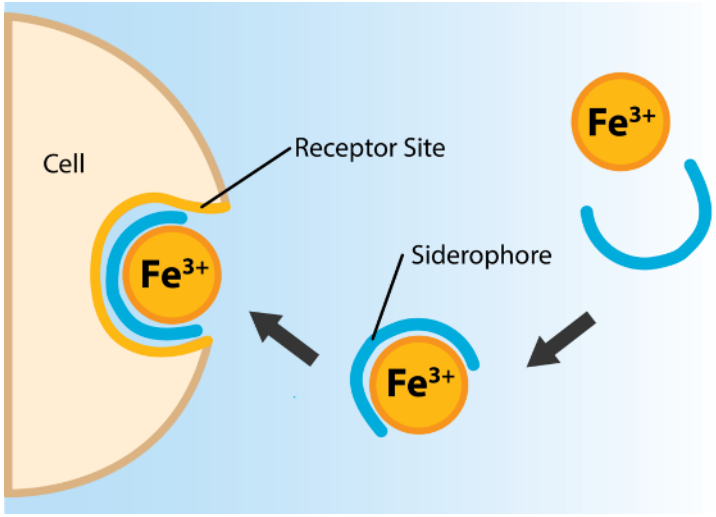
One of the best studied examples of group translocation is the **phosphoenolpyruvate: sugar phosphotransferase system (PTS)**, which uses energy from the high-energy molecule **phosphoenolpyruvate (PEP)** to transport sugars into the cell. A phosphate is transferred from the PEP to the incoming sugar during the process of transportation.



Group Translocation via PTS.

Iron Uptake

Iron is required by microbes for the function of their cytochromes and enzymes, resulting in it being a growth-limiting micronutrient. However, little free iron is available in environments, due to its insolubility. Many bacteria have evolved **siderophores**, organic molecules that chelate or bind ferric iron with high affinity. Siderophores are released by the organism to the surrounding environment, whereby they bind any available ferric iron. The iron-siderophore complex is then bound by a specific receptor on the outside of the cell, allowing the iron to be transported into the cell.



Siderophores and Receptor Sites.

Key Words

heterotroph, autotroph, phototroph, chemotroph, lithotroph, organotroph, photolithoautotroph, photoorganoheterotroph, chemoorganoheterotroph, chemolithoautotroph, chemolithoheterotroph, macronutrients, growth factors, passive/simple diffusion, facilitated diffusion, carrier protein/permease, active transport, primary active transport, ABC system, ATP-binding cassette transporter, ABC transporter, secondary active transport, proton motive force (PMF), uniport, symport, antiport, porter, uniporter, symporter, antiporter, group translocation, phosphoenolpyruvate: sugar phosphotransferase system (PTS), phosphoenolpyruvate (PEP), siderophore.

Study Questions

1. What are the different terms associated with microbial nutritional types? How can these terms be combined to define the nutritional types of microbes in terms of their sources of carbon, electrons, and energy?
2. What are macroelements and why are they important to a cell? What are growth factors and what is their significance to a cell?
3. What is the importance of nutrient uptake for a cell? What are the common features of nutrient uptake by bacteria?

4. What is transported into a bacteria cell by passive diffusion and how does this affect a bacterial cell?
5. Explain diffusion (passive and facilitated) and active transport.
6. What are the 3 types of active transport? Be able to diagram each processes. What is required for each of these processes? How are they similar, how are they different?
7. Why is iron uptake important for a cell? What is used to accomplish this?

Exploratory Questions (OPTIONAL)

1. What is the largest bacterium or archaean ever discovered? What is the smallest eukaryote ever discovered?

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SECTION OVERVIEW

4.3: Enzyme Catalysis and Kinetics

4.3.1: Introduction

4.3.2: Enzymes

4.3.3: Key Words and Terms

Thumbnail: diagram showing the induced fit model in enzymes (Public Domain; LadyofHats).

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4.3.1: Introduction

In this chapter, we look at the properties and mechanism of action of enzymes. These include allosteric change (***induced fit***, ***enzyme regulation***), energetic events (changes in ***activation energy***), and how enzymes work in open and closed (experimental) systems. Any catalyst, by definition, accelerates a chemical reaction. But enzymes and inorganic catalysts differ in important ways (blue and red in the table below).

Enzymes *vs* Inorganic Catalysts

Inorganic Catalysts	Enzymes
e.g., Ni, Pl, Ag, etc.	e.g., pepsin, trypsin, ATP synthase, ribonuclease, etc.
increase rxn rate	increase rxn rate
unchanged at end of rxn	unchanged at end of rxn
non-specific	highly specific
rigid, inflexible	flexible - can undergo *allosteric* change…
cannot be regulated	can be regulated

Enzymes are long polymers that can fold into intricate shapes. As a result, they can be more specific than inorganic catalysts in which substrates they recognize and bind to. Finally, enzymes are flexible and can be regulated in ways that rigid, inflexible, metallic inorganic catalysis cannot. The specificity of an enzyme lies in the structure and flexibility of its ***active site***. We will see that the active site of enzymes undergo conformational change during catalysis. The flexibility of enzymes also explains the effects of enzymes to cellular metabolites that indicate the biochemical status of the cell. When such metabolites bind to an enzyme, they force a conformational change in the enzyme that change the catalytic rate of the reaction, a phenomenon called ***allosteric regulation***. As you might imagine, changing the rate of a biochemical reaction can change the rate of an entire biochemical pathway…, and ultimately the steady state concentrations of products and reactants in the pathway.

To understand the importance of allosteric regulation, we'll look at how we measure the speed of enzyme catalysis. As we consider the classic early 20th century enzyme kinetic studies of Leonor Michaelis and Maud Menten, we'll focus on the significance of the ***Km*** and ***Vmax*** values that they derived from their data. But, before we begin our discussion here, remember that chemical reactions are by definition, reversible. The action of catalysts, either inorganic or organic, depends on this concept of reversibility.

Finally, let's give a nod to recent human ingenuity that enabled enzyme action to turn an *extracellular profit*! You can now find enzymes in household cleaning products like detergents, where they digest and remove stains caused by fats and pigmented proteins. Enzymes added to meat tenderizers also digest (hydrolyze) animal proteins down to smaller peptides. Enzymes can even clean a clogged drain!

Learning objectives

When you have mastered the information in this chapter, you should be able to:

1. describe how the molecular flexibility of protein and RNA molecules make them ideal biological catalysts.
2. compare and contrast the properties of *inorganic* and *organic* catalysts.
3. explain why *catalysts do not change equilibrium concentrations* of a reaction conducted in a closed system.
4. compare the activation energies of catalyzed and un-catalyzed reactions and explain the roles of *allosteric effectors* in enzymatic reactions.
5. discuss how allosteric sites interact with an enzyme's active site and explain the concept of the rate limiting reaction in a biochemical pathway.
6. write simple rate equations for chemical reactions.
7. write the possible rate equations for equations for catalyzed reactions.

8. distinguish between *Vmax* and *Km* in the Michaelis-Menten kinetics equation.

9. state what Vmax and Km say about the progress of an enzyme catalyzed reaction.

10. interpret enzyme kinetic data and the *progress of an enzyme-catalyzed reaction* from this data.

11. more accurately identify Leonor Michaelis and Maud Menten!

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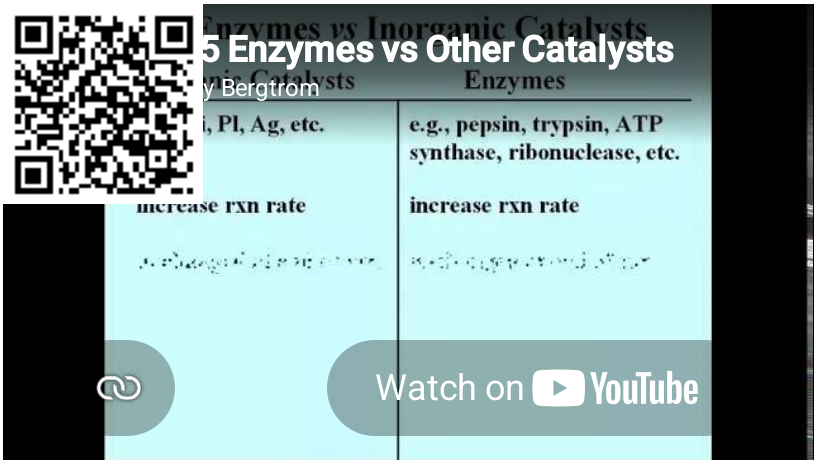
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4.3.2: Enzymes

By 1941, their studies correlating mutations with enzyme deficiencies in *Neurospora crassa* (bread mold) and *Drosophila melanogaster* led George Beadle and Edward Tatum to propose the ***one-gene/one-enzyme hypothesis*** in 1941. In 1958, they shared Nobel Prize in Physiology and Medicine for this work. By the time of the award, their hypothesis had morphed twice: first into the ***one-gene/one-prot*ein**, and then the ***one-gene/one- polypeptide*** hypothesis. This rightfully revered history helped launch the age of molecular biology, making the discovery of RNA catalysts quite a surprise! The discovery of RNA catalysts, dubbed ***ribozymes***, earned Sidney Altman and Thomas Cech the Nobel Prize in Chemistry in 1989. Ribozymes are now known that catalyze RNA splicing (the removal of unwanted regions of a precursor RNA. ***Ribozymes*** are also associated with a region of ribosomal RNA, where they participate in the catalysis of protein synthesis. Here, the focus here is based on the long history of *protein enzyme catalysis*, but you should recognize the mechanisms of enzyme catalytic mechanisms to be discussed involve essential features in all biocatalysts.

Enzymes are generally soluble in or outside cells while a few are part of membranes or other cellular structures. In all cases, they bind to soluble ***substrates*** (the reactants in enzyme-catalyzed reactions). The large size and exquisite diversity of protein structures make enzymes highly specific catalysts. The specificity of an enzyme results from the shape of the ***active*** site of the enzyme, which is dependent on the three-dimensional arrangement of amino acids in and around the region. The *substrates* of a catalyzed biochemical reaction are bound to, and held in place on the enzyme while rapid bond rearrangements take place. Because of their flexibility, enzymes undergo change in shape at the active site during catalysis itself. In addition, this flexibility enables small metabolites in cells to interact with and change the shapes of many enzymes. The latter phenomenon enables ***allosteric regulation***, allowing cells to control the rates and even the direction of biochemical reactions and pathways. As we will see, enzymes may also be bound to *prosthetic groups* or ions that contribute to the shape and activity of the enzyme.

Almost no chemical reaction occurs that is not directly the result of enzyme catalysis, from the digestion of nutrients in your mouth, stomach and small intestines to pretty much every chemical reaction inside your cells [check out Kornberg A (1989) *Never a Dull Enzyme.* Ann. Rev. Biochem. 58:1-30].



A. The Mechanisms of Enzyme Catalysis

We describe the action of biological catalysis in two ways. One way takes into account structural features of the enzyme (active site shape, overall conformation, the *affinities* of the enzyme for its substrates). The other way involves the energetic of enzyme action. We'll see that enzymes lower the ***activation energy*** of a chemical reaction. Activation energy is an inherent energy barrier to the reaction. Of course, structural and energy considerations of enzyme catalysis are related.

1. Structural Considerations of Catalysis

From a chemistry course, you may recall that the rate of an uncatalyzed reaction is dependent on the concentration of the reactants in solution. This is the *Law of Mass Action*, recognized in the 19th century. Look at this simple reaction:

$$\mathrm{A} + \mathrm{B} \rightleftharpoons \mathrm{C} + \mathrm{D} \tag{4.3.2.1}$$

The *Law of Mass Action* makes two key assumptions:

a. At any given time following the start of the reaction, the rate of product formation is proportional to the concentrations of the reactants and products ([A], [B], [C] and [D] in this case).
b. Chemical reactions in the laboratory eventually reach equilibrium, at which point the net rate of formation of reaction products is zero (i.e., the forward and reverse reactions occur at the same rate).

At the start of the reaction written above, since there are no products yet, the reaction rate should be directly proportional only to the concentration of the reactants. Therefore, the *Law of Mass Action* predicts that a chemical reaction will occur faster at higher concentrations of A & B. This is because there are more reactant molecules in solution and a greater likelihood that they will collide in an orientation that allows the bond rearrangements for the reaction to occur.

Of course, reactant concentrations decline as products accumulate over time. Then the rate of formation of C & D should slows down, now affected by product as well as reactant concentrations; remember, all chemical reactions are inherently reversible! You may recognize the chemical rate equations from a chemistry course; these enable quantitation of reaction rates for our sample reaction. Here is the rate of formation of the products, C and D:

Misplaced '&'

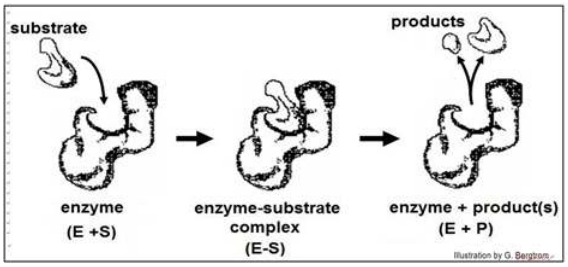
This equation recognizes that the reaction is reversible. Thus, the net reaction rate is equal to the *rate of the forward reaction* $k_1[A][B]$ minus the *rate of the back reaction* $k_{-1}[C][D]$. The equation is valid (applicable) at any time during the reaction. k_1 and k_{-1} are ***rate constants*** for the forward and reverse reactions, respectively.

So how do catalysts work? Catalysts increase chemical reaction rates by bringing reactants together more rapidly than they would encounter each other based just on random molecular motion in solution. This is possible because catalysts have an ***affinity*** for their substrates.

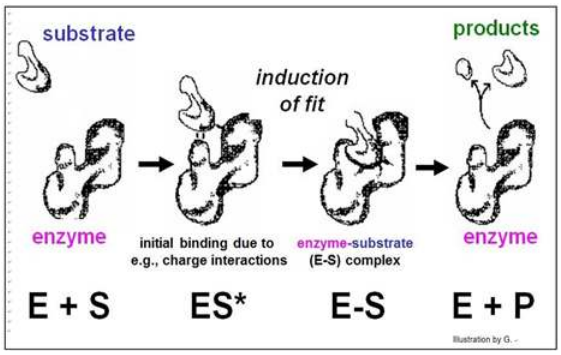
In the case of inorganic catalysts, relatively weak, generic forces account for the affinity of reactants and inorganic catalysts. Thus, a metallic catalyst (e.g., silver, platinum) attracts molecules with the appropriate (e.g., charge) configuration. If the attraction (*affinity*) is sufficient, the metal will hold reactants in place long enough to catalyze the bond rearrangements of a chemical reaction.

Unlike inorganic catalysts, enzymes have evolved highly specific shapes with physical-chemical properties. As a result, enzymes typically attract only the substrates necessary for a particular biochemical reaction. The active site of an enzyme has the exquisitely selective affinity for its substrate(s). This affinity is many times greater than those of inorganic catalysts for generic reactants. The result is that enzymes are more efficient, faster catalysts.

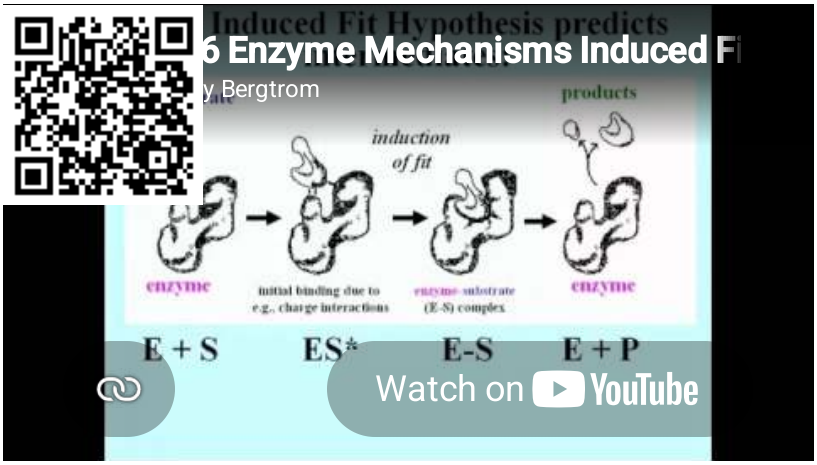
Early ideas of how substrate-enzyme interaction could be so specific suggested a ***Lock and Key*** mechanism, illustrated below.



According to this model, the affinity of enzyme for substrate brings them together, after which the substrate uniquely fits into the active site like a key into a lock. Once in the active site, the substrate(s) would undergo the bond rearrangements specific for the catalyzed reaction to generate products and regenerate an unchanged enzyme. But X-ray crystallography of enzyme-substrate interaction revealed that the active site of the enzyme changes shape during catalysis. This *allosteric change* suggested the revised, ***Induced Fit*** mechanism of enzyme action modeled below.



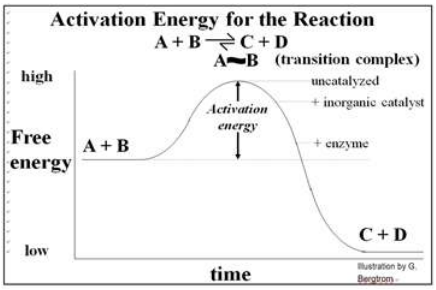
In this model, enzyme-substrate affinity causes the substrate to bind to the enzyme surface. Once bound, the enzyme undergoes an allosteric change, drawing the substrate(s) more tightly into the active site and catalyzing the reaction. Of course, after the reaction products come off, the enzyme returns to its original shape.



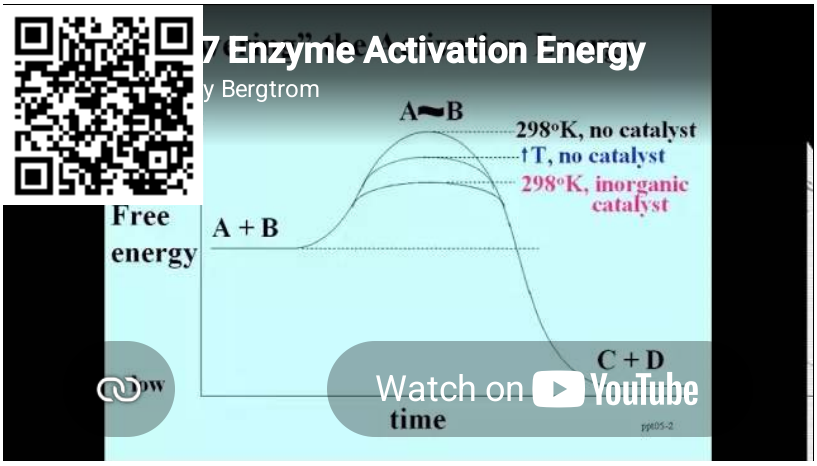
2. *Energetic Considerations of Catalysis*

Catalysts work by lowering the ***activation energy*** (E_a) for a reaction, thereby dramatically increasing the rate of the reaction. Activation energy is essentially a barrier to getting interacting substrates together to actually undergo a biochemical reaction. Compare the random motion of substrates in solution that occasionally encounter one another. They even more rarely bump into one another in just the right way to cause a reaction. This explains why adding more reactants or increasing the temperature of a reaction can speed it up…, by increasing the number of random as well as productive molecular collisions. Unlike molecules and reactions in a test tube, living organisms do not have these options for conducting fast biochemical reactions, or controlling reaction rates.

Inorganic catalytic surfaces attract reactants where catalysis can occur. The attractions are weak compared to those of enzymes and their substrates. An enzyme's active site attracts otherwise randomly distributed substrates very strongly, making enzyme catalysis faster than inorganic catalysis. Again, cells cannot use inorganic catalysts, most of which are insoluble and would attract reactants indiscriminately... not a good way for cells to control metabolism! The advent of enzymes with their specificity and high rate of catalysis was a key event in *chemical evolution* required for the origins of life. As we saw, allosteric change during the 'induction of fit' enables specific catalysis. In fact, a catalyzed reaction will be faster than the same reaction catalyzed by a piece of metal, and of course much faster (millions of times faster!) than the uncatalyzed reaction. The energetic of catalysis helps to explain why. Take a look at the energetic of a simple reaction in which A & B are converted to C & D, shown below.

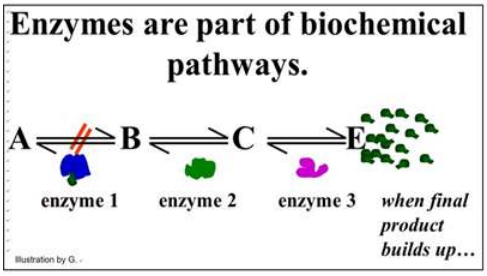


Conducted in a closed system, enzyme-catalyzed reactions reach their equilibrium more rapidly. As with all catalysts, enzymes are not consumed by the reactions they catalyze, nor do they alter the equilibrium concentrations of reactants and products of these reactions. The roughly 4000 biochemical reactions known to be catalyzed in cells are undoubtedly an underestimate! But remember too, that we estimate that the human genome has only 20,000 to 25,000 different genes!



B. Enzyme Regulation

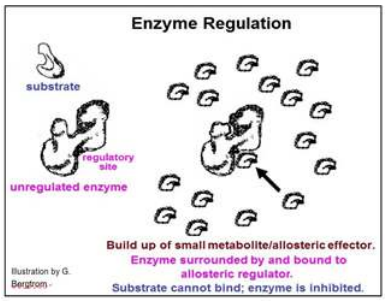
We noted that some enzymes are regulated, which just means that factors in the cell can slow down or speed up their rate of catalysis. In this way, the cell can respond quickly to metabolic needs reflected by the intracellular levels of these factors. Factors that slow down catalysis are called ***inhibitors***. Those that speed up catalysis are called ***activators***. In addition to responding to intracellular molecular indicators of the metabolic status of the cell, enzymes may be inhibited by drugs, poisons or changes in the chemical milieu (e.g. pH). Since cellular reactions occur as part of biochemical pathways, regulating a single enzyme can affect an entire pathway. For example, look at the generic pathway illustrated below.

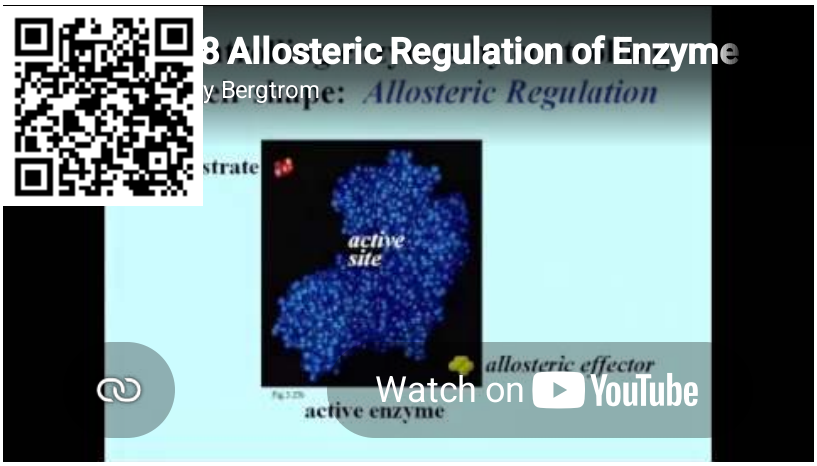


This pathway exists to produce substance **E**. Under normal conditions, another series of metabolic reactions would consume **E**. However, if the cell is meeting its metabolic needs and no longer needs so much **E**, it will accumulate in the cell. If there is an excess of **E** in the cell, it might bind to one of the enzymes. In the pathway shown, **E** binds to *enzyme 1*. This binding causes an allosteric change inhibiting catalysis and slowing down the entire pathway. In this example, of ***allosteric regulation***, we can assume that inhibitory regulation of **enzyme 1** evolved to control the rate of production of substance **E**. This is a common mode of enzyme allosteric regulation, called ***feedback inhibition***.

Enzymes can be regulated precisely because they can be *bent out of shape* (or into shape for that matter!). Some small metabolites become chemical information when they accumulate in cells, becoming the indicators of cellular metabolic status. The result is a decrease or increase enzyme activities to achieve an appropriate cellular response.

Whether an activator or an inhibitor of enzyme catalysis, regulatory molecules typically bind to enzymes at ***allosteric regulatory*** sites, causing local allosteric changes that is transmitted to the active site. *Enzyme inhibition* will occur if a change in shape reduces the affinity of enzyme for substrate or the rate of the bond rearrangements after the substrate has entered the active site. *Enzyme activation* would occur if the allosteric effect were to increase this affinity and/or catalytic rate. The mechanism of allosteric regulation of enzyme activity is illustrated below.





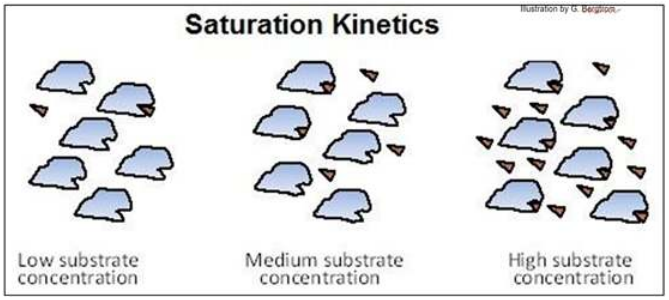
We can understand the effects changing rates of enzyme catalysis by determining *enzyme kinetics*. By comparing kinetic data for each enzyme in a biochemical pathway, one can determine a standard *rate-limiting reaction* under a given set of conditions. For example, if clinical tests reveal that a patient is producing too much of a biochemical metabolite, then the catalytic rate of the normally rate-limiting enzyme in its pathway of synthesis may have increased. What then, if the patient is producing too little of the metabolite? Either the catalytic rate of the rate-limiting enzyme has decreased or the catalytic rate of another enzyme in the biochemical pathway has become rate limiting. Reasons why a cellular biochemical would deviate from 'normal' levels include:

1. ***Viral & bacterial infection or environmental poisons:*** these can interfere with a specific reaction in a metabolic pathway; remedies depend on this information!
2. ***Chronic illness resulting from mutational enzyme deficiencies:*** treatments might include medications designed to enhance or inhibit (as appropriate) enzyme activity.
3. ***Genetic illness tied to metabolic deficiency:*** if a specific enzyme is the culprit, investigation of a pre- and/or post-natal course of treatment might be possible.
4. ***Life-style changes and choices:*** these might include eating habits, usually remediated by a change in diet.
5. ***Life-Style changes brought on by circumstance rather than choice:*** these are changes due to aging, such as the possibility of onset of Type 2 Diabetes; this can be delayed by switching to a low carb diet favoring hormonal changes that improve proper sugar metabolism.

Knowing the rate-limiting reaction(s) in biochemical pathways can identify regulated enzymes and lead to a remedy to correct a metabolic imbalance. As noted, ribozymes are RNA molecules that catalyze biochemical reactions; their kinetics can also be analyzed and classified. Next, we look at an overview of enzyme kinetics (for clear, detailed explanations of enzyme catalytic mechanisms, check out Jencks WP [1987, *Catalysis in Chemistry and Enzymology*. Mineola, NY, Courier Dover Publications]). We will consider how enzymes are regulated later, when we discuss glycolysis, a biochemical pathway that most living things use to extract energy from nutrients.

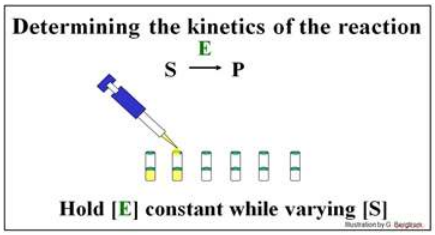
C. Enzyme Kinetics

All catalyzed chemical reactions display *saturation kinetics*, as shown below.

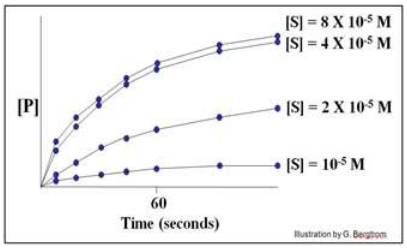


Note how at high substrate concentration, the active sites on all the enzyme molecules are bound to substrate molecules.

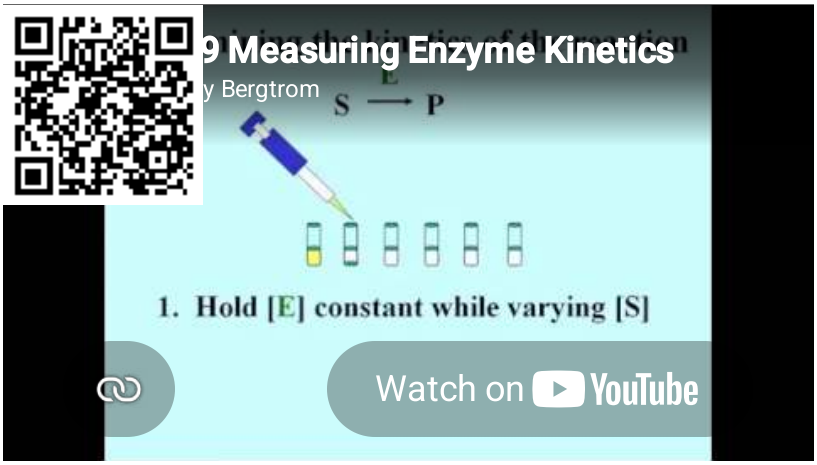
The experiment described below will determine the kinetics of the conversion of S to P by enzyme E.



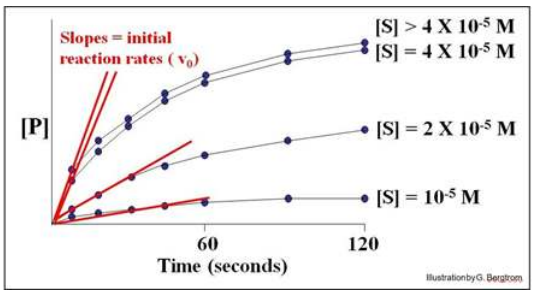
A series of reaction tubes are set up, each containing the same concentration of enzyme ([E]) but different concentrations of substrate ([S]). The concentration of P ([P]) produced at different times just after the start of the reaction in each tube is plotted to determine the *initial rate* of P formation for each concentration of substrate tested (see below).



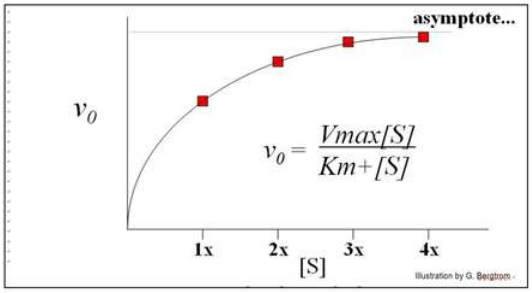
In this hypothetical example, the rates of the reactions (amount of P made over time) do not increase at substrate concentrations higher than 4 $X10^{-5}$ M. The upper curves therefore represent the maximal rate of the reaction at the experimental concentration of enzyme. We say that the maximal reaction rate occurs at ***saturation***.



Next, we can estimate the initial reaction rate (v_o) at each substrate concentration by plotting the slope of the first few time points through the origin of each curve in the graph. Consider the graph below, of the initial reaction rates estimated in this way.



Each straight line is the v_o for the reaction at a different [S] near the very beginning of the reaction, when [S] is high and [P] is vanishingly low. Next, we plot these rates (slopes, or v_o values) against the different concentrations of S in the experiment to get the curve of the reaction kinetics below.



This is an example of Michaelis-Menten kinetics common to many enzymes, named after the two biochemists who realized that the curve described ***rectangular hyperbola***.

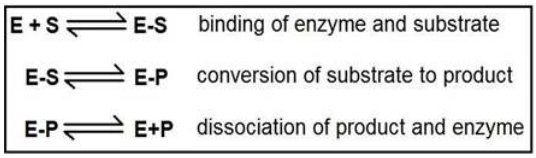
Put another way, the equation mathematically describes the mechanism of catalysis of the enzyme. The equation below mathematically describes a rectangular hyperbola:

$$y = \frac{xa}{x + b} \tag{4.3.2.2}$$

You might be asked to understand the derivation of (or even derive!) the Michaelis- Menten equation in a Biochemistry course. Suffice it to say here that Michaelis and Menten started with some simple assumptions about how an enzyme-catalyzed reaction would proceed and wrote reasonable chemical and rate equations for those reactions. Here is one way to write the chemical equation for a simple reaction in which an enzyme (E) catalyzes the conversion of substrate (S) to product (P):

$$S \underset{E}{\rightleftharpoons} P \tag{4.3.2.3}$$

Michaelis and Menten rationalized that this reaction might actually proceed in three steps. In each step, **E**, the enzyme is treated as a reactant in the conversion of S to P. The resulting chemical equations are shown below.



Reasoning that the middle reaction (the conversion of E-S to E-P) would be the fastest one, and therefore would not be the *rate-limiting reaction of catalysis*, they only considered the first and third reactions to be relevant in determining the overall kinetics of product formation. Then they wrote the following rate equations for just these two chemical reactions (as one would in an introductory chemistry course):

$$V_{\text{E-S formation}} = \mathrm{k_1[E][S] - k_{-1}[E\text{-}S]} \tag{4.3.2.4}$$

$$V_{\text{P formation}} = \mathrm{k_2[E\text{-}S] - k_{-2}[E][P]} \tag{4.3.2.5}$$

Both of these equations describe a straight line, which does not describe the observed hyperbolic reaction kinetics. Solving one for e.g., E-S and substituting the solution for E-S in the other equation left a single equation that also described a straight line. Again, not the expected rectangular hyperbola. To arrive at a chemical rate equation consistent with a rectangular hyperbola, Michaelis and Menten made several assumptions, including those made by G. E. Briggs and J. B. S. Haldane about how E, S and P would behave in a catalyzed reaction.

It was those assumptions allowed them to re-write each equation, combine and rewrite them into a single mathematical equation that did indeed describe a rectangular hyperbola. Here are Briggs and Haldane's assumptions:

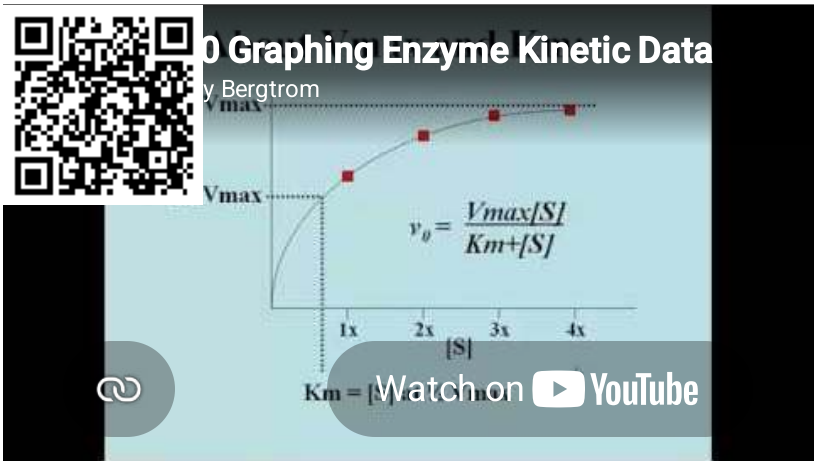
1. **[S] >> [E] at start and during the 'steady state'**
2. **[P] << [S] at start of reaction**
3. **All E is bound to S at start of reaction**
4. **$[E]_{total} = [E]_{free} + [E\text{-}S]$ at all times**

We have already seen the equation that Michaelis and Menten derived and now known as the Michaelis-Menten equation:

$$\mathrm{v_0} = \frac{\mathrm{Vmax[S]}}{\mathrm{Km + [S]}} \tag{4.3.2.6}$$

The take-home message here is that the assumptions about an enzyme-catalyzed reaction are a good approximation of how the reaction proceeds over time.

Michaelis and Menten defined Vmax and Km as key kinetic factors in enzymatic reactions. In the generic example of substrate conversion to product, we saw that increasing [S] results in a higher rate of product formation because a higher rate of encounters of enzyme and substrate molecules. At some point however, increasing [S] does not increase the initial reaction rate any further. Instead, v_o ***asymptotically*** approaches a theoretical maximum for the reaction, defined as ***Vmax***, the *maximum initial rate*. As we have already seen, *Vmax* occurs when all available enzyme active sites are saturated (occupied by substrate). At this point, the intrinsic catalytic rate determines the *turnover rate* of the enzyme. The substrate concentration at which the reaction rate has reached *½Vmax* is defined as $\boldsymbol{K_M}$ (the *Michaelis-Menten constant*). The Km is a ratio of rate constants remaining after rewriting the rate equations for the catalyzed reaction.



To recapitulate, the two most important kinetic properties of an enzyme are:

1. how quickly the enzyme becomes saturated with a particular substrate, which is related to the *Km* for the reaction, and
2. the maximum rate of the catalyzed reaction, described by the *Vmax* for the reaction.

Knowing these properties suggests how an enzyme might behave under cellular conditions, and can show how the enzyme should respond to allosteric regulation by natural inhibitory or activating factors…, and to poisons or other anomalous chemicals. You can find more details of how kinetic equations are derived (a necessary step in understanding how the enzyme works) in any good biochemistry textbook, or check out the *Michaelis-Menten Kinetics* entry in in the Enzymes Wikipedia link.

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4.3.3: Key Words and Terms

activation energy	**enzyme**	**Michaelis-Menten constant**
active site	**enzyme activation**	**Michaelis-Menten kinetics**
allosteric change	**enzyme inhibition**	**rate-limiting reaction**
allosteric regulation	**enzyme kinetics**	**ribozyme**
allosteric site	**enzyme regulation**	**saturation kinetics**
biochemical pathway	**induced fit**	**substrate specificity**
catalytic RNAs	**inorganic catalyst**	**substrates**
conformation	**Km**	**Vmax**

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SECTION OVERVIEW

4.4: Microbial Metabolism

Throughout earth's history, microbial metabolism has been a driving force behind the development and maintenance of the planet's biosphere. Eukaryotic organisms such as plants and animals typically depend on organic molecules for energy, growth, and reproduction. Prokaryotes, on the other hand, can metabolize a wide range of organic as well as inorganic matter, from complex organic molecules like cellulose to inorganic molecules and ions such as atmospheric nitrogen (N_2), molecular hydrogen (H_2), sulfide (S^{2-}), manganese (II) ions (Mn^{2+}), ferrous iron (Fe^{2+}), and ferric iron (Fe^{3+}), to name a few. By metabolizing such substances, microbes chemically convert them to other forms. In some cases, microbial metabolism produces chemicals that can be harmful to other organisms; in others, it produces substances that are essential to the metabolism and survival of other life forms (Figure 4.4.1).



Figure 4.4.1: Prokaryotes have great metabolic diversity with important consequences to other forms of life. Acidic mine drainage (left) is a serious environmental problem resulting from the introduction of water and oxygen to sulfide-oxidizing bacteria during mining processes. These bacteria produce large amounts of sulfuric acid as a byproduct of their metabolism, resulting in a low-pH environment that can kill many aquatic plants and animals. On the other hand, some prokaryotes are essential to other life forms. Root nodules of many plants (right) house nitrogen-fixing bacteria that convert atmospheric nitrogen into ammonia, providing a usable nitrogen source for these plants. (credit left: modification of work by D. Hardesty, USGS Columbia Environment Research Center; credit right: modification of work by Celmow SR, Clairmont L, Madsen LH, and Guinel FC)

4.4.1: Energy, Matter, and Enzymes

4.4.2: Catabolism of Carbohydrates

4.4.3: Cellular Respiration

4.4.4: Fermentation

4.4.5: Catabolism of Lipids and Proteins

4.4.6: Photosynthesis and the Importance of Light

4.4.7: Biogeochemical Cycles

4.4.E: Microbial Metabolism (Exercises)

Thumbnail: The Krebs cycle, also known as the citric acid cycle, is summarized here. Note incoming two-carbon acetyl results in the main outputs per turn of two CO_2, three NADH, one $FADH_2$, and one ATP (or GTP) molecules made by substrate-level phosphorylation. Two turns of the Krebs cycle are required to process all of the carbon from one glucose molecule. (CC BY 4.0; OpenStax)

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4.4.1: Energy, Matter, and Enzymes

Learning Objectives

- Define and describe metabolism
- Compare and contrast autotrophs and heterotrophs
- Describe the importance of oxidation-reduction reactions in metabolism
- Describe why ATP, FAD, NAD^+, and $NADP^+$ are important in a cell
- Identify the structure and structural components of an enzyme
- Describe the differences between competitive and noncompetitive enzyme inhibitors

Clinical Focus: Part 1

Hannah is a 15-month-old girl from Washington state. She is spending the summer in Gambia, where her parents are working for a nongovernmental organization. About 3 weeks after her arrival in Gambia, Hannah's appetite began to diminish and her parents noticed that she seemed unusually sluggish, fatigued, and confused. She also seemed very irritable when she was outdoors, especially during the day. When she began vomiting, her parents figured she had caught a 24-hour virus, but when her symptoms persisted, they took her to a clinic. The local physician noticed that Hannah's reflexes seemed abnormally slow, and when he examined her eyes with a light, she seemed unusually light sensitive. She also seemed to be experiencing a stiff neck.

Exercise 4.4.1.1

What are some possible causes of Hannah's symptoms?

The term used to describe all of the chemical reactions inside a cell is metabolism (Figure 4.4.1.1). Cellular processes such as the building or breaking down of complex molecules occur through series of stepwise, interconnected chemical reactions called metabolic pathways. Reactions that are spontaneous and release energy are exergonic reactions, whereas endergonic reactions require energy to proceed. The term anabolism refers to those endergonic metabolic pathways involved in biosynthesis, converting simple molecular building blocks into more complex molecules, and fueled by the use of cellular energy. Conversely, the term catabolism refers to exergonic pathways that break down complex molecules into simpler ones. Molecular energy stored in the bonds of complex molecules is released in catabolic pathways and harvested in such a way that it can be used to produce high-energy molecules, which are used to drive anabolic pathways. Thus, in terms of energy and molecules, cells are continually balancing catabolism with anabolism.

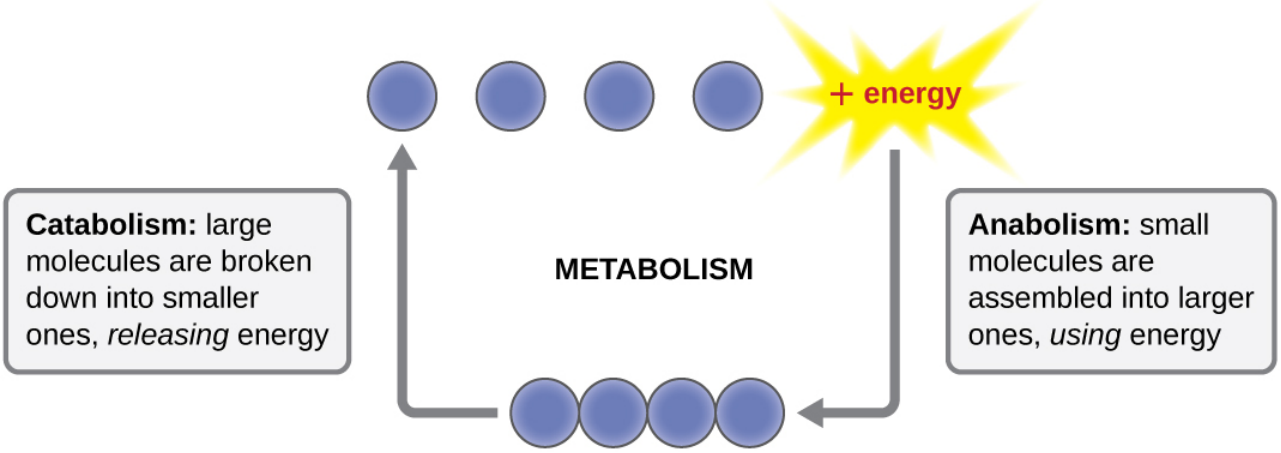


Figure 4.4.1.1: Metabolism includes catabolism and anabolism. Anabolic pathways require energy to synthesize larger molecules. Catabolic pathways generate energy by breaking down larger molecules. Both types of pathways are required for maintaining the cell's energy balance.

Classification by Carbon and Energy Source

Organisms can be identified according to the source of carbon they use for metabolism as well as their energy source. The prefixes auto- (“self”) and hetero- (“other”) refer to the origins of the carbon sources various organisms can use. Organisms that convert inorganic carbon dioxide (CO_2) into organic carbon compounds are autotrophs. Plants and cyanobacteria are well-known examples of autotrophs. Conversely, heterotrophs rely on more complex organic carbon compounds as nutrients; these are provided to them initially by autotrophs. Many organisms, ranging from humans to many prokaryotes, including the well-studied *Escherichia coli*, are heterotrophic.

Organisms can also be identified by the energy source they use. All energy is derived from the transfer of electrons, but the source of electrons differs between various types of organisms. The prefixes photo- (“light”) and chemo- (“chemical”) refer to the energy sources that various organisms use. Those that get their energy for electron transfer from light are phototrophs, whereas chemotrophs obtain energy for electron transfer by breaking chemical bonds. There are two types of chemotrophs: organotrophs and lithotrophs. Organotrophs, including humans, fungi, and many prokaryotes, are chemotrophs that obtain energy from organic compounds. Lithotrophs (“litho” means “rock”) are chemotrophs that get energy from inorganic compounds, including hydrogen sulfide (H_2S) and reduced iron. Lithotrophy is unique to the microbial world.

The strategies used to obtain both carbon and energy can be combined for the classification of organisms according to nutritional type. Most organisms are chemoheterotrophs because they use organic molecules as both their electron and carbon sources. Table 4.4.1.1 summarizes this and the other classifications.

Table 4.4.1.1: Classifications of Organisms by Energy and Carbon Source

Classifications		Energy Source	Carbon Source	Examples
Chemotrophs	Chemoautotrophs	Chemical	Inorganic	Hydrogen-, sulfur-, iron-, nitrogen-, and carbon monoxide-oxidizing bacteria
	Chemoheterotrophs	Chemical	Organic compounds	All animals, most fungi, protozoa, and bacteria
Phototrophs	Photoautotrophs	Light	Inorganic	All plants, algae, cyanobacteria, and green and purple sulfur bacteria
	Photoheterotrophs	Light	Organic compounds	Green and purple nonsulfur bacteria, heliobacteria

? Exercise 4.4.1.2

1. Explain the difference between catabolism and anabolism.
2. Explain the difference between autotrophs and heterotrophs.

Oxidation and Reduction in Metabolism

The transfer of electrons between molecules is important because most of the energy stored in atoms and used to fuel cell functions is in the form of high-energy electrons. The transfer of energy in the form of electrons allows the cell to transfer and use energy incrementally; that is, in small packages rather than a single, destructive burst. Reactions that remove electrons from donor molecules, leaving them oxidized, are oxidation reactions; those that add electrons to acceptor molecules, leaving them reduced, are reduction reactions. Because electrons can move from one molecule to another, oxidation and reduction occur in tandem. These pairs of reactions are called oxidation-reduction reactions, or redox reactions.

Energy Carriers: NAD^+, $NADP^+$, FAD, and ATP

The energy released from the breakdown of the chemical bonds within nutrients can be stored either through the reduction of electron carriers or in the bonds of adenosine triphosphate (ATP). In living systems, a small class of compounds functions as mobile electron carriers, molecules that bind to and shuttle high-energy electrons between compounds in pathways. The principal electron carriers we will consider originate from the B vitamin group and are derivatives of nucleotides; they are nicotinamide adenine dinucleotide, nicotine adenine dinucleotide phosphate, and flavin adenine dinucleotide. These compounds can be easily reduced or oxidized. Nicotinamide adenine dinucleotide (NAD^+/NADH) is the most common mobile electron carrier used in catabolism. NAD^+ is the oxidized form of the molecule; NADH is the reduced form of the molecule. Nicotine adenine dinucleotide phosphate ($NADP^+$), the oxidized form of an NAD^+ variant that contains an extra phosphate group, is another important electron carrier; it forms NADPH when reduced. The oxidized form of flavin adenine dinucleotide is FAD, and its reduced form is $FADH_2$. Both NAD^+/NADH and FAD/$FADH_2$ are extensively used in energy extraction from sugars during catabolism in chemoheterotrophs, whereas $NADP^+$/NADPH plays an important role in anabolic reactions and photosynthesis. Collectively, $FADH_2$, NADH, and NADPH are often referred to as having reducing power due to their ability to donate electrons to various chemical reactions.

A living cell must be able to handle the energy released during catabolism in a way that enables the cell to store energy safely and release it for use only as needed. Living cells accomplish this by using the compound adenosine triphosphate (ATP). ATP is often called the “energy currency” of the cell, and, like currency, this versatile compound can be used to fill any energy need of the cell. At the heart of ATP is a molecule of adenosine monophosphate (AMP), which is composed of an adenine molecule bonded to a ribose molecule and a single phosphate group. Ribose is a five-carbon sugar found in RNA, and AMP is one of the nucleotides in RNA. The addition of a second phosphate group to this core molecule results in the formation of adenosine diphosphate (ADP); the addition of a third phosphate group forms ATP (Figure 4.4.1.2). Adding a phosphate group to a molecule, a process called phosphorylation, requires energy. Phosphate groups are negatively charged and thus repel one another when they are arranged in series, as they are in ADP and ATP. This repulsion makes the ADP and ATP molecules inherently unstable. Thus, the bonds between phosphate groups (one in ADP and two in ATP) are called high-energy phosphate bonds. When these high-energy bonds are broken to release one phosphate (called inorganic phosphate [P_i]) or two connected phosphate groups (called pyrophosphate [PP_i]) from ATP through a process called dephosphorylation, energy is released to drive endergonic reactions (Figure 4.4.1.3).

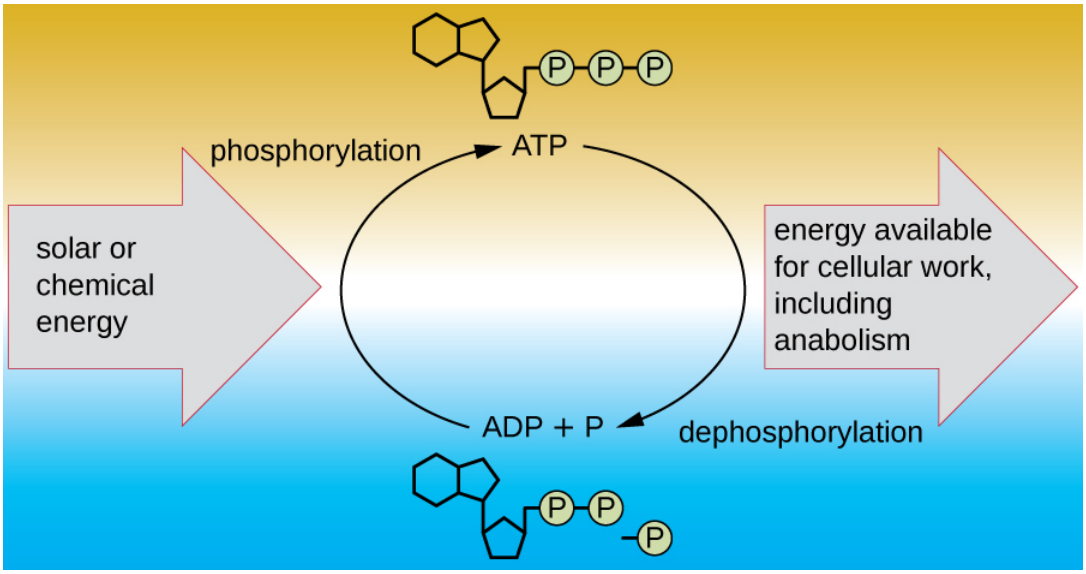


Figure 4.4.1.2: The energy released from dephosphorylation of ATP is used to drive cellular work, including anabolic pathways. ATP is regenerated through phosphorylation, harnessing the energy found in chemicals or from sunlight. (credit: modification of work by Robert Bear, David Rintoul)

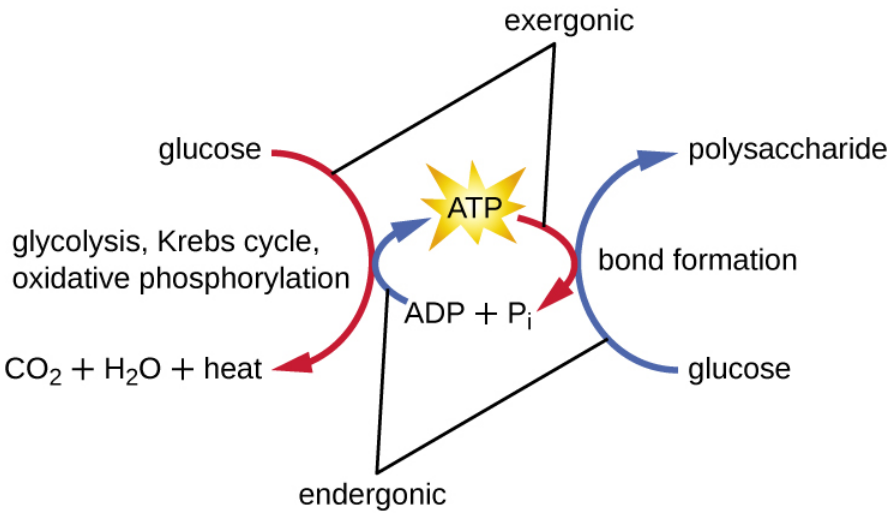


Figure 4.4.1.3: Exergonic reactions are coupled to endergonic ones, making the combination favorable. Here, the endergonic reaction of ATP phosphorylation is coupled to the exergonic reactions of catabolism. Similarly, the exergonic reaction of ATP dephosphorylation is coupled to the endergonic reaction of polypeptide formation, an example of anabolism.

? Exercise 4.4.1.3

What is the function of an electron carrier?

Enzyme Structure and Function

A substance that helps speed up a chemical reaction is a catalyst. Catalysts are not used or changed during chemical reactions and, therefore, are reusable. Whereas inorganic molecules may serve as catalysts for a wide range of chemical reactions, proteins called enzymes serve as catalysts for biochemical reactions inside cells. Enzymes thus play an important role in controlling cellular metabolism.

An enzyme functions by lowering the activation energy of a chemical reaction inside the cell. Activation energy is the energy needed to form or break chemical bonds and convert reactants to products (Figure 4.4.1.4). Enzymes lower the activation energy by binding to the reactant molecules and holding them in such a way as to speed up the reaction.

The chemical reactants to which an enzyme binds are called substrates, and the location within the enzyme where the substrate binds is called the enzyme's active site. The characteristics of the amino acids near the active site create a very specific chemical environment within the active site that induces suitability to binding, albeit briefly, to a specific substrate (or substrates). Due to this jigsaw puzzle-like match between an enzyme and its substrates, enzymes are known for their specificity. In fact, as an enzyme binds to its substrate(s), the enzyme structure changes slightly to find the best fit between the transition state (a structural intermediate between the substrate and product) and the active site, just as a rubber glove molds to a hand inserted into it. This active-site modification in the presence of substrate, along with the simultaneous formation of the transition state, is called induced fit (Figure 4.4.1.5). Overall, there is a specifically matched enzyme for each substrate and, thus, for each chemical reaction; however, there is some flexibility as well. Some enzymes have the ability to act on several different structurally related substrates.

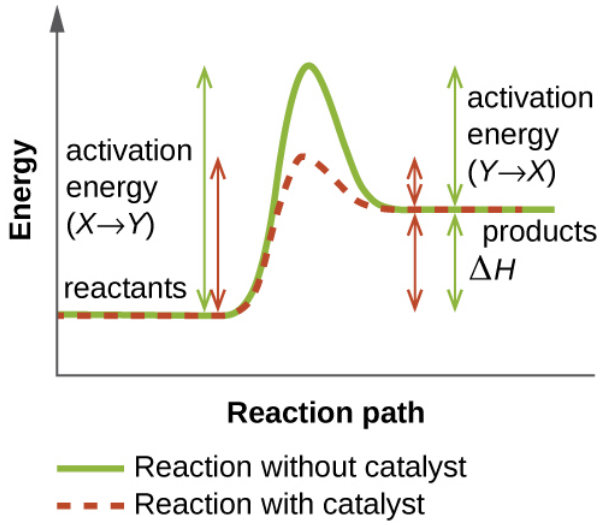


Figure 4.4.1.4: Enzymes lower the activation energy of a chemical reaction.

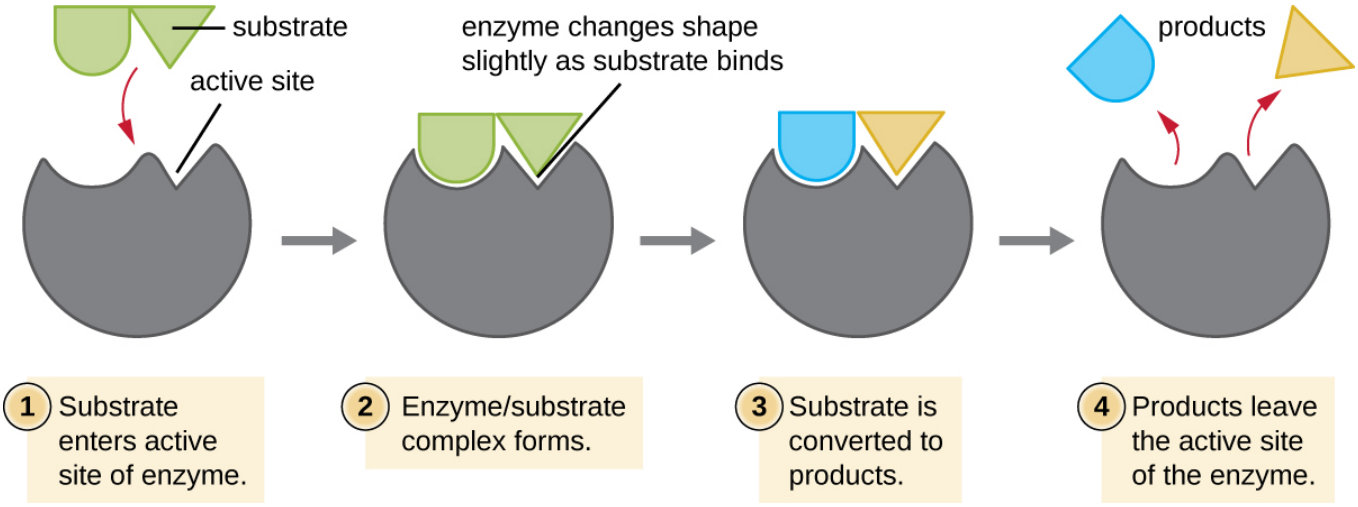


Figure 4.4.1.5: According to the induced-fit model, the active site of the enzyme undergoes conformational changes upon binding with the substrate.

Enzymes are subject to influences by local environmental conditions such as pH, substrate concentration, and temperature. Although increasing the environmental temperature generally increases reaction rates, enzyme catalyzed or otherwise, increasing or decreasing the temperature outside of an optimal range can affect chemical bonds within the active site, making them less well suited to bind substrates. High temperatures will eventually cause enzymes, like other biological molecules, to denature, losing their three-dimensional structure and function. Enzymes are also suited to function best within a certain pH range, and, as with temperature, extreme environmental pH values (acidic or basic) can cause enzymes to denature. Active-site amino-acid side chains have their own acidic or basic properties that are optimal for catalysis and, therefore, are sensitive to changes in pH.

Another factor that influences enzyme activity is substrate concentration: Enzyme activity is increased at higher concentrations of substrate until it reaches a saturation point at which the enzyme can bind no additional substrate. Overall, enzymes are optimized to work best under the environmental conditions in which the organisms that produce them live. For example, while microbes that inhabit hot springs have enzymes that work best at high temperatures, human pathogens have enzymes that work best at 37°C. Similarly, while enzymes produced by most organisms work best at a neutral pH, microbes growing in acidic environments make enzymes optimized to low pH conditions, allowing for their growth at those conditions.

Many enzymes do not work optimally, or even at all, unless bound to other specific nonprotein helper molecules, either temporarily through ionic or hydrogen bonds or permanently through stronger covalent bonds. Binding to these molecules promotes optimal conformation and function for their respective enzymes. Two types of helper molecules are cofactors and coenzymes. Cofactors are inorganic ions such as iron (Fe^{2+}) and magnesium (Mg^{2+}) that help stabilize enzyme conformation and function. One example of an

enzyme that requires a metal ion as a cofactor is the enzyme that builds DNA molecules, DNA polymerase, which requires a bound zinc ion (Zn^{2+}) to function.

Coenzymes are organic helper molecules that are required for enzyme action. Like enzymes, they are not consumed and, hence, are reusable. The most common sources of coenzymes are dietary vitamins. Some vitamins are precursors to coenzymes and others act directly as coenzymes.

Some cofactors and coenzymes, like coenzyme A (CoA), often bind to the enzyme's active site, aiding in the chemistry of the transition of a substrate to a product (Figure 4.4.1.6). In such cases, an enzyme lacking a necessary cofactor or coenzyme is called an apoenzyme and is inactive. Conversely, an enzyme with the necessary associated cofactor or coenzyme is called a holoenzyme and is active. NADH and ATP are also both examples of commonly used coenzymes that provide high-energy electrons or phosphate groups, respectively, which bind to enzymes, thereby activating them.

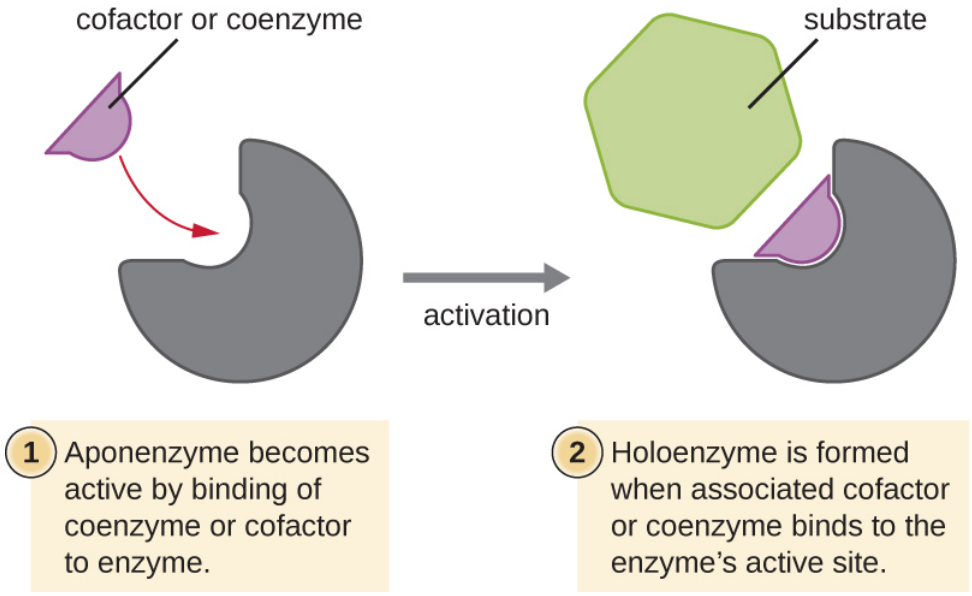


Figure 4.4.1.6: The binding of a coenzyme or cofactor to an apoenzyme is often required to form an active holoenzyme.

? Exercise 4.4.1.4

What role do enzymes play in a chemical reaction?

Enzyme Inhibitors

Enzymes can be regulated in ways that either promote or reduce their activity. There are many different kinds of molecules that inhibit or promote enzyme function, and various mechanisms exist for doing so (Figure 4.4.1.7). A competitive inhibitor is a molecule similar enough to a substrate that it can compete with the substrate for binding to the active site by simply blocking the substrate from binding. For a competitive inhibitor to be effective, the inhibitor concentration needs to be approximately equal to the substrate concentration. Sulfa drugs provide a good example of competitive competition. They are used to treat bacterial infections because they bind to the active site of an enzyme within the bacterial folic acid synthesis pathway. When present in a sufficient dose, a sulfa drug prevents folic acid synthesis, and bacteria are unable to grow because they cannot synthesize DNA, RNA, and proteins. Humans are unaffected because we obtain folic acid from our diets.

On the other hand, a noncompetitive (allosteric) inhibitor binds to the enzyme at an allosteric site, a location other than the active site, and still manages to block substrate binding to the active site by inducing a conformational change that reduces the affinity of the enzyme for its substrate (Figure 4.4.1.8). Because only one inhibitor molecule is needed per enzyme for effective inhibition, the concentration of inhibitors needed for noncompetitive inhibition is typically much lower than the substrate concentration.

In addition to allosteric inhibitors, there are allosteric activators that bind to locations on an enzyme away from the active site, inducing a conformational change that increases the affinity of the enzyme's active site(s) for its substrate(s).

Allosteric control is an important mechanism of regulation of metabolic pathways involved in both catabolism and anabolism. In a most efficient and elegant way, cells have evolved also to use the products of their own metabolic reactions for feedback inhibition of enzyme activity. Feedback inhibition involves the use of a pathway product to regulate its own further production. The cell responds to the abundance of specific products by slowing production during anabolic or catabolic reactions (Figure 4.4.1.8).

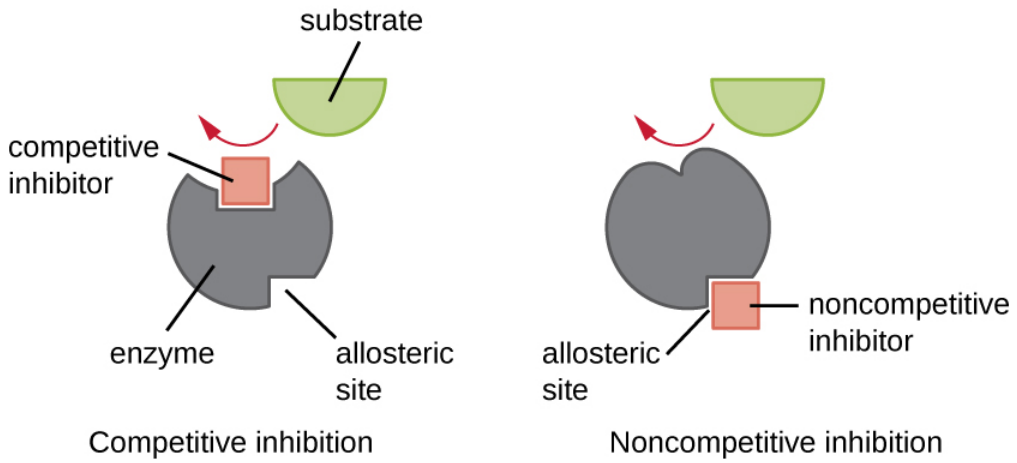


Figure 4.4.1.7: Enzyme activity can be regulated by either competitive inhibitors, which bind to the active site, or noncompetitive inhibitors, which bind to an allosteric site.

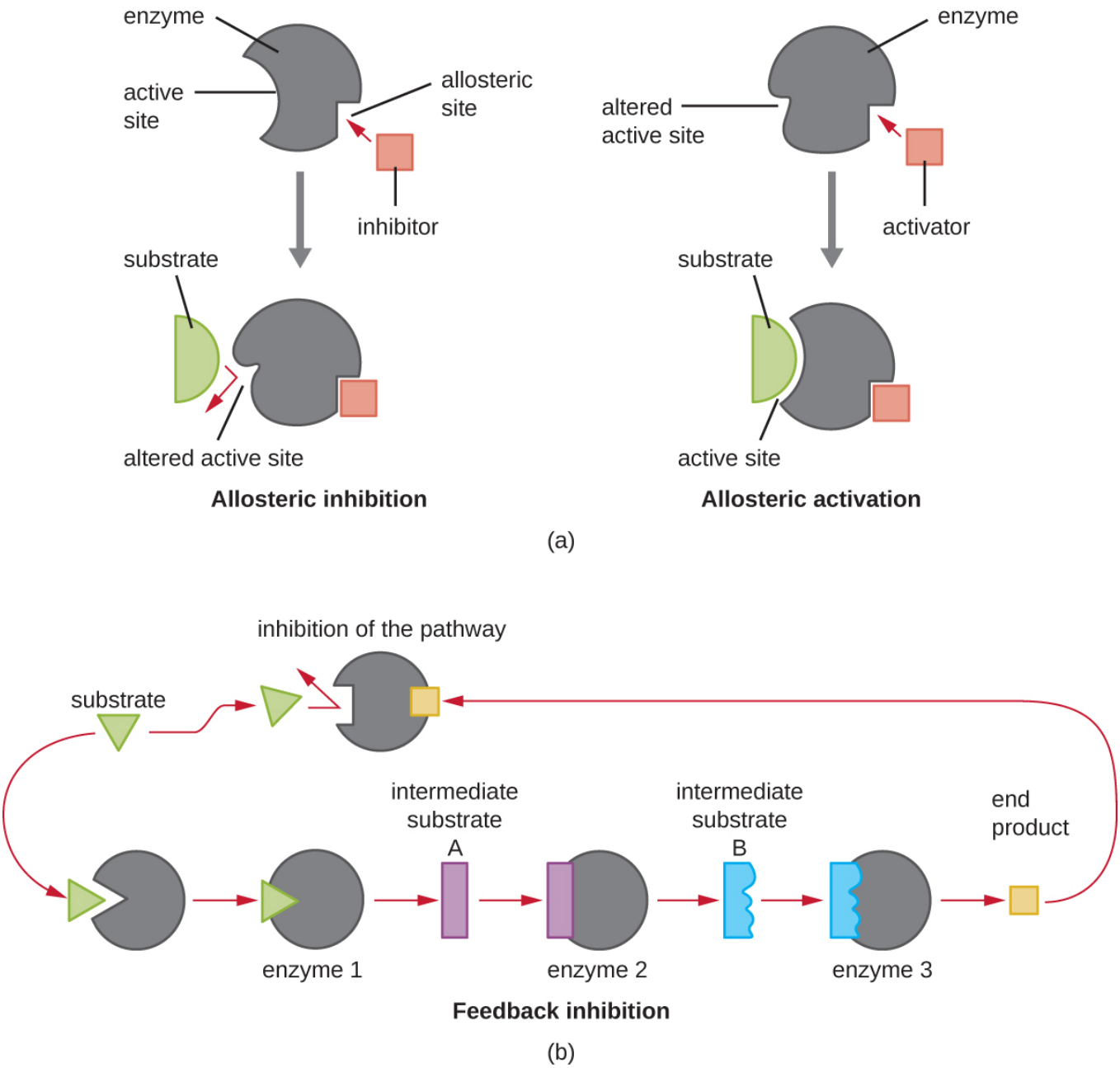


Figure 4.4.1.8: (a) Binding of an allosteric inhibitor reduces enzyme activity, but binding of an allosteric activator increases enzyme activity. (b) Feedback inhibition, where the end product of the pathway serves as a noncompetitive inhibitor to an enzyme early in the pathway, is an important mechanism of allosteric regulation in cells.

? Exercise 4.4.1.5

Explain the difference between a competitive inhibitor and a noncompetitive inhibitor.

Key Concepts and Summary

- **Metabolism** includes chemical reactions that break down complex molecules (**catabolism**) and those that build complex molecules (**anabolism**).
- Organisms may be classified according to their source of carbon. **Autotrophs** convert inorganic carbon dioxide into organic carbon; **heterotrophs** use fixed organic carbon compounds.

- Organisms may also be classified according to their energy source. **Phototrophs** obtain their energy from light. **Chemotrophs** get their energy from chemical compounds. **Organotrophs** use organic molecules, and **lithotrophs** use inorganic chemicals.
- Cellular **electron carriers** accept high-energy electrons from foods and later serve as electron donors in subsequent **redox reactions**. **FAD/$FADH_2$, NAD^+/NADH, and $NADP^+$/NADPH** are important electron carriers.
- **Adenosine triphosphate (ATP)** serves as the energy currency of the cell, safely storing chemical energy in its two **high-energy phosphate bonds** for later use to drive processes requiring energy.
- **Enzymes** are biological **catalysts** that increase the rate of chemical reactions inside cells by lowering the activation energy required for the reaction to proceed.
- In nature, **exergonic reactions** do not require energy beyond activation energy to proceed, and they release energy. They may proceed without enzymes, but at a slow rate. Conversely, **endergonic reactions** require energy beyond activation energy to occur. In cells, endergonic reactions are coupled to exergonic reactions, making the combination energetically favorable.
- **Substrates** bind to the enzyme's **active site**. This process typically alters the structures of both the active site and the substrate, favoring transition-state formation; this is known as **induced fit**.
- **Cofactors** are inorganic ions that stabilize enzyme conformation and function. **Coenzymes** are organic molecules required for proper enzyme function and are often derived from vitamins. An enzyme lacking a cofactor or coenzyme is an **apoenzyme;** an enzyme with a bound cofactor or coenzyme is a **holoenzyme**.
- **Competitive inhibitors** regulate enzymes by binding to an enzyme's active site, preventing substrate binding. **Noncompetitive (allosteric) inhibitors** bind to **allosteric sites**, inducing a conformational change in the enzyme that prevents it from functioning. **Feedback inhibition** occurs when the product of a metabolic pathway noncompetitively binds to an enzyme early on in the pathway, ultimately preventing the synthesis of the product.

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4.4.2: Catabolism of Carbohydrates

Learning Objectives

- Describe why glycolysis is not oxygen dependent
- Define and describe the net yield of three-carbon molecules, ATP, and NADH from glycolysis
- Explain how three-carbon pyruvate molecules are converted into two-carbon acetyl groups that can be funneled into the Krebs cycle.
- Define and describe the net yield of CO_2, GTP/ATP, $FADH_2$, and NADH from the Krebs cycle
- Explain how intermediate carbon molecules of the Krebs cycle can be used in a cell

Extensive enzyme pathways exist for breaking down carbohydrates to capture energy in ATP bonds. In addition, many catabolic pathways produce intermediate molecules that are also used as building blocks for anabolism. Understanding these processes is important for several reasons. First, because the main metabolic processes involved are common to a wide range of chemoheterotrophic organisms, we can learn a great deal about human metabolism by studying metabolism in more easily manipulated bacteria like *E. coli*. Second, because animal and human pathogens are also chemoheterotrophs, learning about the details of metabolism in these bacteria, including possible differences between bacterial and human pathways, is useful for the diagnosis of pathogens as well as for the discovery of antimicrobial therapies targeting specific pathogens. Last, learning specifically about the pathways involved in chemoheterotrophic metabolism also serves as a basis for comparing other more unusual metabolic strategies used by microbes. Although the chemical source of electrons initiating electron transfer is different between chemoheterorophs and chemoautotrophs, many similar processes are used in both types of organisms.

The typical example used to introduce concepts of metabolism to students is carbohydrate catabolism. For chemoheterotrophs, our examples of metabolism start with the catabolism of polysaccharides such as glycogen, starch, or cellulose. Enzymes such as amylase, which breaks down glycogen or starch, and cellulases, which break down cellulose, can cause the hydrolysis of glycosidic bonds between the glucose monomers in these polymers, releasing glucose for further catabolism.

Glycolysis

For bacteria, eukaryotes, and most archaea, glycolysis is the most common pathway for the catabolism of glucose; it produces energy, reduced electron carriers, and precursor molecules for cellular metabolism. Every living organism carries out some form of glycolysis, suggesting this mechanism is an ancient universal metabolic process. The process itself does not use oxygen; however, glycolysis can be coupled with additional metabolic processes that are either aerobic or anaerobic. Glycolysis takes place in the cytoplasm of prokaryotic and eukaryotic cells. It begins with a single six-carbon glucose molecule and ends with two molecules of a three-carbon sugar called pyruvate. Pyruvate may be broken down further after glycolysis to harness more energy through aerobic or anaerobic respiration, but many organisms, including many microbes, may be unable to respire; for these organisms, glycolysis may be their only source of generating ATP.

The type of glycolysis found in animals and that is most common in microbes is the Embden-Meyerhof-Parnas (EMP) pathway, named after Gustav Embden (1874–1933), Otto Meyerhof (1884–1951), and Jakub Parnas (1884–1949). Glycolysis using the EMP pathway consists of two distinct phases (Figure 4.4.2.1). The first part of the pathway, called the energy investment phase, uses energy from two ATP molecules to modify a glucose molecule so that the six-carbon sugar molecule can be split evenly into two phosphorylated three-carbon molecules called glyceraldehyde 3-phosphate (G3P). The second part of the pathway, called the energy payoff phase, extracts energy by oxidizing G3P to pyruvate, producing four ATP molecules and reducing two molecules of NAD^+ to two molecules of NADH, using electrons that originated from glucose. (A discussion and illustration of the full EMP pathway with chemical structures and enzyme names appear in Appendix C.)

The ATP molecules produced during the energy payoff phase of glycolysis are formed by substrate-level phosphorylation (Figure 4.4.2.1), one of two mechanisms for producing ATP. In substrate-level phosphorylation, a phosphate group is removed from an organic molecule and is directly transferred to an available ADP molecule, producing ATP. During glycolysis, high-energy phosphate groups from the intermediate molecules are added to ADP to make ATP.

Overall, in this process of glycolysis, the net gain from the breakdown of a single glucose molecule is:

- two ATP molecules

- two ATP molecules
- two NADH molecule, and
- two pyruvate molecules.

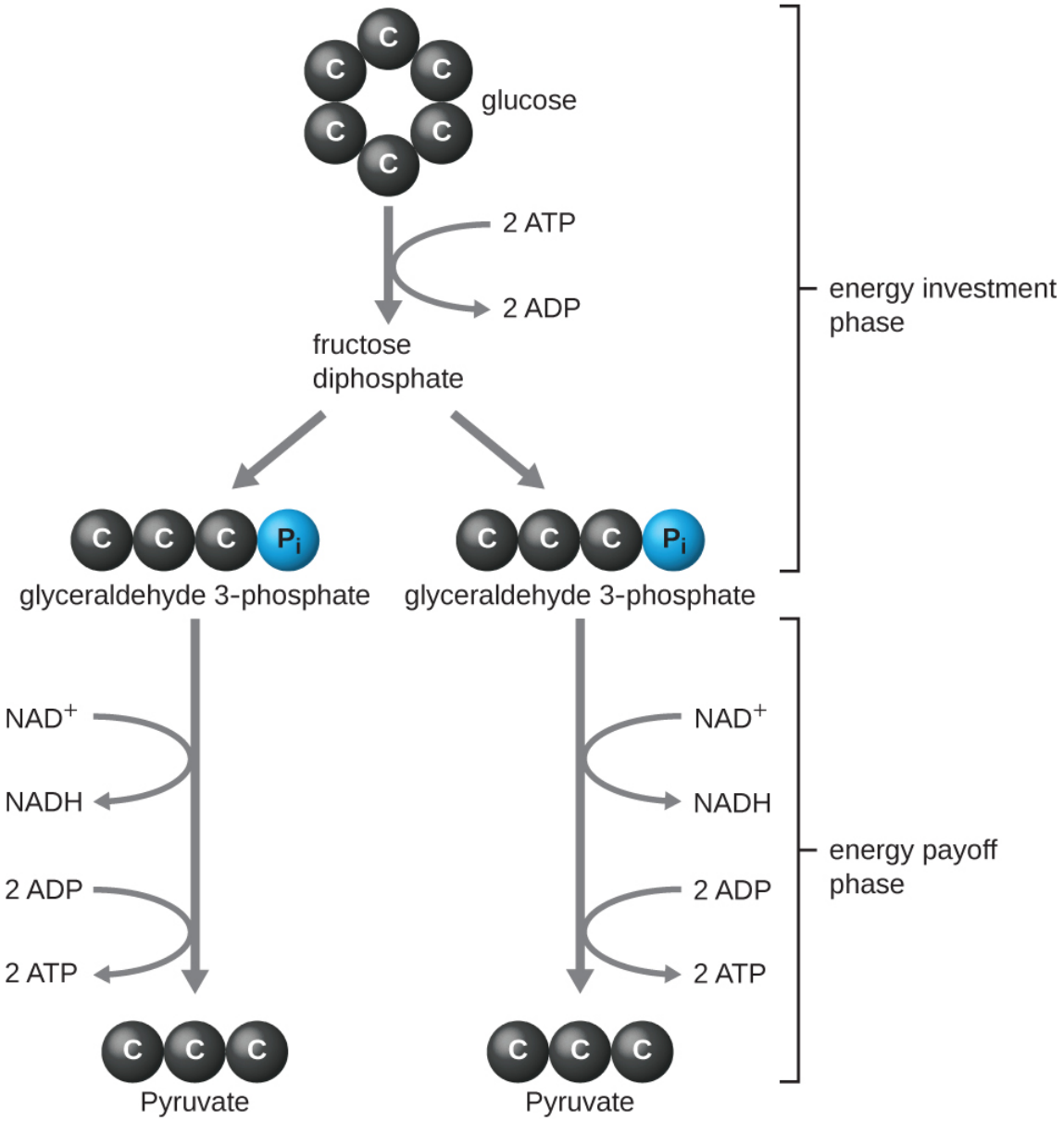


Figure 4.4.2.1: The energy investment phase of the Embden-Meyerhof-Parnas glycolysis pathway uses two ATP molecules to phosphorylate glucose, forming two glyceraldehyde 3-phosphate (G3P) molecules. The energy payoff phase harnesses the energy in the G3P molecules, producing four ATP molecules, two NADH molecules, and two pyruvates.

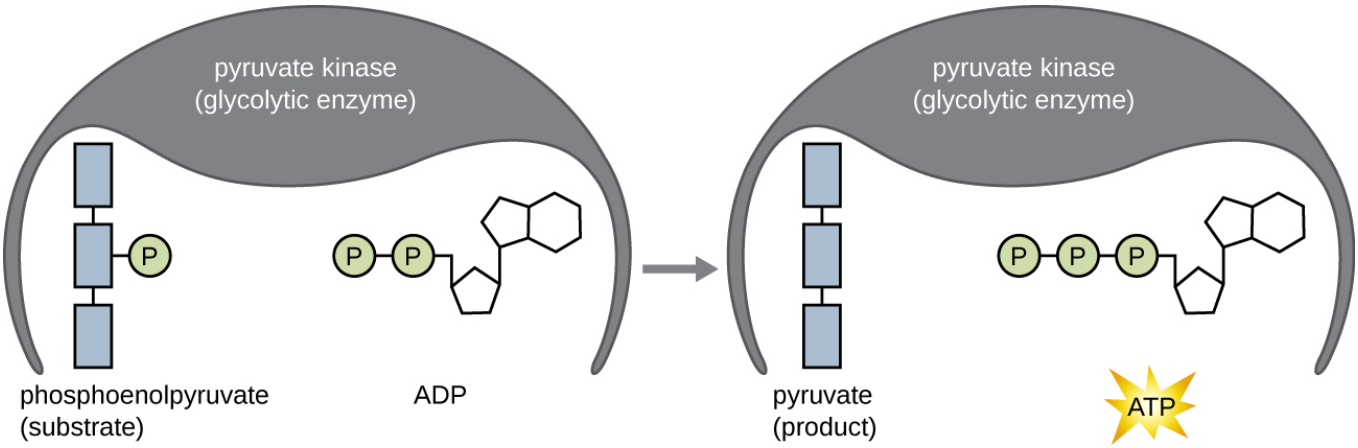


Figure 4.4.2.2: The ATP made during glycolysis is a result of substrate-level phosphorylation. One of the two enzymatic reactions in the energy payoff phase of Embden Meyerhof-Parnas glycolysis that produce ATP in this way is shown here.

Other Glycolytic Pathways

When we refer to glycolysis, unless otherwise indicated, we are referring to the EMP pathway used by animals and many bacteria. However, some prokaryotes use alternative glycolytic pathways. One important alternative is the Entner-Doudoroff (ED) pathway, named after its discoverers Nathan Entner and Michael Doudoroff (1911–1975). Although some bacteria, including the opportunistic gram-negative pathogen *Pseudomonas aeruginosa*, contain only the ED pathway for glycolysis, other bacteria, like *E. coli*, have the ability to use either the ED pathway or the EMP pathway.

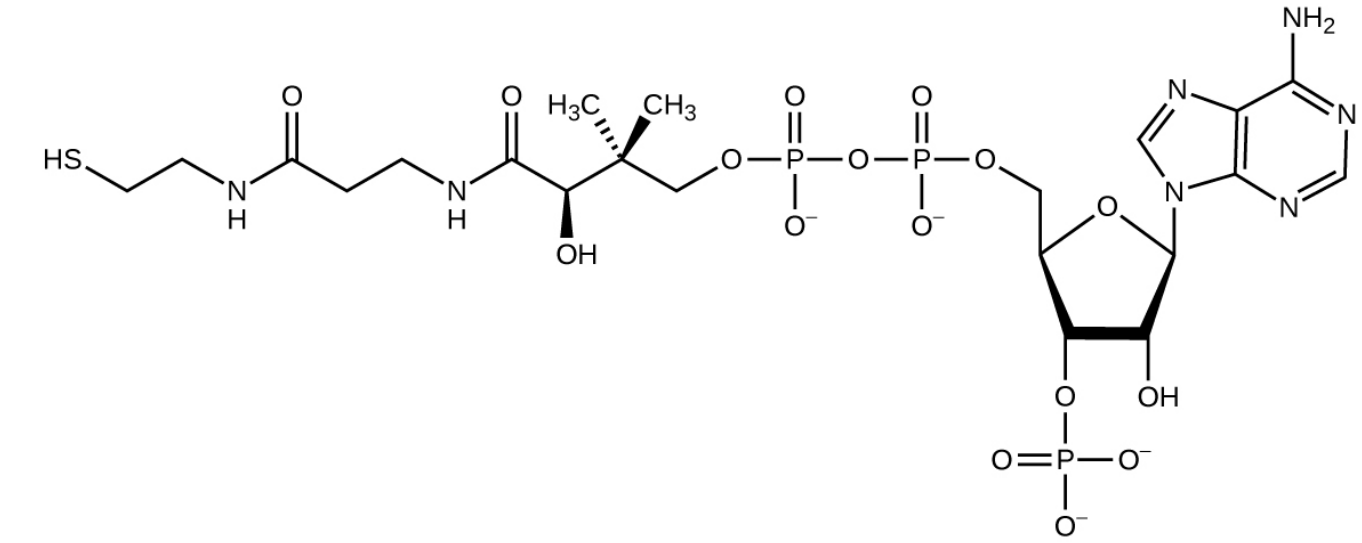
A third type of glycolytic pathway that occurs in all cells, which is quite different from the previous two pathways, is the pentose phosphate pathway (PPP) also called the phosphogluconate pathway or the hexose monophosphate shunt. Evidence suggests that the PPP may be the most ancient universal glycolytic pathway. The intermediates from the PPP are used for the biosynthesis of nucleotides and amino acids. Therefore, this glycolytic pathway may be favored when the cell has need for nucleic acid and/or protein synthesis, respectively. A discussion and illustration of the complete ED pathway and PPP with chemical structures and enzyme names appear in Appendix C.

? Exercise 4.4.2.1

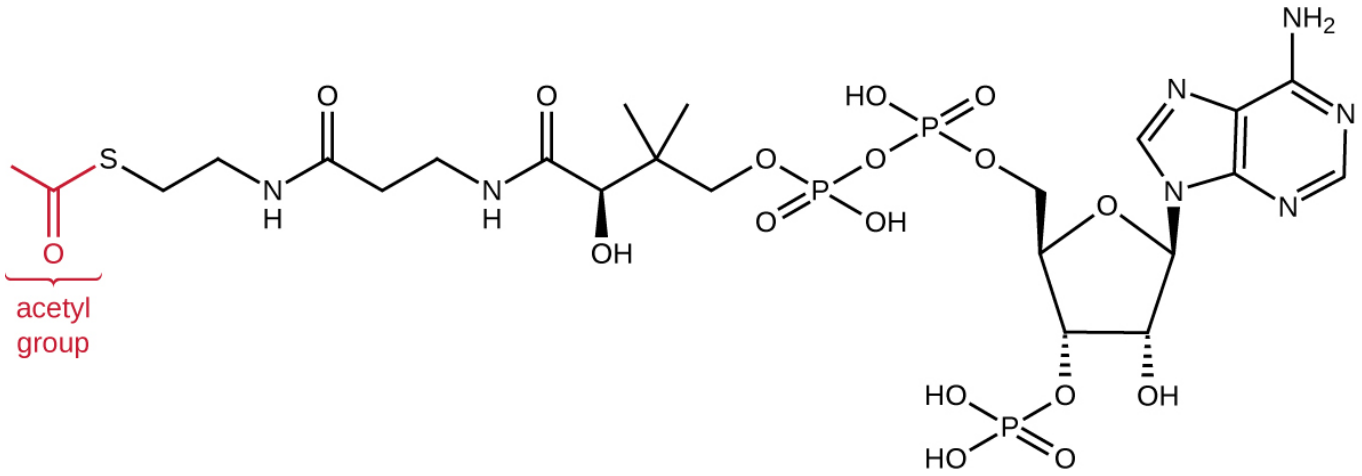
When might an organism use the ED pathway or the PPP for glycolysis?

Transition Reaction, Coenzyme A, and the Krebs Cycle

Glycolysis produces pyruvate, which can be further oxidized to capture more energy. For pyruvate to enter the next oxidative pathway, it must first be decarboxylated by the enzyme complex pyruvate dehydrogenase to a two-carbon acetyl group in the transition reaction, also called the bridge reaction (see Appendix C and Figure 4.4.2.3). In the transition reaction, electrons are also transferred to NAD^+ to form NADH. To proceed to the next phase of this metabolic process, the comparatively tiny two-carbon acetyl must be attached to a very large carrier compound called coenzyme A (CoA). The transition reaction occurs in the mitochondrial matrix of eukaryotes; in prokaryotes, it occurs in the cytoplasm because prokaryotes lack membrane-enclosed organelles.



(a) coenzyme A without an attached acetyl group



(b) coenzyme A with an attached acetyl group

Figure 4.4.2.3: (a) Coenzyme A is shown here without an attached acetyl group. (b) Coenzyme A is shown here with an attached acetyl group.

The Krebs cycle transfers remaining electrons from the acetyl group produced during the transition reaction to electron carrier molecules, thus reducing them. The Krebs cycle also occurs in the cytoplasm of prokaryotes along with glycolysis and the transition reaction, but it takes place in the mitochondrial matrix of eukaryotic cells where the transition reaction also occurs. The Krebs cycle is named after its discoverer, British scientist Hans Adolf Krebs (1900–1981) and is also called the citric acid cycle, or the tricarboxylic acid cycle (TCA) because citric acid has three carboxyl groups in its structure. Unlike glycolysis, the Krebs cycle is a closed loop: The last part of the pathway regenerates the compound used in the first step (Figure 4.4.2.4). The eight steps of the cycle are a series of chemical reactions that capture the two-carbon acetyl group (the CoA carrier does not enter the Krebs cycle) from the transition reaction, which is added to a four-carbon intermediate in the Krebs cycle, producing the six-carbon intermediate citric acid (giving the alternate name for this cycle). As one turn of the cycle returns to the starting point of the four-carbon intermediate, the cycle produces two CO_2 molecules, one ATP molecule (or an equivalent, such as guanosine triphosphate [GTP]) produced by substrate-level phosphorylation, and three molecules of NADH and one of $FADH_2$. (A discussion and detailed illustration of the full Krebs cycle appear in Appendix C.)

Although many organisms use the Krebs cycle as described as part of glucose metabolism, several of the intermediate compounds in the Krebs cycle can be used in synthesizing a wide variety of important cellular molecules, including amino acids, chlorophylls,

fatty acids, and nucleotides; therefore, the cycle is both anabolic and catabolic (Figure 4.4.2.5).

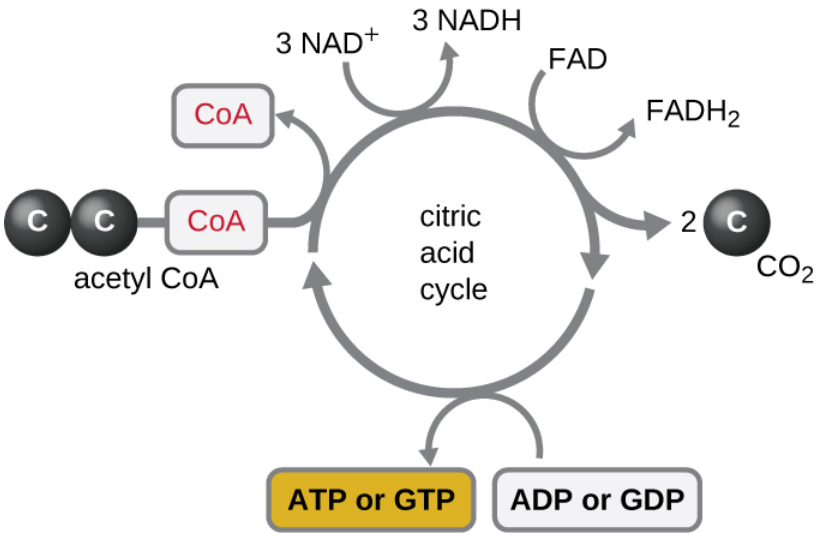


Figure 4.4.2.4: The Krebs cycle, also known as the citric acid cycle, is summarized here. Note incoming two-carbon acetyl results in the main outputs per turn of two CO_2, three NADH, one $FADH_2$, and one ATP (or GTP) molecules made by substrate-level phosphorylation. Two turns of the Krebs cycle are required to process all of the carbon from one glucose molecule.

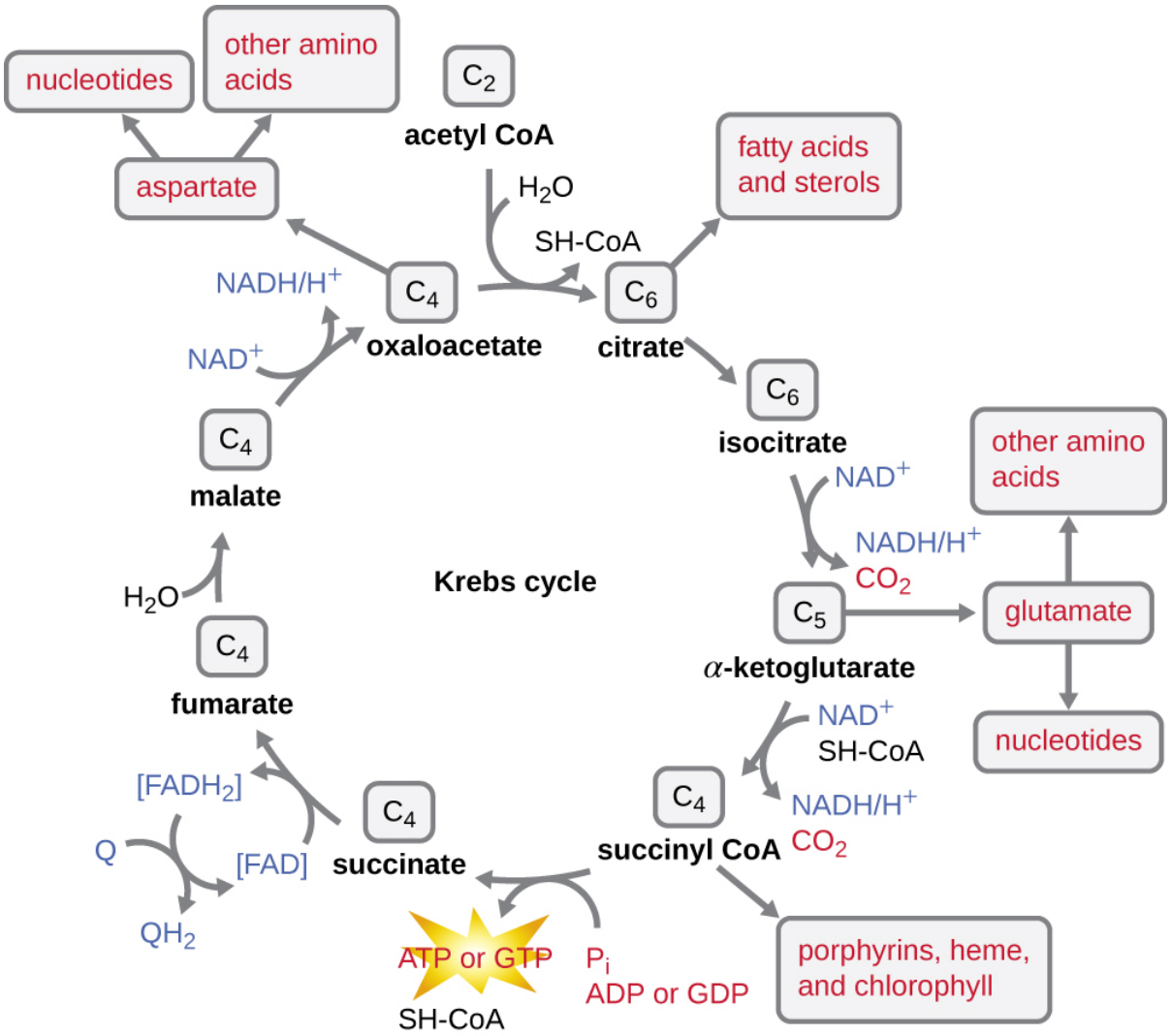


Figure 4.4.2.5: Many organisms use intermediates from the Krebs cycle, such as amino acids, fatty acids, and nucleotides, as building blocks for biosynthesis.

Key Concepts and Summary

- **Glycolysis** is the first step in the breakdown of glucose, resulting in the formation of ATP, which is produced by **substrate-level phosphorylation**; NADH; and two pyruvate molecules. Glycolysis does not use oxygen and is not oxygen dependent.
- After glycolysis, a three-carbon pyruvate is decarboxylated to form a two-carbon acetyl group, coupled with the formation of NADH. The acetyl group is attached to a large carrier compound called coenzyme A.
- After the transition step, coenzyme A transports the two-carbon acetyl to the **Krebs cycle**, where the two carbons enter the cycle. Per turn of the cycle, one acetyl group derived from glycolysis is further oxidized, producing three NADH molecules, one $FADH_2$, and one ATP by **substrate-level phosphorylation**, and releasing two CO_2 molecules.
- The Krebs cycle may be used for other purposes. Many of the intermediates are used to synthesize important cellular molecules, including amino acids, chlorophylls, fatty acids, and nucleotides.

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4.4.3: Cellular Respiration

Learning Objectives

- Compare and contrast the electron transport system location and function in a prokaryotic cell and a eukaryotic cell
- Compare and contrast the differences between substrate-level and oxidative phosphorylation
- Explain the relationship between chemiosmosis and proton motive force
- Describe the function and location of ATP synthase in a prokaryotic versus eukaryotic cell
- Compare and contrast aerobic and anaerobic respiration

We have just discussed two pathways in glucose catabolism—glycolysis and the Krebs cycle—that generate ATP by substrate-level phosphorylation. Most ATP, however, is generated during a separate process called oxidative phosphorylation, which occurs during cellular respiration. Cellular respiration begins when electrons are transferred from NADH and $FADH_2$—made in glycolysis, the transition reaction, and the Krebs cycle—through a series of chemical reactions to a final inorganic electron acceptor (either oxygen in aerobic respiration or non-oxygen inorganic molecules in anaerobic respiration). These electron transfers take place on the inner part of the cell membrane of prokaryotic cells or in specialized protein complexes in the inner membrane of the mitochondria of eukaryotic cells. The energy of the electrons is harvested to generate an electrochemical gradient across the membrane, which is used to make ATP by oxidative phosphorylation.

Electron Transport System

The electron transport system (ETS) is the last component involved in the process of cellular respiration; it comprises a series of membrane-associated protein complexes and associated mobile accessory electron carriers. Electron transport is a series of chemical reactions that resembles a bucket brigade in that electrons from NADH and $FADH_2$ are passed rapidly from one ETS electron carrier to the next. These carriers can pass electrons along in the ETS because of their redox potential. For a protein or chemical to accept electrons, it must have a more positive redox potential than the electron donor. Therefore, electrons move from electron carriers with more negative redox potential to those with more positive redox potential. The four major classes of electron carriers involved in both eukaryotic and prokaryotic electron transport systems are the cytochromes, flavoproteins, iron-sulfur proteins, and the quinones.

In aerobic respiration, the final electron acceptor (i.e., the one having the most positive redox potential) at the end of the ETS is an oxygen molecule (O_2) that becomes reduced to water (H_2O) by the final ETS carrier. This electron carrier, cytochrome oxidase, differs between bacterial types and can be used to differentiate closely related bacteria for diagnoses. For example, the gram-negative opportunist *Pseudomonas aeruginosa* and the gram-negative cholera-causing *Vibrio cholerae* use cytochrome c oxidase, which can be detected by the oxidase test, whereas other gram-negative Enterobacteriaceae, like *E. coli*, are negative for this test because they produce different cytochrome oxidase types.

There are many circumstances under which aerobic respiration is not possible, including any one or more of the following:

- The cell lacks genes encoding an appropriate cytochrome oxidase for transferring electrons to oxygen at the end of the electron transport system.
- The cell lacks genes encoding enzymes to minimize the severely damaging effects of dangerous oxygen radicals produced during aerobic respiration, such as hydrogen peroxide (H_2O_2) or superoxide (O_2^-).
- The cell lacks a sufficient amount of oxygen to carry out aerobic respiration.

One possible alternative to aerobic respiration is anaerobic respiration, using an inorganic molecule other than oxygen as a final electron acceptor. There are many types of anaerobic respiration found in bacteria and archaea. Denitrifiers are important soil bacteria that use nitrate (NO_3^-) and nitrite (NO_2^-) as final electron acceptors, producing nitrogen gas (N_2). Many aerobically respiring bacteria, including *E. coli*, switch to using nitrate as a final electron acceptor and producing nitrite when oxygen levels have been depleted.

Microbes using anaerobic respiration commonly have an intact Krebs cycle, so these organisms can access the energy of the NADH and $FADH_2$ molecules formed. However, anaerobic respirers use altered ETS carriers encoded by their genomes, including

distinct complexes for electron transfer to their final electron acceptors. Smaller electrochemical gradients are generated from these electron transfer systems, so less ATP is formed through anaerobic respiration.

? Exercise 4.4.3.1

Do both aerobic respiration and anaerobic respiration use an electron transport chain?

Chemiosmosis, Proton Motive Force, and Oxidative Phosphorylation

In each transfer of an electron through the ETS, the electron loses energy, but with some transfers, the energy is stored as potential energy by using it to pump hydrogen ions (H^+) across a membrane. In prokaryotic cells, H^+ is pumped to the outside of the cytoplasmic membrane (called the periplasmic space in gram-negative and gram-positive bacteria), and in eukaryotic cells, they are pumped from the mitochondrial matrix across the inner mitochondrial membrane into the intermembrane space. There is an uneven distribution of H^+ across the membrane that establishes an electrochemical gradient because H^+ ions are positively charged (electrical) and there is a higher concentration (chemical) on one side of the membrane. This electrochemical gradient formed by the accumulation of H^+ (also known as a proton) on one side of the membrane compared with the other is referred to as the proton motive force (PMF). Because the ions involved are H^+, a pH gradient is also established, with the side of the membrane having the higher concentration of H^+ being more acidic. Beyond the use of the PMF to make ATP, as discussed in this chapter, the PMF can also be used to drive other energetically unfavorable processes, including nutrient transport and flagella rotation for motility.

The potential energy of this electrochemical gradient generated by the ETS causes the H^+ to diffuse across a membrane (the plasma membrane in prokaryotic cells and the inner membrane in mitochondria in eukaryotic cells). This flow of hydrogen ions across the membrane, called chemiosmosis, must occur through a channel in the membrane via a membrane-bound enzyme complex called ATP synthase (Figure 4.4.3.1). The tendency for movement in this way is much like water accumulated on one side of a dam, moving through the dam when opened. ATP synthase (like a combination of the intake and generator of a hydroelectric dam) is a complex protein that acts as a tiny generator, turning by the force of the H^+ diffusing through the enzyme, down their electrochemical gradient from where there are many mutually repelling H^+ to where there are fewer H^+. In prokaryotic cells, H^+ flows from the outside of the cytoplasmic membrane into the cytoplasm, whereas in eukaryotic mitochondria, H^+ flows from the intermembrane space to the mitochondrial matrix. The turning of the parts of this molecular machine regenerates ATP from ADP and inorganic phosphate (P_i) by oxidative phosphorylation, a second mechanism for making ATP that harvests the potential energy stored within an electrochemical gradient.

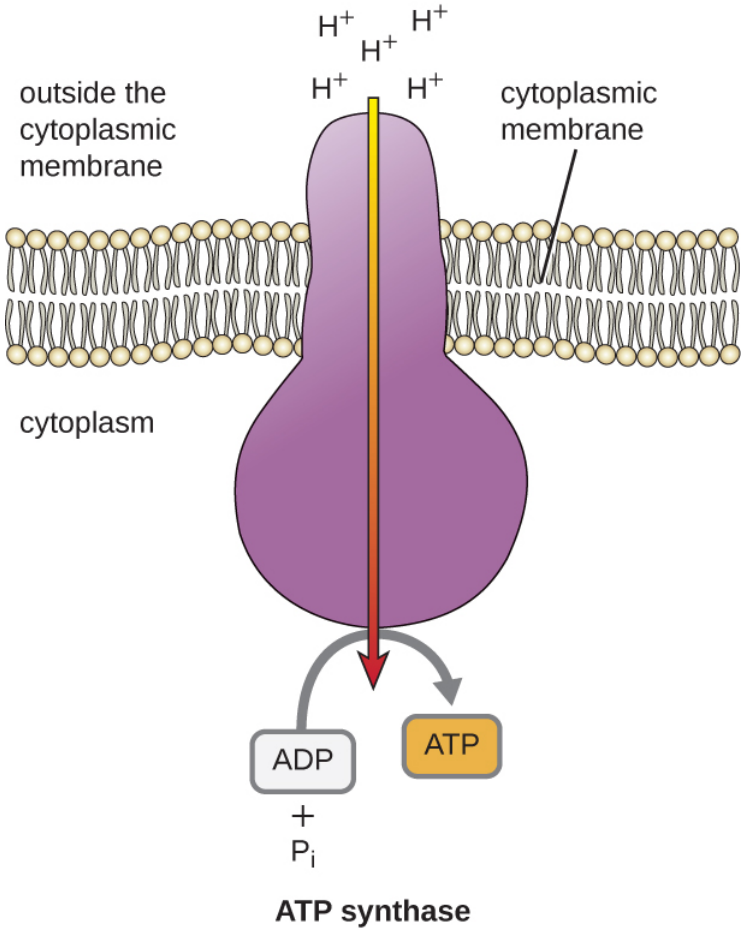


Figure 4.4.3.1: ATP synthase is a complex integral membrane protein through which H^+ flows down an electrochemical gradient, providing the energy for ATP production by oxidative phosphorylation. (credit: modification of work by Klaus Hoffmeier)

The number of ATP molecules generated from the catabolism of glucose varies. For example, the number of hydrogen ions that the electron transport system complexes can pump through the membrane varies between different species of organisms. In aerobic respiration in mitochondria, the passage of electrons from one molecule of NADH generates enough proton motive force to make three ATP molecules by oxidative phosphorylation, whereas the passage of electrons from one molecule of $FADH_2$ generates enough proton motive force to make only two ATP molecules. Thus, the 10 NADH molecules made per glucose during glycolysis, the transition reaction, and the Krebs cycle carry enough energy to make 30 ATP molecules, whereas the two $FADH_2$ molecules made per glucose during these processes provide enough energy to make four ATP molecules. Overall, the theoretical maximum yield of ATP made during the complete aerobic respiration of glucose is 38 molecules, with four being made by substrate-level phosphorylation and 34 being made by oxidative phosphorylation (Figure 4.4.3.2). In reality, the total ATP yield is usually less, ranging from one to 34 ATP molecules, depending on whether the cell is using aerobic respiration or anaerobic respiration; in eukaryotic cells, some energy is expended to transport intermediates from the cytoplasm into the mitochondria, affecting ATP yield.

Figure 4.4.3.2 summarizes the theoretical maximum yields of ATP from various processes during the complete aerobic respiration of one glucose molecule.

Source	Carbon Flow	Molecules of Reduced Coenzymes Produced	Net ATP Molecules Made by Substrate-Level Phosphory-lation	Net ATP Molecules Made by Oxidative Phosphory-lation	Theoretical Maximum Yield of ATP Molecules
Glycolysis (EMP)	Glucose (6C) ⟶ 2 pyruvates (2C)	2 NADH	2 ATP	6 ATP from 2 NADH	8
Transition reaction	2 pyruvates (3C) ⟶ 2 acetyl (2C) + 2 CO_2	2 NADH		6 ATP from 2 NADH	6
Krebs cycle	2 acetyl (2C) ⟶ 4 CO_2	6 NADH 2 $FADH_2$	2 ATP	18 ATP from 6 NADH 4 ATP from 2 $FADH_2$	24
Total:	glucose (6C) ⟶ 6 CO_2	10 NADH 2 $FADH_2$	4 ATP	34 ATP	38 ATP

Figure 4.4.3.2: Theoretical maximum yields of ATP from various processes during the complete aerobic respiration of one glucose molecule.

? Exercise 4.4.3.1

What are the functions of the proton motive force?

Summary

- Most ATP generated during the cellular respiration of glucose is made by **oxidative phosphorylation**.
- An **electron transport system (ETS)** is composed of a series of membrane-associated protein complexes and associated mobile accessory electron carriers. The ETS is embedded in the cytoplasmic membrane of prokaryotes and the inner mitochondrial membrane of eukaryotes.
- Each ETS complex has a different redox potential, and electrons move from electron carriers with more negative redox potential to those with more positive redox potential.
- To carry out **aerobic respiration**, a cell requires oxygen as the final electron acceptor. A cell also needs a complete Krebs cycle, an appropriate cytochrome oxidase, and oxygen detoxification enzymes to prevent the harmful effects of oxygen radicals produced during aerobic respiration.
- Organisms performing **anaerobic respiration** use alternative electron transport system carriers for the ultimate transfer of electrons to the final non-oxygen electron acceptors.
- Microbes show great variation in the composition of their electron transport systems, which can be used for diagnostic purposes to help identify certain pathogens.
- As electrons are passed from NADH and $FADH_2$ through an ETS, the electron loses energy. This energy is stored through the pumping of H^+ across the membrane, generating a **proton motive force**.
- The energy of this proton motive force can be harnessed by allowing hydrogen ions to diffuse back through the membrane by **chemiosmosis** using **ATP synthase**. As hydrogen ions diffuse through down their electrochemical gradient, components of ATP synthase spin, making ATP from ADP and P_i by oxidative phosphorylation.

- Aerobic respiration forms more ATP (a maximum of 34 ATP molecules) during oxidative phosphorylation than does anaerobic respiration (between one and 32 ATP molecules).

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4.4.4: Fermentation

Learning Objectives

- Define fermentation and explain why it does not require oxygen
- Describe the fermentation pathways and their end products and give examples of microorganisms that use these pathways
- Compare and contrast fermentation and anaerobic respiration

Many cells are unable to carry out respiration because of one or more of the following circumstances:

1. The cell lacks a sufficient amount of any appropriate, inorganic, final electron acceptor to carry out cellular respiration.
2. The cell lacks genes to make appropriate complexes and electron carriers in the electron transport system.
3. The cell lacks genes to make one or more enzymes in the Krebs cycle.

Whereas lack of an appropriate inorganic final electron acceptor is environmentally dependent, the other two conditions are genetically determined. Thus, many prokaryotes, including members of the clinically important genus *Streptococcus*, are permanently incapable of respiration, even in the presence of oxygen. Conversely, many prokaryotes are facultative, meaning that, should the environmental conditions change to provide an appropriate inorganic final electron acceptor for respiration, organisms containing all the genes required to do so will switch to cellular respiration for glucose metabolism because respiration allows for much greater ATP production per glucose molecule.

If respiration does not occur, NADH must be reoxidized to NAD^+ for reuse as an electron carrier for glycolysis, the cell's only mechanism for producing any ATP, to continue. Some living systems use an organic molecule (commonly pyruvate) as a final electron acceptor through a process called fermentation. Fermentation does not involve an electron transport system and does not directly produce any additional ATP beyond that produced during glycolysis by substrate-level phosphorylation. Organisms carrying out fermentation, called fermenters, produce a maximum of two ATP molecules per glucose during glycolysis. Table 4.4.4.1 compares the final electron acceptors and methods of ATP synthesis in aerobic respiration, anaerobic respiration, and fermentation. Note that the number of ATP molecules shown for glycolysis assumes the Embden-Meyerhof-Parnas pathway. The number of ATP molecules made by substrate-level phosphorylation (SLP) versus oxidative phosphorylation (OP) are indicated.

Table 4.4.4.1: Comparison of Respiration Versus Fermentation

Type of Metabolism	Example	Final Electron Acceptor	Pathways Involved in ATP Synthesis (Type of Phosphorylation)	Maximum Yield of ATP Molecules
Aerobic respiration	*Pseudomonas aeruginosa*	O_2	EMP glycolysis (SLP) Krebs cycle (SLP) Electron transport and chemiosmosis (OP):	2 2 34
			Total	**38**
Anaerobic respiration	*Paracoccus denitrificans*	NO_3^-, SO_4^{-2}, Fe^{+3}, CO_2, other inorganics	EMP glycolysis (SLP) Krebs cycle (SLP) Electron transport and chemiosmosis (OP):	2 2 1–32
			Total	**5–36**
Fermentation	*Candida albicans*	Organics (usually pyruvate)	EMP glycolysis (SLP) Fermentation	2 0
			Total	**2**

Microbial fermentation processes have been manipulated by humans and are used extensively in the production of various foods and other commercial products, including pharmaceuticals. Microbial fermentation can also be useful for identifying microbes for

diagnostic purposes.

Fermentation by some bacteria, like those in yogurt and other soured food products, and by animals in muscles during oxygen depletion, is lactic acid fermentation. The chemical reaction of lactic acid fermentation is as follows:

$$\text{Pyruvate} + \text{NADH} \leftrightarrow \text{lactic acid} + \text{NAD}^+ \tag{4.4.4.1}$$

Bacteria of several gram-positive genera, including *Lactobacillus*, *Leuconostoc*, and *Streptococcus*, are collectively known as the lactic acid bacteria (LAB), and various strains are important in food production. During yogurt and cheese production, the highly acidic environment generated by lactic acid fermentation denatures proteins contained in milk, causing it to solidify. When lactic acid is the only fermentation product, the process is said to be homolactic fermentation; such is the case for *Lactobacillus delbrueckii* and *S. thermophiles* used in yogurt production. However, many bacteria perform heterolactic fermentation, producing a mixture of lactic acid, ethanol and/or acetic acid, and CO_2 as a result, because of their use of the branched pentose phosphate pathway instead of the EMP pathway for glycolysis. One important heterolactic fermenter is *Leuconostoc mesenteroides*, which is used for souring vegetables like cucumbers and cabbage, producing pickles and sauerkraut, respectively.

Lactic acid bacteria are also important medically. The production of low pH environments within the body inhibits the establishment and growth of pathogens in these areas. For example, the vaginal microbiota is composed largely of lactic acid bacteria, but when these bacteria are reduced, yeast can proliferate, causing a yeast infection. Additionally, lactic acid bacteria are important in maintaining the health of the gastrointestinal tract and, as such, are the primary component of probiotics.

Another familiar fermentation process is alcohol fermentation, which produces ethanol. The ethanol fermentation reaction is shown in Figure 4.4.4.1. In the first reaction, the enzyme pyruvate decarboxylase removes a carboxyl group from pyruvate, releasing CO_2 gas while producing the two-carbon molecule acetaldehyde. The second reaction, catalyzed by the enzyme alcohol dehydrogenase, transfers an electron from NADH to acetaldehyde, producing ethanol and NAD^+. The ethanol fermentation of pyruvate by the yeast *Saccharomyces cerevisiae* is used in the production of alcoholic beverages and also makes bread products rise due to CO_2 production. Outside of the food industry, ethanol fermentation of plant products is important in biofuel production.

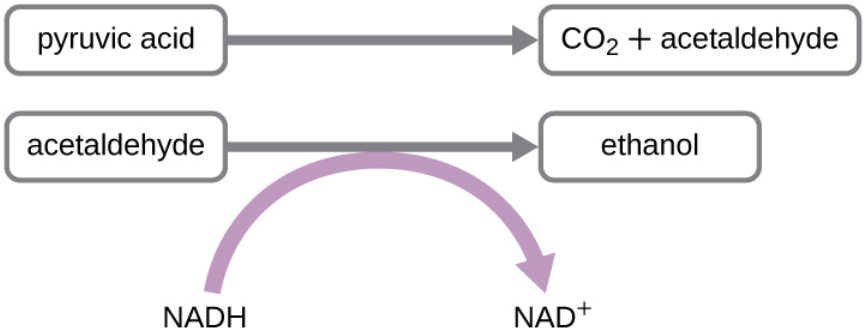


Figure 4.4.4.1: The chemical reactions of alcohol fermentation are shown here. Ethanol fermentation is important in the production of alcoholic beverages and bread.

Beyond lactic acid fermentation and alcohol fermentation, many other fermentation methods occur in prokaryotes, all for the purpose of ensuring an adequate supply of NAD^+ for glycolysis (Table 4.4.4.2). Without these pathways, glycolysis would not occur and no ATP would be harvested from the breakdown of glucose. It should be noted that most forms of fermentation besides homolactic fermentation produce gas, commonly CO_2 and/or hydrogen gas. Many of these different types of fermentation pathways are also used in food production and each results in the production of different organic acids, contributing to the unique flavor of a particular fermented food product. The propionic acid produced during propionic acid fermentation contributes to the distinctive flavor of Swiss cheese, for example.

Several fermentation products are important commercially outside of the food industry. For example, chemical solvents such as acetone and butanol are produced during acetone-butanol-ethanol fermentation. Complex organic pharmaceutical compounds used in antibiotics (e.g., penicillin), vaccines, and vitamins are produced through mixed acid fermentation. Fermentation products are used in the laboratory to differentiate various bacteria for diagnostic purposes. For example, enteric bacteria are known for their ability to perform mixed acid fermentation, reducing the pH, which can be detected using a pH indicator. Similarly, the bacterial production of acetoin during butanediol fermentation can also be detected. Gas production from fermentation can also be seen in an inverted Durham tube that traps produced gas in a broth culture.

Microbes can also be differentiated according to the substrates they can ferment. For example, *E. coli* can ferment lactose, forming gas, whereas some of its close gram-negative relatives cannot. The ability to ferment the sugar alcohol sorbitol is used to identify the pathogenic enterohemorrhagic O157:H7 strain of *E. coli* because, unlike other *E. coli* strains, it is unable to ferment sorbitol. Last, mannitol fermentation differentiates the mannitol-fermenting *Staphylococcus aureus* from other non–mannitol-fermenting staphylococci.

Table 4.4.4.2: Common Fermentation Pathways

Pathway	End Products	Example Microbes	Commercial Products
Acetone-butanol-ethanol	Acetone, butanol, ethanol, CO_2	*Clostridium acetobutylicum*	Commercial solvents, gasoline alternative
Alcohol	Ethanol, CO_2	*Candida*, *Saccharomyces*	Beer, bread
Butanediol	Formic and lactic acid; ethanol; acetoin; 2,3 butanediol; CO_2; hydrogen gas	*Klebsiella*, *Enterobacter*	Chardonnay wine
Butyric acid	Butyric acid, CO_2, hydrogen gas	*Clostridium butyricum*	Butter
Lactic acid	Lactic acid	*Streptococcus*, *Lactobacillus*	Sauerkraut, yogurt, cheese
Mixed acid	Acetic, formic, lactic, and succinic acids; ethanol, CO_2, hydrogen gas	*Escherichia*, *Shigella*	Vinegar, cosmetics, pharmaceuticals
Propionic acid	Acetic acid, propionic acid, CO_2	*Propionibacterium*, *Bifidobacterium*	Swiss cheese

? Exercise 4.4.4.1

When would a metabolically versatile microbe perform fermentation rather than cellular respiration?

Identifying Bacteria by Using API Test Panels

Identification of a microbial isolate is essential for the proper diagnosis and appropriate treatment of patients. Scientists have developed techniques that identify bacteria according to their biochemical characteristics. Typically, they either examine the use of specific carbon sources as substrates for fermentation or other metabolic reactions, or they identify fermentation products or specific enzymes present in reactions. In the past, microbiologists have used individual test tubes and plates to conduct biochemical testing. However, scientists, especially those in clinical laboratories, now more frequently use plastic, disposable, multitest panels that contain a number of miniature reaction tubes, each typically including a specific substrate and pH indicator. After inoculation of the test panel with a small sample of the microbe in question and incubation, scientists can compare the results to a database that includes the expected results for specific biochemical reactions for known microbes, thus enabling rapid identification of a sample microbe. These test panels have allowed scientists to reduce costs while improving efficiency and reproducibility by performing a larger number of tests simultaneously.

Many commercial, miniaturized biochemical test panels cover a number of clinically important groups of bacteria and yeasts. One of the earliest and most popular test panels is the Analytical Profile Index (API) panel invented in the 1970s. Once some basic laboratory characterization of a given strain has been performed, such as determining the strain's Gram morphology, an appropriate test strip that contains 10 to 20 different biochemical tests for differentiating strains within that microbial group can be used. Currently, the various API strips can be used to quickly and easily identify more than 600 species of bacteria, both aerobic and anaerobic, and approximately 100 different types of yeasts. Based on the colors of the reactions when metabolic end products are present, due to the presence of pH indicators, a metabolic profile is created from the results (Figure 4.4.4.2). Microbiologists can then compare the sample's profile to the database to identify the specific microbe.



Figure 4.4.4.2: The API 20NE test strip is used to identify specific strains of gram-negative bacteria outside the Enterobacteriaceae. Here is an API 20NE test strip result for *Photobacterium damselae* ssp. *piscicida*.

Clinical Focus: Part 2

Many of Hannah's symptoms are consistent with several different infections, including influenza and pneumonia. However, her sluggish reflexes along with her light sensitivity and stiff neck suggest some possible involvement of the central nervous system, perhaps indicating meningitis. Meningitis is an infection of the cerebrospinal fluid (CSF) around the brain and spinal cord that causes inflammation of the meninges, the protective layers covering the brain. Meningitis can be caused by viruses, bacteria, or fungi. Although all forms of meningitis are serious, bacterial meningitis is particularly serious. Bacterial meningitis may be caused by several different bacteria, but the bacterium *Neisseria meningitidis*, a gram-negative, bean-shaped diplococcus, is a common cause and leads to death within 1 to 2 days in 5% to 10% of patients.

Given the potential seriousness of Hannah's conditions, her physician advised her parents to take her to the hospital in the Gambian capital of Banjul and there have her tested and treated for possible meningitis. After a 3-hour drive to the hospital, Hannah was immediately admitted. Physicians took a blood sample and performed a lumbar puncture to test her CSF. They also immediately started her on a course of the antibiotic ceftriaxone, the drug of choice for treatment of meningitis caused by *N. meningitidis*, without waiting for laboratory test results.

Exercise 4.4.4.2

1. How might biochemical testing be used to confirm the identity of *N. meningitidis*?
2. Why did Hannah's doctors decide to administer antibiotics without waiting for the test results?

Key Concepts and Summary

- Fermentation uses an organic molecule as a final electron acceptor to regenerate NAD^+ from NADH so that glycolysis can continue.
- Fermentation does not involve an electron transport system, and no ATP is made by the fermentation process directly. Fermenters make very little ATP—only two ATP molecules per glucose molecule during glycolysis.
- Microbial fermentation processes have been used for the production of foods and pharmaceuticals, and for the identification of microbes.
- During lactic acid fermentation, pyruvate accepts electrons from NADH and is reduced to lactic acid. Microbes performing **homolactic fermentation** produce only lactic acid as the fermentation product; microbes performing **heterolactic fermentation** produce a mixture of lactic acid, ethanol and/or acetic acid, and CO_2.
- Lactic acid production by the normal microbiota prevents growth of pathogens in certain body regions and is important for the health of the gastrointestinal tract.
- During ethanol fermentation, pyruvate is first decarboxylated (releasing CO_2) to acetaldehyde, which then accepts electrons from NADH, reducing acetaldehyde to ethanol. Ethanol fermentation is used for the production of alcoholic beverages, for making bread products rise, and for biofuel production.
- Fermentation products of pathways (e.g., propionic acid fermentation) provide distinctive flavors to food products. Fermentation is used to produce chemical solvents (acetone-butanol-ethanol fermentation) and pharmaceuticals (mixed acid fermentation).
- Specific types of microbes may be distinguished by their fermentation pathways and products. Microbes may also be differentiated according to the substrates they are able to ferment.

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4.4.5: Catabolism of Lipids and Proteins

Learning Objectives

- Describe how lipids are catabolized
- Describe how lipid catabolism can be used to identify microbes
- Describe how proteins are catabolized
- Describe how protein catabolism can be used to identify bacteria

Previous sections have discussed the catabolism of glucose, which provides energy to living cells, as well as how polysaccharides like glycogen, starch, and cellulose are degraded to glucose monomers. But microbes consume more than just carbohydrates for food. In fact, the microbial world is known for its ability to degrade a wide range of molecules, both naturally occurring and those made by human processes, for use as carbon sources. In this section, we will see that the pathways for both lipid and protein catabolism connect to those used for carbohydrate catabolism, eventually leading into glycolysis, the transition reaction, and the Krebs cycle pathways. Metabolic pathways should be considered to be porous—that is, substances enter from other pathways, and intermediates leave for other pathways. These pathways are not closed systems. Many of the substrates, intermediates, and products in a particular pathway are reactants in other pathways.

Lipid Catabolism

Triglycerides are a form of long-term energy storage in animals. They are made of glycerol and three fatty acids (see Figure 7.3.1). Phospholipids compose the cell and organelle membranes of all organisms except the archaea. Phospholipid structure is similar to triglycerides except that one of the fatty acids is replaced by a phosphorylated head group (see Figure 7.3.2). Triglycerides and phospholipids are broken down first by releasing fatty acid chains (and/or the phosphorylated head group, in the case of phospholipids) from the three-carbon glycerol backbone. The reactions breaking down triglycerides are catalyzed by lipases and those involving phospholipids are catalyzed by phospholipases. These enzymes contribute to the virulence of certain microbes, such as the bacterium *Staphylococcus aureus* and the fungus *Cryptococcus neoformans*. These microbes use phospholipases to destroy lipids and phospholipids in host cells and then use the catabolic products for energy (see Virulence Factors of Bacterial and Viral Pathogens).

The resulting products of lipid catabolism, glycerol and fatty acids, can be further degraded. Glycerol can be phosphorylated to glycerol-3-phosphate and easily converted to glyceraldehyde 3-phosphate, which continues through glycolysis. The released fatty acids are catabolized in a process called β-oxidation, which sequentially removes two-carbon acetyl groups from the ends of fatty acid chains, reducing NAD^+ and FAD to produce NADH and $FADH_2$, respectively, whose electrons can be used to make ATP by oxidative phosphorylation. The acetyl groups produced during β-oxidation are carried by coenzyme A to the Krebs cycle, and their movement through this cycle results in their degradation to CO_2, producing ATP by substrate-level phosphorylation and additional NADH and $FADH_2$ molecules (see Appendix C for a detailed illustration of β-oxidation).

Other types of lipids can also be degraded by certain microbes. For example, the ability of certain pathogens, like *Mycobacterium tuberculosis*, to degrade cholesterol contributes to their virulence. The side chains of cholesterol can be easily removed enzymatically, but degradation of the remaining fused rings is more problematic. The four fused rings are sequentially broken in a multistep process facilitated by specific enzymes, and the resulting products, including pyruvate, can be further catabolized in the Krebs cycle.

Exercise 4.4.5.1

How can lipases and phospholipases contribute to virulence in microbes?

Protein Catabolism

Proteins are degraded through the concerted action of a variety of microbial protease enzymes. Extracellular proteases cut proteins internally at specific amino acid sequences, breaking them down into smaller peptides that can then be taken up by cells. Some clinically important pathogens can be identified by their ability to produce a specific type of extracellular protease. For example,

the production of the extracellular protease gelatinase by members of the genera *Proteus* and *Serratia* can be used to distinguish them from other gram-negative enteric bacteria. Following inoculation and growth of microbes in gelatin broth, degradation of the gelatin protein due to gelatinase production prevents solidification of gelatin when refrigerated. Other pathogens can be distinguished by their ability to degrade casein, the main protein found in milk. When grown on skim milk agar, production of the extracellular protease caseinase causes degradation of casein, which appears as a zone of clearing around the microbial growth. Caseinase production by the opportunist pathogen *Pseudomonas aeruginosa* can be used to distinguish it from other related gram-negative bacteria.

After extracellular protease degradation and uptake of peptides in the cell, the peptides can then be broken down further into individual amino acids by additional intracellular proteases, and each amino acid can be enzymatically deaminated to remove the amino group. The remaining molecules can then enter the transition reaction or the Krebs cycle.

? Exercise 4.4.5.2

How can protein catabolism help identify microbes?

Clinical Focus: Part 3

Because bacterial meningitis progresses so rapidly, Hannah's doctors had decided to treat her aggressively with antibiotics, based on empirical observation of her symptoms. However, laboratory testing to confirm the cause of Hannah's meningitis was still important for several reasons. *N. meningitidis* is an infectious pathogen that can be spread from person to person through close contact; therefore, if tests confirm *N. meningitidis* as the cause of Hannah's symptoms, Hannah's parents and others who came into close contact with her might need to be vaccinated or receive prophylactic antibiotics to lower their risk of contracting the disease. On the other hand, if it turns out that *N. meningitidis* is not the cause, Hannah's doctors might need to change her treatment.

The clinical laboratory performed a Gram stain on Hannah's blood and CSF samples. The Gram stain showed the presence of a bean-shaped gram-negative diplococcus. The technician in the hospital lab cultured Hannah's blood sample on both blood agar and chocolate agar, and the bacterium that grew on both media formed gray, nonhemolytic colonies. Next, he performed an oxidase test on this bacterium and determined that it was oxidase positive. Last, he examined the repertoire of sugars that the bacterium could use as a carbon source and found that the bacterium was positive for glucose and maltose use but negative for lactose and sucrose use. All of these test results are consistent with characteristics of *N. meningitidis*.

Exercise 4.4.5.3

1. What do these test results tell us about the metabolic pathways of *N. meningitidis*?
2. Why do you think that the hospital used these biochemical tests for identification in lieu of molecular analysis by DNA testing?

Key Concepts and Summary

- Collectively, microbes have the ability to degrade a wide variety of carbon sources besides carbohydrates, including lipids and proteins. The catabolic pathways for all of these molecules eventually connect into glycolysis and the Krebs cycle.
- Several types of lipids can be microbially degraded. Triglycerides are degraded by extracellular **lipases**, releasing fatty acids from the glycerol backbone. Phospholipids are degraded by **phospholipases**, releasing fatty acids and the phosphorylated head group from the glycerol backbone. Lipases and phospholipases act as virulence factors for certain pathogenic microbes.
- Fatty acids can be further degraded inside the cell through **β-oxidation**, which sequentially removes two-carbon acetyl groups from the ends of fatty acid chains.
- Protein degradation involves extracellular **proteases** that degrade large proteins into smaller peptides. Detection of the extracellular proteases gelatinase and caseinase can be used to differentiate clinically relevant bacteria.

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4.4.6: Photosynthesis and the Importance of Light

Learning Objectives

- Describe the function and locations of photosynthetic pigments in eukaryotes and prokaryotes
- Describe the major products of the light-dependent and light-independent reactions
- Describe the reactions that produce glucose in a photosynthetic cell
- Compare and contrast cyclic and noncyclic photophosphorylation

Heterotrophic organisms ranging from *E. coli* to humans rely on the chemical energy found mainly in carbohydrate molecules. Many of these carbohydrates are produced by photosynthesis, the biochemical process by which phototrophic organisms convert solar energy (sunlight) into chemical energy. Although photosynthesis is most commonly associated with plants, microbial photosynthesis is also a significant supplier of chemical energy, fueling many diverse ecosystems. In this section, we will focus on microbial photosynthesis.

Photosynthesis takes place in two sequential stages: the light-dependent reactions and the light-independent reactions (Figure 4.4.6.1). In the light-dependent reactions, energy from sunlight is absorbed by pigment molecules in photosynthetic membranes and converted into stored chemical energy. In the light-independent reactions, the chemical ener gy produced by the light-dependent reactions is used to drive the assembly of sugar molecules using CO_2; however, these reactions are still light dependent because the products of the light-dependent reactions necessary for driving them are short-lived. The light-dependent reactions produce ATP and either NADPH or NADH to temporarily store energy. These energy carriers are used in the light-independent reactions to drive the energetically unfavorable process of "fixing" inorganic CO_2 in an organic form, sugar.

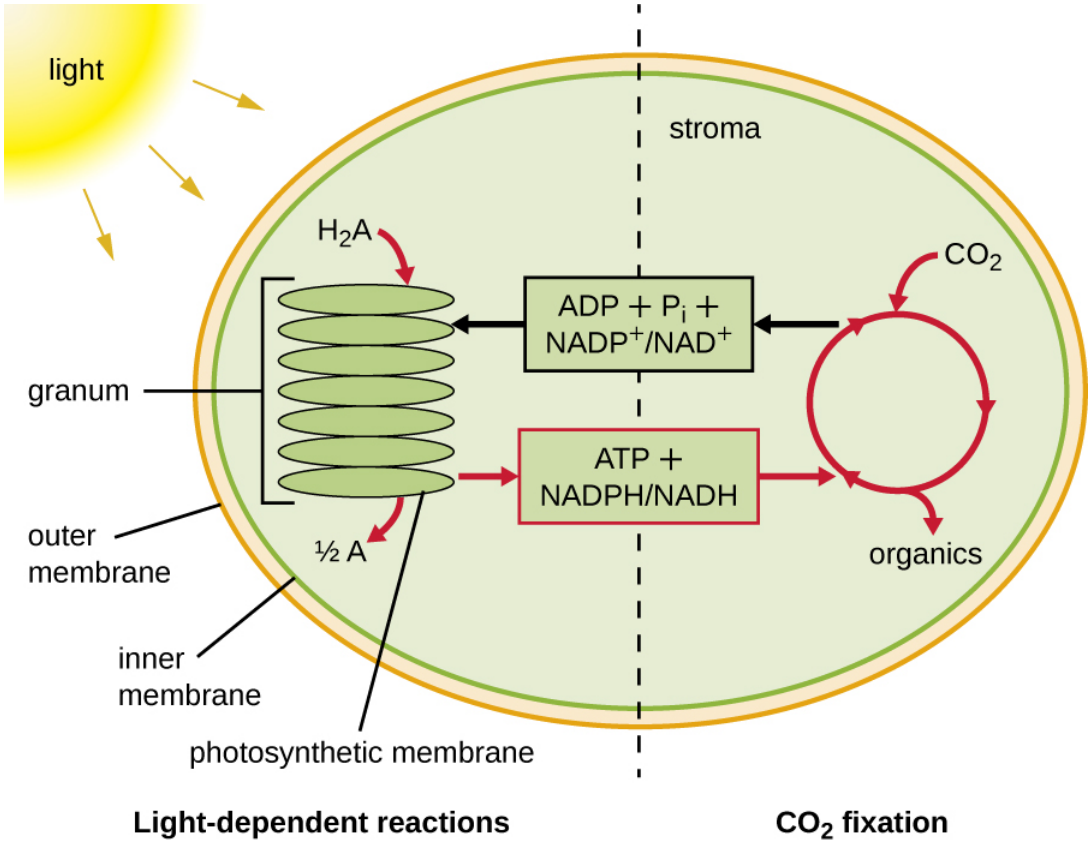


Figure 4.4.6.1: The light-dependent reactions of photosynthesis (left) convert light energy into chemical energy, forming ATP and NADPH. These products are used by the light-independent reactions to fix CO_2, producing organic carbon molecules.

Photosynthetic Structures in Eukaryotes and Prokaryotes

In all phototrophic eukaryotes, photosynthesis takes place inside a chloroplast, an organelle that arose in eukaryotes by endosymbiosis of a photosynthetic bacterium (see Unique Characteristics of Eukaryotic Cells). These chloroplasts are enclosed by a double membrane with inner and outer layers. Within the chloroplast is a third membrane that forms stacked, disc-shaped photosynthetic structures called thylakoids (Figure 4.4.6.2). A stack of thylakoids is called a granum, and the space surrounding the granum within the chloroplast is called stroma.

Photosynthetic membranes in prokaryotes, by contrast, are not organized into distinct membrane-enclosed organelles; rather, they are infolded regions of the plasma membrane. In cyanobacteria, for example, these infolded regions are also referred to as thylakoids. In either case, embedded within the thylakoid membranes or other photosynthetic bacterial membranes are photosynthetic pigment molecules organized into one or more photosystems, where light energy is actually converted into chemical energy.

Photosynthetic pigments within the photosynthetic membranes are organized into photosystems, each of which is composed of a light-harvesting (antennae) complex and a reaction center. The light-harvesting complex consists of multiple proteins and associated pigments that each may absorb light energy and, thus, become excited. This energy is transferred from one pigment molecule to another until eventually (after about a millionth of a second) it is delivered to the reaction center. Up to this point, only energy—not electrons—has been transferred between molecules. The reaction center contains a pigment molecule that can undergo oxidation upon excitation, actually giving up an electron. It is at this step in photosynthesis that light energy is converted into an excited electron.

Different kinds of light-harvesting pigments absorb unique patterns of wavelengths (colors) of visible light. Pigments reflect or transmit the wavelengths they cannot absorb, making them appear the corresponding color. Examples of photosynthetic pigments (molecules used to absorb solar energy) are bacteriochlorophylls (green, purple, or red), carotenoids (orange, red, or yellow), chlorophylls (green), phycocyanins (blue), and phycoerythrins (red). By having mixtures of pigments, an organism can absorb energy from more wavelengths. Because photosynthetic bacteria commonly grow in competition for sunlight, each type of photosynthetic bacteria is optimized for harvesting the wavelengths of light to which it is commonly exposed, leading to stratification of microbial communities in aquatic and soil ecosystems by light quality and penetration.

Once the light harvesting complex transfers the energy to the reaction center, the reaction center delivers its high-energy electrons, one by one, to an electron carrier in an electron transport system, and electron transfer through the ETS is initiated. The ETS is similar to that used in cellular respiration and is embedded within the photosynthetic membrane. Ultimately, the electron is used to produce NADH or NADPH. The electrochemical gradient that forms across the photosynthetic membrane is used to generate ATP by chemiosmosis through the process of photophosphorylation, another example of oxidative phosphorylation (Figure 4.4.6.3).

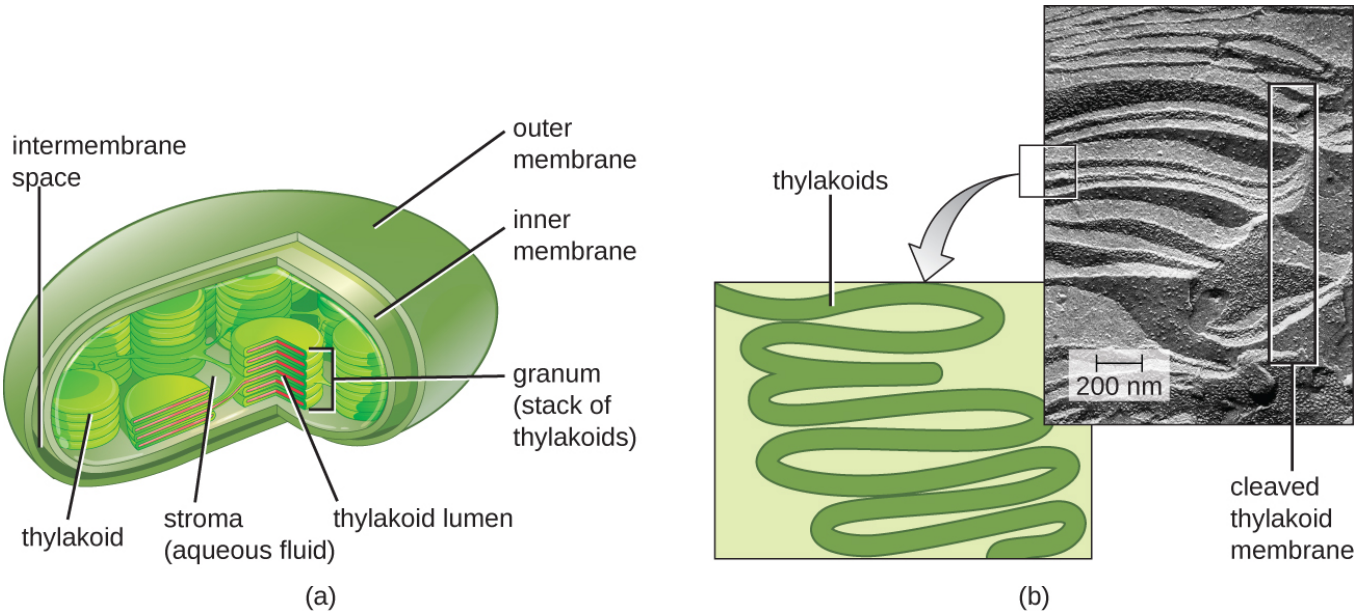


Figure 4.4.6.2: (a) Photosynthesis in eukaryotes takes place in chloroplasts, which contain thylakoids stacked into grana. (b) A photosynthetic prokaryote has infolded regions of the plasma membrane that function like thylakoids. (credit: scale bar data from Matt Russell.)

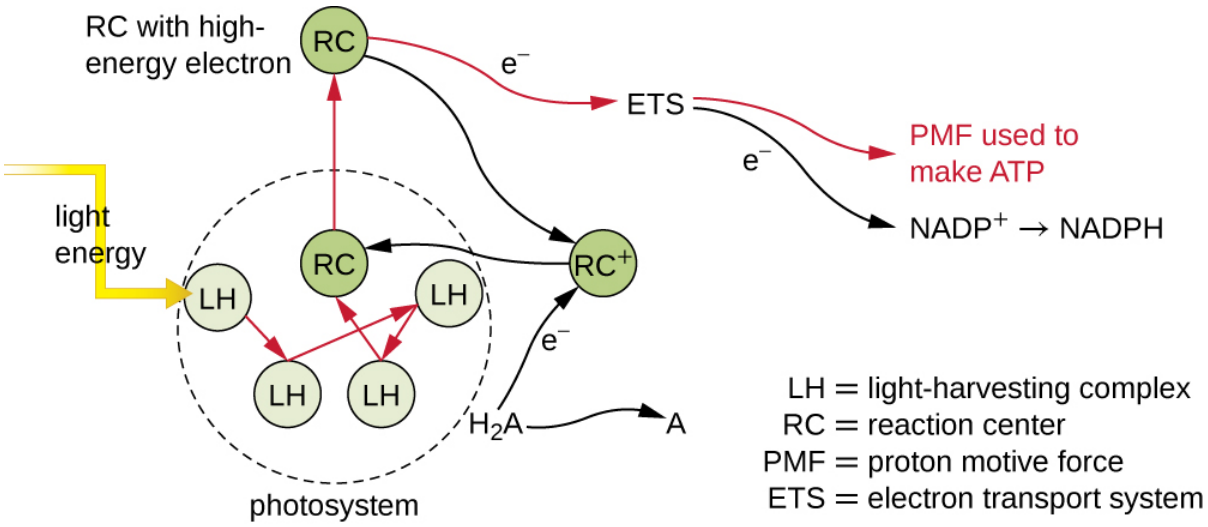


Figure 4.4.6.3: This figure summarizes how a photosystem works. Light harvesting (LH) pigments absorb light energy, converting it to chemical energy. The energy is passed from one LH pigment to another until it reaches a reaction center (RC) pigment, exciting an electron. This high-energy electron is lost from the RC pigment and passed through an electron transport system (ETS), ultimately producing NADH or NADPH and ATP. A reduced molecule (H_2A) donates an electron, replacing electrons to the electron-deficient RC pigment.

? Exercise 4.4.6.1

In a phototrophic eukaryote, where does photosynthesis take place?

Oxygenic and Anoxygenic Photosynthesis

For photosynthesis to continue, the electron lost from the reaction center pigment must be replaced. The source of this electron (H_2A) differentiates the oxygenic photosynthesis of plants and cyanobacteria from anoxygenic photosynthesis carried out by other types of bacterial phototrophs (Figure 4.4.6.4). In oxygenic photosynthesis, H_2O is split and supplies the electron to the reaction center. Because oxygen is generated as a byproduct and is released, this type of photosynthesis is referred to as oxygenic photosynthesis. However, when other reduced compounds serve as the electron donor, oxygen is not generated; these types of

photosynthesis are called anoxygenic photosynthesis. Hydrogen sulfide (H_2S) or thiosulfate $(S_2O_3^{2-})$ can serve as the electron donor, generating elemental sulfur and sulfate (SO_4^{2-}) ions, respectively, as a result.

Photosystems have been classified into two types: photosystem I (PSI) and photosystem II (PSII) (Figure 4.4.6.5). Cyanobacteria and plant chloroplasts have both photosystems, whereas anoxygenic photosynthetic bacteria use only one of the photosystems. Both photosystems are excited by light energy simultaneously. If the cell requires both ATP and NADPH for biosynthesis, then it will carry out noncyclic photophosphorylation. Upon passing of the PSII reaction center electron to the ETS that connects PSII and PSI, the lost electron from the PSII reaction center is replaced by the splitting of water. The excited PSI reaction center electron is used to reduce $NADP^+$ to NADPH and is replaced by the electron exiting the ETS. The flow of electrons in this way is called the Z-scheme.

If a cell's need for ATP is significantly greater than its need for NADPH, it may bypass the production of reducing power through cyclic photophosphorylation. Only PSI is used during cyclic photophosphorylation; the high-energy electron of the PSI reaction center is passed to an ETS carrier and then ultimately returns to the oxidized PSI reaction center pigment, thereby reducing it.

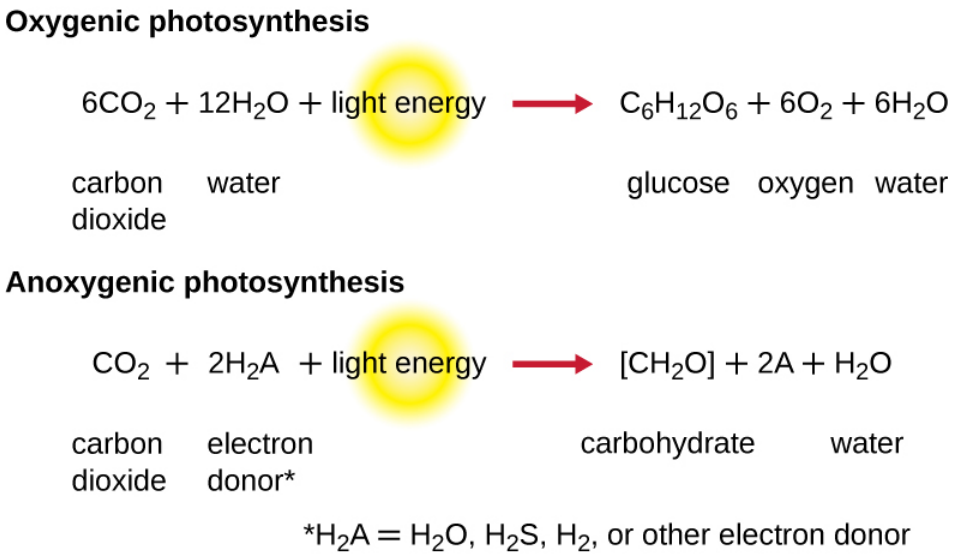
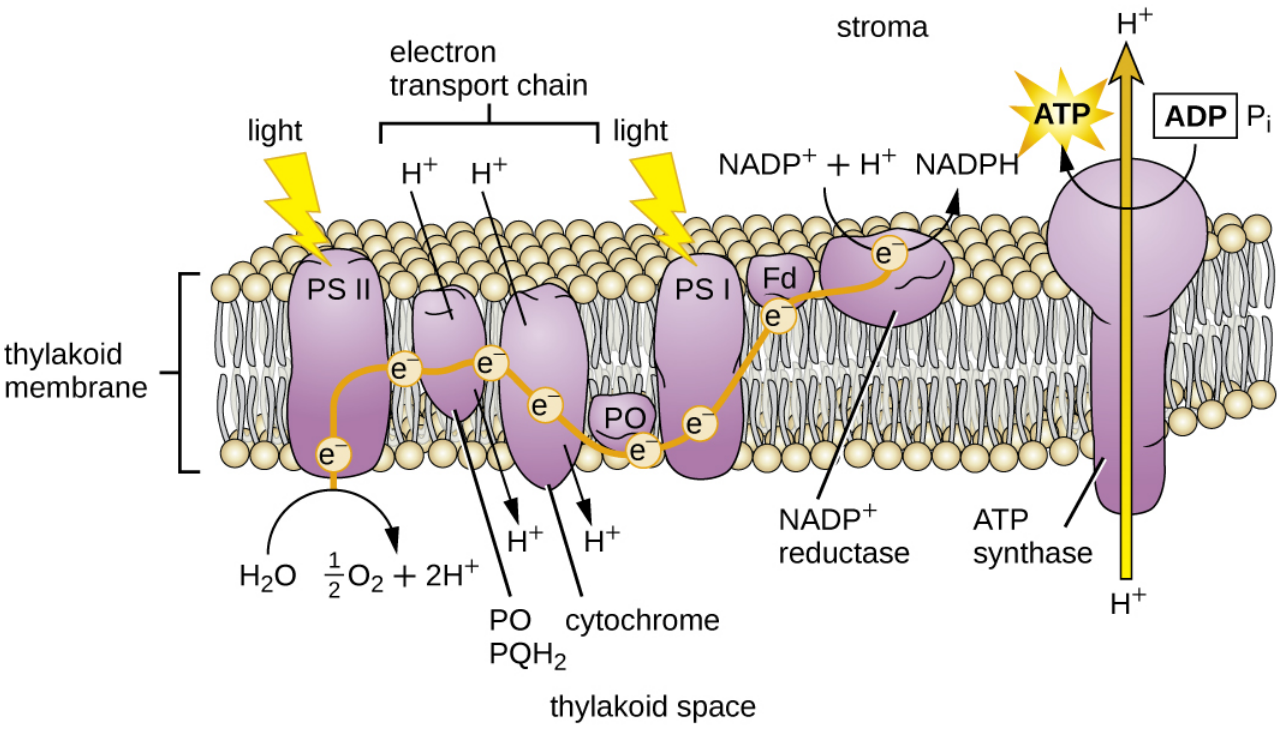
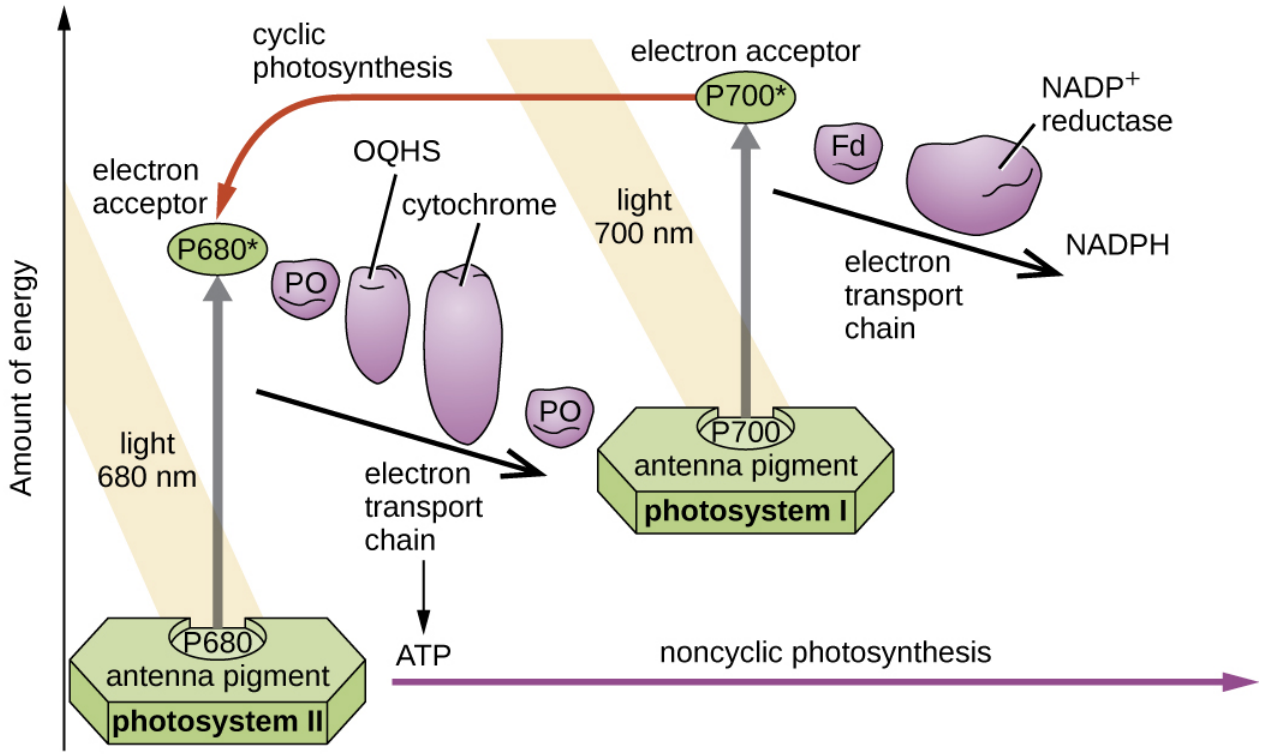


Figure 4.4.6.4: Eukaryotes and cyanobacteria carry out oxygenic photosynthesis, producing oxygen, whereas other bacteria carry out anoxygenic photosynthesis, which does not produce oxygen.


stroma
H+
electron
transport chain
light
light
ATP
ADP
Pi
H+ H+
NADP+ + H+
NADPH
PS II
PS I
Fd
e−
thylakoid
membrane
PO
H2O
½O2 + 2H+
H+
H+
NADP+
reductase
ATP
synthase
H+
PO
PQH2
cytochrome
thylakoid space

(a)


cyclic
photosynthesis
electron acceptor
P700*
NADP+
reductase
Fd
OQHS
electron
acceptor
cytochrome
light
700 nm
P680*
PO
NADPH
electron
transport
chain
Amount of energy
PO
light
680 nm
P700
antenna pigment
photosystem I
electron
transport
chain
P680
antenna pigment
photosystem II
ATP
noncyclic photosynthesis

(b)

Figure 4.4.6.5: (a) PSI and PSII are found on the thylakoid membrane. The high-energy electron from PSII is passed to an ETS, which generates a proton motive force for ATP synthesis by chemiosmosis, and ultimately replaces the electron lost by the PSI reaction center. The PSI reaction center electron is used to make NADPH. (b) When both ATP and NADPH are required, noncyclic photophosphorylation (in cyanobacteria and plants) provides both. The electron flow described here is referred to as the Z-scheme (shown in yellow in [a]). When the cell's ATP needs outweigh those for NADPH, cyanobacteria and plants will use only PSI, and its reaction center electron is passed to the ETS to generate a proton motive force used for ATP synthesis.

? Exercise 4.4.6.2

Why would a photosynthetic bacterium have different pigments?

Light-Independent Reactions

After the energy from the sun is converted into chemical energy and temporarily stored in ATP and NADPH molecules (having lifespans of millionths of a second), photoautotrophs have the fuel needed to build multicarbon carbohydrate molecules, which can survive for hundreds of millions of years, for long-term energy storage. The carbon comes from CO_2, the gas that is a waste product of cellular respiration.

The Calvin-Benson cycle (named for Melvin Calvin [1911–1997] and Andrew Benson [1917–2015]), the biochemical pathway used for fixation of CO_2, is located within the cytoplasm of photosynthetic bacteria and in the stroma of eukaryotic chloroplasts. The light-independent reactions of the Calvin cycle can be organized into three basic stages: fixation, reduction, and regeneration (see Appendix C for a detailed illustration of the Calvin cycle).

- **Fixation**: The enzyme ribulose bisphosphate carboxylase (RuBisCO) catalyzes the addition of a CO_2 to ribulose bisphosphate (RuBP). This results in the production of 3-phosphoglycerate (3-PGA).
- **Reduction**: Six molecules of both ATP and NADPH (from the light-dependent reactions) are used to convert 3-PGA into glyceraldehyde 3-phosphate (G3P). Some G3P is then used to build glucose.
- **Regeneration**: The remaining G3P not used to synthesize glucose is used to regenerate RuBP, enabling the system to continue CO_2 fixation. Three more molecules of ATP are used in these regeneration reactions.

The Calvin cycle is used extensively by plants and photoautotrophic bacteria, and the enzyme RuBisCO is said to be the most plentiful enzyme on earth, composing 30%–50% of the total soluble protein in plant chloroplasts.[1] However, besides its prevalent use in photoautotrophs, the Calvin cycle is also used by many nonphotosynthetic chemoautotrophs to fix CO_2. Additionally, other bacteria and archaea use alternative systems for CO_2 fixation. Although most bacteria using Calvin cycle alternatives are chemoautotrophic, certain green sulfur photoautotrophic bacteria have been also shown to use an alternative CO_2 fixation pathway.

? Exercise 4.4.6.3

Describe the three stages of the Calvin cycle.

Key Concepts and Summary

- Heterotrophs depend on the carbohydrates produced by autotrophs, many of which are photosynthetic, converting solar energy into chemical energy.
- Different photosynthetic organisms use different mixtures of **photosynthetic pigments**, which increase the range of the wavelengths of light an organism can absorb.
- **Photosystems** (PSI and PSII) each contain a **light-harvesting complex**, composed of multiple proteins and associated pigments that absorb light energy. The **light-dependent reactions** of photosynthesis convert solar energy into chemical energy, producing ATP and NADPH or NADH to temporarily store this energy.
- In **oxygenic photosynthesis**, H_2O serves as the electron donor to replace the reaction center electron, and oxygen is formed as a byproduct. In **anoxygenic photosynthesis**, other reduced molecules like H_2S or thiosulfate may be used as the electron donor; as such, oxygen is not formed as a byproduct.
- **Noncyclic photophosphorylation** is used in oxygenic photosynthesis when there is a need for both ATP and NADPH production. If a cell's needs for ATP outweigh its needs for NADPH, then it may carry out **cyclic photophosphorylation** instead, producing only ATP.

- The **light-independent reactions** of photosynthesis use the ATP and NADPH from the light-dependent reactions to fix CO_2 into organic sugar molecules.

Footnotes

1. 1 A. Dhingra et al. “Enhanced Translation of a Chloroplast-Expressed *Rbc*S Gene Restores Small Subunit Levels and Photosynthesis in Nuclear *Rbc*S Antisense Plants.” *Proceedings of the National Academy of Sciences of the United States of America* 101 no. 16 (2004):6315–6320.

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4.4.7: Biogeochemical Cycles

Learning Objectives

- Define and describe the importance of microorganisms in the biogeochemical cycles of carbon, nitrogen, and sulfur
- Define and give an example of bioremediation

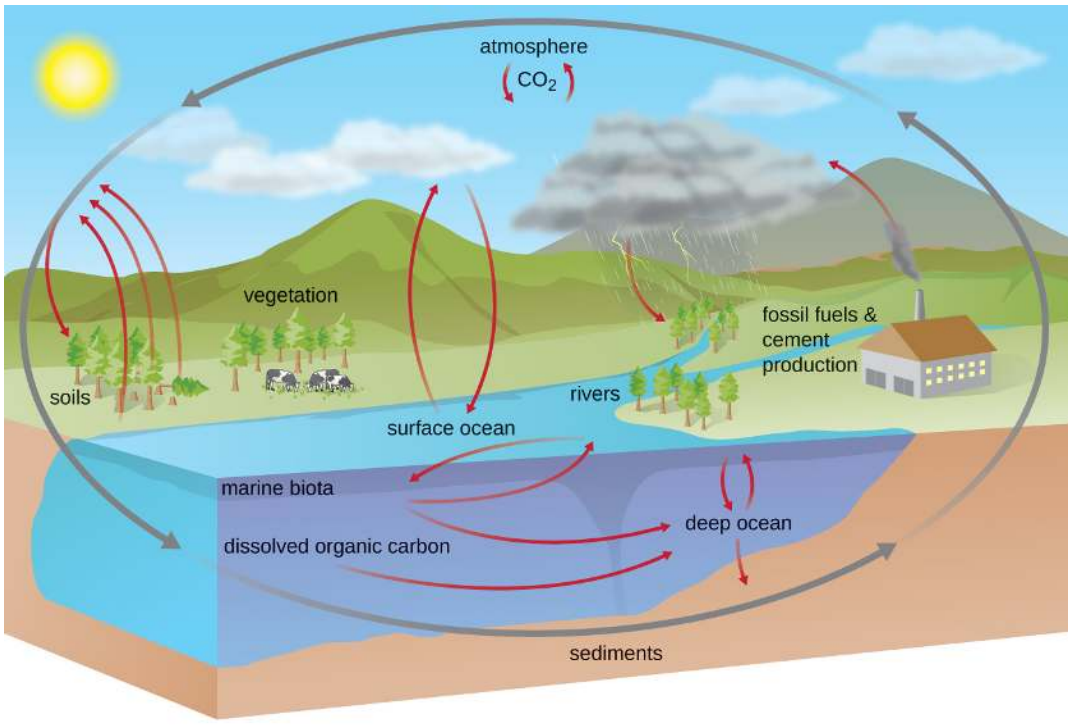
Energy flows directionally through ecosystems, entering as sunlight for phototrophs or as inorganic molecules for chemoautotrophs. The six most common elements associated with organic molecules—carbon, hydrogen, nitrogen, oxygen, phosphorus, and sulfur—take a variety of chemical forms and may exist for long periods in the atmosphere, on land, in water, or beneath earth's surface. Geologic processes, such as erosion, water drainage, the movement of the continental plates, and weathering, all are involved in the cycling of elements on earth. Because geology and chemistry have major roles in the study of this process, the recycling of inorganic matter between living organisms and their nonliving environment is called a biogeochemical cycle. Here, we will focus on the function of microorganisms in these cycles, which play roles at each step, most frequently interconverting oxidized versions of molecules with reduced ones.

Carbon Cycle

Carbon is one of the most important elements to living organisms, as shown by its abundance and presence in all organic molecules. The carbon cycle exemplifies the connection between organisms in various ecosystems. Carbon is exchanged between heterotrophs and autotrophs within and between ecosystems primarily by way of atmospheric CO_2, a fully oxidized version of carbon that serves as the basic building block that autotrophs use to build multicarbon, high-energy organic molecules such as glucose. Photoautotrophs and chemoautotrophs harness energy from the sun and from inorganic chemical compounds, respectively, to covalently bond carbon atoms together into reduced organic compounds whose energy can be later accessed through the processes of respiration and fermentation (Figure 4.4.7.1).

Overall, there is a constant exchange of CO_2 between the heterotrophs (which produce CO_2 as a result of respiration or fermentation) and the autotrophs (which use the CO_2 for fixation). Autotrophs also respire or ferment, consuming the organic molecules they form; they do not fix carbon for heterotrophs, but rather use it for their own metabolic needs.

Bacteria and archaea that use methane as their carbon source are called methanotrophs. Reduced one-carbon compounds like methane accumulate in certain anaerobic environments when CO_2 is used as a terminal electron acceptor in anaerobic respiration by archaea called methanogens. Some methanogens also ferment acetate (carbons) to produce methane and CO_2. Methane accumulation due to methanogenesis occurs in both natural anaerobic soil and aquatic environments; methane accumulation also occurs as a result of animal husbandry because methanogens are members of the normal microbiota of ruminants. Environmental methane accumulation due to methanogenesis is of consequence because it is a strong greenhouse gas, and methanotrophs help to reduce atmospheric methane levels.



Carbon cycle

Figure 4.4.7.1: This figure summarizes the carbon cycle. Eukaryotes participate in aerobic respiration, fermentation, and oxygenic photosynthesis. Prokaryotes participate in all the steps shown. (credit: modification of work by NOAA)

? Exercise 4.4.7.1

Describe the interaction between heterotrophs and autotrophs in the carbon cycle.

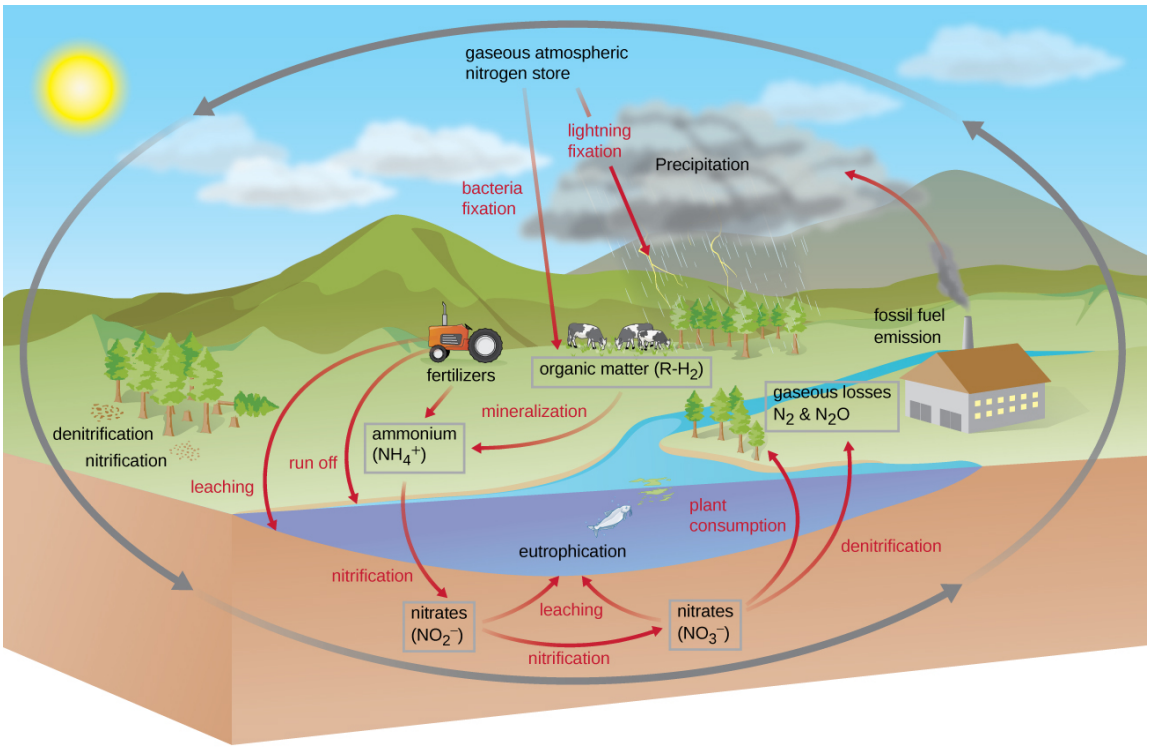
Nitrogen Cycle

Many biological macromolecules, including proteins and nucleic acids, contain nitrogen; however, getting nitrogen into living organisms is difficult. Prokaryotes play essential roles in the nitrogen cycle (Figure 4.4.7.2), transforming nitrogen between various forms for their own needs, benefiting other organisms indirectly. Plants and phytoplankton cannot incorporate nitrogen from the atmosphere (where it exists as tightly bonded, triple covalent N_2), even though this molecule composes approximately 78% of the atmosphere. Nitrogen enters the living world through free-living and symbiotic bacteria, which incorporate nitrogen into their macromolecules through specialized biochemical pathways called nitrogen fixation. Cyanobacteria in aquatic ecosystems fix inorganic nitrogen (from nitrogen gas) into ammonia (NH_3) that can be easily incorporated into biological macromolecules. *Rhizobium* bacteria (Figure 8.1) also fix nitrogen and live symbiotically in the root nodules of legumes (such as beans, peanuts, and peas), providing them with needed organic nitrogen while receiving fixed carbon as sugar in exchange. Free-living bacteria, such as members of the genus *Azotobacter*, are also able to fix nitrogen.

The nitrogen that enters living systems by nitrogen fixation is eventually converted from organic nitrogen back into nitrogen gas by microbes through three steps: ammonification, nitrification, and denitrification. In terrestrial systems, the first step is the ammonification process, in which certain bacteria and fungi convert nitrogenous waste from living animals or from the remains of dead organisms into ammonia (NH_3). This ammonia is then oxidized to nitrite (NO_2^-), then to nitrate (NO_3^-), by nitrifying soil bacteria such as members of the genus *Nitrosomonas*, through the process of nitrification. Last, the process of denitrification occurs, whereby soil bacteria, such as members of the genera *Pseudomonas* and *Clostridium*, use nitrate as a terminal electron acceptor in anaerobic respiration, converting it into nitrogen gas that reenters the atmosphere. A similar process occurs in the marine nitrogen cycle, where these three processes are performed by marine bacteria and archaea.

Human activity releases nitrogen into the environment by the use of artificial fertilizers that contain nitrogen and phosphorus compounds, which are then washed into lakes, rivers, and streams by surface runoff. A major effect from fertilizer runoff is

saltwater and freshwater eutrophication, in which nutrient runoff causes the overgrowth and subsequent death of aquatic algae, making water sources anaerobic and inhospitable for the survival of aquatic organisms.



Nitrogen cycle

Figure 4.4.7.2: This figure summarizes the nitrogen cycle. Note that specific groups of prokaryotes each participate in every step in the cycle. (credit: modification of work by NOAA)

? Exercise 4.4.7.2

What are the three steps of the nitrogen cycle?

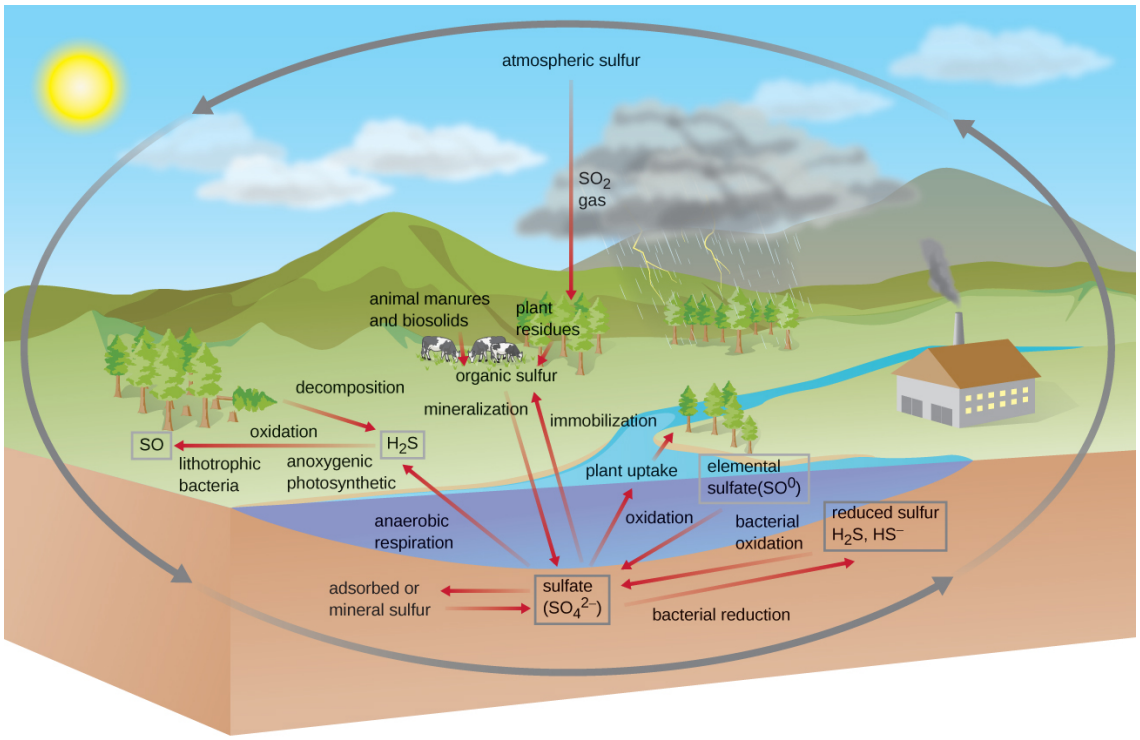
Link to Learning

To learn more about the nitrogen cycle, visit the PBS website.

Sulfur Cycle

Sulfur is an essential element for the macromolecules of living organisms. As part of the amino acids cysteine and methionine, it is involved in the formation of proteins. It is also found in several vitamins necessary for the synthesis of important biological molecules like coenzyme A. Several groups of microbes are responsible for carrying out processes involved in the sulfur cycle (Figure 4.4.7.3). Anoxygenic photosynthetic bacteria as well as chemoautotrophic archaea and bacteria use hydrogen sulfide as an electron donor, oxidizing it first to elemental sulfur (S^0), then to sulfate (SO_4^{2-}).This leads to stratification of hydrogen sulfide in soil, with levels increasing at deeper, more anaerobic depths.

Many bacteria and plants can use sulfate as a sulfur source. Decomposition dead organisms by fungi and bacteria remove sulfur groups from amino acids, producing hydrogen sulfide, returning inorganic sulfur to the environment.



Sulfur cycle

Figure 4.4.7.3: This figure summarizes the sulfur cycle. Note that specific groups of prokaryotes each may participate in every step in the cycle. (credit: modification of work by NOAA)

? Exercise 4.4.7.3

Which groups of microbes carry out the sulfur cycle?

Other Biogeochemical Cycles

Beyond their involvement in the carbon, nitrogen, and sulfur cycles, prokaryotes are involved in other biogeochemical cycles as well. Like the carbon, nitrogen, and sulfur cycles, several of these additional biogeochemical cycles, such as the iron (Fe), manganese (Mn), and chromium (Cr) cycles, also involve redox chemistry, with prokaryotes playing roles in both oxidation and reduction. Several other elements undergo chemical cycles that do not involve redox chemistry. Examples of these are phosphorus (P), calcium (Ca), and silica (Si) cycles. The cycling of these elements is particularly important in oceans because large quantities of these elements are incorporated into the exoskeletons of marine organisms. These biogeochemical cycles do not involve redox chemistry but instead involve fluctuations in the solubility of compounds containing calcium, phosphorous, and silica. The overgrowth of naturally occurring microbial communities is typically limited by the availability of nitrogen (as previously mentioned), phosphorus, and iron. Human activities introducing excessive amounts of iron, nitrogen, or phosphorus (typically from detergents) may lead to eutrophication.

Bioremediation

Microbial bioremediation leverages microbial metabolism to remove xenobiotics or other pollutants. Xenobiotics are compounds synthesized by humans and introduced into the environment in much higher concentrations than would naturally occur. Such environmental contamination may involve adhesives, dyes, flame retardants, lubricants, oil and petroleum products, organic solvents, pesticides, and products of the combustion of gasoline and oil. Many xenobiotics resist breakdown, and some accumulate in the food chain after being consumed or absorbed by fish and wildlife, which, in turn, may be eaten by humans. Of particular concern are contaminants like polycyclic aromatic hydrocarbon (PAH), a carcinogenic xenobiotic found in crude oil, and trichloroethylene (TCE), a common groundwater contaminant.

Bioremediation processes can be categorized as in situ or ex situ. Bioremediation conducted at the site of contamination is called in situ bioremediation and does not involve movement of contaminated material. In contrast, ex situ bioremediation involves the removal of contaminated material from the original site so that it can be treated elsewhere, typically in a large, lined pit where conditions are optimized for degradation of the contaminant.

Some bioremediation processes rely on microorganisms that are indigenous to the contaminated site or material. Enhanced bioremediation techniques, which may be applied to either in situ or ex situ processing, involve the addition of nutrients and/or air to encourage the growth of pollution-degrading microbes; they may also involve the addition of non-native microbes known for their ability to degrade contaminants. For example, certain bacteria of the genera *Rhodococcus* and *Pseudomonas* are known for their ability to degrade many environmental contaminants, including aromatic compounds like those found in oil, down to CO_2. The genes encoding their degradatory enzymes are commonly found on plasmids. Others, like *Alcanivorax borkumensis*, produce surfactants that are useful in the solubilization of the hydrophobic molecules found in oil, making them more accessible to other microbes for degradation.

? Exercise 4.4.7.4

Compare and contrast the benefits of in situ and ex situ bioremediation.

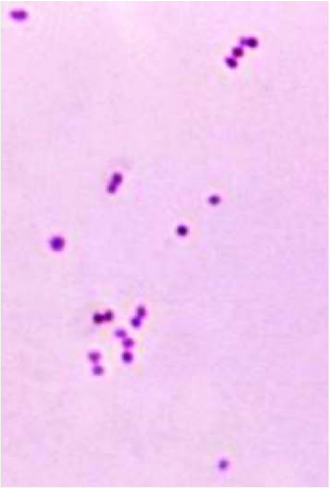
Clinical Focus: Resolution

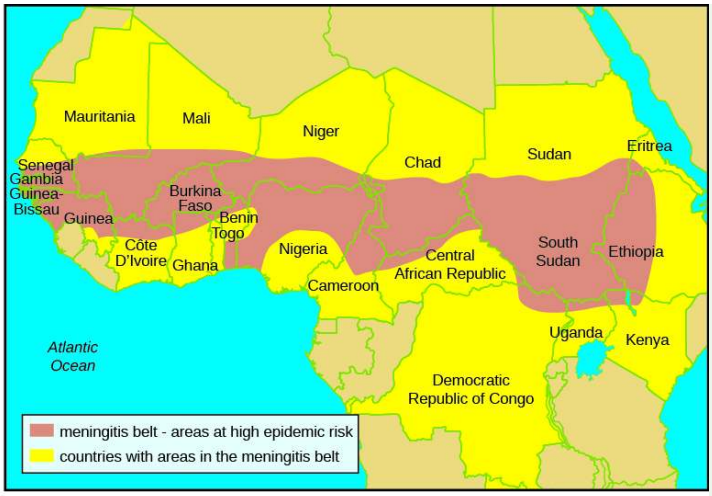
Although there is a DNA test specific for *Neisseria meningitidis*, it is not practical for use in some developing countries because it requires expensive equipment and a high level of expertise to perform. The hospital in Banjul was not equipped to perform DNA testing. Biochemical testing, however, is much less expensive and is still effective for microbial identification.

Fortunately for Hannah, her symptoms began to resolve with antibiotic therapy. Patients who survive bacterial meningitis often suffer from long-term complications such as brain damage, hearing loss, and seizures, but after several weeks of recovery, Hannah did not seem to be exhibiting any long-term effects and her behavior returned to normal. Because of her age, her parents were advised to monitor her closely for any signs of developmental issues and have her regularly evaluated by her pediatrician.

N. meningitidis is found in the normal respiratory microbiota in 10%–20% of the human population.[1] In most cases, it does not cause disease, but for reasons not fully understood, the bacterium can sometimes invade the bloodstream and cause infections in other areas of the body, including the brain. The disease is more common in infants and children, like Hannah.

The prevalence of meningitis caused by *N. meningitidis* is particularly high in the so-called meningitis belt, a region of sub-Saharan African that includes 26 countries stretching from Senegal to Ethiopia (Figure 4.4.7.4). The reasons for this high prevalence are not clear, but several factors may contribute to higher rates of transmission, such as the dry, dusty climate; overcrowding and low standards of living; and the relatively low immunocompetence and nutritional status of the population.[2] A vaccine against four bacterial strains of *N. meningitidis* is available. Vaccination is recommended for 11- and 12-year-old children, with a booster at age 16 years. Vaccination is also recommended for young people who live in close quarters with others (e.g., college dormitories, military barracks), where the disease is more easily transmitted. Travelers visiting the "meningitis belt" should also be vaccinated, especially during the dry season (December through June) when the prevalence is highest.[3,4]





(a) (b)

Figure 4.4.7.4: (a) *Neisseria meningitidis* is a gram-negative diplococcus, as shown in this gram-stained sample. (b) The "meningitis belt" is the area of sub-Saharan Africa with high prevalence of meningitis caused by *N. meningitidis*. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Key Concepts and Summary

- The recycling of inorganic matter between living organisms and their nonliving environment is called a **biogeochemical cycle**. Microbes play significant roles in these cycles.
- In the **carbon cycle**, heterotrophs degrade reduced organic molecule to produce carbon dioxide, whereas autotrophs fix carbon dioxide to produce organics. **Methanogens** typically form methane by using CO_2 as a final electron acceptor during anaerobic respiration; methanotrophs oxidize the methane, using it as their carbon source.
- In the **nitrogen cycle**, nitrogen-fixing bacteria convert atmospheric nitrogen into ammonia (ammonification). The ammonia can then be oxidized to nitrite and nitrate (nitrification). Nitrates can then be assimilated by plants. Soil bacteria convert nitrate back to nitrogen gas (denitrification).
- In **sulfur cycling**, many anoxygenic photosynthesizers and chemoautotrophs use hydrogen sulfide as an electron donor, producing elemental sulfur and then sulfate; sulfate-reducing bacteria and archaea then use sulfate as a final electron acceptor in anaerobic respiration, converting it back to hydrogen sulfide.
- Human activities that introduce excessive amounts of naturally limited nutrients (like iron, nitrogen, or phosphorus) to aquatic systems may lead to eutrophication.
- Microbial **bioremediation** is the use of microbial metabolism to remove or degrade **xenobiotics** and other environmental contaminants and pollutants. Enhanced bioremediation techniques may involve the introduction of non-native microbes specifically chosen or engineered for their ability to degrade contaminants.

Footnotes

1. 1 Centers for Disease Control and Prevention. "Meningococcal Disease: Causes and Transmission." www.cdc.gov/meningococcal/abo...nsmission.html. Accessed September 12, 2016.
2. 2 Centers for Disease Control and Prevention. "Meningococcal Disease in Other Countries." http://www.cdc.gov/meningococcal/global.html. Accessed September 12, 2016.
3. 3 Centers for Disease Control and Prevention. "Health Information for Travelers to the Gambia: Traveler View." wwwnc.cdc.gov/travel/destinat...one/the-gambia. Accessed September 12, 2016.
4. 4 Centers for Disease Control and Prevention. "Meningococcal: Who Needs to Be Vaccinated?" www.cdc.gov/vaccines/vpd-vac/...-vaccinate.htm. Accessed September 12, 2016.

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4.4.E: Microbial Metabolism (Exercises)

8.1: Energy, Matter, and Enzymes

Cellular processes such as the building or breaking down of complex molecules occur through series of stepwise, interconnected chemical reactions called metabolic pathways. The term anabolism refers to those endergonic metabolic pathways involved in biosynthesis, converting simple molecular building blocks into more complex molecules, and fueled by the use of cellular energy.

Multiple Choice

Which of the following is an organism that obtains its energy from the transfer of electrons originating from chemical compounds and its carbon from an inorganic source?

A. chemoautotroph
B. chemoheterotroph
C. photoheterotroph
D. photoautotroph

Answer

A

Which of the following molecules is reduced?

A. NAD^+
B. FAD
C. O_2
D. NADPH

Answer

D

Enzymes work by which of the following?

A. increasing the activation energy
B. reducing the activation energy
C. making exergonic reactions endergonic
D. making endergonic reactions exergonic

Answer

B

To which of the following does a competitive inhibitor most structurally resemble?

A. the active site
B. the allosteric site
C. the substrate
D. a coenzyme

Answer

C

Which of the following are organic molecules that help enzymes work correctly?

A. cofactors
B. coenzymes
C. holoenzymes

D. apoenzymes

Answer

B

Fill in the Blank

Processes in which cellular energy is used to make complex molecules from simpler ones are described as _____.

Answer

anabolic

The loss of an electron from a molecule is called _____.

Answer

oxidation

The part of an enzyme to which a substrate binds is called the _____.

Answer

active site

True/False

Competitive inhibitors bind to allosteric sites.

Answer

False

Short Answer

In cells, can an oxidation reaction happen in the absence of a reduction reaction? Explain.

What is the function of molecules like NAD^+/NADH and FAD/$FADH_2$ in cells?

8.2: Catabolism of Carbohydrates

Glycolysis is the first step in the breakdown of glucose, resulting in the formation of ATP, which is produced by substrate-level phosphorylation; NADH; and two pyruvate molecules. Glycolysis does not use oxygen and is not oxygen dependent. After glycolysis, a three-carbon pyruvate is decarboxylated to form a two-carbon acetyl group, coupled with the formation of NADH. The acetyl group is attached to a large carrier compound called coenzyme A.

Multiple Choice

During which of the following is ATP not made by substrate-level phosphorylation?

A. Embden-Meyerhof pathway
B. Transition reaction
C. Krebs cycle
D. Entner-Doudoroff pathway

Answer

B

Which of the following products is made during Embden-Meyerhof glycolysis?

A. NAD^+
B. pyruvate

C. CO_2
D. two-carbon acetyl

Answer

B

During the catabolism of glucose, which of the following is produced only in the Krebs cycle?

A. ATP
B. NADH
C. NADPH
D. $FADH_2$

Answer

D

Which of the following is not a name for the cycle resulting in the conversion of a two-carbon acetyl to one ATP, two CO_2, one $FADH_2$, and three NADH molecules?

A. Krebs cycle
B. tricarboxylic acid cycle
C. Calvin cycle
D. citric acid cycle

Answer

C

True/False

Glycolysis requires oxygen or another inorganic final electron acceptor to proceed.

Answer

False

Fill in the Blank

Per turn of the Krebs cycle, one acetyl is oxidized, forming ____ CO_2, ____ ATP, ____ NADH, and ____ $FADH_2$molecules.

Answer

2; 1; 3; 1

Most commonly, glycolysis occurs by the _____ pathway.

Answer

Embden-Meyerhof

Short Answer

What is substrate-level phosphorylation? When does it occur during the breakdown of glucose to CO_2?

Why is the Krebs cycle important in both catabolism and anabolism?

Critical Thinking

What would be the consequences to a cell of having a mutation that knocks out coenzyme A synthesis?

8.3: Cellular Respiration

Cellular respiration begins when electrons are transferred from NADH and $FADH_2$—through a series of chemical reactions to a final inorganic electron acceptor (either oxygen in aerobic respiration or non-oxygen inorganic molecules in anaerobic respiration). These electron transfers take place on the inner part of the cell membrane of prokaryotic cells or in specialized protein complexes in the inner membrane of the mitochondria of eukaryotic cells.

Multiple Choice

Which is the location of electron transports systems in prokaryotes?

A. the outer mitochondrial membrane
B. the cytoplasm
C. the inner mitochondrial membrane
D. the cytoplasmic membrane

Answer

D

Which is the source of the energy used to make ATP by oxidative phosphorylation?

A. oxygen
B. high-energy phosphate bonds
C. the proton motive force
D. P_i

Answer

C

A cell might perform anaerobic respiration for which of the following reasons?

A. It lacks glucose for degradation.
B. It lacks the transition reaction to convert pyruvate to acetyl-CoA.
C. It lacks Krebs cycle enzymes for processing acetyl-CoA to CO_2.
D. It lacks a cytochrome oxidase for passing electrons to oxygen.

Answer

D

In prokaryotes, which of the following is true?

A. As electrons are transferred through an ETS, H^+ is pumped out of the cell.
B. As electrons are transferred through an ETS, H^+ is pumped into the cell.
C. As protons are transferred through an ETS, electrons are pumped out of the cell.
D. As protons are transferred through an ETS, electrons are pumped into the cell.

Answer

A

Which of the following is not an electron carrier within an electron transport system?

A. flavoprotein
B. ATP synthase
C. ubiquinone
D. cytochrome oxidase

Answer

B

Fill in the Blank

The final ETS complex used in aerobic respiration that transfers energy-depleted electrons to oxygen to form H_2O is called _____.

Answer

cytochrome oxidase

The passage of hydrogen ions through _____ down their electrochemical gradient harnesses the energy needed for ATP synthesis by oxidative phosphorylation.

Answer

ATP synthase

True/False

All organisms that use aerobic cellular respiration have cytochrome oxidase.

Answer

True

Short Answer

What is the relationship between chemiosmosis and the proton motive force?

How does oxidative phosphorylation differ from substrate-level phosphorylation?

How does the location of ATP synthase differ between prokaryotes and eukaryotes? Where do protons accumulate as a result of the ETS in each cell type?

8.4: Fermentation

Fermentation uses an organic molecule as a final electron acceptor to regenerate NAD^+ from NADH so that glycolysis can continue. Fermentation does not involve an electron transport system, and no ATP is made by the fermentation process directly. Fermenters make very little ATP—only two ATP molecules per glucose molecule during glycolysis. Microbial fermentation processes have been used for the production of foods and pharmaceuticals, and for the identification of microbes.

Multiple Choice

Which of the following is the purpose of fermentation?

A. to make ATP
B. to make carbon molecule intermediates for anabolism
C. to make NADH
D. to make NAD^+

Answer

D

Which molecule typically serves as the final electron acceptor during fermentation?

A. oxygen
B. NAD^+
C. pyruvate
D. CO_2

Answer

https://bio.libretexts.org/@go/page/89222

C

Which fermentation product is important for making bread rise?

A. ethanol
B. CO_2
C. lactic acid
D. hydrogen gas

Answer

B

Which of the following is not a commercially important fermentation product?

A. ethanol
B. pyruvate
C. butanol
D. penicillin

Answer

B

Fill in the Blank

The microbe responsible for ethanol fermentation for the purpose of producing alcoholic beverages is _____.

Answer

yeast (*Saccharomyces cerevisiae*)

_____ results in the production of a mixture of fermentation products, including lactic acid, ethanol and/or acetic acid, and CO_2.

Answer

Heterolactic fermentation

Fermenting organisms make ATP through the process of _____.

Answer

glycolysis

Matching

Match the fermentation pathway with the correct commercial product it is used to produce:

___acetone-butanol-ethanol fermentation	a. bread
___alcohol fermentation	b. pharmaceuticals
___lactic acid fermentation	c. Swiss cheese
___mixed acid fermentation	d. yogurt
___propionic acid fermentation	e. industrial solvents

Answer

e; 2. a; 3. d; 4. b; 5. c

Short Answer

Why are some microbes, including *Streptococcus* spp., unable to perform aerobic respiration, even in the presence of oxygen?

How can fermentation be used to differentiate various types of microbes?

Critical Thinking

The bacterium *E. coli* is capable of performing aerobic respiration, anaerobic respiration, and fermentation. When would it perform each process and why? How is ATP made in each case?

8.5: Catabolism of Lipids and Proteins

Collectively, microbes have the ability to degrade a wide variety of carbon sources besides carbohydrates, including lipids and proteins. The catabolic pathways for all of these molecules eventually connect into glycolysis and the Krebs cycle. Several types of lipids can be microbially degraded. Triglycerides are degraded by extracellular lipases, releasing fatty acids from the glycerol backbone. Phospholipids are degraded by phospholipases, releasing fatty acids and phosphorylated head groups.

Multiple Choice

Which of the following molecules is not produced during the breakdown of phospholipids?

A. glucose
B. glycerol
C. acetyl groups
D. fatty acids

Answer

A

Caseinase is which type of enzyme?

A. phospholipase
B. lipase
C. extracellular protease
D. intracellular protease

Answer

C

Which of the following is the first step in triglyceride degradation?

A. removal of fatty acids
B. β-oxidation
C. breakage of fused rings
D. formation of smaller peptides

Answer

A

Fill in the Blank

The process by which two-carbon units are sequentially removed from fatty acids, producing acetyl-CoA, $FADH_2$, and NADH is called _____.

Answer

β-oxidation

The NADH and $FADH_2$ produced during β-oxidation are used to make _____.

Answer

ATP by oxidative phosphorylation

_____ is a type of medium used to detect the production of an extracellular protease called caseinase.

Answer

Skim milk agar

Short Answer

How are the products of lipid and protein degradation connected to glucose metabolism pathways?

What is the general strategy used by microbes for the degradation of macromolecules?

Critical Thinking

Do you think that β-oxidation can occur in an organism incapable of cellular respiration? Why or why not?

8.6: Photosynthesis and the Importance of Light

Heterotrophic organisms ranging from *E. coli* to humans rely on the chemical energy found mainly in carbohydrate molecules. Many of these carbohydrates are produced by photosynthesis, the biochemical process by which phototrophic organisms convert solar energy (sunlight) into chemical energy. Although photosynthesis is most commonly associated with plants, microbial photosynthesis is also a significant supplier of chemical energy, fueling many diverse ecosystems.

Multiple Choice

During the light-dependent reactions, which molecule loses an electron?

A. a light-harvesting pigment molecule
B. a reaction center pigment molecule
C. NADPH
D. 3-phosphoglycerate

Answer

B

In prokaryotes, in which direction are hydrogen ions pumped by the electron transport system of photosynthetic membranes?

A. to the outside of the plasma membrane
B. to the inside (cytoplasm) of the cell
C. to the stroma
D. to the intermembrane space of the chloroplast

Answer

A

Which of the following does not occur during cyclic photophosphorylation in cyanobacteria?

A. electron transport through an ETS
B. photosystem I use
C. ATP synthesis
D. NADPH formation

Answer

D

Which are two products of the light-dependent reactions are _____.

A. glucose and NADPH
B. NADPH and ATP
C. glyceraldehyde 3-phosphate and CO_2
D. glucose and oxygen

Answer

B

True/False

Photosynthesis always results in the formation of oxygen.

Answer

False

Fill in the Blank

The enzyme responsible for CO_2 fixation during the Calvin cycle is called _____.

Answer

ribulose bisphosphate carboxylase (RuBisCO)

The types of pigment molecules found in plants, algae, and cyanobacteria are _____ and _____.

Answer

chlorophylls and carotenoids

Short Answer

Why would an organism perform cyclic phosphorylation instead of noncyclic phosphorylation?

What is the function of photosynthetic pigments in the light-harvesting complex?

Critical Thinking

Is life dependent on the carbon fixation that occurs during the light-independent reactions of photosynthesis? Explain.

8.7: Biogeochemical Cycles

Energy flows directionally through ecosystems, entering as sunlight for phototrophs or as inorganic molecules for chemoautotrophs. The six most common elements associated with organic molecules—carbon, hydrogen, nitrogen, oxygen, phosphorus, and sulfur—take a variety of chemical forms and may exist for long periods in the atmosphere, on land, in water, or beneath earth's surface.

Multiple Choice

Which of the following is the group of archaea that can use CO_2 as their final electron acceptor during anaerobic respiration, producing CH_4?

A. methylotrophs
B. methanotrophs
C. methanogens
D. anoxygenic photosynthesizers

Answer

C

Which of the following processes is not involved in the conversion of organic nitrogen to nitrogen gas?

A. nitrogen fixation
B. ammonification
C. nitrification
D. denitrification

Answer

A

Which of the following processes produces hydrogen sulfide?

A. anoxygenic photosynthesis
B. oxygenic photosynthesis
C. anaerobic respiration
D. chemoautrophy

Answer

C

The biogeochemical cycle of which of the following elements is based on changes in solubility rather than redox chemistry?

A. carbon
B. sulfur
C. nitrogen
D. phosphorus

Answer

D

Fill in the Blank

The molecule central to the carbon cycle that is exchanged within and between ecosystems, being produced by heterotrophs and used by autotrophs, is _____.

Answer

carbon dioxide

The use of microbes to remove pollutants from a contaminated system is called _____.

Answer

bioremediation

True/False

There are many naturally occurring microbes that have the ability to degrade several of the compounds found in oil.

Answer

True

Short Answer

Why must autotrophic organisms also respire or ferment in addition to fixing CO_2?

How can human activity lead to eutrophication?

Critical Thinking

In considering the symbiotic relationship between *Rhizobium* species and their plant hosts, what metabolic activity does each organism perform that benefits the other member of the pair?

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CHAPTER OVERVIEW

5: Interactions between Microbes and Humans and Antimicrobial Treatment

Topic hierarchy

5.1: Control of Microbial Growth

5.1.1: Controlling Microbial Growth

5.1.2: Using Physical Methods to Control Microorganisms

5.1.3: Using Chemicals to Control Microorganisms

5.1.4: Testing the Effectiveness of Antiseptics and Disinfectants

5.1.E: Control of Microbial Growth (Exercises)

5.2: Bacterial Pathogenicity

5.3: Antimicrobial Drugs

5.3.1: Discovering Antimicrobial Drugs

5.3.2: Antibacterial Drugs

5.3.3: Drugs Targeting Other Microorganisms

5.3.4: Clinical Considerations

5.3.5: Testing the Effectiveness of Antimicrobials

5.3.6: The Emergence of Drug Resistance

5.3.E: Antimicrobial Drugs (Exercises)

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SECTION OVERVIEW

5.1: Control of Microbial Growth

How clean is clean? People wash their cars and vacuum the carpets, but most would not want to eat from these surfaces. Similarly, we might eat with silverware cleaned in a dishwasher, but we could not use the same dishwasher to clean surgical instruments. As these examples illustrate, “clean” is a relative term. Car washing, vacuuming, and dishwashing all reduce the microbial load on the items treated, thus making them “cleaner.” But whether they are “clean enough” depends on their intended use. Because people do not normally eat from cars or carpets, these items do not require the same level of cleanliness that silverware does. Likewise, because silverware is not used for invasive surgery, these utensils do not require the same level of cleanliness as surgical equipment, which requires sterilization to prevent infection.

Why not play it safe and sterilize everything? Sterilizing everything we come in contact with is impractical, as well as potentially dangerous. As this chapter will demonstrate, sterilization protocols often require time- and labor-intensive treatments that may degrade the quality of the item being treated or have toxic effects on users. Therefore, the user must consider the item’s intended application when choosing a cleaning method to ensure that it is “clean enough.”

Location	Average number CFUs per 6.5 × 6.5 cm area
Door latch	256
Door lock	14
Door lock control	182
Door handle	29
Window control	4
Cruise control button	69
Steering wheel	239
Interior steering wheel	390
Radio volume knob	99
Gear shifter	115
Center console	506



Figure 5.1.1: Most environments, including cars, are not sterile. A study[1] analyzed 11 locations within 18 different cars to determine the number of microbial colony-forming units (CFUs) present. The center console harbored by far the most microbes (506 CFUs), possibly because that is where drinks are placed (and often spilled). Frequently touched sites also had high concentrations. (credit “photo”: modification of work by Jeff Wilcox)

5.1.1: Controlling Microbial Growth

5.1.2: Using Physical Methods to Control Microorganisms

5.1.3: Using Chemicals to Control Microorganisms

5.1.4: Testing the Effectiveness of Antiseptics and Disinfectants

5.1.E: Control of Microbial Growth (Exercises)

Footnotes

1. 1 R.E. Stephenson et al. “Elucidation of Bacteria Found in Car Interiors and Strategies to Reduce the Presence of Potential Pathogens.” *Biofouling* 30 no. 3 (2014):337–346.

Thumbnail: Scanning electron microscope image of *Vibrio cholerae* bacteria, which infect the digestive system. (Public Domain; T.J. Kirn, M.J. Lafferty, C.M.P Sandoe and R.K. Taylor).

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5.1.1: Controlling Microbial Growth

Learning Objectives

- Compare disinfectants, antiseptics, and sterilants
- Describe the principles of controlling the presence of microorganisms through sterilization and disinfection
- Differentiate between microorganisms of various biological safety levels and explain methods used for handling microbes at each level

Clinical Focus: Part 1

Roberta is a 46-year-old real estate agent who recently underwent a cholecystectomy (surgery to remove painful gallstones). The surgery was performed laparoscopically with the aid of a duodenoscope, a specialized endoscope that allows surgeons to see inside the body with the aid of a tiny camera. On returning home from the hospital, Roberta developed abdominal pain and a high fever. She also experienced a burning sensation during urination and noticed blood in her urine. She notified her surgeon of these symptoms, per her postoperative instructions.

Exercise 5.1.1.1

What are some possible causes of Roberta's symptoms?

To prevent the spread of human disease, it is necessary to control the growth and abundance of microbes in or on various items frequently used by humans. Inanimate items, such as doorknobs, toys, or towels, which may harbor microbes and aid in disease transmission, are called **fomites**. Two factors heavily influence the level of cleanliness required for a particular fomite and, hence, the protocol chosen to achieve this level. The first factor is the application for which the item will be used. For example, invasive applications that require insertion into the human body require a much higher level of cleanliness than applications that do not. The second factor is the level of resistance to antimicrobial treatment by potential pathogens. For example, foods preserved by canning often become contaminated with the bacterium *Clostridium botulinum*, which produces the neurotoxin that causes botulism. Because *C. botulinum* can produce endospores that can survive harsh conditions, extreme temperatures and pressures must be used to eliminate the endospores. Other organisms may not require such extreme measures and can be controlled by a procedure such as washing clothes in a laundry machine.

Laboratory Biological Safety Levels

For researchers or laboratory personnel working with pathogens, the risks associated with specific pathogens determine the levels of cleanliness and control required. The Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) have established four classification levels, called "biological safety levels" (BSLs). Various organizations around the world, including the World Health Organization (WHO) and the European Union (EU), use a similar classification scheme. According to the CDC, the BSL is determined by the agent's infectivity, ease of transmission, and potential disease severity, as well as the type of work being done with the agent.[1]

Each BSL requires a different level of biocontainment to prevent contamination and spread of infectious agents to laboratory personnel and, ultimately, the community. For example, the lowest BSL, BSL-1, requires the fewest precautions because it applies to situations with the lowest risk for microbial infection.

BSL-1 agents are those that generally do not cause infection in healthy human adults. These include noninfectious bacteria, such as nonpathogenic strains of *Escherichia coli* and *Bacillus subtilis*, and viruses known to infect animals other than humans, such as baculoviruses (insect viruses). Because working with BSL-1 agents poses very little risk, few precautions are necessary. Laboratory workers use standard aseptic technique and may work with these agents at an open laboratory bench or table, wearing personal protective equipment (PPE) such as a laboratory coat, goggles, and gloves, as needed. Other than a sink for handwashing and doors to separate the laboratory from the rest of the building, no additional modifications are needed.

Agents classified as BSL-2 include those that pose moderate risk to laboratory workers and the community, and are typically "indigenous," meaning that they are commonly found in that geographical area. These include bacteria such as *Staphylococcus aureus* and *Salmonella* spp., and viruses like hepatitis, mumps, and measles viruses. BSL-2 laboratories require additional precautions beyond those of BSL-1, including restricted access; required PPE, including a face shield in some circumstances; and the use of biological safety cabinets for procedures that may disperse agents through the air (called "aerosolization"). BSL-2 laboratories are equipped with self-closing doors, an eyewash station, and an autoclave, which is a specialized device for sterilizing materials with pressurized steam before use or disposal. BSL-1 laboratories may also have an autoclave.

BSL-3 agents have the potential to cause lethal infections by inhalation. These may be either indigenous or "exotic," meaning that they are derived from a foreign location, and include pathogens such as *Mycobacterium tuberculosis*, *Bacillus anthracis*, West Nile virus, and human immunodeficiency virus (HIV). Because of the serious nature of the infections caused by BSL-3 agents, laboratories working with them require restricted access. Laboratory workers are under medical surveillance, possibly receiving vaccinations for the microbes with which they work. In addition to the standard PPE already mentioned, laboratory personnel in BSL-3 laboratories must also wear a respirator and work with microbes and infectious agents in a biological safety cabinet at all times. BSL-3 laboratories require a hands-free sink, an eyewash station near the exit, and two sets of self-closing and locking doors at the entrance. These laboratories are equipped with directional airflow, meaning that clean air is pulled through the laboratory from clean areas to potentially contaminated areas. This air cannot be recirculated, so a constant supply of clean air is required.

BSL-4 agents are the most dangerous and often fatal. These microbes are typically exotic, are easily transmitted by inhalation, and cause infections for which there are no treatments or vaccinations. Examples include Ebola virus and Marburg virus, both of which cause hemorrhagic fevers, and smallpox virus. There are only a small number of laboratories in the United States and around the world appropriately equipped to work with these agents. In addition to BSL-3 precautions, laboratory workers in BSL-4 facilities must also change their clothing on entering the laboratory, shower on exiting, and decontaminate all material on exiting. While working in the laboratory, they must either wear a full-body protective suit with a designated air supply or conduct all work within a biological safety cabinet with a high-efficiency particulate air (HEPA)-filtered air supply and a doubly HEPA-filtered exhaust. If wearing a suit, the air pressure within the suit must be higher than that outside the suit, so that if a leak in the suit occurs, laboratory air that may be contaminated cannot be drawn into the suit (Figure 5.1.1.1). The laboratory itself must be located either in a separate building or in an isolated portion of a building and have its own air supply and exhaust system, as well as its own decontamination system. The BSLs are summarized in Figure 5.1.1.2.



Figure 5.1.1.1: A protective suit like this one is an additional precaution for those who work in BSL-4 laboratories. This suit has its own air supply and maintains a positive pressure relative to the outside, so that if a leak occurs, air will flow out of the suit, not into it from the laboratory. (credit: modification of work by Centers for Disease Control and Prevention)

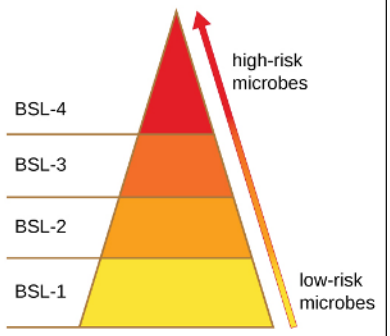
Biosafety Levels			
Biological Safety Levels	**Description**	**Examples**	**CDC Classification**
BSL-4	Microbes are dangerous and exotic, posing a high risk of aerosol-transmitted infections, which are frequently fatal without treatment or vaccines. Few labs are at this level.	Ebola and Marburg viruses	
BSL-3	Microbes are indigenous or exotic and cause serious or potentially lethal diseases through respiratory transmission.	*Mycobacterium tuberculosis*	
BSL-2	Microbes are typically indigenous and are associated with diseases of varying severity. They pose moderate risk to workers and the environment.	*Staphylococcus aureus*	
BSL-1	Microbes are not known to cause disease in healthy hosts and pose minimal risk to workers and the environment.	Nonpathogenic strains of *Escherichia coli*	

Figure 5.1.1.2: The CDC classifies infectious agents into four biosafety levels based on potential risk to laboratory personnel and the community. Each level requires a progressively greater level of precaution. (credit "pyramid": modification of work by Centers for Disease Control and Prevention)

Link to Learning

To learn more about the four BSLs, visit the CDC's website.

Exercise 5.1.1.2

What are some factors used to determine the BSL necessary for working with a specific pathogen?

Sterilization

The most extreme protocols for microbial control aim to achieve sterilization: the complete removal or killing of all vegetative cells, endospores, and viruses from the targeted item or environment. Sterilization protocols are generally reserved for laboratory, medical, manufacturing, and food industry settings, where it may be imperative for certain items to be completely free of potentially infectious agents. Sterilization can be accomplished through either physical means, such as exposure to high heat, pressure, or filtration through an appropriate filter, or by chemical means. Chemicals that can be used to achieve sterilization are called sterilants. Sterilants effectively kill all microbes and viruses, and, with appropriate exposure time, can also kill endospores.

For many clinical purposes, aseptic technique is necessary to prevent contamination of sterile surfaces. Aseptic technique involves a combination of protocols that collectively maintain sterility, or asepsis, thus preventing contamination of the patient with microbes and infectious agents. Failure to practice aseptic technique during many types of clinical procedures may introduce microbes to the patient's body and put the patient at risk for sepsis, a systemic inflammatory response to an infection that results in high fever, increased heart and respiratory rates, shock, and, possibly, death. Medical procedures that carry risk of contamination must be performed in a sterile field, a designated area that is kept free of all vegetative microbes, endospores, and viruses. Sterile fields are created according to protocols requiring the use of sterilized materials, such as packaging and drapings, and strict procedures for washing and application of sterilants. Other protocols are followed to maintain the sterile field while the medical procedure is being performed.

One food sterilization protocol, commercial sterilization, uses heat at a temperature low enough to preserve food quality but high enough to destroy common pathogens responsible for food poisoning, such as *C. botulinum*. Because *C. botulinum* and its endospores are commonly found in soil, they may easily contaminate crops during harvesting, and these endospores can later germinate within the anaerobic environment once foods are canned. Metal cans of food contaminated with *C. botulinum* will bulge

due to the microbe's production of gases; contaminated jars of food typically bulge at the metal lid. To eliminate the risk for *C. botulinum* contamination, commercial food-canning protocols are designed with a large margin of error. They assume an impossibly large population of endospores (10^{12} per can) and aim to reduce this population to 1 endospore per can to ensure the safety of canned foods. For example, low- and medium-acid foods are heated to 121 °C for a minimum of 2.52 minutes, which is the time it would take to reduce a population of 10^{12} endospores per can down to 1 endospore at this temperature. Even so, commercial sterilization does not eliminate the presence of all microbes; rather, it targets those pathogens that cause spoilage and foodborne diseases, while allowing many nonpathogenic organisms to survive. Therefore, "sterilization" is somewhat of a misnomer in this context, and commercial sterilization may be more accurately described as "quasi-sterilization."

? Exercise 5.1.1.3

What is the difference between sterilization and aseptic technique?

Link to Learning

The Association of Surgical Technologists publishes standards for aseptic technique, including creating and maintaining a sterile field.

Other Methods of Control

Sterilization protocols require procedures that are not practical, or necessary, in many settings. Various other methods are used in clinical and nonclinical settings to reduce the microbial load on items. Although the terms for these methods are often used interchangeably, there are important distinctions (Figure 5.1.1.3).

The process of disinfection inactivates most microbes on the surface of a fomite by using antimicrobial chemicals or heat. Because some microbes remain, the disinfected item is not considered sterile. Ideally, disinfectants should be fast acting, stable, easy to prepare, inexpensive, and easy to use. An example of a natural disinfectant is vinegar; its acidity kills most microbes. Chemical disinfectants, such as chlorine bleach or products containing chlorine, are used to clean nonliving surfaces such as laboratory benches, clinical surfaces, and bathroom sinks. Typical disinfection does not lead to sterilization because endospores tend to survive even when all vegetative cells have been killed.

Unlike disinfectants, antiseptics are antimicrobial chemicals safe for use on living skin or tissues. Examples of antiseptics include hydrogen peroxide and isopropyl alcohol. The process of applying an antiseptic is called antisepsis. In addition to the characteristics of a good disinfectant, antiseptics must also be selectively effective against microorganisms and able to penetrate tissue deeply without causing tissue damage.

The type of protocol required to achieve the desired level of cleanliness depends on the particular item to be cleaned. For example, those used clinically are categorized as critical, semicritical, and noncritical. Critical items must be sterile because they will be used inside the body, often penetrating sterile tissues or the bloodstream; examples of critical items include surgical instruments, catheters, and intravenous fluids. Gastrointestinal endoscopes and various types of equipment for respiratory therapies are examples of semicritical items; they may contact mucous membranes or nonintact skin but do not penetrate tissues. Semicritical items do not typically need to be sterilized but do require a high level of disinfection. Items that may contact but not penetrate intact skin are noncritical items; examples are bed linens, furniture, crutches, stethoscopes, and blood pressure cuffs. These articles need to be clean but not highly disinfected.

The act of handwashing is an example of degerming, in which microbial numbers are significantly reduced by gently scrubbing living tissue, most commonly skin, with a mild chemical (e.g., soap) to avoid the transmission of pathogenic microbes. Wiping the skin with an alcohol swab at an injection site is another example of degerming. These degerming methods remove most (but not all) microbes from the skin's surface.

The term sanitization refers to the cleansing of fomites to remove enough microbes to achieve levels deemed safe for public health. For example, commercial dishwashers used in the food service industry typically use very hot water and air for washing and drying; the high temperatures kill most microbes, sanitizing the dishes. Surfaces in hospital rooms are commonly sanitized using a

chemical disinfectant to prevent disease transmission between patients. Figure 5.1.1.3 summarizes common protocols, definitions, applications, and agents used to control microbial growth.

Common Protocols for Control of Microbial Growth			
Protocol	**Definition**	**Common Application**	**Common Agents**
For Use on Fomites			
Disinfection	Reduces or destroys microbial load of an inanimate item through application of heat or antimicrobial chemicals	Cleaning surfaces like laboratory benches, clinical surfaces, and bathrooms	Chlorine bleach, phenols (e.g., Lysol), glutaraldehyde
Sanitization	Reduces microbial load of an inanimate item to safe public health levels through application of heat or antimicrobial chemicals	Commercial dishwashing of eating utensils, cleaning public restrooms	Detergents containing phosphates (e.g., Finish), industrial-strength cleaners containing quaternary ammonium compounds
Sterilization	Completely eliminates all vegetative cells, endospores, and viruses from an inanimate item	Preparation of surgical equipment and of needles used for injection	Pressurized steam (autoclave), chemicals, radiation
For Use on Living Tissue			
Antisepsis	Reduces microbial load on skin or tissue through application of an antimicrobial chemical	Cleaning skin broken due to injury; cleaning skin before surgery	Boric acid, isopropyl alcohol, hydrogen peroxide, iodine (betadine)
Degerming	Reduces microbial load on skin or tissue through gentle to firm scrubbing and the use of mild chemicals	Handwashing	Soap, alcohol swab

Figure 5.1.1.3: Common protocols for control of microbial growth

? Exercise 5.1.1.4

1. What is the difference between a disinfectant and an antiseptic?
2. Which is most effective at removing microbes from a product: sanitization, degerming, or sterilization? Explain.

Clinical Focus: Part 2

Roberta's physician suspected that a bacterial infection was responsible for her sudden-onset high fever, abdominal pain, and bloody urine. Based on these symptoms, the physician diagnosed a urinary tract infection (UTI). A wide variety of bacteria may cause UTIs, which typically occur when bacteria from the lower gastrointestinal tract are introduced to the urinary tract. However, Roberta's recent gallstone surgery caused the physician to suspect that she had contracted a nosocomial (hospital-acquired) infection during her surgery. The physician took a urine sample and ordered a urine culture to check for the presence of white blood cells, red blood cells, and bacteria. The results of this test would help determine the cause of the infection. The physician also prescribed a course of the antibiotic ciprofloxacin, confident that it would clear Roberta's infection.

Exercise 5.1.1.5

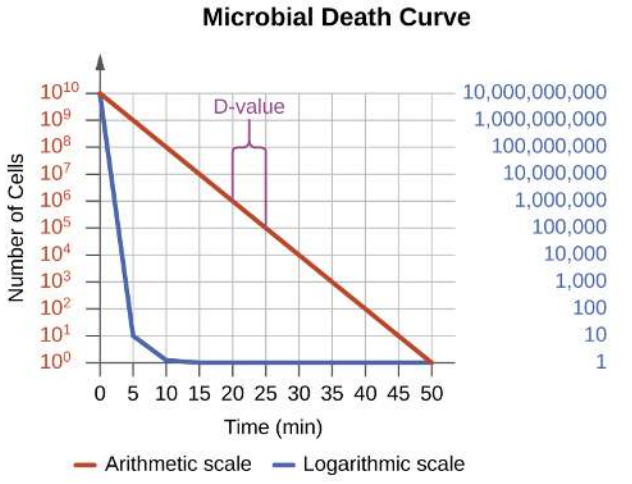
What are some possible ways that bacteria could have been introduced to Roberta's urinary tract during her surgery?

Measuring Microbial Control

Physical and chemical methods of microbial control that kill the targeted microorganism are identified by the suffix *-cide* (or *-cidal*). The prefix indicates the type of microbe or infectious agent killed by the treatment method: bactericide**s** kill bacteria, viricide**s** kill or inactivate viruses, and fungicide**s** kill fungi. Other methods do not kill organisms but, instead, stop their growth, making their population static; such methods are identified by the suffix *-stat* (or *-static*). For example, bacteriostatic treatments inhibit the growth of bacteria, whereas fungistatic treatments inhibit the growth of fungi. Factors that determine whether a particular treatment is *-cidal* or *-static* include the types of microorganisms targeted, the concentration of the chemical used, and the nature of the treatment applied.

Although *-static* treatments do not actually kill infectious agents, they are often less toxic to humans and other animals, and may also better preserve the integrity of the item treated. Such treatments are typically sufficient to keep the microbial population of an item in check. The reduced toxicity of some of these *-static* chemicals also allows them to be impregnated safely into plastics to prevent the growth of microbes on these surfaces. Such plastics are used in products such as toys for children and cutting boards for food preparation. When used to treat an infection, *-static* treatments are typically sufficient in an otherwise healthy individual, preventing the pathogen from multiplying, thus allowing the individual's immune system to clear the infection.

The degree of microbial control can be evaluated using a microbial death curve to describe the progress and effectiveness of a particular protocol. When exposed to a particular microbial control protocol, a fixed percentage of the microbes within the population will die. Because the rate of killing remains constant even when the population size varies, the percentage killed is more useful information than the absolute number of microbes killed. Death curves are often plotted as semilog plots just like microbial growth curves because the reduction in microorganisms is typically logarithmic (Figure 5.1.1.4). The amount of time it takes for a specific protocol to produce a one order-of-magnitude decrease in the number of organisms, or the death of 90% of the population, is called the decimal reduction time (DRT) or D-value.



Time (min)	Number of cells
0	10^{10}
5	10^{9}
10	10^{8}
15	10^{7}
20	10^{6}
25	10^{5}
30	10^{4}
35	10^{3}
40	10^{2}
45	10^{1}
50	10^{0}

Figure 5.1.1.4: Microbial death is logarithmic and easily observed using a semilog plot instead of an arithmetic one. The decimal reduction time (D-value) is the time it takes to kill 90% of the population (a 1-log decrease in the total population) when exposed to a specific microbial control protocol, as indicated by the purple bracket.

Several factors contribute to the effectiveness of a disinfecting agent or microbial control protocol. First, as demonstrated in Figure 5.1.1.4, the length of time of exposure is important. Longer exposure times kill more microbes. Because microbial death of a population exposed to a specific protocol is logarithmic, it takes longer to kill a high-population load than a low-population load exposed to the same protocol. A shorter treatment time (measured in multiples of the D-value) is needed when starting with a smaller number of organisms. Effectiveness also depends on the susceptibility of the agent to that disinfecting agent or protocol. The concentration of disinfecting agent or intensity of exposure is also important. For example, higher temperatures and higher concentrations of disinfectants kill microbes more quickly and effectively. Conditions that limit contact between the agent and the targeted cells cells—for example, the presence of bodily fluids, tissue, organic debris (e.g., mud or feces), or biofilms on surfaces—increase the cleaning time or intensity of the microbial control protocol required to reach the desired level of cleanliness. All these factors must be considered when choosing the appropriate protocol to control microbial growth in a given situation.

? Exercise 5.1.1.6

1. What are two possible reasons for choosing a bacteriostatic treatment over a bactericidal one?
2. Name at least two factors that can compromise the effectiveness of a disinfecting agent.

Key Concepts and Summary

- Inanimate items that may harbor microbes and aid in their transmission are called **fomites**. The level of cleanliness required for a fomite depends both on the item's use and the infectious agent with which the item may be contaminated.
- The CDC and the NIH have established four **biological safety levels (BSLs)** for laboratories performing research on infectious agents. Each level is designed to protect laboratory personnel and the community. These BSLs are determined by the agent's infectivity, ease of transmission, and potential disease severity, as well as the type of work being performed with the agent.
- **Disinfection** removes potential pathogens from a fomite, whereas **antisepsis** uses antimicrobial chemicals safe enough for tissues; in both cases, microbial load is reduced, but microbes may remain unless the chemical used is strong enough to be a **sterilant**.
- The amount of cleanliness (**sterilization** versus high-level disinfection versus general cleanliness) required for items used clinically depends on whether the item will come into contact with sterile tissues (**critical item)**, mucous membranes (**semicritical item**), or intact skin (**noncritical item**).
- Medical procedures with a risk for contamination should be carried out in a **sterile field** maintained by proper **aseptic technique** to prevent **sepsis**.
- Sterilization is necessary for some medical applications as well as in the food industry, where endospores of *Clostridium botulinum* are killed through **commercial sterilization** protocols.
- Physical or chemical methods to control microbial growth that result in death of the microbe are indicated by the suffixes *-cide* or *-cidal* (e.g., as with **bactericides**, **viricides**, and **fungicides**), whereas those that inhibit microbial growth are indicated by the suffixes *-stat* or*-static* (e.g., **bacteriostatic**, **fungistatic**).
- **Microbial death curves** display the logarithmic decline of living microbes exposed to a method of microbial control. The time it takes for a protocol to yield a 1-log (90%) reduction in the microbial population is the **decimal reduction time**, or **D-value**.
- When choosing a microbial control protocol, factors to consider include the length of exposure time, the type of microbe targeted, its susceptibility to the protocol, the intensity of the treatment, the presence of organics that may interfere with the protocol, and the environmental conditions that may alter the effectiveness of the protocol.

Footnotes

1. 1 US Centers for Disease Control and Prevention. "Recognizing the Biosafety Levels." http://www.cdc.gov/training/quicklearns/biosafety/. Accessed June 7, 2016.

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5.1.2: Using Physical Methods to Control Microorganisms

Learning Objectives

- Understand and compare various physical methods of controlling microbial growth, including heating, refrigeration, freezing, high-pressure treatment, desiccation, lyophilization, irradiation, and filtration

For thousands of years, humans have used various physical methods of microbial control for food preservation. Common control methods include the application of high temperatures, radiation, filtration, and desiccation (drying), among others. Many of these methods nonspecifically kill cells by disrupting membranes, changing membrane permeability, or damaging proteins and nucleic acids by denaturation, degradation, or chemical modification. Various physical methods used for microbial control are described in this section.

Heat

Heating is one of the most common—and oldest—forms of microbial control. It is used in simple techniques like cooking and canning. Heat can kill microbes by altering their membranes and denaturing proteins. The **thermal death point (TDP)** of a microorganism is the lowest temperature at which all microbes are killed in a 10-minute exposure. Different microorganisms will respond differently to high temperatures, with some (e.g., endospore-formers such as *C. botulinum*) being more heat tolerant. A similar parameter, the **thermal death time (TDT)**, is the length of time needed to kill all microorganisms in a sample at a given temperature. These parameters are often used to describe sterilization procedures that use high heat, such as autoclaving. Boiling is one of the oldest methods of moist-heat control of microbes, and it is typically quite effective at killing vegetative cells and some viruses. However, boiling is less effective at killing endospores; some endospores are able to survive up to 20 hours of boiling. Additionally, boiling may be less effective at higher altitudes, where the boiling point of water is lower and the boiling time needed to kill microbes is therefore longer. For these reasons, boiling is not considered a useful sterilization technique in the laboratory or clinical setting.

Many different heating protocols can be used for sterilization in the laboratory or clinic, and these protocols can be broken down into two main categories: **dry-heat sterilization** and **moist-heat sterilization**. Aseptic technique in the laboratory typically involves some dry-heat sterilization protocols using direct application of high heat, such as sterilizing inoculating loops (Figure 5.1.2.1). Incineration at very high temperatures destroys all microorganisms. Dry heat can also be applied for relatively long periods of time (at least 2 hours) at temperatures up to 170 °C by using a dry-heat sterilizer, such as an oven. However, moist-heat sterilization is typically the more effective protocol because it penetrates cells better than dry heat does.



(a) (b)

Figure 5.1.2.1: (a) Sterilizing a loop, often referred to as “flaming a loop,” is a common component of aseptic technique in the microbiology laboratory and is used to incinerate any microorganisms on the loop. (b) Alternatively, a bactericinerator may be used to reduce aerosolization of microbes and remove the presence of an open flame in the laboratory. These are examples of dry-heat sterilization by the direct application of high heat capable of incineration. (credit a: modification of work by Anh-Hue Tu; credit b: modification of work by Brian Forster)

Autoclaves

Autoclaves rely on moist-heat sterilization. They are used to raise temperatures above the boiling point of water to sterilize items such as surgical equipment from vegetative cells, viruses, and especially endospores, which are known to survive boiling temperatures, without damaging the items. Charles Chamberland (1851–1908) designed the modern autoclave in 1879 while working in the laboratory of Louis Pasteur. The autoclave is still considered the most effective method of sterilization (Figure 5.1.2.2). Outside laboratory and clinical settings, large industrial autoclaves called retorts allow for moist-heat sterilization on a large scale.

In general, the air in the chamber of an autoclave is removed and replaced with increasing amounts of steam trapped within the enclosed chamber, resulting in increased interior pressure and temperatures above the boiling point of water. The two main types of autoclaves differ in the way that air is removed from the chamber. In gravity displacement autoclaves, steam is introduced into the chamber from the top or sides. Air, which is heavier than steam, sinks to the bottom of the chamber, where it is forced out through a vent. Complete displacement of air is difficult, especially in larger loads, so longer cycles may be required for such loads. In prevacuum sterilizers, air is removed completely using a high-speed vacuum before introducing steam into the chamber. Because air is more completely eliminated, the steam can more easily penetrate wrapped items. Many autoclaves are capable of both gravity and prevacuum cycles, using the former for the decontamination of waste and sterilization of media and unwrapped glassware, and the latter for sterilization of packaged instruments.

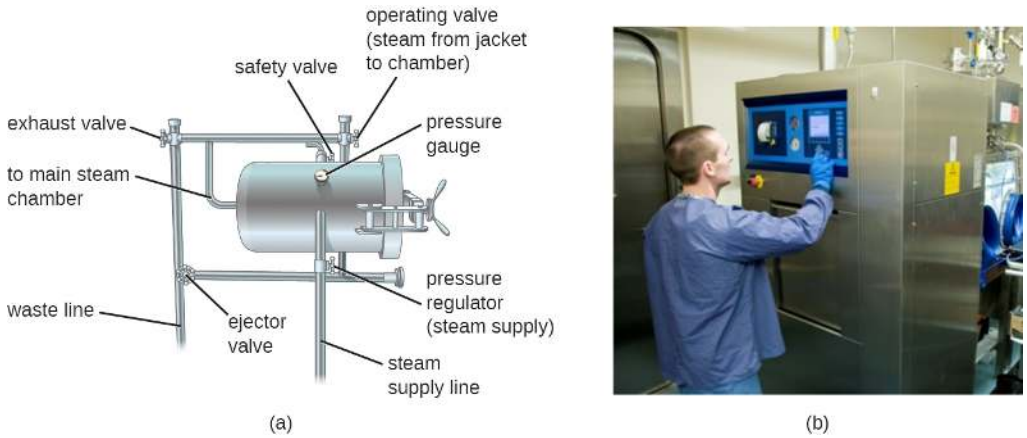


Figure 5.1.2.2: (a) An autoclave is commonly used for sterilization in the laboratory and in clinical settings. By displacing the air in the chamber with increasing amounts of steam, pressure increases, and temperatures exceeding 100 °C can be achieved, allowing for complete sterilization. (b) A researcher programs an autoclave to sterilize a sample. (credit a: modification of work by Courtney Harrington; credit b: modification of work by Lackemeyer MG, Kok-Mercado Fd, Wada J, Bollinger L, Kindrachuk J, Wahl-Jensen V, Kuhn JH, Jahrling PB)

Standard operating temperatures for autoclaves are 121 °C or, in some cases, 132 °C, typically at a pressure of 15 to 20 pounds per square inch (psi). The length of exposure depends on the volume and nature of material being sterilized, but it is typically 20 minutes or more, with larger volumes requiring longer exposure times to ensure sufficient heat transfer to the materials being sterilized. The steam must directly contact the liquids or dry materials being sterilized, so containers are left loosely closed and instruments are loosely wrapped in paper or foil. The key to autoclaving is that the temperature must be high enough to kill endospores to achieve complete sterilization.

Because sterilization is so important to safe medical and laboratory protocols, quality control is essential. Autoclaves may be equipped with recorders to document the pressures and temperatures achieved during each run. Additionally, internal indicators of various types should be autoclaved along with the materials to be sterilized to ensure that the proper sterilization temperature has been reached (Figure 5.1.2.3). One common type of indicator is the use of heat-sensitive autoclave tape, which has white stripes that turn black when the appropriate temperature is achieved during a successful autoclave run. This type of indicator is relatively inexpensive and can be used during every run. However, autoclave tape provides no indication of length of exposure, so it cannot be used as an indicator of sterility. Another type of indicator, a biological indicator spore test, uses either a strip of paper or a liquid suspension of the endospores of *Geobacillus stearothermophilus* to determine whether the endospores are killed by the process. The endospores of the obligate thermophilic bacterium *G. stearothermophilus* are the gold standard used for this purpose because of their extreme heat resistance. Biological spore indicators can also be used to test the effectiveness of other sterilization protocols,

including ethylene oxide, dry heat, formaldehyde, gamma radiation, and hydrogen peroxide plasma sterilization using either *G. stearothermophilus*, *Bacillus atrophaeus*, *B. subtilis*, or *B. pumilus* spores. In the case of validating autoclave function, the endospores are incubated after autoclaving to ensure no viable endospores remain. Bacterial growth subsequent to endospore germination can be monitored by biological indicator spore tests that detect acid metabolites or fluorescence produced by enzymes derived from viable *G. stearothermophilus*. A third type of autoclave indicator is the Diack tube, a glass ampule containing a temperature-sensitive pellet that melts at the proper sterilization temperature. Spore strips or Diack tubes are used periodically to ensure the autoclave is functioning properly.

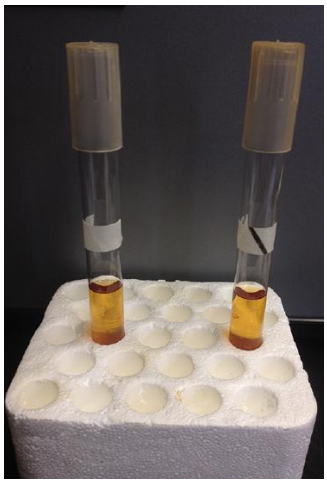


Figure 5.1.2.3: The white strips on autoclave tape (left tube) turn dark during a successful autoclave run (right tube). (credit: modification of work by Brian Forster)

Pasteurization

Although complete sterilization is ideal for many medical applications, it is not always practical for other applications and may also alter the quality of the product. Boiling and autoclaving are not ideal ways to control microbial growth in many foods because these methods may ruin the consistency and other organoleptic (sensory) qualities of the food. Pasteurization is a form of microbial control for food that uses heat but does not render the food sterile. Traditional pasteurization kills pathogens and reduces the number of spoilage-causing microbes while maintaining food quality. The process of pasteurization was first developed by Louis Pasteur in the 1860s as a method for preventing the spoilage of beer and wine. Today, pasteurization is most commonly used to kill heat-sensitive pathogens in milk and other food products (e.g., apple juice and honey) (Figure 5.1.2.4). However, because pasteurized food products are not sterile, they will eventually spoil.

The methods used for milk pasteurization balance the temperature and the length of time of treatment. One method, high-temperature short-time (HTST) pasteurization, exposes milk to a temperature of 72 °C for 15 seconds, which lowers bacterial numbers while preserving the quality of the milk. An alternative is ultra-high-temperature (UHT) pasteurization, in which the milk is exposed to a temperature of 138 °C for 2 or more seconds. UHT pasteurized milk can be stored for a long time in sealed containers without being refrigerated; however, the very high temperatures alter the proteins in the milk, causing slight changes in the taste and smell. Still, this method of pasteurization is advantageous in regions where access to refrigeration is limited.

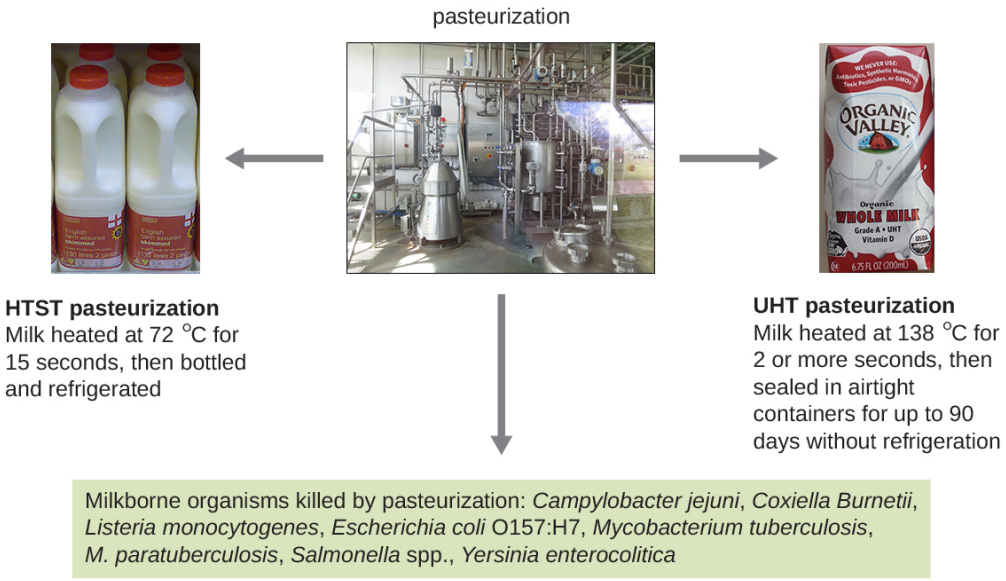


Figure 5.1.2.4: Two different methods of pasteurization, HTST and UHT, are commonly used to kill pathogens associated with milk spoilage. (credit left: modification of work by Mark Hillary; credit right: modification of work by Kerry Ceszyk)

? Exercise 5.1.2.1

1. In an autoclave, how are temperatures above boiling achieved?
2. How would the onset of spoilage compare between HTST-pasteurized and UHT-pasteurized milk?
3. Why is boiling not used as a sterilization method in a clinical setting?

Refrigeration and Freezing

Just as high temperatures are effective for controlling microbial growth, exposing microbes to low temperatures can also be an easy and effective method of microbial control, with the exception of psychrophiles, which prefer cold temperatures (see Temperature and Microbial Growth). Refrigerators used in home kitchens or in the laboratory maintain temperatures between 0 °C and 7 °C. This temperature range inhibits microbial metabolism, slowing the growth of microorganisms significantly and helping preserve refrigerated products such as foods or medical supplies. Certain types of laboratory cultures can be preserved by refrigeration for later use.

Freezing below −2 °C may stop microbial growth and even kill susceptible organisms. According to the US Department of Agriculture (USDA), the only safe ways that frozen foods can be thawed are in the refrigerator, immersed in cold water changed every 30 minutes, or in the microwave, keeping the food at temperatures not conducive for bacterial growth.[1] In addition, halted bacterial growth can restart in thawed foods, so thawed foods should be treated like fresh perishables.

Bacterial cultures and medical specimens requiring long-term storage or transport are often frozen at ultra-low temperatures of −70 °C or lower. These ultra-low temperatures can be achieved by storing specimens on dry ice in an ultra-low freezer or in special liquid nitrogen tanks, which maintain temperatures lower than −196 °C (Figure 5.1.2.5).



(a) (b)

Figure 5.1.2.5: Cultures and other medical specimens can be stored for long periods at ultra-low temperatures. (a) An ultra-low freezer maintains temperatures at or below −70 °C. (b) Even lower temperatures can be achieved through freezing and storage in liquid nitrogen. (credit a: modification of work by “Expert Infantry”/Flickr; credit b: modification of work by USDA)

? Exercise 5.1.2.2

Does placing food in a refrigerator kill bacteria on the food?

Pressure

Exposure to high pressure kills many microbes. In the food industry, high-pressure processing (also called pascalization) is used to kill bacteria, yeast, molds, parasites, and viruses in foods while maintaining food quality and extending shelf life. The application of high pressure between 100 and 800 MPa (sea level atmospheric pressure is about 0.1 MPa) is sufficient to kill vegetative cells by protein denaturation, but endospores may survive these pressures.[23]

In clinical settings, hyperbaric oxygen therapy is sometimes used to treat infections. In this form of therapy, a patient breathes pure oxygen at a pressure higher than normal atmospheric pressure, typically between 1 and 3 atmospheres (atm). This is achieved by placing the patient in a hyperbaric chamber or by supplying the pressurized oxygen through a breathing tube. Hyperbaric oxygen therapy helps increase oxygen saturation in tissues that become hypoxic due to infection and inflammation. This increased oxygen concentration enhances the body’s immune response by increasing the activities of neutrophils and macrophages, white blood cells that fight infections. Increased oxygen levels also contribute to the formation of toxic free radicals that inhibit the growth of oxygen-sensitive or anaerobic bacteria like as *Clostridium perfringens*, a common cause of gas gangrene. In *C. perfringens* infections, hyperbaric oxygen therapy can also reduce secretion of a bacterial toxin that causes tissue destruction. Hyperbaric oxygen therapy also seems to enhance the effectiveness of antibiotic treatments. Unfortunately, some rare risks include oxygen toxicity and effects on delicate tissues, such as the eyes, middle ear, and lungs, which may be damaged by the increased air pressure.

High pressure processing is not commonly used for disinfection or sterilization of fomites. Although the application of pressure and steam in an autoclave is effective for killing endospores, it is the high temperature achieved, and not the pressure directly, that results in endospore death.

A Streak of Bad Potluck

One Monday in spring 2015, an Ohio woman began to experience blurred, double vision; difficulty swallowing; and drooping eyelids. She was rushed to the emergency department of her local hospital. During the examination, she began to experience abdominal cramping, nausea, paralysis, dry mouth, weakness of facial muscles, and difficulty speaking and breathing. Based on these symptoms, the hospital’s incident command center was activated, and Ohio public health officials were notified of a possible case of botulism. Meanwhile, other patients with similar symptoms began showing up at other local hospitals.

Because of the suspicion of botulism, antitoxin was shipped overnight from the CDC to these medical facilities, to be administered to the affected patients. The first patient died of respiratory failure as a result of paralysis, and about half of the remaining victims required additional hospitalization following antitoxin administration, with at least two requiring ventilators for breathing.

Public health officials investigated each of the cases and determined that all of the patients had attended the same church potluck the day before. Moreover, they traced the source of the outbreak to a potato salad made with home-canned potatoes. More than likely, the potatoes were canned using boiling water, a method that allows endospores of *Clostridium botulinum* to survive. *C. botulinum* produces botulinum toxin, a neurotoxin that is often deadly once ingested. According to the CDC, the Ohio case was the largest botulism outbreak in the United States in nearly 40 years.[4]

Killing *C. botulinum* endospores requires a minimum temperature of 116 °C (240 °F), well above the boiling point of water. This temperature can only be reached in a pressure canner, which is recommended for home canning of low-acid foods such as meat, fish, poultry, and vegetables (Figure 5.1.2.6). Additionally, the CDC recommends boiling home-canned foods for about 10 minutes before consumption. Since the botulinum toxin is heat labile (meaning that it is denatured by heat), 10 minutes of boiling will render nonfunctional any botulinum toxin that the food may contain.



Figure 5.1.2.6: (a) *Clostridium botulinum* is the causative agent of botulism. (b) A pressure canner is recommended for home canning because endospores of *C. botulinum* can survive temperatures above the boiling point of water. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by National Center for Home Food Preservation)

Link to Learning

To learn more about proper home-canning techniques, visit the CDC's website.

Desiccation

Drying, also known as desiccation or dehydration, is a method that has been used for millennia to preserve foods such as raisins, prunes, and jerky. It works because all cells, including microbes, require water for their metabolism and survival. Although drying controls microbial growth, it might not kill all microbes or their endospores, which may start to regrow when conditions are more favorable and water content is restored.

In some cases, foods are dried in the sun, relying on evaporation to achieve desiccation. Freeze-drying, or lyophilization, is another method of dessication in which an item is rapidly frozen ("snap-frozen") and placed under vacuum so that water is lost by sublimation. Lyophilization combines both exposure to cold temperatures and desiccation, making it quite effective for controlling microbial growth. In addition, lyophilization causes less damage to an item than conventional desiccation and better preserves the item's original qualities. Lyophilized items may be stored at room temperature if packaged appropriately to prevent moisture acquisition. Lyophilization is used for preservation in the food industry and is also used in the laboratory for the long-term storage and transportation of microbial cultures.

The water content of foods and materials, called the water activity, can be lowered without physical drying by the addition of solutes such as salts or sugars. At very high concentrations of salts or sugars, the amount of available water in microbial cells is reduced dramatically because water will be drawn from an area of low solute concentration (inside the cell) to an area of high solute concentration (outside the cell) (Figure 5.1.2.7). Many microorganisms do not survive these conditions of high osmotic

pressure. Honey, for example, is 80% sucrose, an environment in which very few microorganisms are capable of growing, thereby eliminating the need for refrigeration. Salted meats and fish, like ham and cod, respectively, were critically important foods before the age of refrigeration. Fruits were preserved by adding sugar, making jams and jellies. However, certain microbes, such as molds and yeasts, tend to be more tolerant of desiccation and high osmotic pressures, and, thus, may still contaminate these types of foods.



Figure 5.1.2.7: (a) The addition of a solute creates a hypertonic environment, drawing water out of cells. (b) Some foods can be dried directly, like raisins and jerky. Other foods are dried with the addition of salt, as in the case of salted fish, or sugar, as in the case of jam. (credit a: modification of work by "Bruce Blaus"/Wikimedia Commons; credit raisins: modification of work by Christian Schnettelker; credit jerky: modification of work by Larry Jacobsen; credit salted fish: modification of work by "The Photographer"/Wikimedia Commons; credit jam: modification of work by Kim Becker)

? Exercise 5.1.2.3

How does the addition of salt or sugar to food affect its water activity?

Radiation

Radiation in various forms, from high-energy radiation to sunlight, can be used to kill microbes or inhibit their growth. **Ionizing radiation** includes X-rays, gamma rays, and high-energy electron beams. Ionizing radiation is strong enough to pass into the cell, where it alters molecular structures and damages cell components. For example, ionizing radiation introduces double-strand breaks in DNA molecules. This may directly cause DNA mutations to occur, or mutations may be introduced when the cell attempts to repair the DNA damage. As these mutations accumulate, they eventually lead to cell death.

Both X-rays and gamma rays easily penetrate paper and plastic and can therefore be used to sterilize many packaged materials. In the laboratory, ionizing radiation is commonly used to sterilize materials that cannot be autoclaved, such as plastic Petri dishes and disposable plastic inoculating loops. For clinical use, ionizing radiation is used to sterilize gloves, intravenous tubing, and other latex and plastic items used for patient care. Ionizing radiation is also used for the sterilization of other types of delicate, heat-sensitive materials used clinically, including tissues for transplantation, pharmaceutical drugs, and medical equipment.

In Europe, gamma irradiation for food preservation is widely used, although it has been slow to catch on in the United States (see the Micro Connections box on this topic). Packaged dried spices are also often gamma-irradiated. Because of their ability to penetrate paper, plastic, thin sheets of wood and metal, and tissue, great care must be taken when using X-rays and gamma irradiation. These types of ionizing irradiation cannot penetrate thick layers of iron or lead, so these metals are commonly used to protect humans who may be potentially exposed.

Another type of radiation, nonionizing radiation, is commonly used for sterilization and uses less energy than ionizing radiation. It does not penetrate cells or packaging. Ultraviolet (UV) light is one example; it causes thymine dimers to form between adjacent thymines within a single strand of DNA (Figure 5.1.2.8). When DNA polymerase encounters the thymine dimer, it does not always incorporate the appropriate complementary nucleotides (two adenines), and this leads to formation of mutations that can ultimately kill microorganisms.

UV light can be used effectively by both consumers and laboratory personnel to control microbial growth. UV lamps are now commonly incorporated into water purification systems for use in homes. In addition, small portable UV lights are commonly used by campers to purify water from natural environments before drinking. Germicidal lamps are also used in surgical suites, biological

safety cabinets, and transfer hoods, typically emitting UV light at a wavelength of 260 nm. Because UV light does not penetrate surfaces and will not pass through plastics or glass, cells must be exposed directly to the light source.

Sunlight has a very broad spectrum that includes UV and visible light. In some cases, sunlight can be effective against certain bacteria because of both the formation of thymine dimers by UV light and by the production of reactive oxygen products induced in low amounts by exposure to visible light.

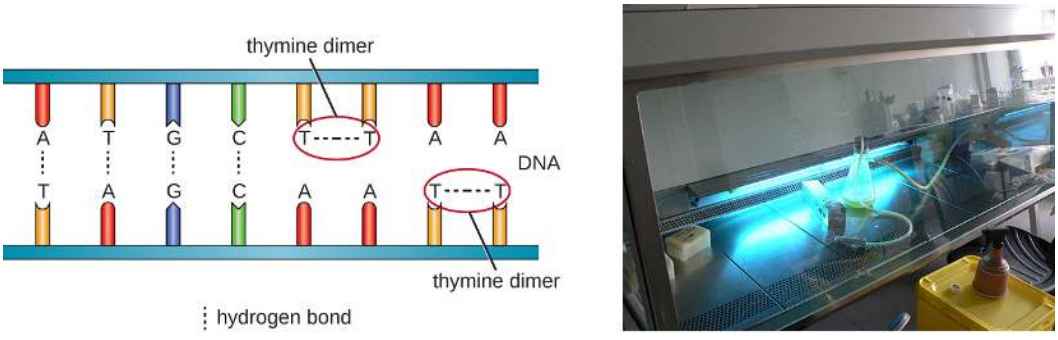


Figure 5.1.2.8: (a) UV radiation causes the formation of thymine dimers in DNA, leading to lethal mutations in the exposed microbes. (b) Germicidal lamps that emit UV light are commonly used in the laboratory to sterilize equipment.

? Exercise 5.1.2.4

1. What are two advantages of ionizing radiation as a sterilization method?
2. How does the effectiveness of ionizing radiation compare with that of nonionizing radiation?

Irradiated Food: Would You Eat That?

Of all the ways to prevent food spoilage and foodborne illness, gamma irradiation may be the most unappetizing. Although gamma irradiation is a proven method of eliminating potentially harmful microbes from food, the public has yet to buy in. Most of their concerns, however, stem from misinformation and a poor understanding of the basic principles of radiation.

The most common method of irradiation is to expose food to cobalt-60 or cesium-137 by passing it through a radiation chamber on a conveyor belt. The food does not directly contact the radioactive material and does not become radioactive itself. Thus, there is no risk for exposure to radioactive material through eating gamma-irradiated foods. Additionally, irradiated foods are not significantly altered in terms of nutritional quality, aside from the loss of certain vitamins, which is also exacerbated by extended storage. Alterations in taste or smell may occur in irradiated foods with high fat content, such as fatty meats and dairy products, but this effect can be minimized by using lower doses of radiation at colder temperatures.

In the United States, the CDC, Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA) have deemed irradiation safe and effective for various types of meats, poultry, shellfish, fresh fruits and vegetables, eggs with shells, and spices and seasonings. Gamma irradiation of foods has also been approved for use in many other countries, including France, the Netherlands, Portugal, Israel, Russia, China, Thailand, Belgium, Australia, and South Africa. To help ameliorate consumer concern and assist with education efforts, irradiated foods are now clearly labeled and marked with the international irradiation symbol, called the “radura” (Figure 5.1.2.9). Consumer acceptance seems to be rising, as indicated by several recent studies.



(a) (b)

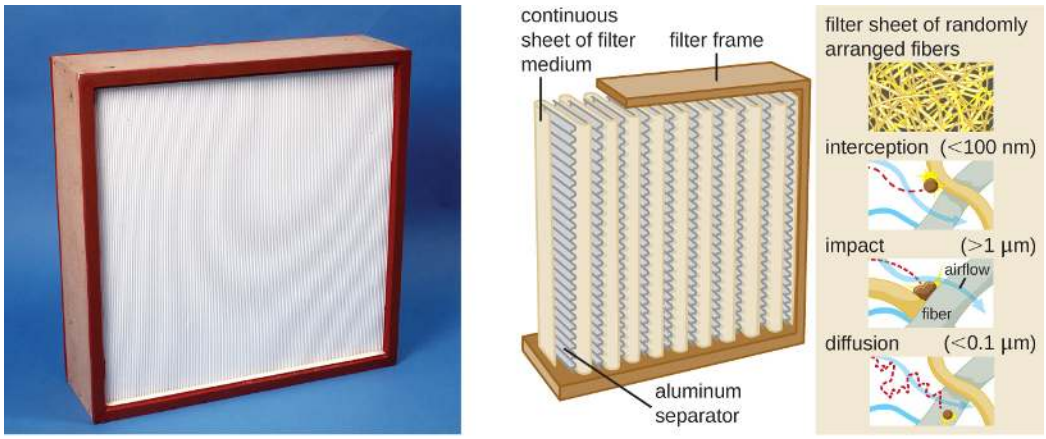
Figure 5.1.2.9: (a) Foods are exposed to gamma radiation by passage on a conveyor belt through a radiation chamber. (b) Gamma-irradiated foods must be clearly labeled and display the irradiation symbol, known as the “radura.” (credit a, b: modification of work by U.S. Department of Agriculture)

Sonication

The use of high-frequency ultrasound waves to disrupt cell structures is called sonication. Application of ultrasound waves causes rapid changes in pressure within the intracellular liquid; this leads to cavitation, the formation of bubbles inside the cell, which can disrupt cell structures and eventually cause the cell to lyse or collapse. Sonication is useful in the laboratory for efficiently lysing cells to release their contents for further research; outside the laboratory, sonication is used for cleaning surgical instruments, lenses, and a variety of other objects such as coins, tools, and musical instruments.

Filtration

Filtration is a method of physically separating microbes from samples. Air is commonly filtered through high-efficiency particulate air (HEPA) filters (Figure 5.1.2.10). HEPA filters have effective pore sizes of 0.3 µm, small enough to capture bacterial cells, endospores, and many viruses, as air passes through these filters, nearly sterilizing the air on the other side of the filter. HEPA filters have a variety of applications and are used widely in clinical settings, in cars and airplanes, and even in the home. For example, they may be found in vacuum cleaners, heating and air-conditioning systems, and air purifiers.



(a) (b)

Figure 5.1.2.10: (a) HEPA filters like this one remove microbes, endospores, and viruses as air flows through them. (b) A schematic of a HEPA filter. (credit a: modification of work by CSIRO; credit b: modification of work by “LadyofHats”/Mariana Ruiz Villareal)

Biological Safety Cabinets

Biological safety cabinets are a good example of the use of HEPA filters. HEPA filters in biological safety cabinets (BSCs) are used to remove particulates in the air either entering the cabinet (air intake), leaving the cabinet (air exhaust), or treating both the intake and exhaust. Use of an air-intake HEPA filter prevents environmental contaminants from entering the BSC, creating a clean area for handling biological materials. Use of an air-exhaust HEPA filter prevents laboratory pathogens from contaminating the laboratory, thus maintaining a safe work area for laboratory personnel.

There are three classes of BSCs: I, II, and III. Each class is designed to provide a different level of protection for laboratory personnel and the environment; BSC II and III are also designed to protect the materials or devices in the cabinet. Table 5.1.2.1 summarizes the level of safety provided by each class of BSC for each BSL.

Table 5.1.2.1: Biological risks and BSCs

Biological Risk Assessed	BSC Class	Protection of Personnel	Protection of Environment	Protection of Product
BSL-1, BSL-2, BSL-3	I	Yes	Yes	No
BSL-1, BSL-2, BSL-3	II	Yes	Yes	Yes
BSL-4	III; II when used in suit room with suit	Yes	Yes	Yes

Class I BSCs protect laboratory workers and the environment from a low to moderate risk for exposure to biological agents used in the laboratory. Air is drawn into the cabinet and then filtered before exiting through the building's exhaust system. Class II BSCs use directional air flow and partial barrier systems to contain infectious agents. Class III BSCs are designed for working with highly infectious agents like those used in BSL-4 laboratories. They are gas tight, and materials entering or exiting the cabinet must be passed through a double-door system, allowing the intervening space to be decontaminated between uses. All air is passed through one or two HEPA filters and an air incineration system before being exhausted directly to the outdoors (not through the building's exhaust system). Personnel can manipulate materials inside the Class III cabinet by using long rubber gloves sealed to the cabinet.

Link to Learning

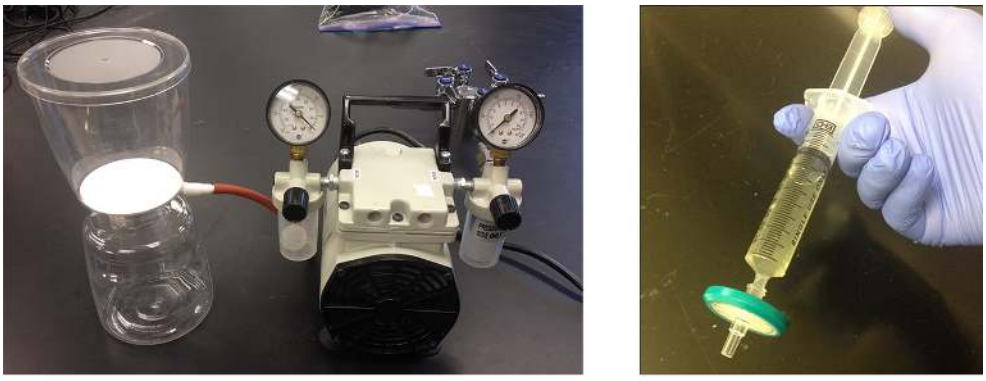
This video shows how BSCs are designed and explains how they protect personnel, the environment, and the product.

Filtration in Hospitals

HEPA filters are also commonly used in hospitals and surgical suites to prevent contamination and the spread of airborne microbes through ventilation systems. HEPA filtration systems may be designed for entire buildings or for individual rooms. For example, burn units, operating rooms, or isolation units may require special HEPA-filtration systems to remove opportunistic pathogens from the environment because patients in these rooms are particularly vulnerable to infection.

Membrane Filters

Filtration can also be used to remove microbes from liquid samples using membrane filtration. Membrane filters for liquids function similarly to HEPA filters for air. Typically, membrane filters that are used to remove bacteria have an effective pore size of 0.2 µm, smaller than the average size of a bacterium (1 µm), but filters with smaller pore sizes are available for more specific needs. Membrane filtration is useful for removing bacteria from various types of heat-sensitive solutions used in the laboratory, such as antibiotic solutions and vitamin solutions. Large volumes of culture media may also be filter sterilized rather than autoclaved to protect heat-sensitive components. Often when filtering small volumes, syringe filters are used, but vacuum filters are typically used for filtering larger volumes (Figure 5.1.2.11).



(a) (b)

Figure 5.1.2.11: Membrane filters come in a variety of sizes, depending on the volume of solution being filtered. (a) Larger volumes are filtered in units like these. The solution is drawn through the filter by connecting the unit to a vacuum. (b) Smaller volumes are often filtered using syringe filters, which are units that fit on the end of a syringe. In this case, the solution is pushed through by depressing the syringe's plunger. (credit a, b: modification of work by Brian Forster)

? Exercise 5.1.2.5

1. Would membrane filtration with a 0.2-µm filter likely remove viruses from a solution? Explain.
2. Name at least two common uses of HEPA filtration in clinical or laboratory settings.

Figure 5.1.2.12 and Figure 5.1.2.13 summarize the physical methods of control discussed in this section.

Physical Methods of Control			
Method	**Conditions**	**Mode of Action**	**Example Uses**
Heat			
Boiling	100 °C at sea level	Denatures proteins and alters membranes	Cooking, personal use, preparing certain laboratory media
Dry-heat oven	170 °C for 2 hours	Denatures proteins and alters membranes, dehydration, desiccation	Sterilization of heat-stable medical and laboratory equipment and glassware
Incineration	Exposure to flame	Destroy by burning	Flaming loop, microincinerator
Autoclave	Typical settings: 121 °C for 15 minutes at 15 pounds per square inch (psi)	Denatures proteins and alters membranes	Sterilization of microbiological media, heat-stable medical and laboratory equipment, and other heat-stable items
Pasteurization	Can vary. One type is 72 °C for 15 seconds (HTST)	Denatures proteins and alters membranes	Prevents spoilage of milk, apple juice, honey, and other ingestible liquids
Cold			
Refrigeration	0 °C to 7 °C	Inhibits metabolism (slows or arrests cell division)	Preservation of food or laboratory materials (solutions, cultures)
Freezing	Below −2 °C	Stops metabolism, may kill microbes	Long-term storage of food, laboratory cultures, or medical specimens
Pressure			
High-pressure processing	100–800 MPa	Denatures proteins and can cause cell lysis	Preservation of food
Hyberbaric oxygen therapy	Air pressure three times higher than normal	Inhibits metabolism and growth of anaerobic microbes	Treatment of certain infections (e.g., gas gangrene)
Desiccation			
Simple desiccation	Drying	Inhibits metabolism	Dried fruits, jerky
Reduce water activity	Addition of salt or water	Inhibits metabolism and can cause lysis	Salted meats and fish, honey, jams and jellies
Lyophilization	Rapid freezing under vacuum	Inhibits metabolism	Preservation of food, laboratory cultures, or reagents
Radiation			
Ionizing radiation	Exposure to X-rays or gamma rays	Alters molecular structures, introduces double-strand breaks into DNA	Sterilization of spices and heat-sensitive laboratory and medical items; used for food sterilization in Europe but not widely accepted in US
Nonionizing radiation	Exposure to ultraviolet light	Introduces thymine dimers, leading to mutations	Surface sterilization of laboratory materials, water purification

Figure 5.1.2.12: Physical methods of control

Physical Methods of Control (continued)			
Method	**Conditions**	**Mode of Action**	**Example Uses**
Sonication			
Sonication	Exposure to ultrasonic waves	Cavitation (formation of empty space) disrupts cells, lysing them	Laboratory research to lyse cells; cleaning jewelry, lenses, and equipment
Filtration			
HEPA filtration	Use of high-efficiency particulate air (HEPA) filter with 0.3 μm pore size	Physically removes microbes from air	Laboratory biological safety cabinets, operating rooms, isolation units, heating and air conditioning systems, vacuum cleaners
Membrane filtration	Use of membrane filter with 0.2-μm or smaller pore size	Physically removes microbes from liquid solutions	Removal of bacteria from heat-sensitive solutions like vitamins, antibiotics, and media with heat-sensitive components

Figure 5.1.2.13: Physical methods of control (continued)

Key Concepts and Summary

- Heat is a widely used and highly effective method for controlling microbial growth.
- **Dry-heat sterilization** protocols are used commonly in aseptic techniques in the laboratory. However, **moist-heat sterilization** is typically the more effective protocol because it penetrates cells better than dry heat does.
- **Pasteurization** is used to kill pathogens and reduce the number of microbes that cause food spoilage. **High-temperature, short-time pasteurization** is commonly used to pasteurize milk that will be refrigerated; **ultra-high temperature pasteurization** can be used to pasteurize milk for long-term storage without refrigeration.
- Refrigeration slows microbial growth; freezing stops growth, killing some organisms. Laboratory and medical specimens may be frozen on dry ice or at ultra-low temperatures for storage and transport.
- High-pressure processing can be used to kill microbes in food. Hyperbaric oxygen therapy to increase oxygen saturation has also been used to treat certain infections.
- **Desiccation** has long been used to preserve foods and is accelerated through the addition of salt or sugar, which decrease water activity in foods.
- **Lyophilization** combines cold exposure and desiccation for the long-term storage of foods and laboratory materials, but microbes remain and can be rehydrated.
- **Ionizing radiation**, including gamma irradiation, is an effective way to sterilize heat-sensitive and packaged materials. **Nonionizing radiation**, like ultraviolet light, is unable to penetrate surfaces but is useful for surface sterilization.
- **HEPA** filtration is commonly used in hospital ventilation systems and biological safety cabinets in laboratories to prevent transmission of airborne microbes. **Membrane filtration** is commonly used to remove bacteria from heat-sensitive solutions.

Footnotes

1. 1 US Department of Agriculture. “Freezing and Food Safety.” 2013. http://www.fsis.usda.gov/wps/portal/...afety/CT_Index. Accessed June 8, 2016.
2. 2 C. Ferstl. “High Pressure Processing: Insights on Technology and Regulatory Requirements.” Food for Thought/White Paper. Series Volume 10. Livermore, CA: The National Food Lab; July 2013.
3. 3 US Food and Drug Administration. “Kinetics of Microbial Inactivation for Alternative Food Processing Technologies: High Pressure Processing.” 2000. www.fda.gov/Food/FoodScienceR.../ucm101456.htm. Accessed July 19, 2106.
4. 4 CL McCarty et al. “Large Outbreak of Botulism Associated with a Church Potluck Meal-Ohio, 2015.” *Morbidity and Mortality Weekly Report* 64, no. 29 (2015):802–803.
5. 5 AM Johnson et al. “Consumer Acceptance of Electron-Beam Irradiated Ready-to-Eat Poultry Meats.” *Food Processing Preservation*, 28 no. 4 (2004):302–319.

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5.1.3: Using Chemicals to Control Microorganisms

Learning Objectives

- Understand and compare various chemicals used to control microbial growth, including their uses, advantages and disadvantages, chemical structure, and mode of action

In addition to physical methods of microbial control, chemicals are also used to control microbial growth. A wide variety of chemicals can be used as disinfectants or antiseptics. When choosing which to use, it is important to consider the type of microbe targeted; how clean the item needs to be; the disinfectant's effect on the item's integrity; its safety to animals, humans, and the environment; its expense; and its ease of use. This section describes the variety of chemicals used as disinfectants and antiseptics, including their mechanisms of action and common uses.

Phenolics

In the 1800s, scientists began experimenting with a variety of chemicals for disinfection. In the 1860s, British surgeon Joseph Lister (1827–1912) began using carbolic acid, known as phenol, as a disinfectant for the treatment of surgical wounds (see Foundations of Modern Cell Theory). In 1879, Lister's work inspired the American chemist Joseph Lawrence (1836–1909) to develop Listerine, an alcohol-based mixture of several related compounds that is still used today as an oral antiseptic. Today, carbolic acid is no longer used as a surgical disinfectant because it is a skin irritant, but the chemical compounds found in antiseptic mouthwashes and throat lozenges are called phenolics.

Chemically, phenol consists of a benzene ring with an –OH group, and phenolics are compounds that have this group as part of their chemical structure (Figure 5.1.3.1). Phenolics such as thymol and eucalyptol occur naturally in plants. Other phenolics can be derived from creosote, a component of coal tar. Phenolics tend to be stable, persistent on surfaces, and less toxic than phenol. They inhibit microbial growth by denaturing proteins and disrupting membranes.

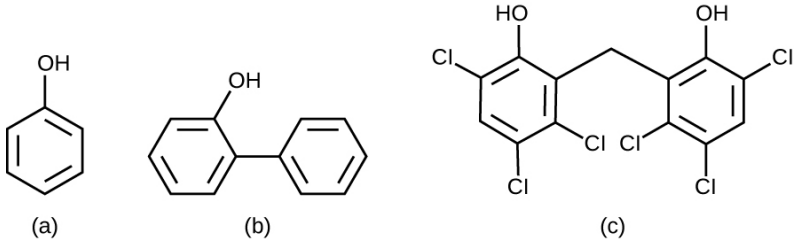


Figure 5.1.3.1: Phenol and phenolic compounds have been used to control microbial growth. (a) Chemical structure of phenol, also known as carbolic acid. (b) o-Phenylphenol, a type of phenolic, has been used as a disinfectant as well as to control bacterial and fungal growth on harvested citrus fruits. (c) Hexachlorophene, another phenol, known as a bisphenol (two rings), is the active ingredient in pHisoHex.

Since Lister's time, several phenolic compounds have been used to control microbial growth. Phenolics like cresols(methylated phenols) and o-phenylphenol were active ingredients in various formulations of Lysol since its invention in 1889. o-Phenylphenol was also commonly used in agriculture to control bacterial and fungal growth on harvested crops, especially citrus fruits, but its use in the United States is now far more limited. The bisphenol hexachlorophene, a disinfectant, is the active ingredient in pHisoHex, a topical cleansing detergent widely used for handwashing in hospital settings. pHisoHex is particularly effective against gram-positive bacteria, including those causing staphylococcal and streptococcal skin infections. pHisoHex was formerly used for bathing infants, but this practice has been discontinued because it has been shown that exposure to hexachlorophene can lead to neurological problems.

Triclosan is another bisphenol compound that has seen widespread application in antibacterial products over the last several decades. Initially used in toothpastes, triclosan is now commonly used in hand soaps and is frequently impregnated into a wide variety of other products, including cutting boards, knives, shower curtains, clothing, and concrete, to make them antimicrobial. It is particularly effective against gram-positive bacteria on the skin, as well as certain gram-negative bacteria and yeasts.[1]

Triclosan: Antibacterial Overkill?

Hand soaps and other cleaning products are often marketed as “antibacterial,” suggesting that they provide a level of cleanliness superior to that of conventional soaps and cleansers. But are the antibacterial ingredients in these products really safe and effective?

About 75% of antibacterial liquid hand soaps and 30% of bar soaps contain the chemical triclosan, a phenolic, (Figure 5.1.3.2).[1] Triclosan blocks an enzyme in the bacterial fatty acid-biosynthesis pathway that is not found in the comparable human pathway. Although the use of triclosan in the home increased dramatically during the 1990s, more than 40 years of research by the FDA have turned up no conclusive evidence that washing with triclosan-containing products provides increased health benefits compared with washing with traditional soap. Although some studies indicate that fewer bacteria may remain on a person’s hands after washing with triclosan-based soap, compared with traditional soap, no evidence points to any reduction in the transmission of bacteria that cause respiratory and gastrointestinal illness. In short, soaps with triclosan may remove or kill a few more germs but not enough to reduce the spread of disease.

Perhaps more disturbing, some clear risks associated with triclosan-based soaps have come to light. The widespread use of triclosan has led to an increase in triclosan-resistant bacterial strains, including those of clinical importance, such as *Salmonella enterica*; this resistance may render triclosan useless as an antibacterial in the long run.[3][4] Bacteria can easily gain resistance to triclosan through a change to a single gene encoding the targeted enzyme in the bacterial fatty acid-synthesis pathway. Other disinfectants with a less specific mode of action are much less prone to engendering resistance because it would take much more than a single genetic change.

Use of triclosan over the last several decades has also led to a buildup of the chemical in the environment. Triclosan in hand soap is directly introduced into wastewater and sewage systems as a result of the handwashing process. There, its antibacterial properties can inhibit or kill bacteria responsible for the decomposition of sewage, causing septic systems to clog and back up. Eventually, triclosan in wastewater finds its way into surface waters, streams, lakes, sediments, and soils, disrupting natural populations of bacteria that carry out important environmental functions, such as inhibiting algae. Triclosan also finds its way into the bodies of amphibians and fish, where it can act as an endocrine disruptor. Detectable levels of triclosan have also been found in various human bodily fluids, including breast milk, plasma, and urine.[5] In fact, a study conducted by the CDC found detectable levels of triclosan in the urine of 75% of 2,517 people tested in 2003–2004.[6] This finding is even more troubling given the evidence that triclosan may affect immune function in humans.[7]

In December 2013, the FDA gave soap manufacturers until 2016 to prove that antibacterial soaps provide a significant benefit over traditional soaps; if unable to do so, manufacturers will be forced to remove these products from the market.

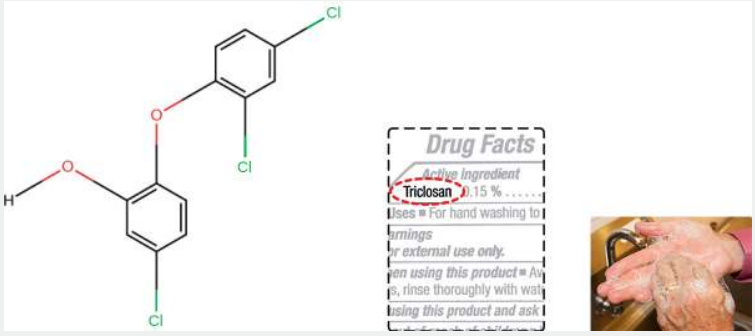


Figure 5.1.3.2: Triclosan is a common ingredient in antibacterial soaps despite evidence that it poses environmental and health risks and offers no significant health benefit compared to conventional soaps. (credit b, c: modification of work by FDA)

Exercise 5.1.3.1

Why is triclosan more like an antibiotic than a traditional disinfectant?

Heavy Metals

Some of the first chemical disinfectants and antiseptics to be used were heavy metals. Heavy metals kill microbes by binding to proteins, thus inhibiting enzymatic activity (Figure 5.1.3.3). Heavy metals are oligodynamic, meaning that very small concentrations show significant antimicrobial activity. Ions of heavy metals bind to sulfur-containing amino acids strongly and bioaccumulate within cells, allowing these metals to reach high localized concentrations. This causes proteins to denature.

Heavy metals are not selectively toxic to microbial cells. They may bioaccumulate in human or animal cells, as well, and excessive concentrations can have toxic effects on humans. If too much silver accumulates in the body, for example, it can result in a condition called argyria, in which the skin turns irreversibly blue-gray. One way to reduce the potential toxicity of heavy metals is by carefully controlling the duration of exposure and concentration of the heavy metal.



(a) (b) (c) (d) (e)

Figure 5.1.3.3: Heavy metals denature proteins, impairing cell function and, thus, giving them strong antimicrobial properties. (a) Copper in fixtures like this door handle kills microbes that otherwise might accumulate on frequently touched surfaces. (b) Eating utensils contain small amounts of silver to inhibit microbial growth. (c) Copper commonly lines incubators to minimize contamination of cell cultures stored inside. (d) Antiseptic mouthwashes commonly contain zinc chloride. (e) This patient is suffering from argyria, an irreversible condition caused by bioaccumulation of silver in the body. (credit b: modification of work by "Shoshanah"/Flickr; credit e: modification of work by Herbert L. Fred and Hendrik A. van Dijk)

Mercury

Mercury is an example of a heavy metal that has been used for many years to control microbial growth. It was used for many centuries to treat syphilis. Mercury compounds like mercuric chloride are mainly bacteriostatic and have a very broad spectrum of activity. Various forms of mercury bind to sulfur-containing amino acids within proteins, inhibiting their functions.

In recent decades, the use of such compounds has diminished because of mercury's toxicity. It is toxic to the central nervous, digestive, and renal systems at high concentrations, and has negative environmental effects, including bioaccumulation in fish. Topical antiseptics such as mercurochrome, which contains mercury in low concentrations, and merthiolate, a tincture (a solution of mercury dissolved in alcohol) were once commonly used. However, because of concerns about using mercury compounds, these antiseptics are no longer sold in the United States.

Silver

Silver has long been used as an antiseptic. In ancient times, drinking water was stored in silver jugs.[8] Silvadene cream is commonly used to treat topical wounds and is particularly helpful in preventing infection in burn wounds. Silver nitrate drops were once routinely applied to the eyes of newborns to protect against ophthalmia neonatorum, eye infections that can occur due to exposure to pathogens in the birth canal, but antibiotic creams are more now commonly used. Silver is often combined with antibiotics, making the antibiotics thousands of times more effective.[9] Silver is also commonly incorporated into catheters and bandages, rendering them antimicrobial; however, there is evidence that heavy metals may also enhance selection for antibiotic resistance.[10]

Copper, Nickel, and Zinc

Several other heavy metals also exhibit antimicrobial activity. Copper sulfate is a common algicide used to control algal growth in swimming pools and fish tanks. The use of metallic copper to minimize microbial growth is also becoming more widespread. Copper linings in incubators help reduce contamination of cell cultures. The use of copper pots for water storage in underdeveloped

countries is being investigated as a way to combat diarrheal diseases. Copper coatings are also becoming popular for frequently handled objects such as doorknobs, cabinet hardware, and other fixtures in health-care facilities in an attempt to reduce the spread of microbes.

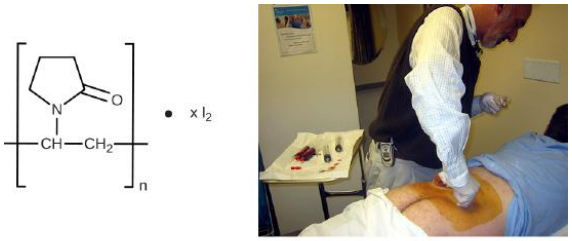
Nickel and zinc coatings are now being used in a similar way. Other forms of zinc, including zinc chloride and zinc oxide, are also used commercially. Zinc chloride is quite safe for humans and is commonly found in mouthwashes, substantially increasing their length of effectiveness. Zinc oxide is found in a variety of products, including topical antiseptic creams such as calamine lotion, diaper ointments, baby powder, and dandruff shampoos.

? Exercise 5.1.3.2

Why are many heavy metals both antimicrobial and toxic to humans?

Halogens

Other chemicals commonly used for disinfection are the halogens iodine, chlorine, and fluorine. Iodine works by oxidizing cellular components, including sulfur-containing amino acids, nucleotides, and fatty acids, and destabilizing the macromolecules that contain these molecules. It is often used as a topical tincture, but it may cause staining or skin irritation. An iodophor is a compound of iodine complexed with an organic molecule, thereby increasing iodine's stability and, in turn, its efficacy. One common iodophor is povidone-iodine, which includes a wetting agent that releases iodine relatively slowly. Betadine is a brand of povidone-iodine commonly used as a hand scrub by medical personnel before surgery and for topical antisepsis of a patient's skin before incision (Figure 5.1.3.4).



(a) (b)

Figure 5.1.3.4: (a) Betadine is a solution of the iodophor povidone-iodine. (b) It is commonly used as a topical antiseptic on a patient's skin before incision during surgery. (credit b: modification of work by Andrew Ratto)

Chlorine is another halogen commonly used for disinfection. When chlorine gas is mixed with water, it produces a strong oxidant called hypochlorous acid, which is uncharged and enters cells easily. Chlorine gas is commonly used in municipal drinking water and wastewater treatment plants, with the resulting hypochlorous acid producing the actual antimicrobial effect. Those working at water treatment facilities need to take great care to minimize personal exposure to chlorine gas. Sodium hypochlorite is the chemical component of common household bleach, and it is also used for a wide variety of disinfecting purposes. Hypochlorite salts, including sodium and calcium hypochlorites, are used to disinfect swimming pools. Chlorine gas, sodium hypochlorite, and calcium hypochlorite are also commonly used disinfectants in the food processing and restaurant industries to reduce the spread of foodborne diseases. Workers in these industries also need to take care to use these products correctly to ensure their own safety as well as the safety of consumers. A recent joint statement published by the Food and Agriculture Organization (FAO) of the United Nations and WHO indicated that none of the many beneficial uses of chlorine products in food processing to reduce the spread of foodborne illness posed risks to consumers.[11]

Another class of chlorinated compounds called chloramines are widely used as disinfectants. Chloramines are relatively stable, releasing chlorine over long periods time. Chloramines are derivatives of ammonia by substitution of one, two, or all three hydrogen atoms with chlorine atoms (Figure 5.1.3.5).

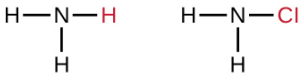


Figure 5.1.3.5: Monochloroamine, one of the chloramines, is derived from ammonia by the replacement of one hydrogen atom with a chlorine atom.

Chloramines and other cholorine compounds may be used for disinfection of drinking water, and chloramine tablets are frequently used by the military for this purpose. After a natural disaster or other event that compromises the public water supply, the CDC recommends disinfecting tap water by adding small amounts of regular household bleach. Recent research suggests that sodium dichloroisocyanurate (NaDCC) may also be a good alternative for drinking water disinfection. Currently, NaDCC tablets are available for general use and for use by the military, campers, or those with emergency needs; for these uses, NaDCC is preferable to chloramine tablets. Chlorine dioxide, a gaseous agent used for fumigation and sterilization of enclosed areas, is also commonly used for the disinfection of water.

Although chlorinated compounds are relatively effective disinfectants, they have their disadvantages. Some may irritate the skin, nose, or eyes of some individuals, and they may not completely eliminate certain hardy organisms from contaminated drinking water. The fungus *Cryptosporidium*, for example, has a protective outer shell that makes it resistant to chlorinated disinfectants. Thus, boiling of drinking water in emergency situations is recommended when possible.

The halogen fluorine is also known to have antimicrobial properties that contribute to the prevention of dental caries(cavities).[12] Fluoride is the main active ingredient of toothpaste and is also commonly added to tap water to help communities maintain oral health. Chemically, fluoride can become incorporated into the hydroxyapatite of tooth enamel, making it more resistant to corrosive acids produced by the fermentation of oral microbes. Fluoride also enhances the uptake of calcium and phosphate ions in tooth enamel, promoting remineralization. In addition to strengthening enamel, fluoride also seems to be bacteriostatic. It accumulates in plaque-forming bacteria, interfering with their metabolism and reducing their production of the acids that contribute to tooth decay.

? Exercise 5.1.3.3

What is a benefit of a chloramine over hypochlorite for disinfecting?

Alcohols

Alcohols make up another group of chemicals commonly used as disinfectants and antiseptics. They work by rapidly denaturing proteins, which inhibits cell metabolism, and by disrupting membranes, which leads to cell lysis. Once denatured, the proteins may potentially refold if enough water is present in the solution. Alcohols are typically used at concentrations of about 70% aqueous solution and, in fact, work better in aqueous solutions than 100% alcohol solutions. This is because alcohols coagulate proteins. In higher alcohol concentrations, rapid coagulation of surface proteins prevents effective penetration of cells. The most commonly used alcohols for disinfection are ethyl alcohol(ethanol) and isopropyl alcohol (isopropanol, rubbing alcohol) (Figure 5.1.3.6).

Alcohols tend to be bactericidal and fungicidal, but may also be viricidal for enveloped viruses only. Although alcohols are not sporicidal, they do inhibit the processes of sporulation and germination. Alcohols are volatile and dry quickly, but they may also cause skin irritation because they dehydrate the skin at the site of application. One common clinical use of alcohols is swabbing the skin for degerming before needle injection. Alcohols also are the active ingredients in instant hand sanitizers, which have gained popularity in recent years. The alcohol in these hand sanitizers works both by denaturing proteins and by disrupting the microbial cell membrane, but will not work effectively in the presence of visible dirt.

Last, alcohols are used to make tinctures with other antiseptics, such as the iodine tinctures discussed previously in this chapter. All in all, alcohols are inexpensive and quite effective for the disinfection of a broad range of vegetative microbes. However, one disadvantage of alcohols is their high volatility, limiting their effectiveness to immediately after application.



Figure 5.1.3.6: (a) Ethyl alcohol, the intoxicating ingredient found in alcoholic drinks, is also used commonly as a disinfectant. (b) Isopropyl alcohol, also called rubbing alcohol, has a related molecular structure and is another commonly used disinfectant. (credit a photo: modification of work by D Coetzee; credit b photo: modification of work by Craig Spurrier)

? Exercise 5.1.3.4

1. Name at least three advantages of alcohols as disinfectants.
2. Describe several specific applications of alcohols used in disinfectant products.

Surfactants

Surface-active agents, or surfactants, are a group of chemical compounds that lower the surface tension of water. Surfactants are the major ingredients in soaps and detergents. Soaps are salts of long-chain fatty acids and have both polar and nonpolar regions, allowing them to interact with polar and nonpolar regions in other molecules (Figure 5.1.3.7). They can interact with nonpolar oils and grease to create emulsions in water, loosening and lifting away dirt and microbes from surfaces and skin. Soaps do not kill or inhibit microbial growth and so are not considered antiseptics or disinfectants. However, proper use of soaps mechanically carries away microorganisms, effectively degerming a surface. Some soaps contain added bacteriostatic agents such as triclocarban or cloflucarban, compounds structurally related to triclosan, that introduce antiseptic or disinfectant properties to the soaps.

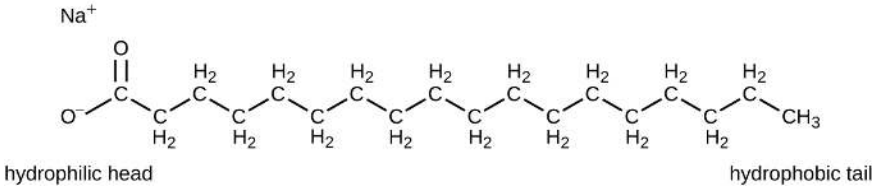
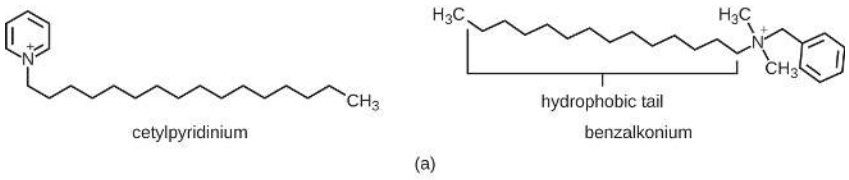
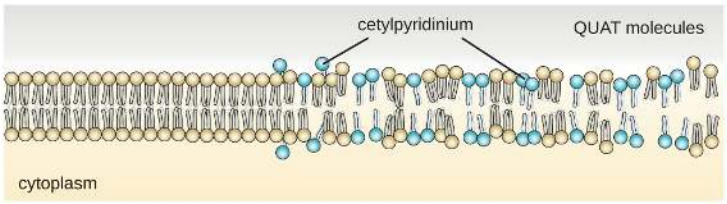


Figure 5.1.3.7: Soaps are the salts (sodium salt in the illustration) of fatty acids and have the ability to emulsify lipids, fats, and oils by interacting with water through their hydrophilic heads and with the lipid at their hydrophobic tails.

Soaps, however, often form films that are difficult to rinse away, especially in hard water, which contains high concentrations of calcium and magnesium mineral salts. Detergents contain synthetic surfactant molecules with both polar and nonpolar regions that have strong cleansing activity but are more soluble, even in hard water, and, therefore, leave behind no soapy deposits. Anionic detergents, such as those used for laundry, have a negatively charged anion at one end attached to a long hydrophobic chain, whereas cationic detergents have a positively charged cation instead. Cationic detergents include an important class of disinfectants and antiseptics called the quaternary ammonium salts (quats), named for the characteristic quaternary nitrogen atom that confers the positive charge (Figure 5.1.3.8). Overall, quats have properties similar to phospholipids, having hydrophilic and hydrophobic ends. As such, quats have the ability to insert into the bacterial phospholipid bilayer and disrupt membrane integrity. The cationic charge of quats appears to confer their antimicrobial properties, which are diminished when neutralized. Quats have several useful properties. They are stable, nontoxic, inexpensive, colorless, odorless, and tasteless. They tend to be bactericidal by disrupting membranes. They are also active against fungi, protozoans, and enveloped viruses, but endospores are unaffected. In clinical settings, they may be used as antiseptics or to disinfect surfaces. Mixtures of quats are also commonly found in household cleaners and disinfectants, including many current formulations of Lysol brand products, which contain benzalkonium chlorides as the active ingredients. Benzalkonium chlorides, along with the quat cetylpyrimidine chloride, are also found in products such as skin antiseptics, oral rinses, and mouthwashes.



(a)



(b)

Figure 5.1.3.8: (a) Two common quats are benzylalkonium chloride and cetylpyrimidine chloride. Note the hydrophobic nonpolar carbon chain at one end and the nitrogen-containing cationic component at the other end. (b) Quats are able to infiltrate the phospholipid plasma membranes of bacterial cells and disrupt their integrity, leading to death of the cell.

? Exercise 5.1.3.5

Why are soaps not considered disinfectants?

Handwashing the Right Way

Handwashing is critical for public health and should be emphasized in a clinical setting. For the general public, the CDC recommends handwashing before, during, and after food handling; before eating; before and after interacting with someone who is ill; before and after treating a wound; after using the toilet or changing diapers; after coughing, sneezing, or blowing the nose; after handling garbage; and after interacting with an animal, its feed, or its waste. Figure 5.1.3.9 illustrates the five steps of proper handwashing recommended by the CDC.

Handwashing is even more important for health-care workers, who should wash their hands thoroughly between every patient contact, after the removal of gloves, after contact with bodily fluids and potentially infectious fomites, and before and after assisting a surgeon with invasive procedures. Even with the use of proper surgical attire, including gloves, scrubbing for surgery is more involved than routine handwashing. The goal of surgical scrubbing is to reduce the normal microbiota on the skin's surface to prevent the introduction of these microbes into a patient's surgical wounds.

There is no single widely accepted protocol for surgical scrubbing. Protocols for length of time spent scrubbing may depend on the antimicrobial used; health-care workers should always check the manufacturer's recommendations. According to the Association of Surgical Technologists (AST), surgical scrubs may be performed with or without the use of brushes (Figure 5.1.3.9).

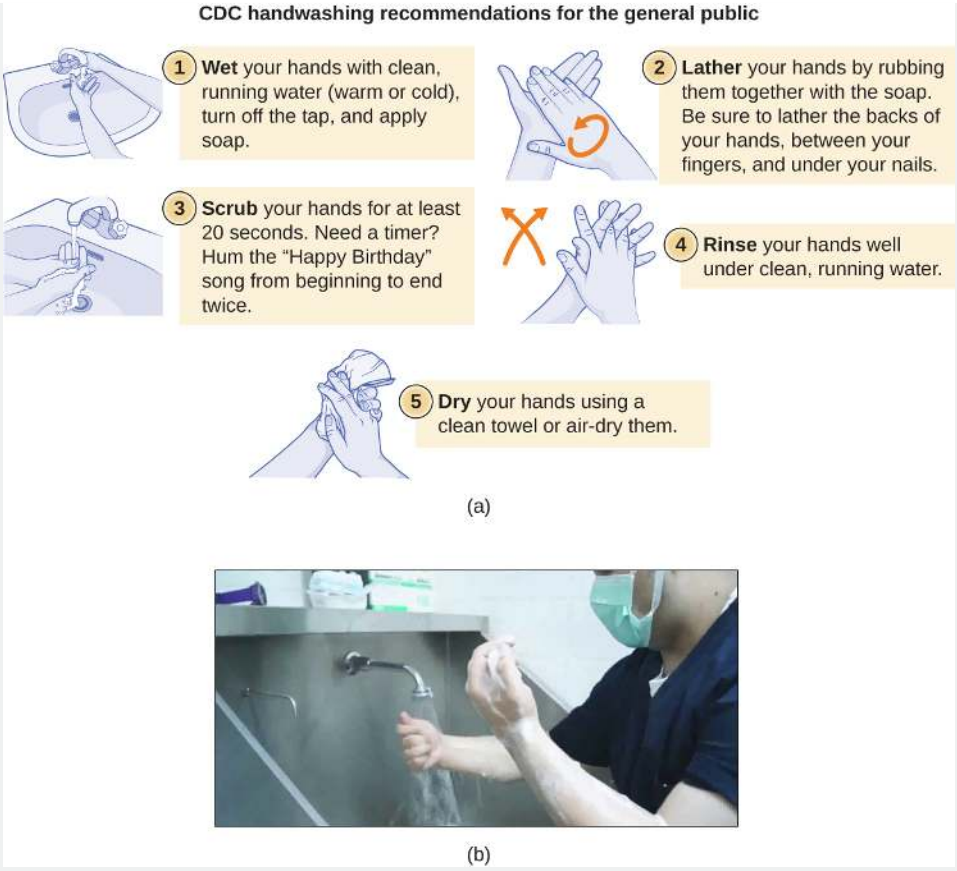


Figure 5.1.3.9: (a) The CDC recommends five steps as part of typical handwashing for the general public. (b) Surgical scrubbing is more extensive, requiring scrubbing starting from the fingertips, extending to the hands and forearms, and then up beyond the elbows, as shown here. (credit a: modification of work by World Health Organization)

Link to Learning

To learn more about proper handwashing, visit the CDC's website.

Bisbiguanides

Bisbiguanides were first synthesized in the 20th century and are cationic (positively charged) molecules known for their antiseptic properties (Figure 5.1.3.10). One important bisbiguanide antiseptic is chlorhexidine. It has broad-spectrum activity against yeasts, gram-positive bacteria, and gram-negative bacteria, with the exception of *Pseudomonas aeruginosa*, which may develop resistance on repeated exposure.[13] Chlorhexidine disrupts cell membranes and is bacteriostatic at lower concentrations or bactericidal at higher concentrations, in which it actually causes the cells' cytoplasmic contents to congeal. It also has activity against enveloped viruses. However, chlorhexidine is poorly effective against *Mycobacterium tuberculosis* and nonenveloped viruses, and it is not sporicidal. Chlorhexidine is typically used in the clinical setting as a surgical scrub and for other handwashing needs for medical personnel, as well as for topical antisepsis for patients before surgery or needle injection. It is more persistent than iodophors, providing long-lasting antimicrobial activity. Chlorhexidine solutions may also be used as oral rinses after oral procedures or to treat gingivitis. Another bisbiguanide, alexidine, is gaining popularity as a surgical scrub and an oral rinse because it acts faster than chlorhexidine.

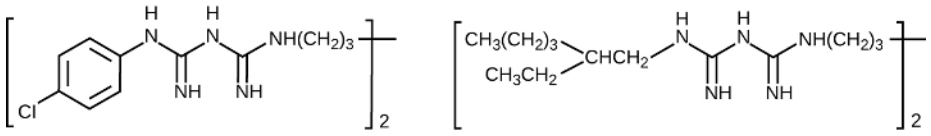


Figure 5.1.3.10: The bisbiguanides chlorhexadine and alexidine are cationic antiseptic compounds commonly used as surgical scrubs.

? Exercise 5.1.3.6

What two effects does chlorhexidine have on bacterial cells?

Alkylating Agents

The alkylating agents are a group of strong disinfecting chemicals that act by replacing a hydrogen atom within a molecule with an alkyl group (C_nH_{2n+1}), thereby inactivating enzymes and nucleic acids (Figure 5.1.3.11). The alkylating agent formaldehyde (CH_2OH) is commonly used in solution at a concentration of 37% (known as formalin) or as a gaseous disinfectant and biocide. It is a strong, broad-spectrum disinfectant and biocide that has the ability to kill bacteria, viruses, fungi, and endospores, leading to sterilization at low temperatures, which is sometimes a convenient alternative to the more labor-intensive heat sterilization methods. It also cross-links proteins and has been widely used as a chemical fixative. Because of this, it is used for the storage of tissue specimens and as an embalming fluid. It also has been used to inactivate infectious agents in vaccine preparation. Formaldehyde is very irritating to living tissues and is also carcinogenic; therefore, it is not used as an antiseptic.

Glutaraldehyde is structurally similar to formaldehyde but has two reactive aldehyde groups, allowing it to act more quickly than formaldehyde. It is commonly used as a 2% solution for sterilization and is marketed under the brand name Cidex. It is used to disinfect a variety of surfaces and surgical and medical equipment. However, similar to formaldehyde, glutaraldehyde irritates the skin and is not used as an antiseptic.

A new type of disinfectant gaining popularity for the disinfection of medical equipment is o-phthalaldehyde (OPA), which is found in some newer formulations of Cidex and similar products, replacing glutaraldehyde. o-Phthalaldehyde also has two reactive aldehyde groups, but they are linked by an aromatic bridge. o-Phthalaldehyde is thought to work similarly to glutaraldehyde and formaldehyde, but is much less irritating to skin and nasal passages, produces a minimal odor, does not require processing before use, and is more effective against mycobacteria.

Ethylene oxide is a type of alkylating agent that is used for gaseous sterilization. It is highly penetrating and can sterilize items within plastic bags such as catheters, disposable items in laboratories and clinical settings (like packaged Petri dishes), and other pieces of equipment. Ethylene oxide exposure is a form of cold sterilization, making it useful for the sterilization of heat-sensitive items. Great care needs to be taken with the use of ethylene oxide, however; it is carcinogenic, like the other alkylating agents, and is also highly explosive. With careful use and proper aeration of the products after treatment, ethylene oxide is highly effective, and ethylene oxide sterilizers are commonly found in medical settings for sterilizing packaged materials.

β-Propionolactone is an alkylating agent with a different chemical structure than the others already discussed. Like other alkylating agents, β-propionolactone binds to DNA, thereby inactivating it (Figure 5.1.3.11). It is a clear liquid with a strong odor and has the ability to kill endospores. As such, it has been used in either liquid form or as a vapor for the sterilization of medical instruments and tissue grafts, and it is a common component of vaccines, used to maintain their sterility. It has also been used for the sterilization of nutrient broth, as well as blood plasma, milk, and water. It is quickly metabolized by animals and humans to lactic acid. It is also an irritant, however, and may lead to permanent damage of the eyes, kidneys, or liver. Additionally, it has been shown to be carcinogenic in animals; thus, precautions are necessary to minimize human exposure to β-propionolactone.[14]

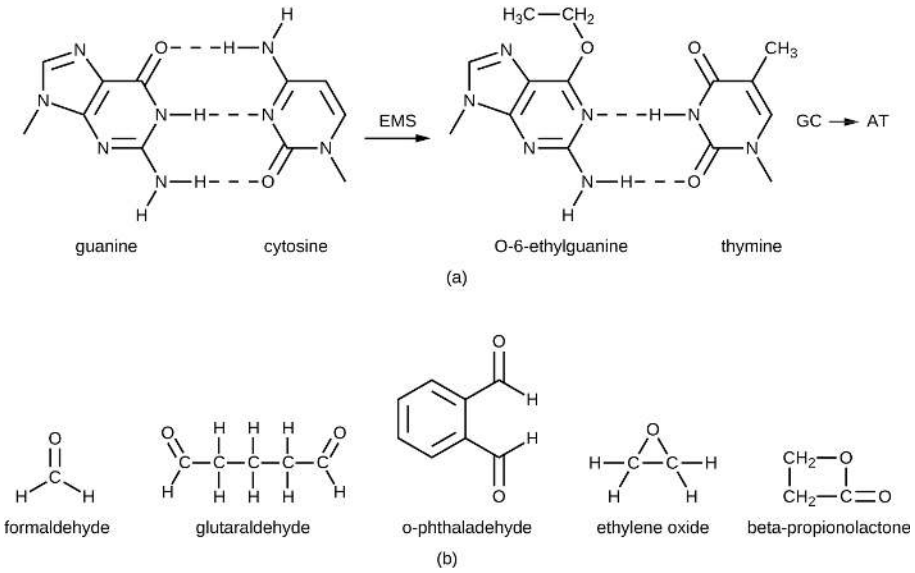


Figure 5.1.3.11: (a) Alkylating agents replace hydrogen atoms with alkyl groups. Here, guanine is alkylated, resulting in its hydrogen bonding with thymine, instead of cytosine. (b) The chemical structures of several alkylating agents.

? Exercise 5.1.3.7

1. What chemical reaction do alkylating agents participate in?
2. Why are alkylating agents not used as antiseptics?

Diehard Prions

Prions, the acellular, misfolded proteins responsible for incurable and fatal diseases such as kuru and Creutzfeldt-Jakob disease (see Viroids, Virusoids, and Prions), are notoriously difficult to destroy. Prions are extremely resistant to heat, chemicals, and radiation. They are also extremely infectious and deadly; thus, handling and disposing of prion-infected items requires extensive training and extreme caution.

Typical methods of disinfection can reduce but not eliminate the infectivity of prions. Autoclaving is not completely effective, nor are chemicals such as phenol, alcohols, formalin, and β-propiolactone. Even when fixed in formalin, affected brain and spinal cord tissues remain infectious.

Personnel who handle contaminated specimens or equipment or work with infected patients must wear a protective coat, face protection, and cut-resistant gloves. Any contact with skin must be immediately washed with detergent and warm water without scrubbing. The skin should then be washed with 1 N NaOH or a 1:10 dilution of bleach for 1 minute. Contaminated waste must be incinerated or autoclaved in a strong basic solution, and instruments must be cleaned and soaked in a strong basic solution.

Link to Learning

For more information on the handling of animals and prion-contaminated materials, visit the guidelines published on the CDC and WHO websites.

Peroxygens

Peroxygens are strong oxidizing agents that can be used as disinfectants or antiseptics. The most widely used peroxygen is hydrogen peroxide (H_2O_2), which is often used in solution to disinfect surfaces and may also be used as a gaseous agent. Hydrogen peroxide solutions are inexpensive skin antiseptics that break down into water and oxygen gas, both of which are environmentally safe. This decomposition is accelerated in the presence of light, so hydrogen peroxide solutions typically are sold in brown or

opaque bottles. One disadvantage of using hydrogen peroxide as an antiseptic is that it also causes damage to skin that may delay healing or lead to scarring. Contact lens cleaners often include hydrogen peroxide as a disinfectant.

Hydrogen peroxide works by producing free radicals that damage cellular macromolecules. Hydrogen peroxide has broad-spectrum activity, working against gram-positive and gram-negative bacteria (with slightly greater efficacy against gram-positive bacteria), fungi, viruses, and endospores. However, bacteria that produce the oxygen-detoxifying enzymes catalase or peroxidase may have inherent tolerance to low hydrogen peroxide concentrations (Figure 5.1.3.12). To kill endospores, the length of exposure or concentration of solutions of hydrogen peroxide must be increased. Gaseous hydrogen peroxide has greater efficacy and can be used as a sterilant for rooms or equipment.

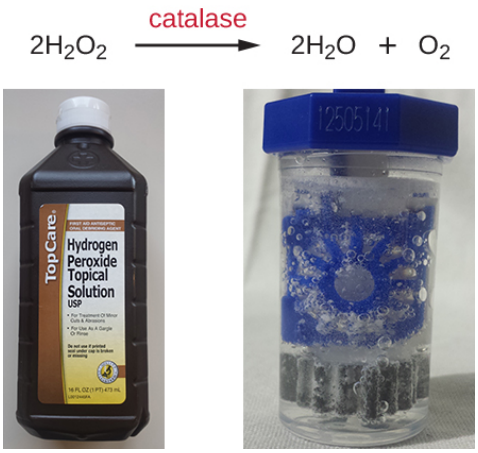


Figure 5.1.3.12: Catalase enzymatically converts highly reactive hydrogen peroxide (H_2O_2) into water and oxygen. Hydrogen peroxide can be used to clean wounds. Hydrogen peroxide is used to sterilize items such as contact lenses. (credit photos: modification of work by Kerry Ceszyk)

Plasma, a hot, ionized gas, described as the fourth state of matter, is useful for sterilizing equipment because it penetrates surfaces and kills vegetative cells and endospores. Hydrogen peroxide and peracetic acid, another commonly used peroxygen, each may be introduced as a plasma. Peracetic acid can be used as a liquid or plasma sterilant insofar as it readily kills endospores, is more effective than hydrogen peroxide even at rather low concentrations, and is immune to inactivation by catalases and peroxidases. It also breaks down to environmentally innocuous compounds; in this case, acetic acid and oxygen.

Other examples of peroxygens include benzoyl peroxide and carbamide peroxide. Benzoyl peroxide is a peroxygen that used in acne medication solutions. It kills the bacterium *Propionibacterium acnes*, which is associated with acne. Carbamide peroxide, an ingredient used in toothpaste, is a peroxygen that combats oral biofilms that cause tooth discoloration and halitosis (bad breath).[15] Last, ozone gas is a peroxygen with disinfectant qualities and is used to clean air or water supplies. Overall, peroxygens are highly effective and commonly used, with no associated environmental hazard.

? Exercise 5.1.3.8

How do peroxides kill cells?

Supercritical Fluids

Within the last 15 years, the use of supercritical fluids, especially supercritical carbon dioxide ($scCO_2$), has gained popularity for certain sterilizing applications. When carbon dioxide is brought to approximately 10 times atmospheric pressure, it reaches a supercritical state that has physical properties between those of liquids and gases. Materials put into a chamber in which carbon dioxide is pressurized in this way can be sterilized because of the ability of $scCO_2$ to penetrate surfaces.

Supercritical carbon dioxide works by penetrating cells and forming carbonic acid, thereby lowering the cell pH considerably. This technique is effective against vegetative cells and is also used in combination with peracetic acid to kill endospores. Its efficacy can also be augmented with increased temperature or by rapid cycles of pressurization and depressurization, which more likely produce cell lysis.

Benefits of $scCO_2$ include the nonreactive, nontoxic, and nonflammable properties of carbon dioxide, and this protocol is effective at low temperatures. Unlike other methods, such as heat and irradiation, that can degrade the object being sterilized, the use of $scCO_2$ preserves the object's integrity and is commonly used for treating foods (including spices and juices) and medical devices such as endoscopes. It is also gaining popularity for disinfecting tissues such as skin, bones, tendons, and ligaments prior to transplantation. $scCO_2$ can also be used for pest control because it can kill insect eggs and larvae within products.

? Exercise 5.1.3.9

Why is the use of supercritical carbon dioxide gaining popularity for commercial and medical uses?

Chemical Food Preservatives

Chemical preservatives are used to inhibit microbial growth and minimize spoilage in some foods. Commonly used chemical preservatives include sorbic acid, benzoic acid, and propionic acid, and their more soluble salts potassium sorbate, sodium benzoate, and calcium propionate, all of which are used to control the growth of molds in acidic foods. Each of these preservatives is nontoxic and readily metabolized by humans. They are also flavorless, so they do not compromise the flavor of the foods they preserve.

Sorbic and benzoic acids exhibit increased efficacy as the pH decreases. Sorbic acid is thought to work by inhibiting various cellular enzymes, including those in the citric acid cycle, as well as catalases and peroxidases. It is added as a preservative in a wide variety of foods, including dairy, bread, fruit, and vegetable products. Benzoic acid is found naturally in many types of fruits and berries, spices, and fermented products. It is thought to work by decreasing intracellular pH, interfering with mechanisms such as oxidative phosphorylation and the uptake of molecules such as amino acids into cells. Foods preserved with benzoic acid or sodium benzoate include fruit juices, jams, ice creams, pastries, soft drinks, chewing gum, and pickles.

Propionic acid is thought to both inhibit enzymes and decrease intracellular pH, working similarly to benzoic acid. However, propionic acid is a more effective preservative at a higher pH than either sorbic acid or benzoic acid. Propionic acid is naturally produced by some cheeses during their ripening and is added to other types of cheese and baked goods to prevent mold contamination. It is also added to raw dough to prevent contamination by the bacterium *Bacillus mesentericus*, which causes bread to become ropy.

Other commonly used chemical preservatives include sulfur dioxide and nitrites. Sulfur dioxide prevents browning of foods and is used for the preservation of dried fruits; it has been used in winemaking since ancient times. Sulfur dioxide gas dissolves in water readily, forming sulfites. Although sulfites can be metabolized by the body, some people have sulfite allergies, including asthmatic reactions. Additionally, sulfites degrade thiamine, an important nutrient in some foods. The mode of action of sulfites is not entirely clear, but they may interfere with the disulfide bond (see Figure 7.4.5) formation in proteins, inhibiting enzymatic activity. Alternatively, they may reduce the intracellular pH of the cell, interfering with proton motive force-driven mechanisms.

Nitrites are added to processed meats to maintain color and stop the germination of *Clostridium botulinum* endospores. Nitrites are reduced to nitric oxide, which reacts with heme groups and iron-sulfur groups. When nitric oxide reacts with the heme group within the myoglobin of meats, a red product forms, giving meat its red color. Alternatively, it is thought that when nitric acid reacts with the iron-sulfur enzyme ferredoxin within bacteria, this electron transport-chain carrier is destroyed, preventing ATP synthesis. Nitrosamines, however, are carcinogenic and can be produced through exposure of nitrite-preserved meats (e.g., hot dogs, lunch meat, breakfast sausage, bacon, meat in canned soups) to heat during cooking.

Natural Chemical Food Preservatives

The discovery of natural antimicrobial substances produced by other microbes has added to the arsenal of preservatives used in food. Nisin is an antimicrobial peptide produced by the bacterium *Lactococcus lactis* and is particularly effective against gram-positive organisms. Nisin works by disrupting cell wall production, leaving cells more prone to lysis. It is used to preserve cheeses, meats, and beverages.

Natamycin is an antifungal macrolide antibiotic produced by the bacterium *Streptomyces natalensis*. It was approved by the FDA in 1982 and is used to prevent fungal growth in various types of dairy products, including cottage cheese, sliced cheese, and shredded cheese. Natamycin is also used for meat preservation in countries outside the United States.

? Exercise 5.1.3.10

What are the advantages and drawbacks of using sulfites and nitrites as food preservatives?

Key Concepts and Summary

- **Heavy metals**, including mercury, silver, copper, and zinc, have long been used for disinfection and preservation, although some have toxicity and environmental risks associated with them.
- **Halogens**, including chlorine, fluorine, and iodine, are also commonly used for disinfection. Chlorine compounds, including **sodium hypochlorite**, **chloramines**, and **chlorine dioxide**, are commonly used for water disinfection. Iodine, in both **tincture** and **iodophor** forms, is an effective antiseptic.
- **Alcohols**, including ethyl alcohol and isopropyl alcohol, are commonly used antiseptics that act by denaturing proteins and disrupting membranes.
- **Phenolics** are stable, long-acting disinfectants that denature proteins and disrupt membranes. They are commonly found in household cleaners, mouthwashes, and hospital disinfectants, and are also used to preserve harvested crops.
- The phenolic compound **triclosan**, found in antibacterial soaps, plastics, and textiles is technically an antibiotic because of its specific mode of action of inhibiting bacterial fatty-acid synthesis..
- **Surfactants**, including soaps and detergents, lower the surface tension of water to create emulsions that mechanically carry away microbes. Soaps are long-chain fatty acids, whereas detergents are synthetic surfactants.
- **Quaternary ammonium compounds** (**quats**) are cationic detergents that disrupt membranes. They are used in household cleaners, skin disinfectants, oral rinses, and mouthwashes.
- **Bisbiguanides** disrupt cell membranes, causing cell contents to gel. **Chlorhexidine** and **alexidine** are commonly used for surgical scrubs, for handwashing in clinical settings, and in prescription oral rinses.
- **Alkylating agents** effectively sterilize materials at low temperatures but are carcinogenic and may also irritate tissue. **Glutaraldehyde** and **o-phthalaldehyde** are used as hospital disinfectants but not as antiseptics. **Formaldehyde** is used for the storage of tissue specimens, as an embalming fluid, and in vaccine preparation to inactivate infectious agents. **Ethylene oxide** is a gas sterilant that can permeate heat-sensitive packaged materials, but it is also explosive and carcinogenic.
- **Peroxygens**, including **hydrogen peroxide**, **peracetic acid**, **benzoyl peroxide**, and ozone gas, are strong oxidizing agents that produce free radicals in cells, damaging their macromolecules. They are environmentally safe and are highly effective disinfectants and antiseptics.
- Pressurized carbon dioxide in the form of a **supercritical fluid** easily permeates packaged materials and cells, forming carbonic acid and lowering intracellular pH. Supercritical carbon dioxide is nonreactive, nontoxic, nonflammable, and effective at low temperatures for sterilization of medical devices, implants, and transplanted tissues.
- Chemical preservatives are added to a variety of foods. **Sorbic acid**, **benzoic acid**, **propionic acid**, and their more soluble salts inhibit enzymes or reduce intracellular pH.
- **Sulfites** are used in winemaking and food processing to prevent browning of foods.
- **Nitrites** are used to preserve meats and maintain color, but cooking nitrite-preserved meats may produce carcinogenic nitrosamines.
- **Nisin** and **natamycin** are naturally produced preservatives used in cheeses and meats. Nisin is effective against gram-positive bacteria and natamycin against fungi.

Footnotes

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5.1.4: Testing the Effectiveness of Antiseptics and Disinfectants

Learning Objectives

- Describe why the phenol coefficient is used
- Compare and contrast the disk-diffusion, use-dilution, and in-use methods for testing the effectiveness of antiseptics, disinfectants, and sterilants

The effectiveness of various chemical disinfectants is reflected in the terms used to describe them. Chemical disinfectants are grouped by the power of their activity, with each category reflecting the types of microbes and viruses its component disinfectants are effective against. High-level germicides have the ability to kill vegetative cells, fungi, viruses, and endospores, leading to sterilization, with extended use. Intermediate-level germicides, as their name suggests, are less effective against endospores and certain viruses, and low-level germicides kill only vegetative cells and certain enveloped viruses, and are ineffective against endospores.

However, several environmental conditions influence the potency of an antimicrobial agent and its effectiveness. For example, length of exposure is particularly important, with longer exposure increasing efficacy. Similarly, the concentration of the chemical agent is also important, with higher concentrations being more effective than lower ones. Temperature, pH, and other factors can also affect the potency of a disinfecting agent.

One method to determine the effectiveness of a chemical agent includes swabbing surfaces before and after use to confirm whether a sterile field was maintained during use. Additional tests are described in the sections that follow. These tests allow for the maintenance of appropriate disinfection protocols in clinical settings, controlling microbial growth to protect patients, health-care workers, and the community.

Phenol Coefficient

The effectiveness of a disinfectant or antiseptic can be determined in a number of ways. Historically, a chemical agent's effectiveness was often compared with that of phenol, the first chemical agent used by Joseph Lister. In 1903, British chemists Samuel Rideal (1863–1929) and J. T. Ainslie Walker (1868–1930) established a protocol to compare the effectiveness of a variety of chemicals with that of phenol, using as their test organisms *Staphylococcus aureus* (a gram-positive bacterium) and *Salmonella enterica* serovar Typhi (a gram-negative bacterium). They exposed the test bacteria to the antimicrobial chemical solutions diluted in water for 7.5 minutes. They then calculated a phenol coefficient for each chemical for each of the two bacteria tested. A phenol coefficient of 1.0 means that the chemical agent has about the same level of effectiveness as phenol. A chemical agent with a phenol coefficient of less than 1.0 is less effective than phenol. An example is formalin, with phenol coefficients of 0.3 (*S. aureus*) and 0.7 (*S. enterica* serovar Typhi). A chemical agent with a phenol coefficient greater than 1.0 is more effective than phenol, such as chloramine, with phenol coefficients of 133 and 100, respectively. Although the phenol coefficient was once a useful measure of effectiveness, it is no longer commonly used because the conditions and organisms used were arbitrarily chosen.

Exercise 5.1.4.1

What are the differences between the three levels of disinfectant effectiveness?

Disk-Diffusion Method

The disk-diffusion method involves applying different chemicals to separate, sterile filter paper disks (Figure 5.1.4.1). The disks are then placed on an agar plate that has been inoculated with the targeted bacterium and the chemicals diffuse out of the disks into the agar where the bacteria have been inoculated. As the "lawn" of bacteria grows, zones of inhibition of microbial growth are observed as clear areas around the disks. Although there are other factors that contribute to the sizes of zones of inhibition (e.g., whether the agent is water soluble and able to diffuse in the agar), larger zones typically correlate to increased inhibition effectiveness of the chemical agent. The diameter across each zone is measured in millimeters.

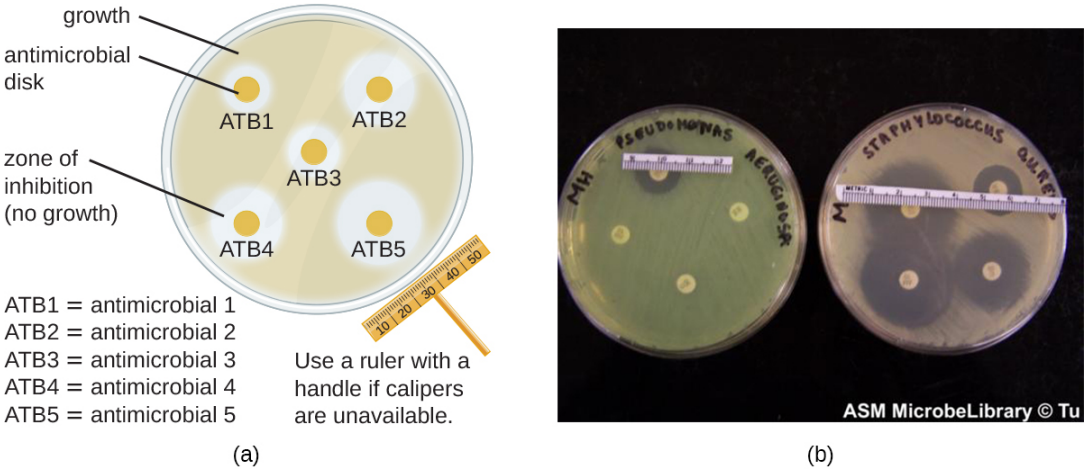


Figure 5.1.4.1: A disk-diffusion assay is used to determine the effectiveness of chemical agents against a particular microbe. (a) A plate is inoculated with various antimicrobial discs. The zone of inhibition around each disc indicates how effective that antimicrobial is against the particular species being tested. (b) On these plates, four antimicrobial agents are tested for efficacy in killing *Pseudomonas aeruginosa* (left) and *Staphylococcus aureus* (right). These antimicrobials are much more effective at killing *S. aureus*, as indicated by the size of the zones of inhibition. (credit b: modification of work by American Society for Microbiology)

? Exercise 5.1.4.2

When comparing the activities of two disinfectants against the same microbe, using the disk-diffusion assay, and assuming both are water soluble and can easily diffuse in the agar, would a more effective disinfectant have a larger zone of inhibition or a smaller one?

Use-Dilution Test

Other methods are also used for measuring the effectiveness of a chemical agent in clinical settings. The use-dilution test is commonly used to determine a chemical's disinfection effectiveness on an inanimate surface. For this test, a cylinder of stainless steel is dipped in a culture of the targeted microorganism and then dried. The cylinder is then dipped in solutions of disinfectant at various concentrations for a specified amount of time. Finally, the cylinder is transferred to a new test tube containing fresh sterile medium that does not contain disinfectant, and this test tube is incubated. Bacterial survival is demonstrated by the presence of turbidity in the medium, whereas killing of the target organism on the cylinder by the disinfectant will produce no turbidity.

The Association of Official Agricultural Chemists International (AOAC), a nonprofit group that establishes many protocol standards, has determined that a minimum of 59 of 60 replicates must show no growth in such a test to achieve a passing result, and the results must be repeatable from different batches of disinfectant and when performed on different days. Disinfectant manufacturers perform use-dilution tests to validate the efficacy claims for their products, as designated by the EPA.

? Exercise 5.1.4.3

Is the use-dilution test performed in a clinical setting? Why?

In-Use Test

An in-use test can determine whether an actively used solution of disinfectant in a clinical setting is microbially contaminated (Figure 5.1.4.2). A 1-mL sample of the used disinfectant is diluted into 9 mL of sterile broth medium that also contains a compound to inactivate the disinfectant. Ten drops, totaling approximately 0.2 mL of this mixture, are then inoculated onto each of two agar plates. One plate is incubated at 37 °C for 3 days and the other is incubated at room temperature for 7 days. The plates are monitored for growth of microbial colonies. Growth of five or more colonies on either plate suggests that viable microbial cells existed in the disinfectant solution and that it is contaminated. Such in-use tests monitor the effectiveness of disinfectants in the clinical setting.

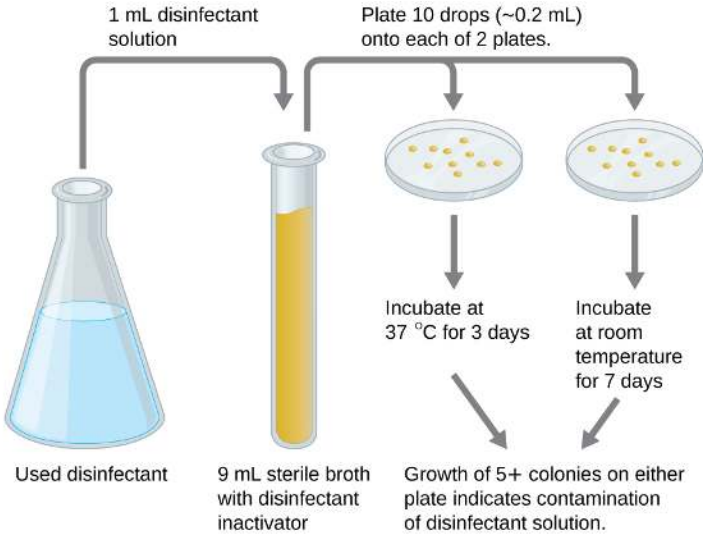


Figure 5.1.4.2: Used disinfectant solutions in a clinical setting can be checked with the in-use test for contamination with microbes.

? Exercise 5.1.4.4

What does a positive in-use test indicate?

Clinical Focus: Resolution

Despite antibiotic treatment, Roberta's symptoms worsened. She developed pyelonephritis, a severe kidney infection, and was rehospitalized in the intensive care unit (ICU). Her condition continued to deteriorate, and she developed symptoms of septic shock. At this point, her physician ordered a culture from her urine to determine the exact cause of her infection, as well as a drug sensitivity test to determine what antibiotics would be effective against the causative bacterium. The results of this test indicated resistance to a wide range of antibiotics, including the carbapenems, a class of antibiotics that are used as the last resort for many types of bacterial infections. This was an alarming outcome, suggesting that Roberta's infection was caused by a so-called superbug: a bacterial strain that has developed resistance to the majority of commonly used antibiotics. In this case, the causative agent belonged to the carbapenem-resistant Enterobacteriaceae (CRE), a drug-resistant family of bacteria normally found in the digestive system (Figure 5.1.4.3). When CRE is introduced to other body systems, as might occur through improperly cleaned surgical instruments, catheters, or endoscopes, aggressive infections can occur.

CRE infections are notoriously difficult to treat, with a 40%–50% fatality rate. To treat her kidney infection and septic shock, Roberta was treated with dialysis, intravenous fluids, and medications to maintain blood pressure and prevent blood clotting. She was also started on aggressive treatment with intravenous administration of a new drug called tigecycline, which has been successful in treating infections caused by drug-resistant bacteria.

After several weeks in the ICU, Roberta recovered from her CRE infection. However, public health officials soon noticed that Roberta's case was not isolated. Several patients who underwent similar procedures at the same hospital also developed CRE infections, some dying as a result. Ultimately, the source of the infection was traced to the duodenoscopes used in the procedures. Despite the hospital staff meticulously following manufacturer protocols for disinfection, bacteria, including CRE, remained within the instruments and were introduced to patients during procedures.



Figure 5.1.4.3: CRE is an extremely drug-resistant strain of bacteria that is typically associated with nosocomial infections. (credit: Centers for Disease Control and Prevention)

Who Is Responsible?

Carbapenem-resistant Enterobacteriaceae infections due to contaminated endoscopes have become a high-profile problem in recent years. Several CRE outbreaks have been traced to endoscopes, including a case at Ronald Reagan UCLA Medical Center in early 2015 in which 179 patients may have been exposed to a contaminated endoscope. Seven of the patients developed infections, and two later died. Several lawsuits have been filed against Olympus, the manufacturer of the endoscopes. Some claim that Olympus did not obtain FDA approval for design changes that may have led to contamination, and others claim that the manufacturer knowingly withheld information from hospitals concerning defects in the endoscopes.

Lawsuits like these raise difficult-to-answer questions about liability. Invasive procedures are inherently risky, but negative outcomes can be minimized by strict adherence to established protocols. Who is responsible, however, when negative outcomes occur due to flawed protocols or faulty equipment? Can hospitals or health-care workers be held liable if they have strictly followed a flawed procedure? Should manufacturers be held liable—and perhaps be driven out of business—if their lifesaving equipment fails or is found defective? What is the government's role in ensuring that use and maintenance of medical equipment and protocols are fail-safe?

Protocols for cleaning or sterilizing medical equipment are often developed by government agencies like the FDA, and other groups, like the AOAC, a nonprofit scientific organization that establishes many protocols for standard use globally. These procedures and protocols are then adopted by medical device and equipment manufacturers. Ultimately, the end-users (hospitals and their staff) are responsible for following these procedures and can be held liable if a breach occurs and patients become ill from improperly cleaned equipment.

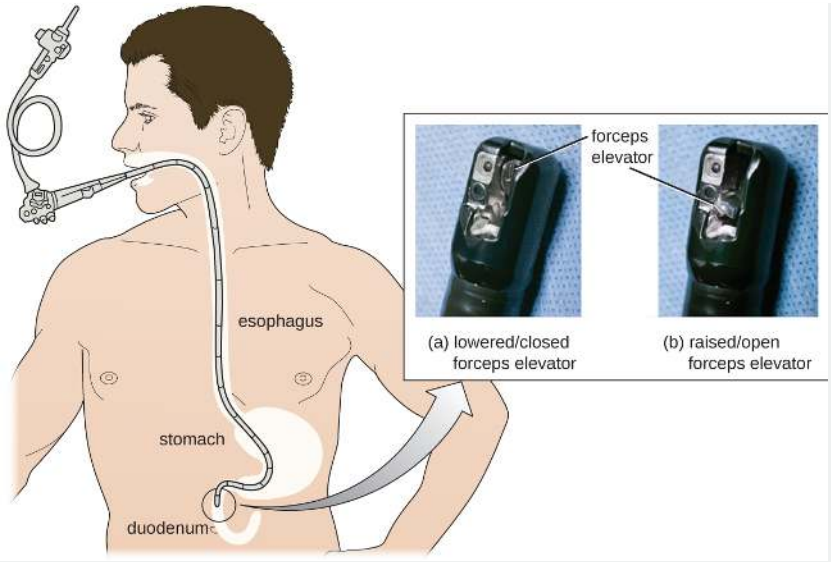


Figure 5.1.4.4: The elevator mechanism in a duodenoscope contains crevices that are difficult to disinfect. Pathogens that survive disinfection protocols can be passed from one patient to another, causing serious infections. (credit "photos": modification of work by Centers for Disease Control and Prevention)

Unfortunately, protocols are not infallible, and sometimes it takes negative outcomes to reveal their flaws. In 2008, the FDA had approved a disinfection protocol for endoscopes, using glutaraldehyde (at a lower concentration when mixed with phenol), o-phthalaldehyde, hydrogen peroxide, peracetic acid, and a mix of hydrogen peroxide with peracetic acid. However, subsequent CRE outbreaks from endoscope use showed that this protocol alone was inadequate.

As a result of CRE outbreaks, hospitals, manufacturers, and the FDA are investigating solutions. Many hospitals are instituting more rigorous cleaning procedures than those mandated by the FDA. Manufacturers are looking for ways to redesign duodenoscopes to minimize hard-to-reach crevices where bacteria can escape disinfectants, and the FDA is updating its protocols. In February 2015, the FDA added new recommendations for careful hand cleaning of the duodenoscope elevator mechanism (the location where microbes are most likely to escape disinfection), and issued more careful documentation about quality control of disinfection protocols (Figure 5.1.4.4).

There is no guarantee that new procedures, protocols, or equipment will completely eliminate the risk for infection associated with endoscopes. Yet these devices are used successfully in 500,000–650,000 procedures annually in the United States, many of them lifesaving. At what point do the risks outweigh the benefits of these devices, and who should be held responsible when negative outcomes occur?

Key Concepts and Summary

- Chemical disinfectants are grouped by the types of microbes and infectious agents they are effective against. **High-level germicides** kill vegetative cells, fungi, viruses, and endospores, and can ultimately lead to sterilization. **Intermediate-level germicides** cannot kill all viruses and are less effective against endospores. **Low-level germicides** kill vegetative cells and some enveloped viruses, but are ineffective against endospores.
- The effectiveness of a disinfectant is influenced by several factors, including length of exposure, concentration of disinfectant, temperature, and pH.
- Historically, the effectiveness of a chemical disinfectant was compared with that of phenol at killing *Staphylococcus aureus* and *Salmonella enterica* serovar Typhi, and a **phenol coefficient** was calculated.
- The **disk-diffusion method** is used to test the effectiveness of a chemical disinfectant against a particular microbe.
- The **use-dilution test** determines the effectiveness of a disinfectant on a surface. **In-use tests** can determine whether disinfectant solutions are being used correctly in clinical settings.

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5.1.E: Control of Microbial Growth (Exercises)

13.1: Controlling Microbial Growth

Inanimate items, such as doorknobs, toys, or towels, which may harbor microbes and aid in disease transmission, are called fomites. Two factors heavily influence the level of cleanliness required for a particular fomite and, hence, the protocol chosen to achieve this level. The first factor is the application for which the item will be used and the second factor is the level of resistance to antimicrobial treatment by potential pathogens.

Multiple Choice

Which of the following types of medical items requires sterilization?

A. needles
B. bed linens
C. respiratory masks
D. blood pressure cuffs

Answer

A

Which of the following is suitable for use on tissues for microbial control to prevent infection?

A. disinfectant
B. antiseptic
C. sterilant
D. water

Answer

B

Which biosafety level is appropriate for research with microbes or infectious agents that pose moderate risk to laboratory workers and the community, and are typically indigenous?

A. BSL-1
B. BSL-2
C. BSL-3
D. BSL-4

Answer

B

Which of the following best describes a microbial control protocol that inhibits the growth of molds and yeast?

A. bacteriostatic
B. fungicidal
C. bactericidal
D. fungistatic

Answer

D

The decimal reduction time refers to the amount of time it takes to which of the following?

A. reduce a microbial population by 10%
B. reduce a microbial population by 0.1%

C. reduce a microbial population by 90%
D. completely eliminate a microbial population

Answer

C

Fill in the Blank

A medical item that comes into contact with intact skin and does not penetrate sterile tissues or come into contact with mucous membranes is called a(n) _____ item.

Answer

noncritical

The goal of _____ _____ protocols is to rid canned produce of *Clostridium botulinum* endospores.

Answer

commercial sterilization

True/False

Sanitization leaves an object free of microbes.

Answer

False

Short Answer

What are some characteristics of microbes and infectious agents that would require handling in a BSL-3 laboratory?

What is the purpose of degerming? Does it completely eliminate microbes?

What are some factors that alter the effectiveness of a disinfectant?

Critical Thinking

When plotting microbial death curves, how might they look different for bactericidal versus bacteriostatic treatments?

What are the benefits of cleaning something to a level of cleanliness beyond what is required? What are some possible disadvantages of doing so?

13.2: Using Physical Methods to Control Microorganisms

For thousands of years, humans have used various physical methods of microbial control for food preservation. Common control methods include the application of high temperatures, radiation, filtration, and desiccation (drying), among others. Many of these methods nonspecifically kill cells by disrupting membranes, changing membrane permeability, or damaging proteins and nucleic acids by denaturation, degradation, or chemical modification.

Multiple Choice

Which of the following methods brings about cell lysis due to cavitation induced by rapid localized pressure changes?

A. microwaving
B. gamma irradiation
C. ultraviolet radiation
D. sonication

Answer

D

Which of the following terms is used to describe the time required to kill all of the microbes within a sample at a given temperature?

A. D-value
B. thermal death point
C. thermal death time
D. decimal reduction time

Answer

C

Which of the following microbial control methods does not actually kill microbes or inhibit their growth but instead removes them physically from samples?

A. filtration
B. desiccation
C. lyophilization
D. nonionizing radiation

Answer

A

Fill in the Blank

In an autoclave, the application of pressure to _____ is increased to allow the steam to achieve temperatures above the boiling point of water.

Answer

steam

True/False

Ionizing radiation can penetrate surfaces, but nonionizing radiation cannot.

Answer

True

Moist-heat sterilization protocols require the use of higher temperatures for longer periods of time than do dry-heat sterilization protocols do.

Answer

False

Short Answer

What is the advantage of HTST pasteurization compared with sterilization? What is an advantage of UHT treatment?

How does the addition of salt or sugar help preserve food?

Which is more effective at killing microbes: autoclaving or freezing? Explain.

Critical Thinking

In 2001, endospores of *Bacillus anthracis*, the causative agent of anthrax, were sent to government officials and news agencies via the mail. In response, the US Postal Service began to irradiate mail with UV light. Was this an effective strategy? Why or why not?

13.3: Using Chemicals to Control Microorganisms

In addition to physical methods of microbial control, chemicals are also used to control microbial growth. A wide variety of chemicals can be used as disinfectants or antiseptics. This section describes the variety of chemicals used as disinfectants and antiseptics, including their mechanisms of action and common uses.

Multiple Choice

Which of the following refers to a disinfecting chemical dissolved in alcohol?

A. iodophor
B. tincture
C. phenolic
D. peroxygen

Answer

B

Which of the following peroxygens is widely used as a household disinfectant, is inexpensive, and breaks down into water and oxygen gas?

A. hydrogen peroxide
B. peracetic acid
C. benzoyl peroxide
D. ozone

Answer

A

Which of the following chemical food preservatives is used in the wine industry but may cause asthmatic reactions in some individuals?

A. nitrites
B. sulfites
C. propionic acid
D. benzoic acid

Answer

B

Bleach is an example of which group of chemicals used for disinfection?

A. heavy metals
B. halogens
C. quats
D. bisbiguanides

Answer

B

Which chemical disinfectant works by methylating enzymes and nucleic acids and is known for being toxic and carcinogenic?

A. sorbic acid
B. triclosan
C. formaldehyde
D. hexaclorophene

Answer

C

Fill in the Blank

Doorknobs and other surfaces in clinical settings are often coated with _____, _____, or _____ to prevent the transmission of microbes.

Answer

copper, nickel, zinc

True/False

Soaps are classified as disinfectants.

Answer

False

Mercury-based compounds have fallen out of favor for use as preservatives and antiseptics.

Answer

True

Short Answer

Which solution of ethyl alcohol is more effective at inhibiting microbial growth: a 70% solution or a 100% solution? Why?

When might a gas treatment be used to control microbial growth instead of autoclaving? What are some examples?

What is the advantage of using an iodophor rather than iodine or an iodine tincture?

Critical Thinking

Looking at Figure 13.3.11 and reviewing the functional groups in Figure 7.1.5, which alkylating agent shown lacks an aldehyde group?

Do you think naturally produced antimicrobial products like nisin and natamycin should replace sorbic acid for food preservation? Why or why not?

Why is the use of skin disinfecting compounds required for surgical scrubbing and not for everyday handwashing?

13.4: Testing the Effectiveness of Antiseptics and Disinfectants

Several environmental conditions influence the potency of an antimicrobial agent and its effectiveness. For example, length of exposure is particularly important, with longer exposure increasing efficacy. Similarly, the concentration of the chemical agent is also important, with higher concentrations being more effective than lower ones. Temperature, pH, and other factors can also affect the potency of a disinfecting agent.

Multiple Choice

Which type of test is used to determine whether disinfectant solutions actively used in a clinical setting are being used correctly?

A. disk-diffusion assay
B. phenol coefficient test
C. in-use test
D. use-dilution test

Answer

C

The effectiveness of chemical disinfectants has historically been compared to that of which of the following?

A. phenol
B. ethyl alcohol
C. bleach
D. formaldehyde

Answer

A

Which of the following refers to a germicide that can kill vegetative cells and certain enveloped viruses but not endospores?

A. high-level germicide
B. intermediate-level germicide
C. low-level germicide
D. sterilant

Answer

C

Fill in the Blank

If a chemical disinfectant is more effective than phenol, then its phenol coefficient would be _____ than 1.0.

Answer

greater

If used for extended periods of time, _____ germicides may lead to sterility.

Answer

high-level

In the disk-diffusion assay, a large zone of inhibition around a disk to which a chemical disinfectant has been applied indicates _____ of the test microbe to the chemical disinfectant.

Answer

susceptibility or sensitivity

Short Answer

Why were chemical disinfectants once commonly compared with phenol?

Why is length of exposure to a chemical disinfectant important for its activity?

Critical Thinking

What are some advantages of use-dilution and in-use tests compared with the disk-diffusion assay?

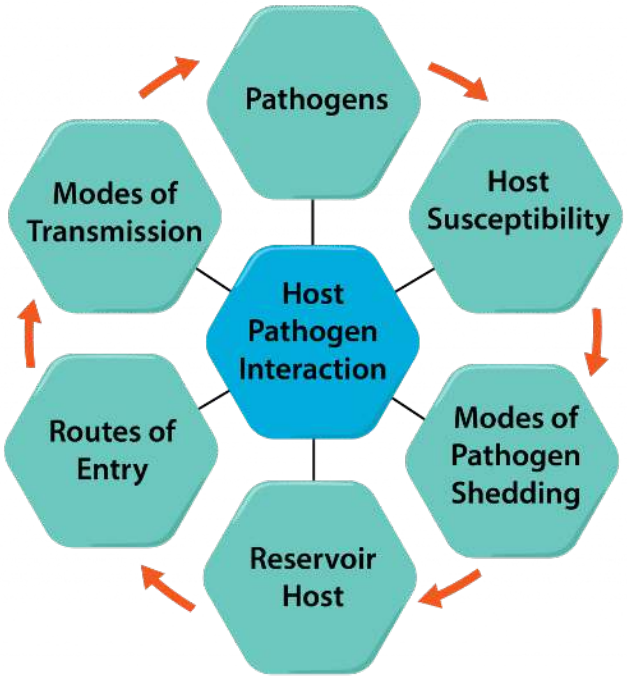
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5.2: Bacterial Pathogenicity

A microbe that is capable of causing disease is referred to as a **pathogen,** while the organism being infected is called a **host**. The ability to cause disease is referred to as **pathogenicity**, with pathogens varying in their ability. An **opportunistic pathogen** is a microbe that typically infects a host that is compromised in some way, either by a weakened immune system or breach to the body's natural defenses, such as a wound. The measurement of pathogenicity is called **virulence**, with highly virulent pathogens being more likely to cause disease in a host.

It is important to remember that there are many variables to take into account in a host-pathogen interaction, which is a dynamic relationship that is constantly changing. The virulence of the pathogen is important, but so is the number of microbes that gained entry to the host, the location of entry, the overall health of the host, and the state of the host's defenses. Exposure to a pathogen does not ensure that disease will occur, since a host might be able to fight off the infection before disease signs/symptoms develop.



Host-Pathogen Interactions.

Pathogen Transmission

An infection starts with exposure to a pathogen. The natural site or home for a pathogen is known as a **reservoir** and can either be animate (human or animal) or inanimate (water, soil, food). A pathogen can be picked up from its reservoir and then spread from one infected host to another. **Carriers** play an important role in the spread of disease, since they carry the pathogen but show no obvious symptoms of disease. A disease that primarily occurs within animal populations but can be spread to humans is called a **zoonosis**, while a hospital-acquired infection is known as a **nosocomial infection**.

The mechanism by which a pathogen is picked up by a host is referred to as **mode of transmission**, with the main mechanisms listed below:

Direct contact

Direct contact includes host-to-host contact, such as through kissing or sexual intercourse, where one person might come in contact with another person's skin or body fluids. An expectant mother may transmit a pathogen to her infant by **vertical contact** while pregnant, or during the act of giving birth.

Droplet transmission

Droplet transmission is often considered to be a form of direct contact as well. It involves transmission by respiratory droplets, where an infected host expels the pathogen in tiny droplets by coughing or sneezing, which are then inhaled by a host nearby. These droplets are not transmitted through the air over long distances, nor do they remain infectious for very long.

Indirect contact

Indirect contact involves the transfer of the infectious agent through some type of intermediary, such as a contaminated object or person. The pathogen might be deposited on an inanimate object, called a **fomite**, which is then used by another person. This could include a shared toy or commonly-touched surface, like a doorknob or computer keyboard. Alternatively, a healthcare worked might transmit a pathogen from one patient to another, if they did not change their gloves between patients.

Airborne transmission

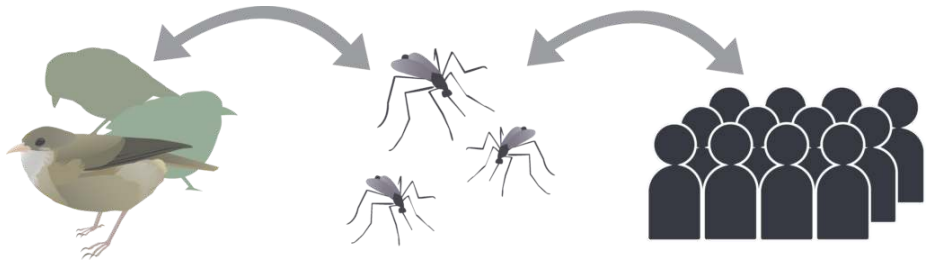
Airborne transmission occurs due to pathogens that are in small particles or droplets in the environment, which can remain infectious over time and distance. An example might be fungal spores that are inhaled during a dust storm.

Fecal-oral transmission

Fecal-oral transmission occurs when an infected host is shedding the pathogen in their feces which contaminate food or water that is consumed by the next host.

Vectorborne transmission

Vectorborne transmission occurs when an arthropod vector, such as mosquitoes, flies, ticks, are involves in the transmission. Sometimes the vector just picks up the infectious agents on their external body parts and carries it to another host, but typically the vector picks up the infectious agent when biting an infected host. The agent is picked up in the blood, and then spread to the next host when the vector moves on to bite someone else.



Pathogen Transmission.

Virulence Factors

In order for a bacterium to be virulent, it must have capabilities that allow it to infect a host. These capabilities arise from physical structures that the bacterium has or chemical substances that the bacterium can produce. Collectively the characteristics that contribute to virulence are called **virulence factors**. The genes that code for virulence factors are commonly found clustered on the pathogen's chromosome or plasmid DNA, called **pathogenicity islands**. These pathogenicity islands can be distinguished by a G+C content that differs from the rest of the genome and the presence of insertion-like sequences flanking the gene cluster. Pathogenicity islands facilitate the sharing of virulence factors between bacteria due to horizontal gene transfer, leading to the development of new pathogens over time.

Often the genes for virulence factors are controlled by quorum sensing, to ensure gene activation when the pathogen population is at an optimal density. Triggering the genes too soon could alert the host's immune system to the invader, cutting short the bacterial infection.

Adherence and Colonization

Bacterial pathogens must be able to grab onto host cells or tissue, and resist removal by physical means (such as sneezing) or mechanical means (such as movement of the cilated cells that line our airway). **Adherence** can involve polysaccharide layers made

by the bacteria, such as a capsule or slime layer, which provide adhesion to host cells as well as resistance from phagocytosis. Adherence can also be accomplished by physical structures such as a pilus or flagellum.

Once cells are successfully adhering to a surface, they increase in number, utilizing resources available at the site. This **colonization** is important for pathogen survival and invasion to other sites, which will yield increased nutrients and space for the growing population.

Invasion

Invasion refers to the ability of the pathogen to spread to other locations in the host, by invading host cells or tissue. It is typically at this point when disease or obvious signs/symptoms of illness will occur. While physical structures can still play a role in invasion, most bacterial pathogens produce a wide array of chemicals, specifically enzymes that effect the host's cells and tissue. Enzymes such as collagenase, which allows the pathogen to spread by breaking down the collagen found in connective tissue. Or leukocidins, which destroy the host's white blood cells, decreasing resistance. Hemolysins lyse the host's red blood cells, releasing iron, a growth-limiting factor for bacteria.

Bacteria in the bloodstream, a condition known as **bacteremia**, can quickly spread to locations throughout the host. This can result in a massive, systemic infection known as **septicemia**, which can result in septic shock and death, as the host becomes overwhelmed by the bacterial pathogen and its products.

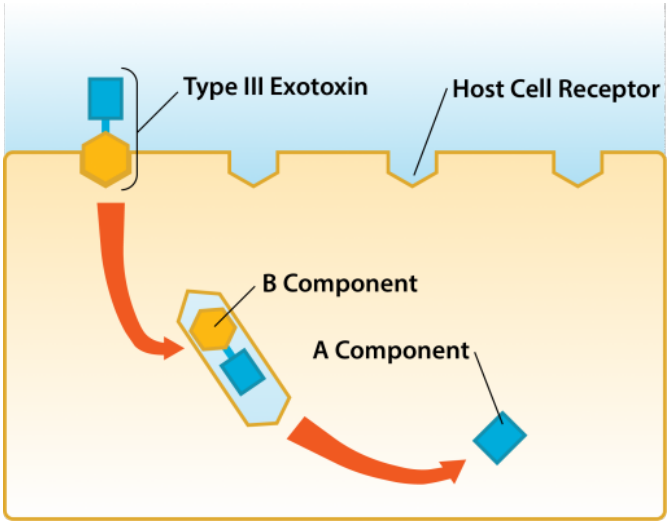
Toxins

Toxins are a very specific virulence factor produced by some bacterial pathogens, in the form of substances that are poisonous to the host. **Toxigenicity** refers to an organism's ability to make toxins. For bacteria, there are two categories of toxins, the exotoxins and the endotoxins.

Exotoxins

Exotoxins are heat-sensitive soluble proteins that are released into the surrounding environment by a living organism. These incredibly potent substances can spread throughout the host's body, causing damage distant from the original site of infection. Exotoxins are associated with specific diseases, with the toxin genes often carried on plasmids or by prophages. There are many different bacteria that produce exotoxins, causing diseases such as botulism, tetanus, and diphtheria. There are three categories of exotoxins:

1. **Type I: cell surface-active** – these toxins bind to cell receptors and stimulate cell responses. One example is **superantigen**, that stimulates the host's **T cells**, an important component of the immune system. The stimulated T cells produce an excessive amount of the signaling molecule **cytokine**, causing massive inflammation and tissue damage.
2. **Type II: membrane-damaging –** these toxins exert their effect on the host cell membrane, often by forming pores in the membrane of the target cell. This can lead to cell lysis as cytoplasmic contents rush out and water rushes in, disrupting the osmotic balance of the cell.
3. **Type III: intracellular –** these toxins gain access to a particular host cell and stimulate a reaction within the target cell. One example is the **AB-toxin** – these toxins are composed of two subunits, an **A portion** and a **B portion**. The B subunit is the binding portion of the toxin, responsible for recognizing and binding to the correct cell type. The A subunit is the portion with enzymatic activity. Once delivered into the correct cell by the B subunit, the A subunit enacts some mechanism on the cell, leading to decreased cell function and/or cell death. An example is the tetanus toxin produced by the bacterium *Clostridrium tetani*. Once delivered to a neuron, the A subunit will cleave the cellular synaptobreven, resulting in a decrease in neurotransmitter release. This results in spastic paralysis of the host. Each AB-toxin is associated with a different disease.



AB-toxin: Host Cell Binding.

Endotoxins

Endotoxins are made by gram negative bacteria, as a component of the outer membrane of their cell wall. The outer membrane contains lipopolysaccharide or LPS, with the toxic component being the lipid part known as **lipid A**. Lipid A is heat-stable and is only released when the bacterial cell is lysed. The effect on the host is the same, regardless of what bacterium made the lipid A – fever, diarrhea, weakness, and blood coagulation. A massive release of endotoxin in a host can cause **endotoxin shock**, which can be deadly.

Key Words

pathogen, host, pathogenicity, opportunistic pathogen, virulence, reservoir, carrier, nosocomial infection, mode of transmission, direct contact, vertical contact, droplet transmission, indirect contact, fomite, airborne transmission, fecal-oral transmission, vectorborne transmission, virulence factor, pathogenicity island, adherence, colonization, invasion, bacteremia, septicemia, toxin, toxigenicity, exotoxin, Type I/cell surface-active toxin, superantigen, T cell, cytokine, Type II/membrane-damaging toxin, Type III/intracellular toxin, AB toxin, endotoxin, lipid A, endotoxin shock.

Study Questions

1. What are the different terms associated with bacterial pathogenesis? How do they differ and what to they refer to?
2. What are the components that play a role in the host-pathogen interaction?
3. What terms are associated with pathogen transmission? What are the different ways in which pathogens can be transmitted? What is involved for each mode of transmission?
4. What are virulence factors? What role does pathogenicity islands play in the dispersal of virulence factors?
5. Why are adherence and colonization important to a bacterial pathogen? How does invasion differ?
6. What types of toxins are made by bacterial pathogens? What characteristics do they have?

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SECTION OVERVIEW

5.3: Antimicrobial Drugs

In nature, some microbes produce substances that inhibit or kill other microbes that might otherwise compete for the same resources. Humans have successfully exploited these abilities, using microbes to mass-produce substances that can be used as antimicrobial drugs. Since their discovery, antimicrobial drugs have saved countless lives, and they remain an essential tool for treating and controlling infectious disease. But their widespread and often unnecessary use has had an unintended side effect: the rise of multidrug-resistant microbial strains. In this chapter, we will discuss how antimicrobial drugs work, why microbes develop resistance, and what health professionals can do to encourage responsible use of antimicrobials.



Figure 5.3.1: First mass produced in the 1940s, penicillin was instrumental in saving millions of lives during World War II and was considered a wonder drug.[1] Today, overprescription of antibiotics (especially for childhood illnesses) has contributed to the evolution of drug-resistant pathogens. (credit left: modification of work by Chemical Heritage Foundation; Credit right: DFID / Flickr; CC-BY)

5.3.1: Discovering Antimicrobial Drugs

5.3.2: Antibacterial Drugs

5.3.3: Drugs Targeting Other Microorganisms

5.3.4: Clinical Considerations

5.3.5: Testing the Effectiveness of Antimicrobials

5.3.6: The Emergence of Drug Resistance

5.3.E: Antimicrobial Drugs (Exercises)

Footnotes

1. 1 "Treatment of War Wounds: A Historical Review." *Clinical Orthopaedics and Related Research* 467 no. 8 (2009):2168–2191.

Thumbnail: Staphylococcus aureus - Antibiotics Test plate. (Public Domain; CDC / Provider: Don Stalons).

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5.3.1: Discovering Antimicrobial Drugs

Learning Objectives

- Compare and contrast natural, semisynthetic, and synthetic antimicrobial drugs
- Describe the chemotherapeutic approaches of ancient societies
- Describe the historically important individuals and events that led to the development of antimicrobial drugs

Clinical Focus: Part 1

Marisa, a 52-year-old woman, was suffering from severe abdominal pain, swollen lymph nodes, fatigue, and a fever. She had just returned home from visiting extended family in her native country of Cambodia. While abroad, she received medical care in neighboring Vietnam for a compressed spinal cord. She still had discomfort when leaving Cambodia, but the pain increased as her trip home continued and her husband drove her straight from the airport to the emergency room.

Her doctor considers whether Marisa could be suffering from appendicitis, a urinary tract infection (UTI), or pelvic inflammatory disease (PID). However, each of those conditions is typically preceded or accompanied by additional symptoms. He considers the treatment she received in Vietnam for her compressed spinal cord, but abdominal pain is not usually associated with spinal cord compression. He examines her health history further.

Exercise 5.3.1.1

1. What type of infection or other condition may be responsible?
2. What type of lab tests might the doctor order?

Most people associate the term chemotherapy with treatments for cancer. However, chemotherapy is actually a broader term that refers to any use of chemicals or drugs to treat disease. Chemotherapy may involve drugs that target cancerous cells or tissues, or it may involve antimicrobial drugs that target infectious microorganisms. Antimicrobial drugs typically work by destroying or interfering with microbial structures and enzymes, either killing microbial cells or inhibiting of their growth. But before we examine how these drugs work, we will briefly explore the history of humans' use of antimicrobials for the purpose of chemotherapy.

Use of Antimicrobials in Ancient Societies

Although the discovery of antimicrobials and their subsequent widespread use is commonly associated with modern medicine, there is evidence that humans have been exposed to antimicrobial compounds for millennia. Chemical analyses of the skeletal remains of people from Nubia[1] (now found in present-day Sudan) dating from between 350 and 550 AD have shown residue of the antimicrobial agent tetracycline in high enough quantities to suggest the purposeful fermentation of tetracycline-producing *Streptomyces* during the beer-making process. The resulting beer, which was thick and gruel-like, was used to treat a variety of ailments in both adults and children, including gum disease and wounds. The antimicrobial properties of certain plants may also have been recognized by various cultures around the world, including Indian and Chinese herbalists (Figure 5.3.1.1) who have long used plants for a wide variety of medical purposes. Healers of many cultures understood the antimicrobial properties of fungi and their use of moldy bread or other mold-containing products to treat wounds has been well documented for centuries.[2] Today, while about 80% of the world's population still relies on plant-derived medicines,[3] scientists are now discovering the active compounds conferring the medicinal benefits contained in many of these traditionally used plants.



Figure 5.3.1.1: For millennia, Chinese herbalists have used many different species of plants for the treatment of a wide variety of human ailments.

? Exercise 5.3.1.2

Give examples of how antimicrobials were used in ancient societies

The First Antimicrobial Drugs

Societies relied on traditional medicine for thousands of years; however, the first half of the 20th century brought an era of strategic drug discovery. In the early 1900s, the German physician and scientist Paul Ehrlich (1854–1915) set out to discover or synthesize chemical compounds capable of killing infectious microbes without harming the patient. In 1909, after screening more than 600 arsenic-containing compounds, Ehrlich's assistant Sahachiro Hata (1873–1938) found one such "magic bullet." Compound 606 targeted the bacterium *Treponema pallidum*, the causative agent of syphilis. Compound 606 was found to successfully cure syphilis in rabbits and soon after was marketed under the name Salvarsan as a remedy for the disease in humans (Figure 5.3.1.2). Ehrlich's innovative approach of systematically screening a wide variety of compounds remains a common strategy for the discovery of new antimicrobial agents even today.

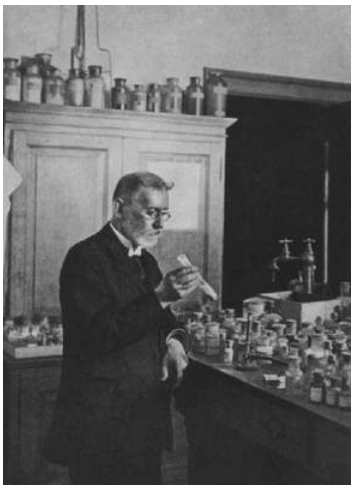
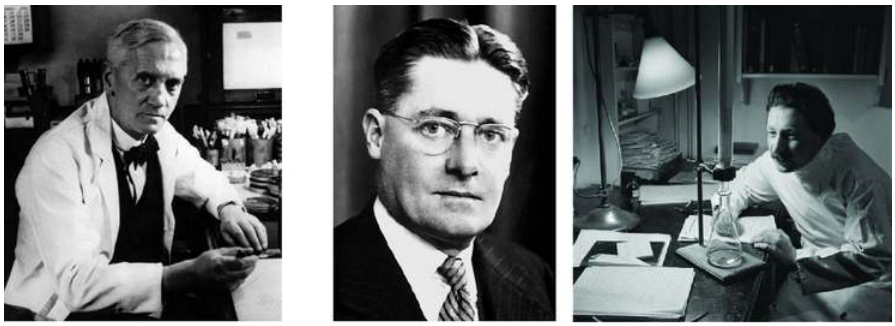


Figure 5.3.1.2: Paul Ehrlich was influential in the discovery of Compound 606, an antimicrobial agent that proved to be an effective treatment for syphilis.

A few decades later, German scientists Josef Klarer, Fritz Mietzsch, and Gerhard Domagk discovered the antibacterial activity of a synthetic dye, prontosil, that could treat streptococcal and staphylococcal infections in mice. Domagk's own daughter was one of the first human recipients of the drug, which completely cured her of a severe streptococcal infection that had resulted from a poke with an embroidery needle. Gerhard Domagk (1895–1964) was awarded the Nobel Prize in Medicine in 1939 for his work with prontosil and sulfanilamide, the active breakdown product of prontosil in the body. Sulfanilamide, the first synthetic antimicrobial

created, served as the foundation for the chemical development of a family of sulfa drugs. A synthetic antimicrobial is a drug that is developed from a chemical not found in nature. The success of the sulfa drugs led to the discovery and production of additional important classes of synthetic antimicrobials, including the quinolines and oxazolidinones.

A few years before the discovery of prontosil, scientist Alexander Fleming (1881–1955) made his own accidental discovery that turned out to be monumental. In 1928, Fleming returned from holiday and examined some old plates of staphylococci in his research laboratory at St. Mary's Hospital in London. He observed that contaminating mold growth (subsequently identified as a strain of *Penicillium notatum*) inhibited staphylococcal growth on one plate. Fleming, therefore, is credited with the discovery of penicillin, the first natural antibiotic, (Figure 5.3.1.3). Further experimentation showed that penicillin from the mold was antibacterial against streptococci, meningococci, and *Corynebacterium diphtheriae*, the causative agent of diphtheria.



(a) (b)

Figure 5.3.1.3: (a) Alexander Fleming was the first to discover a naturally produced antimicrobial, penicillin, in 1928. (b) Howard Florey and Ernst Chain discovered how to scale up penicillin production. Then they figured out how to purify it and showed its efficacy as an antimicrobial in animal and human trials in the early 1940s.

Fleming and his colleagues were credited with discovering and identifying penicillin, but its isolation and mass production were accomplished by a team of researchers at Oxford University under the direction of Howard Florey(1898–1968) and Ernst Chain (1906–1979) (Figure 5.3.1.3). In 1940, the research team purified penicillin and reported its success as an antimicrobial agent against streptococcal infections in mice. Their subsequent work with human subjects also showed penicillin to be very effective. Because of their important work, Fleming, Florey, and Chain were awarded the Nobel Prize in Physiology and Medicine in 1945.

In the early 1940s, scientist Dorothy Hodgkin (1910–1994), who studied crystallography at Oxford University, used X-rays to analyze the structure of a variety of natural products. In 1946, she determined the structure of penicillin, for which she was awarded the Nobel Prize in Chemistry in 1964. Once the structure was understood, scientists could modify it to produce a variety of semisynthetic penicillins. A semisynthetic antimicrobial is a chemically modified derivative of a natural antibiotic. The chemical modifications are generally designed to increase the range of bacteria targeted, increase stability, decrease toxicity, or confer other properties beneficial for treating infections.

Penicillin is only one example of a natural antibiotic. Also in the 1940s, Selman Waksman (1888–1973) (Figure 5.3.1.4), a prominent soil microbiologist at Rutgers University, led a research team that discovered several antimicrobials, including actinomycin, streptomycin, and neomycin. The discoveries of these antimicrobials stemmed from Waksman's study of fungi and the Actinobacteria, including soil bacteria in the genus *Streptomyces*, known for their natural production of a wide variety of antimicrobials. His work earned him the Nobel Prize in Physiology and Medicine in 1952. The actinomycetes are the source of more than half of all natural antibiotics[4] and continue to serve as an excellent reservoir for the discovery of novel antimicrobial agents. Some researchers argue that we have not yet come close to tapping the full antimicrobial potential of this group.[5]



Figure 5.3.1.4: Selman Waksman was the first to show the vast antimicrobial production capabilities of a group of soil bacteria, the actinomycetes.

? Exercise 5.3.1.3

Why is the soil a reservoir for antimicrobial resistance genes?

Key Concepts and Summary

- **Antimicrobial drugs** produced by purposeful fermentation and/or contained in plants have been used as traditional medicines in many cultures for millennia.
- The purposeful and systematic search for a chemical "magic bullet" that specifically target infectious microbes was initiated by Paul Ehrlich in the early 20th century.
- The discovery of the **natural antibiotic**, penicillin, by Alexander Fleming in 1928 started the modern age of antimicrobial discovery and research.
- Sulfanilamide, the first **synthetic antimicrobial**, was discovered by Gerhard Domagk and colleagues and is a breakdown product of the synthetic dye, prontosil.

Footnotes

1. 1 M.L. Nelson et al. "Brief Communication: Mass Spectroscopic Characterization of Tetracycline in the Skeletal Remains of an Ancient Population from Sudanese Nubia 350–550 CE." *American Journal of Physical Anthropology* 143 no. 1 (2010):151–154.
2. 2 M. Wainwright. "Moulds in Ancient and More Recent Medicine." *Mycologist* 3 no. 1 (1989):21–23.
3. 3 S. Verma, S.P. Singh. "Current and Future Status of Herbal Medicines." *Veterinary World* 1 no. 11 (2008):347–350.
4. 4 J. Berdy. "Bioactive Microbial Metabolites." *The Journal of Antibiotics* 58 no. 1 (2005):1–26.
5. 5 M. Baltz. "Antimicrobials from Actinomycetes: Back to the Future." *Microbe* 2 no. 3 (2007):125–131.

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5.3.2: Antibacterial Drugs

Learning Objectives

- Contrast bacteriostatic versus bactericidal antibacterial activities
- Contrast broad-spectrum drugs versus narrow-spectrum drugs
- Explain the significance of superinfections
- Discuss the significance of dosage and the route of administration of a drug
- Identify factors and variables that can influence the side effects of a drug
- Describe the significance of positive and negative interactions between drugs

Several factors are important in choosing the most appropriate antimicrobial drug therapy, including bacteriostatic versus bactericidal mechanisms, spectrum of activity, dosage and route of administration, the potential for side effects, and the potential interactions between drugs. The following discussion will focus primarily on antibacterial drugs, but the concepts translate to other antimicrobial classes.

Bacteriostatic Versus Bactericidal

Antibacterial drugs can be either bacteriostatic or bactericidal in their interactions with target bacteria. Bacteriostatic drugs cause a reversible inhibition of growth, with bacterial growth restarting after elimination of the drug. By contrast, bactericidal drugs kill their target bacteria. The decision of whether to use a bacteriostatic or bactericidal drugs depends on the type of infection and the immune status of the patient. In a patient with strong immune defenses, bacteriostatic and bactericidal drugs can be effective in achieving clinical cure. However, when a patient is immunocompromised, a bactericidal drug is essential for the successful treatment of infections. Regardless of the immune status of the patient, life-threatening infections such as acute endocarditis require the use of a bactericidal drug.

Spectrum of Activity

The spectrum of activity of an antibacterial drug relates to diversity of targeted bacteria. A narrow-spectrum antimicrobial targets only specific subsets of bacterial pathogens. For example, some narrow-spectrum drugs only target gram-positive bacteria, whereas others target only gram-negative bacteria. If the pathogen causing an infection has been identified, it is best to use a narrow-spectrum antimicrobial and minimize collateral damage to the normal microbiota. A broad-spectrum antimicrobial targets a wide variety of bacterial pathogens, including both gram-positive and gram-negative species, and is frequently used as empiric therapy to cover a wide range of potential pathogens while waiting on the laboratory identification of the infecting pathogen. Broad-spectrum antimicrobials are also used for polymicrobic infections (mixed infection with multiple bacterial species), or as prophylactic prevention of infections with surgery/invasive procedures. Finally, broad-spectrum antimicrobials may be selected to treat an infection when a narrow-spectrum drug fails because of development of drug resistance by the target pathogen.

The risk associated with using broad-spectrum antimicrobials is that they will also target a broad spectrum of the normal microbiota, increasing the risk of a superinfection, a secondary infection in a patient having a preexisting infection. A superinfection develops when the antibacterial intended for the preexisting infection kills the protective microbiota, allowing another pathogen resistant to the antibacterial to proliferate and cause a secondary infection (Figure 5.3.2.1). Common examples of superinfections that develop as a result of antimicrobial usage include yeast infections (candidiasis) and pseudomembranous colitis caused by *Clostridium difficile*, which can be fatal.

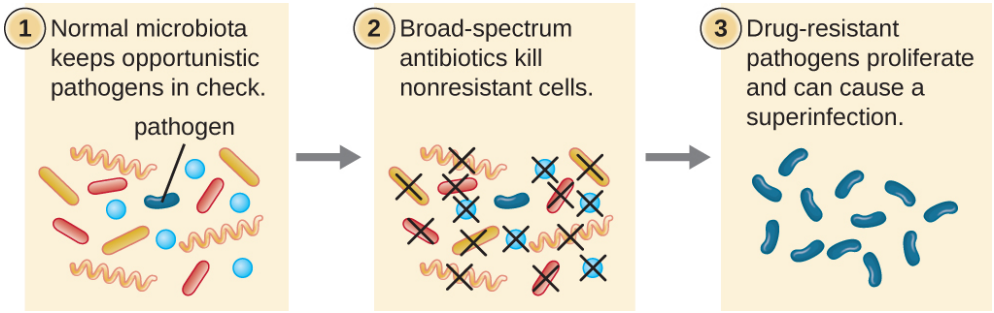


Figure 5.3.2.1: Broad-spectrum antimicrobial use may lead to the development of a superinfection. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 5.3.2.1

What is a superinfection and how does one arise?

Dosage and Route of Administration

The amount of medication given during a certain time interval is the dosage, and it must be determined carefully to ensure that optimum therapeutic drug levels are achieved at the site of infection without causing significant toxicity(side effects) to the patient. Each drug class is associated with a variety of potential side effects, and some of these are described for specific drugs later in this chapter. Despite best efforts to optimize dosing, allergic reactions and other potentially serious side effects do occur. Therefore, the goal is to select the optimum dosage that will minimize the risk of side effects while still achieving clinical cure, and there are important factors to consider when selecting the best dose and dosage interval. For example, in children, dose is based upon the patient's mass. However, the same is not true for adults and children 12 years of age and older, for which there is typically a single standard dose regardless of the patient's mass. With the great variability in adult body mass, some experts have argued that mass should be considered for all patients when determining appropriate dosage.[1] An additional consideration is how drugs are metabolized and eliminated from the body. In general, patients with a history of liver or kidney dysfunction may experience reduced drug metabolism or clearance from the body, resulting in increased drug levels that may lead to toxicity and make them more prone to side effects.

There are also some factors specific to the drugs themselves that influence appropriate dose and time interval between doses. For example, the half-life, or rate at which 50% of a drug is eliminated from the plasma, can vary significantly between drugs. Some drugs have a short half-life of only 1 hour and must be given multiple times a day, whereas other drugs have half-lives exceeding 12 hours and can be given as a single dose every 24 hours. Although a longer half-life can be considered an advantage for an antibacterial when it comes to convenient dosing intervals, the longer half-life can also be a concern for a drug that has serious side effects because drug levels may remain toxic for a longer time. Last, some drugs are dose dependent, meaning they are more effective when administered in large doses to provide high levels for a short time at the site of infection. Others are time dependent, meaning they are more effective when lower optimum levels are maintained over a longer period of time.

The route of administration, the method used to introduce a drug into the body, is also an important consideration for drug therapy. Drugs that can be administered orally are generally preferred because patients can more conveniently take these drugs at home. However, some drugs are not absorbed easily from the gastrointestinal (GI) tract into the bloodstream. These drugs are often useful for treating diseases of the intestinal tract, such as tapeworms treated with niclosamide, or for decontaminating the bowel, as with colistin. Some drugs that are not absorbed easily, such as bacitracin, polymyxin, and several antifungals, are available as topical preparations for treatment of superficial skin infections. Sometimes, patients may not initially be able to take oral medications because of their illness (e.g., vomiting, intubation for respirator). When this occurs, and when a chosen drug is not absorbed in the GI tract, administration of the drug by a parenteral route (intravenous or intramuscular injection) is preferred and typically is performed in health-care settings. For most drugs, the plasma levels achieved by intravenous administration is substantially higher than levels achieved by oral or intramuscular administration, and this can also be an important consideration when choosing the route of administration for treating an infection (Figure 5.3.2.2).

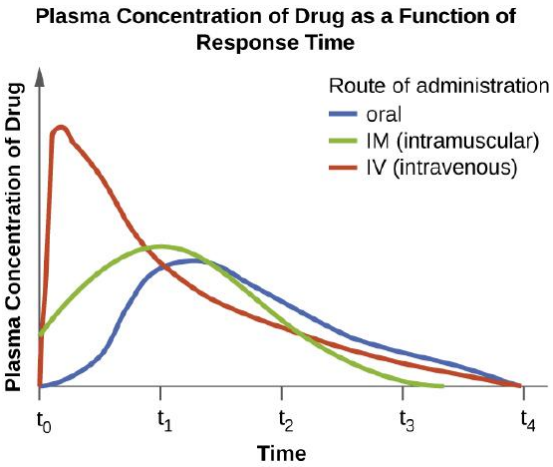


Figure 5.3.2.2: On this graph, t_0 represents the time at which a drug dose is administered. The curves illustrate how plasma concentration of the drug changes over specific intervals of time (t_1 through t_4). As the graph shows, when a drug is administered intravenously, the concentration peaks very quickly and then gradually decreases. When drugs are administered orally or intramuscularly, it takes longer for the concentration to reach its peak.

? Exercise 5.3.2.2

1. List five factors to consider when determining the dosage of a drug.
2. Name some typical side effects associated with drugs and identify some factors that might contribute to these side effects.

Drug Interactions

For the optimum treatment of some infections, two antibacterial drugs may be administered together to provide a synergistic interaction that is better than the efficacy of either drug alone. A classic example of synergistic combinations is trimethoprim and sulfamethoxazole (Bactrim). Individually, these two drugs provide only bacteriostatic inhibition of bacterial growth, but combined, the drugs are bactericidal.

Whereas synergistic drug interactions provide a benefit to the patient, antagonistic interactions produce harmful effects. Antagonism can occur between two antimicrobials or between antimicrobials and nonantimicrobials being used to treat other conditions. The effects vary depending on the drugs involved, but antagonistic interactions may cause loss of drug activity, decreased therapeutic levels due to increased metabolism and elimination, or increased potential for toxicitydue to decreased metabolism and elimination. As an example, some antibacterials are absorbed most effectively from the acidic environment of the stomach. If a patient takes antacids, however, this increases the pH of the stomach and negatively impacts the absorption of these antimicrobials, decreasing their effectiveness in treating an infection. Studies have also shown an association between use of some antimicrobials and failure of oral contraceptives.[2]

? Exercise 5.3.2.3

Explain the difference between synergistic and antagonistic drug interactions.

Resistance Police

In the United States and many other countries, most antimicrobial drugs are self-administered by patients at home. Unfortunately, many patients stop taking antimicrobials once their symptoms dissipate and they feel better. If a 10-day course of treatment is prescribed, many patients only take the drug for 5 or 6 days, unaware of the negative consequences of not completing the full course of treatment. A shorter course of treatment not only fails to kill the target organisms to expected levels, it also selects for drug-resistant variants within the target population and within the patient's microbiota.

Patients' nonadherence especially amplifies drug resistance when the recommended course of treatment is long. Treatment for tuberculosis (TB) is a case in point, with the recommended treatment lasting from 6 months to a year. The CDC estimates that about one-third of the world's population is infected with TB, most living in underdeveloped or underserved regions where

antimicrobial drugs are available over the counter. In such countries, there may be even lower rates of adherence than in developed areas. Nonadherence leads to antibiotic resistance and more difficulty in controlling pathogens. As a direct result, the emergence of multidrug-resistant and extensively drug-resistant strains of TB is becoming a huge problem.

Overprescription of antimicrobials also contributes to antibiotic resistance. Patients often demand antibiotics for diseases that do not require them, like viral colds and ear infections. Pharmaceutical companies aggressively market drugs to physicians and clinics, making it easy for them to give free samples to patients, and some pharmacies even offer certain antibiotics free to low-income patients with a prescription.

In recent years, various initiatives have aimed to educate parents and clinicians about the judicious use of antibiotics. However, a recent study showed that, between 2000 and 2013, the parental expectation for antimicrobial prescriptions for children actually increased (Figure 5.3.2.3).

One possible solution is a regimen called directly observed therapy (DOT), which involves the supervised administration of medications to patients. Patients are either required to visit a health-care facility to receive their medications, or health-care providers must administer medication in patients' homes or another designated location. DOT has been implemented in many cases for the treatment of TB and has been shown to be effective; indeed, DOT is an integral part of WHO's global strategy for eradicating TB.[3,4] But is this a practical strategy for all antibiotics? Would patients taking penicillin, for example, be more or less likely to adhere to the full course of treatment if they had to travel to a health-care facility for each dose? And who would pay for the increased cost associated with DOT? When it comes to overprescription, should someone be policing physicians or drug companies to enforce best practices? What group should assume this responsibility, and what penalties would be effective in discouraging overprescription?

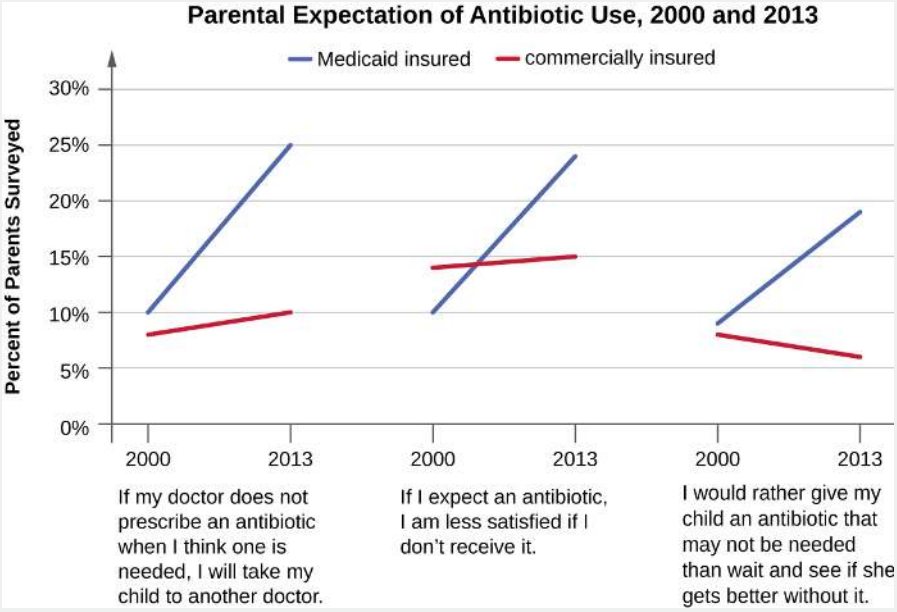


Figure 5.3.2.3: This graph indicates trends in parental expectations related to prescription of antibiotics based on a recent study.[5] Among parents of Medicaid-insured children, there was a clear upward trend in parental expectations for prescription antibiotics. Expectations were relatively stable (and lesser) among parents whose children were commercially insured, suggesting that these parents were somewhat better informed than those with Medicaid-insured children.

Key Concepts and Summary

- Antimicrobial drugs can be **bacteriostatic** or **bactericidal**, and these characteristics are important considerations when selecting the most appropriate drug.
- The use of **narrow-spectrum** antimicrobial drugs is preferred in many cases to avoid **superinfection** and the development of antimicrobial resistance.
- **Broad-spectrum** antimicrobial use is warranted for serious systemic infections when there is no time to determine the causative agent, when narrow-spectrum antimicrobials fail, or for the treatment or prevention of infections with multiple types of microbes.

- The **dosage** and **route of administration** are important considerations when selecting an antimicrobial to treat and infection. Other considerations include the patient's age, mass, ability to take oral medications, liver and kidney function, and possible interactions with other drugs the patient may be taking.

Footnotes

1. 1 M.E. Falagas, D.E. Karageorgopoulos. "Adjustment of Dosing of Antimicrobial Agents for Bodyweight in Adults." *The Lancet* 375 no. 9710 (2010):248–251.
2. 2 B.D. Dickinson et al. "Drug Interactions between Oral Contraceptives and Antibiotics." *Obstetrics & Gynecology* 98, no. 5 (2001):853–860.
3. 3 Centers for Disease Control and Prevention. "Tuberculosis (TB)." www.cdc.gov/tb/education/ssmo...s9reading2.htm. Accessed June 2, 2016.
4. 4 World Health Organization. "Tuberculosis (TB): The Five Elements of DOTS." http://www.who.int/tb/dots/whatisdots/en/. Accessed June 2, 2016.
5. 5 Vaz, L.E., et al. "Prevalence of Parental Misconceptions About Antibiotic Use." *Pediatrics* 136 no.2 (August 2015). DOI: 10.1542/peds.2015-0883.

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5.3.3: Drugs Targeting Other Microorganisms

Learning Objectives

- Describe the mechanisms of action associated with drugs that inhibit cell wall biosynthesis, protein synthesis, membrane function, nucleic acid synthesis, and metabolic pathway.

An important quality for an antimicrobial drug is selective toxicity, meaning that it selectively kills or inhibits the growth of microbial targets while causing minimal or no harm to the host. Most antimicrobial drugs currently in clinical use are antibacterial because the prokaryotic cell provides a greater variety of unique targets for selective toxicity, in comparison to fungi, parasites, and viruses. Each class of antibacterial drugs has a unique mode of action (the way in which a drug affects microbes at the cellular level), and these are summarized in Figure 5.3.3.1 and Table 5.3.3.1.

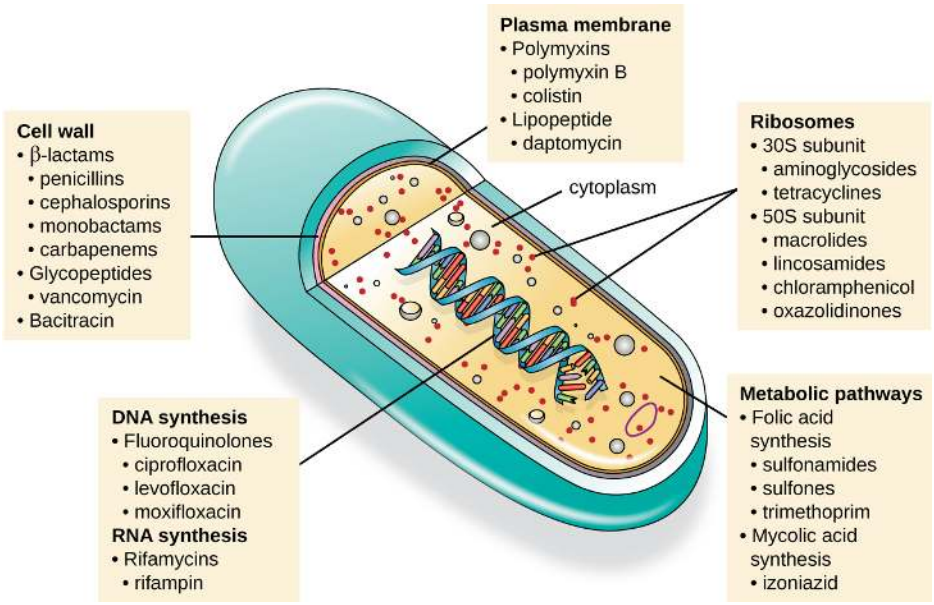


Figure 5.3.3.1: There are several classes of antibacterial compounds that are typically classified based on their bacterial target.

Table 5.3.3.1: Common Antibacterial Drugs by Mode of Action

Mode of Action	Target	Drug Class
Inhibit cell wall biosynthesis	Penicillin-binding proteins	β-lactams: penicillins, cephalosporins, monobactams, carbapenems
	Peptidoglycan subunits	Glycopeptides
	Peptidoglycan subunit transport	Bacitracin
Inhibit biosynthesis of proteins	30S ribosomal subunit	Aminoglycosides, tetracyclines
	50S ribosomal subunit	Macrolides, lincosamides, chloramphenicol, oxazolidinones
Disrupt membranes	Lipopolysaccharide, inner and outer membranes	Polymyxin B, colistin, daptomycin
Inhibit nucleic acid synthesis	RNA	Rifamycin
	DNA	Fluoroquinolones
Antimetabolites	Folic acid synthesis enzyme	Sulfonamides, trimethoprim
	Mycolic acid synthesis enzyme	Isonicotinic acid hydrazide
Mycobacterial adenosine triphosphate (ATP) synthase inhibitor	Mycobacterial ATP synthase	Diarylquinoline

Inhibitors of Cell Wall Biosynthesis

Several different classes of antibacterials block steps in the biosynthesis of peptidoglycan, making cells more susceptible to osmotic lysis (Table 5.3.3.2). Therefore, antibacterials that target cell wall biosynthesis are bactericidal in their action. Because human cells do not make peptidoglycan, this mode of action is an excellent example of selective toxicity.

Penicillin, the first antibiotic discovered, is one of several antibacterials within a class called β-lactams. This group of compounds includes the penicillins, cephalosporins, monobactams, and carbapenems, and is characterized by the presence of a β-lactam ring found within the central structure of the drug molecule (Figure 5.3.3.2). The β-lactam antibacterials block the crosslinking of peptide chains during the biosynthesis of new peptidoglycan in the bacterial cell wall. They are able to block this process because the β-lactam structure is similar to the structure of the peptidoglycan subunit component that is recognized by the crosslinking transpeptidase enzyme, also known as a penicillin-binding protein (PBP). Although the β-lactam ring must remain unchanged for these drugs to retain their antibacterial activity, strategic chemical changes to the R groups have allowed for development of a wide variety of semisynthetic β-lactam drugs with increased potency, expanded spectrum of activity, and longer half-lives for better dosing, among other characteristics.

Penicillin G and penicillin V are natural antibiotics from fungi and are primarily active against gram-positive bacterial pathogens, and a few gram-negative bacterial pathogens such as *Pasteurella multocida*. Figure 5.3.3.2 summarizes the semisynthetic development of some of the penicillins. Adding an amino group (-NH_2) to penicillin G created the aminopenicillins (i.e., ampicillin and amoxicillin) that have increased spectrum of activity against more gram-negative pathogens. Furthermore, the addition of a hydroxyl group (-OH) to amoxicillin increased acid stability, which allows for improved oral absorption. Methicillin is a semisynthetic penicillin that was developed to address the spread of enzymes (penicillinases) that were inactivating the other penicillins. Changing the R group of penicillin G to the more bulky dimethoxyphenyl group provided protection of the β-lactam ring from enzymatic destruction by penicillinases, giving us the first penicillinase-resistant penicillin.

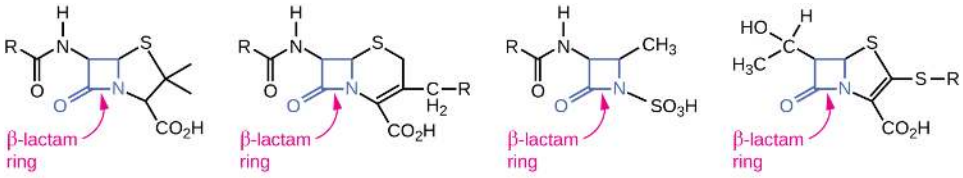
Similar to the penicillins, cephalosporins contain a β-lactam ring (Figure 5.3.3.2) and block the transpeptidase activity of penicillin-binding proteins. However, the β-lactam ring of cephalosporins is fused to a six-member ring, rather than the five-member ring found in penicillins. This chemical difference provides cephalosporins with an increased resistance to enzymatic inactivation by β-lactamases. The drug cephalosporin C was originally isolated from the fungus *Cephalosporium acremonium* in the 1950s and has a similar spectrum of activity to that of penicillin against gram-positive bacteria but is active against more gram-negative bacteria

than penicillin. Another important structural difference is that cephalosporin C possesses two R groups, compared with just one R group for penicillin, and this provides for greater diversity in chemical alterations and development of semisynthetic cephalosporins. The family of semisynthetic cephalosporins is much larger than the penicillins, and these drugs have been classified into generations based primarily on their spectrum of activity, increasing in spectrum from the narrow-spectrum, first-generation cephalosporins to the broad-spectrum, fourth-generation cephalosporins. A new fifth-generation cephalosporin has been developed that is active against methicillin-resistant *Staphylococcus aureus* (MRSA).

The carbapenems and monobactams also have a β-lactam ring as part of their core structure, and they inhibit the transpeptidase activity of penicillin-binding proteins. The only monobactam used clinically is aztreonam. It is a narrow-spectrum antibacterial with activity only against gram-negative bacteria. In contrast, the carbapenem family includes a variety of semisynthetic drugs (imipenem, meropenem, and doripenem) that provide very broad-spectrum activity against gram-positive and gram-negative bacterial pathogens.

The drug vancomycin, a member of a class of compounds called the glycopeptides, was discovered in the 1950s as a natural antibiotic from the actinomycete *Amycolatopsis orientalis*. Similar to the β-lactams, vancomycin inhibits cell wall biosynthesis and is bactericidal. However, in contrast to the β-lactams, the structure of vancomycin is not similar to that of cell-wall peptidoglycan subunits and does not directly inactivate penicillin-binding proteins. Rather, vancomycin is a very large, complex molecule that binds to the end of the peptide chain of cell wall precursors, creating a structural blockage that prevents the cell wall subunits from being incorporated into the growing N-acetylglucosamine and N-acetylmuramic acid (NAM-NAG) backbone of the peptidoglycan structure (transglycosylation). Vancomycin also structurally blocks transpeptidation. Vancomycin is bactericidal against gram-positive bacterial pathogens, but it is not active against gram-negative bacteria because of its inability to penetrate the protective outer membrane.

The drug bacitracin consists of a group of structurally similar peptide antibiotics originally isolated from *Bacillus subtilis*. Bacitracin blocks the activity of a specific cell-membrane molecule that is responsible for the movement of peptidoglycan precursors from the cytoplasm to the exterior of the cell, ultimately preventing their incorporation into the cell wall. Bacitracin is effective against a wide range of bacteria, including gram-positive organisms found on the skin, such as *Staphylococcus* and *Streptococcus*. Although it may be administered orally or intramuscularly in some circumstances, bacitracin has been shown to be nephrotoxic (damaging to the kidneys). Therefore, it is more commonly combined with neomycin and polymyxin in topical ointments such as Neosporin.



penicillin | cephalosporin | monobactam | carbapenem

R group	—CH_2—	CH_2—O—	—CH(—NH_2)—	—CH(—NH_2)—OH	CH_3O
Drug name	penicillin G	penicillin V	ampicillin	amoxicillin	methicillin
Spectrum of activity	G+ and a few G−	similar to penicillin G	G+ and more G− than penicillin	similar to ampicillin	G+ only, including β-lactamase producers
Route of administration	parenteral	oral	parenteral and oral	oral (better than ampicillin)	parenteral

Figure 5.3.3.2: Penicillins, cephalosporins, monobactams, and carbapenems all contain a β-lactam ring, the site of attack by inactivating β-lactamase enzymes. Although they all share the same nucleus, various penicillins differ from each other in the structure of their R groups. Chemical changes to the R groups provided increased spectrum of activity, acid stability, and resistance to β-lactamase degradation.

Table 5.3.3.2: Drugs that Inhibit Bacterial Cell Wall Synthesis

Mechanism of Action	Drug Class	Specific Drugs	Natural or Semisynthetic	Spectrum of Activity
Interact directly with PBPs and inhibit transpeptidase activity	Penicillins	Penicillin G, penicillin V	Natural	Narrow-spectrum against gram-positive and a few gram-negative bacteria
		Ampicillin, amoxicillin	Semisynthetic	Narrow-spectrum against gram-positive bacteria but with increased gram-negative spectrum
		Methicillin	Semisynthetic	Narrow-spectrum against gram-positive bacteria only, including strains producing penicillinase
	Cephalosporins	Cephalosporin C	Natural	Narrow-spectrum similar to penicillin but with increased gram-negative spectrum
		First-generation cephalosporins	Semisynthetic	Narrow-spectrum similar to cephalosporin C
		Second-generation cephalosporins	Semisynthetic	Narrow-spectrum but with increased gram-negative spectrum compared with first generation
		Third- and fourth-generation cephalosporins	Semisynthetic	Broad-spectrum against gram-positive and gram-negative bacteria, including some β-lactamase producers
		Fifth-generation cephalosporins	Semisynthetic	Broad-spectrum against gram-positive and gram-negative bacteria, including MRSA
	Monobactams	Aztreonam	Semisynthetic	Narrow-spectrum against gram-negative bacteria, including some β-lactamase producers
	Carbapenems	Imipenem, meropenem, doripenem	Semisynthetic	Broadest spectrum of the β-lactams against gram-positive and gram-negative bacteria, including many β-lactamase producers
Large molecules that bind to the peptide chain of peptidoglycan subunits, blocking	Glycopeptides	Vancomycin	Natural	Narrow spectrum against gram-positive bacteria only, including multidrug-resistant strains

Mechanism of Action	Drug Class	Specific Drugs	Natural or Semisynthetic	Spectrum of Activity
transglycosylation and transpeptidation				
Block transport of peptidoglycan subunits across cytoplasmic membrane	Bacitracin	Bacitracin	Natural	Broad-spectrum against gram-positive and gram-negative bacteria

? Exercise 5.3.3.1

Describe the mode of action of β-lactams.

Inhibitors of Protein Biosynthesis

The cytoplasmic ribosomes found in animal cells (80S) are structurally distinct from those found in bacterial cells (70S), making protein biosynthesis a good selective target for antibacterial drugs. Several types of protein biosynthesis inhibitors are discussed in this section and are summarized in Figure 5.3.3.3.

Protein Synthesis Inhibitors That Bind the 30S Subunit

Aminoglycosides are large, highly polar antibacterial drugs that bind to the 30S subunit of bacterial ribosomes, impairing the proofreading ability of the ribosomal complex. This impairment causes mismatches between codons and anticodons, resulting in the production of proteins with incorrect amino acids and shortened proteins that insert into the cytoplasmic membrane. Disruption of the cytoplasmic membrane by the faulty proteins kills the bacterial cells. The aminoglycosides, which include drugs such as streptomycin, gentamicin, neomycin, and kanamycin, are potent broad-spectrum antibacterials. However, aminoglycosides have been shown to be nephrotoxic (damaging to kidney), neurotoxic (damaging to the nervous system), and ototoxic (damaging to the ear).

Another class of antibacterial compounds that bind to the 30S subunit is the tetracyclines. In contrast to aminoglycosides, these drugs are bacteriostatic and inhibit protein synthesis by blocking the association of tRNAs with the ribosome during translation. Naturally occurring tetracyclines produced by various strains of *Streptomyces* were first discovered in the 1940s, and several semisynthetic tetracyclines, including doxycycline and tigecycline have also been produced. Although the tetracyclines are broad spectrum in their coverage of bacterial pathogens, side effects that can limit their use include phototoxicity, permanent discoloration of developing teeth, and liver toxicity with high doses or in patients with kidney impairment.

Protein Synthesis Inhibitors That Bind the 50S Subunit

There are several classes of antibacterial drugs that work through binding to the 50S subunit of bacterial ribosomes. The macrolide antibacterial drugs have a large, complex ring structure and are part of a larger class of naturally produced secondary metabolites called polyketides, complex compounds produced in a stepwise fashion through the repeated addition of two-carbon units by a mechanism similar to that used for fatty acid synthesis. Macrolides are broad-spectrum, bacteriostatic drugs that block elongation of proteins by inhibiting peptide bond formation between specific combinations of amino acids. The first macrolide was erythromycin. It was isolated in 1952 from *Streptomyces erythreus* and prevents translocation. Semisynthetic macrolides include azithromycin and telithromycin. Compared with erythromycin, azithromycin has a broader spectrum of activity, fewer side effects, and a significantly longer half-life (1.5 hours for erythromycin versus 68 hours for azithromycin) that allows for once-daily dosing and a short 3-day course of therapy (i.e., Zpac formulation) for most infections. Telithromycin is the first semisynthetic within the class known as ketolides. Although telithromycin shows increased potency and activity against macrolide-resistant pathogens, the US Food and Drug Administration (FDA) has limited its use to treatment of community-acquired pneumonia and requires the strongest “black box warning” label for the drug because of serious hepatotoxicity.

The lincosamides include the naturally produced lincomycin and semisynthetic clindamycin. Although structurally distinct from macrolides, lincosamides are similar in their mode of action to the macrolides through binding to the 50S ribosomal subunit and preventing peptide bond formation. Lincosamides are particularly active against streptococcal and staphylococcal infections.

The drug chloramphenicol represents yet another structurally distinct class of antibacterials that also bind to the 50S ribosome, inhibiting peptide bond formation. Chloramphenicol, produced by *Streptomyces venezuelae*, was discovered in 1947; in 1949, it became the first broad-spectrum antibiotic that was approved by the FDA. Although it is a natural antibiotic, it is also easily synthesized and was the first antibacterial drug synthetically mass produced. As a result of its mass production, broad-spectrum coverage, and ability to penetrate into tissues efficiently, chloramphenicol was historically used to treat a wide range of infections, from meningitis to typhoid fever to conjunctivitis. Unfortunately, serious side effects, such as lethal gray baby syndrome, and suppression of bone marrow production, have limited its clinical role. Chloramphenicol also causes anemia in two different ways. One mechanism involves the targeting of mitochondrial ribosomes within hematopoietic stem cells, causing a reversible, dose-dependent suppression of blood cell production. Once chloramphenicol dosing is discontinued, blood cell production returns to normal. This mechanism highlights the similarity between 70S ribosomes of bacteria and the 70S ribosomes within our mitochondria. The second mechanism of anemia is idiosyncratic (i.e., the mechanism is not understood), and involves an irreversible lethal loss of blood cell production known as aplastic anemia. This mechanism of aplastic anemia is not dose dependent and can develop after therapy has stopped. Because of toxicity concerns, chloramphenicol usage in humans is now rare in the United States and is limited to severe infections unable to be treated by less toxic antibiotics. Because its side effects are much less severe in animals, it is used in veterinary medicine.

The oxazolidinones, including linezolid, are a new broad-spectrum class of synthetic protein synthesis inhibitors that bind to the 50S ribosomal subunit of both gram-positive and gram-negative bacteria. However, their mechanism of action seems somewhat different from that of the other 50S subunit-binding protein synthesis inhibitors already discussed. Instead, they seem to interfere with formation of the initiation complex (association of the 50S subunit, 30S subunit, and other factors) for translation, and they prevent translocation of the growing protein from the ribosomal A site to the P site. Table 5.3.3.3 summarizes the protein synthesis inhibitors.

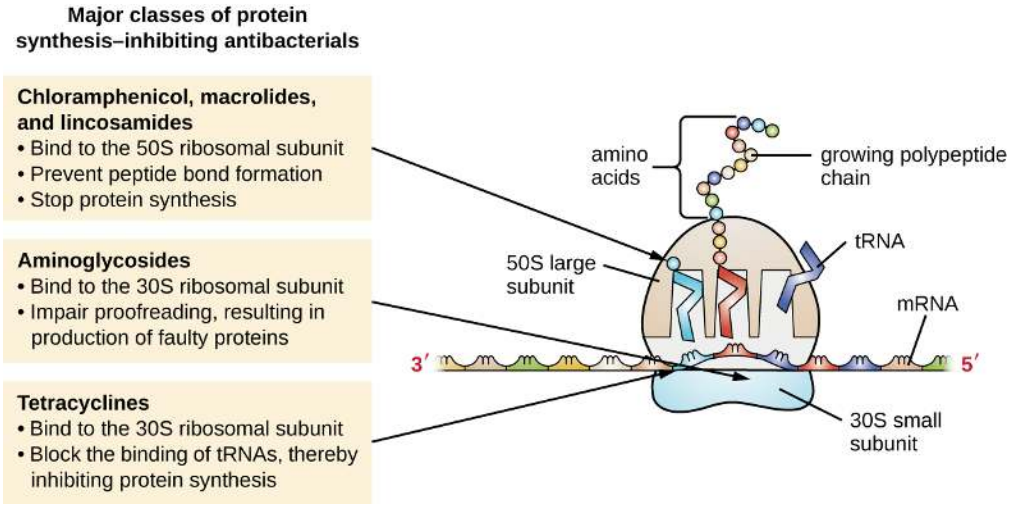


Figure 5.3.3.3: The major classes of protein synthesis inhibitors target the 30S or 50S subunits of cytoplasmic ribosomes.

Table 5.3.3.3: Drugs That Inhibit Bacterial Protein Synthesis

Molecular Target	Mechanism of Action	Drug Class	Specific Drugs	Bactericidal or Bactericidal	Spectrum of Activity
30S subunit	Causes mismatches between codons and anticodons, leading to faulty proteins that insert into and disrupt cytoplasmic membrane	Aminoglycosides	Streptomycin, gentamicin, neomycin, kanamycin	Bactericidal	Broad spectrum
	Blocks association of tRNAs with ribosome	Tetracyclines	Tetracycline, doxycycline, tigecycline	Bacteriostatic	Broad spectrum
50S subunit	Blocks peptide bond formation between amino acids	Macrolides	Erythromycin, azithromycin, telithromycin	Bacteriostatic	Broad spectrum
		Lincosamides	Lincomycin, clindamycin	Bacteriostatic	Narrow spectrum
		Not applicable	Chloramphenicol	Bacteriostatic	Broad spectrum
	Interferes with the formation of the initiation complex between 50S and 30S subunits and other factors.	Oxazolidinones	Linezolid	Bacteriostatic	Broad spectrum

? Exercise 5.3.3.2

Compare and contrast the different types of protein synthesis inhibitors.

Inhibitors of Membrane Function

A small group of antibacterials target the bacterial membrane as their mode of action (Table 5.3.3.4). The polymyxins are natural polypeptide antibiotics that were first discovered in 1947 as products of *Bacillus polymyxa*; only polymyxin B and polymyxin E (colistin) have been used clinically. They are lipophilic with detergent-like properties and interact with the lipopolysaccharide component of the outer membrane of gram-negative bacteria, ultimately disrupting both their outer and inner membranes and killing the bacterial cells. Unfortunately, the membrane-targeting mechanism is not a selective toxicity, and these drugs also target and damage the membrane of cells in the kidney and nervous system when administered systemically. Because of these serious side effects and their poor absorption from the digestive tract, polymyxin B is used in over-the-counter topical antibiotic ointments (e.g., Neosporin), and oral colistin was historically used only for bowel decontamination to prevent infections originating from bowel microbes in immunocompromised patients or for those undergoing certain abdominal surgeries. However, the emergence and spread of multidrug-resistant pathogens has led to increased use of intravenous colistin in hospitals, often as a drug of last resort to treat serious infections. The antibacterial daptomycin is a cyclic lipopeptide produced by *Streptomyces roseosporus* that seems to work like the polymyxins, inserting in the bacterial cell membrane and disrupting it. However, in contrast to polymyxin B and colistin, which target only gram-negative bacteria, daptomycin specifically targets gram-positive bacteria. It is typically administered intravenously and seems to be well tolerated, showing reversible toxicity in skeletal muscles.

Table 5.3.3.4: Drugs That Inhibit Bacterial Membrane Function

Mechanism of Action	Drug Class	Specific Drugs	Spectrum of Activity	Clinical Use
Interacts with lipopolysaccharide in the outer membrane of gram-negative bacteria, killing the cell through the eventual disruption of the outer membrane and cytoplasmic membrane	Polymyxins	Polymyxin B	Narrow spectrum against gram-negative bacteria, including multidrug-resistant strains	Topical preparations to prevent infections in wounds
		Polymyxin E (colistin)	Narrow spectrum against gram-negative bacteria, including multidrug-resistant strains	Oral dosing to decontaminate bowels to prevent infections in immunocompromised patients or patients undergoing invasive surgery/procedures.
				Intravenous dosing to treat serious systemic infections caused by multidrug-resistant pathogens
Inserts into the cytoplasmic membrane of gram-positive bacteria, disrupting the membrane and killing the cell	Lipopeptide	Daptomycin	Narrow spectrum against gram-positive bacteria, including multidrug-resistant strains	Complicated skin and skin-structure infections and bacteremia caused by gram-positive pathogens, including MRSA

? Exercise 5.3.3.3

How do polymyxins inhibit membrane function?

Inhibitors of Nucleic Acid Synthesis

Some antibacterial drugs work by inhibiting nucleic acid synthesis (Table 5.3.3.5). For example, metronidazole is a semisynthetic member of the nitroimidazole family that is also an antiprotozoan. It interferes with DNA replication in target cells. The drug rifampin is a semisynthetic member of the rifamycin family and functions by blocking RNA polymerase activity in bacteria. The RNA polymerase enzymes in bacteria are structurally different from those in eukaryotes, providing for selective toxicity against bacterial cells. It is used for the treatment of a variety of infections, but its primary use, often in a cocktail with other antibacterial drugs, is against mycobacteria that cause tuberculosis. Despite the selectivity of its mechanism, rifampin can induce liver enzymes to increase metabolism of other drugs being administered (antagonism), leading to hepatotoxicity (liver toxicity) and negatively influencing the bioavailability and therapeutic effect of the companion drugs.

One member of the quinolone family, a group of synthetic antimicrobials, is nalidixic acid. It was discovered in 1962 as a byproduct during the synthesis of chloroquine, an antimalarial drug. Nalidixic acid selectively inhibits the activity of bacterial DNA gyrase, blocking DNA replication. Chemical modifications to the original quinolone backbone have resulted in the production of fluoroquinolones, like ciprofloxacin and levofloxacin, which also inhibit the activity of DNA gyrase. Ciprofloxacin and levofloxacin are effective against a broad spectrum of gram-positive or gram-negative bacteria, and are among the most commonly prescribed antibiotics used to treat a wide range of infections, including urinary tract infections, respiratory infections, abdominal infections, and skin infections. However, despite their selective toxicity against DNA gyrase, side effects associated with different fluoroquinolones include phototoxicity, neurotoxicity, cardiotoxicity, glucose metabolism dysfunction, and increased risk for tendon rupture.

Table 5.3.3.5: Drugs That Inhibit Bacterial Nucleic Acid Synthesis

Mechanisms of Action	Drug Class	Specific Drugs	Spectrum of activity	Clinical Use
Inhibits bacterial RNA polymerase activity and blocks transcription, killing the cell	Rifamycin	Rifampin	Narrow spectrum with activity against gram-positive and limited numbers of gram-negative bacteria. Also active against *Mycobacterium tuberculosis.*	Combination therapy for treatment of tuberculosis
Inhibits the activity of DNA gyrase and blocks DNA replication, killing the cell	Fluoroquinolones	Ciprofloxacin, ofloxacin, moxifloxacin	Broad spectrum against gram-positive and gram-negative bacteria	Wide variety of skin and systemic infections

? Exercise 5.3.3.4

Why do inhibitors of bacterial nucleic acid synthesis not target host cells?

Inhibitors of Metabolic Pathways

Some synthetic drugs control bacterial infections by functioning as antimetabolites, competitive inhibitors for bacterial metabolic enzymes (Table 5.3.3.6). The sulfonamides (sulfa drugs) are the oldest synthetic antibacterial agents and are structural analogues of *para*-aminobenzoic acid (PABA), an early intermediate in folic acid synthesis (Figure 5.3.3.4). By inhibiting the enzyme involved in the production of dihydrofolic acid, sulfonamides block bacterial biosynthesis of folic acid and, subsequently, pyrimidines and purines required for nucleic acid synthesis. This mechanism of action provides bacteriostatic inhibition of growth against a wide spectrum of gram-positive and gram-negative pathogens. Because humans obtain folic acid from food instead of synthesizing it intracellularly, sulfonamides are selectively toxic for bacteria. However, allergic reactions to sulfa drugs are common. The sulfones are structurally similar to sulfonamides but are not commonly used today except for the treatment of Hansen's disease (leprosy).

Trimethoprim is a synthetic antimicrobial compound that serves as an antimetabolite within the same folic acid synthesis pathway as sulfonamides. However, trimethoprim is a structural analogue of dihydrofolic acid and inhibits a later step in the metabolic pathway (Figure 5.3.3.4). Trimethoprim is used in combination with the sulfa drug sulfamethoxazole to treat urinary tract infections, ear infections, and bronchitis. As discussed, the combination of trimethoprim and sulfamethoxazole is an example of antibacterial synergy. When used alone, each antimetabolite only decreases production of folic acid to a level where bacteriostatic inhibition of growth occurs. However, when used in combination, inhibition of both steps in the metabolic pathway decreases folic acid synthesis to a level that is lethal to the bacterial cell. Because of the importance of folic acid during fetal development, sulfa drugs and trimethoprim use should be carefully considered during early pregnancy.

The drug isoniazid is an antimetabolite with specific toxicity for mycobacteria and has long been used in combination with rifampin or streptomycin in the treatment of tuberculosis. It is administered as a prodrug, requiring activation through the action of an intracellular bacterial peroxidase enzyme, forming isoniazid-nicotinamide adenine dinucleotide (NAD) and isoniazid-nicotinamide adenine dinucleotide phosphate (NADP), ultimately preventing the synthesis of mycolic acid, which is essential for mycobacterial cell walls. Possible side effects of isoniazid use include hepatotoxicity, neurotoxicity, and hematologic toxicity (anemia).

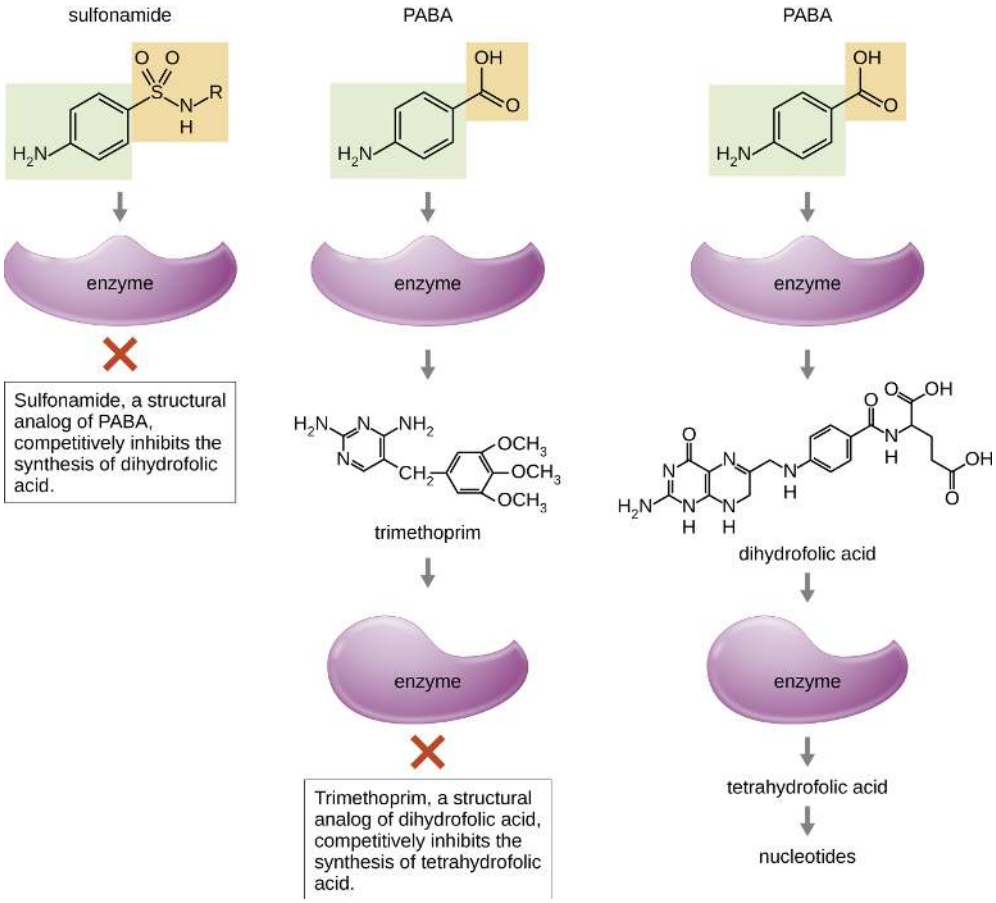


Figure 5.3.3.4: Sulfonamides and trimethoprim are examples of antimetabolites that interfere in the bacterial synthesis of folic acid by blocking purine and pyrimidine biosynthesis, thus inhibiting bacterial growth.

Table 5.3.3.6: Antimetabolite Drugs

Metabolic Pathway Target	Mechanism of Action	Drug Class	Specific Drugs	Spectrum of Activity
Folic acid synthesis	Inhibits the enzyme involved in production of dihydrofolic acid	Sulfonamides	Sulfamethoxazole	Broad spectrum against gram-positive and gram-negative bacteria
		Sulfones	Dapsone	
	Inhibits the enzyme involved in the production of tetrahydrofolic acid	Not applicable	Trimethoprim	Broad spectrum against gram-positive and gram-negative bacteria
Mycolic acid synthesis	Interferes with the synthesis of mycolic acid	Not applicable	Isoniazid	Narrow spectrum against *Mycobacterium* spp., including *M. tuberculosis*

? Exercise 5.3.3.5

How do sulfonamides and trimethoprim selectively target bacteria?

Inhibitor of ATP Synthase

Bedaquiline, representing the synthetic antibacterial class of compounds called the diarylquinolones, uses a novel mode of action that specifically inhibits mycobacterial growth. Although the specific mechanism has yet to be elucidated, this compound appears

to interfere with the function of ATP synthases, perhaps by interfering with the use of the hydrogen ion gradient for ATP synthesis by oxidative phosphorylation, leading to reduced ATP production. Due to its side effects, including hepatotoxicity and potentially lethal heart arrhythmia, its use is reserved for serious, otherwise untreatable cases of tuberculosis.

Clinical Focus: Part 2

Reading thorough Marisa's health history, the doctor noticed that during her hospitalization in Vietnam, she was catheterized and received the antimicrobial drugs ceftazidime and metronidazole. Upon learning this, the doctor ordered a CT scan of Marisa's abdomen to rule out appendicitis; the doctor also requested blood work to see if she had an elevated white blood cell count, and ordered a urine analysis test and urine culture to look for the presence of white blood cells, red blood cells, and bacteria.

Marisa's urine sample came back positive for the presence of bacteria, indicating a urinary tract infection (UTI). The doctor prescribed ciprofloxacin. In the meantime, her urine was cultured to grow the bacterium for further testing.

Exercise 5.3.3.6

1. What types of antimicrobials are typically prescribed for UTIs?
2. Based upon the antimicrobial drugs she was given in Vietnam, which of the antimicrobials for treatment of a UTI would you predict to be ineffective?

Key Concepts and Summary

- Antibacterial compounds exhibit **selective toxicity**, largely due to differences between prokaryotic and eukaryotic cell structure.
- Cell wall synthesis inhibitors, including the **β-lactams**, the **glycopeptides**, and **bacitracin**, interfere with peptidoglycan synthesis, making bacterial cells more prone to osmotic lysis.
- There are a variety of broad-spectrum, bacterial protein synthesis inhibitors that selectively target the prokaryotic 70S ribosome, including those that bind to the 30S subunit (**aminoglycosides** and **tetracyclines**) and others that bind to the 50S subunit (**macrolides**, **lincosamides**, **chloramphenicol**, and **oxazolidinones**).
- **Polymyxins** are lipophilic polypeptide antibiotics that target the lipopolysaccharide component of gram-negative bacteria and ultimately disrupt the integrity of the outer and inner membranes of these bacteria.
- The nucleic acid synthesis inhibitors rifamycins and **fluoroquinolones** target bacterial RNA transcription and DNA replication, respectively.
- Some antibacterial drugs are **antimetabolites**, acting as competitive inhibitors for bacterial metabolic enzymes. **Sulfonamides** and **trimethoprim** are antimetabolites that interfere with bacterial folic acid synthesis. **Isoniazid** is an antimetabolite that interferes with mycolic acid synthesis in mycobacteria.

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5.3.4: Clinical Considerations

Learning Objectives

- Explain the differences between modes of action of drugs that target fungi, protozoa, helminths, and viruses

Because fungi, protozoa, and helminths are eukaryotic, their cells are very similar to human cells, making it more difficult to develop drugs with selective toxicity. Additionally, viruses replicate within human host cells, making it difficult to develop drugs that are selectively toxic to viruses or virus-infected cells. Despite these challenges, there are antimicrobial drugs that target fungi, protozoa, helminths, and viruses, and some even target more than one type of microbe. Table 5.3.4.1, Table 5.3.4.2, Table 5.3.4.3, and Table 5.3.4.4 provide examples for antimicrobial drugs in these various classes.

Antifungal Drugs

The most common mode of action for antifungal drugs is the disruption of the cell membrane. Antifungals take advantage of small differences between fungi and humans in the biochemical pathways that synthesize sterols. The sterols are important in maintaining proper membrane fluidity and, hence, proper function of the cell membrane. For most fungi, the predominant membrane sterol is ergosterol. Because human cell membranes use cholesterol, instead of ergosterol, antifungal drugs that target ergosterol synthesis are selectively toxic (Figure 5.3.4.1).

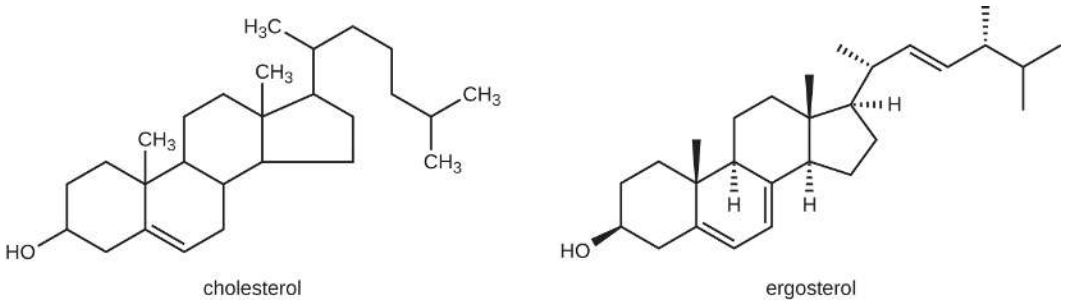


Figure 5.3.4.1: The predominant sterol found in human cells is cholesterol, whereas the predominant sterol found in fungi is ergosterol, making ergosterol a good target for antifungal drug development.

The imidazoles are synthetic fungicides that disrupt ergosterol biosynthesis; they are commonly used in medical applications and also in agriculture to keep seeds and harvested crops from molding. Examples include miconazole, ketoconazole, and clotrimazole, which are used to treat fungal skin infections such as ringworm, specifically tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis. These infections are commonly caused by dermatophytes of the genera *Trichophyton*, *Epidermophyton*, and *Microsporum*. Miconazole is also used predominantly for the treatment of vaginal yeast infections caused by the fungus *Candida*, and ketoconazole is used for the treatment of tinea versicolor and dandruff, which both can be caused by the fungus *Malassezia*.

The triazole drugs, including fluconazole, also inhibit ergosterol biosynthesis. However, they can be administered orally or intravenously for the treatment of several types of systemic yeast infections, including oral thrush and cryptococcal meningitis, both of which are prevalent in patients with AIDS. The triazoles also exhibit more selective toxicity, compared with the imidazoles, and are associated with fewer side effects.

The allylamines, a structurally different class of synthetic antifungal drugs, inhibit an earlier step in ergosterol biosynthesis. The most commonly used allylamine is terbinafine (marketed under the brand name Lamisil), which is used topically for the treatment of dermatophytic skin infections like athlete's foot, ringworm, and jock itch. Oral treatment with terbinafine is also used for the treatment of fingernail and toenail fungus, but it can be associated with the rare side effect of hepatotoxicity.

The polyenes are a class of antifungal agents naturally produced by certain actinomycete soil bacteria and are structurally related to macrolides. These large, lipophilic molecules bind to ergosterol in fungal cytoplasmic membranes, thus creating pores. Common examples include nystatin and amphotericin B. Nystatin is typically used as a topical treatment for yeast infections of the skin, mouth, and vagina, but may also be used for intestinal fungal infections. The drug amphotericin B is used for systemic fungal infections like aspergillosis, cryptococcal meningitis, histoplasmosis, blastomycosis, and candidiasis. Amphotericin B was the only

antifungal drug available for several decades, but its use is associated with some serious side effects, including nephrotoxicity (kidney toxicity).

Amphotericin B is often used in combination with flucytosine, a fluorinated pyrimidine analog that is converted by a fungal-specific enzyme into a toxic product that interferes with both DNA replication and protein synthesis in fungi. Flucytosine is also associated with hepatotoxicity (liver toxicity) and bone marrow depression.

Beyond targeting ergosterol in fungal cell membranes, there are a few antifungal drugs that target other fungal structures (Figure 5.3.4.2). The echinocandins, including caspofungin, are a group of naturally produced antifungal compounds that block the synthesis of β(1→3) glucan found in fungal cell walls but not found in human cells. This drug class has the nickname "penicillin for fungi." Caspofungin is used for the treatment of aspergillosis as well as systemic yeast infections.

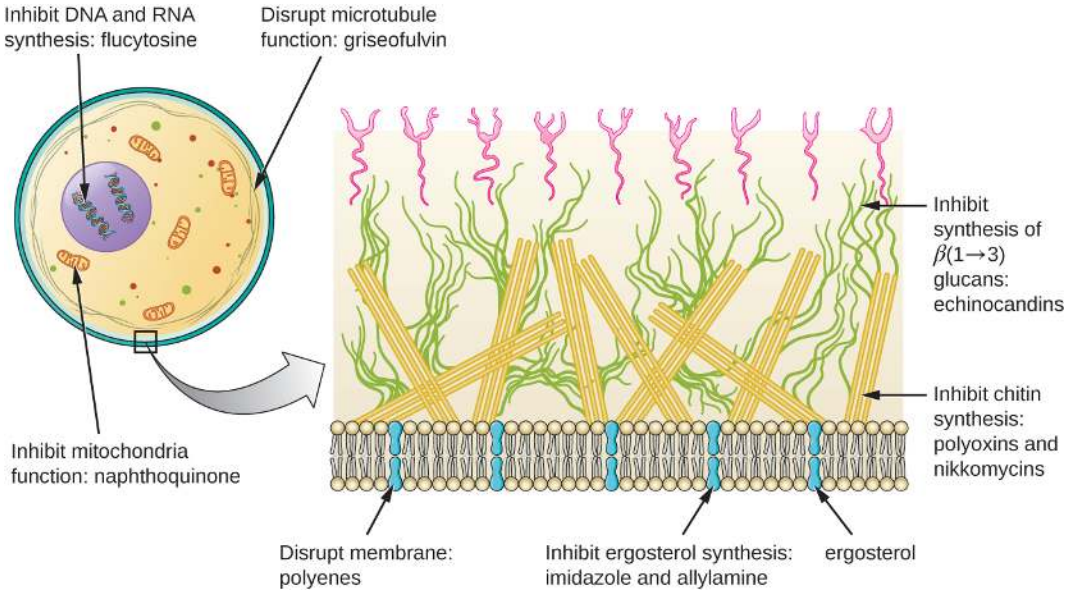


Figure 5.3.4.2: Antifungal drugs target several different cell structures. (credit right: modification of work by "Maya and Rike"/Wikimedia Commons)

Although chitin is only a minor constituent of fungal cell walls, it is also absent in human cells, making it a selective target. The polyoxins and nikkomycins are naturally produced antifungals that target chitin synthesis. Polyoxins are used to control fungi for agricultural purposes, and nikkomycin Z is currently under development for use in humans to treat yeast infections and Valley fever (coccidioidomycosis), a fungal disease prevalent in the southwestern US.[1]

The naturally produced antifungal griseofulvin is thought to specifically disrupt fungal cell division by interfering with microtubules involved in spindle formation during mitosis. It was one of the first antifungals, but its use is associated with hepatotoxicity. It is typically administered orally to treat various types of dermatophytic skin infections when other topical antifungal treatments are ineffective.

There are a few drugs that act as antimetabolites against fungal processes. For example, atovaquone, a representative of the naphthoquinone drug class, is a semisynthetic antimetabolite for fungal and protozoal versions of a mitochondrial cytochrome important in electron transport. Structurally, it is an analog of coenzyme Q, with which it competes for electron binding. It is particularly useful for the treatment of *Pneumocystis* pneumonia caused by *Pneumocystis jirovecii*. The antibacterial sulfamethoxazole-trimethoprim combination also acts as an antimetabolite against *P. jirovecii*.

Table 5.3.4.1 shows the various therapeutic classes of antifungal drugs, categorized by mode of action, with examples of each.

Table 5.3.4.1: Common Antifungal Drugs

Mechanism of Action	Drug Class	Specific Drugs	Clinical Uses
Inhibit ergosterol synthesis	Imidazoles	Miconazole, ketoconazole, clotrimazole	Fungal skin infections and vaginal yeast infections
	Triazoles	Fluconazole	Systemic yeast infections, oral thrush, and cryptococcal meningitis
	Allylamines	Terbinafine	Dermatophytic skin infections (athlete's foot, ring worm, jock itch), and infections of fingernails and toenails
Bind ergosterol in the cell membrane and create pores that disrupt the membrane	Polyenes	Nystatin	Used topically for yeast infections of skin, mouth, and vagina; also used for fungal infections of the intestine
		Amphotericin B	Variety systemic fungal infections
Inhibit cell wall synthesis	Echinocandins	Caspofungin	Aspergillosis and systemic yeast infections
	Not applicable	Nikkomycin Z	Coccidioidomycosis (Valley fever) and yeast infections
Inhibit microtubules and cell division	Not applicable	Griseofulvin	Dermatophytic skin infections

? Exercise 5.3.4.1

How is disruption of ergosterol biosynthesis an effective mode of action for antifungals?

Treating a Fungal Infection of the Lungs

Jack, a 48-year-old engineer, is HIV positive but generally healthy thanks to antiretroviral therapy (ART). However, after a particularly intense week at work, he developed a fever and a dry cough. He assumed that he just had a cold or mild flu due to overexertion and didn't think much of it. However, after about a week, he began to experience fatigue, weight loss, and shortness of breath. He decided to visit his physician, who found that Jack had a low level of blood oxygenation. The physician ordered blood testing, a chest X-ray, and the collection of an induced sputum sample for analysis. His X-ray showed a fine cloudiness and several pneumatoceles (thin-walled pockets of air), which indicated *Pneumocystis* pneumonia (PCP), a type of pneumonia caused by the fungus *Pneumocystis jirovecii*. Jack's physician admitted him to the hospital and prescribed Bactrim, a combination of sulfamethoxazole and trimethoprim, to be administered intravenously.

P. jirovecii is a yeast-like fungus with a life cycle similar to that of protozoans. As such, it was classified as a protozoan until the 1980s. It lives only in the lung tissue of infected persons and is transmitted from person to person, with many people exposed as children. Typically, *P. jirovecii* only causes pneumonia in immunocompromised individuals. Healthy people may carry the fungus in their lungs with no symptoms of disease. PCP is particularly problematic among HIV patients with compromised immune systems.

PCP is usually treated with oral or intravenous Bactrim, but atovaquone or pentamidine(another antiparasitic drug) are alternatives. If not treated, PCP can progress, leading to a collapsed lung and nearly 100% mortality. Even with antimicrobial drug therapy, PCP still is responsible for 10% of HIV-related deaths.

The cytological examination, using direct immunofluorescence assay (DFA), of a smear from Jack's sputum sample confirmed the presence of *P. jirovecii* (Figure 5.3.4.3). Additionally, the results of Jack's blood tests revealed that his white blood cell count had dipped, making him more susceptible to the fungus. His physician reviewed his ART regimen and made adjustments. After a few days of hospitalization, Jack was released to continue his antimicrobial therapy at home. With the adjustments to his ART therapy, Jack's CD4 counts began to increase and he was able to go back to work.

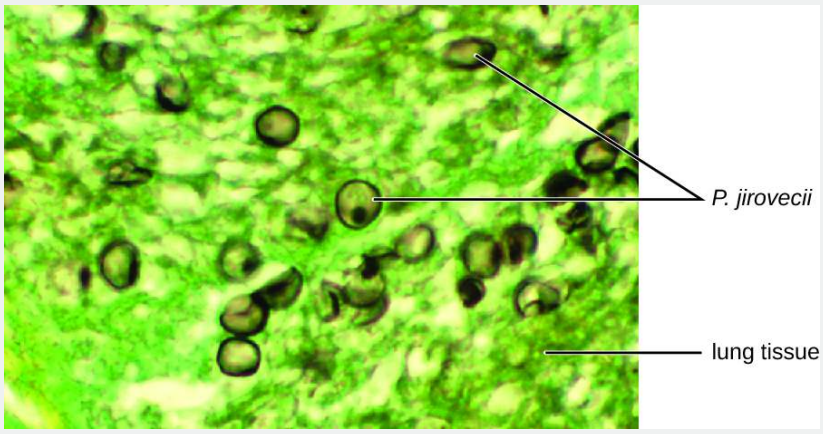


Figure 5.3.4.3: Microscopic examination of an induced sputum sample or bronchoaveolar lavage sample typically reveals the organism, as shown here. (credit: modification of work by the Centers for Disease Control and Prevention)

Antiprotozoan Drugs

There are a few mechanisms by which antiprotozoan drugs target infectious protozoans (Table 5.3.4.3). Some are antimetabolites, such as atovaquone, proguanil, and artemisinins. Atovaquone, in addition to being antifungal, blocks electron transport in protozoans and is used for the treatment of protozoan infections including malaria, babesiosis, and toxoplasmosis. Proguanil is another synthetic antimetabolite that is processed in parasitic cells into its active form, which inhibits protozoan folic acid synthesis. It is often used in combination with atovaquone, and the combination is marketed as Malarone for both malaria treatment and prevention.

Artemisinin, a plant-derived antifungal first discovered by Chinese scientists in the 1970s, is quite effective against malaria. Semisynthetic derivatives of artemisinin are more water soluble than the natural version, which makes them more bioavailable. Although the exact mechanism of action is unclear, artemisinins appear to act as prodrugs that are metabolized by target cells to produce reactive oxygen species (ROS) that damage target cells. Due to the rise in resistance to antimalarial drugs, artemisinins are also commonly used in combination with other antimalarial compounds in artemisinin-based combination therapy (ACT).

Several antimetabolites are used for the treatment of toxoplasmosis caused by the parasite *Toxoplasma gondii*. The synthetic sulfa drug sulfadiazine competitively inhibits an enzyme in folic acid production in parasites and can be used to treat malaria and toxoplasmosis. Pyrimethamine is a synthetic drug that inhibits a different enzyme in the folic acid production pathway and is often used in combination with sulfadoxine (another sulfa drug) for the treatment of malariaor in combination with sulfadiazine for the treatment of toxoplasmosis. Side effects of pyrimethamine include decreased bone marrow activity that may cause increased bruising and low red blood cell counts. When toxicity is a concern, spiramycin, a macrolide protein synthesis inhibitor, is typically administered for the treatment of toxoplasmosis.

Two classes of antiprotozoan drugs interfere with nucleic acid synthesis: nitroimidazoles and quinolines. Nitroimidazoles, including semisynthetic metronidazole, which was discussed previously as an antibacterial drug, and synthetic tinidazole, are useful in combating a wide variety of protozoan pathogens, such as *Giardia lamblia*, *Entamoeba histolytica*, and *Trichomonas vaginalis*. Upon introduction into these cells in low-oxygen environments, nitroimidazoles become activated and introduce DNA strand breakage, interfering with DNA replication in target cells. Unfortunately, metronidazole is associated with carcinogenesis (the development of cancer) in humans.

Another type of synthetic antiprotozoan drug that has long been thought to specifically interfere with DNA replication in certain pathogens is pentamidine. It has historically been used for the treatment of African sleeping sickness (caused by the protozoan *Trypanosoma brucei*) and leishmaniasis (caused by protozoa of the genus *Leishmania*), but it is also an alternative treatment for the

fungus *Pneumocystis*. Some studies indicate that it specifically binds to the DNA found within kinetoplasts (kDNA; long mitochondrion-like structures unique to trypanosomes), leading to the cleavage of kDNA. However, nuclear DNA of both the parasite and host remain unaffected. It also appears to bind to tRNA, inhibiting the addition of amino acids to tRNA, thus preventing protein synthesis. Possible side effects of pentamidine use include pancreatic dysfunction and liver damage.

The quinolines are a class of synthetic compounds related to quinine, which has a long history of use against malaria. Quinolines are thought to interfere with heme detoxification, which is necessary for the parasite's effective breakdown of hemoglobin into amino acids inside red blood cells. The synthetic derivatives chloroquine, quinacrine (also called mepacrine), and mefloquine are commonly used as antimalarials, and chloroquine is also used to treat amebiasis typically caused by *Entamoeba histolytica*. Long-term prophylactic use of chloroquine or mefloquine may result in serious side effects, including hallucinations or cardiac issues. Patients with glucose-6-phosphate dehydrogenase deficiency experience severe anemia when treated with chloroquine.

Table 5.3.4.2: Common Antiprotozoan Drugs

Mechanism of Action	Drug Class	Specific Drugs	Clinical Uses
Inhibit electron transport in mitochondria	Naphthoquinone	Atovaquone	Malaria, babesiosis, and toxoplasmosis
Inhibit folic acid synthesis	Not applicable	Proquanil	Combination therapy with atovaquone for malaria treatment and prevention
	Sulfonamide	Sulfadiazine	Malaria and toxoplasmosis
	Not applicable	Pyrimethamine	Combination therapy with sulfadoxine (sulfa drug) for malaria
Produces damaging reactive oxygen species	Not applicable	Artemisinin	Combination therapy to treat malaria
Inhibit DNA synthesis	Nitroimidazoles	Metronidazole, tinidazole	Infections caused by *Giardia lamblia*, *Entamoeba histolytica*, and *Trichomonas vaginalis*
	Not applicable	Pentamidine	African sleeping sickness and leishmaniasis
Inhibit heme detoxification	Quinolines	Chloroquine	Malaria and infections with *E. histolytica*
		Mepacrine, mefloquine	Malaria

? Exercise 5.3.4.2

List two modes of action for antiprotozoan drugs.

Antihelminthic Drugs

Because helminths are multicellular eukaryotes like humans, developing drugs with selective toxicity against them is extremely challenging. Despite this, several effective classes have been developed (Table 5.3.4.3). Synthetic benzimidazoles, like mebendazole and albendazole, bind to helminthic β-tubulin, preventing microtubule formation. Microtubules in the intestinal cells of the worms seem to be particularly affected, leading to a reduction in glucose uptake. Besides their activity against a broad range of helminths, benzimidazoles are also active against many protozoans, fungi, and viruses, and their use for inhibiting mitosis and cell cycle progression in cancer cells is under study.[2] Possible side effects of their use include liver damage and bone marrow suppression.

The avermectins are members of the macrolide family that were first discovered from a Japanese soil isolate, *Streptomyces avermectinius*. A more potent semisynthetic derivative of avermectin is ivermectin, which binds to glutamate-gated chloride channels specific to invertebrates including helminths, blocking neuronal transmission and causing starvation, paralysis, and death of the worms. Ivermectin is used to treat roundworm diseases, including onchocerciasis (also called river blindness, caused by the worm *Onchocerca volvulus*) and strongyloidiasis (caused by the worm *Strongyloides stercoralis* or *S. fuelleborni*). Ivermectin also can also treat parasitic insects like mites, lice, and bed bugs, and is nontoxic to humans.

Niclosamide is a synthetic drug that has been used for over 50 years to treat tapeworm infections. Although its mode of action is not entirely clear, niclosamide appears to inhibit ATP formation under anaerobic conditions and inhibit oxidative phosphorylation in the mitochondria of its target pathogens. Niclosamide is not absorbed from the gastrointestinal tract, thus it can achieve high localized intestinal concentrations in patients. Recently, it has been shown to also have antibacterial, antiviral, and antitumor activities.[345]

Another synthetic antihelminthic drug is praziquantel, which used for the treatment of parasitic tapeworms and liver flukes, and is particularly useful for the treatment of schistosomiasis (caused by blood flukes from three genera of *Schistosoma*). Its mode of action remains unclear, but it appears to cause the influx of calcium into the worm, resulting in intense spasm and paralysis of the worm. It is often used as a preferred alternative to niclosamide in the treatment of tapeworms when gastrointestinal discomfort limits niclosamide use.

The thioxanthenones, another class of synthetic drugs structurally related to quinine, exhibit antischistosomal activity by inhibiting RNA synthesis. The thioxanthenone lucanthone and its metabolite hycanthone were the first used clinically, but serious neurological, gastrointestinal, cardiovascular, and hepatic side effects led to their discontinuation. Oxamniquine, a less toxic derivative of hycanthone, is only effective against *S. mansoni*, one of the three species known to cause schistosomiasis in humans. Praziquantel was developed to target the other two schistosome species, but concerns about increasing resistance have renewed interest in developing additional derivatives of oxamniquine to target all three clinically important schistosome species.

Table 5.3.4.3: Common Antihelminthic Drugs

Mechanism of Action	Drug Class	Specific Drugs	Clinical Uses
Inhibit microtubule formation, reducing glucose uptake	Benzimidazoles	Mebendazole, albendazole	Variety of helminth infections
Block neuronal transmission, causing paralysis and starvation	Avermectins	Ivermectin	Roundworm diseases, including river blindness and strongyloidiasis, and treatment of parasitic insects
Inhibit ATP production	Not applicable	Niclosamide	Intestinal tapeworm infections
Induce calcium influx	Not applicable	Praziquantel	Schistosomiasis (blood flukes)
Inhibit RNA synthesis	Thioxanthenones	Lucanthone, hycanthone, oxamniquine	Schistosomiasis (blood flukes)

? Exercise 5.3.4.3

Why are antihelminthic drugs difficult to develop?

Antiviral Drugs

Unlike the complex structure of fungi, protozoa, and helminths, viral structure is simple, consisting of nucleic acid, a protein coat, viral enzymes, and, sometimes, a lipid envelope. Furthermore, viruses are obligate intracellular pathogens that use the host's cellular machinery to replicate. These characteristics make it difficult to develop drugs with selective toxicity against viruses.

Many antiviral drugs are nucleoside analogs and function by inhibiting nucleic acid biosynthesis. For example, acyclovir(marketed as Zovirax) is a synthetic analog of the nucleoside guanosine (Figure 5.3.4.4). It is activated by the herpes simplex viral enzyme

thymidine kinase and, when added to a growing DNA strand during replication, causes chain termination. Its specificity for virus-infected cells comes from both the need for a viral enzyme to activate it and the increased affinity of the activated form for viral DNA polymerase compared to host cell DNA polymerase. Acyclovir and its derivatives are frequently used for the treatment of herpes virus infections, including genital herpes, chickenpox, shingles, Epstein-Barr virus infections, and cytomegalovirus infections. Acyclovir can be administered either topically or systemically, depending on the infection. One possible side effect of its use includes nephrotoxicity. The drug adenine-arabinoside, marketed as vidarabine, is a synthetic analog to deoxyadenosine that has a mechanism of action similar to that of acyclovir. It is also effective for the treatment of various human herpes viruses. However, because of possible side effects involving low white blood cell counts and neurotoxicity, treatment with acyclovir is now preferred.

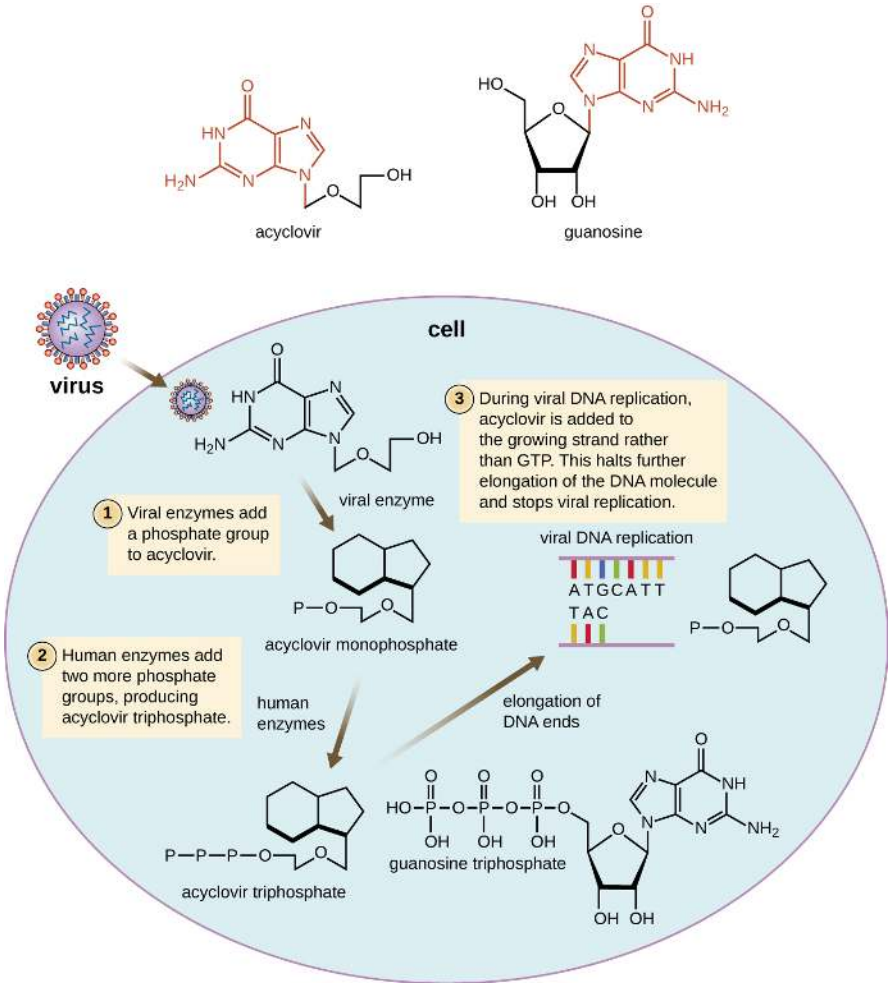


Figure 5.3.4.4: Acyclovir is a structural analog of guanosine. It is specifically activated by the viral enzyme thymidine kinase and then preferentially binds to viral DNA polymerase, leading to chain termination during DNA replication.

Ribavirin, another synthetic guanosine analog, works by a mechanism of action that is not entirely clear. It appears to interfere with both DNA and RNA synthesis, perhaps by reducing intracellular pools of guanosine triphosphate (GTP). Ribavarin also appears to inhibit the RNA polymerase of hepatitis C virus. It is primarily used for the treatment of the RNA viruses like hepatitis C (in combination therapy with interferon) and respiratory syncytial virus. Possible side effects of ribavirin use include anemia and developmental effects on unborn children in pregnant patients. In recent years, another nucleotide analog, sofosbuvir (Solvaldi), has also been developed for the treatment of hepatitis C. Sofosbuvir is a uridine analog that interferes with viral polymerase activity. It is commonly coadministered with ribavirin, with and without interferon.

Inhibition of nucleic acid synthesis is not the only target of synthetic antivirals. Although the mode of action of amantadine and its relative rimantadine are not entirely clear, these drugs appear to bind to a transmembrane protein that is involved in the escape of the influenza virus from endosomes. Blocking escape of the virus also prevents viral RNA release into host cells and subsequent

viral replication. Increasing resistance has limited the use of amantadine and rimantadine in the treatment of influenza A. Use of amantadine can result in neurological side effects, but the side effects of rimantadine seem less severe. Interestingly, because of their effects on brain chemicals such as dopamine and NMDA (N-methyl D-aspartate), amantadine and rimantadine are also used for the treatment of Parkinson's disease.

Neuraminidase inhibitors, including olsetamivir (Tamiflu), zanamivir (Relenza), and peramivir (Rapivab), specifically target influenza viruses by blocking the activity of influenza virus neuraminidase, preventing the release of the virus from infected cells. These three antivirals can decrease flu symptoms and shorten the duration of illness, but they differ in their modes of administration: olsetamivir is administered orally, zanamivir is inhaled, and peramivir is administered intravenously. Resistance to these neuraminidase inhibitors still seems to be minimal.

Pleconaril is a synthetic antiviral under development that showed promise for the treatment of picornaviruses. Use of pleconaril for the treatment of the common cold caused by rhinoviruses was not approved by the FDA in 2002 because of lack of proven effectiveness, lack of stability, and association with irregular menstruation. Its further development for this purpose was halted in 2007. However, pleconaril is still being investigated for use in the treatment of life-threatening complications of enteroviruses, such as meningitis and sepsis. It is also being investigated for use in the global eradication of a specific enterovirus, polio.[6] Pleconaril seems to work by binding to the viral capsid and preventing the uncoating of viral particles inside host cells during viral infection.

Viruses with complex life cycles, such as HIV, can be more difficult to treat. First, HIV targets CD4-positive white blood cells, which are necessary for a normal immune response to infection. Second, HIV is a retrovirus, meaning that it converts its RNA genome into a DNA copy that integrates into the host cell's genome, thus hiding within host cell DNA. Third, the HIV reverse transcriptase lacks proofreading activity and introduces mutations that allow for rapid development of antiviral drug resistance. To help prevent the emergence of resistance, a combination of specific synthetic antiviral drugs is typically used in ART for HIV (Figure 5.3.4.5).

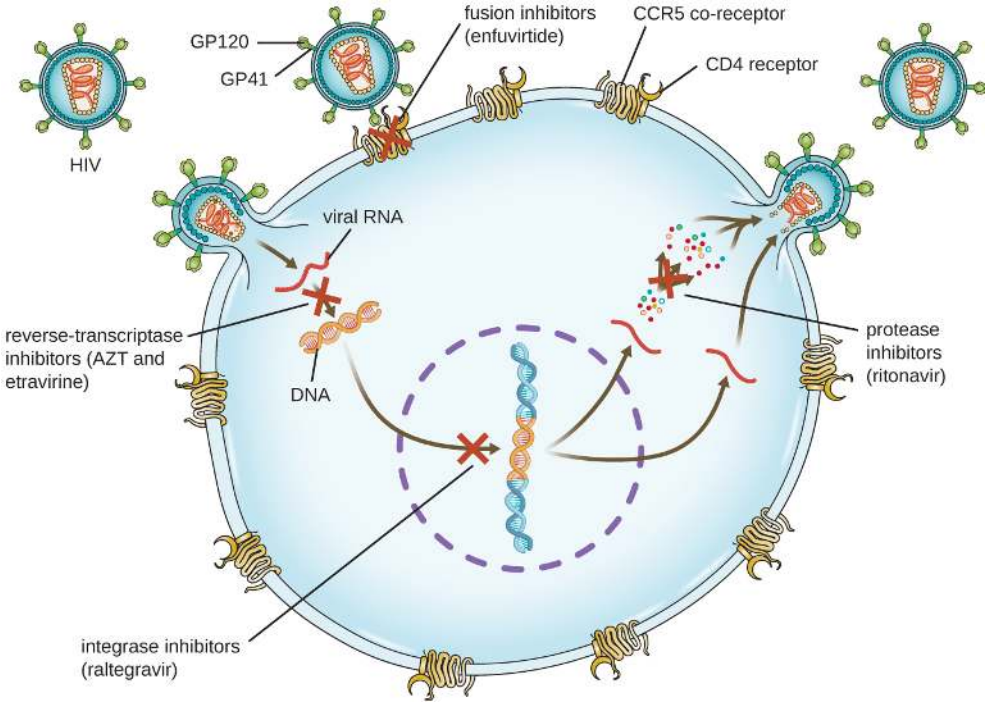


Figure 5.3.4.5: Antiretroviral therapy (ART) is typically used for the treatment of HIV. The targets of drug classes currently in use are shown here. (credit: modification of work by Thomas Splettstoesser)

The reverse transcriptase inhibitors block the early step of converting viral RNA genome into DNA, and can include competitive nucleoside analog inhibitors (e.g., azidothymidine/zidovudine, or AZT) and non-nucleoside noncompetitive inhibitors (e.g., etravirine) that bind reverse transcriptase and cause an inactivating conformational change. Drugs called protease inhibitors (e.g., ritonavir) block the processing of viral proteins and prevent viral maturation. Protease inhibitors are also being developed for the treatment of other viral types.[7] For example, simeprevir (Olysio) has been approved for the treatment of hepatitis C and is

administered with ribavirin and interferon in combination therapy. The integrase inhibitors (e.g., raltegravir), block the activity of the HIV integrase responsible for the recombination of a DNA copy of the viral genome into the host cell chromosome. Additional drug classes for HIV treatment include the CCR5 antagonists and the fusion inhibitors (e.g., enfuviritide), which prevent the binding of HIV to the host cell coreceptor (chemokine receptor type 5 [CCR5]) and the merging of the viral envelope with the host cell membrane, respectively. Table 5.3.4.4 shows the various therapeutic classes of antiviral drugs, categorized by mode of action, with examples of each.

Table 5.3.4.4: Common Antiviral Drugs

Mechanism of Action	Drug	Clinical Uses
Nucleoside analog inhibition of nucleic acid synthesis	Acyclovir	Herpes virus infections
	Azidothymidine/zidovudine (AZT)	HIV infections
	Ribavirin	Hepatitis C virus and respiratory syncytial virus infections
	Vidarabine	Herpes virus infections
	Sofosbuvir	Hepatitis C virus infections
Non-nucleoside noncompetitive inhibition	Etravirine	HIV infections
Inhibit escape of virus from endosomes	Amantadine, rimantadine	Infections with influenza virus
Inhibit neuraminadase	Olsetamivir, zanamivir, peramivir	Infections with influenza virus
Inhibit viral uncoating	Pleconaril	Serious enterovirus infections
Inhibition of protease	Ritonavir	HIV infections
	Simeprevir	Hepatitis C virus infections
Inhibition of integrase	Raltegravir	HIV infections
Inhibition of membrane fusion	Enfuviritide	HIV infections

? Exercise 5.3.4.4

Why is HIV difficult to treat with antivirals?

Link to Learning

To learn more about the various classes of antiretroviral drugs used in the ART of HIV infection, explore each of the drugs in the HIV drug classes provided by US Department of Health and Human Services at this website.

Key Concepts and Summary

- Because fungi, protozoans, and helminths are eukaryotic organisms like human cells, it is more challenging to develop antimicrobial drugs that specifically target them. Similarly, it is hard to target viruses because human viruses replicate inside of human cells.
- **Antifungal drugs** interfere with ergosterol synthesis, bind to ergosterol to disrupt fungal cell membrane integrity, or target cell wall-specific components or other cellular proteins.
- **Antiprotozoan drugs** increase cellular levels of reactive oxygen species, interfere with protozoal DNA replication (nuclear versus kDNA, respectively), and disrupt heme detoxification.
- **Antihelminthic drugs** disrupt helminthic and protozoan microtubule formation; block neuronal transmissions; inhibit anaerobic ATP formation and/or oxidative phosphorylation; induce a calcium influx in tapeworms, leading to spasms and paralysis; and interfere with RNA synthesis in schistosomes.

- **Antiviral drugs** inhibit viral entry, inhibit viral uncoating, inhibit nucleic acid biosynthesis, prevent viral escape from endosomes in host cells, and prevent viral release from infected cells.
- Because it can easily mutate to become drug resistant, HIV is typically treated with a combination of several **antiretroviral drugs**, which may include **reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors**, and drugs that interfere with viral binding and fusion to initiate infection.

Footnotes

1. 1 Centers for Disease Control and Prevention. “Valley Fever: Awareness Is Key.” www.cdc.gov/features/valleyfever/. Accessed June 1, 2016.
2. 2 B. Chu et al. “A Benzimidazole Derivative Exhibiting Antitumor Activity Blocks EGFR and HER2 Activity and Upregulates DR5 in Breast Cancer Cells.” *Cell Death and Disease* 6 (2015):e1686
3. 3 J.-X. Pan et al. “Niclosamide, An Old Antihelminthic Agent, Demonstrates Antitumor Activity by Blocking Multiple Signaling Pathways of Cancer Stem Cells.” *Chinese Journal of Cancer* 31 no. 4 (2012):178–184.
4. 4 F. Imperi et al. “New Life for an Old Drug: The Anthelmintic Drug Niclosamide Inhibits *Pseudomonas aeruginosa* Quorum Sensing.” *Antimicrobial Agents and Chemotherapy* 57 no. 2 (2013):996-1005.
5. 5 A. Jurgeit et al. “Niclosamide Is a Proton Carrier and Targets Acidic Endosomes with Broad Antiviral Effects.” *PLoS Pathogens* 8 no. 10 (2012):e1002976.
6. 6 M.J. Abzug. “The Enteroviruses: Problems in Need of Treatments.” *Journal of Infection* 68 no. S1 (2014):108–14.
7. 7 B.L. Pearlman. “Protease Inhibitors for the Treatment of Chronic Hepatitis C Genotype-1 Infection: The New Standard of Care.” *Lancet Infectious Diseases* 12 no. 9 (2012):717–728.

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5.3.5: Testing the Effectiveness of Antimicrobials

Learning Objectives

- Explain the concept of drug resistance
- Describe how microorganisms develop or acquire drug resistance
- Describe the different mechanisms of antimicrobial drug resistance

Antimicrobial resistance is not a new phenomenon. In nature, microbes are constantly evolving in order to overcome the antimicrobial compounds produced by other microorganisms. Human development of antimicrobial drugs and their widespread clinical use has simply provided another selective pressure that promotes further evolution. Several important factors can accelerate the evolution of drug resistance. These include the overuse and misuse of antimicrobials, inappropriate use of antimicrobials, subtherapeutic dosing, and patient noncompliance with the recommended course of treatment.

Exposure of a pathogen to an antimicrobial compound can select for chromosomal mutations conferring resistance, which can be transferred vertically to subsequent microbial generations and eventually become predominant in a microbial population that is repeatedly exposed to the antimicrobial. Alternatively, many genes responsible for drug resistance are found on plasmids or in transposons that can be transferred easily between microbes through horizontal gene transfer (see How Asexual Prokaryotes Achieve Genetic Diversity). Transposons also have the ability to move resistance genes between plasmids and chromosomes to further promote the spread of resistance.

Mechanisms for Drug Resistance

There are several common mechanisms for drug resistance, which are summarized in Figure 5.3.5.1. These mechanisms include enzymatic modification of the drug, modification of the antimicrobial target, and prevention of drug penetration or accumulation.

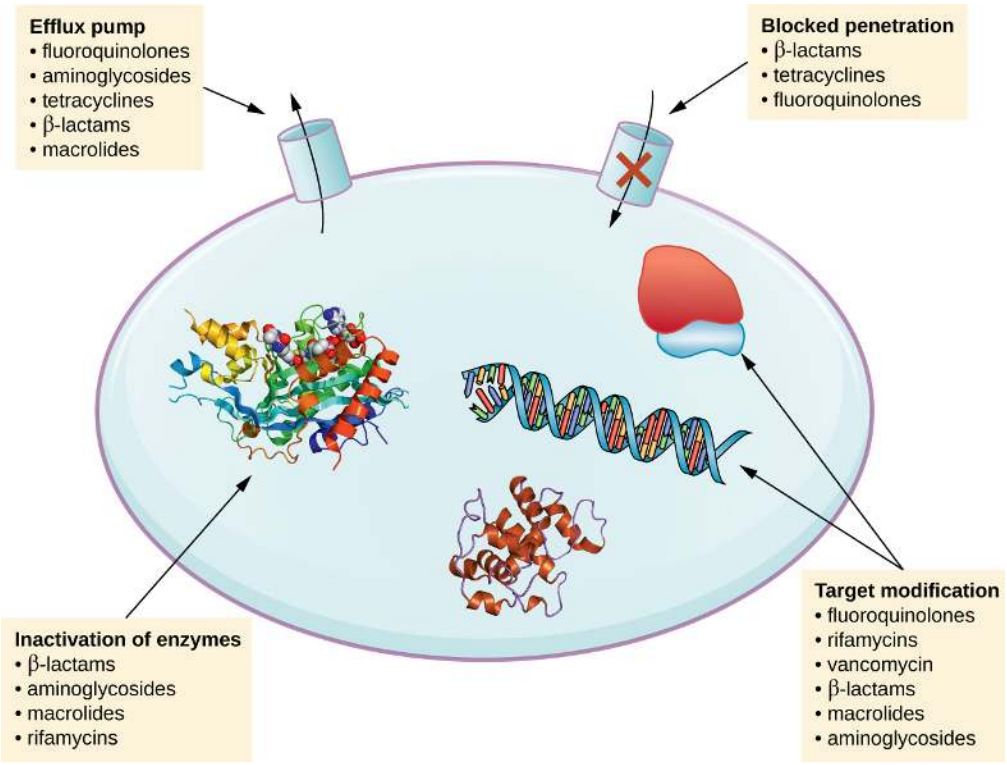


Figure 5.3.5.1: There are multiple strategies that microbes use to develop resistance to antimicrobial drugs. (Not shown: target overproduction, target mimicry, and enzymatic bypass). (credit: modification of work by Gerard D Wright)

Drug Modification or Inactivation

Resistance genes may code for enzymes that chemically modify an antimicrobial, thereby inactivating it, or destroy an antimicrobial through hydrolysis. Resistance to many types of antimicrobials occurs through this mechanism. For example, aminoglycoside resistance can occur through enzymatic transfer of chemical groups to the drug molecule, impairing the binding of the drug to its bacterial target. For β-lactams, bacterial resistance can involve the enzymatic hydrolysis of the β-lactam bond within the β-lactam ring of the drug molecule. Once the β-lactam bond is broken, the drug loses its antibacterial activity. This mechanism of resistance is mediated by β-lactamases, which are the most common mechanism of β-lactam resistance. Inactivation of rifampin commonly occurs through glycosylation, phosphorylation, or adenosine diphosphate (ADP) ribosylation, and resistance to macrolides and lincosamides can also occur due to enzymatic inactivation of the drug or modification.

Prevention of Cellular Uptake or Efflux

Microbes may develop resistance mechanisms that involve inhibiting the accumulation of an antimicrobial drug, which then prevents the drug from reaching its cellular target. This strategy is common among gram-negative pathogens and can involve changes in outer membrane lipid composition, porin channel selectivity, and/or porin channel concentrations. For example, a common mechanism of carbapenem resistance among *Pseudomonas aeruginosa* is to decrease the amount of its OprD porin, which is the primary portal of entry for carbapenems through the outer membrane of this pathogen. Additionally, many gram-positive and gram-negative pathogenic bacteria produce efflux pumps that actively transport an antimicrobial drug out of the cell and prevent the accumulation of drug to a level that would be antibacterial. For example, resistance to β-lactams, tetracyclines, and fluoroquinolones commonly occurs through active efflux out of the cell, and it is rather common for a single efflux pump to have the ability to translocate multiple types of antimicrobials.

Target Modification

Because antimicrobial drugs have very specific targets, structural changes to those targets can prevent drug binding, rendering the drug ineffective. Through spontaneous mutations in the genes encoding antibacterial drug targets, bacteria have an evolutionary advantage that allows them to develop resistance to drugs. This mechanism of resistance development is quite common. Genetic changes impacting the active site of penicillin-binding proteins (PBPs) can inhibit the binding of β-lactam drugs and provide resistance to multiple drugs within this class. This mechanism is very common among strains of *Streptococcus pneumoniae*, which alter their own PBPs through genetic mechanisms. In contrast, strains of *Staphylococcus aureus* develop resistance to methicillin (MRSA) through the acquisition of a new low-affinity PBP, rather than structurally alter their existing PBPs. Not only does this new low-affinity PBP provide resistance to methicillin but it provides resistance to virtually all β-lactam drugs, with the exception of the newer fifth-generation cephalosporins designed specifically to kill MRSA. Other examples of this resistance strategy include alterations in

- ribosome subunits, providing resistance to macrolides, tetracyclines, and aminoglycosides;
- lipopolysaccharide (LPS) structure, providing resistance to polymyxins;
- RNA polymerase, providing resistance to rifampin;
- DNA gyrase, providing resistance to fluoroquinolones;
- metabolic enzymes, providing resistance to sulfa drugs, sulfones, and trimethoprim; and
- peptidoglycan subunit peptide chains, providing resistance to glycopeptides.

Target Overproduction or Enzymatic Bypass

When an antimicrobial drug functions as an antimetabolite, targeting a specific enzyme to inhibit its activity, there are additional ways that microbial resistance may occur. First, the microbe may overproduce the target enzyme such that there is a sufficient amount of antimicrobial-free enzyme to carry out the proper enzymatic reaction. Second, the bacterial cell may develop a bypass that circumvents the need for the functional target enzyme. Both of these strategies have been found as mechanisms of sulfonamide resistance. Vancomycin resistance among *S. aureus* has been shown to involve the decreased cross-linkage of peptide chains in the bacterial cell wall, which provides an increase in targets for vancomycin to bind to in the outer cell wall. Increased binding of vancomycin in the outer cell wall provides a blockage that prevents free drug molecules from penetrating to where they can block new cell wall synthesis.

Target Mimicry

A recently discovered mechanism of resistance called target mimicry involves the production of proteins that bind and sequester drugs, preventing the drugs from binding to their target. For example, *Mycobacterium tuberculosis*produces a protein with regular pentapeptide repeats that appears to mimic the structure of DNA. This protein binds fluoroquinolones, sequestering them and keeping them from binding to DNA, providing *M. tuberculosis* resistance to fluoroquinolones. Proteins that mimic the A-site of the bacterial ribosome have been found to contribute to aminoglycoside resistance as well.[1]

? Exercise 5.3.5.1

List several mechanisms for drug resistance.

Multidrug-Resistant Microbes and Cross Resistance

From a clinical perspective, our greatest concerns are multidrug-resistant microbes (MDRs) and cross resistance. MDRs are colloquially known as “superbugs” and carry one or more resistance mechanism(s), making them resistant to multiple antimicrobials. In cross-resistance, a single resistance mechanism confers resistance to multiple antimicrobial drugs. For example, having an efflux pump that can export multiple antimicrobial drugs is a common way for microbes to be resistant to multiple drugs by using a single resistance mechanism. In recent years, several clinically important superbugs have emerged, and the CDC reports that superbugs are responsible for more than 2 million infections in the US annually, resulting in at least 23,000 fatalities.[2] Several of the superbugs discussed in the following sections have been dubbed the ESKAPE pathogens. This acronym refers to the names of the pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.) but it is also fitting in that these pathogens are able to “escape” many conventional forms of antimicrobial therapy. As such, infections by ESKAPE pathogens can be difficult to treat and they cause a large number of nosocomial infections.

Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Methicillin, a semisynthetic penicillin, was designed to resist inactivation by β-lactamases. Unfortunately, soon after the introduction of methicillin to clinical practice, methicillin-resistant strains of *S. aureus* appeared and started to spread. The mechanism of resistance, acquisition of a new low-affinity PBP, provided *S. aureus* with resistance to all available β-lactams. Strains of methicillin-resistant *S. aureus* (MRSA) are widespread opportunistic pathogens and a particular concern for skin and other wound infections, but may also cause pneumonia and septicemia. Although originally a problem in health-care settings (hospital-acquired MRSA [HA-MRSA]), MRSA infections are now also acquired through contact with contaminated members of the general public, called community-associated MRSA (CA-MRSA). Approximately one-third of the population carries *S. aureus* as a member of their normal nasal microbiota without illness, and about 6% of these strains are methicillin resistant.[3,4]

Clavulanic Acid: Penicillin’s Little Helper

With the introduction of penicillin in the early 1940s, and its subsequent mass production, society began to think of antibiotics as miracle cures for a wide range of infectious diseases. Unfortunately, as early as 1945, penicillin resistance was first documented and started to spread. Greater than 90% of current *S. aureus* clinical isolates are resistant to penicillin.[5]

Although developing new antimicrobial drugs is one solution to this problem, scientists have explored new approaches, including the development of compounds that inactivate resistance mechanisms. The development of clavulanic acid represents an early example of this strategy. Clavulanic acid is a molecule produced by the bacterium *Streptococcus clavuligerus*. It contains a β-lactam ring, making it structurally similar to penicillin and other β-lactams, but shows no clinical effectiveness when administered on its own. Instead, clavulanic acid binds irreversibly within the active site of β-lactamases and prevents them from inactivating a coadministered penicillin.

Clavulanic acid was first developed in the 1970s and was mass marketed in combination with amoxicillin beginning in the 1980s under the brand name Augmentin. As is typically the case, resistance to the amoxicillin-clavulanic acid combination soon appeared. Resistance most commonly results from bacteria increasing production of their β-lactamase and overwhelming the inhibitory effects of clavulanic acid, mutating their β-lactamase so it is no longer inhibited by clavulanic acid, or from

acquiring a new β-lactamase that is not inhibited by clavulanic acid. Despite increasing resistance concerns, clavulanic acid and related β-lactamase inhibitors (sulbactam and tazobactam) represent an important new strategy: the development of compounds that directly inhibit antimicrobial resistance-conferring enzymes.

Vancomycin-Resistant Enterococci and *Staphylococcus aureus*

Vancomycin is only effective against gram-positive organisms, and it is used to treat wound infections, septic infections, endocarditis, and meningitis that are caused by pathogens resistant to other antibiotics. It is considered one of the last lines of defense against such resistant infections, including MRSA. With the rise of antibiotic resistance in the 1970s and 1980s, vancomycin use increased, and it is not surprising that we saw the emergence and spread of vancomycin-resistant enterococci (VRE), vancomycin-resistant *S. aureus* (VRSA), and vancomycin-intermediate *S. aureus*(VISA). The mechanism of vancomycin resistance among enterococci is target modification involving a structural change to the peptide component of the peptidoglycan subunits, preventing vancomycin from binding. These strains are typically spread among patients in clinical settings by contact with health-care workers and contaminated surfaces and medical equipment.

VISA and VRSA strains differ from each other in the mechanism of resistance and the degree of resistance each mechanism confers. VISA strains exhibit intermediate resistance, with a minimum inhibitory concentration (MIC) of 4–8 μg/mL, and the mechanism involves an increase in vancomycin targets. VISA strains decrease the crosslinking of peptide chains in the cell wall, providing an increase in vancomycin targets that trap vancomycin in the outer cell wall. In contrast, VRSA strains acquire vancomycin resistance through horizontal transfer of resistance genes from VRE, an opportunity provided in individuals coinfected with both VRE and MRSA. VRSA exhibit a higher level of resistance, with MICs of 16 μg/mL or higher.[6] In the case of all three types of vancomycin-resistant bacteria, rapid clinical identification is necessary so proper procedures to limit spread can be implemented. The oxazolidinones like linezolid are useful for the treatment of these vancomycin-resistant, opportunistic pathogens, as well as MRSA.

Extended-Spectrum β-Lactamase–Producing Gram-Negative Pathogens

Gram-negative pathogens that produce extended-spectrum β-lactamases (ESBLs) show resistance well beyond just penicillins. The spectrum of β-lactams inactivated by ESBLs provides for resistance to all penicillins, cephalosporins, monobactams, and the β-lactamase-inhibitor combinations, but not the carbapenems. An even greater concern is that the genes encoding for ESBLs are usually found on mobile plasmids that also contain genes for resistance to other drug classes (e.g., fluoroquinolones, aminoglycosides, tetracyclines), and may be readily spread to other bacteria by horizontal gene transfer. These multidrug-resistant bacteria are members of the intestinal microbiota of some individuals, but they are also important causes of opportunistic infections in hospitalized patients, from whom they can be spread to other people.

Carbapenem-Resistant Gram-Negative Bacteria

The occurrence of carbapenem-resistant Enterobacteriaceae (CRE) and carbapenem resistance among other gram-negative bacteria (e.g., *P. aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophila*) is a growing health-care concern. These pathogens develop resistance to carbapenems through a variety of mechanisms, including production of carbapenemases (broad-spectrum β-lactamases that inactivate all β-lactams, including carbapenems), active efflux of carbapenems out of the cell, and/or prevention of carbapenem entry through porin channels. Similar to concerns with ESBLs, carbapenem-resistant, gram-negative pathogens are usually resistant to multiple classes of antibacterials, and some have even developed pan-resistance (resistance to all available antibacterials). Infections with carbapenem-resistant, gram-negative pathogens commonly occur in health-care settings through interaction with contaminated individuals or medical devices, or as a result of surgery.

Multidrug-Resistant Mycobacterium tuberculosis

The emergence of multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) and extensively drug-resistant*Mycobacterium tuberculosis* (XDR-TB) is also of significant global concern. MDR-TB strains are resistant to both rifampin and isoniazid, the drug combination typically prescribed for treatment of tuberculosis. XDR-TB strains are additionally resistant to any fluoroquinolone and at least one of three other drugs (amikacin, kanamycin, or capreomycin) used as a second line of treatment, leaving these patients very few treatment options. Both types of pathogens are particularly problematic in immunocompromised persons,

including those suffering from HIV infection. The development of resistance in these strains often results from the incorrect use of antimicrobials for tuberculosistreatment, selecting for resistance.

Exercise 5.3.5.2

How does drug resistance lead to superbugs?

Link to Learning

To learn more about the top 18 drug-resistant threats to the US, visit the CDC's website.

Factory Farming and Drug Resistance

Although animal husbandry has long been a major part of agriculture in America, the rise of concentrated animal feeding operations (CAFOs) since the 1950s has brought about some new environmental issues, including the contamination of water and air with biological waste, and ethical issues regarding animal rights also are associated with growing animals in this way. Additionally, the increase in CAFOs involves the extensive use of antimicrobial drugs in raising livestock. Antimicrobials are used to prevent the development of infectious disease in the close quarters of CAFOs; however, the majority of antimicrobials used in factory farming are for the promotion of growth—in other words, to grow larger animals.

The mechanism underlying this enhanced growth remains unclear. These antibiotics may not necessarily be the same as those used clinically for humans, but they are structurally related to drugs used for humans. As a result, use of antimicrobial drugs in animals can select for antimicrobial resistance, with these resistant bacteria becoming cross-resistant to drugs typically used in humans. For example, tylosin use in animals appears to select for bacteria also cross-resistant to other macrolides, including erythromycin, commonly used in humans.

Concentrations of the drug-resistant bacterial strains generated by CAFOs become increased in water and soil surrounding these farms. If not directly pathogenic in humans, these resistant bacteria may serve as a reservoir of mobile genetic elements that can then pass resistance genes to human pathogens. Fortunately, the cooking process typically inactivates any antimicrobials remaining in meat, so humans typically are not directly ingesting these drugs. Nevertheless, many people are calling for more judicious use of these drugs, perhaps charging farmers user fees to reduce indiscriminate use. In fact, in 2012, the FDA published guidelines for farmers who voluntarily phase out the use of antimicrobial drugs except under veterinary supervision and when necessary to ensure animal health. Although following the guidelines is voluntary at this time, the FDA does recommend what it calls "judicious" use of antimicrobial drugs in food-producing animals in an effort to decrease antimicrobial resistance.

Clinical Focus: Part 3

Unfortunately, Marisa's urinary tract infection did not resolve with ciprofloxacin treatment. Laboratory testing showed that her infection was caused by a strain of *Klebsiella pneumoniae* with significant antimicrobial resistance. The resistance profile of this *K. pneumoniae* included resistance to the carbapenem class of antibacterials, a group of β-lactams that is typically reserved for the treatment of highly resistant bacteria. *K. pneumoniae* is an opportunistic, capsulated, gram-negative rod that may be a member of the normal microbiota of the intestinal tract, but may also cause a number of diseases, including pneumonia and UTIs.

Specific laboratory tests looking for carbapenemase production were performed on Marisa's samples and came back positive. Based upon this result, in combination with her health history, production of a carbapenemase known as the New Delhi Metallo-β-lactamase (NDM) was suspected. Although the origin of the NDM carbapenemase is not completely known, many patients infected with NDM-containing strains have travel histories involving hospitalizations in India or surrounding countries.

Exercise 5.3.5.1

How would doctors determine which types of antimicrobial drugs should be administered?

Key Concepts and Summary

- **Antimicrobial resistance** is on the rise and is the result of selection of drug-resistant strains in clinical environments, the overuse and misuse of antibacterials, the use of subtherapeutic doses of antibacterial drugs, and poor patient compliance with antibacterial drug therapies.
- Drug resistance genes are often carried on plasmids or in transposons that can undergo vertical transfer easily and between microbes through horizontal gene transfer.
- Common modes of antimicrobial drug resistance include drug modification or inactivation, prevention of cellular uptake or efflux, target modification, target overproduction or enzymatic bypass, and target mimicry.
- Problematic microbial strains showing extensive antimicrobial resistance are emerging; many of these strains can reside as members of the normal microbiota in individuals but also can cause opportunistic infection. The transmission of many of these highly resistant microbial strains often occurs in clinical settings, but can also be community-acquired.

Footnotes

1. 1 D.H. Fong, A.M. Berghuis. “Substrate Promiscuity of an Aminoglycoside Antibiotic Resistance Enzyme Via Target Mimicry.” *EMBO Journal* 21 no. 10 (2002):2323–2331.
2. 2 Centers for Disease Control and Prevention. “Antibiotic/Antimicrobial Resistance.” http://www.cdc.gov/drugresistance/index.html. Accessed June 2, 2016.
3. 3 A.S. Kalokhe et al. “Multidrug-Resistant Tuberculosis Drug Susceptibility and Molecular Diagnostic Testing: A Review of the Literature. *American Journal of the Medical Sciences* 345 no. 2 (2013):143–148.
4. 4 Centers for Disease Control and Prevention. “Methicillin-Resistant *Staphylococcus aureus* (MRSA): General Information About MRSA in the Community.” http://www.cdc.gov/mrsa/community/index.html. Accessed June 2, 2016
5. 5 F.D. Lowy. “Antimicrobial Resistance: The Example of *Staphylococcus aureus*.” *Journal of Clinical Investigation* 111 no. 9 (2003):1265–1273.
6. 6 Centers for Disease Control and Prevention. “Healthcare-Associated Infections (HIA): General Information about VISA/VRSA.” www.cdc.gov/HAI/organisms/vis...visa_vrsa.html. Accessed June 2, 2016.

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5.3.6: The Emergence of Drug Resistance

Learning Objectives

- Describe how the Kirby-Bauer disk diffusion test determines the susceptibility of a microbe to an antibacterial drug.
- Explain the significance of the minimal inhibitory concentration and the minimal bactericidal concentration relative to the effectiveness of an antimicrobial drug.

Testing the effectiveness of antimicrobial drugs against specific organisms is important in identifying their spectrum of activity and the therapeutic dosage. This type of test, generally described as antimicrobial susceptibility testing (AST), is commonly performed in a clinical laboratory. In this section, we will discuss common methods of testing the effectiveness of antimicrobials.

The Kirby-Bauer Disk Diffusion Test

The Kirby-Bauer disk diffusion test has long been used as a starting point for determining the susceptibility of specific microbes to various antimicrobial drugs. The Kirby-Bauer assay starts with a Mueller-Hinton agar plate on which a confluent lawn is inoculated with a patient's isolated bacterial pathogen. Filter paper disks impregnated with known amounts of antibacterial drugs to be tested are then placed on the agar plate. As the bacterial inoculum grows, antibiotic diffuses from the circular disk into the agar and interacts with the growing bacteria. Antibacterial activity is observed as a clear circular zone of inhibition around the drug-impregnated disk, similar to the disk-diffusion assay. The diameter of the zone of inhibition, measured in millimeters and compared to a standardized chart, determines the susceptibility or resistance of the bacterial pathogen to the drug.

There are multiple factors that determine the size of a zone of inhibition in this assay, including drug solubility, rate of drug diffusion through agar, the thickness of the agar medium, and the drug concentration impregnated into the disk. Due to a lack of standardization of these factors, interpretation of the Kirby-Bauer disk diffusion assay provides only limited information on susceptibility and resistance to the drugs tested. The assay cannot distinguish between bacteriostatic and bactericidal activities, and differences in zone sizes cannot be used to compare drug potencies or efficacies. Comparison of zone sizes to a standardized chart will only provide information on the antibacterials to which a bacterial pathogen is susceptible or resistant.

Exercise 5.3.6.1

How does one use the information from a Kirby-Bauer assay to predict the therapeutic effectiveness of an antimicrobial drug in a patient?

Antibiograms: Taking Some of the Guesswork Out of Prescriptions

Unfortunately, infectious diseases don't take a time-out for lab work. As a result, physicians rarely have the luxury of conducting susceptibility testing before they write a prescription. Instead, they rely primarily on the empirical evidence (i.e., the signs and symptoms of disease) and their professional experience to make an educated guess as to the diagnosis, causative agent(s), and drug most likely to be effective. This approach allows treatment to begin sooner so the patient does not have to wait for lab test results. In many cases, the prescription is effective; however, in an age of increased antimicrobial resistance, it is becoming increasingly more difficult to select the most appropriate empiric therapy. Selecting an inappropriate empiric therapy not only puts the patient at risk but may promote greater resistance to the drug prescribed.

Recently, studies have shown that antibiograms are useful tools in the decision-making process of selecting appropriate empiric therapy. An antibiogram is a compilation of local antibiotic susceptibility data broken down by bacterial pathogen. In a November 2014 study published in the journal *Infection Control and Hospital Epidemiology*, researchers determined that 85% of the prescriptions ordered in skilled nursing facilities were decided upon empirically, but only 35% of those prescriptions were deemed appropriate when compared with the eventual pathogen identification and susceptibility profile obtained from the clinical laboratory. However, in one nursing facility where use of antibiograms was implemented to direct selection of empiric therapy, appropriateness of empiric therapy increased from 32% before antibiogram implementation to 45% after implementation of antibiograms.[1] Although these data are preliminary, they do suggest that health-care facilities can reduce the

number of inappropriate prescriptions by using antibiograms to select empiric therapy, thus benefiting patients and minimizing opportunities for antimicrobial resistance to develop.

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Visit this website to view an interactive antibiogram provided by Stanford University.

Dilution Tests

As discussed, the limitations of the Kirby-Bauer disk diffusion test do not allow for a direct comparison of antibacterial potencies to guide selection of the best therapeutic choice. However, antibacterial dilution tests can be used to determine a particular drug's minimal inhibitory concentration (MIC), the lowest concentration of drug that inhibits visible bacterial growth, and minimal bactericidal concentration (MBC), the lowest drug concentration that kills ≥99.9% of the starting inoculum. Determining these concentrations helps identify the correct drug for a particular pathogen. For the macrobroth dilution assay, a dilution series of the drug in broth is made in test tubes and the same number of cells of a test bacterial strain is added to each tube (Figure 5.3.6.1). The MIC is determined by examining the tubes to find the lowest drug concentration that inhibits visible growth; this is observed as turbidity (cloudiness) in the broth. Tubes with no visible growth are then inoculated onto agar media without antibiotic to determine the MBC. Generally, serum levels of an antibacterial should be at least three to five times above the MIC for treatment of an infection.

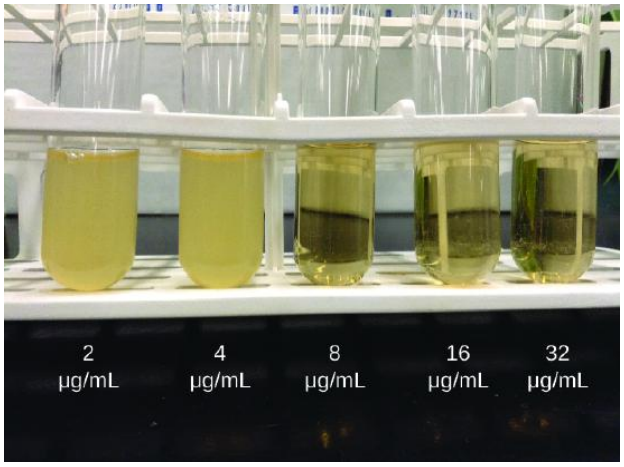


Figure 5.3.6.1: In a dilution test, the lowest dilution that inhibits turbidity (cloudiness) is the MIC. In this example, the MIC is 8 µg/mL. Broth from samples without turbidity can be inoculated onto plates lacking the antimicrobial drug. The lowest dilution that kills ≥99.9% of the starting inoculum is observed on the plates is the MBC. (credit: modification of work by Suzanne Wakim)

The MIC assay can also be performed using 96-well microdilution trays, which allow for the use of small volumes and automated dispensing devices, as well as the testing of multiple antimicrobials and/or microorganisms in one tray (Figure 5.3.6.2). MICs are interpreted as the lowest concentration that inhibits visible growth, the same as for the macrobroth dilution in test tubes. Growth may also be interpreted visually or by using a spectrophotometer or similar device to detect turbidity or a color change if an appropriate biochemical substrate that changes color in the presence of bacterial growth is also included in each well.

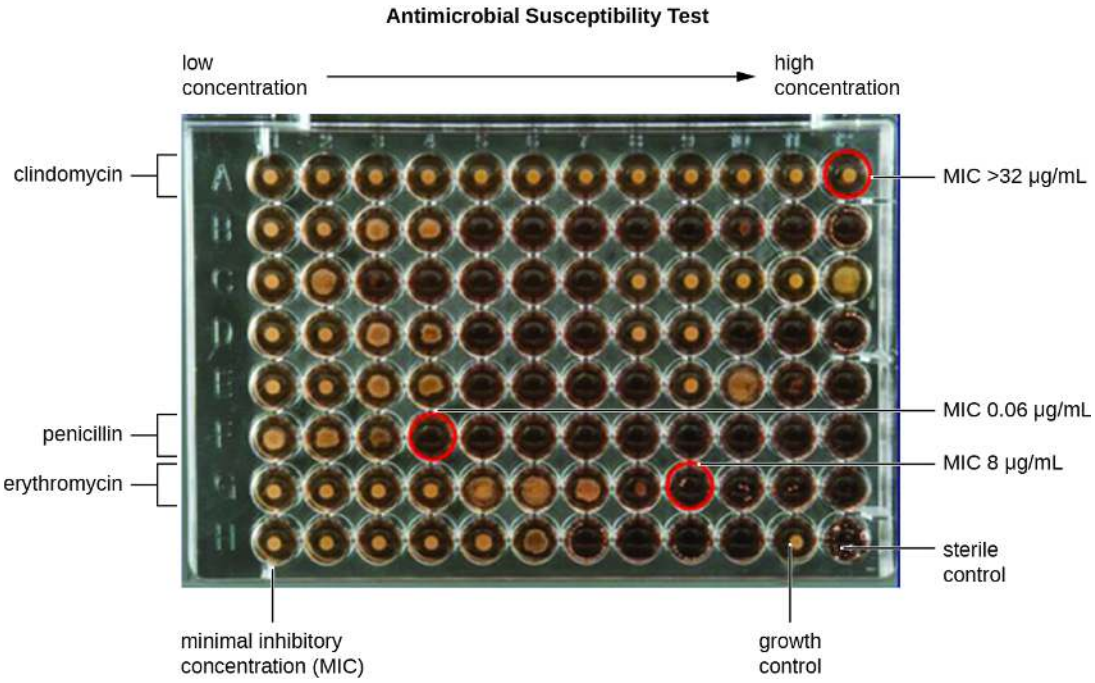


Figure 5.3.6.2: A microdilution tray can also be used to determine MICs of multiple antimicrobial drugs in a single assay. In this example, the drug concentrations increase from left to right and the rows with clindamycin, penicillin, and erythromycin have been indicated to the left of the plate. For penicillin and erythromycin, the lowest concentrations that inhibited visible growth are indicated by red circles and were 0.06 µg/mL for penicillin and 8 µg/mL for erythromycin. For clindamycin, visible bacterial growth was observed at every concentration up to 32 µg/mL and the MIC is interpreted as >32 µg/mL. (credit: modification of work by Centers for Disease Control and Prevention)

The Etest is an alternative method used to determine MIC, and is a combination of the Kirby-Bauer disk diffusion testand dilution methods. Similar to the Kirby-Bauer assay, a confluent lawn of a bacterial isolate is inoculated onto the surface of an agar plate. Rather than using circular disks impregnated with one concentration of drug, however, commercially available plastic strips that contain a gradient of an antibacterial are placed on the surface of the inoculated agar plate (Figure 5.3.6.3). As the bacterial inoculum grows, antibiotic diffuses from the plastic strips into the agar and interacts with the bacterial cells. Because the rate of drug diffusion is directly related to concentration, an elliptical zone of inhibition is observed with the Etest drug gradient, rather than a circular zone of inhibition observed with the Kirby-Bauer assay. To interpret the results, the intersection of the elliptical zone with the gradient on the drug-containing strip indicates the MIC. Because multiple strips containing different antimicrobials can be placed on the same plate, the MIC of multiple antimicrobials can be determined concurrently and directly compared. However, unlike the macrobroth and microbroth dilution methods, the MBC cannot be determined with the Etest.



Figure 5.3.6.3: The Etest can be used to determine the MIC of an antibiotic. In this Etest, vancomycin is shown to have a MIC of 1.5 µg/mL against *Staphylococcus aureus*.

? Exercise 5.3.6.2

Compare and contrast MIC and MBC.

Clinical Focus: Resolution

Marisa's UTI was likely caused by the catheterizations she had in Vietnam. Most bacteria that cause UTIs are members of the normal gut microbiota, but they can cause infections when introduced to the urinary tract, as might have occurred when the catheter was inserted. Alternatively, if the catheter itself was not sterile, bacteria on its surface could have been introduced into Marisa's body. The antimicrobial therapy Marisa received in Cambodia may also have been a complicating factor because it may have selected for antimicrobial-resistant strains already present in her body. These bacteria would have already contained genes for antimicrobial resistance, either acquired by spontaneous mutation or through horizontal gene transfer, and, therefore, had the best evolutionary advantage for adaptation and growth in the presence of the antimicrobial therapy. As a result, one of these resistant strains may have been subsequently introduced into her urinary tract.

Laboratory testing at the CDC confirmed that the strain of *Klebsiella pneumoniae* from Marisa's urine sample was positive for the presence of NDM, a very active carbapenemasethat is beginning to emerge as a new problem in antimicrobial resistance. While NDM-positive strains are resistant to a wide range of antimicrobials, they have shown susceptibility to tigecycline (structurally related to tetracycline) and the polymyxins B and E (colistin).

To prevent her infection from spreading, Marisa was isolated from the other patients in a separate room. All hospital staff interacting with her were advised to follow strict protocols to prevent surface and equipment contamination. This would include especially stringent hand hygiene practices and careful disinfection of all items coming into contact with her.

Marisa's infection finally responded to tigecycline and eventually cleared. She was discharged a few weeks after admission, and a follow-up stool sample showed her stool to be free of NDM-containing *K. pneumoniae*, meaning that she was no longer harboring the highly resistant bacterium.

Key Concepts and Summary

- The **Kirby-Bauer disk diffusion** test helps determine the susceptibility of a microorganism to various antimicrobial drugs. However, the **zones of inhibition** measured must be correlated to known standards to determine susceptibility and resistance, and do not provide information on bactericidal versus bacteriostatic activity, or allow for direct comparison of drug potencies.
- Antibiograms are useful for monitoring local trends in antimicrobial resistance/susceptibility and for directing appropriate selection of empiric antibacterial therapy.
- There are several laboratory methods available for determining the **minimum inhibitory concentration (MIC)** of an antimicrobial drug against a specific microbe. The **minimal bactericidal concentration (MBC)** can also be determined, typically as a follow-up experiment to MIC determination using the tube dilution method.

Footnotes

1. 1 J.P. Furuno et al. "Using Antibiograms to Improve Antibiotic Prescribing in Skilled Nursing Facilities." *Infection Control and Hospital Epidemiology* 35 no. Suppl S3 (2014):S56–61.

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5.3.E: Antimicrobial Drugs (Exercises)

14.1: Discovering Antimicrobial Drugs

Antimicrobial drugs produced by purposeful fermentation and/or contained in plants have been used as traditional medicines in many cultures for millennia. The purposeful and systematic search for a chemical “magic bullet” that specifically target infectious microbes was initiated by Paul Ehrlich in the early 20th century. The discovery of the natural antibiotic, penicillin, by Alexander Fleming in 1928 started the modern age of antimicrobial discovery and research.

Multiple Choice

A scientist discovers that a soil bacterium he has been studying produces an antimicrobial that kills gram-negative bacteria. She isolates and purifies the antimicrobial compound, then chemically converts a chemical side chain to a hydroxyl group. When she tests the antimicrobial properties of this new version, she finds that this antimicrobial drug can now also kill gram-positive bacteria. The new antimicrobial drug with broad-spectrum activity is considered to be which of the following?

A. resistant
B. semisynthetic
C. synthetic
D. natural

Answer

B

Which of the following antimicrobial drugs is synthetic?

A. sulfanilamide
B. penicillin
C. actinomycin
D. neomycin

Answer

A

Fill in the Blank

The group of soil bacteria known for their ability to produce a wide variety of antimicrobials is called the _____.

Answer

actinomycetes

Short Answer

Where do antimicrobials come from naturally? Why?

Why was Salvarsan considered to be a “magic bullet” for the treatment of syphilis?

Critical Thinking

In nature, why do antimicrobial-producing microbes commonly also have antimicrobial resistance genes?

14.2: Antibacterial Drugs

Antimicrobial drugs can be bacteriostatic or bactericidal, and these characteristics are important considerations when selecting the most appropriate drug. The use of narrow-spectrum antimicrobial drugs is preferred in many cases to avoid superinfection and the development of antimicrobial resistance. Broad-spectrum antimicrobial use is warranted for serious systemic infections when there is no time to determine the causative agent or when narrow-spectrum antimicrobials fail.

Multiple Choice

Which of the following combinations would most likely contribute to the development of a superinfection?

A. long-term use of narrow-spectrum antimicrobials
B. long-term use of broad-spectrum antimicrobials
C. short-term use of narrow-spectrum antimicrobials
D. short-term use of broad-spectrum antimicrobials

Answer

B

Which of the following routes of administration would be appropriate and convenient for home administration of an antimicrobial to treat a systemic infection?

A. oral
B. intravenous
C. topical
D. parenteral

Answer

A

Which clinical situation would be appropriate for treatment with a narrow-spectrum antimicrobial drug?

A. treatment of a polymicrobic mixed infection in the intestine
B. prophylaxis against infection after a surgical procedure
C. treatment of strep throat caused by culture identified *Streptococcus pyogenes*
D. empiric therapy of pneumonia while waiting for culture results

Answer

C

Fill in the Blank

The bacterium known for causing pseudomembranous colitis, a potentially deadly superinfection, is _____.

Answer

Clostridium difficile

True/False

Narrow-spectrum antimicrobials are commonly used for prophylaxis following surgery.

Answer

False

Short Answer

When prescribing antibiotics, what aspects of the patient's health history should the clinician ask about and why?

When is using a broad-spectrum antimicrobial drug warranted?

Critical Thinking

Why are yeast infections a common type of superinfection that results from long-term use of broad-spectrum antimicrobials?

Too often patients will stop taking antimicrobial drugs before the prescription is finished. What are factors that cause a patient to stop too soon, and what negative impacts could this have?

14.3: Drugs Targeting Other Microorganisms

Antibacterial compounds exhibit selective toxicity, largely due to differences between prokaryotic and eukaryotic cell structure. Cell wall synthesis inhibitors, including the β-lactams, the glycopeptides, and bacitracin, interfere with peptidoglycan synthesis, making bacterial cells more prone to osmotic lysis. There are a variety of broad-spectrum, bacterial protein synthesis inhibitors that selectively target the prokaryotic 70S ribosome, including those that bind to the 30S and 50S subunits.

Multiple Choice

Which of the following terms refers to the ability of an antimicrobial drug to harm the target microbe without harming the host?

A. mode of action
B. therapeutic level
C. spectrum of activity
D. selective toxicity

Answer

D

Which of the following is not a type of β-lactam antimicrobial?

A. penicillins
B. glycopeptides
C. cephalosporins
D. monobactams

Answer

B

Which of the following does not bind to the 50S ribosomal subunit?

A. tetracyclines
B. lincosamides
C. macrolides
D. chloramphenicol

Answer

A

Which of the following antimicrobials inhibits the activity of DNA gyrase?

A. polymyxin B
B. clindamycin
C. nalidixic acid
D. rifampin

Answer

C

Fill in the Blank

Selective toxicity antimicrobials are easier to develop against bacteria because they are _____ cells, whereas human cells are eukaryotic.

Answer

prokaryotic

True/False

β-lactamases can degrade vancomycin.

Answer

false

Short Answer

If human cells and bacterial cells perform transcription, how are the rifamycins specific for bacterial infections?

What bacterial structural target would make an antibacterial drug selective for gram-negative bacteria? Provide one example of an antimicrobial compound that targets this structure.

Critical Thinking

In considering the cell structure of prokaryotes compared with that of eukaryotes, propose one possible reason for side effects in humans due to treatment of bacterial infections with protein synthesis inhibitors.

14.4: Clinical Considerations

Because fungi, protozoans, and helminths are eukaryotic organisms like human cells, it is more challenging to develop antimicrobial drugs that specifically target them. Similarly, it is hard to target viruses because human viruses replicate inside of human cells.

Multiple Choice

Which of the following is not an appropriate target for antifungal drugs?

A. ergosterol
B. chitin
C. cholesterol
D. β(1→3) glucan

Answer

C

Which of the following drug classes specifically inhibits neuronal transmission in helminths?

A. quinolines
B. avermectins
C. amantadines
D. imidazoles

Answer

B

Which of the following is a nucleoside analog commonly used as a reverse transcriptase inhibitor in the treatment of HIV?

A. acyclovir
B. ribavirin
C. adenine-arabinoside
D. azidothymidine

Answer

D

Which of the following is an antimalarial drug that is thought to increase ROS levels in target cells?

A. artemisinin
B. amphotericin b
C. praziquantel
D. pleconaril

Answer

A

Fill in the Blank

Antiviral drugs, like Tamiflu and Relenza, that are effective against the influenza virus by preventing viral escape from host cells are called _____.

Answer

neuraminidase inhibitors

True/False

Echinocandins, known as “penicillin for fungi,” target β(1→3) glucan in fungal cell walls.

Answer

true

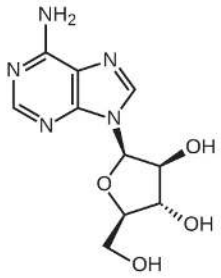
Short Answer

How does the biology of HIV necessitate the need to treat HIV infections with multiple drugs?

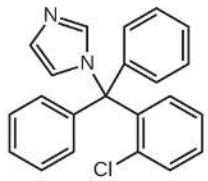
Niclosamide is insoluble and thus is not readily absorbed from the stomach into the bloodstream. How does the insolubility of niclosamide aid its effectiveness as a treatment for tapeworm infection?

Critical Thinking

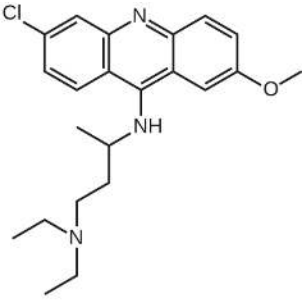
Which of the following molecules is an example of a nucleoside analog?



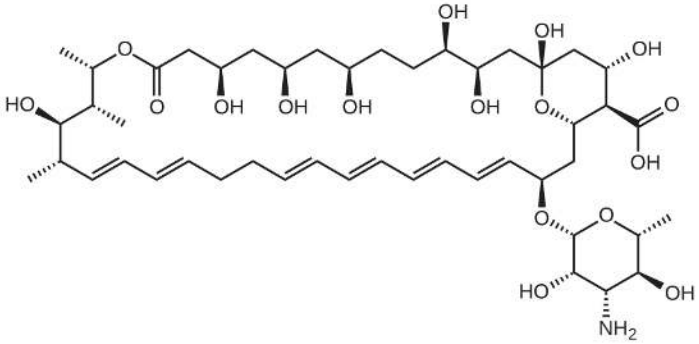
A



B



C



D

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Why can’t drugs used to treat influenza, like amantadines and neuraminidase inhibitors, be used to treat a wider variety of viral infections?

14.5: Testing the Effectiveness of Antimicrobials

Antimicrobial resistance is on the rise and is the result of selection of drug-resistant strains in clinical environments, the overuse and misuse of antibacterials, the use of subtherapeutic doses of antibacterial drugs, and poor patient compliance with antibacterial drug therapies. Drug resistance genes are often carried on plasmids or in transposons that can undergo vertical transfer easily and between microbes through horizontal gene transfer.

Multiple Choice

Which of the following resistance mechanisms describes the function of β-lactamase?

A. efflux pump
B. target mimicry
C. drug inactivation
D. target overproduction

Answer

C

Which of the following resistance mechanisms is commonly effective against a wide range of antimicrobials in multiple classes?

A. efflux pump
B. target mimicry
C. target modification
D. target overproduction

Answer

A

Which of the following resistance mechanisms is the most nonspecific to a particular class of antimicrobials?

A. drug modification
B. target mimicry
C. target modification
D. efflux pump

Answer

D

Which of the following types of drug-resistant bacteria do not typically persist in individuals as a member of their intestinal microbiota?

A. MRSA
B. VRE
C. CRE
D. ESBL-producing bacteria

Answer

A

Fill in the Blank

Staphylococcus aureus, including MRSA strains, may commonly be carried as a normal member of the _____ microbiota in some people.

Answer

nasal

Short Answer

Why does the length of time of antimicrobial treatment for tuberculosis contribute to the rise of resistant strains?

What is the difference between multidrug resistance and cross-resistance?

14.6: The Emergence of Drug Resistance

The Kirby-Bauer disk diffusion test helps determine the susceptibility of a microorganism to various antimicrobial drugs. However, the zones of inhibition measured must be correlated to known standards to determine susceptibility and resistance, and do not provide information on bactericidal versus bacteriostatic activity, or allow for direct comparison of drug potencies. Antibiograms are useful for monitoring local trends in antimicrobial resistance/susceptibility.

Multiple Choice

In the Kirby-Bauer disk diffusion test, the _____ of the zone of inhibition is measured and used for interpretation.

A. diameter
B. microbial population
C. circumference
D. depth

Answer

A

Which of the following techniques cannot be used to determine the minimum inhibitory concentration of an antimicrobial drug against a particular microbe?

A. Etest
B. microbroth dilution test
C. Kirby-Bauer disk diffusion test
D. macrobroth dilution test

Answer

C

The utility of an antibiogram is that it shows antimicrobial susceptibility trends

A. over a large geographic area.
B. for an individual patient.
C. in research laboratory strains.
D. in a localized population.

Answer

D

Fill in the Blank

The method that can determine the MICs of multiple antimicrobial drugs against a microbial strain using a single agar plate is called the _____.

Answer

Etest

True/False

If drug A produces a larger zone of inhibition than drug B on the Kirby-Bauer disk diffusion test, drug A should always be prescribed.

Answer

false

Short Answer

How is the information from a Kirby-Bauer disk diffusion test used for the recommendation of the clinical use of an antimicrobial drug?

What is the difference between MIC and MBC?

Critical Thinking

Can an Etest be used to find the MBC of a drug? Explain.

14.7: Current Strategies for Antimicrobial Discovery

With the continued evolution and spread of antimicrobial resistance, and now the identification of pan-resistant bacterial pathogens, the search for new antimicrobials is essential for preventing the postantibiotic era.

Multiple Choice

Which of the following has yielded compounds with the most antimicrobial activity?

A. water
B. air
C. volcanoes
D. soil

Answer

D

True/False

The rate of discovery of antimicrobial drugs has decreased significantly in recent decades.

Answer

true

Critical Thinking

Who should be responsible for discovering and developing new antibiotics? Support your answer with reasoning.

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CHAPTER OVERVIEW

6: The Immune System, Nonspecific and Specific Defenses

Topic hierarchy

6.1: The Lymphatic and Immune System

6.1.1: Introduction

6.1.2: Anatomy of the Lymphatic and Immune Systems

6.1.3: Barrier Defenses and the Innate Immune Response

6.1.4: The Adaptive Immune Response - T Lymphocytes and Their Functional Types

6.1.5: The Adaptive Immune Response - B Lymphocytes and Antibodies

6.1.6: The Immune Response Against Pathogens

6.1.7: Diseases Associated with Depressed or Overactive Immune Responses

6.1.8: Transplantation and Cancer Immunology

6.2: Innate Nonspecific Host Defenses

6.2.1: Physical Defenses

6.2.2: Chemical Defenses

6.2.3: Cellular Defenses

6.2.4: Pathogen Recognition and Phagocytosis

6.2.5: Inflammation and Fever

6.2.E: Innate Nonspecific Host Defenses (Exercises)

6.3: Specific Adaptive Host Defenses

6.3.1: Architecture of the Immune System

6.3.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes

6.3.3: T Lymphocytes

6.3.4: B Lymphocytes and Antibodies

6.3.5: Vaccines

6.3.E: Specific Adaptive Host Defenses (Exercises)

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SECTION OVERVIEW

6.1: The Lymphatic and Immune System

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6.1.8: Transplantation and Cancer Immunology

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6.1.1: Introduction

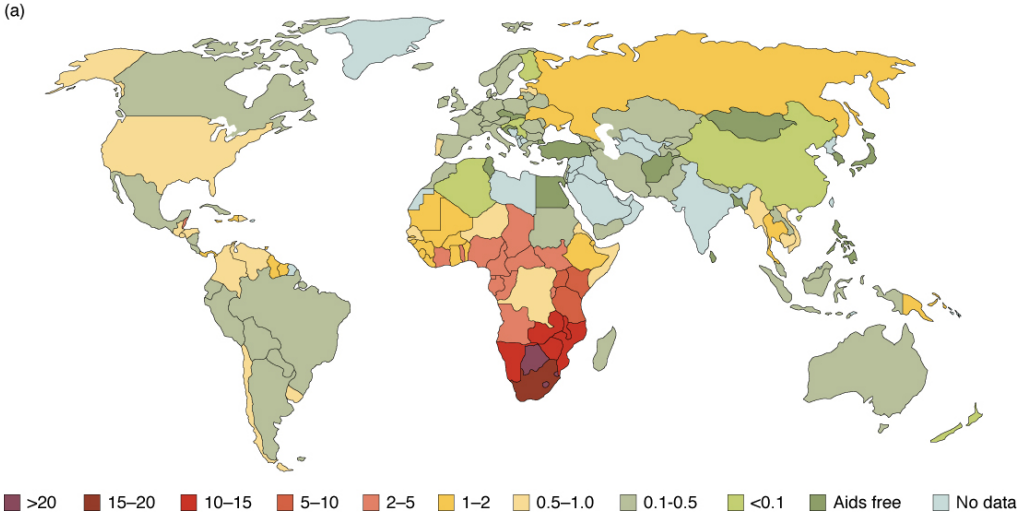
In June 1981, the Centers for Disease Control and Prevention (CDC), in Atlanta, Georgia, published a report of an unusual cluster of five patients in Los Angeles, California. All five were diagnosed with a rare pneumonia caused by a fungus called *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*).

Why was this unusual? Although commonly found in the lungs of healthy individuals, this fungus is an opportunistic pathogen that causes disease in individuals with suppressed or underdeveloped immune systems. The very young, whose immune systems have yet to mature, and the elderly, whose immune systems have declined with age, are particularly susceptible. The five patients from LA, though, were between 29 and 36 years of age and should have been in the prime of their lives, immunologically speaking. What could be going on?

A few days later, a cluster of eight cases was reported in New York City, also involving young patients, this time exhibiting a rare form of skin cancer known as Kaposi's sarcoma. This cancer of the cells that line the blood and lymphatic vessels was previously observed as a relatively innocuous disease of the elderly. The disease that doctors saw in 1981 was frighteningly more severe, with multiple, fast-growing lesions that spread to all parts of the body, including the trunk and face. Could the immune systems of these young patients have been compromised in some way? Indeed, when they were tested, they exhibited extremely low numbers of a specific type of white blood cell in their bloodstreams, indicating that they had somehow lost a major part of the immune system.

Acquired immune deficiency syndrome, or AIDS, turned out to be a new disease caused by the previously unknown human immunodeficiency virus (HIV). Although nearly 100 percent fatal in those with active HIV infections in the early years, the development of anti-HIV drugs has transformed HIV infection into a chronic, manageable disease and not the certain death sentence it once was. One positive outcome resulting from the emergence of HIV disease was that the public's attention became focused as never before on the importance of having a functional and healthy immune system.

(a)



(b)

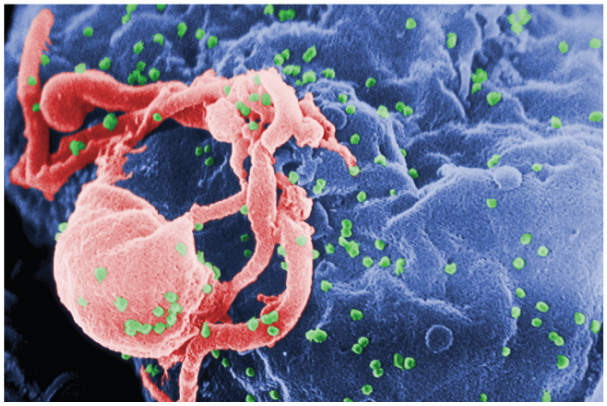


Figure 6.1.1.1: The Worldwide AIDS Epidemic. (a) As of 2008, more than 15 percent of adults were infected with HIV in certain African countries. This grim picture had changed little by 2012. (b) In this scanning electron micrograph, HIV virions (green particles) are budding off the surface of a macrophage (pink structure). (credit b: C. Goldsmith)

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6.1.2: Anatomy of the Lymphatic and Immune Systems

Learning Objectives

- Describe the structure and function of the lymphatic tissue (lymph fluid, vessels, ducts, and organs)
- Describe the structure and function of the primary and secondary lymphatic organs
- Discuss the cells of the immune system, how they function, and their relationship with the lymphatic system

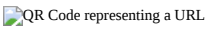
The **immune system** is the complex collection of cells and organs that destroys or neutralizes pathogens that would otherwise cause disease or death. The lymphatic system, for most people, is associated with the immune system to such a degree that the two systems are virtually indistinguishable. The **lymphatic system** is the system of vessels, cells, and organs that carries excess fluids to the bloodstream and filters pathogens from the blood. The swelling of lymph nodes during an infection and the transport of lymphocytes via the lymphatic vessels are but two examples of the many connections between these critical organ systems.

Functions of the Lymphatic System

A major function of the lymphatic system is to drain body fluids and return them to the bloodstream. Blood pressure causes leakage of fluid from the capillaries, resulting in the accumulation of fluid in the interstitial space—that is, spaces between individual cells in the tissues. In humans, 20 liters of plasma is released into the interstitial space of the tissues each day due to capillary filtration. Once this filtrate is out of the bloodstream and in the tissue spaces, it is referred to as interstitial fluid. Of this, 17 liters is reabsorbed directly by the blood vessels. But what happens to the remaining three liters? This is where the lymphatic system comes into play. It drains the excess fluid and empties it back into the bloodstream via a series of vessels, trunks, and ducts. **Lymph** is the term used to describe interstitial fluid once it has entered the lymphatic system. When the lymphatic system is damaged in some way, such as by being blocked by cancer cells or destroyed by injury, protein-rich interstitial fluid accumulates (sometimes “backs up” from the lymph vessels) in the tissue spaces. This inappropriate accumulation of fluid referred to as lymphedema may lead to serious medical consequences.

As the vertebrate immune system evolved, the network of lymphatic vessels became convenient avenues for transporting the cells of the immune system. Additionally, the transport of dietary lipids and fat-soluble vitamins absorbed in the gut uses this system.

Cells of the immune system not only use lymphatic vessels to make their way from interstitial spaces back into the circulation, but they also use lymph nodes as major staging areas for the development of critical immune responses. A **lymph node** is one of the small, bean-shaped organs located throughout the lymphatic system.



Visit this website for an overview of the lymphatic system. What are the three main components of the lymphatic system?

Structure of the Lymphatic System

The lymphatic vessels begin as open-ended capillaries, which feed into larger and larger lymphatic vessels, and eventually empty into the bloodstream by a series of ducts. Along the way, the lymph travels through the lymph nodes, which are commonly found near the groin, armpits, neck, chest, and abdomen. Humans have about 500–600 lymph nodes throughout the body (Figure 6.1.2.1).

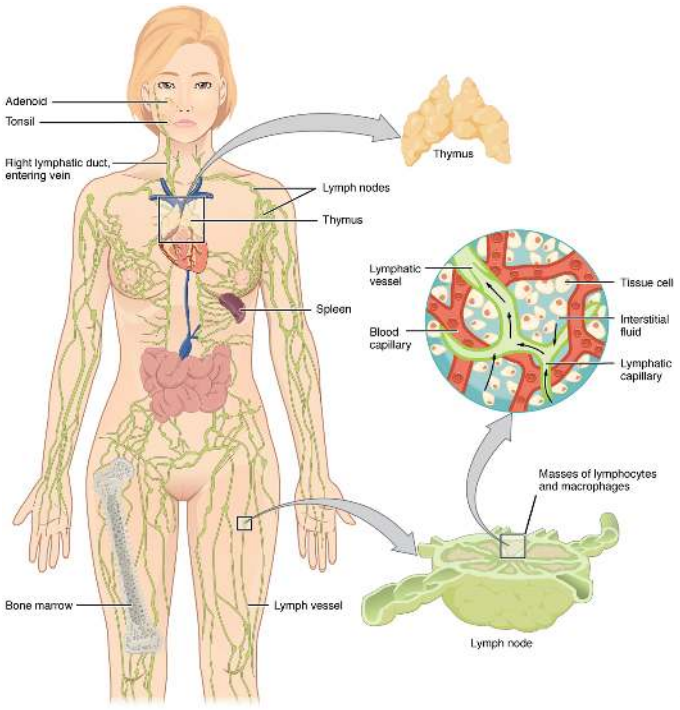


Figure 6.1.2.1: Anatomy of the Lymphatic System. Lymphatic vessels in the arms and legs convey lymph to the larger lymphatic vessels in the torso.

A major distinction between the lymphatic and cardiovascular systems in humans is that lymph is not actively pumped by the heart, but is forced through the vessels by the movements of the body, the contraction of skeletal muscles during body movements, and breathing. One-way valves (semi-lunar valves) in lymphatic vessels keep the lymph moving toward the heart. Lymph flows from the lymphatic capillaries, through lymphatic vessels, and then is dumped into the circulatory system via the lymphatic ducts located at the junction of the jugular and subclavian veins in the neck.

Lymphatic Capillaries

Lymphatic capillaries, also called the terminal lymphatics, are vessels where interstitial fluid enters the lymphatic system to become lymph fluid. Located in almost every tissue in the body, these vessels are interlaced among the arterioles and venules of the circulatory system in the soft connective tissues of the body (Figure 6.1.2.2). Exceptions are the central nervous system, bone marrow, bones, teeth, and the cornea of the eye, which do not contain lymph vessels.

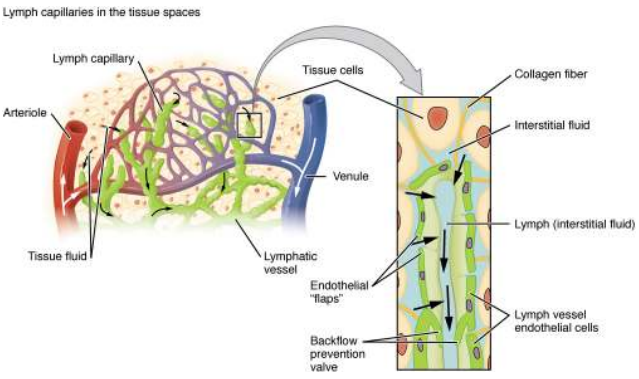


Figure 6.1.2.2: Lymphatic Capillaries. Lymphatic capillaries are interlaced with the arterioles and venules of the cardiovascular system. Collagen fibers anchor a lymphatic capillary in the tissue (inset). Interstitial fluid slips through spaces between the overlapping endothelial cells that compose the lymphatic capillary.

Lymphatic capillaries are formed by a one cell-thick layer of endothelial cells and represent the open end of the system, allowing interstitial fluid to flow into them via overlapping cells (see Figure 6.1.2.2). When interstitial pressure is low, the endothelial flaps close to prevent “backflow.” As interstitial pressure increases, the spaces between the cells open up, allowing the fluid to enter. Entry of fluid into lymphatic capillaries is also enabled by the collagen filaments that anchor the capillaries to surrounding

structures. As interstitial pressure increases, the filaments pull on the endothelial cell flaps, opening up them even further to allow easy entry of fluid.

In the small intestine, lymphatic capillaries called lacteals are critical for the transport of dietary lipids and lipid-soluble vitamins to the bloodstream. In the small intestine, dietary triglycerides combine with other lipids and proteins, and enter the lacteals to form a milky fluid called **chyle**. The chyle then travels through the lymphatic system, eventually entering the liver and then the bloodstream.

Larger Lymphatic Vessels, Trunks, and Ducts

The lymphatic capillaries empty into larger lymphatic vessels, which are similar to veins in terms of their three-tunic structure and the presence of valves. These one-way valves are located fairly close to one another, and each one causes a bulge in the lymphatic vessel, giving the vessels a beaded appearance (see Figure 6.1.2.2).

The superficial and deep lymphatics eventually merge to form larger lymphatic vessels known as **lymphatic trunks**. On the right side of the body, the right sides of the head, thorax, and right upper limb drain lymph fluid into the right subclavian vein via the right lymphatic duct (Figure 6.1.2.3). On the left side of the body, the remaining portions of the body drain into the larger thoracic duct, which drains into the left subclavian vein. The thoracic duct itself begins just beneath the diaphragm in the **cisterna chyli**, a sac-like chamber that receives lymph from the lower abdomen, pelvis, and lower limbs by way of the left and right lumbar trunks and the intestinal trunk.

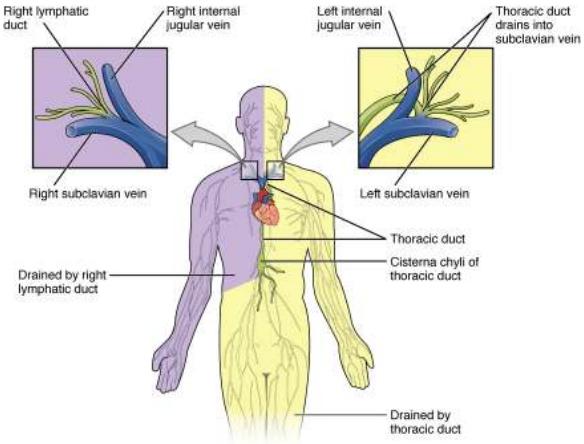


Figure 6.1.2.3: Major Trunks and Ducts of the Lymphatic System. The thoracic duct drains a much larger portion of the body than does the right lymphatic duct.

The overall drainage system of the body is asymmetrical (see Figure 6.1.2.3). The **right lymphatic duct** receives lymph from only the upper right side of the body. The lymph from the rest of the body enters the bloodstream through the **thoracic duct** via all the remaining lymphatic trunks. In general, lymphatic vessels of the subcutaneous tissues of the skin, that is, the superficial lymphatics, follow the same routes as veins, whereas the deep lymphatic vessels of the viscera generally follow the paths of arteries.

The Organization of Immune Function

The immune system is a collection of barriers, cells, and soluble proteins that interact and communicate with each other in extraordinarily complex ways. The modern model of immune function is organized into three phases based on the timing of their effects. The three temporal phases consist of the following:

- **Barrier defenses** such as the skin and mucous membranes, which act instantaneously to prevent pathogenic invasion into the body tissues
- The rapid but nonspecific **innate immune response**, which consists of a variety of specialized cells and soluble factors
- The slower but more specific and effective **adaptive immune response**, which involves many cell types and soluble factors, but is primarily controlled by white blood cells (leukocytes) known as **lymphocytes**, which help control immune responses

The cells of the blood, including all those involved in the immune response, arise in the bone marrow via various differentiation pathways from hematopoietic stem cells (Figure 6.1.2.4). In contrast with embryonic stem cells, hematopoietic stem cells are

present throughout adulthood and allow for the continuous differentiation of blood cells to replace those lost to age or function. These cells can be divided into three classes based on function:

- Phagocytic cells, which ingest pathogens to destroy them
- Lymphocytes, which specifically coordinate the activities of adaptive immunity
- Cells containing cytoplasmic granules, which help mediate immune responses against parasites and intracellular pathogens such as viruses

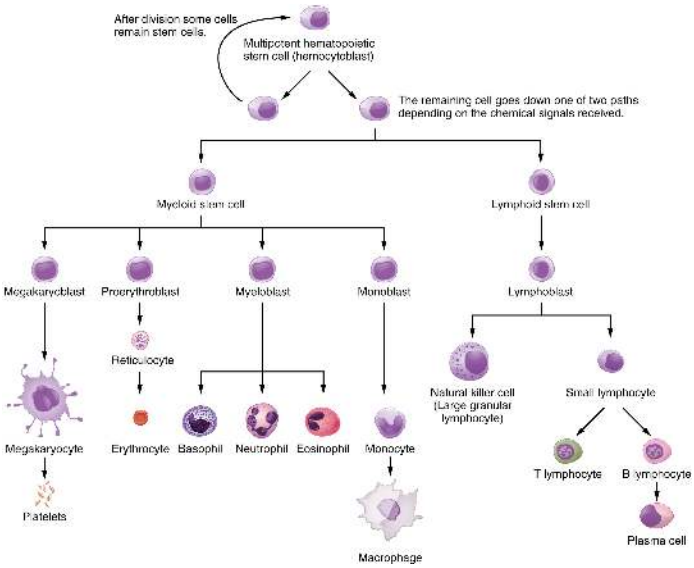


Figure 6.1.2.4: Hematopoietic System of the Bone Marrow. All the cells of the immune response as well as of the blood arise by differentiation from hematopoietic stem cells. Platelets are cell fragments involved in the clotting of blood.

Lymphocytes: B Cells, T Cells, Plasma Cells, and Natural Killer Cells

As stated above, lymphocytes are the primary cells of adaptive immune responses (Table). The two basic types of lymphocytes, B cells and T cells, are identical morphologically with a large central nucleus surrounded by a thin layer of cytoplasm. They are distinguished from each other by their surface protein markers as well as by the molecules they secrete. While B cells mature in red bone marrow and T cells mature in the thymus, they both initially develop from bone marrow. T cells migrate from bone marrow to the thymus gland where they further mature. B cells and T cells are found in many parts of the body, circulating in the bloodstream and lymph, and residing in secondary lymphoid organs, including the spleen and lymph nodes, which will be described later in this section. The human body contains approximately 10^{12} lymphocytes.

B Cells

B cells are immune cells that function primarily by producing antibodies. An **antibody** is any of the group of proteins that binds specifically to pathogen-associated molecules known as antigens. An **antigen** is a chemical structure on the surface of a pathogen that binds to T or B lymphocyte antigen receptors. Once activated by binding to antigen, B cells differentiate into cells that secrete a soluble form of their surface antibodies. These activated B cells are known as plasma cells.

T Cells

The **T cell**, on the other hand, does not secrete antibody but performs a variety of functions in the adaptive immune response. Different T cell types have the ability to either secrete soluble factors that communicate with other cells of the adaptive immune response or destroy cells infected with intracellular pathogens. The roles of T and B lymphocytes in the adaptive immune response will be discussed further in this chapter.

Plasma Cells

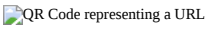
Another type of lymphocyte of importance is the plasma cell. A **plasma cell** is a B cell that has differentiated in response to antigen binding, and has thereby gained the ability to secrete soluble antibodies. These cells differ in morphology from standard B and T

cells in that they contain a large amount of cytoplasm packed with the protein-synthesizing machinery known as rough endoplasmic reticulum.

Natural Killer Cells

A fourth important lymphocyte is the natural killer cell, a participant in the innate immune response. A **natural killer cell (NK)** is a circulating blood cell that contains cytotoxic (cell-killing) granules in its extensive cytoplasm. It shares this mechanism with the cytotoxic T cells of the adaptive immune response. NK cells are among the body's first lines of defense against viruses and certain types of cancer.

Lymphocytes	
Type of lymphocyte	Primary function
B lymphocyte	Generates diverse antibodies
T lymphocyte	Secretes chemical messengers
Plasma cell	Secretes antibodies
NK cell	Destroys virally infected cells



Visit this website to learn about the many different cell types in the immune system and their very specialized jobs. What is the role of the dendritic cell in an HIV infection?

Primary Lymphoid Organs and Lymphocyte Development

Understanding the differentiation and development of B and T cells is critical to the understanding of the adaptive immune response. It is through this process that the body (ideally) learns to destroy only pathogens and leaves the body's own cells relatively intact. The **primary lymphoid organs** are the bone marrow, spleen, and thymus gland. The lymphoid organs are where lymphocytes mature, proliferate, and are selected, which enables them to attack pathogens without harming the cells of the body.

Bone Marrow

In the embryo, blood cells are made in the yolk sac. As development proceeds, this function is taken over by the spleen, lymph nodes, and liver. Later, the bone marrow takes over most hematopoietic functions, although the final stages of the differentiation of some cells may take place in other organs. The red **bone marrow** is a loose collection of cells where hematopoiesis occurs, and the yellow bone marrow is a site of energy storage, which consists largely of fat cells (Figure 6.1.2.5). The B cell undergoes nearly all of its development in the red bone marrow, whereas the immature T cell, called a **thymocyte**, leaves the bone marrow and matures largely in the thymus gland.



Figure 6.1.2.5: Bone Marrow. Red bone marrow fills the head of the femur, and a spot of yellow bone marrow is visible in the center. The white reference bar is 1 cm.

Thymus

The **thymus** gland is a bilobed organ found in the space between the sternum and the aorta of the heart (Figure 6.1.2.6). Connective tissue holds the lobes closely together but also separates them and forms a capsule.

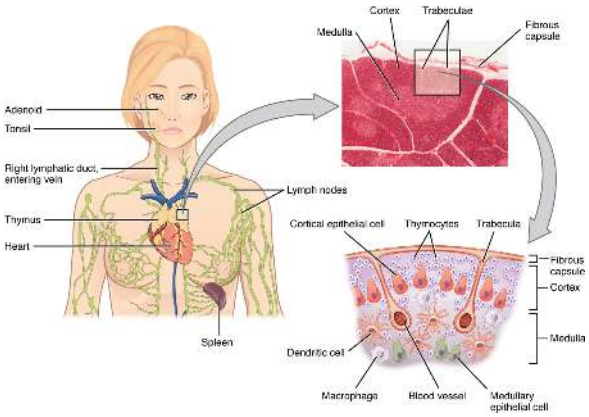


Figure 6.1.2.6: Location, Structure, and Histology of the Thymus. The thymus lies above the heart. The trabeculae and lobules, including the darkly staining cortex and the lighter staining medulla of each lobule, are clearly visible in the light micrograph of the thymus of a newborn. LM × 100. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

QR Code representing a URL

View the University of Michigan WebScope to explore the tissue sample in greater detail.

The connective tissue capsule further divides the thymus into lobules via extensions called trabeculae. The outer region of the organ is known as the cortex and contains large numbers of thymocytes with some epithelial cells, macrophages, and dendritic cells (two types of phagocytic cells that are derived from monocytes). The cortex is densely packed so it stains more intensely than the rest of the thymus (see Figure 6.1.2.6). The medulla, where thymocytes migrate before leaving the thymus, contains a less dense collection of thymocytes, epithelial cells, and dendritic cells.

AGING AND THE...

Immune System

By the year 2050, 25 percent of the population of the United States will be 60 years of age or older. The CDC estimates that 80 percent of those 60 years and older have one or more chronic disease associated with deficiencies of the immune systems. This loss of immune function with age is called immunosenescence. To treat this growing population, medical professionals must better understand the aging process. One major cause of age-related immune deficiencies is thymic involution, the shrinking of the thymus gland that begins at birth, at a rate of about three percent tissue loss per year, and continues until 35–45 years of age, when the rate declines to about one percent loss per year for the rest of one's life. At that pace, the total loss of thymic epithelial tissue and thymocytes would occur at about 120 years of age. Thus, this age is a theoretical limit to a healthy human lifespan.

Thymic involution has been observed in all vertebrate species that have a thymus gland. Animal studies have shown that transplanted thymic grafts between inbred strains of mice involuted according to the age of the donor and not of the recipient, implying the process is genetically programmed. There is evidence that the thymic microenvironment, so vital to the development of naïve T cells, loses thymic epithelial cells according to the decreasing expression of the FOXN1 gene with age.

It is also known that thymic involution can be altered by hormone levels. Sex hormones such as estrogen and testosterone enhance involution, and the hormonal changes in pregnant women cause a temporary thymic involution that reverses itself, when the size of the thymus and its hormone levels return to normal, usually after lactation ceases. What does all this tell us? Can we reverse immunosenescence, or at least slow it down? The potential is there for using thymic transplants from younger donors to keep thymic output of naïve T cells high. Gene therapies that target gene expression are also seen as future possibilities. The more we learn through immunosenescence research, the more opportunities there will be to develop therapies, even though these therapies will likely take decades to develop. The ultimate goal is for everyone to live and be healthy longer, but there may be limits to immortality imposed by our genes and hormones.

Secondary Lymphoid Organs and their Roles in Active Immune Responses

Lymphocytes develop and mature in the primary lymphoid organs, but they mount immune responses from the **secondary lymphoid organs**. A **naïve lymphocyte** is one that has left the primary organ and entered a secondary lymphoid organ. Naïve

lymphocytes are fully functional immunologically, but have yet to encounter an antigen to respond to. In addition to circulating in the blood and lymph, lymphocytes concentrate in secondary lymphoid organs, which include the lymph nodes, spleen, and lymphoid nodules. All of these tissues have many features in common, including the following:

- The presence of lymphoid follicles, the sites of the formation of lymphocytes, with specific B cell-rich and T cell-rich areas
- An internal structure of reticular fibers with associated fixed macrophages
- **Germinal centers**, which are the sites of rapidly dividing B lymphocytes and plasma cells, with the exception of the spleen
- Specialized post-capillary vessels known as **high endothelial venules**; the cells lining these venules are thicker and more columnar than normal endothelial cells, which allow cells from the blood to directly enter these tissues

Lymph Nodes

Lymph nodes function to remove debris and pathogens from the lymph, and are thus sometimes referred to as the “filters of the lymph” (Figure 6.1.2.7). Any bacteria that infect the interstitial fluid are taken up by the lymphatic capillaries and transported to a regional lymph node. Dendritic cells and macrophages within this organ internalize and kill many of the pathogens that pass through, thereby removing them from the body. The lymph node is also the site of adaptive immune responses mediated by T cells, B cells, and accessory cells of the adaptive immune system. Like the thymus, the bean-shaped lymph nodes are surrounded by a tough capsule of connective tissue and are separated into compartments by trabeculae, the extensions of the capsule. In addition to the structure provided by the capsule and trabeculae, the structural support of the lymph node is provided by a series of reticular fibers laid down by fibroblasts.

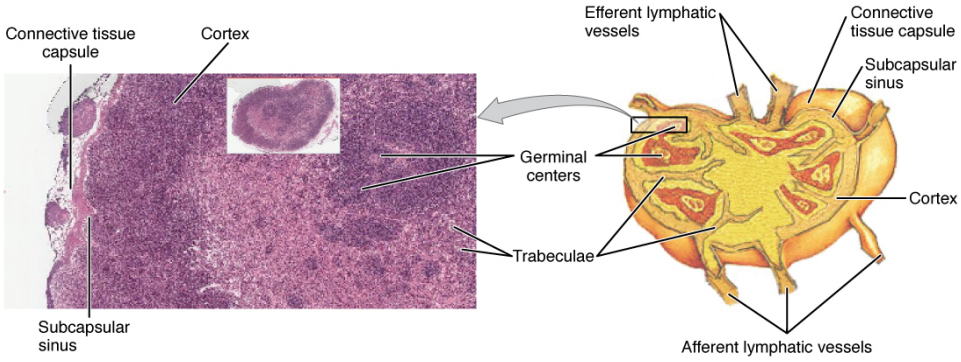


Figure 6.1.2.7: Structure and Histology of a Lymph Node. Lymph nodes are masses of lymphatic tissue located along the larger lymph vessels. The micrograph of the lymph nodes shows a germinal center, which consists of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. LM × 128. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

View the University of Michigan WebScope to explore the tissue sample in greater detail.

The major routes into the lymph node are via **afferent lymphatic vessels** (see Figure 6.1.2.7). Cells and lymph fluid that leave the lymph node may do so by another set of vessels known as the **efferent lymphatic vessels**. Lymph enters the lymph node via the subcapsular sinus, which is occupied by dendritic cells, macrophages, and reticular fibers. Within the cortex of the lymph node are lymphoid follicles, which consist of germinal centers of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. As the lymph continues to flow through the node, it enters the medulla, which consists of medullary cords of B cells and plasma cells, and the medullary sinuses where the lymph collects before leaving the node via the efferent lymphatic vessels.

Spleen

In addition to the lymph nodes, the **spleen** is a major secondary lymphoid organ (Figure 6.1.2.8). It is about 12 cm (5 in) long and is attached to the lateral border of the stomach via the gastrosplenic ligament. The spleen is a fragile organ without a strong capsule, and is dark red due to its extensive vascularization. The spleen is sometimes called the “filter of the blood” because of its extensive

vascularization and the presence of macrophages and dendritic cells that remove microbes and other materials from the blood, including dying red blood cells. The spleen also functions as the location of immune responses to blood-borne pathogens.

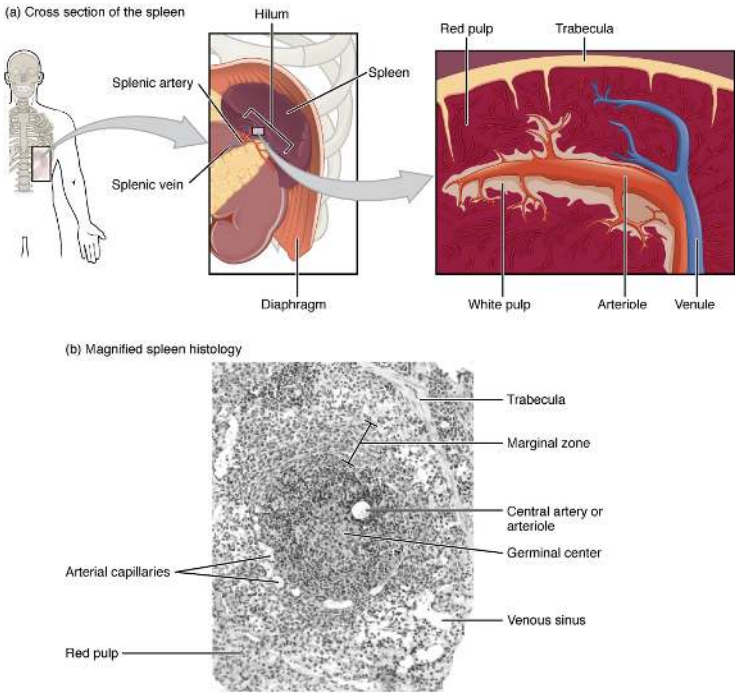


Figure 6.1.2.8: Spleen. (a) The spleen is attached to the stomach. (b) A micrograph of spleen tissue shows the germinal center. The marginal zone is the region between the red pulp and white pulp, which sequesters particulate antigens from the circulation and presents these antigens to lymphocytes in the white pulp. EM × 660. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

The spleen is also divided by trabeculae of connective tissue, and within each splenic nodule is an area of red pulp, consisting of mostly red blood cells, and white pulp, which resembles the lymphoid follicles of the lymph nodes. Upon entering the spleen, the splenic artery splits into several arterioles (surrounded by white pulp) and eventually into sinusoids. Blood from the capillaries subsequently collects in the venous sinuses and leaves via the splenic vein. The red pulp consists of reticular fibers with fixed macrophages attached, free macrophages, and all of the other cells typical of the blood, including some lymphocytes. The white pulp surrounds a central arteriole and consists of germinal centers of dividing B cells surrounded by T cells and accessory cells, including macrophages and dendritic cells. Thus, the red pulp primarily functions as a filtration system of the blood, using cells of the relatively nonspecific immune response, and white pulp is where adaptive T and B cell responses are mounted.

Lymphoid Nodules

The other lymphoid tissues, the **lymphoid nodules**, have a simpler architecture than the spleen and lymph nodes in that they consist of a dense cluster of lymphocytes without a surrounding fibrous capsule. These nodules are located in the respiratory and digestive tracts, areas routinely exposed to environmental pathogens.

Tonsils are lymphoid nodules located along the inner surface of the pharynx and are important in developing immunity to oral pathogens (Figure 6.1.2.9). The tonsil located at the back of the throat, the pharyngeal tonsil, is sometimes referred to as the adenoid when swollen. Such swelling is an indication of an active immune response to infection. Histologically, tonsils do not contain a complete capsule, and the epithelial layer invaginates deeply into the interior of the tonsil to form tonsillar crypts. These structures, which accumulate all sorts of materials taken into the body through eating and breathing, actually “encourage” pathogens to penetrate deep into the tonsillar tissues where they are acted upon by numerous lymphoid follicles and eliminated. This seems to be the major function of tonsils—to help children’s bodies recognize, destroy, and develop immunity to common environmental pathogens so that they will be protected in their later lives. Tonsils are often removed in those children who have recurring throat infections, especially those involving the palatine tonsils on either side of the throat, whose swelling may interfere with their breathing and/or swallowing.

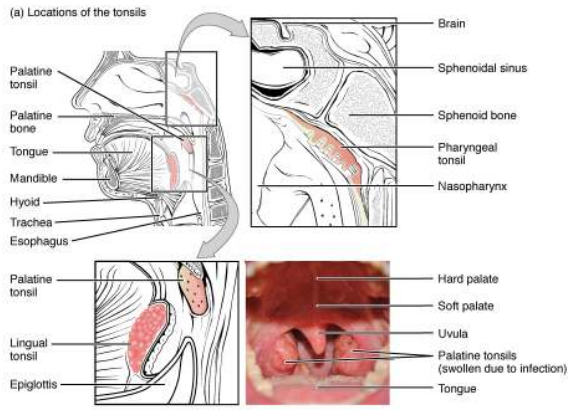


Figure 6.1.2.9: Locations and Histology of the Tonsils. (a) The pharyngeal tonsil is located on the roof of the posterior superior wall of the nasopharynx. The palatine tonsils lay on each side of the pharynx. (b) A micrograph shows the palatine tonsil tissue. LM × 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

QR Code representing a URL

View the University of Michigan WebScope to explore the tissue sample in greater detail.

Mucosa-associated lymphoid tissue (MALT) consists of an aggregate of lymphoid follicles directly associated with the mucous membrane epithelia. MALT makes up dome-shaped structures found underlying the mucosa of the gastrointestinal tract, breast tissue, lungs, and eyes. Peyer's patches, a type of MALT in the small intestine, are especially important for immune responses against ingested substances (Figure 6.1.2.10). Peyer's patches contain specialized endothelial cells called M (or microfold) cells that sample material from the intestinal lumen and transport it to nearby follicles so that adaptive immune responses to potential pathogens can be mounted.



Figure 6.1.2.10: Mucosa-associated Lymphoid Tissue (MALT) Nodule. LM × 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Bronchus-associated lymphoid tissue (BALT) consists of lymphoid follicular structures with an overlying epithelial layer found along the bifurcations of the bronchi, and between bronchi and arteries. They also have the typically less-organized structure of other lymphoid nodules. These tissues, in addition to the tonsils, are effective against inhaled pathogens.

Chapter Review

The lymphatic system is a series of vessels, ducts, and trunks that remove interstitial fluid from the tissues and return it the blood. The lymphatics are also used to transport dietary lipids and cells of the immune system. Cells of the immune system all come from the hematopoietic system of the bone marrow. Primary lymphoid organs, the bone marrow and thymus gland, are the locations where lymphocytes of the adaptive immune system proliferate and mature. Secondary lymphoid organs are site in which mature lymphocytes congregate to mount immune responses. Many immune system cells use the lymphatic and circulatory systems for transport throughout the body to search for and then protect against pathogens.

Interactive Link Questions

Visit this website for an overview of the lymphatic system. What are the three main components of the lymphatic system?

> Answer: The three main components are the lymph vessels, the lymph nodes, and the lymph.

Visit this website to learn about the many different cell types in the immune system and their very specialized jobs. What is the role of the dendritic cell in infection by HIV?

> Answer: The dendritic cell transports the virus to a lymph node.

Review Questions

Q. Which of the following cells is phagocytic?

A. plasma cell

B. macrophage

C. B cell

D. NK cell

> Answer: B

Q. Which structure allows lymph from the lower right limb to enter the bloodstream?

A. thoracic duct

B. right lymphatic duct

C. right lymphatic trunk

D. left lymphatic trunk

> Answer: A

Q. Which of the following cells is important in the innate immune response?

A. B cells

B. T cells

C. macrophages

D. plasma cells

> Answer: C

Q. Which of the following cells would be most active in early, antiviral immune responses the first time one is exposed to pathogen?

A. macrophage

B. T cell

E. neutrophil

D. natural killer cell

Answer: D

Q. Which of the lymphoid nodules is most likely to see food antigens first?

A. tonsils

B. Peyer’s patches

C. bronchus-associated lymphoid tissue

D. mucosa-associated lymphoid tissue

Answer: A

Critical Thinking Questions

Q. Describe the flow of lymph from its origins in interstitial fluid to its emptying into the venous bloodstream.

A. The lymph enters through lymphatic capillaries, and then into larger lymphatic vessels. The lymph can only go in one direction due to valves in the vessels. The larger lymphatics merge to form trunks that enter into the blood via lymphatic ducts.

Glossary

adaptive immune response
relatively slow but very specific and effective immune response controlled by lymphocytes

afferent lymphatic vessels
lead into a lymph node

antibody
antigen-specific protein secreted by plasma cells; immunoglobulin

antigen
molecule recognized by the receptors of B and T lymphocytes

barrier defenses
antipathogen defenses deriving from a barrier that physically prevents pathogens from entering the body to establish an infection

B cells
lymphocytes that act by differentiating into an antibody-secreting plasma cell

bone marrow
tissue found inside bones; the site of all blood cell differentiation and maturation of B lymphocytes

bronchus-associated lymphoid tissue (BALT)
lymphoid nodule associated with the respiratory tract

chyle
lipid-rich lymph inside the lymphatic capillaries of the small intestine

cisterna chyli
bag-like vessel that forms the beginning of the thoracic duct

efferent lymphatic vessels
lead out of a lymph node

germinal centers
clusters of rapidly proliferating B cells found in secondary lymphoid tissues

high endothelial venules
vessels containing unique endothelial cells specialized to allow migration of lymphocytes from the blood to the lymph node

immune system
series of barriers, cells, and soluble mediators that combine to response to infections of the body with pathogenic organisms

innate immune response
rapid but relatively nonspecific immune response

lymph
fluid contained within the lymphatic system

lymph node
one of the bean-shaped organs found associated with the lymphatic vessels

lymphatic capillaries
smallest of the lymphatic vessels and the origin of lymph flow

lymphatic system
network of lymphatic vessels, lymph nodes, and ducts that carries lymph from the tissues and back to the bloodstream.

lymphatic trunks
large lymphatics that collect lymph from smaller lymphatic vessels and empties into the blood via lymphatic ducts

lymphocytes
white blood cells characterized by a large nucleus and small rim of cytoplasm

lymphoid nodules
unencapsulated patches of lymphoid tissue found throughout the body

mucosa-associated lymphoid tissue (MALT)
lymphoid nodule associated with the mucosa

naïve lymphocyte
mature B or T cell that has not yet encountered antigen for the first time

natural killer cell (NK)
cytotoxic lymphocyte of innate immune response

plasma cell

differentiated B cell that is actively secreting antibody

primary lymphoid organ

site where lymphocytes mature and proliferate; red bone marrow and thymus gland

right lymphatic duct

drains lymph fluid from the upper right side of body into the right subclavian vein

secondary lymphoid organs

sites where lymphocytes mount adaptive immune responses; examples include lymph nodes and spleen

spleen

secondary lymphoid organ that filters pathogens from the blood (white pulp) and removes degenerating or damaged blood cells (red pulp)

T cell

lymphocyte that acts by secreting molecules that regulate the immune system or by causing the destruction of foreign cells, viruses, and cancer cells

thoracic duct

large duct that drains lymph from the lower limbs, left thorax, left upper limb, and the left side of the head

thymocyte

immature T cell found in the thymus

thymus

primary lymphoid organ; where T lymphocytes proliferate and mature

tonsils

lymphoid nodules associated with the nasopharynx

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6.1.3: Barrier Defenses and the Innate Immune Response

Learning Objectives

- Describe the barrier defenses of the body
- Show how the innate immune response is important and how it helps guide and prepare the body for adaptive immune responses
- Describe various soluble factors that are part of the innate immune response
- Explain the steps of inflammation and how they lead to destruction of a pathogen
- Discuss early induced immune responses and their level of effectiveness

The immune system can be divided into two overlapping mechanisms to destroy pathogens: the innate immune response, which is relatively rapid but nonspecific and thus not always effective, and the adaptive immune response, which is slower in its development during an initial infection with a pathogen, but is highly specific and effective at attacking a wide variety of pathogens (Figure 6.1.3.1).

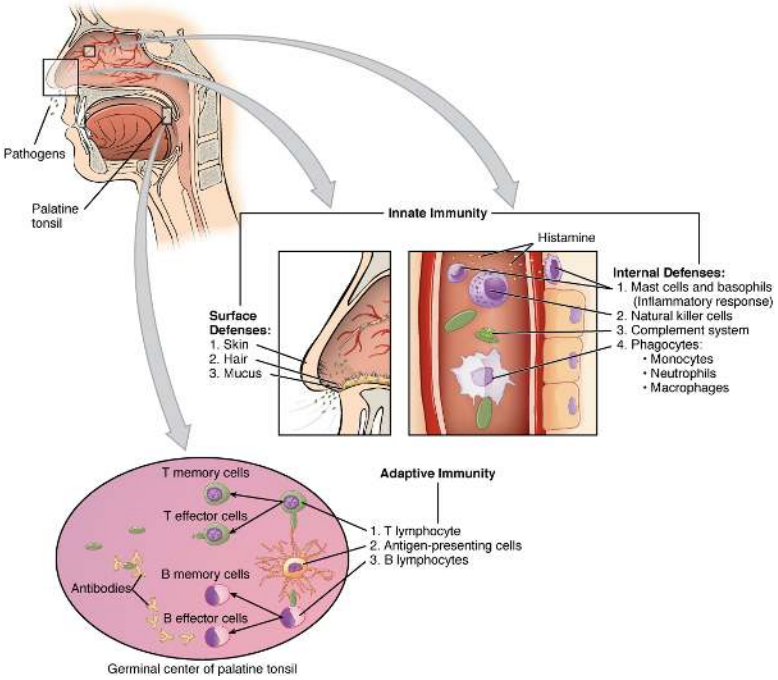


Figure 6.1.3.1: Cooperation between Innate and Adaptive Immune Responses. The innate immune system enhances adaptive immune responses so they can be more effective.

Any discussion of the innate immune response usually begins with the physical barriers that prevent pathogens from entering the body, destroy them after they enter, or flush them out before they can establish themselves in the hospitable environment of the body's soft tissues. Barrier defenses are part of the body's most basic defense mechanisms. The barrier defenses are not a response to infections, but they are continuously working to protect against a broad range of pathogens.

The different modes of barrier defenses are associated with the external surfaces of the body, where pathogens may try to enter (Table). The primary barrier to the entrance of microorganisms into the body is the skin. Not only is the skin covered with a layer of dead, keratinized epithelium that is too dry for bacteria in which to grow, but as these cells are continuously sloughed off from the skin, they carry bacteria and other pathogens with them. Additionally, sweat and other skin secretions may lower pH, contain toxic lipids, and physically wash microbes away.

Barrier Defenses		
Site	Specific defense	Protective aspect
Skin	Epidermal surface	Keratinized cells of surface, Langerhans cells
Skin (sweat/secretions)	Sweat glands, sebaceous glands	Low pH, washing action
Oral cavity	Salivary glands	Lysozyme
Stomach	Gastrointestinal tract	Low pH
Mucosal surfaces	Mucosal epithelium	Nonkeratinized epithelial cells
Normal flora (nonpathogenic bacteria)	Mucosal tissues	Prevent pathogens from growing on mucosal surfaces

Another barrier is the saliva in the mouth, which is rich in lysozyme—an enzyme that destroys bacteria by digesting their cell walls. The acidic environment of the stomach, which is fatal to many pathogens, is also a barrier. Additionally, the mucus layer of the gastrointestinal tract, respiratory tract, reproductive tract, eyes, ears, and nose traps both microbes and debris, and facilitates their removal. In the case of the upper respiratory tract, ciliated epithelial cells move potentially contaminated mucus upwards to the mouth, where it is then swallowed into the digestive tract, ending up in the harsh acidic environment of the stomach. Considering how often you breathe compared to how often you eat or perform other activities that expose you to pathogens, it is not surprising that multiple barrier mechanisms have evolved to work in concert to protect this vital area.

Cells of the Innate Immune Response

A phagocyte is a cell that is able to surround and engulf a particle or cell, a process called **phagocytosis**. The phagocytes of the immune system engulf other particles or cells, either to clean an area of debris, old cells, or to kill pathogenic organisms such as bacteria. The phagocytes are the body's fast acting, first line of immunological defense against organisms that have breached barrier defenses and have entered the vulnerable tissues of the body.

Phagocytes: Macrophages and Neutrophils

Many of the cells of the immune system have a phagocytic ability, at least at some point during their life cycles. Phagocytosis is an important and effective mechanism of destroying pathogens during innate immune responses. The phagocyte takes the organism inside itself as a phagosome, which subsequently fuses with a lysosome and its digestive enzymes, effectively killing many pathogens. On the other hand, some bacteria including *Mycobacteria tuberculosis*, the cause of tuberculosis, may be resistant to these enzymes and are therefore much more difficult to clear from the body. Macrophages, neutrophils, and dendritic cells are the major phagocytes of the immune system.

A **macrophage** is an irregularly shaped phagocyte that is amoeboid in nature and is the most versatile of the phagocytes in the body. Macrophages move through tissues and squeeze through capillary walls using pseudopodia. They not only participate in innate immune responses but have also evolved to cooperate with lymphocytes as part of the adaptive immune response. Macrophages exist in many tissues of the body, either freely roaming through connective tissues or fixed to reticular fibers within specific tissues such as lymph nodes. When pathogens breach the body's barrier defenses, macrophages are the first line of defense (Table). They are called different names, depending on the tissue: Kupffer cells in the liver, histiocytes in connective tissue, and alveolar macrophages in the lungs.

A **neutrophil** is a phagocytic cell that is attracted via chemotaxis from the bloodstream to infected tissues. These spherical cells are granulocytes. A granulocyte contains cytoplasmic granules, which in turn contain a variety of vasoactive mediators such as histamine. In contrast, macrophages are agranulocytes. An agranulocyte has few or no cytoplasmic granules. Whereas macrophages act like sentries, always on guard against infection, neutrophils can be thought of as military reinforcements that are called into a battle to hasten the destruction of the enemy. Although, usually thought of as the primary pathogen-killing cell of the inflammatory process of the innate immune response, new research has suggested that neutrophils play a role in the adaptive immune response as well, just as macrophages do.

A **monocyte** is a circulating precursor cell that differentiates into either a macrophage or dendritic cell, which can be rapidly attracted to areas of infection by signal molecules of inflammation.

Phagocytic Cells of the Innate Immune System			
Cell	Cell type	Primary location	Function in the innate immune response
Macrophage	Agranulocyte	Body cavities/organs	Phagocytosis
Neutrophil	Granulocyte	Blood	Phagocytosis
Monocyte	Agranulocyte	Blood	Precursor of macrophage/dendritic cell

Natural Killer Cells

NK cells are a type of lymphocyte that have the ability to induce apoptosis, that is, programmed cell death, in cells infected with intracellular pathogens such as obligate intracellular bacteria and viruses. NK cells recognize these cells by mechanisms that are still not well understood, but that presumably involve their surface receptors. NK cells can induce apoptosis, in which a cascade of events inside the cell causes its own death by either of two mechanisms:

1) NK cells are able to respond to chemical signals and express the fas ligand. The **fas ligand** is a surface molecule that binds to the fas molecule on the surface of the infected cell, sending it apoptotic signals, thus killing the cell and the pathogen within it; or

2) The granules of the NK cells release perforins and granzymes. A **perforin** is a protein that forms pores in the membranes of infected cells. A **granzyme** is a protein-digesting enzyme that enters the cell via the perforin pores and triggers apoptosis intracellularly.

Both mechanisms are especially effective against virally infected cells. If apoptosis is induced before the virus has the ability to synthesize and assemble all its components, no infectious virus will be released from the cell, thus preventing further infection.

Recognition of Pathogens

Cells of the innate immune response, the phagocytic cells, and the cytotoxic NK cells recognize patterns of pathogen-specific molecules, such as bacterial cell wall components or bacterial flagellar proteins, using pattern recognition receptors. A **pattern recognition receptor (PRR)** is a membrane-bound receptor that recognizes characteristic features of a pathogen and molecules released by stressed or damaged cells.

These receptors, which are thought to have evolved prior to the adaptive immune response, are present on the cell surface whether they are needed or not. Their variety, however, is limited by two factors. First, the fact that each receptor type must be encoded by a specific gene requires the cell to allocate most or all of its DNA to make receptors able to recognize all pathogens. Secondly, the variety of receptors is limited by the finite surface area of the cell membrane. Thus, the innate immune system must “get by” using only a limited number of receptors that are active against as wide a variety of pathogens as possible. This strategy is in stark contrast to the approach used by the adaptive immune system, which uses large numbers of different receptors, each highly specific to a particular pathogen.

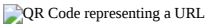
Should the cells of the innate immune system come into contact with a species of pathogen they recognize, the cell will bind to the pathogen and initiate phagocytosis (or cellular apoptosis in the case of an intracellular pathogen) in an effort to destroy the offending microbe. Receptors vary somewhat according to cell type, but they usually include receptors for bacterial components and for complement, discussed below.

Soluble Mediators of the Innate Immune Response

The previous discussions have alluded to chemical signals that can induce cells to change various physiological characteristics, such as the expression of a particular receptor. These soluble factors are secreted during innate or early induced responses, and later during adaptive immune responses.

Cytokines and Chemokines

A **cytokine** is signaling molecule that allows cells to communicate with each other over short distances. Cytokines are secreted into the intercellular space, and the action of the cytokine induces the receiving cell to change its physiology. A **chemokine** is a soluble chemical mediator similar to cytokines except that its function is to attract cells (chemotaxis) from longer distances.



Visit this website to learn about phagocyte chemotaxis. Phagocyte chemotaxis is the movement of phagocytes according to the secretion of chemical messengers in the form of interleukins and other chemokines. By what means does a phagocyte destroy a bacterium that it has ingested?

Early induced Proteins

Early induced proteins are those that are not constitutively present in the body, but are made as they are needed early during the innate immune response. **Interferons** are an example of early induced proteins. Cells infected with viruses secrete interferons that travel to adjacent cells and induce them to make antiviral proteins. Thus, even though the initial cell is sacrificed, the surrounding cells are protected. Other early induced proteins specific for bacterial cell wall components are mannose-binding protein and C-reactive protein, made in the liver, which bind specifically to polysaccharide components of the bacterial cell wall. Phagocytes such as macrophages have receptors for these proteins, and they are thus able to recognize them as they are bound to the bacteria. This brings the phagocyte and bacterium into close proximity and enhances the phagocytosis of the bacterium by the process known as opsonization. **Opsonization** is the tagging of a pathogen for phagocytosis by the binding of an antibody or an antimicrobial protein.

Complement System

The **complement** system is a series of proteins constitutively found in the blood plasma. As such, these proteins are not considered part of the **early induced immune response**, even though they share features with some of the antibacterial proteins of this class. Made in the liver, they have a variety of functions in the innate immune response, using what is known as the “alternate pathway” of complement activation. Additionally, complement functions in the adaptive immune response as well, in what is called the classical pathway. The complement system consists of several proteins that enzymatically alter and fragment later proteins in a series, which is why it is termed cascade. Once activated, the series of reactions is irreversible, and releases fragments that have the following actions:

- Bind to the cell membrane of the pathogen that activates it, labeling it for phagocytosis (opsonization)
- Diffuse away from the pathogen and act as chemotactic agents to attract phagocytic cells to the site of inflammation
- Form damaging pores in the plasma membrane of the pathogen

Figure 6.1.3.2 shows the classical pathway, which requires antibodies of the adaptive immune response. The alternate pathway does not require an antibody to become activated.

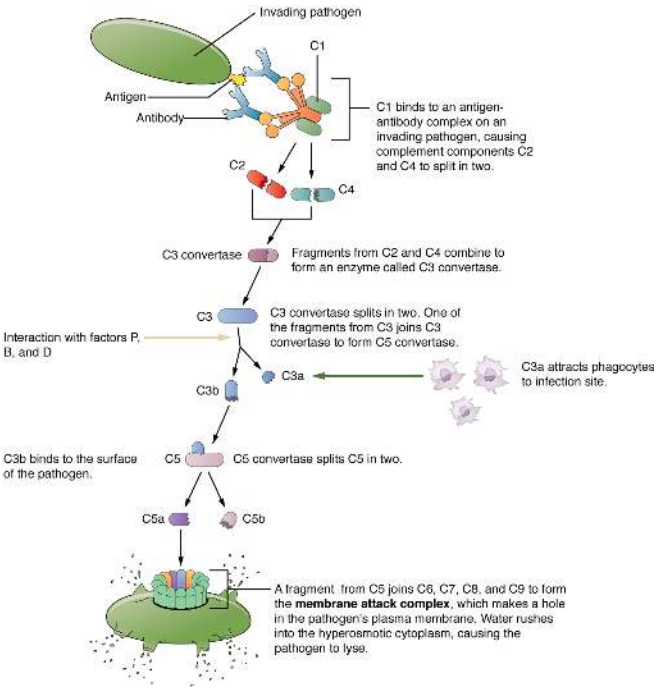


Figure 6.1.3.2: Complement Cascade and Function. The classical pathway, used during adaptive immune responses, occurs when C1 reacts with antibodies that have bound an antigen.

The splitting of the C3 protein is the common step to both pathways. In the alternate pathway, C3 is activated spontaneously and, after reacting with the molecules factor P, factor B, and factor D, splits apart. The larger fragment, C3b, binds to the surface of the pathogen and C3a, the smaller fragment, diffuses outward from the site of activation and attracts phagocytes to the site of infection. Surface-bound C3b then activates the rest of the cascade, with the last five proteins, C5–C9, forming the membrane-attack complex (MAC). The MAC can kill certain pathogens by disrupting their osmotic balance. The MAC is especially effective against a broad range of bacteria. The classical pathway is similar, except the early stages of activation require the presence of antibody bound to antigen, and thus is dependent on the adaptive immune response. The earlier fragments of the cascade also have important functions. Phagocytic cells such as macrophages and neutrophils are attracted to an infection site by chemotactic attraction to smaller complement fragments. Additionally, once they arrive, their receptors for surface-bound C3b opsonize the pathogen for phagocytosis and destruction.

Inflammatory Response

The hallmark of the innate immune response is **inflammation**. Inflammation is something everyone has experienced. Stub a toe, cut a finger, or do any activity that causes tissue damage and inflammation will result, with its four characteristics: heat, redness, pain, and swelling (“loss of function” is sometimes mentioned as a fifth characteristic). It is important to note that inflammation does not have to be initiated by an infection, but can also be caused by tissue injuries. The release of damaged cellular contents into the site of injury is enough to stimulate the response, even in the absence of breaks in physical barriers that would allow pathogens to enter (by hitting your thumb with a hammer, for example). The inflammatory reaction brings in phagocytic cells to the damaged area to clear cellular debris and to set the stage for wound repair (Figure 6.1.3.3).

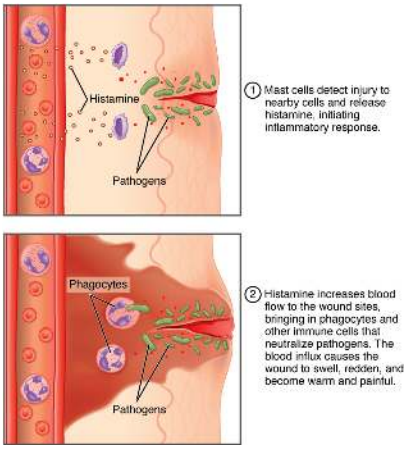


Figure 6.1.3.3.

This reaction also brings in the cells of the innate immune system, allowing them to get rid of the sources of a possible infection. Inflammation is part of a very basic form of immune response. The process not only brings fluid and cells into the site to destroy the pathogen and remove it and debris from the site, but also helps to isolate the site, limiting the spread of the pathogen. **Acute inflammation** is a short-term inflammatory response to an insult to the body. If the cause of the inflammation is not resolved, however, it can lead to chronic inflammation, which is associated with major tissue destruction and fibrosis. **Chronic inflammation** is ongoing inflammation. It can be caused by foreign bodies, persistent pathogens, and autoimmune diseases such as rheumatoid arthritis.

There are four important parts to the inflammatory response:

- *Tissue Injury.* The released contents of injured cells stimulate the release of **mast cell** granules and their potent inflammatory mediators such as histamine, leukotrienes, and prostaglandins. **Histamine** increases the diameter of local blood vessels (vasodilation), causing an increase in blood flow. Histamine also increases the permeability of local capillaries, causing plasma to leak out and form interstitial fluid. This causes the swelling associated with inflammation. Additionally, injured cells, phagocytes, and basophils are sources of inflammatory mediators, including prostaglandins and leukotrienes. Leukotrienes attract neutrophils from the blood by chemotaxis and increase vascular permeability. Prostaglandins cause vasodilation by relaxing vascular smooth muscle and are a major cause of the pain associated with inflammation. Nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen relieve pain by inhibiting prostaglandin production.
- *Vasodilation.* Many inflammatory mediators such as histamine are vasodilators that increase the diameters of local capillaries. This causes increased blood flow and is responsible for the heat and redness of inflamed tissue. It allows greater access of the blood to the site of inflammation.
- *Increased Vascular Permeability.* At the same time, inflammatory mediators increase the permeability of the local vasculature, causing leakage of fluid into the interstitial space, resulting in the swelling, or edema, associated with inflammation.
- *Recruitment of Phagocytes.* Leukotrienes are particularly good at attracting neutrophils from the blood to the site of infection by chemotaxis. Following an early neutrophil infiltrate stimulated by macrophage cytokines, more macrophages are recruited to clean up the debris left over at the site. When local infections are severe, neutrophils are attracted to the sites of infections in large numbers, and as they phagocytose the pathogens and subsequently die, their accumulated cellular remains are visible as pus at the infection site.

Overall, inflammation is valuable for many reasons. Not only are the pathogens killed and debris removed, but the increase in vascular permeability encourages the entry of clotting factors, the first step towards wound repair. Inflammation also facilitates the transport of antigen to lymph nodes by dendritic cells for the development of the adaptive immune response.

Chapter Review

Innate immune responses are critical to the early control of infections. Whereas barrier defenses are the body's first line of physical defense against pathogens, innate immune responses are the first line of physiological defense. Innate responses occur rapidly, but with less specificity and effectiveness than the adaptive immune response. Innate responses can be caused by a variety of cells, mediators, and antibacterial proteins such as complement. Within the first few days of an infection, another series of antibacterial proteins are induced, each with activities against certain bacteria, including opsonization of certain species. Additionally,

interferons are induced that protect cells from viruses in their vicinity. Finally, the innate immune response does not stop when the adaptive immune response is developed. In fact, both can cooperate and one can influence the other in their responses against pathogens.

Interactive Link Questions

Visit this website to learn about phagocyte chemotaxis. Phagocyte chemotaxis is the movement of phagocytes according to the secretion of chemical messengers in the form of interleukins and other chemokines. By what means does a phagocyte destroy a bacterium that it has ingested?

Answer: The bacterium is digested by the phagocyte's digestive enzymes (contained in its lysosomes).

Review Questions

Q. Which of the following signs is *not* characteristic of inflammation?

A. redness

B. pain

C. cold

D. swelling

Answer: C

Q. Which of the following is *not* important in the antiviral innate immune response?

A. interferons

B. natural killer cells

C. complement

D. microphages

Answer: D

Q. Enhanced phagocytosis of a cell by the binding of a specific protein is called _____.

A. endocytosis

B. opsonization

C. anaphylaxis

D. complement activation

Answer: B

Q. Which of the following leads to the redness of inflammation?

A. increased vascular permeability

B. anaphylactic shock

C. increased blood flow

D. complement activation

Answer: C

Critical Thinking Questions

Q. Describe the process of inflammation in an area that has been traumatized, but not infected.

A. The cell debris and damaged cells induce macrophages to begin to clean them up. Macrophages release cytokines that attract neutrophils, followed by more macrophages. Other mediators released by mast cells increase blood flow to the area and also vascular permeability, allowing the recruited cells to get from the blood to the site of infection, where they can phagocytose the dead cells and debris, preparing the site for wound repair.

Q. Describe two early induced responses and what pathogens they affect.

A. Interferons are produced in virally infected cells and cause them to secrete signals for surrounding cells to make antiviral proteins. C-reactive protein is induced to be made by the liver and will opsonize certain species of bacteria.

Glossary

acute inflammation
inflammation occurring for a limited time period; rapidly developing

chemokine
soluble, long-range, cell-to-cell communication molecule

chronic inflammation
inflammation occurring for long periods of time

complement
enzymatic cascade of constitutive blood proteins that have antipathogen effects, including the direct killing of bacteria

cytokine
soluble, short-range, cell-to-cell communication molecule

early induced immune response
includes antimicrobial proteins stimulated during the first several days of an infection

fas ligand
molecule expressed on cytotoxic T cells and NK cells that binds to the fas molecule on a target cell and induces it do undergo apoptosis

granzyme
apoptosis-inducing substance contained in granules of NK cells and cytotoxic T cells

histamine
vasoactive mediator in granules of mast cells and is the primary cause of allergies and anaphylactic shock

inflammation
basic innate immune response characterized by heat, redness, pain, and swelling

interferons
early induced proteins made in virally infected cells that cause nearby cells to make antiviral proteins

macrophage

ameboid phagocyte found in several tissues throughout the body

mast cell
cell found in the skin and the lining of body cells that contains cytoplasmic granules with vasoactive mediators such as histamine

monocyte
precursor to macrophages and dendritic cells seen in the blood

neutrophil
phagocytic white blood cell recruited from the bloodstream to the site of infection via the bloodstream

opsonization
enhancement of phagocytosis by the binding of antibody or antimicrobial protein

pattern recognition receptor (PRR)
leukocyte receptor that binds to specific cell wall components of different bacterial species

perforin
molecule in NK cell and cytotoxic T cell granules that form pores in the membrane of a target cell

phagocytosis
movement of material from the outside to the inside of the cells via vesicles made from invaginations of the plasma membrane

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6.1.4: The Adaptive Immune Response - T Lymphocytes and Their Functional Types

Learning Objectives

- Explain the advantages of the adaptive immune response over the innate immune response
- List the various characteristics of an antigen
- Describe the types of T cell antigen receptors
- Outline the steps of T cell development
- Describe the major T cell types and their functions

Innate immune responses (and early induced responses) are in many cases ineffective at completely controlling pathogen growth. However, they slow pathogen growth and allow time for the adaptive immune response to strengthen and either control or eliminate the pathogen. The innate immune system also sends signals to the cells of the adaptive immune system, guiding them in how to attack the pathogen. Thus, these are the two important arms of the immune response.

The Benefits of the Adaptive Immune Response

The specificity of the adaptive immune response—its ability to specifically recognize and make a response against a wide variety of pathogens—is its great strength. Antigens, the small chemical groups often associated with pathogens, are recognized by receptors on the surface of B and T lymphocytes. The adaptive immune response to these antigens is so versatile that it can respond to nearly any pathogen. This increase in specificity comes because the adaptive immune response has a unique way to develop as many as 10^{11}, or 100 trillion, different receptors to recognize nearly every conceivable pathogen. How could so many different types of antibodies be encoded? And what about the many specificities of T cells? There is not nearly enough DNA in a cell to have a separate gene for each specificity. The mechanism was finally worked out in the 1970s and 1980s using the new tools of molecular genetics

Primary Disease and Immunological Memory

The immune system's first exposure to a pathogen is called a **primary adaptive response**. Symptoms of a first infection, called primary disease, are always relatively severe because it takes time for an initial adaptive immune response to a pathogen to become effective.

Upon re-exposure to the same pathogen, a secondary adaptive immune response is generated, which is stronger and faster that the primary response. The **secondary adaptive response** often eliminates a pathogen before it can cause significant tissue damage or any symptoms. Without symptoms, there is no disease, and the individual is not even aware of the infection. This secondary response is the basis of **immunological memory**, which protects us from getting diseases repeatedly from the same pathogen. By this mechanism, an individual's exposure to pathogens early in life spares the person from these diseases later in life.

Self Recognition

A third important feature of the adaptive immune response is its ability to distinguish between self-antigens, those that are normally present in the body, and foreign antigens, those that might be on a potential pathogen. As T and B cells mature, there are mechanisms in place that prevent them from recognizing self-antigen, preventing a damaging immune response against the body. These mechanisms are not 100 percent effective, however, and their breakdown leads to autoimmune diseases, which will be discussed later in this chapter.

T Cell-Mediated Immune Responses

The primary cells that control the adaptive immune response are the lymphocytes, the T and B cells. T cells are particularly important, as they not only control a multitude of immune responses directly, but also control B cell immune responses in many cases as well. Thus, many of the decisions about how to attack a pathogen are made at the T cell level, and knowledge of their functional types is crucial to understanding the functioning and regulation of adaptive immune responses as a whole.

T lymphocytes recognize antigens based on a two-chain protein receptor. The most common and important of these are the alpha-beta T cell receptors (Figure 6.1.4.1).

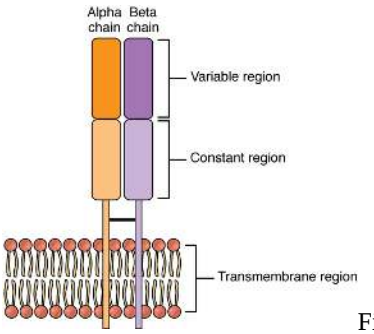


Figure 6.1.4.1: Alpha-beta T Cell Receptor. Notice the constant and variable regions of each chain, anchored by the transmembrane region.

There are two chains in the T cell receptor, and each chain consists of two domains. The **variable region domain** is furthest away from the T cell membrane and is so named because its amino acid sequence varies between receptors. In contrast, the **constant region domain** has less variation. The differences in the amino acid sequences of the variable domains are the molecular basis of the diversity of antigens the receptor can recognize. Thus, the antigen-binding site of the receptor consists of the terminal ends of both receptor chains, and the amino acid sequences of those two areas combine to determine its antigenic specificity. Each T cell produces only one type of receptor and thus is specific for a single particular antigen.

Antigens

Antigens on pathogens are usually large and complex, and consist of many antigenic determinants. An **antigenic determinant** (epitope) is one of the small regions within an antigen to which a receptor can bind, and antigenic determinants are limited by the size of the receptor itself. They usually consist of six or fewer amino acid residues in a protein, or one or two sugar moieties in a carbohydrate antigen. Antigenic determinants on a carbohydrate antigen are usually less diverse than on a protein antigen. Carbohydrate antigens are found on bacterial cell walls and on red blood cells (the ABO blood group antigens). Protein antigens are complex because of the variety of three-dimensional shapes that proteins can assume, and are especially important for the immune responses to viruses and worm parasites. It is the interaction of the shape of the antigen and the complementary shape of the amino acids of the antigen-binding site that accounts for the chemical basis of specificity (Figure 6.1.4.2).

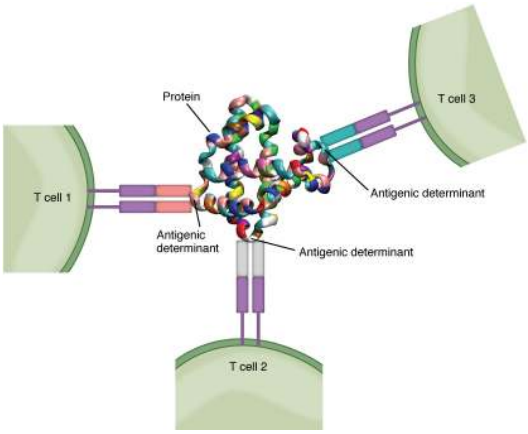


Figure 6.1.4.2: Antigenic Determinants. A typical protein antigen has multiple antigenic determinants, shown by the ability of T cells with three different specificities to bind to different parts of the same antigen.

Antigen Processing and Presentation

Although Figure 6.1.4.2 shows T cell receptors interacting with antigenic determinants directly, the mechanism that T cells use to recognize antigens is, in reality, much more complex. T cells do not recognize free-floating or cell-bound antigens as they appear on the surface of the pathogen. They only recognize antigen on the surface of specialized cells called antigen-presenting cells. Antigens are internalized by these cells. **Antigen processing** is a mechanism that enzymatically cleaves the antigen into smaller pieces. The antigen fragments are then brought to the cell's surface and associated with a specialized type of antigen-presenting protein known as a **major histocompatibility complex (MHC)** molecule. The MHC is the cluster of genes that encode these antigen-presenting molecules. The association of the antigen fragments with an MHC molecule on the surface of a cell is known as

antigen presentation and results in the recognition of antigen by a T cell. This association of antigen and MHC occurs inside the cell, and it is the complex of the two that is brought to the surface. The peptide-binding cleft is a small indentation at the end of the MHC molecule that is furthest away from the cell membrane; it is here that the processed fragment of antigen sits. MHC molecules are capable of presenting a variety of antigens, depending on the amino acid sequence, in their peptide-binding clefts. It is the combination of the MHC molecule and the fragment of the original peptide or carbohydrate that is actually physically recognized by the T cell receptor (Figure 6.1.4.3).

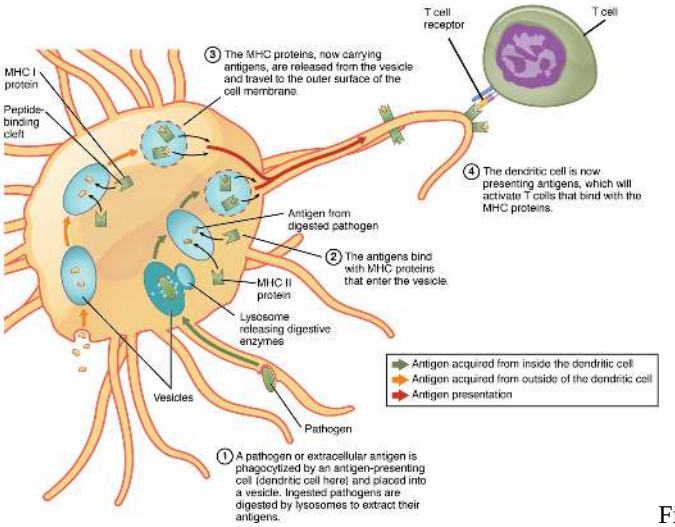


Figure 6.1.4.3: Antigen Processing and Presentation.

Two distinct types of MHC molecules, **MHC class I** and **MHC class II**, play roles in antigen presentation. Although produced from different genes, they both have similar functions. They bring processed antigen to the surface of the cell via a transport vesicle and present the antigen to the T cell and its receptor. Antigens from different classes of pathogens, however, use different MHC classes and take different routes through the cell to get to the surface for presentation. The basic mechanism, though, is the same. Antigens are processed by digestion, are brought into the endomembrane system of the cell, and then are expressed on the surface of the antigen-presenting cell for antigen recognition by a T cell. Intracellular antigens are typical of viruses, which replicate inside the cell, and certain other intracellular parasites and bacteria. These antigens are processed in the cytosol by an enzyme complex known as the proteasome and are then brought into the endoplasmic reticulum by the transporter associated with antigen processing (TAP) system, where they interact with class I MHC molecules and are eventually transported to the cell surface by a transport vesicle.

Extracellular antigens, characteristic of many bacteria, parasites, and fungi that do not replicate inside the cell's cytoplasm, are brought into the endomembrane system of the cell by receptor-mediated endocytosis. The resulting vesicle fuses with vesicles from the Golgi complex, which contain pre-formed MHC class II molecules. After fusion of these two vesicles and the association of antigen and MHC, the new vesicle makes its way to the cell surface.

Professional Antigen-presenting Cells

Many cell types express class I molecules for the presentation of intracellular antigens. These MHC molecules may then stimulate a cytotoxic T cell immune response, eventually destroying the cell and the pathogen within. This is especially important when it comes to the most common class of intracellular pathogens, the virus. Viruses infect nearly every tissue of the body, so all these tissues must necessarily be able to express class I MHC or no T cell response can be made.

On the other hand, class II MHC molecules are expressed only on the cells of the immune system, specifically cells that affect other arms of the immune response. Thus, these cells are called "professional" antigen-presenting cells to distinguish them from those that bear class I MHC. The three types of professional antigen presenters are macrophages, dendritic cells, and B cells (Table).

Macrophages stimulate T cells to release cytokines that enhance phagocytosis. Dendritic cells also kill pathogens by phagocytosis (see Figure 6.1.4.3), but their major function is to bring antigens to regional draining lymph nodes. The lymph nodes are the locations in which most T cell responses against pathogens of the interstitial tissues are mounted. Macrophages are found in the

skin and in the lining of mucosal surfaces, such as the nasopharynx, stomach, lungs, and intestines. B cells may also present antigens to T cells, which are necessary for certain types of antibody responses, to be covered later in this chapter.

Classes of Antigen-presenting Cells			
MHC	Cell type	Phagocytic?	Function
Class I	Many	No	Stimulates cytotoxic T cell immune response
Class II	Macrophage	Yes	Stimulates phagocytosis and presentation at primary infection site
Class II	Dendritic	Yes, in tissues	Brings antigens to regional lymph nodes
Class II	B cell	Yes, internalizes surface Ig and antigen	Stimulates antibody secretion by B cells

T Cell Development and Differentiation

The process of eliminating T cells that might attack the cells of one's own body is referred to as **T cell tolerance**. While thymocytes are in the cortex of the thymus, they are referred to as "double negatives," meaning that they do not bear the CD4 or CD8 molecules that you can use to follow their pathways of differentiation (Figure 6.1.4.4). In the cortex of the thymus, they are exposed to cortical epithelial cells. In a process known as **positive selection**, double-negative thymocytes bind to the MHC molecules they observe on the thymic epithelia, and the MHC molecules of "self" are selected. This mechanism kills many thymocytes during T cell differentiation. In fact, only two percent of the thymocytes that enter the thymus leave it as mature, functional T cells.

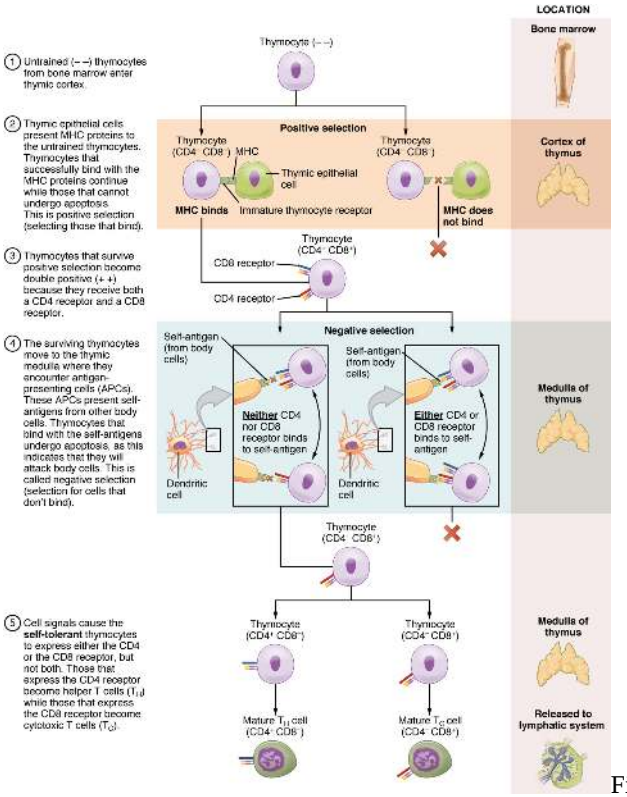


Figure 6.1.4.4: Differentiation of T Cells within the Thymus.

Thymocytes enter the thymus and go through a series of developmental stages that ensures both function and tolerance before they leave and become functional components of the adaptive immune response.

Later, the cells become double positives that express both CD4 and CD8 markers and move from the cortex to the junction between the cortex and medulla. It is here that negative selection takes place. In **negative selection**, self-antigens are brought into the thymus from other parts of the body by professional antigen-presenting cells. The T cells that bind to these self-antigens are selected for negatively and are killed by apoptosis. In summary, the only T cells left are those that can bind to MHC molecules of the body with foreign antigens presented on their binding clefts, preventing an attack on one's own body tissues, at least under normal circumstances. Tolerance can be broken, however, by the development of an autoimmune response, to be discussed later in this chapter.

The cells that leave the thymus become single positives, expressing either CD4 or CD8, but not both (see Figure 6.1.4.4). The $CD4^+$ T cells will bind to class II MHC and the $CD8^+$ cells will bind to class I MHC. The discussion that follows explains the functions of these molecules and how they can be used to differentiate between the different T cell functional types.

Mechanisms of T Cell-mediated Immune Responses

Mature T cells become activated by recognizing processed foreign antigen in association with a self-MHC molecule and begin dividing rapidly by mitosis. This proliferation of T cells is called **clonal expansion** and is necessary to make the immune response strong enough to effectively control a pathogen. How does the body select only those T cells that are needed against a specific pathogen? Again, the specificity of a T cell is based on the amino acid sequence and the three-dimensional shape of the antigen-binding site formed by the variable regions of the two chains of the T cell receptor (Figure 6.1.4.5). **Clonal selection** is the process of antigen binding only to those T cells that have receptors specific to that antigen. Each T cell that is activated has a specific receptor "hard-wired" into its DNA, and all of its progeny will have identical DNA and T cell receptors, forming clones of the original T cell.

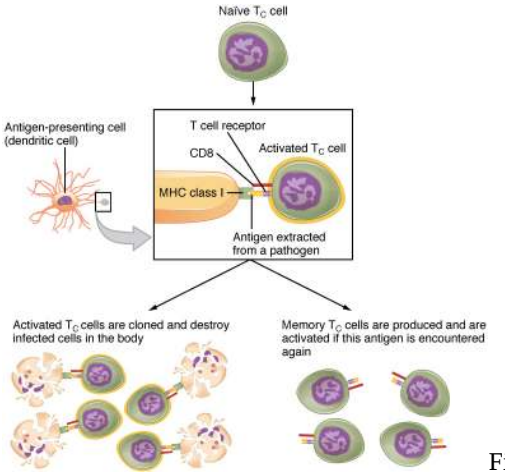


Figure 6.1.4.5: Clonal Selection and Expansion of T Lymphocytes. Stem cells differentiate into T cells with specific receptors, called clones. The clones with receptors specific for antigens on the pathogen are selected for and expanded.

Clonal Selection and Expansion

The clonal selection theory was proposed by Frank Burnet in the 1950s. However, the term clonal selection is not a complete description of the theory, as clonal expansion goes hand in glove with the selection process. The main tenet of the theory is that a typical individual has a multitude (10^{11}) of different types of T cell clones based on their receptors. In this use, a **clone** is a group of lymphocytes that share the same **antigen receptor**. Each clone is necessarily present in the body in low numbers. Otherwise, the body would not have room for lymphocytes with so many specificities.

Only those clones of lymphocytes whose receptors are activated by the antigen are stimulated to proliferate. Keep in mind that most antigens have multiple antigenic determinants, so a T cell response to a typical antigen involves a polyclonal response. A **polyclonal response** is the stimulation of multiple T cell clones. Once activated, the selected clones increase in number and make many copies of each cell type, each clone with its unique receptor. By the time this process is complete, the body will have large numbers of specific lymphocytes available to fight the infection (see Figure 6.1.4.5).

The Cellular Basis of Immunological Memory

As already discussed, one of the major features of an adaptive immune response is the development of immunological memory.

During a primary adaptive immune response, both **memory T cells** and **effector T cells** are generated. Memory T cells are long-lived and can even persist for a lifetime. Memory cells are primed to act rapidly. Thus, any subsequent exposure to the pathogen will elicit a very rapid T cell response. This rapid, secondary adaptive response generates large numbers of effector T cells so fast that the pathogen is often overwhelmed before it can cause any symptoms of disease. This is what is meant by immunity to a disease. The same pattern of primary and secondary immune responses occurs in B cells and the antibody response, as will be discussed later in the chapter.

T Cell Types and their Functions

In the discussion of T cell development, you saw that mature T cells express either the CD4 marker or the CD8 marker, but not both. These markers are cell adhesion molecules that keep the T cell in close contact with the antigen-presenting cell by directly binding to the MHC molecule (to a different part of the molecule than does the antigen). Thus, T cells and antigen-presenting cells are held together in two ways: by CD4 or CD8 attaching to MHC and by the T cell receptor binding to antigen (Figure 6.1.4.6).

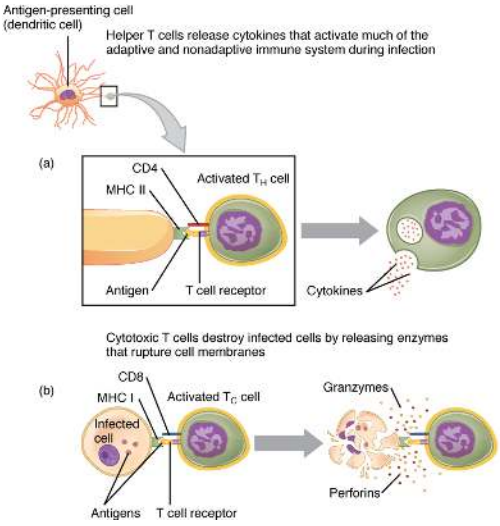


Figure 6.1.4.6: Pathogen Presentation. (a) CD4 is associated with helper and regulatory T cells. An extracellular pathogen is processed and presented in the binding cleft of a class II MHC molecule, and this interaction is strengthened by the CD4 molecule. (b) CD8 is associated with cytotoxic T cells. An intracellular pathogen is presented by a class I MHC molecule, and CD8 interacts with it.

Although the correlation is not 100 percent, CD4-bearing T cells are associated with helper functions and CD8-bearing T cells are associated with cytotoxicity. These functional distinctions based on CD4 and CD8 markers are useful in defining the function of each type.

Helper T Cells and their Cytokines

Helper T cells (Th), bearing the CD4 molecule, function by secreting cytokines that act to enhance other immune responses. There are two classes of Th cells, and they act on different components of the immune response. These cells are not distinguished by their surface molecules but by the characteristic set of cytokines they secrete (Table).

Th1 cells are a type of helper T cell that secretes cytokines that regulate the immunological activity and development of a variety of cells, including macrophages and other types of T cells.

Th2 cells, on the other hand, are cytokine-secreting cells that act on B cells to drive their differentiation into plasma cells that make antibody. In fact, T cell help is required for antibody responses to most protein antigens, and these are called T cell-dependent antigens.

Cytotoxic T cells

Cytotoxic T cells (Tc) are T cells that kill target cells by inducing apoptosis using the same mechanism as NK cells. They either express Fas ligand, which binds to the fas molecule on the target cell, or act by using perforins and granzymes contained in their

cytoplasmic granules. As was discussed earlier with NK cells, killing a virally infected cell before the virus can complete its replication cycle results in the production of no infectious particles. As more Tc cells are developed during an immune response, they overwhelm the ability of the virus to cause disease. In addition, each Tc cell can kill more than one target cell, making them especially effective. Tc cells are so important in the antiviral immune response that some speculate that this was the main reason the adaptive immune response evolved in the first place.

Regulatory T Cells

Regulatory T cells (Treg), or suppressor T cells, are the most recently discovered of the types listed here, so less is understood about them. In addition to CD4, they bear the molecules CD25 and FOXP3. Exactly how they function is still under investigation, but it is known that they suppress other T cell immune responses. This is an important feature of the immune response, because if clonal expansion during immune responses were allowed to continue uncontrolled, these responses could lead to autoimmune diseases and other medical issues.

Not only do T cells directly destroy pathogens, but they regulate nearly all other types of the adaptive immune response as well, as evidenced by the functions of the T cell types, their surface markers, the cells they work on, and the types of pathogens they work against (see Table).

Functions of T Cell Types and Their Cytokines

T cell	Main target	Function	Pathogen	Surface marker	MHC	Cytokines or mediators
Tc	Infected cells	Cytotoxicity	Intracellular	CD8	Class I	Perforins, granzymes, and fas ligand
Th1	Macrophage	Helper inducer	Extracellular	CD4	Class II	Interferon-γ and TGF-β
Th2	B cell	Helper inducer	Extracellular	CD4	Class II	IL-4, IL-6, IL-10, and others
Treg	Th cell	Suppressor	None	CD4, CD25	?	TGF-β and IL-10

Chapter Review

T cells recognize antigens with their antigen receptor, a complex of two protein chains on their surface. They do not recognize self-antigens, however, but only processed antigen presented on their surfaces in a binding groove of a major histocompatibility complex molecule. T cells develop in the thymus, where they learn to use self-MHC molecules to recognize only foreign antigens, thus making them tolerant to self-antigens. There are several functional types of T lymphocytes, the major ones being helper, regulatory, and cytotoxic T cells.

Review Chapter

Q. T cells that secrete cytokines that help antibody responses are called _____.

A. Th1

B. Th2

C. regulatory T cells

D. thymocytes

Answer: B

Q. The taking in of antigen and digesting it for later presentation is called _____.

A. antigen presentation

B. antigen processing

C. endocytosis

D. exocytosis

Answer: B

Q. Why is clonal expansion so important?

A. to select for specific cells

B. to secrete cytokines

C. to kill target cells

D. to increase the numbers of specific cells

Answer: D

Q. The elimination of self-reactive thymocytes is called _____.

A. positive selection.

B. negative selection.

C. tolerance.

D. clonal selection.

Answer: B

Q. Which type of T cell is most effective against viruses?

A. Th1

B. Th2

C. cytotoxic T cells

D. regulatory T cells

Answer: C

Critical Thinking Questions

Q. Describe the processing and presentation of an intracellular antigen.

A. The antigen is digested by the proteasome, brought into the endoplasmic reticulum by the TAP transporter system, where it binds to class I MHC molecules. These are taken to the cell surface by transport vesicles.

Q. Describe clonal selection and expansion.

A. Antigen-specific clones are stimulated as their antigen receptor binds to antigen. They are then activated and proliferate, expanding their numbers. The result is a large number of antigen-specific lymphocytes.

Glossary

antigenic determinant

(also, epitope) one of the chemical groups recognized by a single type of lymphocyte antigen receptor

antigen presentation

binding of processed antigen to the protein-binding cleft of a major histocompatibility complex molecule

antigen processing
internalization and digestion of antigen in an antigen-presenting cell

antigen receptor
two-chain receptor by which lymphocytes recognize antigen

clone
group of lymphocytes sharing the same antigen receptor

clonal expansion
growth of a clone of selected lymphocytes

clonal selection
stimulating growth of lymphocytes that have specific receptors

constant region domain
part of a lymphocyte antigen receptor that does not vary much between different receptor types

cytotoxic T cells (Tc)
T lymphocytes with the ability to induce apoptosis in target cells

effector T cells
immune cells with a direct, adverse effect on a pathogen

helper T cells (Th)
T cells that secrete cytokines to enhance other immune responses, involved in activation of both B and T cell lymphocytes

immunological memory
ability of the adaptive immune response to mount a stronger and faster immune response upon re-exposure to a pathogen

major histocompatibility complex (MHC)
gene cluster whose proteins present antigens to T cells

memory T cells
long-lived immune cell reserved for future exposure to an pathogen

MHC class I
found on most cells of the body, it binds to the CD8 molecule on T cells

MHC class II
found on macrophages, dendritic cells, and B cells, it binds to CD4 molecules on T cells

negative selection
selection against thymocytes in the thymus that react with self-antigen

polyclonal response
response by multiple clones to a complex antigen with many determinants

primary adaptive response
immune system’s response to the first exposure to a pathogen

positive selection

selection of thymocytes within the thymus that interact with self, but not non-self, MHC molecules

regulatory T cells (Treg)
(also, suppressor T cells) class of CD4 T cells that regulates other T cell responses

secondary adaptive response
immune response observed upon re-exposure to a pathogen, which is stronger and faster than a primary response

T cell tolerance
process during T cell differentiation where most T cells that recognize antigens from one's own body are destroyed

Th1 cells
cells that secrete cytokines that enhance the activity of macrophages and other cells

Th2 cells
cells that secrete cytokines that induce B cells to differentiate into antibody-secreting plasma cells

variable region domain
part of a lymphocyte antigen receptor that varies considerably between different receptor types

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6.1.5: The Adaptive Immune Response - B Lymphocytes and Antibodies

Learning Objectives

- Explain how B cells mature and how B cell tolerance develops
- Discuss how B cells are activated and differentiate into plasma cells
- Describe the structure of the antibody classes and their functions

Antibodies were the first component of the adaptive immune response to be characterized by scientists working on the immune system. It was already known that individuals who survived a bacterial infection were immune to re-infection with the same pathogen. Early microbiologists took serum from an immune patient and mixed it with a fresh culture of the same type of bacteria, then observed the bacteria under a microscope. The bacteria became clumped in a process called agglutination. When a different bacterial species was used, the agglutination did not happen. Thus, there was something in the serum of immune individuals that could specifically bind to and agglutinate bacteria.

Scientists now know the cause of the agglutination is an antibody molecule, also called an **immunoglobulin**. What is an antibody? An antibody protein is essentially a secreted form of a B cell receptor. (In fact, surface immunoglobulin is another name for the B cell receptor.) Not surprisingly, the same genes encode both the secreted antibodies and the surface immunoglobulins. One minor difference in the way these proteins are synthesized distinguishes a naïve B cell with antibody on its surface from an antibody-secreting plasma cell with no antibodies on its surface. The antibodies of the plasma cell have the exact same antigen-binding site and specificity as their B cell precursors.

There are five different classes of antibody found in humans: IgM, IgD, IgG, IgA, and IgE. Each of these has specific functions in the immune response, so by learning about them, researchers can learn about the great variety of antibody functions critical to many adaptive immune responses.

B cells do not recognize antigen in the complex fashion of T cells. B cells can recognize native, unprocessed antigen and do not require the participation of MHC molecules and antigen-presenting cells.

B Cell Differentiation and Activation

B cells differentiate in the bone marrow. During the process of maturation, up to 100 trillion different clones of B cells are generated, which is similar to the diversity of antigen receptors seen in T cells.

B cell differentiation and the development of tolerance are not quite as well understood as it is in T cells. **Central tolerance** is the destruction or inactivation of B cells that recognize self-antigens in the bone marrow, and its role is critical and well established. In the process of **clonal deletion**, immature B cells that bind strongly to self-antigens expressed on tissues are signaled to commit suicide by apoptosis, removing them from the population. In the process of **clonal anergy**, however, B cells exposed to soluble antigen in the bone marrow are not physically deleted, but become unable to function.

Another mechanism called peripheral tolerance is a direct result of T cell tolerance. In **peripheral tolerance**, functional, mature B cells leave the bone marrow but have yet to be exposed to self-antigen. Most protein antigens require signals from helper T cells (Th2) to proceed to make antibody. When a B cell binds to a self-antigen but receives no signals from a nearby Th2 cell to produce antibody, the cell is signaled to undergo apoptosis and is destroyed. This is yet another example of the control that T cells have over the adaptive immune response.

After B cells are activated by their binding to antigen, they differentiate into plasma cells. Plasma cells often leave the secondary lymphoid organs, where the response is generated, and migrate back to the bone marrow, where the whole differentiation process started. After secreting antibodies for a specific period, they die, as most of their energy is devoted to making antibodies and not to maintaining themselves. Thus, plasma cells are said to be terminally differentiated.

The final B cell of interest is the memory B cell, which results from the clonal expansion of an activated B cell. Memory B cells function in a way similar to memory T cells. They lead to a stronger and faster secondary response when compared to the primary response, as illustrated below.

Antibody Structure

Antibodies are glycoproteins consisting of two types of polypeptide chains with attached carbohydrates. The **heavy chain** and the **light chain** are the two polypeptides that form the antibody. The main differences between the classes of antibodies are in the differences between their heavy chains, but as you shall see, the light chains have an important role, forming part of the antigen-binding site on the antibody molecules.

Four-chain Models of Antibody Structures

All antibody molecules have two identical heavy chains and two identical light chains. (Some antibodies contain multiple units of this four-chain structure.) The **Fc region** of the antibody is formed by the two heavy chains coming together, usually linked by disulfide bonds (Figure 6.1.5.1). The Fc portion of the antibody is important in that many effector cells of the immune system have Fc receptors. Cells having these receptors can then bind to antibody-coated pathogens, greatly increasing the specificity of the effector cells. At the other end of the molecule are two identical antigen-binding sites.

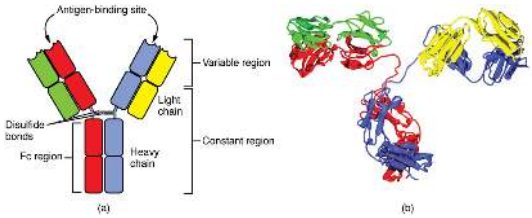


Figure 6.1.5.1: Antibody and IgG2 Structures. The typical four chain structure of a generic antibody (a) and the corresponding three-dimensional structure of the antibody IgG2 (b). (credit b: modification of work by Tim Vickers)

Five Classes of Antibodies and their Functions

In general, antibodies have two basic functions. They can act as the B cell antigen receptor or they can be secreted, circulate, and bind to a pathogen, often labeling it for identification by other forms of the immune response. Of the five antibody classes, notice that only two can function as the antigen receptor for naïve B cells: IgM and **IgD** (Figure 6.1.5.2). Mature B cells that leave the bone marrow express both IgM and IgD, but both antibodies have the same antigen specificity. Only IgM is secreted, however, and no other nonreceptor function for IgD has been discovered.

The Five Immunoglobulin (Ig) Classes

	IgM pentamer	IgG monomer	Secretory IgA dimer	IgE monomer	IgD monomer
			Secretory component		
Heavy chains	μ	γ	α	ε	δ
Number of antigen binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000
Percentage of total antibody in serum	6%	80%	13%	0.002%	1%
Crosses placenta	no	yes	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to		phagocytes		mast cells and basophils	
Function	Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor	Main blood antibody of secondary responses, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva, colostrum	Antibody of allergy and antiparasitic activity	B cell receptor

Figure 6.1.5.2: Five Classes of Antibodies.

IgM consists of five four-chain structures (20 total chains with 10 identical antigen-binding sites) and is thus the largest of the antibody molecules. IgM is usually the first antibody made during a primary response. Its 10 antigen-binding sites and large shape allow it to bind well to many bacterial surfaces. It is excellent at binding complement proteins and activating the complement cascade, consistent with its role in promoting chemotaxis, opsonization, and cell lysis. Thus, it is a very effective antibody against bacteria at early stages of a primary antibody response. As the primary response proceeds, the antibody produced in a B cell can change to IgG, IgA, or IgE by the process known as class switching. **Class switching** is the change of one antibody class to another. While the class of antibody changes, the specificity and the antigen-binding sites do not. Thus, the antibodies made are still specific to the pathogen that stimulated the initial IgM response.

IgG is a major antibody of late primary responses and the main antibody of secondary responses in the blood. This is because class switching occurs during primary responses. IgG is a monomeric antibody that clears pathogens from the blood and can activate complement proteins (although not as well as IgM), taking advantage of its antibacterial activities. Furthermore, this class of antibody is the one that crosses the placenta to protect the developing fetus from disease exits the blood to the interstitial fluid to fight extracellular pathogens.

IgA exists in two forms, a four-chain monomer in the blood and an eight-chain structure, or dimer, in exocrine gland secretions of the mucous membranes, including mucus, saliva, and tears. Thus, dimeric IgA is the only antibody to leave the interior of the body to protect body surfaces. IgA is also of importance to newborns, because this antibody is present in mother's breast milk (colostrum), which serves to protect the infant from disease.

IgE is usually associated with allergies and anaphylaxis. It is present in the lowest concentration in the blood, because its Fc region binds strongly to an IgE-specific Fc receptor on the surfaces of mast cells. IgE makes mast cell degranulation very specific, such that if a person is allergic to peanuts, there will be peanut-specific IgE bound to his or her mast cells. In this person, eating peanuts will cause the mast cells to degranulate, sometimes causing severe allergic reactions, including anaphylaxis, a severe, systemic allergic response that can cause death.

Clonal Selection of B Cells

Clonal selection and expansion work much the same way in B cells as in T cells. Only B cells with appropriate antigen specificity are selected for and expanded (Figure 6.1.5.3). Eventually, the plasma cells secrete antibodies with antigenic specificity identical to those that were on the surfaces of the selected B cells. Notice in the figure that both plasma cells and memory B cells are generated simultaneously.

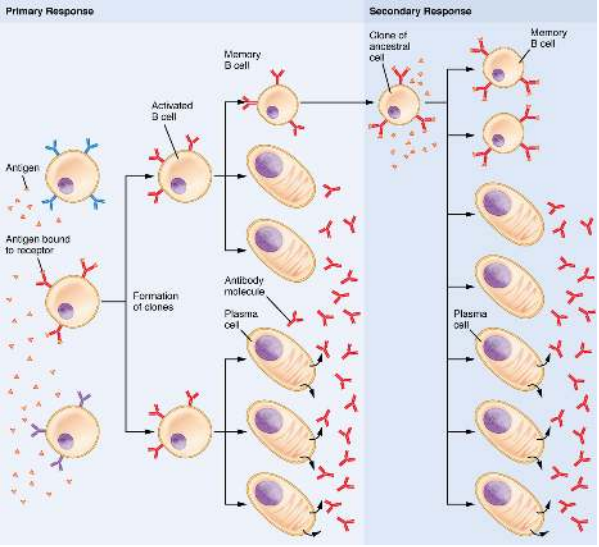


Figure 6.1.5.3: Clonal Selection of B Cells. During a primary B cell immune response, both antibody-secreting plasma cells and memory B cells are produced. These memory cells lead to the differentiation of more plasma cells and memory B cells during secondary responses.

Primary versus Secondary B Cell Responses

Primary and secondary responses as they relate to T cells were discussed earlier. This section will look at these responses with B cells and antibody production. Because antibodies are easily obtained from blood samples, they are easy to follow and graph (Figure 6.1.5.4). As you will see from the figure, the primary response to an antigen (representing a pathogen) is delayed by several days. This is the time it takes for the B cell clones to expand and differentiate into plasma cells. The level of antibody produced is low, but it is sufficient for immune protection. The second time a person encounters the same antigen, there is no time delay, and the amount of antibody made is much higher. Thus, the secondary antibody response overwhelms the pathogens quickly and, in most situations, no symptoms are felt. When a different antigen is used, another primary response is made with its low antibody levels and time delay.

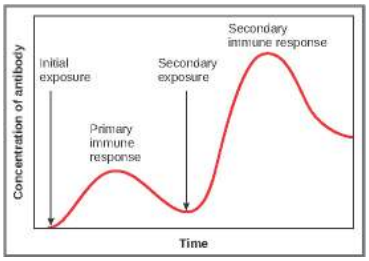


Figure 6.1.5.4: Primary and Secondary Antibody Responses. Antigen A is given once to generate a primary response and later to generate a secondary response. When a different antigen is given for the first time, a new primary response is made.

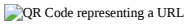
Active versus Passive Immunity

Immunity to pathogens, and the ability to control pathogen growth so that damage to the tissues of the body is limited, can be acquired by (1) the active development of an immune response in the infected individual or (2) the passive transfer of immune components from an immune individual to a nonimmune one. Both active and passive immunity have examples in the natural world and as part of medicine.

Active immunity is the resistance to pathogens acquired during an adaptive immune response within an individual (Table). Naturally acquired active immunity, the response to a pathogen, is the focus of this chapter. Artificially acquired active immunity involves the use of vaccines. A vaccine is a killed or weakened pathogen or its components that, when administered to a healthy individual, leads to the development of immunological memory (a weakened primary immune response) without causing much in the way of symptoms. Thus, with the use of vaccines, one can avoid the damage from disease that results from the first exposure to the pathogen, yet reap the benefits of protection from immunological memory. The advent of vaccines was one of the major medical advances of the twentieth century and led to the eradication of smallpox and the control of many infectious diseases, including polio, measles, and whooping cough.

Active versus Passive Immunity		
	Natural	Artificial
Active	Adaptive immune response	Vaccine response
Passive	Trans-placental antibodies/breastfeeding	Immune globulin injections

Passive immunity arises from the transfer of antibodies to an individual without requiring them to mount their own active immune response. Naturally acquired passive immunity is seen during fetal development. IgG is transferred from the maternal circulation to the fetus via the placenta, protecting the fetus from infection and protecting the newborn for the first few months of its life. As already stated, a newborn benefits from the IgA antibodies it obtains from milk during breastfeeding. The fetus and newborn thus benefit from the immunological memory of the mother to the pathogens to which she has been exposed. In medicine, artificially acquired passive immunity usually involves injections of immunoglobulins, taken from animals previously exposed to a specific pathogen. This treatment is a fast-acting method of temporarily protecting an individual who was possibly exposed to a pathogen. The downside to both types of passive immunity is the lack of the development of immunological memory. Once the antibodies are transferred, they are effective for only a limited time before they degrade.



Immunity can be acquired in an active or passive way, and it can be natural or artificial. Watch this video to see an animated discussion of passive and active immunity. What is an example of natural immunity acquired passively?

T cell-dependent versus T cell-independent Antigens

As discussed previously, Th2 cells secrete cytokines that drive the production of antibodies in a B cell, responding to complex antigens such as those made by proteins. On the other hand, some antigens are T cell independent. A **T cell-independent antigen** usually is in the form of repeated carbohydrate moieties found on the cell walls of bacteria. Each antibody on the B cell surface has two binding sites, and the repeated nature of T cell-independent antigen leads to crosslinking of the surface antibodies on the B cell. The crosslinking is enough to activate it in the absence of T cell cytokines.

A **T cell-dependent antigen**, on the other hand, usually is not repeated to the same degree on the pathogen and thus does not crosslink surface antibody with the same efficiency. To elicit a response to such antigens, the B and T cells must come close together (Figure 6.1.5.5). The B cell must receive two signals to become activated. Its surface immunoglobulin must recognize native antigen. Some of this antigen is internalized, processed, and presented to the Th2 cells on a class II MHC molecule. The T cell then binds using its antigen receptor and is activated to secrete cytokines that diffuse to the B cell, finally activating it completely. Thus, the B cell receives signals from both its surface antibody and the T cell via its cytokines, and acts as a professional antigen-presenting cell in the process.

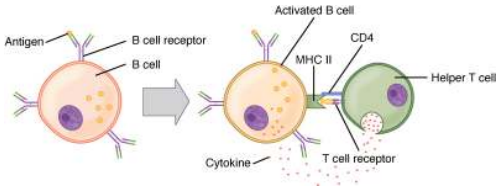


Figure 6.1.5.5: T and B Cell Binding. To elicit a response to a T cell-dependent antigen, the B and T cells must come close together. To become fully activated, the B cell must receive two signals from the native antigen and the T cell's cytokines.

Chapter Review

B cells, which develop within the bone marrow, are responsible for making five different classes of antibodies, each with its own functions. B cells have their own mechanisms for tolerance, but in peripheral tolerance, the B cells that leave the bone marrow remain inactive due to T cell tolerance. Some B cells do not need T cell cytokines to make antibody, and they bypass this need by the crosslinking of their surface immunoglobulin by repeated carbohydrate residues found in the cell walls of many bacterial species. Others require T cells to become activated.

Interactive Link Questions

Immunity can be acquired in an active or passive way, and it can be natural or artificial. Watch this video to see an animated discussion of passive and active immunity. What is an example of natural immunity acquired passively?

Answer: Breastfeeding is an example of natural immunity acquired passively.

Review Chapter

Q. Removing functionality from a B cell without killing it is called _____.

A. clonal selection

B. clonal expansion

C. clonal deletion

D. clonal anergy

Answer: D

Q. Which class of antibody crosses the placenta in pregnant women?

A. IgM

B. IgA

C. IgE

D. IgG

Answer: D

Q. Which class of antibody has no known function other than as an antigen receptor?

A. IgM

B. IgA

C. IgE

D. IgD

Answer: D

Q. When does class switching occur?

A. primary response

B. secondary response

C. tolerance

D. memory response

Answer: A

Q. Which class of antibody is found in mucus?

A. IgM

B. IgA

C. IgE

D. IgD

Answer: B

Critical Thinking Questions

Q. Describe how secondary B cell responses are developed.

A. B cells activated during a primary response differentiate either into terminally differentiated plasma cells or into memory B cells. These memory B cells are what respond during a secondary or memory antibody response.

Q. Describe the role of IgM in immunity.

A. IgM is an antigen receptor on naïve B cells. Upon activation, naïve B cells make IgM first. IgM is good at binding complement and thus has good antibacterial effects. IgM is replaced with other classes of antibodies later on in the primary response due to class switching.

Glossary

active immunity
immunity developed from an individual's own immune system

central tolerance
B cell tolerance induced in immature B cells of the bone marrow

class switching
ability of B cells to change the class of antibody they produce without altering the specificity for antigen

clonal anergy
process whereby B cells that react to soluble antigens in bone marrow are made nonfunctional

clonal deletion
removal of self-reactive B cells by inducing apoptosis

Fc region
in an antibody molecule, the site where the two termini of the heavy chains come together; many cells have receptors for this portion of the antibody, adding functionality to these molecules

heavy chain
larger protein chain of an antibody

IgA
antibody whose dimer is secreted by exocrine glands, is especially effective against digestive and respiratory pathogens, and can pass immunity to an infant through breastfeeding

IgD
class of antibody whose only known function is as a receptor on naive B cells; important in B cell activation

IgE
antibody that binds to mast cells and causes antigen-specific degranulation during an allergic response

IgG
main blood antibody of late primary and early secondary responses; passed from mother to unborn child via placenta

IgM
antibody whose monomer is a surface receptor of naive B cells; the pentamer is the first antibody made blood plasma during primary responses

immunoglobulin
protein antibody; occurs as one of five main classes

light chain
small protein chain of an antibody

passive immunity
transfer of immunity to a pathogen to an individual that lacks immunity to this pathogen usually by the injection of antibodies

peripheral tolerance
mature B cell made tolerant by lack of T cell help

T cell-dependent antigen
antigen that binds to B cells, which requires signals from T cells to make antibody

T cell-independent antigen
binds to B cells, which do not require signals from T cells to make antibody

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6.1.6: The Immune Response Against Pathogens

Learning Objectives

- Explain the development of immunological competence
- Describe the mucosal immune response
- Discuss immune responses against bacterial, viral, fungal, and animal pathogens
- Describe different ways pathogens evade immune responses

Now that you understand the development of mature, naïve B cells and T cells, and some of their major functions, how do all of these various cells, proteins, and cytokines come together to actually resolve an infection? Ideally, the immune response will rid the body of a pathogen entirely. The adaptive immune response, with its rapid clonal expansion, is well suited to this purpose. Think of a primary infection as a race between the pathogen and the immune system. The pathogen bypasses barrier defenses and starts multiplying in the host's body. During the first 4 to 5 days, the innate immune response will partially control, but not stop, pathogen growth. As the adaptive immune response gears up, however, it will begin to clear the pathogen from the body, while at the same time becoming stronger and stronger. When following antibody responses in patients with a particular disease such as a virus, this clearance is referred to as seroconversion (sero- = "serum"). **Seroconversion** is the reciprocal relationship between virus levels in the blood and antibody levels. As the antibody levels rise, the virus levels decline, and this is a sign that the immune response is being at least partially effective (partially, because in many diseases, seroconversion does not necessarily mean a patient is getting well).

An excellent example of this is seroconversion during HIV disease (Figure 6.1.6.1). Notice that antibodies are made early in this disease, and the increase in anti-HIV antibodies correlates with a decrease in detectable virus in the blood. Although these antibodies are an important marker for diagnosing the disease, they are not sufficient to completely clear the virus. Several years later, the vast majority of these individuals, if untreated, will lose their entire adaptive immune response, including the ability to make antibodies, during the final stages of AIDS.

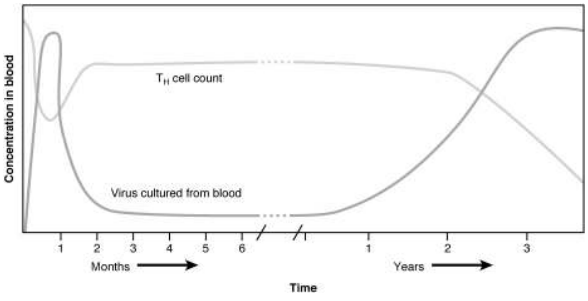


Figure 6.1.6.1: HIV Disease Progression. Seroconversion, the rise of anti-HIV antibody levels and the concomitant decline in measurable virus levels, happens during the first several months of HIV disease. Unfortunately, this antibody response is ineffective at controlling the disease, as seen by the progression of the disease towards AIDS, in which all adaptive immune responses are compromised.

EVERYDAY CONNECTION

Disinfectants: Fighting the Good Fight?

"Wash your hands!" Parents have been telling their children this for generations. Dirty hands can spread disease. But is it possible to get rid of enough pathogens that children will never get sick? Are children who avoid exposure to pathogens better off? The answers to both these questions appears to be no.

Antibacterial wipes, soaps, gels, and even toys with antibacterial substances embedded in their plastic are ubiquitous in our society. Still, these products do not rid the skin and gastrointestinal tract of bacteria, and it would be harmful to our health if they did. We need these nonpathogenic bacteria on and within our bodies to keep the pathogenic ones from growing. The urge to keep children perfectly clean is thus probably misguided. Children will get sick anyway, and the later benefits of immunological memory far outweigh the minor discomforts of most childhood diseases. In fact, getting diseases such as chickenpox or measles later in life is much harder on the adult and are associated with symptoms significantly worse than

those seen in the childhood illnesses. Of course, vaccinations help children avoid some illnesses, but there are so many pathogens, we will never be immune to them all.

Could over-cleanliness be the reason that allergies are increasing in more developed countries? Some scientists think so. Allergies are based on an IgE antibody response. Many scientists think the system evolved to help the body rid itself of worm parasites. The hygiene theory is the idea that the immune system is geared to respond to antigens, and if pathogens are not present, it will respond instead to inappropriate antigens such as allergens and self-antigens. This is one explanation for the rising incidence of allergies in developed countries, where the response to nonpathogens like pollen, shrimp, and cat dander cause allergic responses while not serving any protective function.

The Mucosal Immune Response

Mucosal tissues are major barriers to the entry of pathogens into the body. The IgA (and sometimes IgM) antibodies in mucus and other secretions can bind to the pathogen, and in the cases of many viruses and bacteria, neutralize them. **Neutralization** is the process of coating a pathogen with antibodies, making it physically impossible for the pathogen to bind to receptors. Neutralization, which occurs in the blood, lymph, and other body fluids and secretions, protects the body constantly. Neutralizing antibodies are the basis for the disease protection offered by vaccines. Vaccinations for diseases that commonly enter the body via mucous membranes, such as influenza, are usually formulated to enhance IgA production.

Immune responses in some mucosal tissues such as the Peyer's patches (see [link]) in the small intestine take up particulate antigens by specialized cells known as microfold or M cells (Figure 6.1.6.2). These cells allow the body to sample potential pathogens from the intestinal lumen. Dendritic cells then take the antigen to the regional lymph nodes, where an immune response is mounted.

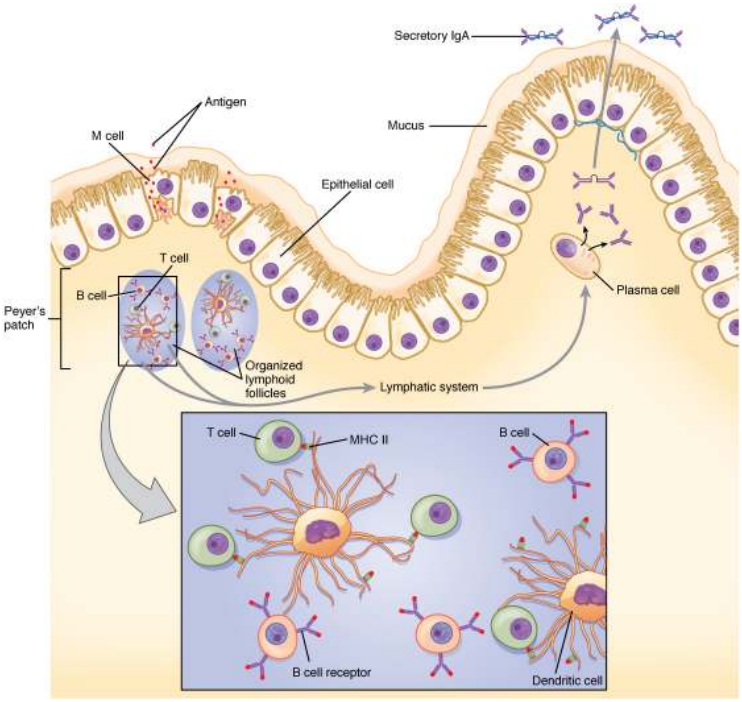


Figure 6.1.6.2: IgA Immunity. The nasal-associated lymphoid tissue and Peyer's patches of the small intestine generate IgA immunity. Both use M cells to transport antigen inside the body so that immune responses can be mounted.

Defenses against Bacteria and Fungi

The body fights bacterial pathogens with a wide variety of immunological mechanisms, essentially trying to find one that is effective. Bacteria such as *Mycobacterium leprae*, the cause of leprosy, are resistant to lysosomal enzymes and can persist in macrophage organelles or escape into the cytosol. In such situations, infected macrophages receiving cytokine signals from Th1 cells turn on special metabolic pathways. **Macrophage oxidative metabolism** is hostile to intracellular bacteria, often relying on the production of nitric oxide to kill the bacteria inside the macrophage.

Fungal infections, such as those from *Aspergillus*, *Candida*, and *Pneumocystis*, are largely opportunistic infections that take advantage of suppressed immune responses. Most of the same immune mechanisms effective against bacteria have similar effects on fungi, both of which have characteristic cell wall structures that protect their cells.

Defenses against Parasites

Worm parasites such as helminths are seen as the primary reason why the mucosal immune response, IgE-mediated allergy and asthma, and eosinophils evolved. These parasites were at one time very common in human society. When infecting a human, often via contaminated food, some worms take up residence in the gastrointestinal tract. Eosinophils are attracted to the site by T cell cytokines, which release their granule contents upon their arrival. Mast cell degranulation also occurs, and the fluid leakage caused by the increase in local vascular permeability is thought to have a flushing action on the parasite, expelling its larvae from the body. Furthermore, if IgE labels the parasite, the eosinophils can bind to it by its Fc receptor.

Defenses against Viruses

The primary mechanisms against viruses are NK cells, interferons, and cytotoxic T cells. Antibodies are effective against viruses mostly during protection, where an immune individual can neutralize them based on a previous exposure. Antibodies have no effect on viruses or other intracellular pathogens once they enter the cell, since antibodies are not able to penetrate the plasma membrane of the cell. Many cells respond to viral infections by downregulating their expression of MHC class I molecules. This is to the advantage of the virus, because without class I expression, cytotoxic T cells have no activity. NK cells, however, can recognize virally infected class I-negative cells and destroy them. Thus, NK and cytotoxic T cells have complementary activities against virally infected cells.

Interferons have activity in slowing viral replication and are used in the treatment of certain viral diseases, such as hepatitis B and C, but their ability to eliminate the virus completely is limited. The cytotoxic T cell response, though, is key, as it eventually overwhelms the virus and kills infected cells before the virus can complete its replicative cycle. Clonal expansion and the ability of cytotoxic T cells to kill more than one target cell make these cells especially effective against viruses. In fact, without cytotoxic T cells, it is likely that humans would all die at some point from a viral infection (if no vaccine were available).

Evasion of the Immune System by Pathogens

It is important to keep in mind that although the immune system has evolved to be able to control many pathogens, pathogens themselves have evolved ways to evade the immune response. An example already mentioned is in *Mycobactrium tuberculosis*, which has evolved a complex cell wall that is resistant to the digestive enzymes of the macrophages that ingest them, and thus persists in the host, causing the chronic disease tuberculosis. This section briefly summarizes other ways in which pathogens can "outwit" immune responses. But keep in mind, although it seems as if pathogens have a will of their own, they do not. All of these evasive "strategies" arose strictly by evolution, driven by selection.

Bacteria sometimes evade immune responses because they exist in multiple strains, such as different groups of *Staphylococcus aureus*. *S. aureus* is commonly found in minor skin infections, such as boils, and some healthy people harbor it in their nose. One small group of strains of this bacterium, however, called methicillin-resistant *Staphylococcus aureus*, has become resistant to multiple antibiotics and is essentially untreatable. Different bacterial strains differ in the antigens on their surfaces. The immune response against one strain (antigen) does not affect the other; thus, the species survives.

Another method of immune evasion is mutation. Because viruses' surface molecules mutate continuously, viruses like influenza change enough each year that the flu vaccine for one year may not protect against the flu common to the next. New vaccine formulations must be derived for each flu season.

Genetic recombination—the combining of gene segments from two different pathogens—is an efficient form of immune evasion. For example, the influenza virus contains gene segments that can recombine when two different viruses infect the same cell. Recombination between human and pig influenza viruses led to the 2010 H1N1 swine flu outbreak.

Pathogens can produce immunosuppressive molecules that impair immune function, and there are several different types. Viruses are especially good at evading the immune response in this way, and many types of viruses have been shown to suppress the host immune response in ways much more subtle than the wholesale destruction caused by HIV.

Chapter Review

Early childhood is a time when the body develops much of its immunological memory that protects it from diseases in adulthood. The components of the immune response that have the maximum effectiveness against a pathogen are often associated with the class of pathogen involved. Bacteria and fungi are especially susceptible to damage by complement proteins, whereas viruses are taken care of by interferons and cytotoxic T cells. Worms are attacked by eosinophils. Pathogens have shown the ability, however, to evade the body's immune responses, some leading to chronic infections or even death. The immune system and pathogens are in a slow, evolutionary race to see who stays on top. Modern medicine, hopefully, will keep the results skewed in humans' favor.

Review Questions

Q. Which enzymes in macrophages are important for clearing intracellular bacteria?

A. metabolic

B. mitochondrial

C. nuclear

D. lysosomal

Answer: D

Q. What type of chronic lung disease is caused by a *Mycobacterium*?

A. asthma

B. emphysema

C. tuberculosis

D. leprosy

Answer: C

Q. Which type of immune response is most *directly* effective against bacteria?

A. natural killer cells

B. complement

C. cytotoxic T cells

D. helper T cells

Answer: B

Q. What is the reason that you have to be immunized with a new influenza vaccine each year?

A. the vaccine is only protective for a year

B. mutation

C. macrophage oxidative metabolism

D. memory response

Answer: B

Q. Which type of immune response works in concert with cytotoxic T cells against virally infected cells?

A. natural killer cells

B. complement

C. antibodies

D. memory

> Answer: A

Critical Thinking Questions

Q. Describe how seroconversion works in HIV disease.

> A. Seroconversion is the clearance of virus in the serum due to the increase in specific serum antibody levels. Seroconversion happens in the early stages of HIV disease. Unfortunately, the antibody cannot completely clear the virus from the body and thus it most often progresses to AIDS.

Q. Describe tuberculosis and the innocent bystander effect.

> A. Tuberculosis is caused by bacteria resistant to lysosomal enzymes in alveolar macrophages, resulting in chronic infection. The immune response to these bacteria actually causes most of the lung damage that is characteristic of this life-threatening disease.

Glossary

macrophage oxidative metabolism
metabolism turned on in macrophages by T cell signals that help destroy intracellular bacteria

neutralization
inactivation of a virus by the binding of specific antibody

seroconversion
clearance of pathogen in the serum and the simultaneous rise of serum antibody

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6.1.7: Diseases Associated with Depressed or Overactive Immune Responses

Learning Objectives

- Discuss inherited and acquired immunodeficiencies
- Explain the four types of hypersensitivity and how they differ
- Give an example of how autoimmune disease breaks tolerance

This section is about how the immune system goes wrong. When it goes haywire, and becomes too weak or too strong, it leads to a state of disease. The factors that maintain immunological homeostasis are complex and incompletely understood.

Immunodeficiencies

As you have seen, the immune system is quite complex. It has many pathways using many cell types and signals. Because it is so complex, there are many ways for it to go wrong. Inherited immunodeficiencies arise from gene mutations that affect specific components of the immune response. There are also acquired immunodeficiencies with potentially devastating effects on the immune system, such as HIV.

Inherited Immunodeficiencies

A list of all inherited immunodeficiencies is well beyond the scope of this book. The list is almost as long as the list of cells, proteins, and signaling molecules of the immune system itself. Some deficiencies, such as those for complement, cause only a higher susceptibility to some Gram-negative bacteria. Others are more severe in their consequences. Certainly, the most serious of the inherited immunodeficiencies is **severe combined immunodeficiency disease (SCID)**. This disease is complex because it is caused by many different genetic defects. What groups them together is the fact that both the B cell and T cell arms of the adaptive immune response are affected.

Children with this disease usually die of opportunistic infections within their first year of life unless they receive a bone marrow transplant. Such a procedure had not yet been perfected for David Vetter, the “boy in the bubble,” who was treated for SCID by having to live almost his entire life in a sterile plastic cocoon for the 12 years before his death from infection in 1984. One of the features that make bone marrow transplants work as well as they do is the proliferative capability of hematopoietic stem cells of the bone marrow. Only a small amount of bone marrow from a healthy donor is given intravenously to the recipient. It finds its own way to the bone where it populates it, eventually reconstituting the patient’s immune system, which is usually destroyed beforehand by treatment with radiation or chemotherapeutic drugs.

New treatments for SCID using gene therapy, inserting nondefective genes into cells taken from the patient and giving them back, have the advantage of not needing the tissue match required for standard transplants. Although not a standard treatment, this approach holds promise, especially for those in whom standard bone marrow transplantation has failed.

Human Immunodeficiency Virus/AIDS

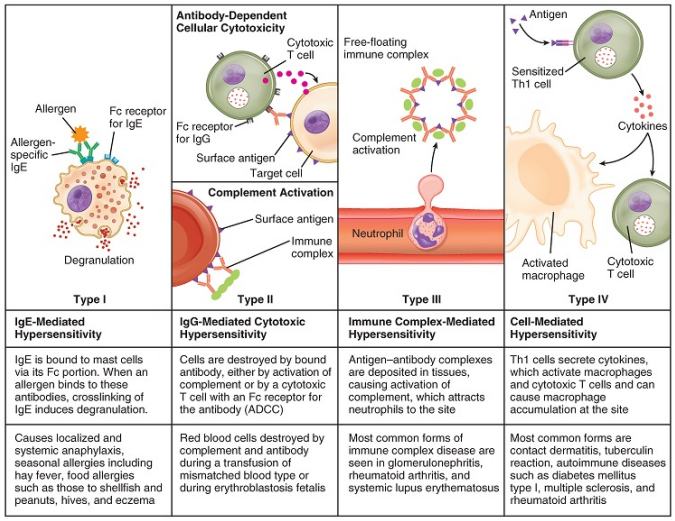
Although many viruses cause suppression of the immune system, only one wipes it out completely, and that is the previously mentioned HIV. It is worth discussing the biology of this virus, which can lead to the well-known AIDS, so that its full effects on the immune system can be understood. The virus is transmitted through semen, vaginal fluids, and blood, and can be caught by risky sexual behaviors and the sharing of needles by intravenous drug users. There are sometimes, but not always, flu-like symptoms in the first 1 to 2 weeks after infection. This is later followed by seroconversion. The anti-HIV antibodies formed during seroconversion are the basis for most initial HIV screening done in the United States. Because seroconversion takes different lengths of time in different individuals, multiple AIDS tests are given months apart to confirm or eliminate the possibility of infection.

After seroconversion, the amount of virus circulating in the blood drops and stays at a low level for several years. During this time, the levels of $CD4^+$ cells, especially helper T cells, decline steadily, until at some point, the immune response is so weak that opportunistic disease and eventually death result. CD4 is the receptor that HIV uses to get inside T cells and reproduce. Given that $CD4^+$ helper T cells play an important role in other in T cell immune responses and antibody responses, it should be no surprise that both types of immune responses are eventually seriously compromised.

Treatment for the disease consists of drugs that target virally encoded proteins that are necessary for viral replication but are absent from normal human cells. By targeting the virus itself and sparing the cells, this approach has been successful in significantly prolonging the lives of HIV-positive individuals. On the other hand, an HIV vaccine has been 30 years in development and is still years away. Because the virus mutates rapidly to evade the immune system, scientists have been looking for parts of the virus that do not change and thus would be good targets for a vaccine candidate.

Hypersensitivities

The word “hypersensitivity” simply means sensitive beyond normal levels of activation. Allergies and inflammatory responses to nonpathogenic environmental substances have been observed since the dawn of history. Hypersensitivity is a medical term describing symptoms that are now known to be caused by unrelated mechanisms of immunity. Still, it is useful for this discussion to use the four types of hypersensitivities as a guide to understand these mechanisms (Figure 6.1.7.1).



IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.	Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)	Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site	Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site
Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema	Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis	Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis

Figure 6.1.7.1: Immune Hypersensitivity. Components of the immune system cause four types of hypersensitivity. Notice that types I–III are B cell mediated, whereas type IV hypersensitivity is exclusively a T cell phenomenon.

Immediate (Type I) Hypersensitivity

Antigens that cause allergic responses are often referred to as allergens. The specificity of the **immediate hypersensitivity** response is predicated on the binding of allergen-specific IgE to the mast cell surface. The process of producing allergen-specific IgE is called sensitization, and is a necessary prerequisite for the symptoms of immediate hypersensitivity to occur. Allergies and allergic asthma are mediated by mast cell degranulation that is caused by the crosslinking of the antigen-specific IgE molecules on the mast cell surface. The mediators released have various vasoactive effects already discussed, but the major symptoms of inhaled allergens are the nasal edema and runny nose caused by the increased vascular permeability and increased blood flow of nasal blood vessels. As these mediators are released with mast cell degranulation, **type I hypersensitivity** reactions are usually rapid and occur within just a few minutes, hence the term immediate hypersensitivity.

Most allergens are in themselves nonpathogenic and therefore innocuous. Some individuals develop mild allergies, which are usually treated with antihistamines. Others develop severe allergies that may cause anaphylactic shock, which can potentially be fatal within 20 to 30 minutes if untreated. This drop in blood pressure (shock) with accompanying contractions of bronchial smooth muscle is caused by systemic mast cell degranulation when an allergen is eaten (for example, shellfish and peanuts), injected (by a bee sting or being administered penicillin), or inhaled (asthma). Because epinephrine raises blood pressure and relaxes bronchial smooth muscle, it is routinely used to counteract the effects of anaphylaxis and can be lifesaving. Patients with known severe allergies are encouraged to keep automatic epinephrine injectors with them at all times, especially when away from easy access to hospitals.

Allergists use skin testing to identify allergens in type I hypersensitivity. In skin testing, allergen extracts are injected into the epidermis, and a positive result of a soft, pale swelling at the site surrounded by a red zone (called the wheal and flare response), caused by the release of histamine and the granule mediators, usually occurs within 30 minutes. The soft center is due to fluid

leaking from the blood vessels and the redness is caused by the increased blood flow to the area that results from the dilation of local blood vessels at the site.

Type II and Type III Hypersensitivities

Type II hypersensitivity, which involves IgG-mediated lysis of cells by complement proteins, occurs during mismatched blood transfusions and blood compatibility diseases such as erythroblastosis fetalis (see section on transplantation). **Type III hypersensitivity** occurs with diseases such as systemic lupus erythematosus, where soluble antigens, mostly DNA and other material from the nucleus, and antibodies accumulate in the blood to the point that the antigen and antibody precipitate along blood vessel linings. These immune complexes often lodge in the kidneys, joints, and other organs where they can activate complement proteins and cause inflammation.

Delayed (Type IV) Hypersensitivity

Delayed hypersensitivity, or type IV hypersensitivity, is basically a standard cellular immune response. In delayed hypersensitivity, the first exposure to an antigen is called **sensitization**, such that on re-exposure, a secondary cellular response results, secreting cytokines that recruit macrophages and other phagocytes to the site. These sensitized T cells, of the Th1 class, will also activate cytotoxic T cells. The time it takes for this reaction to occur accounts for the 24- to 72-hour delay in development.

The classical test for delayed hypersensitivity is the tuberculin test for tuberculosis, where bacterial proteins from *M. tuberculosis* are injected into the skin. A couple of days later, a positive test is indicated by a raised red area that is hard to the touch, called an induration, which is a consequence of the cellular infiltrate, an accumulation of activated macrophages. A positive tuberculin test means that the patient has been exposed to the bacteria and exhibits a cellular immune response to it.

Another type of delayed hypersensitivity is contact sensitivity, where substances such as the metal nickel cause a red and swollen area upon contact with the skin. The individual must have been previously sensitized to the metal. A much more severe case of contact sensitivity is poison ivy, but many of the harshest symptoms of the reaction are associated with the toxicity of its oils and are not T cell mediated.

Autoimmune Responses

The worst cases of the immune system over-reacting are autoimmune diseases. Somehow, tolerance breaks down and the immune systems in individuals with these diseases begin to attack their own bodies, causing significant damage. The trigger for these diseases is, more often than not, unknown, and the treatments are usually based on resolving the symptoms using immunosuppressive and anti-inflammatory drugs such as steroids. These diseases can be localized and crippling, as in rheumatoid arthritis, or diffuse in the body with multiple symptoms that differ in different individuals, as is the case with systemic lupus erythematosus (Figure 6.1.7.2).

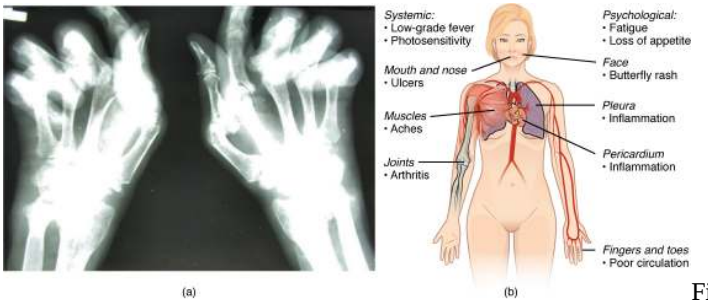


Figure 6.1.7.2: Autoimmune Disorders: Rheumatoid Arthritis and Lupus. (a) Extensive damage to the right hand of a rheumatoid arthritis sufferer is shown in the x-ray. (b) The diagram shows a variety of possible symptoms of systemic lupus erythematosus.

Environmental triggers seem to play large roles in autoimmune responses. One explanation for the breakdown of tolerance is that, after certain bacterial infections, an immune response to a component of the bacterium cross-reacts with a self-antigen. This mechanism is seen in rheumatic fever, a result of infection with *Streptococcus* bacteria, which causes strep throat. The antibodies to this pathogen's M protein cross-react with an antigenic component of heart myosin, a major contractile protein of the heart that is critical to its normal function. The antibody binds to these molecules and activates complement proteins, causing damage to the heart, especially to the heart valves. On the other hand, some theories propose that having multiple common infectious diseases

actually prevents autoimmune responses. The fact that autoimmune diseases are rare in countries that have a high incidence of infectious diseases supports this idea, another example of the hygiene hypothesis discussed earlier in this chapter.

There are genetic factors in autoimmune diseases as well. Some diseases are associated with the MHC genes that an individual expresses. The reason for this association is likely because if one's MHC molecules are not able to present a certain self-antigen, then that particular autoimmune disease cannot occur. Overall, there are more than 80 different autoimmune diseases, which are a significant health problem in the elderly. Table lists several of the most common autoimmune diseases, the antigens that are targeted, and the segment of the adaptive immune response that causes the damage.

Autoimmune Diseases

Disease	Autoantigen	Symptoms
Celiac disease	Tissue transglutaminase	Damage to small intestine
Diabetes mellitus type I	Beta cells of pancreas	Low insulin production; inability to regulate serum glucose
Graves' disease	Thyroid-stimulating hormone receptor (antibody blocks receptor)	Hyperthyroidism
Hashimoto's thyroiditis	Thyroid-stimulating hormone receptor (antibody mimics hormone and stimulates receptor)	Hypothyroidism
Lupus erythematosus	Nuclear DNA and proteins	Damage of many body systems
Myasthenia gravis	Acetylcholine receptor in neuromuscular junctions	Debilitating muscle weakness
Rheumatoid arthritis	Joint capsule antigens	Chronic inflammation of joints

Chapter Review

The immune response can be under-reactive or over-reactive. Suppressed immunity can result from inherited genetic defects or by acquiring viruses. Over-reactive immune responses include the hypersensitivities: B cell- and T cell-mediated immune responses designed to control pathogens, but that lead to symptoms or medical complications. The worst cases of over-reactive immune responses are autoimmune diseases, where an individual's immune system attacks his or her own body because of the breakdown of immunological tolerance. These diseases are more common in the aged, so treating them will be a challenge in the future as the aged population in the world increases.

Review Questions

Q. Which type of hypersensitivity involves soluble antigen-antibody complexes?

A. type I

B. type II

C. type III

D. type IV

Answer: C

Q. What causes the delay in delayed hypersensitivity?

A. inflammation

B. cytokine release

C. recruitment of immune cells

D. histamine release

Answer: C

Q. Which of the following is a critical feature of immediate hypersensitivity?

A. inflammation

B. cytotoxic T cells

C. recruitment of immune cells

D. histamine release

Answer: D

Q. Which of the following is an autoimmune disease of the heart?

A. rheumatoid arthritis

B. lupus

C. rheumatic fever

D. Hashimoto's thyroiditis

Answer: C

Q. What drug is used to counteract the effects of anaphylactic shock?

A. epinephrine

B. antihistamines

C. antibiotics

D. aspirin

Answer: A

Critical Thinking Questions

Q. Describe anaphylactic shock in someone sensitive to peanuts?

A. The peanuts cause high levels of mast cell degranulation in the throats of these individuals. The histamine released increases vascular permeability, causing edema and (swelling), making breathing difficult. This must be treated with epinephrine as soon as possible.

Q. Describe rheumatic fever and how tolerance is broken.

A. Antibody response to the cell walls of β-*Streptococcus* cross-reacts with the heart muscle. Complement is then activated and the heart is damaged, leading to abnormal function. Tolerance is broken because heart myosin antigens are similar to antigens on the β- *Streptococcus* bacteria.

Glossary

delayed hypersensitivity

(type IV) T cell-mediated immune response against pathogens infiltrating interstitial tissues, causing cellular infiltrate

immediate hypersensitivity

(type I) IgE-mediated mast cell degranulation caused by crosslinking of surface IgE by antigen

sensitization

first exposure to an antigen

severe combined immunodeficiency disease (SCID)

genetic mutation that affects both T cell and B cell arms of the immune response

type I hypersensitivity

immediate response mediated by mast cell degranulation caused by the crosslinking of the antigen-specific IgE molecules on the mast cell surface

type II hypersensitivity

cell damage caused by the binding of antibody and the activation of complement, usually against red blood cells

type III hypersensitivity

damage to tissues caused by the deposition of antibody-antigen (immune) complexes followed by the activation of complement

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6.1.8: Transplantation and Cancer Immunology

Learning Objectives

- Explain why blood typing is important and what happens when mismatched blood is used in a transfusion
- Describe how tissue typing is done during organ transplantation and the role of transplant anti-rejection drugs
- Show how the immune response is able to control some cancers and how this immune response might be enhanced by cancer vaccines

The immune responses to transplanted organs and to cancer cells are both important medical issues. With the use of tissue typing and anti-rejection drugs, transplantation of organs and the control of the anti-transplant immune response have made huge strides in the past 50 years. Today, these procedures are commonplace. **Tissue typing** is the determination of MHC molecules in the tissue to be transplanted to better match the donor to the recipient. The immune response to cancer, on the other hand, has been more difficult to understand and control. Although it is clear that the immune system can recognize some cancers and control them, others seem to be resistant to immune mechanisms.

The Rh Factor

Red blood cells can be typed based on their surface antigens. ABO blood type, in which individuals are type A, B, AB, or O according to their genetics, is one example. A separate antigen system seen on red blood cells is the Rh antigen. When someone is "A positive" for example, the positive refers to the presence of the Rh antigen, whereas someone who is "A negative" would lack this molecule.

An interesting consequence of Rh factor expression is seen in **erythroblastosis fetalis**, a hemolytic disease of the newborn (Figure 6.1.8.1). This disease occurs when mothers negative for Rh antigen have multiple Rh-positive children. During the birth of a first Rh-positive child, the mother makes a primary anti-Rh antibody response to the fetal blood cells that enter the maternal bloodstream. If the mother has a second Rh-positive child, IgG antibodies against Rh-positive blood mounted during this secondary response cross the placenta and attack the fetal blood, causing anemia. This is a consequence of the fact that the fetus is not genetically identical to the mother, and thus the mother is capable of mounting an immune response against it. This disease is treated with antibodies specific for Rh factor. These are given to the mother during the subsequent births, destroying any fetal blood that might enter her system and preventing the immune response.

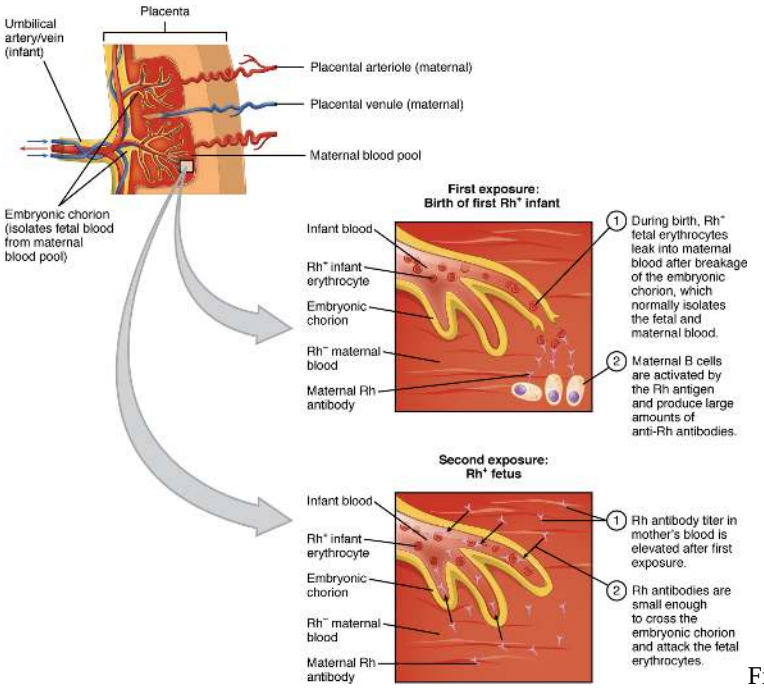


Figure 6.1.8.1: Erythroblastosis Fetalis. Erythroblastosis fetalis (hemolytic disease of the newborn) is the result of an immune response in an Rh-negative mother who has multiple children

with an Rh-positive father. During the first birth, fetal blood enters the mother's circulatory system, and anti-Rh antibodies are made. During the gestation of the second child, these antibodies cross the placenta and attack the blood of the fetus. The treatment for this disease is to give the mother anti-Rh antibodies (RhoGAM) during the first pregnancy to destroy Rh-positive fetal red blood cells from entering her system and causing the anti-Rh antibody response in the first place.

Tissue Transplantation

Tissue transplantation is more complicated than blood transfusions because of two characteristics of MHC molecules. These molecules are the major cause of transplant rejection (hence the name "histocompatibility"). **MHC polygeny** refers to the multiple MHC proteins on cells, and **MHC polymorphism** refers to the multiple alleles for each individual MHC locus. Thus, there are many alleles in the human population that can be expressed (Table and Table). When a donor organ expresses MHC molecules that are different from the recipient, the latter will often mount a cytotoxic T cell response to the organ and reject it. Histologically, if a biopsy of a transplanted organ exhibits massive infiltration of T lymphocytes within the first weeks after transplant, it is a sign that the transplant is likely to fail. The response is a classical, and very specific, primary T cell immune response. As far as medicine is concerned, the immune response in this scenario does the patient no good at all and causes significant harm.

Partial Table of Alleles of the Human MHC (Class I)

Gene	# of alleles	# of possible MHC I protein components
A	2132	1527
B	2798	2110
C	1672	1200
E	11	3
F	22	4
G	50	16

Partial Table of Alleles of the Human MHC (Class II)

Gene	# of alleles	# of possible MHC II protein components
DRA	7	2
DRB	1297	958
DQA1	49	31
DQB1	179	128
DPA1	36	18
DPB1	158	136
DMA	7	4
DMB	13	7
DOA	12	3
DOB	13	5

Immunosuppressive drugs such as cyclosporine A have made transplants more successful, but matching the MHC molecules is still key. In humans, there are six MHC molecules that show the most polymorphisms, three class I molecules (A, B, and C) and three class II molecules called DP, DQ, and DR. A successful transplant usually requires a match between at least 3–4 of these molecules, with more matches associated with greater success. Family members, since they share a similar genetic background, are much more likely to share MHC molecules than unrelated individuals do. In fact, due to the extensive polymorphisms in these MHC

molecules, unrelated donors are found only through a worldwide database. The system is not foolproof however, as there are not enough individuals in the system to provide the organs necessary to treat all patients needing them.

One disease of transplantation occurs with bone marrow transplants, which are used to treat various diseases, including SCID and leukemia. Because the bone marrow cells being transplanted contain lymphocytes capable of mounting an immune response, and because the recipient's immune response has been destroyed before receiving the transplant, the donor cells may attack the recipient tissues, causing **graft-versus-host disease**. Symptoms of this disease, which usually include a rash and damage to the liver and mucosa, are variable, and attempts have been made to moderate the disease by first removing mature T cells from the donor bone marrow before transplanting it.

Immune Responses Against Cancer

It is clear that with some cancers, for example Kaposi's sarcoma, a healthy immune system does a good job at controlling them (Figure 6.1.8.2). This disease, which is caused by the human herpesvirus, is almost never observed in individuals with strong immune systems, such as the young and immunocompetent. Other examples of cancers caused by viruses include liver cancer caused by the hepatitis B virus and cervical cancer caused by the human papilloma virus. As these last two viruses have vaccines available for them, getting vaccinated can help prevent these two types of cancer by stimulating the immune response.

 Figure 6.1.8.2: Karposi's Sarcoma Lesions. (credit: National Cancer Institute)

On the other hand, as cancer cells are often able to divide and mutate rapidly, they may escape the immune response, just as certain pathogens such as HIV do. There are three stages in the immune response to many cancers: elimination, equilibrium, and escape. Elimination occurs when the immune response first develops toward tumor-specific antigens specific to the cancer and actively kills most cancer cells, followed by a period of controlled equilibrium during which the remaining cancer cells are held in check. Unfortunately, many cancers mutate, so they no longer express any specific antigens for the immune system to respond to, and a subpopulation of cancer cells escapes the immune response, continuing the disease process.

This fact has led to extensive research in trying to develop ways to enhance the early immune response to completely eliminate the early cancer and thus prevent a later escape. One method that has shown some success is the use of cancer vaccines, which differ from viral and bacterial vaccines in that they are directed against the cells of one's own body. Treated cancer cells are injected into cancer patients to enhance their anti-cancer immune response and thereby prolong survival. The immune system has the capability to detect these cancer cells and proliferate faster than the cancer cells do, overwhelming the cancer in a similar way as they do for viruses. Cancer vaccines have been developed for malignant melanoma, a highly fatal skin cancer, and renal (kidney) cell carcinoma. These vaccines are still in the development stages, but some positive and encouraging results have been obtained clinically.

It is tempting to focus on the complexity of the immune system and the problems it causes as a negative. The upside to immunity, however, is so much greater: The benefit of staying alive far outweighs the negatives caused when the system does sometimes go awry. Working on "autopilot," the immune system helps to maintain your health and kill pathogens. The only time you really miss the immune response is when it is not being effective and illness results, or, as in the extreme case of HIV disease, the immune system is gone completely.

EVERYDAY CONNECTION

How Stress Affects the Immune Response: The Connections between the Immune, Nervous, and Endocrine Systems of the Body

The immune system cannot exist in isolation. After all, it has to protect the entire body from infection. Therefore, the immune system is required to interact with other organ systems, sometimes in complex ways. Thirty years of research focusing on the connections between the immune system, the central nervous system, and the endocrine system have led to a new science with the unwieldy name of called **psychoneuroimmunology**. The physical connections between these systems have been known for centuries: All primary and secondary organs are connected to sympathetic nerves. What is more complex, though, is the interaction of neurotransmitters, hormones, cytokines, and other soluble signaling molecules,

and the mechanism of “crosstalk” between the systems. For example, white blood cells, including lymphocytes and phagocytes, have receptors for various neurotransmitters released by associated neurons. Additionally, hormones such as cortisol (naturally produced by the adrenal cortex) and prednisone (synthetic) are well known for their abilities to suppress T cell immune mechanisms, hence, their prominent use in medicine as long-term, anti-inflammatory drugs.

One well-established interaction of the immune, nervous, and endocrine systems is the effect of stress on immune health. In the human vertebrate evolutionary past, stress was associated with the fight-or-flight response, largely mediated by the central nervous system and the adrenal medulla. This stress was necessary for survival. The physical action of fighting or running, whichever the animal decides, usually resolves the problem in one way or another. On the other hand, there are no physical actions to resolve most modern day stresses, including short-term stressors like taking examinations and long-term stressors such as being unemployed or losing a spouse. The effect of stress can be felt by nearly every organ system, and the immune system is no exception (Table).

Effects of Stress on Body Systems

System	Stress-related illness
Integumentary system	Acne, skin rashes, irritation
Nervous system	Headaches, depression, anxiety, irritability, loss of appetite, lack of motivation, reduced mental performance
Muscular and skeletal systems	Muscle and joint pain, neck and shoulder pain
Circulatory system	Increased heart rate, hypertension, increased probability of heart attacks
Digestive system	Indigestion, heartburn, stomach pain, nausea, diarrhea, constipation, weight gain or loss
Immune system	Depressed ability to fight infections
Male reproductive system	Lowered sperm production, impotence, reduced sexual desire
Female reproductive system	Irregular menstrual cycle, reduced sexual desire

At one time, it was assumed that all types of stress reduced all aspects of the immune response, but the last few decades of research have painted a different picture. First, most short-term stress does not impair the immune system in healthy individuals enough to lead to a greater incidence of diseases. However, older individuals and those with suppressed immune responses due to disease or immunosuppressive drugs may respond even to short-term stressors by getting sicker more often. It has been found that short-term stress diverts the body’s resources towards enhancing innate immune responses, which have the ability to act fast and would seem to help the body prepare better for possible infections associated with the trauma that may result from a fight-or-flight exchange. The diverting of resources away from the adaptive immune response, however, causes its own share of problems in fighting disease.

Chronic stress, unlike short-term stress, may inhibit immune responses even in otherwise healthy adults. The suppression of both innate and adaptive immune responses is clearly associated with increases in some diseases, as seen when individuals lose a spouse or have other long-term stresses, such as taking care of a spouse with a fatal disease or dementia. The new science of psychoneuroimmunology, while still in its relative infancy, has great potential to make exciting advances in our understanding of how the nervous, endocrine, and immune systems have evolved together and communicate with each other.

Chapter Review

Blood transfusion and organ transplantation both require an understanding of the immune response to prevent medical complications. Blood needs to be typed so that natural antibodies against mismatched blood will not destroy it, causing more harm than good to the recipient. Transplanted organs must be matched by their MHC molecules and, with the use of immunosuppressive

drugs, can be successful even if an exact tissue match cannot be made. Another aspect to the immune response is its ability to control and eradicate cancer. Although this has been shown to occur with some rare cancers and those caused by known viruses, the normal immune response to most cancers is not sufficient to control cancer growth. Thus, cancer vaccines designed to enhance these immune responses show promise for certain types of cancer.

Review Questions

Q. Which of the following terms means “many genes”?

A. polymorphism

B. polygeny

C. polypeptide

D. multiple alleles

Answer: B

Q. Why do we have natural antibodies?

A. We don’t know why.

B. immunity to environmental bacteria

C. immunity to transplants

D. from clonal selection

Answer: B

Q. Which type of cancer is associated with HIV disease?

A. Kaposi’s sarcoma

B. melanoma

C. lymphoma

D. renal cell carcinoma

Answer: A

Q. How does cyclosporine A work?

A. suppresses antibodies

B. suppresses T cells

C. suppresses macrophages

D. suppresses neutrophils

Answer: B

Q. What disease is associated with bone marrow transplants?

A. diabetes mellitus type I

B. melanoma

C. headache

D. graft-versus-host disease

Answer: D

Critical Thinking Questions

Q. Describe how stress affects immune responses.

> A. Stress causes the release of hormones and the activation of nerves that suppress the immune response. Short-term stress has little effect on the health of an already healthy individual, whereas chronic stress does lead to increases in disease in such people.

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Glossary

erythroblastosis fetalis
: disease of Rh factor-positive newborns in Rh-negative mothers with multiple Rh-positive children; resulting from the action of maternal antibodies against fetal blood

graft-versus-host disease
: in bone marrow transplants; occurs when the transplanted cells mount an immune response against the recipient

MHC polygeny
: multiple MHC genes and their proteins found in body cells

MHC polymorphism
: multiple alleles for each individual MHC locus

psychoneuroimmunology
: study of the connections between the immune, nervous, and endocrine systems

tissue typing
: typing of MHC molecules between a recipient and donor for use in a potential transplantation procedure

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SECTION OVERVIEW

6.2: Innate Nonspecific Host Defenses

Despite relatively constant exposure to pathogenic microbes in the environment, humans do not generally suffer from constant infection or disease. Under most circumstances, the body is able to defend itself from the threat of infection thanks to a complex immune system designed to repel, kill, and expel disease-causing invaders. Immunity as a whole can be described as two interrelated parts: nonspecific innate immunity, which is the subject of this chapter, and specific adaptive host defenses, which are discussed in the next chapter.

The nonspecific innate immune response provides a first line of defense that can often prevent infections from gaining a solid foothold in the body. These defenses are described as *nonspecific* because they do not target any specific pathogen; rather, they defend against a wide range of potential pathogens. They are called *innate* because they are built-in mechanisms of the human organism. Unlike the specific adaptive defenses, they are not acquired over time and they have no “memory” (they do not improve after repeated exposures to specific pathogens).

Broadly speaking, nonspecific innate defenses provide an immediate (or very rapid) response against potential pathogens. However, these responses are neither perfect nor impenetrable. They can be circumvented by pathogens on occasion, and sometimes they can even cause damage to the body, contributing to the signs and symptoms of infection (Figure 6.2.1).



Figure 6.2.1: Varicella, or chickenpox, is caused by the highly contagious varicella-zoster virus. The characteristic rash seen here is partly a result of inflammation associated with the body’s immune response to the virus. Inflammation is a response mechanism of innate immunity that helps the body fight off a wide range of infections. (credit: John Noble / CDC; Public Domain)

6.2.1: Physical Defenses

6.2.2: Chemical Defenses

6.2.3: Cellular Defenses

6.2.4: Pathogen Recognition and Phagocytosis

6.2.5: Inflammation and Fever

6.2.E: Innate Nonspecific Host Defenses (Exercises)

Thumbnail: Scanning electron micrograph of a phagocyte (yellow, right) phagocytosing anthrax bacilli (orange, left). (CC BY 2.5; Volker Brinkmann via PLOS).

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6.2.1: Physical Defenses

Learning Objectives

- Describe the various physical barriers and mechanical defenses that protect the human body against infection and disease
- Describe the role of microbiota as a first-line defense against infection and disease

Clinical Focus: Part 1

Angela, a 25-year-old female patient in the emergency department, is having some trouble communicating verbally because of shortness of breath. A nurse observes constriction and swelling of the airway and labored breathing. The nurse asks Angela if she has a history of asthma or allergies. Angela shakes her head no, but there is fear in her eyes. With some difficulty, she explains that her father died suddenly at age 27, when she was just a little girl, of a similar respiratory attack. The underlying cause had never been identified.

Exercise 6.2.1.1

1. What are some possible causes of constriction and swelling of the airway?
2. What causes swelling of body tissues in general?

Nonspecific innate immunity can be characterized as a multifaceted system of defenses that targets invading pathogens in a nonspecific manner. In this chapter, we have divided the numerous defenses that make up this system into three categories: physical defenses, chemical defenses, and cellular defenses. However, it is important to keep in mind that these defenses do not function independently, and the categories often overlap. Table 6.2.1.1 provides an overview of the nonspecific defenses discussed in this chapter.

Table 6.2.1.1: Overview of Nonspecific Innate Immune Defenses

Overview of Nonspecific Innate Immune Defenses	
Physical defenses	Physical barriers
	Mechanical defenses
	Microbiome
Chemical defenses	Chemicals and enzymes in body fluids
	Antimicrobial peptides
	Plasma protein mediators
	Cytokines
	Inflammation-eliciting mediators
Cellular defenses	Granulocytes
	Agranulocytes

Physical defenses provide the body's most basic form of nonspecific defense. They include physical barriers to microbes, such as the skin and mucous membranes, as well as mechanical defenses that physically remove microbes and debris from areas of the body where they might cause harm or infection. In addition, the microbiome provides a measure of physical protection against disease, as microbes of the normal microbiota compete with pathogens for nutrients and cellular binding sites necessary to cause infection.

Physical Barriers

Physical barriers play an important role in preventing microbes from reaching tissues that are susceptible to infection. At the cellular level, barriers consist of cells that are tightly joined to prevent invaders from crossing through to deeper tissue. For example, the endothelial cells that line blood vessels have very tight cell-to-cell junctions, blocking microbes from gaining access to the bloodstream. Cell junctions are generally composed of cell membrane proteins that may connect with the extracellular matrix or with complementary proteins from neighboring cells. Tissues in various parts of the body have different types of cell junctions. These include tight junctions, desmosomes, and gap junctions, as illustrated in Figure 6.2.1.1. Invading microorganisms may attempt to break down these substances chemically, using enzymes such as proteases that can cause structural damage to create a point of entry for pathogens.

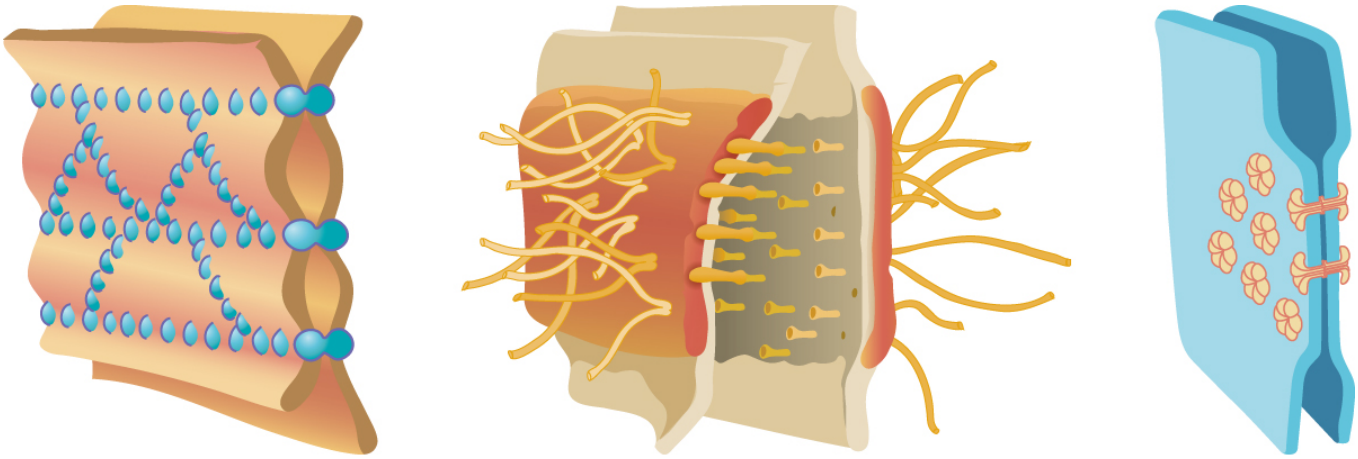


Figure 6.2.1.1: There are multiple types of cell junctions in human tissue, three of which are shown here. Tight junctions rivet two adjacent cells together, preventing or limiting material exchange through the spaces between them. Desmosomes have intermediate fibers that act like shoelaces, tying two cells together, allowing small materials to pass through the resulting spaces. Gap junctions are channels between two cells that permit their communication via signals. (credit: modification of work by Mariana Ruiz Villareal)

The Skin Barrier

One of the body's most important physical barriers is the skin barrier, which is composed of three layers of closely packed cells. The thin upper layer is called the epidermis. A second, thicker layer, called the dermis, contains hair follicles, sweat glands, nerves, and blood vessels. A layer of fatty tissue called the hypodermis lies beneath the dermis and contains blood and lymph vessels (Figure 6.2.1.2).

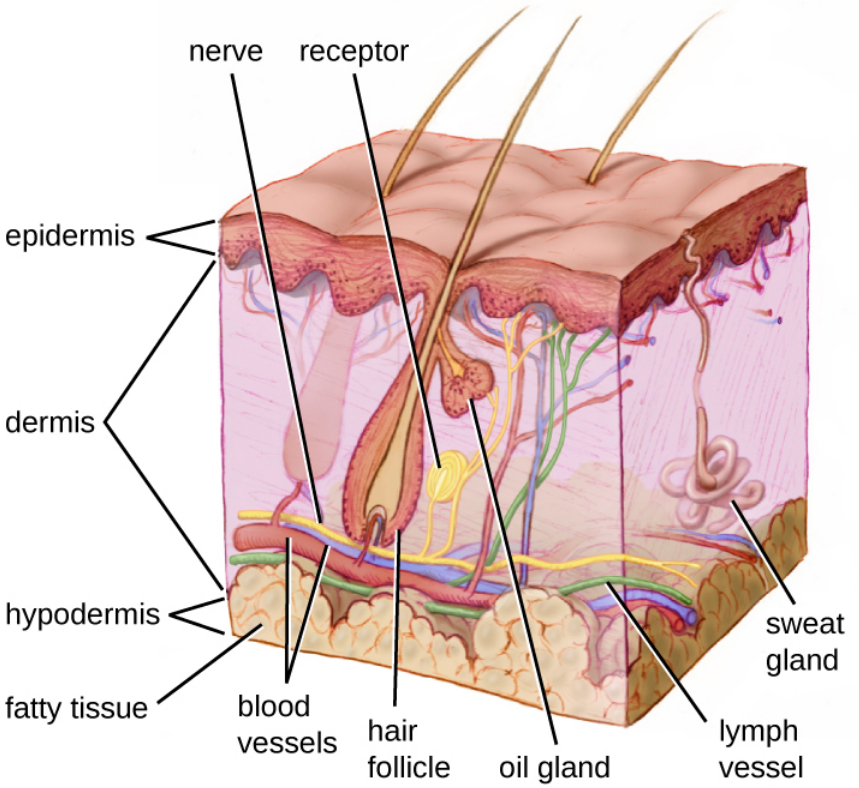


Figure 6.2.1.2: Human skin has three layers, the epidermis, the dermis, and the hypodermis, which provide a thick barrier between microbes outside the body and deeper tissues. Dead skin cells on the surface of the epidermis are continually shed, taking with them microbes on the skin's surface. (credit: modification of work by National Institutes of Health)

The topmost layer of skin, the epidermis, consists of cells that are packed with keratin. These dead cells remain as a tightly connected, dense layer of protein-filled cell husks on the surface of the skin. The keratin makes the skin's surface mechanically tough and resistant to degradation by bacterial enzymes. Fatty acids on the skin's surface create a dry, salty, and acidic environment that inhibits the growth of some microbes and is highly resistant to breakdown by bacterial enzymes. In addition, the dead cells of the epidermis are frequently shed, along with any microbes that may be clinging to them. Shed skin cells are continually replaced with new cells from below, providing a new barrier that will soon be shed in the same way.

Infections can occur when the skin barrier is compromised or broken. A wound can serve as a point of entry for opportunistic pathogens, which can infect the skin tissue surrounding the wound and possibly spread to deeper tissues.

Every Rose Has its Thorn

Mike, a gardener from southern California, recently noticed a small red bump on his left forearm. Initially, he did not think much of it, but soon it grew larger and then ulcerated (opened up), becoming a painful lesion that extended across a large part of his forearm (Figure 6.2.1.3). He went to an urgent care facility, where a physician asked about his occupation. When he said he was a landscaper, the physician immediately suspected a case of sporotrichosis, a type of fungal infection known as rose gardener's disease because it often afflicts landscapers and gardening enthusiasts.

Under most conditions, fungi cannot produce skin infections in healthy individuals. Fungi grow filaments known as hyphae, which are not particularly invasive and can be easily kept at bay by the physical barriers of the skin and mucous membranes. However, small wounds in the skin, such as those caused by thorns, can provide an opening for opportunistic pathogens like *Sporothrix schenkii*, a soil-dwelling fungus and the causative agent of rose gardener's disease. Once it breaches the skin barrier, *S. schenkii* can infect the skin and underlying tissues, producing ulcerated lesions like Mike's. Compounding matters, other pathogens may enter the infected tissue, causing secondary bacterial infections.

Luckily, rose gardener's disease is treatable. Mike's physician wrote him a prescription for some antifungal drugs as well as a course of antibiotics to combat secondary bacterial infections. His lesions eventually healed, and Mike returned to work with a

new appreciation for gloves and protective clothing.





Figure 6.2.1.3: Rose gardener's disease can occur when the fungus *Sporothrix schenkii* breaches the skin through small cuts, such as might be inflicted by thorns. (credit left: modification of work by Elisa Self; credit right: modification of work by Centers for Disease Control and Prevention)

Mucous Membranes

The mucous membranes lining the nose, mouth, lungs, and urinary and digestive tracts provide another nonspecific barrier against potential pathogens. Mucous membranes consist of a layer of epithelial cells bound by tight junctions. The epithelial cells secrete a moist, sticky substance called mucus, which covers and protects the more fragile cell layers beneath it and traps debris and particulate matter, including microbes. Mucus secretions also contain antimicrobial peptides.

In many regions of the body, mechanical actions serve to flush mucus (along with trapped or dead microbes) out of the body or away from potential sites of infection. For example, in the respiratory system, inhalation can bring microbes, dust, mold spores, and other small airborne debris into the body. This debris becomes trapped in the mucus lining the respiratory tract, a layer known as the mucociliary blanket. The epithelial cells lining the upper parts of the respiratory tract are called ciliated epithelial cells because they have hair-like appendages known as cilia. Movement of the cilia propels debris-laden mucus out and away from the lungs. The expelled mucus is then swallowed and destroyed in the stomach, or coughed up, or sneezed out (Figure 6.2.1.4). This system of removal is often called the mucociliary escalator.

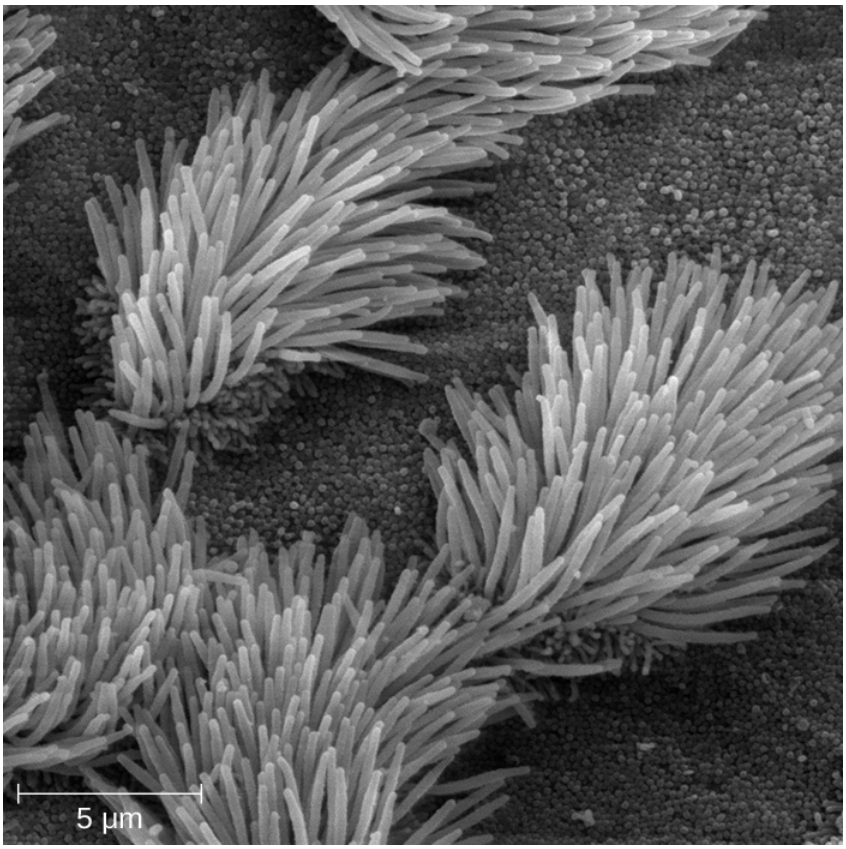


Figure 6.2.1.4: This scanning electron micrograph shows ciliated and nonciliated epithelial cells from the human trachea. The mucociliary escalator pushes mucus away from the lungs, along with any debris or microorganisms that may be trapped in the sticky mucus, and the mucus moves up to the esophagus where it can be removed by swallowing.

The mucociliary escalator is such an effective barrier to microbes that the lungs, the lowermost (and most sensitive) portion of the respiratory tract, were long considered to be a sterile environment in healthy individuals. Only recently has research suggested that healthy lungs may have a small normal microbiota. Disruption of the mucociliary escalator by the damaging effects of smoking or diseases such as cystic fibrosis can lead to increased colonization of bacteria in the lower respiratory tract and frequent infections, which highlights the importance of this physical barrier to host defenses.

Like the respiratory tract, the digestive tract is a portal of entry through which microbes enter the body, and the mucous membranes lining the digestive tract provide a nonspecific physical barrier against ingested microbes. The intestinal tract is lined with epithelial cells, interspersed with mucus-secreting goblet cells (Figure 6.2.1.5). This mucus mixes with material received from the stomach, trapping foodborne microbes and debris. The mechanical action of peristalsis, a series of muscular contractions in the digestive tract, moves the sloughed mucus and other material through the intestines, rectum, and anus, excreting the material in feces.

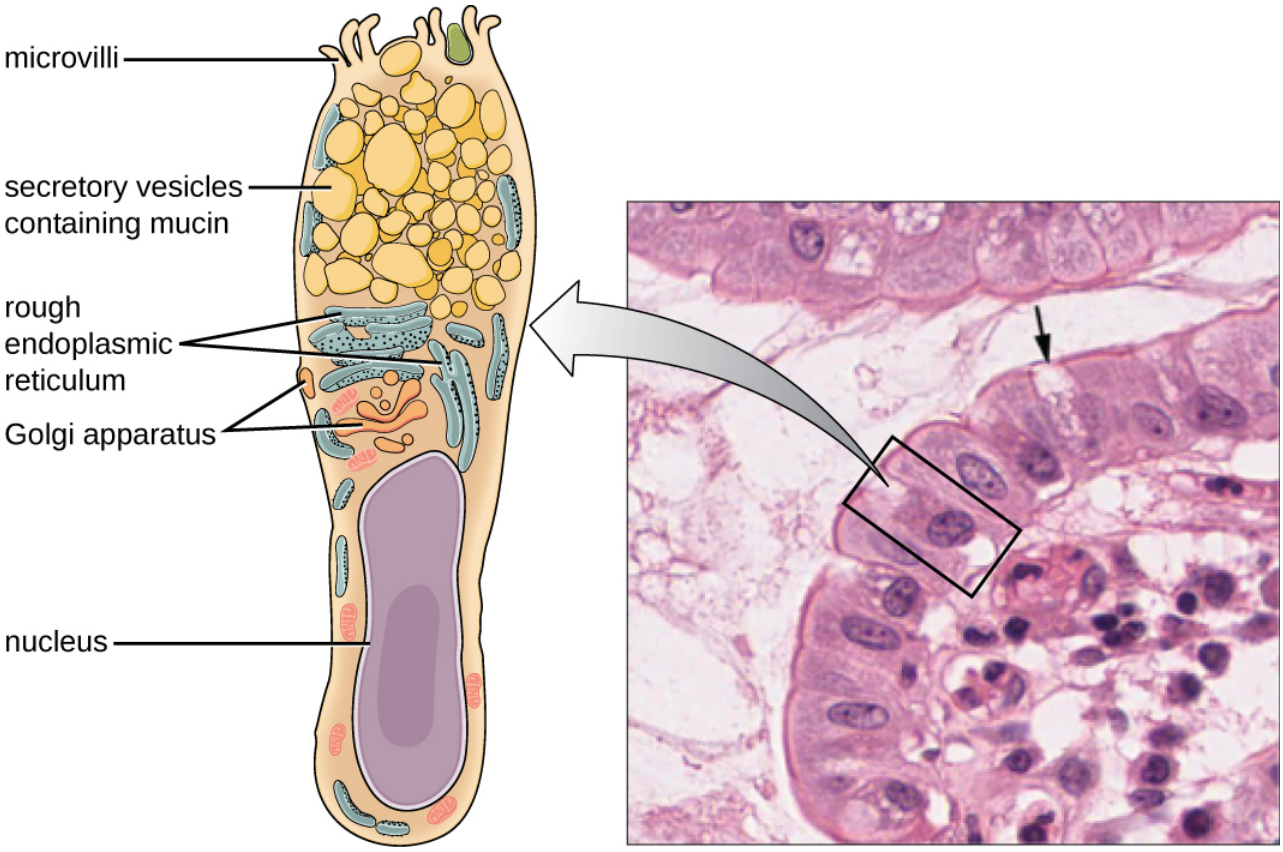


Figure 6.2.1.5: Goblet cells produce and secrete mucus. The arrows in this micrograph point to the mucus-secreting goblet cells (magnification 1600×) in the intestinal epithelium. (credit micrograph: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Endothelia

The epithelial cells lining the urogenital tract, blood vessels, lymphatic vessels, and certain other tissues are known as endothelia. These tightly packed cells provide a particularly effective frontline barrier against invaders. The endothelia of the blood-brain barrier, for example, protect the central nervous system (CNS), which consists of the brain and the spinal cord. The CNS is one of the most sensitive and important areas of the body, as microbial infection of the CNS can quickly lead to serious and often fatal inflammation. The cell junctions in the blood vessels traveling through the CNS are some of the tightest and toughest in the body, preventing any transient microbes in the bloodstream from entering the CNS. This keeps the cerebrospinal fluid that surrounds and bathes the brain and spinal cord sterile under normal conditions.

? Exercise 6.2.1.2

1. Describe how the mucociliary escalator functions.
2. Name two places you would find endothelia.

Mechanical Defenses

In addition to physical barriers that keep microbes out, the body has a number of mechanical defenses that physically remove pathogens from the body, preventing them from taking up residence. We have already discussed several examples of mechanical defenses, including the shedding of skin cells, the expulsion of mucus via the mucociliary escalator, and the excretion of feces through intestinal peristalsis. Other important examples of mechanical defenses include the flushing action of urine and tears, which both serve to carry microbes away from the body. The flushing action of urine is largely responsible for the normally sterile environment of the urinary tract, which includes the kidneys, ureters, and urinary bladder. Urine passing out of the body washes out transient microorganisms, preventing them from taking up residence. The eyes also have physical barriers and mechanical mechanisms for preventing infections. The eyelashes and eyelids prevent dust and airborne microorganisms from reaching the

surface of the eye. Any microbes or debris that make it past these physical barriers may be flushed out by the mechanical action of blinking, which bathes the eye in tears, washing debris away (Figure 6.2.1.6).

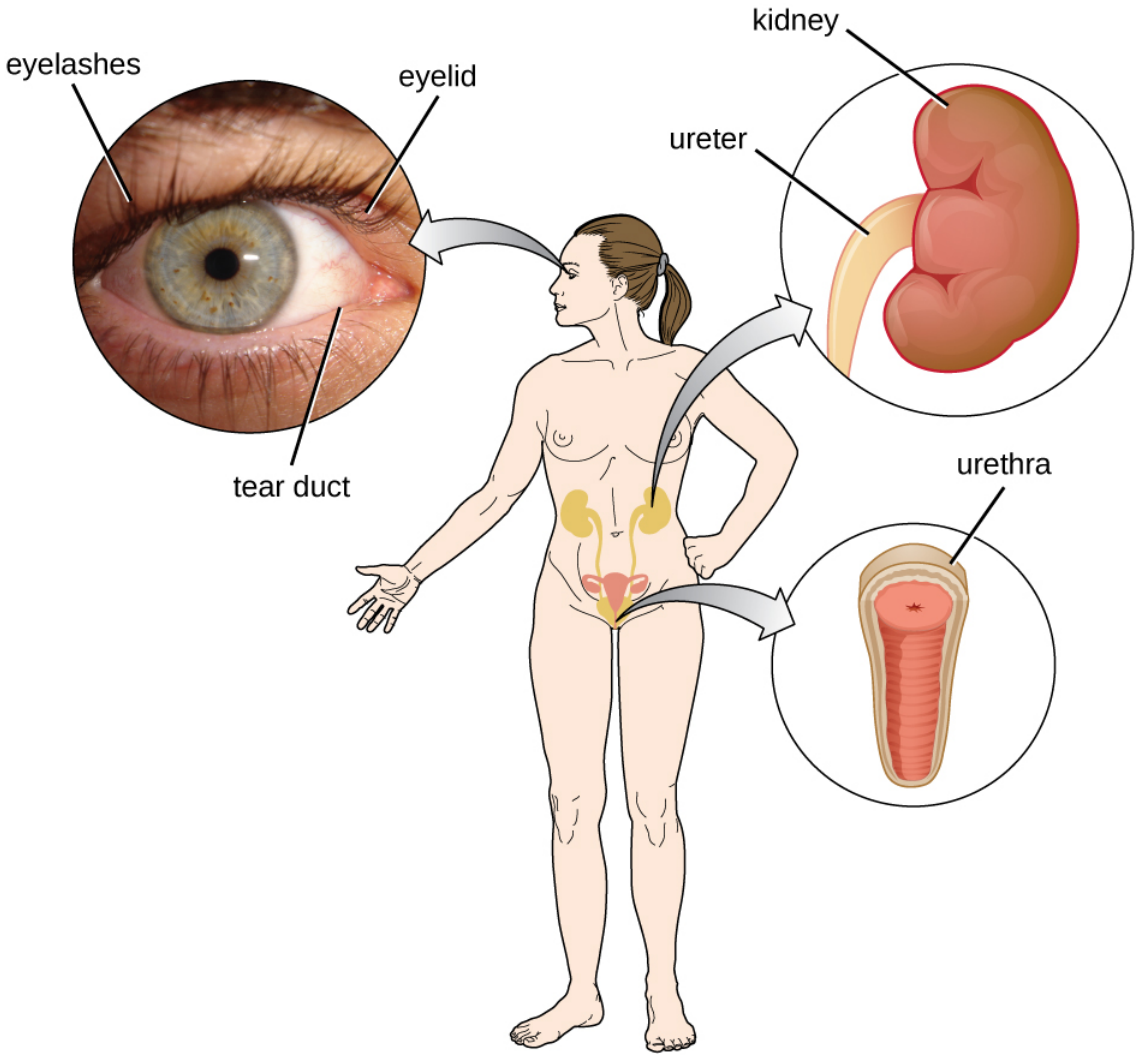


Figure 6.2.1.6: Tears flush microbes away from the surface of the eye. Urine washes microbes out of the urinary tract as it passes through; as a result, the urinary system is normally sterile.

? Exercise 6.2.1.3

Name two mechanical defenses that protect the eyes.

Microbiome

In various regions of the body, resident microbiota serve as an important first-line defense against invading pathogens. Through their occupation of cellular binding sites and competition for available nutrients, the resident microbiota prevent the critical early steps of pathogen attachment and proliferation required for the establishment of an infection. For example, in the vagina, members of the resident microbiota compete with opportunistic pathogens like the yeast *Candida*. This competition prevents infections by limiting the availability of nutrients, thus inhibiting the growth of *Candida*, keeping its population in check. Similar competitions occur between the microbiota and potential pathogens on the skin, in the upper respiratory tract, and in the gastrointestinal tract. As will be discussed later in this chapter, the resident microbiota also contribute to the chemical defenses of the innate nonspecific host defenses.

The importance of the normal microbiota in host defenses is highlighted by the increased susceptibility to infectious diseases when the microbiota is disrupted or eliminated. Treatment with antibiotics can significantly deplete the normal microbiota of the

gastrointestinal tract, providing an advantage for pathogenic bacteria to colonize and cause diarrheal infection. In the case of diarrhea caused by *Clostridium difficile*, the infection can be severe and potentially lethal. One strategy for treating *C. difficile* infections is fecal transplantation, which involves the transfer of fecal material from a donor (screened for potential pathogens) into the intestines of the recipient patient as a method of restoring the normal microbiota and combating *C. difficile* infections.

Table 6.2.1.2 provides a summary of the physical defenses discussed in this section.

Table 6.2.1.2: Physical Defenses of Nonspecific Innate Immunity

Defense	Examples	Function
Cellular barriers	Skin, mucous membranes, endothelial cells	Deny entry to pathogens
Mechanical defenses	Shedding of skin cells, mucociliary sweeping, peristalsis, flushing action of urine and tears	Remove pathogens from potential sites of infection
Microbiome	Resident bacteria of the skin, upper respiratory tract, gastrointestinal tract, and genitourinary tract	Compete with pathogens for cellular binding sites and nutrients

? Exercise 6.2.1.4

List two ways resident microbiota defend against pathogens.

Key Concepts and Summary

- **Nonspecific innate immunity** provides a first line of defense against infection by nonspecifically blocking entry of microbes and targeting them for destruction or removal from the body.
- The physical defenses of innate immunity include physical barriers, mechanical actions that remove microbes and debris, and the microbiome, which competes with and inhibits the growth of pathogens.
- The skin, mucous membranes, and endothelia throughout the body serve as physical barriers that prevent microbes from reaching potential sites of infection. Tight cell junctions in these tissues prevent microbes from passing through.
- Microbes trapped in dead skin cells or **mucus** are removed from the body by mechanical actions such as shedding of skin cells, mucociliary sweeping, coughing, **peristalsis**, and flushing of bodily fluids (e.g., urination, tears)
- The resident microbiota provide a physical defense by occupying available cellular binding sites and competing with pathogens for available nutrients.

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6.2.2: Chemical Defenses

Learning Objectives

- Describe how enzymes in body fluids provide protection against infection or disease
- List and describe the function of antimicrobial peptides, complement components, cytokines, and acute-phase proteins
- Describe similarities and differences among classic, alternate, and lectin complement pathways

In addition to physical defenses, the innate nonspecific immune system uses a number of chemical mediators that inhibit microbial invaders. The term “chemical mediators” encompasses a wide array of substances found in various body fluids and tissues throughout the body. Chemical mediators may work alone or in conjunction with each other to inhibit microbial colonization and infection.

Some chemical mediators are endogenously produced, meaning they are produced by human body cells; others are produced exogenously, meaning that they are produced by certain microbes that are part of the microbiome. Some mediators are produced continually, bathing the area in the antimicrobial substance; others are produced or activated primarily in response to some stimulus, such as the presence of microbes.

Chemical and Enzymatic Mediators Found in Body Fluids

Fluids produced by the skin include examples of both endogenous and exogenous mediators. Sebaceous glands in the dermis secrete an oil called sebum that is released onto the skin surface through hair follicles. This sebum is an endogenous mediator, providing an additional layer of defense by helping seal off the pore of the hair follicle, preventing bacteria on the skin’s surface from invading sweat glands and surrounding tissue (Figure 6.2.2.1). Certain members of the microbiome, such as the bacterium *Propionibacterium acnes* and the fungus *Malassezia*, among others, can use lipase enzymes to degrade sebum, using it as a food source. This produces oleic acid, which creates a mildly acidic environment on the surface of the skin that is inhospitable to many pathogenic microbes. Oleic acid is an example of an exogenously produced mediator because it is produced by resident microbes and not directly by body cells.

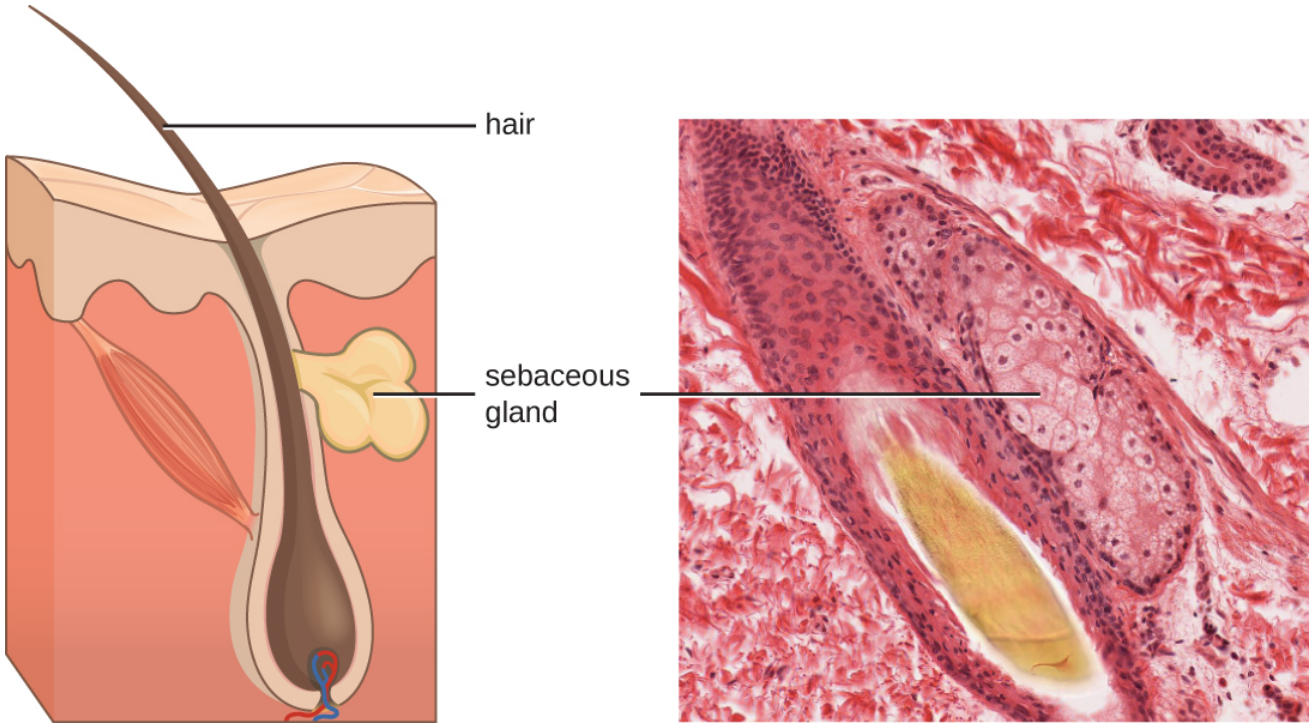


Figure 6.2.2.1: Sebaceous glands secrete sebum, a chemical mediator that lubricates and protect the skin from invading microbes. Sebum is also a food source for resident microbes that produce oleic acid, an exogenously produced mediator. (credit micrograph: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Environmental factors that affect the microbiota of the skin can have a direct impact on the production of chemical mediators. Low humidity or decreased sebum production, for example, could make the skin less habitable for microbes that produce oleic acid, thus making the skin more susceptible to pathogens normally inhibited by the skin's low pH. Many skin moisturizers are formulated to counter such effects by restoring moisture and essential oils to the skin.

The digestive tract also produces a large number of chemical mediators that inhibit or kill microbes. In the oral cavity, saliva contains mediators such as lactoperoxidase enzymes, and mucus secreted by the esophagus contains the antibacterial enzyme lysozyme. In the stomach, highly acidic gastric fluid kills most microbes. In the lower digestive tract, the intestines have pancreatic and intestinal enzymes, antibacterial peptides (cryptins), bile produced from the liver, and specialized Paneth cells that produce lysozyme. Together, these mediators are able to eliminate most pathogens that manage to survive the acidic environment of the stomach.

In the urinary tract, urine flushes microbes out of the body during urination. Furthermore, the slight acidity of urine (the average pH is about 6) inhibits the growth of many microbes and potential pathogens in the urinary tract.

The female reproductive system employs lactate, an exogenously produced chemical mediator, to inhibit microbial growth. The cells and tissue layers composing the vagina produce glycogen, a branched and more complex polymer of glucose. Lactobacilli in the area ferment glycogen to produce lactate, lowering the pH in the vagina and inhibiting transient microbiota, opportunistic pathogens like *Candida* (a yeast associated with vaginal infections), and other pathogens responsible for sexually transmitted diseases.

In the eyes, tears contain the chemical mediators lysozyme and lactoferrin, both of which are capable of eliminating microbes that have found their way to the surface of the eyes. Lysozyme cleaves the bond between NAG and NAM in peptidoglycan, a component of the cell wall in bacteria. It is more effective against gram-positive bacteria, which lack the protective outer membrane associated with gram-negative bacteria. Lactoferrin inhibits microbial growth by chemically binding and sequestering iron. This effectually starves many microbes that require iron for growth.

In the ears, cerumen (earwax) exhibits antimicrobial properties due to the presence of fatty acids, which lower the pH to between 3 and 5.

The respiratory tract uses various chemical mediators in the nasal passages, trachea, and lungs. The mucus produced in the nasal passages contains a mix of antimicrobial molecules similar to those found in tears and saliva (e.g., lysozyme, lactoferrin, lactoperoxidase). Secretions in the trachea and lungs also contain lysozyme and lactoferrin, as well as a diverse group of additional chemical mediators, such as the lipoprotein complex called surfactant, which has antibacterial properties.

? Exercise 6.2.2.1

1. Explain the difference between endogenous and exogenous mediators
2. Describe how pH affects antimicrobial defenses

Antimicrobial Peptides

The antimicrobial peptides (AMPs) are a special class of nonspecific cell-derived mediators with broad-spectrum antimicrobial properties. Some AMPs are produced routinely by the body, whereas others are primarily produced (or produced in greater quantities) in response to the presence of an invading pathogen. Research has begun exploring how AMPs can be used in the diagnosis and treatment of disease.

AMPs may induce cell damage in microorganisms in a variety of ways, including by inflicting damage to membranes, destroying DNA and RNA, or interfering with cell-wall synthesis. Depending on the specific antimicrobial mechanism, a particular AMP may inhibit only certain groups of microbes (e.g., gram-positive or gram-negative bacteria) or it may be more broadly effective against bacteria, fungi, protozoa, and viruses. Many AMPs are found on the skin, but they can also be found in other regions of the body.

A family of AMPs called defensins can be produced by epithelial cells throughout the body as well as by cellular defenses such as macrophages and neutrophils (see Cellular Defenses). Defensins may be secreted or act inside host cells; they combat microorganisms by damaging their plasma membranes. AMPs called bacteriocins are produced exogenously by certain members of

the resident microbiota within the gastrointestinal tract. The genes coding for these types of AMPs are often carried on plasmids and can be passed between different species within the resident microbiota through lateral or horizontal gene transfer.

There are numerous other AMPs throughout the body. The characteristics of a few of the more significant AMPs are summarized in Table 6.2.2.1.

Table 6.2.2.1: Characteristics of Selected Antimicrobial Peptides (AMPs)

AMP	Secreted by	Body site	Pathogens inhibited	Mode of action
Bacteriocins	Resident microbiota	Gastrointestinal tract	Bacteria	Disrupt membrane
Cathelicidin	Epithelial cells, macrophages, and other cell types	Skin	Bacteria and fungi	Disrupts membrane
Defensins	Epithelial cells, macrophages, neutrophils	Throughout the body	Fungi, bacteria, and many viruses	Disrupt membrane
Dermicidin	Sweat glands	Skin	Bacteria and fungi	Disrupts membrane integrity and ion channels
Histatins	Salivary glands	Oral cavity	Fungi	Disrupt intracellular function

? Exercise 6.2.2.2

Why are antimicrobial peptides (AMPs) considered nonspecific defenses?

Plasma Protein Mediators

Many nonspecific innate immune factors are found in plasma, the fluid portion of blood. Plasma contains electrolytes, sugars, lipids, and proteins, each of which helps to maintain homeostasis (i.e., stable internal body functioning), and contains the proteins involved in the clotting of blood. Additional proteins found in blood plasma, such as acute-phase proteins, complement proteins, and cytokines, are involved in the nonspecific innate immune response.

Plasma versus Serum

There are two terms for the fluid portion of blood: plasma and serum. How do they differ if they are both fluid and lack cells? The fluid portion of blood left over after coagulation (blood cell clotting) has taken place is serum. Although molecules such as many vitamins, electrolytes, certain sugars, complement proteins, and antibodies are still present in serum, clotting factors are largely depleted. Plasma, conversely, still contains all the clotting elements. To obtain plasma from blood, an anticoagulant must be used to prevent clotting. Examples of anticoagulants include heparin and ethylene diamine tetraacetic acid (EDTA). Because clotting is inhibited, once obtained, the sample must be gently spun down in a centrifuge. The heavier, denser blood cells form a pellet at the bottom of a centrifuge tube, while the fluid plasma portion, which is lighter and less dense, remains above the cell pellet.

Acute-Phase Proteins

The acute-phase proteins are another class of antimicrobial mediators. Acute-phase proteins are primarily produced in the liver and secreted into the blood in response to inflammatory molecules from the immune system. Examples of acute-phase proteins include C-reactive protein, serum amyloid A, ferritin, transferrin, fibrinogen, and mannose-binding lectin. Each of these proteins has a different chemical structure and inhibits or destroys microbes in some way (Table 6.2.2.1).

Table 6.2.2.2: Some Acute-Phase Proteins and Their Functions

Some Acute-Phase Proteins and Their Functions	
C-reactive protein	Coats bacteria (opsonization), preparing them for ingestion by phagocytes
Serum amyloid A	
Ferritin	Bind and sequester iron, thereby inhibiting the growth of pathogens
Transferrin	
Fibrinogen	Involved in formation of blood clots that trap bacterial pathogens
Mannose-binding lectin	Activates complement cascade

The Complement System

The complement system is a group of plasma protein mediators that can act as an innate nonspecific defense while also serving to connect innate and adaptive immunity (discussed in the next chapter). The complement system is composed of more than 30 proteins (including C1 through C9) that normally circulate as precursor proteins in blood. These precursor proteins become activated when stimulated or triggered by a variety of factors, including the presence of microorganisms. Complement proteins are considered part of innate nonspecific immunity because they are always present in the blood and tissue fluids, allowing them to be activated quickly. Also, when activated through the alternative pathway (described later in this section), complement proteins target pathogens in a nonspecific manner.

The process by which circulating complement precursors become functional is called complement activation. This process is a cascade that can be triggered by one of three different mechanisms, known as the alternative, classical, and lectin pathways.

The alternative pathway is initiated by the spontaneous activation of the complement protein C3. The hydrolysis of C3 produces two products, C3a and C3b. When no invader microbes are present, C3b is very quickly degraded in a hydrolysis reaction using the water in the blood. However, if invading microbes are present, C3b attaches to the surface of these microbes. Once attached, C3b will recruit other complement proteins in a cascade (Figure 6.2.2.2).

The classical pathway provides a more efficient mechanism of activating the complement cascade, but it depends upon the production of antibodies by the specific adaptive immune defenses. To initiate the classical pathway, a specific antibody must first bind to the pathogen to form an antibody-antigen complex. This activates the first protein in the complement cascade, the C1 complex. The C1 complex is a multipart protein complex, and each component participates in the full activation of the overall complex. Following recruitment and activation of the C1 complex, the remaining classical pathway complement proteins are recruited and activated in a cascading sequence (Figure 6.2.2.2).

The lectin activation pathway is similar to the classical pathway, but it is triggered by the binding of mannose-binding lectin, an acute-phase protein, to carbohydrates on the microbial surface. Like other acute-phase proteins, lectins are produced by liver cells and are commonly upregulated in response to inflammatory signals received by the body during an infection (Figure 6.2.2.2).

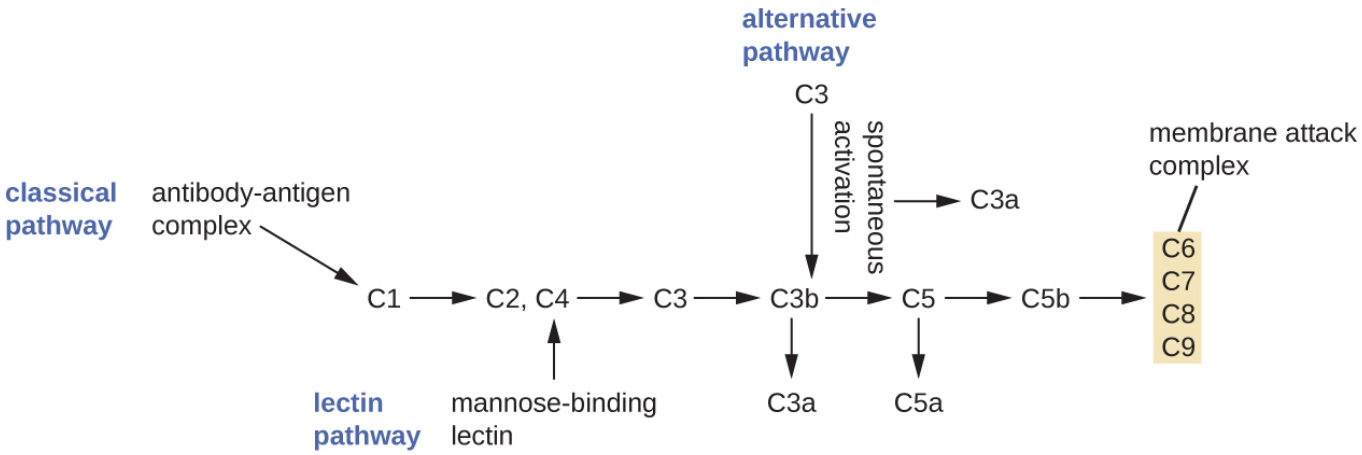


Figure 6.2.2.2: The three complement activation pathways have different triggers, as shown here, but all three result in the activation of the complement protein C3, which produces C3a and C3b. The latter binds to the surface of the target cell and then works with other complement proteins to cleave C5 into C5a and C5b. C5b also binds to the cell surface and then recruits C6 through C9; these molecules form a ring structure called the membrane attack complex (MAC), which punches through the cell membrane of the invading pathogen, causing it to swell and burst.

Although each complement activation pathway is initiated in a different way, they all provide the same protective outcomes: opsonization, inflammation, chemotaxis, and cytolysis. The term opsonization refers to the coating of a pathogen by a chemical substance (called an opsonin) that allows phagocytic cells to recognize, engulf, and destroy it more easily. Opsonins from the complement cascade include C1q, C3b, and C4b. Additional important opsonins include mannose-binding proteins and antibodies. The complement fragments C3a and C5a are well-characterized anaphylatoxins with potent proinflammatory functions. Anaphylatoxins activate mast cells, causing degranulation and the release of inflammatory chemical signals, including mediators that cause vasodilation and increased vascular permeability. C5a is also one of the most potent chemoattractants for neutrophils and other white blood cells, cellular defenses that will be discussed in the next section.

The complement proteins C6, C7, C8, and C9 assemble into a membrane attack complex (MAC), which allows C9 to polymerize into pores in the membranes of gram-negative bacteria. These pores allow water, ions, and other molecules to move freely in and out of the targeted cells, eventually leading to cell lysis and death of the pathogen (Figure 6.2.2.2). However, the MAC is only effective against gram-negative bacteria; it cannot penetrate the thick layer of peptidoglycan associated with cell walls of gram-positive bacteria. Since the MAC does not pose a lethal threat to gram-positive bacterial pathogens, complement-mediated opsonization is more important for their clearance.

Cytokines

Cytokines are soluble proteins that act as communication signals between cells. In a nonspecific innate immune response, various cytokines may be released to stimulate production of chemical mediators or other cell functions, such as cell proliferation, cell differentiation, inhibition of cell division, apoptosis, and chemotaxis.

When a cytokine binds to its target receptor, the effect can vary widely depending on the type of cytokine and the type of cell or receptor to which it has bound. The function of a particular cytokine can be described as autocrine, paracrine, or endocrine (Figure 6.2.2.3). In autocrine function, the same cell that releases the cytokine is the recipient of the signal; in other words, autocrine function is a form of self-stimulation by a cell. In contrast, paracrine function involves the release of cytokines from one cell to other nearby cells, stimulating some response from the recipient cells. Last, endocrine function occurs when cells release cytokines into the bloodstream to be carried to target cells much farther away.

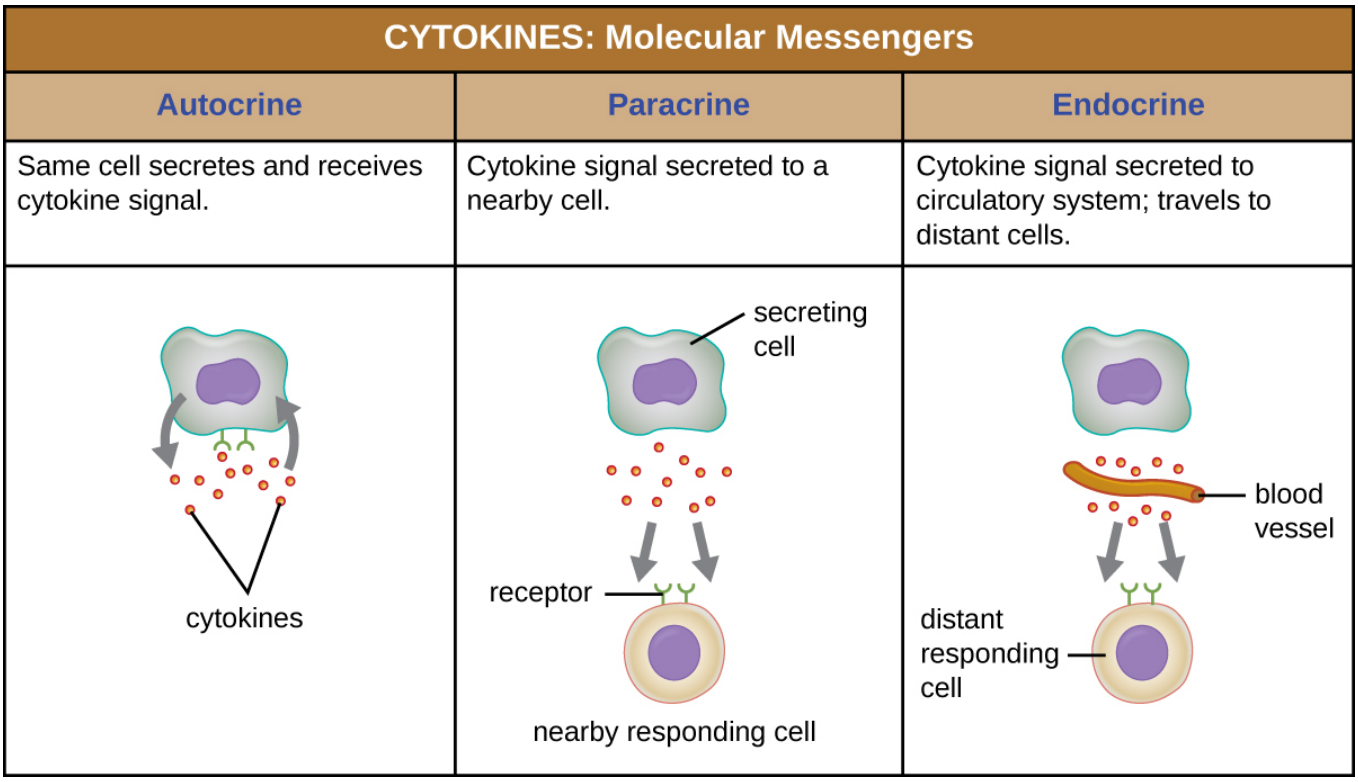


Figure 6.2.2.3: Autocrine, paracrine, and endocrine actions describe which cells are targeted by cytokines and how far the cytokines must travel to bind to their intended target cells' receptors.

Three important classes of cytokines are the interleukins, chemokines, and interferons. The interleukins were originally thought to be produced only by leukocytes (white blood cells) and to only stimulate leukocytes, thus the reasons for their name. Although interleukins are involved in modulating almost every function of the immune system, their role in the body is not restricted to immunity. Interleukins are also produced by and stimulate a variety of cells unrelated to immune defenses.

The chemokines are chemotactic factors that recruit leukocytes to sites of infection, tissue damage, and inflammation. In contrast to more general chemotactic factors, like complement factor C5a, chemokines are very specific in the subsets of leukocytes they recruit.

Interferons are a diverse group of immune signaling molecules and are especially important in our defense against viruses. Type I interferons (interferon-α and interferon-β) are produced and released by cells infected with virus. These interferons stimulate nearby cells to stop production of mRNA, destroy RNA already produced, and reduce protein synthesis. These cellular changes inhibit viral replication and production of mature virus, slowing the spread of the virus. Type I interferons also stimulate various immune cells involved in viral clearance to more aggressively attack virus-infected cells. Type II interferon (interferon-γ) is an important activator of immune cells (Figure 6.2.2.4).

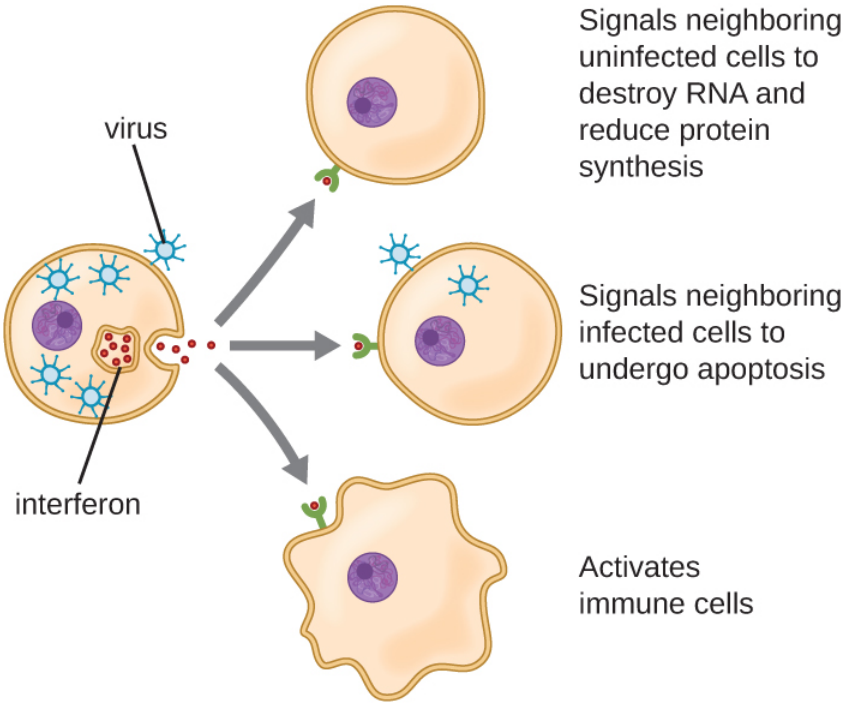


Figure 6.2.2.4: Interferons are cytokines released by a cell infected with a virus. Interferon-α and interferon-β signal uninfected neighboring cells to inhibit mRNA synthesis, destroy RNA, and reduce protein synthesis (top arrow). Interferon-α and interferon-β also promote apoptosis in cells infected with the virus (middle arrow). Interferon-γ alerts neighboring immune cells to an attack (bottom arrow). Although interferons do not cure the cell releasing them or other infected cells, which will soon die, their release may prevent additional cells from becoming infected, thus stemming the infection.

Inflammation-Eliciting Mediators

Many of the chemical mediators discussed in this section contribute in some way to inflammation and fever, which are nonspecific immune responses discussed in more detail in Inflammation and Fever. Cytokines stimulate the production of acute-phase proteins such as C-reactive protein and mannose-binding lectin in the liver. These acute-phase proteins act as opsonins, activating complement cascades through the lectin pathway.

Some cytokines also bind mast cells and basophils, inducing them to release histamine, a proinflammatory compound. Histamine receptors are found on a variety of cells and mediate proinflammatory events, such as bronchoconstriction (tightening of the airways) and smooth muscle contraction.

In addition to histamine, mast cells may release other chemical mediators, such as leukotrienes. Leukotrienes are lipid-based proinflammatory mediators that are produced from the metabolism of arachidonic acid in the cell membrane of leukocytes and tissue cells. Compared with the proinflammatory effects of histamine, those of leukotrienes are more potent and longer lasting. Together, these chemical mediators can induce coughing, vomiting, and diarrhea, which serve to expel pathogens from the body.

Certain cytokines also stimulate the production of prostaglandins, chemical mediators that promote the inflammatory effects of kinins and histamines. Prostaglandins can also help to set the body temperature higher, leading to fever, which promotes the activities of white blood cells and slightly inhibits the growth of pathogenic microbes (see Inflammation and Fever).

Another inflammatory mediator, bradykinin, contributes to edema, which occurs when fluids and leukocytes leak out of the bloodstream and into tissues. It binds to receptors on cells in the capillary walls, causing the capillaries to dilate and become more permeable to fluids.

? Exercise 6.2.2.3

1. What do the three complement activation pathways have in common?
2. Explain autocrine, paracrine, and endocrine signals.
3. Name two important inflammation-eliciting mediators.

Clinical Focus: Part 2

To relieve the constriction of her airways, Angela is immediately treated with antihistamines and administered corticosteroids through an inhaler, and then monitored for a period of time. Though her condition does not worsen, the drugs do not seem to be alleviating her condition. She is admitted to the hospital for further observation, testing, and treatment.

Following admission, a clinician conducts allergy testing to try to determine if something in her environment might be triggering an allergic inflammatory response. A doctor orders blood analysis to check for levels of particular cytokines. A sputum sample is also taken and sent to the lab for microbial staining, culturing, and identification of pathogens that could be causing an infection.

Exercise 6.2.2.4

1. Which aspects of the innate immune system could be contributing to Angela's airway constriction?
2. Why was Angela treated with antihistamines?
3. Why would the doctor be interested in levels of cytokines in Angela's blood?

Table 6.2.2.3 provides a summary of the chemical defenses discussed in this section.

Table 6.2.2.3: Chemical Defenses of Nonspecific Innate Immunity

Defense	Examples	Function
Chemicals and enzymes in body fluids	Sebum from sebaceous glands	Provides oil barrier protecting hair follicle pores from pathogens
	Oleic acid from sebum and skin microbiota	Lowers pH to inhibit pathogens
	Lysozyme in secretions	Kills bacteria by attacking cell wall
	Acid in stomach, urine, and vagina	Inhibits or kills bacteria
	Digestive enzymes and bile	Kill bacteria
	Lactoferrin and transferrin	Bind and sequester iron, inhibiting bacterial growth
	Surfactant in lungs	Kills bacteria
Antimicrobial peptides	Defensins, bacteriocins, dermicidin, cathelicidin, histatins,	Kill bacteria by attacking membranes or interfering with cell functions
Plasma protein mediators	Acute-phase proteins (C-reactive protein, serum amyloid A, ferritin, fibrinogen, transferrin, and mannose-binding lectin)	Inhibit the growth of bacteria and assist in the trapping and killing of bacteria
	Complements C3b and C4b	Opsonization of pathogens to aid phagocytosis
	Complement C5a	Chemoattractant for phagocytes
	Complements C3a and C5a	Proinflammatory anaphylatoxins
Cytokines	Interleukins	Stimulate and modulate most functions of immune system
	Chemokines	Recruit white blood cells to infected area
	Interferons	Alert cells to viral infection, induce apoptosis of virus-infected cells, induce antiviral defenses in infected and nearby uninfected cells, stimulate immune cells to attack virus-infected cells
Inflammation-eliciting mediators	Histamine	Promotes vasodilation, bronchoconstriction, smooth muscle contraction, increased secretion and mucus production
	Leukotrienes	Promote inflammation; stronger and longer lasting than histamine
	Prostaglandins	Promote inflammation and fever
	Bradykinin	Increases vasodilation and vascular permeability, leading to edema

Key Concepts and Summary

- Numerous **chemical mediators** produced endogenously and exogenously exhibit nonspecific antimicrobial functions.
- Many chemical mediators are found in body fluids such as sebum, saliva, mucus, gastric and intestinal fluids, urine, tears, cerumen, and vaginal secretions.

- **Antimicrobial peptides (AMPs)** found on the skin and in other areas of the body are largely produced in response to the presence of pathogens. These include dermcidin, cathelicidin, defensins, histatins, and bacteriocins.
- **Plasma** contains various proteins that serve as chemical mediators, including **acute-phase proteins**, **complement proteins**, and **cytokines**.
- The **complement system** involves numerous precursor proteins that circulate in plasma. These proteins become activated in a cascading sequence in the presence of microbes, resulting in the **opsonization** of pathogens, chemoattraction of leukocytes, induction of inflammation, and cytolysis through the formation of a **membrane attack complex (MAC)**.
- **Cytokines** are proteins that facilitate various nonspecific responses by innate immune cells, including production of other chemical mediators, cell proliferation, cell death, and differentiation.
- Cytokines play a key role in the inflammatory response, triggering production of inflammation-eliciting mediators such as acute-phase proteins, **histamine**, leukotrienes, **prostaglandins**, and **bradykinin**.

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6.2.3: Cellular Defenses

Learning Objectives

- Identify and describe the components of blood
- Explain the process by which the formed elements of blood are formed (hematopoiesis)
- Describe the characteristics of formed elements found in peripheral blood, as well as their respective functions within the innate immune system

In the previous section, we discussed some of the chemical mediators found in plasma, the fluid portion of blood. The nonfluid portion of blood consists of various types of formed elements, so called because they are all formed from the same stem cells found in bone marrow. The three major categories of formed elements are: red blood cells (RBCs), also called erythrocytes; platelets, also called thrombocytes; and white blood cells (WBCs), also called leukocytes.

Red blood cells are primarily responsible for carrying oxygen to tissues. Platelets are cellular fragments that participate in blood clot formation and tissue repair. Several different types of WBCs participate in various nonspecific mechanisms of innate and adaptive immunity. In this section, we will focus primarily on the innate mechanisms of various types of WBCs.

Hematopoiesis

All of the formed elements of blood are derived from pluripotent hematopoietic stem cells (HSCs) in the bone marrow. As the HSCs make copies of themselves in the bone marrow, individual cells receive different cues from the body that control how they develop and mature. As a result, the HSCs differentiate into different types of blood cells that, once mature, circulate in peripheral blood. This process of differentiation, called hematopoiesis, is shown in more detail in Figure 6.2.3.1.

In terms of sheer numbers, the vast majority of HSCs become erythrocytes. Much smaller numbers become leukocytes and platelets. Leukocytes can be further subdivided into granulocytes, which are characterized by numerous granules visible in the cytoplasm, and agranulocytes, which lack granules. Figure 6.2.3.2 provides an overview of the various types of formed elements, including their relative numbers, primary function, and lifespans.

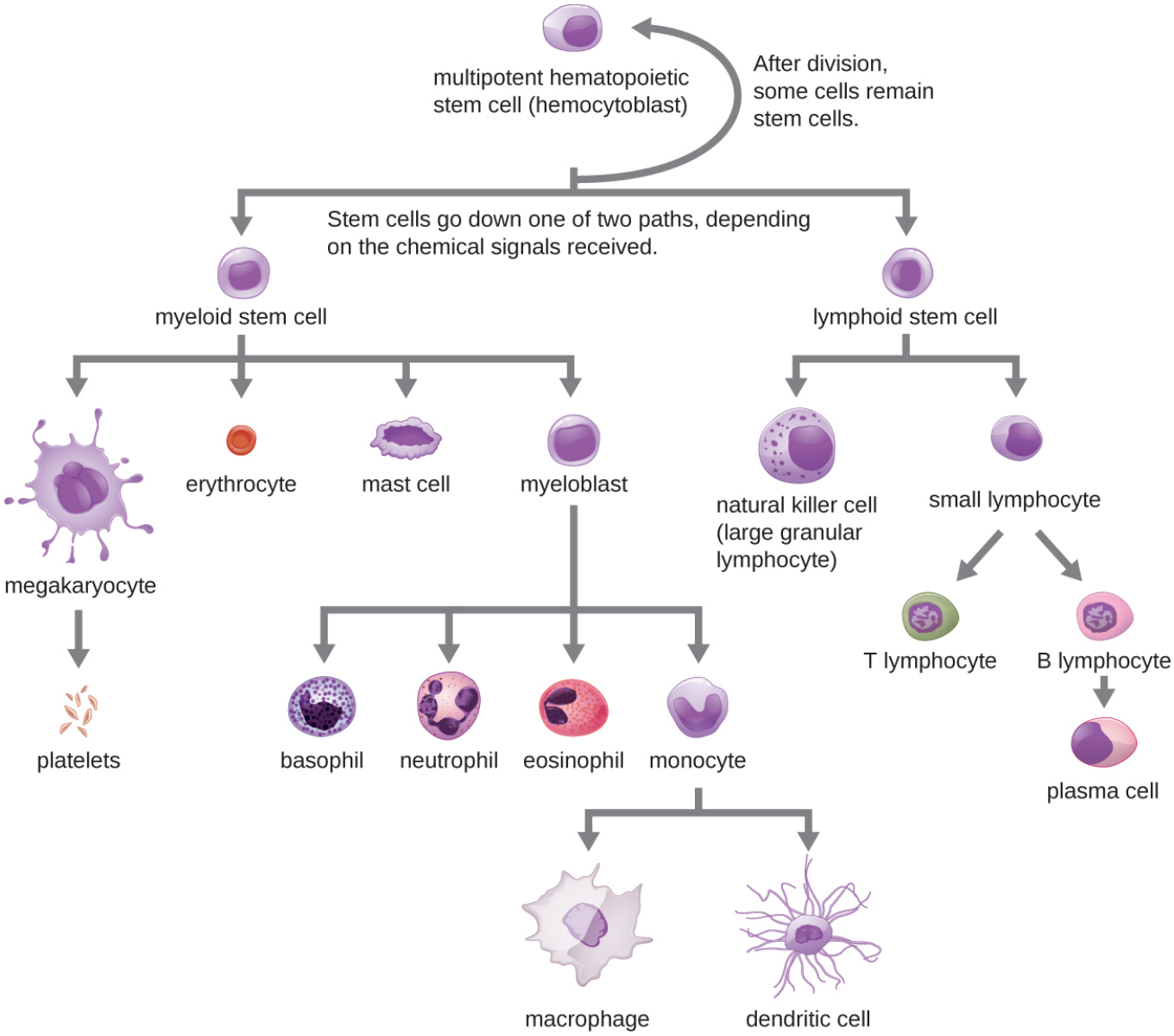


Figure 6.2.3.1: All the formed elements of the blood arise by differentiation of hematopoietic stem cells in the bone marrow.

Formed Element	Major Subtypes		Numbers Present per Microliter (μL) and Mean (Range)	Appearance in a Standard Blood Smear	Summary of Functions	Comments
Erythrocytes (red blood cells) 			5.2 million (4.4–6.0 million)	Flattened biconcave disk; no nucleus; pale red	Transport oxygen and some carbon dioxide between tissue and lungs	Lifespan of approximately 120 days
Leukocytes (white blood cells)			7000 (5000–10,000)	Obvious dark-staining nucleus	All function in body defenses	Exit capillaries and move into tissues; lifespan of usually a few hours or days
	Granulocytes, including neutrophils, eosinophils, and basophils	***Total leukocytes (%)***	4360 (1800–9950)	Abundant granules in cytoplasm; nucleus normally lobed	Nonspecific (innate) resistance to disease	Classified according to membrane-bound granules in cytoplasm
	Neutrophils 	50–70	4150 (1800–7300)	Nucleus lobes increase with age; pale lilac granules	Phagocytic; particularly effective against bacteria; release cytotoxic chemicals from granules	Most common leukocyte; lifespan of minutes to days
	Eosinophils 	1–3	165 (0–700)	Nucleus generally two-lobed; bright red-orange granules	Phagocytic cells; particularly effective with antigen-antibody complexes; release antihistamines; combat parasitic infections	Lifespan of minutes to days
	Basophils 	<1	44 (0–150)	Nucleus generally two-lobed but difficult to see due to presence of heavy, dense, dark purple granules	Pro-inflammatory	Least common leukocyte; lifespan unknown
	Agranulocytes, including lymphocytes and monocytes		2640 (1700–4950)	Lack abundant granules in cytoplasm; have a simple-shaped nucleus that may be indented	Body defenses	Group consists of two major cell types from different lineages
	Lymphocytes 	20–40	2185 (1500–4000)	Spherical cells with a single, often large, nucleus occupying much of the cell's volume; stains purple; seen in large (natural killer cells) and small (B and T cells) variants	Primarily specific (adaptive) immunity: T cells directly attack other cells (cellular immunity); B cells release antibodies (humoral immunity); natural killer cells are similar to T cells but nonspecific	Initial cells originate in bone marrow, but secondary production occurs in lymphatic tissue; several distinct subtypes; memory cells form after exposure to a pathogen and rapidly increase responses to subsequent exposure; lifespan of many years
	Monocytes 	1–6	455 (200–950)	Largest leukocyte; has an indented or horseshoe-shaped nucleus	Very effective phagocytic cells engulfing pathogens or worn-out cells; also serve as antigen-presenting cells (APCs) or other components of the immune system	Produced in red bone marrow; referred to as macrophages and dendritic cells after leaving the circulation
Platelets 			350,000 (150,000–500,000)	Cellular fragments surrounded by a plasma membrane and containing granules; stains purple	Hemostasis; release growth factors for repair and healing of tissue	Formed from megakaryocytes that remain in the red bone marrow and shed platelets into circulation

Figure 6.2.3.2: Formed elements of blood include erythrocytes (red blood cells), leukocytes (white blood cells), and platelets.

Granulocytes

The various types of granulocytes can be distinguished from one another in a blood smear by the appearance of their nuclei and the contents of their granules, which confer different traits, functions, and staining properties. The neutrophils, also called polymorphonuclear neutrophils (PMNs), have a nucleus with three to five lobes and small, numerous, lilac-colored granules. Each lobe of the nucleus is connected by a thin strand of material to the other lobes. The eosinophils have fewer lobes in the nucleus (typically 2–3) and larger granules that stain reddish-orange. The basophils have a two-lobed nucleus and large granules that stain dark blue or purple (Figure 6.2.3.3).

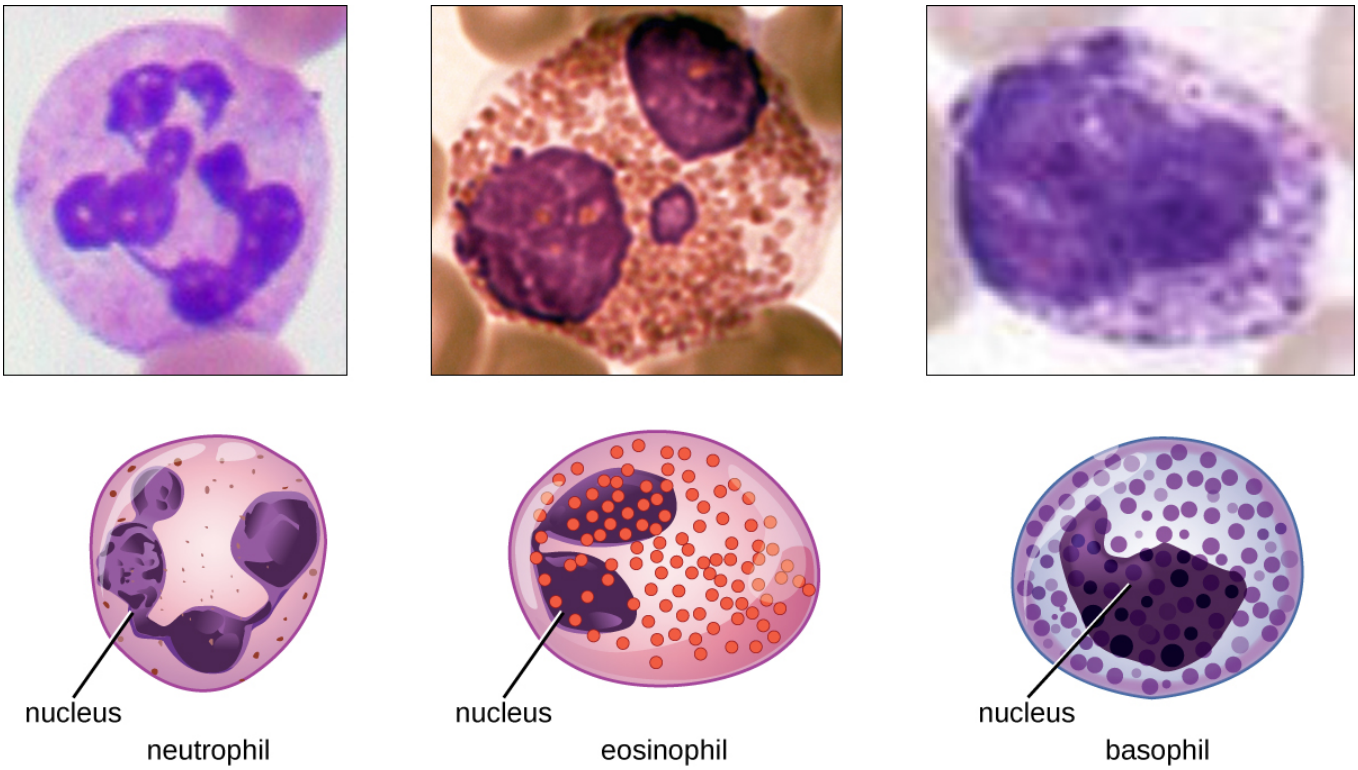


Figure 6.2.3.3: Granulocytes can be distinguished by the number of lobes in their nuclei and the staining properties of their granules. (credit “neutrophil” micrograph: modification of work by Ed Uthman)

Neutrophils (PMNs)

Neutrophils (PMNs) are frequently involved in the elimination and destruction of extracellular bacteria. They are capable of migrating through the walls of blood vessels to areas of bacterial infection and tissue damage, where they seek out and kill infectious bacteria. PMN granules contain a variety of defensins and hydrolytic enzymes that help them destroy bacteria through phagocytosis (described in more detail in Pathogen Recognition and Phagocytosis) In addition, when many neutrophils are brought into an infected area, they can be stimulated to release toxic molecules into the surrounding tissue to better clear infectious agents. This is called degranulation.

Another mechanism used by neutrophils is neutrophil extracellular traps (NETs), which are extruded meshes of chromatin that are closely associated with antimicrobial granule proteins and components. Chromatin is DNA with associated proteins (usually histone proteins, around which DNA wraps for organization and packing within a cell). By creating and releasing a mesh or lattice-like structure of chromatin that is coupled with antimicrobial proteins, the neutrophils can mount a highly concentrated and efficient attack against nearby pathogens. Proteins frequently associated with NETs include lactoferrin, gelatinase, cathepsin G, and myeloperoxidase. Each has a different means of promoting antimicrobial activity, helping neutrophils eliminate pathogens. The toxic proteins in NETs may kill some of the body’s own cells along with invading pathogens. However, this collateral damage can be repaired after the danger of the infection has been eliminated.

As neutrophils fight an infection, a visible accumulation of leukocytes, cellular debris, and bacteria at the site of infection can be observed. This buildup is what we call pus (also known as purulent or suppurative discharge or drainage). The presence of pus is a

sign that the immune defenses have been activated against an infection; historically, some physicians believed that inducing pus formation could actually promote the healing of wounds. The practice of promoting “laudable pus” (by, for instance, wrapping a wound in greasy wool soaked in wine) dates back to the ancient physician Galen in the 2nd century AD, and was practiced in variant forms until the 17th century (though it was not universally accepted). Today, this method is no longer practiced because we now know that it is not effective. Although a small amount of pus formation can indicate a strong immune response, artificially inducing pus formation does not promote recovery.

Eosinophils

Eosinophils are granulocytes that protect against protozoa and helminths; they also play a role in allergic reactions. The granules of eosinophils, which readily absorb the acidic reddish dye eosin, contain histamine, degradative enzymes, and a compound known as major basic protein (MBP) (Figure 6.2.3.3). MBP binds to the surface carbohydrates of parasites, and this binding is associated with disruption of the cell membrane and membrane permeability.

Basophils

Basophils have cytoplasmic granules of varied size and are named for their granules’ ability to absorb the basic dye methylene blue (Figure 6.2.3.3). Their stimulation and degranulation can result from multiple triggering events. Activated complement fragments C3a and C5a, produced in the activation cascades of complement proteins, act as anaphylatoxins by inducing degranulation of basophils and inflammatory responses. This cell type is important in allergic reactions and other responses that involve inflammation. One of the most abundant components of basophil granules is histamine, which is released along with other chemical factors when the basophil is stimulated. These chemicals can be chemotactic and can help to open the gaps between cells in the blood vessels. Other mechanisms for basophil triggering require the assistance of antibodies, as discussed in B Lymphocytes and Humoral Immunity.

Mast Cells

Hematopoiesis also gives rise to mast cells, which appear to be derived from the same common myeloid progenitor cell as neutrophils, eosinophils, and basophils. Functionally, mast cells are very similar to basophils, containing many of the same components in their granules (e.g., histamine) and playing a similar role in allergic responses and other inflammatory reactions. However, unlike basophils, mast cells leave the circulating blood and are most frequently found residing in tissues. They are often associated with blood vessels and nerves or found close to surfaces that interface with the external environment, such as the skin and mucous membranes in various regions of the body (Figure 6.2.3.4).

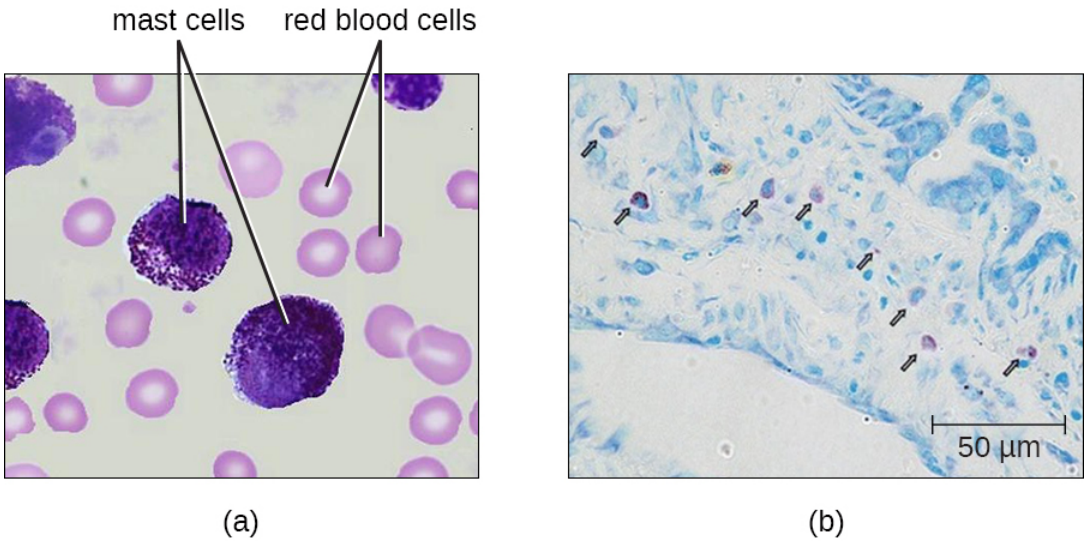


Figure 6.2.3.4: Mast cells function similarly to basophils by inducing and promoting inflammatory responses. (a) This figure shows mast cells in blood. In a blood smear, they are difficult to differentiate from basophils (b). Unlike basophils, mast cells migrate from the blood into various tissues. (credit right: modification of work by Greenland JR, Xu X, Sayah DM, Liu FC, Jones KD, Looney MR, Caughey GH)

Exercise 6.2.3.1

1. Describe the granules and nuclei of neutrophils, eosinophils, basophils, and mast cells.
2. Name three antimicrobial mechanisms of neutrophils

Clinical Focus: Part 3

Angela's tests come back negative for all common allergens, and her sputum samples contain no abnormal presence of pathogenic microbes or elevated levels of members of the normal respiratory microbiota. She does, however, have elevated levels of inflammatory cytokines in her blood.

The swelling of her airway has still not responded to treatment with antihistamines or corticosteroids. Additional blood work shows that Angela has a mildly elevated white blood cell count but normal antibody levels. Also, she has a lower-than-normal level of the complement protein C4.

Exercise 6.2.3.2

1. What does this new information reveal about the cause of Angela's constricted airways?
2. What are some possible conditions that could lead to low levels of complement proteins?

Agranulocytes

As their name suggests, agranulocytes lack visible granules in the cytoplasm. Agranulocytes can be categorized as lymphocytes or monocytes (Figure 6.2.3.2). Among the lymphocytes are natural killer cells, which play an important role in nonspecific innate immune defenses. Lymphocytes also include the B cells and T cells, which are discussed in the next chapter because they are central players in the specific adaptive immune defenses. The monocytes differentiate into macrophages and dendritic cells, which are collectively referred to as the mononuclear phagocyte system.

Natural Killer Cells

Most lymphocytes are primarily involved in the specific adaptive immune response, and thus will be discussed in the following chapter. An exception is the natural killer cells (NK cells); these mononuclear lymphocytes use nonspecific mechanisms to recognize and destroy cells that are abnormal in some way. Cancer cells and cells infected with viruses are two examples of cellular abnormalities that are targeted by NK cells. Recognition of such cells involves a complex process of identifying inhibitory and activating molecular markers on the surface of the target cell. Molecular markers that make up the major histocompatibility complex (MHC) are expressed by healthy cells as an indication of "self." This will be covered in more detail in next chapter. NK cells are able to recognize normal MHC markers on the surface of healthy cells, and these MHC markers serve as an inhibitory signal preventing NK cell activation. However, cancer cells and virus-infected cells actively diminish or eliminate expression of MHC markers on their surface. When these MHC markers are diminished or absent, the NK cell interprets this as an abnormality and a cell in distress. This is one part of the NK cell activation process (Figure 6.2.3.5). NK cells are also activated by binding to activating molecular molecules on the target cell. These activating molecular molecules include "altered self" or "nonself" molecules. When a NK cell recognizes a decrease in inhibitory normal MHC molecules and an increase in activating molecules on the surface of a cell, the NK cell will be activated to eliminate the cell in distress.

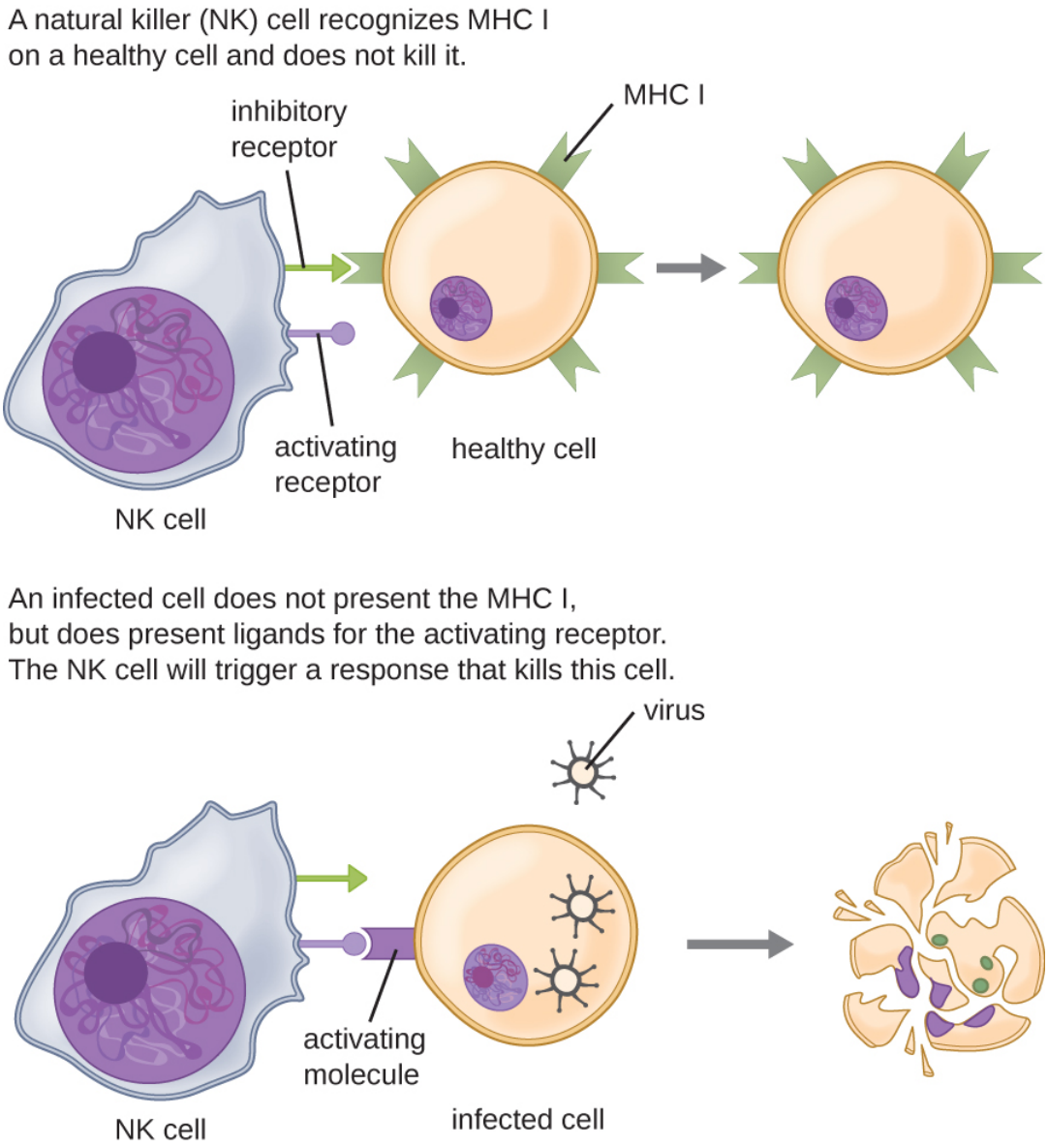


Figure 6.2.3.5: Natural killer (NK) cells are inhibited by the presence of the major histocompatibility cell (MHC) receptor on healthy cells. Cancer cells and virus-infected cells have reduced expression of MHC and increased expression of activating molecules. When a NK cell recognizes decreased MHC and increased activating molecules, it will kill the abnormal cell.

Once a cell has been recognized as a target, the NK cell can use several different mechanisms to kill its target. For example, it may express cytotoxic membrane proteins and cytokines that stimulate the target cell to undergo apoptosis, or controlled cell suicide. NK cells may also use perforin-mediated cytotoxicity to induce apoptosis in target cells. This mechanism relies on two toxins released from granules in the cytoplasm of the NK cell: perforin, a protein that creates pores in the target cell, and granzymes, proteases that enter through the pores into the target cell's cytoplasm, where they trigger a cascade of protein activation that leads to apoptosis. The NK cell binds to the abnormal target cell, releases its destructive payload, and detaches from the target cell. While the target cell undergoes apoptosis, the NK cell synthesizes more perforin and proteases to use on its next target.

NK cells contain these toxic compounds in granules in their cytoplasm. When stained, the granules are azurophilic and can be visualized under a light microscope (Figure 6.2.3.6). Even though they have granules, NK cells are not considered granulocytes because their granules are far less numerous than those found in true granulocytes. Furthermore, NK cells have a different lineage than granulocytes, arising from lymphoid rather than myeloid stem cells (Figure 6.2.3.1).

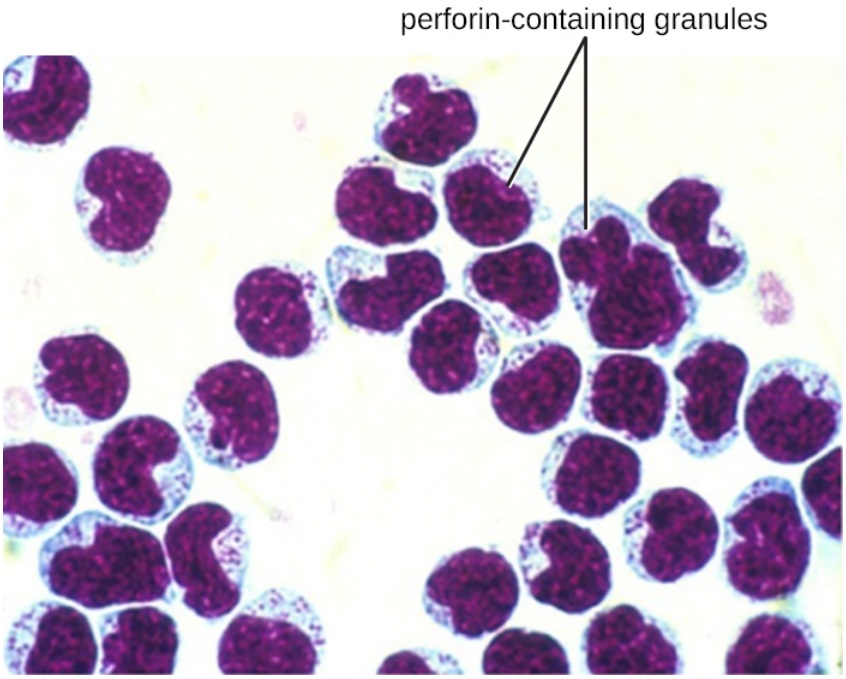


Figure 6.2.3.6: Natural killer cell with perforin-containing granules. (credit: modification of work by Rolstad B)

Monocytes

The largest of the white blood cells, monocytes have a nucleus that lacks lobes, and they also lack granules in the cytoplasm (Figure 6.2.3.7). Nevertheless, they are effective phagocytes, engulfing pathogens and apoptotic cells to help fight infection.

When monocytes leave the bloodstream and enter a specific body tissue, they differentiate into tissue-specific phagocytes called macrophages and dendritic cells. They are particularly important residents of lymphoid tissue, as well as nonlymphoid sites and organs. Macrophages and dendritic cells can reside in body tissues for significant lengths of time. Macrophages in specific body tissues develop characteristics suited to the particular tissue. Not only do they provide immune protection for the tissue in which they reside but they also support normal function of their neighboring tissue cells through the production of cytokines. Macrophages are given tissue-specific names, and a few examples of tissue-specific macrophages are listed in Table 6.2.3.1. Dendritic cells are important sentinels residing in the skin and mucous membranes, which are portals of entry for many pathogens. Monocytes, macrophages, and dendritic cells are all highly phagocytic and important promoters of the immune response through their production and release of cytokines. These cells provide an essential bridge between innate and adaptive immune responses, as discussed in the next section as well as the next chapter.

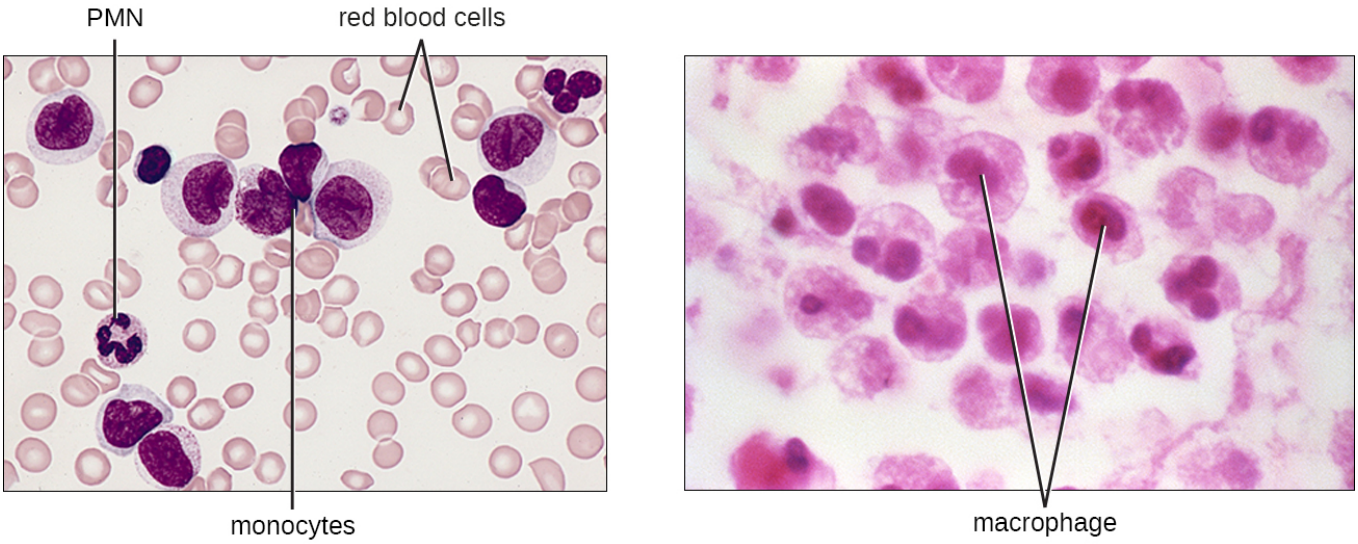


Figure 6.2.3.7: Monocytes are large, agranular white blood cells with a nucleus that lacks lobes. When monocytes leave the bloodstream, they differentiate and become macrophages with tissue-specific properties. (credit left: modification of work by Armed Forces Institute of Pathology; credit right: modification of work by Centers for Disease Control and Prevention)

Table 6.2.3.1: Macrophages Found in Various Body Tissues

Tissue	Macrophage
Brain and central nervous system	Microglial cells
Liver	Kupffer cells
Lungs	Alveolar macrophages (dust cells)
Peritoneal cavity	Peritoneal macrophages

? Exercise 6.2.3.3

1. Describe the signals that activate natural killer cells.
2. What is the difference between monocytes and macrophages?

Key Concepts and Summary

- The **formed elements** of the blood include red blood cells (**erythrocytes**), white blood cells (**leukocytes**), and **platelets (thrombocytes**). Of these, leukocytes are primarily involved in the immune response.
- All formed elements originate in the bone marrow as stem cells (HSCs) that differentiate through **hematopoiesis**.
- **Granulocytes** are leukocytes characterized by a lobed nucleus and granules in the cytoplasm. These include **neutrophils (PMNs)**, **eosinophils**, and **basophils**.
- Neutrophils are the leukocytes found in the largest numbers in the bloodstream and they primarily fight bacterial infections.
- Eosinophils target parasitic infections. Eosinophils and basophils are involved in allergic reactions. Both release histamine and other proinflammatory compounds from their granules upon stimulation.
- **Mast cells** function similarly to basophils but can be found in tissues outside the bloodstream.
- **Natural killer** (**NK**) cells are lymphocytes that recognize and kill abnormal or infected cells by releasing proteins that trigger apoptosis.
- **Monocytes** are large, mononuclear leukocytes that circulate in the bloodstream. They may leave the bloodstream and take up residence in body tissues, where they differentiate and become tissue-specific **macrophages** and **dendritic cells**.

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6.2.4: Pathogen Recognition and Phagocytosis

Learning Objectives

- Explain how leukocytes migrate from peripheral blood into infected tissues
- Explain the mechanisms by which leukocytes recognize pathogens
- Explain the process of phagocytosis and the mechanisms by which phagocytes destroy and degrade pathogens

Several of the cell types discussed in the previous section can be described as phagocytes—cells whose main function is to seek, ingest, and kill pathogens. This process, called phagocytosis, was first observed in starfish in the 1880s by Nobel Prize-winning zoologist Ilya Metchnikoff (1845–1916), who made the connection to white blood cells (WBCs) in humans and other animals. At the time, Pasteur and other scientists believed that WBCs were spreading pathogens rather than killing them (which is true for some diseases, such as tuberculosis). But in most cases, phagocytes provide a strong, swift, and effective defense against a broad range of microbes, making them a critical component of innate nonspecific immunity. This section will focus on the mechanisms by which phagocytes are able to seek, recognize, and destroy pathogens.

Extravasation (Diapedesis) of Leukocytes

Some phagocytes are leukocytes (WBCs) that normally circulate in the bloodstream. To reach pathogens located in infected tissue, leukocytes must pass through the walls of small capillary blood vessels within tissues. This process, called extravasation, or diapedesis, is initiated by complement factor C5a, as well as cytokines released into the immediate vicinity by resident macrophages and tissue cells responding to the presence of the infectious agent (Figure 6.2.4.1). Similar to C5a, many of these cytokines are proinflammatory and chemotactic, and they bind to cells of small capillary blood vessels, initiating a response in the endothelial cells lining the inside of the blood vessel walls. This response involves the upregulation and expression of various cellular adhesion molecules and receptors. Leukocytes passing through will stick slightly to the adhesion molecules, slowing down and rolling along the blood vessel walls near the infected area. When they reach a cellular junction, they will bind to even more of these adhesion molecules, flattening out and squeezing through the cellular junction in a process known as transendothelial migration. This mechanism of “rolling adhesion” allows leukocytes to exit the bloodstream and enter the infected areas, where they can begin phagocytosing the invading pathogens.

Note that extravasation does not occur in arteries or veins. These blood vessels are surrounded by thicker, multilayer protective walls, in contrast to the thin single-cell-layer walls of capillaries. Furthermore, the blood flow in arteries is too turbulent to allow for rolling adhesion. Also, some leukocytes tend to respond to an infection more quickly than others. The first to arrive typically are neutrophils, often within hours of a bacterial infection. By contract, monocytes may take several days to leave the bloodstream and differentiate into macrophages.

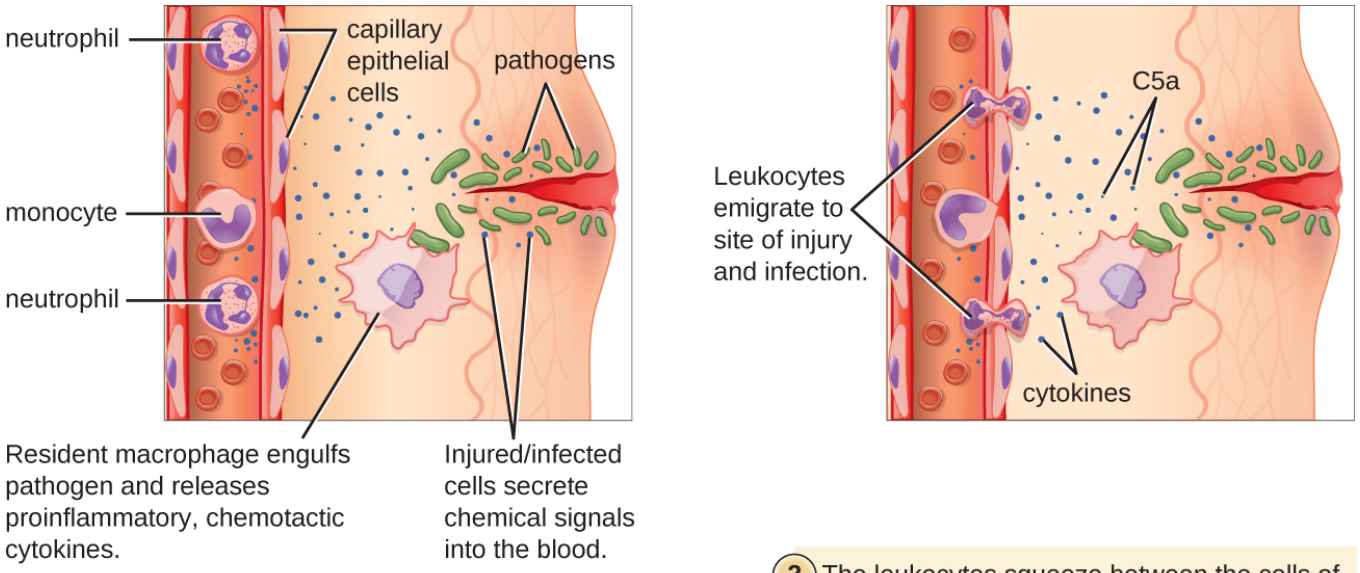


Figure 6.2.4.1: Damaged cells and macrophages that have ingested pathogens release cytokines that are proinflammatory and chemotactic for leukocytes. In addition, activation of complement at the site of infection results in production of the chemotactic and proinflammatory C5a. Leukocytes exit the blood vessel and follow the chemoattractant signal of cytokines and C5a to the site of infection. Granulocytes such as neutrophils release chemicals that destroy pathogens. They are also capable of phagocytosis and intracellular killing of bacterial pathogens.

Link to Learning

Watch the following videos on leukocyte extravasation and leukocyte rolling to learn more.

? Exercise 6.2.4.1

Explain the role of adhesion molecules in the process of extravasation.

Pathogen Recognition

As described in the previous section, opsonization of pathogens by antibody; complement factors C1q, C3b, and C4b; and lectins can assist phagocytic cells in recognition of pathogens and attachment to initiate phagocytosis. However, not all pathogen recognition is opsonin dependent. Phagocytes can also recognize molecular structures that are common to many groups of pathogenic microbes. Such structures are called pathogen-associated molecular patterns (PAMPs). Common PAMPs include the following:

- peptidoglycan, found in bacterial cell walls;
- flagellin, a protein found in bacterial flagella;
- lipopolysaccharide (LPS) from the outer membrane of gram-negative bacteria;
- lipopeptides, molecules expressed by most bacteria; and
- nucleic acids such as viral DNA or RNA.

Like numerous other PAMPs, these substances are integral to the structure of broad classes of microbes.

The structures that allow phagocytic cells to detect PAMPs are called pattern recognition receptors (PRRs). One group of PRRs is the toll-like receptors (TLRs), which bind to various PAMPs and communicate with the nucleus of the phagocyte to elicit a response. Many TLRs (and other PRRs) are located on the surface of a phagocyte, but some can also be found embedded in the membranes of interior compartments and organelles (Figure 6.2.4.2). These interior PRRs can be useful for the binding and recognition of intracellular pathogens that may have gained access to the inside of the cell before phagocytosis could take place. Viral nucleic acids, for example, might encounter an interior PRR, triggering production of the antiviral cytokine interferon.

In addition to providing the first step of pathogen recognition, the interaction between PAMPs and PRRs on macrophages provides an intracellular signal that activates the phagocyte, causing it to transition from a dormant state of readiness and slow proliferation to a state of hyperactivity, proliferation, production/secretion of cytokines, and enhanced intracellular killing. PRRs on macrophages also respond to chemical distress signals from damaged or stressed cells. This allows macrophages to extend their responses beyond protection from infectious diseases to a broader role in the inflammatory response initiated from injuries or other diseases.

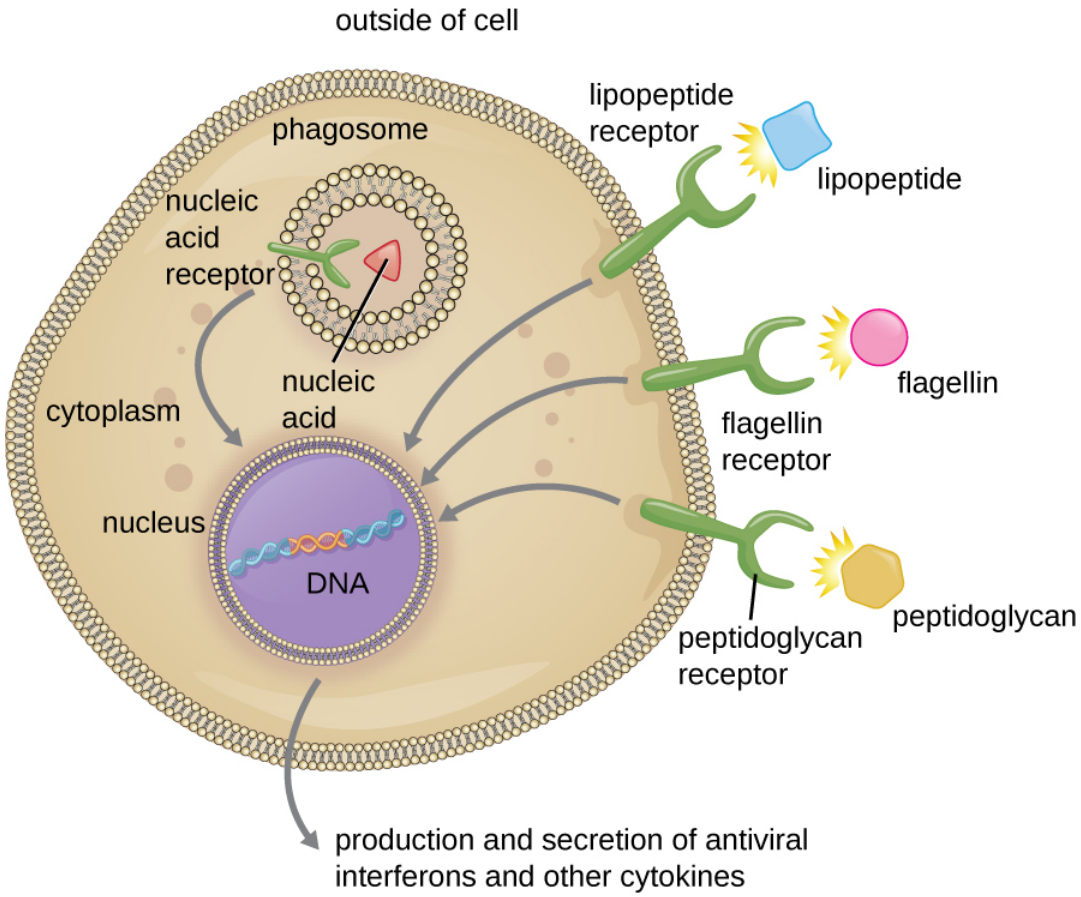


Figure 6.2.4.2: Phagocytic cells contain pattern recognition receptors (PRRs) capable of recognizing various pathogen-associated molecular patterns (PAMPs). These PRRs can be found on the plasma membrane or in internal phagosomes. When a PRR recognizes a PAMP, it sends a signal to the nucleus that activates genes involved in phagocytosis, cellular proliferation, production and secretion of antiviral interferons and proinflammatory cytokines, and enhanced intracellular killing.

? Exercise 6.2.4.2

1. Name four pathogen-associated molecular patterns (PAMPs).
2. Describe the process of phagocyte activation.

Pathogen Degradation

Once pathogen recognition and attachment occurs, the pathogen is engulfed in a vesicle and brought into the internal compartment of the phagocyte in a process called phagocytosis (Figure 6.2.4.3). PRRs can aid in phagocytosis by first binding to the pathogen's surface, but phagocytes are also capable of engulfing nearby items even if they are not bound to specific receptors. To engulf the pathogen, the phagocyte forms a pseudopod that wraps around the pathogen and then pinches it off into a membrane vesicle called a phagosome. Acidification of the phagosome (pH decreases to the range of 4–5) provides an important early antibacterial mechanism. The phagosome containing the pathogen fuses with one or more lysosomes, forming a phagolysosome. Formation of the phagolysosome enhances the acidification, which is essential for activation of pH-dependent digestive lysosomal enzymes and production of hydrogen peroxide and toxic reactive oxygen species. Lysosomal enzymes such as lysozyme, phospholipase, and proteases digest the pathogen. Other enzymes are involved a respiratory burst. During the respiratory burst, phagocytes will increase their uptake and consumption of oxygen, but not for energy production. The increased oxygen consumption is focused on the production of superoxide anion, hydrogen peroxide, hydroxyl radicals, and other reactive oxygen species that are antibacterial.

In addition to the reactive oxygen species produced by the respiratory burst, reactive nitrogen compounds with cytotoxic (cell-killing) potential can also form. For example, nitric oxide can react with superoxide to form peroxynitrite, a highly reactive nitrogen compound with degrading capabilities similar to those of the reactive oxygen species. Some phagocytes even contain an internal storehouse of microbicidal defensin proteins (e.g., neutrophil granules). These destructive forces can be released into the

area around the cell to degrade microbes externally. Neutrophils, especially, can be quite efficient at this secondary antimicrobial mechanism.

Once degradation is complete, leftover waste products are excreted from the cell in an exocytic vesicle. However, it is important to note that not all remains of the pathogen are excreted as waste. Macrophages and dendritic cells are also antigen-presenting cells involved in the specific adaptive immune response. These cells further process the remains of the degraded pathogen and present key antigens (specific pathogen proteins) on their cellular surface. This is an important step for stimulation of some adaptive immune responses, as will be discussed in more detail in the next chapter.

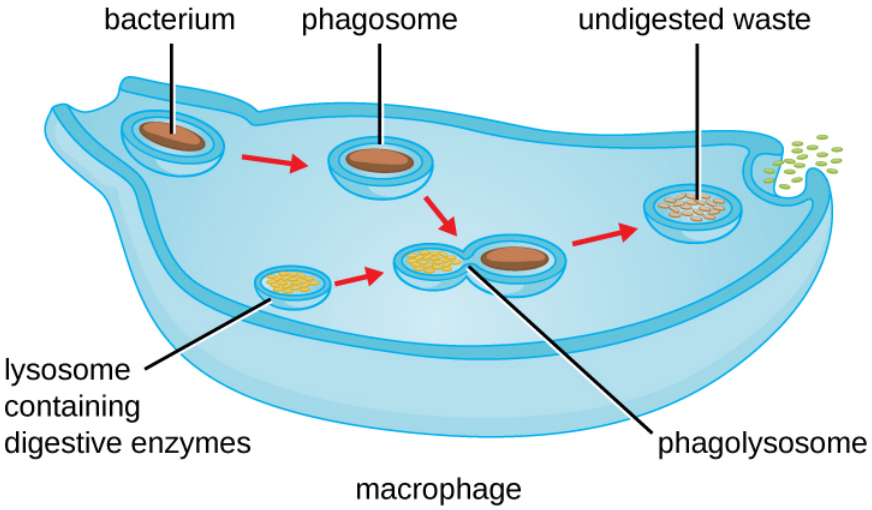


Figure 6.2.4.3: The stages of phagocytosis include the engulfment of a pathogen, the formation of a phagosome, the digestion of the pathogenic particle in the phagolysosome, and the expulsion of undigested materials from the cell.

Link to Learning

Visit this link to view a phagocyte chasing and engulfing a pathogen.

Exercise 6.2.4.3

What is the difference between a phagosome and a lysosome?

When Phagocytosis Fails

Although phagocytosis successfully destroys many pathogens, some are able to survive and even exploit this defense mechanism to multiply in the body and cause widespread infection. Protozoans of the genus *Leishmania* are one example. These obligate intracellular parasites are flagellates transmitted to humans by the bite of a sand fly. Infections cause serious and sometimes disfiguring sores and ulcers in the skin and other tissues (Figure 6.2.4.4). Worldwide, an estimated 1.3 million people are newly infected with leishmaniasis annually.

Salivary peptides from the sand fly activate host macrophages at the site of their bite. The classic or alternate pathway for complement activation ensues with C3b opsonization of the parasite. *Leishmania* cells are phagocytosed, lose their flagella, and multiply in a form known as an amastigote (Leishman-Donovan body) within the phagolysosome. Although many other pathogens are destroyed in the phagolysosome, survival of the *Leishmania* amastigotes is maintained by the presence of surface lipophosphoglycan and acid phosphatase. These substances inhibit the macrophage respiratory burst and lysosomal enzymes. The parasite then multiplies inside the cell and lyses the infected macrophage, releasing the amastigotes to infect other macrophages within the same host. Should another sand fly bite an infected person, it might ingest amastigotes and then transmit them to another individual through another bite.

There are several different forms of leishmaniasis. The most common is a localized cutaneous form of the illness caused by *L. tropica*, which typically resolves spontaneously over time but with some significant lymphocyte infiltration and permanent scarring. A mucocutaneous form of the disease, caused by *L. viannia brasilienfsis*, produces lesions in the tissue of the nose

and mouth and can be life threatening. A visceral form of the illness can be caused by several of the different *Leishmania* species. It affects various organ systems and causes abnormal enlargement of the liver and spleen. Irregular fevers, anemia, liver dysfunction, and weight loss are all signs and symptoms of visceral leishmaniasis. If left untreated, it is typically fatal.

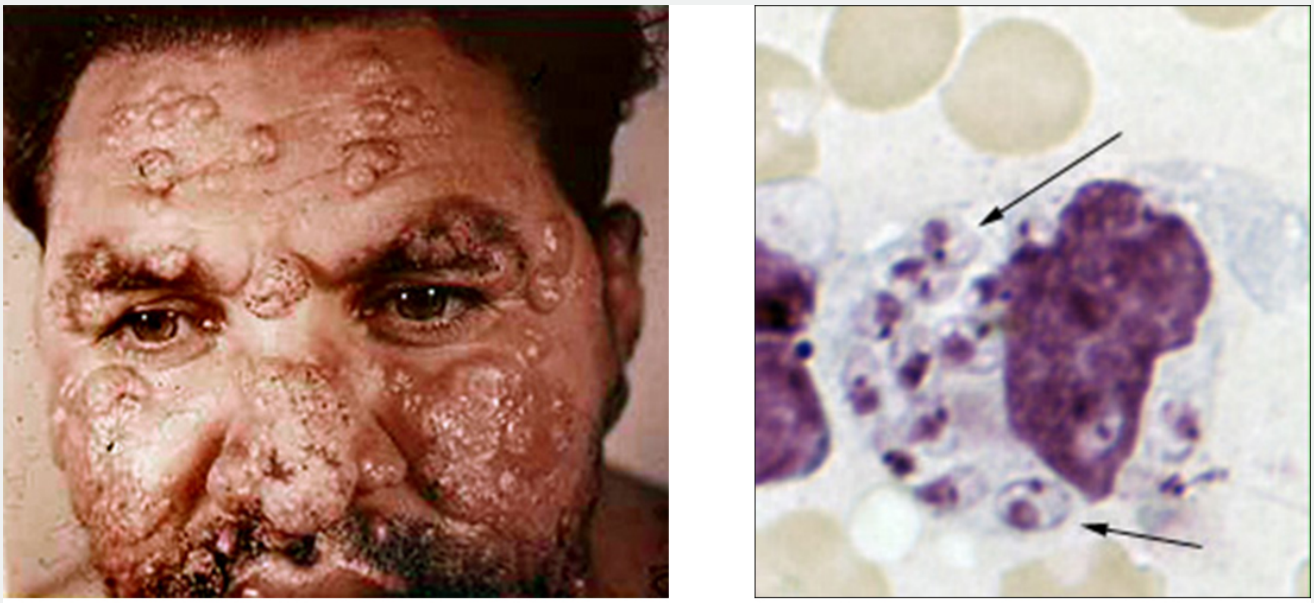


Figure 6.2.4.4: (a) Cutaneous leishmaniasis is a disfiguring disease caused by the intracellular flagellate *Leishmania tropica*, transmitted by the bite of a sand fly. (b) This light micrograph of a sample taken from a skin lesion shows a large cell, which is a macrophage infected with *L. tropica* amastigotes (arrows). The amastigotes have lost their flagella but their nuclei are visible. Soon the amastigotes will lyse the macrophage and be engulfed by other phagocytes, spreading the infection. (credit a: modification of work by Otis Historical Archives of "National Museum of Health & Medicine"; credit b: modification of work by Centers for Disease Control and Prevention)

Key Concepts and Summary

- Phagocytes are cells that recognize pathogens and destroy them through phagocytosis.
- Recognition often takes place by the use of phagocyte receptors that bind molecules commonly found on pathogens, known as **pathogen-associated molecular patterns (PAMPs)**.
- The receptors that bind PAMPs are called **pattern recognition receptors**, or **PRRs**. **Toll-like receptors** (**TLRs**) are one type of PRR found on phagocytes.
- **Extravasation** of white blood cells from the bloodstream into infected tissue occurs through the process of **transendothelial migration**.
- Phagocytes degrade pathogens through **phagocytosis**, which involves engulfing the pathogen, killing and digesting it within a **phagolysosome**, and then excreting undigested matter.

Footnotes

1. 1 World Health Organization. "Leishmaniasis." 2016. http://www.who.int/mediacentre/factsheets/fs375/en/.

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6.2.5: Inflammation and Fever

Learning Objectives

- Identify the signs of inflammation and fever and explain why they occur
- Explain the advantages and risks posed by inflammatory responses

The inflammatory response, or inflammation, is triggered by a cascade of chemical mediators and cellular responses that may occur when cells are damaged and stressed or when pathogens successfully breach the physical barriers of the innate immune system. Although inflammation is typically associated with negative consequences of injury or disease, it is a necessary process insofar as it allows for recruitment of the cellular defenses needed to eliminate pathogens, remove damaged and dead cells, and initiate repair mechanisms. Excessive inflammation, however, can result in local tissue damage and, in severe cases, may even become deadly.

Acute Inflammation

An early, if not immediate, response to tissue injury is acute inflammation. Immediately following an injury, vasoconstriction of blood vessels will occur to minimize blood loss. The amount of vasoconstriction is related to the amount of vascular injury, but it is usually brief. Vasoconstriction is followed by vasodilation and increased vascular permeability, as a direct result of the release of histamine from resident mast cells. Increased blood flow and vascular permeability can dilute toxins and bacterial products at the site of injury or infection. They also contribute to the five observable signs associated with the inflammatory response: erythema (redness), edema (swelling), heat, pain, and altered function. Vasodilation and increased vascular permeability are also associated with an influx of phagocytes at the site of injury and/or infection. This can enhance the inflammatory response because phagocytes may release proinflammatory chemicals when they are activated by cellular distress signals released from damaged cells, by PAMPs, or by opsonins on the surface of pathogens. Activation of the complement system can further enhance the inflammatory response through the production of the anaphylatoxin C5a. Figure 6.2.5.1 illustrates a typical case of acute inflammation at the site of a skin wound.

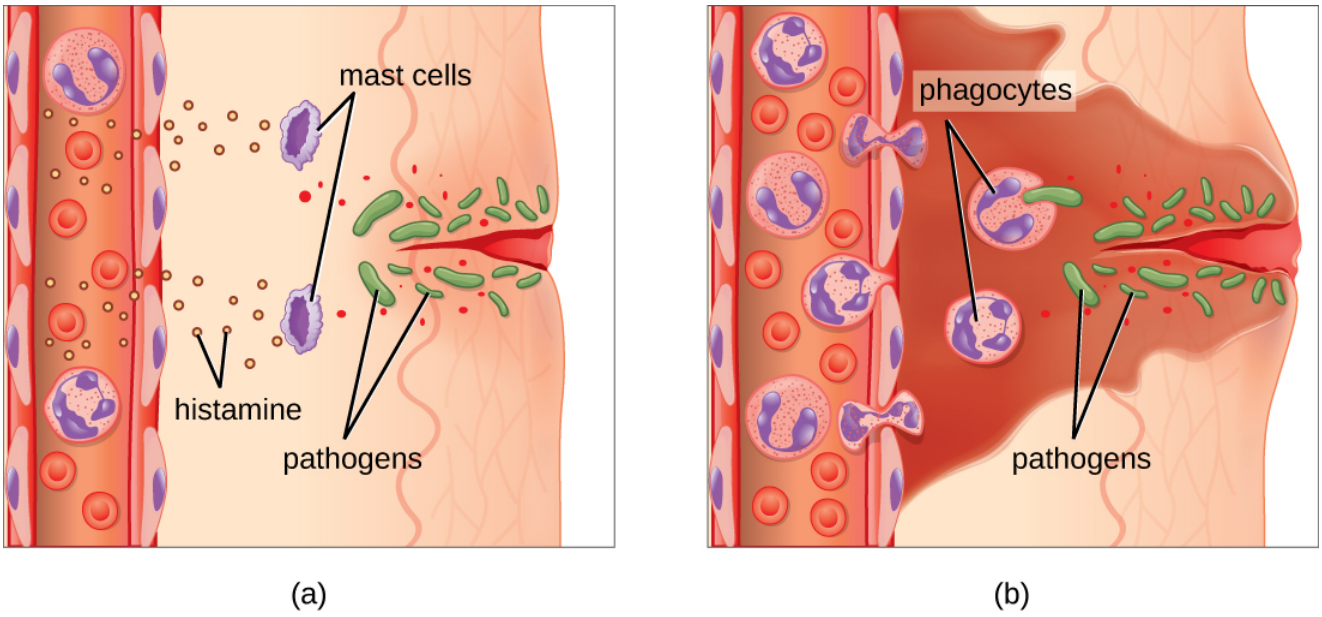


Figure 6.2.5.1: (a) Mast cells detect injury to nearby cells and release histamine, initiating an inflammatory response. (b) Histamine increases blood flow to the wound site, and increased vascular permeability allows fluid, proteins, phagocytes, and other immune cells to enter infected tissue. These events result in the swelling and reddening of the injured site, and the increased blood flow to the injured site causes it to feel warm. Inflammation is also associated with pain due to these events stimulating nerve pain receptors in the tissue. The interaction of phagocyte PRRs with cellular distress signals and PAMPs and opsonins on the surface of pathogens leads to the release of more proinflammatory chemicals, enhancing the inflammatory response.

During the period of inflammation, the release of bradykinin causes capillaries to remain dilated, flooding tissues with fluids and leading to edema. Increasing numbers of neutrophils are recruited to the area to fight pathogens. As the fight rages on, pus forms

from the accumulation of neutrophils, dead cells, tissue fluids, and lymph. Typically, after a few days, macrophages will help to clear out this pus. Eventually, tissue repair can begin in the wounded area.

Chronic Inflammation

When acute inflammation is unable to clear an infectious pathogen, chronic inflammation may occur. This often results in an ongoing (and sometimes futile) lower-level battle between the host organism and the pathogen. The wounded area may heal at a superficial level, but pathogens may still be present in deeper tissues, stimulating ongoing inflammation. Additionally, chronic inflammation may be involved in the progression of degenerative neurological diseases such as Alzheimer's and Parkinson's, heart disease, and metastatic cancer.

Chronic inflammation may lead to the formation of granulomas, pockets of infected tissue walled off and surrounded by WBCs. Macrophages and other phagocytes wage an unsuccessful battle to eliminate the pathogens and dead cellular materials within a granuloma. One example of a disease that produces chronic inflammation is tuberculosis, which results in the formation of granulomas in lung tissues. A tubercular granuloma is called a tubercle (Figure 6.2.5.2). Tuberculosis will be covered in more detail in Bacterial Infections of the Respiratory Tract.

Chronic inflammation is not just associated with bacterial infections. Chronic inflammation can be an important cause of tissue damage from viral infections. The extensive scarring observed with hepatitis C infections and liver cirrhosis is the result of chronic inflammation.

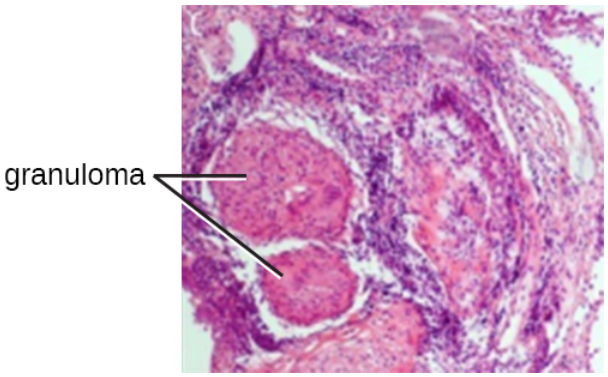


Figure 6.2.5.2: A tubercle is a granuloma in the lung tissue of a patient with tuberculosis. In this micrograph, white blood cells (stained purple) have walled off a pocket of tissue infected with *Mycobacterium tuberculosis*. Granulomas also occur in many other forms of disease. (credit: modification of work by Piotrowski WJ, Górski P, Duda-Szymańska J, Kwiatkowska S)

? Exercise 6.2.5.1

1. Name the five signs of inflammation.
2. Is a granuloma an acute or chronic form of inflammation? Explain.

Chronic Edema

In addition to granulomas, chronic inflammation can also result in long-term edema. A condition known as lymphatic filariasis (also known as elephantiasis) provides an extreme example. Lymphatic filariasis is caused by microscopic nematodes (parasitic worms) whose larvae are transmitted between human hosts by mosquitoes. Adult worms live in the lymphatic vessels, where their presence stimulates infiltration by lymphocytes, plasma cells, eosinophils, and thrombocytes (a condition known as lymphangitis). Because of the chronic nature of the illness, granulomas, fibrosis, and blocking of the lymphatic system may eventually occur. Over time, these blockages may worsen with repeated infections over decades, leading to skin thickened with edema and fibrosis. Lymph (extracellular tissue fluid) may spill out of the lymphatic areas and back into tissues, causing extreme swelling (Figure 6.2.5.3). Secondary bacterial infections commonly follow. Because it is a disease caused by a parasite, eosinophilia (a dramatic rise in the number of eosinophils in the blood) is characteristic of acute infection. However, this increase in antiparasite granulocytes is not sufficient to clear the infection in many cases.

Lymphatic filariasis affects an estimated 120 million people worldwide, mostly concentrated in Africa and Asia. Improved sanitation and mosquito control can reduce transmission rates.



Figure 6.2.5.3: Elephantiasis (chronic edema) of the legs due to filariasis. (credit: modification of work by Centers for Disease Control and Prevention)

Fever

A fever is an inflammatory response that extends beyond the site of infection and affects the entire body, resulting in an overall increase in body temperature. Body temperature is normally regulated and maintained by the hypothalamus, an anatomical section of the brain that functions to maintain homeostasis in the body. However, certain bacterial or viral infections can result in the production of pyrogens, chemicals that effectively alter the “thermostat setting” of the hypothalamus to elevate body temperature and cause fever. Pyrogens may be exogenous or endogenous. For example, the endotoxin lipopolysaccharide (LPS), produced by gram-negative bacteria, is an exogenous pyrogen that may induce the leukocytes to release endogenous pyrogens such as interleukin-1 (IL-1), IL-6, interferon-γ (IFN-γ), and tumor necrosis factor (TNF). In a cascading effect, these molecules can then lead to the release of prostaglandin E2 (PGE_2) from other cells, resetting the hypothalamus to initiate fever (Figure 6.2.5.4).



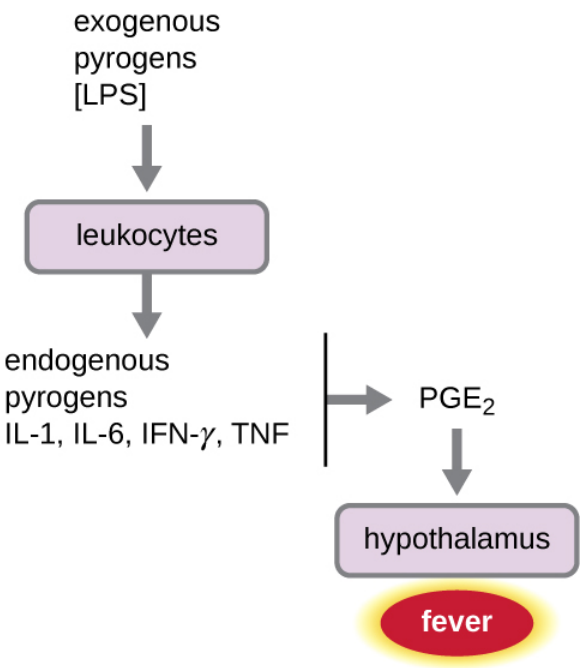


Figure 6.2.5.4: The role of the hypothalamus in the inflammatory response. Macrophages recognize pathogens in an area and release cytokines that trigger inflammation. The cytokines also send a signal up the vagus nerve to the hypothalamus.

Like other forms of inflammation, a fever enhances the innate immune defenses by stimulating leukocytes to kill pathogens. The rise in body temperature also may inhibit the growth of many pathogens since human pathogens are mesophiles with optimum growth occurring around 35 °C (95 °F). In addition, some studies suggest that fever may also stimulate release of iron-sequestering compounds from the liver, thereby starving out microbes that rely on iron for growth.[2]

During fever, the skin may appear pale due to vasoconstriction of the blood vessels in the skin, which is mediated by the hypothalamus to divert blood flow away from extremities, minimizing the loss of heat and raising the core temperature. The hypothalamus will also stimulate shivering of muscles, another effective mechanism of generating heat and raising the core temperature.

The crisis phase occurs when the fever breaks. The hypothalamus stimulates vasodilation, resulting in a return of blood flow to the skin and a subsequent release of heat from the body. The hypothalamus also stimulates sweating, which cools the skin as the sweat evaporates.

Although a low-level fever may help an individual overcome an illness, in some instances, this immune response can be too strong, causing tissue and organ damage and, in severe cases, even death. The inflammatory response to bacterial superantigens is one scenario in which a life-threatening fever may develop. Superantigens are bacterial or viral proteins that can cause an excessive activation of T cells from the specific adaptive immune defense, as well as an excessive release of cytokines that overstimulates the inflammatory response. For example, *Staphylococcus aureus* and *Streptococcus pyogenes* are capable of producing superantigens that cause toxic shock syndrome and scarlet fever, respectively. Both of these conditions can be associated with very high, life-threatening fevers in excess of 42 °C (108 °F).

? Exercise 6.2.5.2

1. Explain the difference between exogenous and endogenous pyrogens.
2. How does a fever inhibit pathogens?

Clinical Focus: Resolution

Given her father's premature death, Angela's doctor suspects that she has hereditary angioedema, a genetic disorder that compromises the function of C1 inhibitor protein. Patients with this genetic abnormality may have occasional episodes of swelling in various parts of the body. In Angela's case, the swelling has occurred in the respiratory tract, leading to difficulty

breathing. Swelling may also occur in the gastrointestinal tract, causing abdominal cramping, diarrhea, and vomiting, or in the muscles of the face or limbs. This swelling may be nonresponsive to steroid treatment and is often misdiagnosed as an allergy.

Because there are three types of hereditary angioedema, the doctor orders a more specific blood test to look for levels of C1-INH, as well as a functional assay of Angela's C1 inhibitors. The results suggest that Angela has type I hereditary angioedema, which accounts for 80%–85% of all cases. This form of the disorder is caused by a deficiency in C1 esterase inhibitors, the proteins that normally help suppress activation of the complement system. When these proteins are deficient or nonfunctional, overstimulation of the system can lead to production of inflammatory anaphylatoxins, which results in swelling and fluid buildup in tissues.

There is no cure for hereditary angioedema, but timely treatment with purified and concentrated C1-INH from blood donors can be effective, preventing tragic outcomes like the one suffered by Angela's father. A number of therapeutic drugs, either currently approved or in late-stage human trials, may also be considered as options for treatment in the near future. These drugs work by inhibiting inflammatory molecules or the receptors for inflammatory molecules.

Thankfully, Angela's condition was quickly diagnosed and treated. Although she may experience additional episodes in the future, her prognosis is good and she can expect to live a relatively normal life provided she seeks treatment at the onset of symptoms.

Key Concepts and Summary

- **Inflammation** results from the collective response of chemical mediators and cellular defenses to an injury or infection.
- **Acute inflammation** is short lived and localized to the site of injury or infection. **Chronic inflammation** occurs when the inflammatory response is unsuccessful, and may result in the formation of **granulomas** (e.g., with tuberculosis) and scarring (e.g., with hepatitis C viral infections and liver cirrhosis).
- The five cardinal signs of inflammation are **erythema**, **edema**, heat, pain, and altered function. These largely result from innate responses that draw increased blood flow to the injured or infected tissue.
- **Fever** is a system-wide sign of inflammation that raises the body temperature and stimulates the immune response.
- Both inflammation and fever can be harmful if the inflammatory response is too severe.

Footnotes

1. 1 Centers for Disease Control and Prevention. "Parasites–Lymphatic Filiariasis." 2016. http://www.cdc.gov/parasites/lymphat...info/faqs.html.
2. 2 N. Parrow et al. "Sequestration and Scavenging of Iron in Infection." *Infection and Immunity* 81 no. 10 (2013):3503–3514

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6.2.E: Innate Nonspecific Host Defenses (Exercises)

17.1: Physical Defenses

Nonspecific innate immunity provides a first line of defense against infection by nonspecifically blocking entry of microbes and targeting them for destruction or removal from the body. The physical defenses of innate immunity include physical barriers, mechanical actions that remove microbes and debris, and the microbiome, which competes with and inhibits the growth of pathogens. The skin, mucous membranes, and endothelia throughout the body serve as physical barriers.

Multiple Choice

Which of the following best describes the innate nonspecific immune system?

A. a targeted and highly specific response to a single pathogen or molecule
B. a generalized and nonspecific set of defenses against a class or group of pathogens
C. a set of barrier mechanisms that adapts to specific pathogens after repeated exposure
D. the production of antibody molecules against pathogens

Answer

B

Which of the following constantly sheds dead cells along with any microbes that may be attached to those cells?

A. epidermis
B. dermis
C. hypodermis
D. mucous membrane

Answer

A

Which of the following uses a particularly dense suite of tight junctions to prevent microbes from entering the underlying tissue?

A. the mucociliary escalator
B. the epidermis
C. the blood-brain barrier
D. the urethra

Answer

C

Fill in the Blank

The muscular contraction of the intestines that results in movement of material through the digestive tract is called _____.

Answer

peristalsis

_____ are the hair-like appendages of cells lining parts of the respiratory tract that sweep debris away from the lungs.

Answer

cilia

Secretions that bathe and moisten the interior of the intestines are produced by _____ cells.

Answer

goblet

Short Answer

Differentiate a physical barrier from a mechanical removal mechanism and give an example of each.

Identify some ways that pathogens can breach the physical barriers of the innate immune system.

17.2: Chemical Defenses

Numerous chemical mediators produced endogenously and exogenously exhibit nonspecific antimicrobial functions. Many chemical mediators are found in body fluids such as sebum, saliva, mucus, gastric and intestinal fluids, urine, tears, cerumen, and vaginal secretions. Antimicrobial peptides (AMPs) found on the skin and in other areas of the body are largely produced in response to the presence of pathogens. These include dermcidin, cathelicidin, defensins, histatins, and bacteriocins.

Multiple Choice

Which of the following serve as chemical signals between cells and stimulate a wide range of nonspecific defenses?

A. cytokines
B. antimicrobial peptides
C. complement proteins
D. antibodies

Answer

A

Bacteriocins and defensins are types of which of the following?

A. leukotrienes
B. cytokines
C. inflammation-eliciting mediators
D. antimicrobial peptides

Answer

D

Which of the following chemical mediators is secreted onto the surface of the skin?

A. cerumen
B. sebum
C. gastric acid
D. prostaglandin

Answer

B

Identify the complement activation pathway that is triggered by the binding of an acute-phase protein to a pathogen.

A. classical
B. alternate
C. lectin
D. cathelicidin

Answer

C

Histamine, leukotrienes, prostaglandins, and bradykinin are examples of which of the following?

A. chemical mediators primarily found in the digestive system
B. chemical mediators that promote inflammation
C. antimicrobial peptides found on the skin
D. complement proteins that form MACs

Answer

B

Fill in the Blank

_____ are antimicrobial peptides produced by members of the normal microbiota.

Answer

bacteriocins

_____ is the fluid portion of a blood sample that has been drawn in the presence of an anticoagulant compound.

Answer

plasma

The process by which cells are drawn or attracted to an area by a microbe invader is known as _____.

Answer

chemotaxis

Short Answer

Differentiate the main activation methods of the classic, alternative, and lectin complement cascades.

What are the four protective outcomes of complement activation?

17.3: Cellular Defenses

The formed elements of the blood include red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (thrombocytes). Of these, leukocytes are primarily involved in the immune response. All formed elements originate in the bone marrow as stem cells (HSCs) that differentiate through hematopoiesis. Granulocytes are leukocytes characterized by a lobed nucleus and granules in the cytoplasm. These include neutrophils (PMNs), eosinophils, and basophils.

Multiple Choice

White blood cells are also referred to as which of the following?

A. platelets
B. erythrocytes
C. leukocytes
D. megakaryocytes

Answer

C

Hematopoiesis occurs inwhich of the following?

A. liver
B. bone marrow
C. kidneys
D. central nervous system

Answer

B

Granulocytes are which type of cell?

A. lymphocyte
B. erythrocyte
C. megakaryocyte
D. leukocyte

Answer

D

Matching

Match each cell type with its description.

___natural killer cell	A. stains with basic dye methylene blue, has large amounts of histamine in granules, and facilitates allergic responses and inflammation
___basophil	B. stains with acidic dye eosin, has histamine and major basic protein in granules, and facilitates responses to protozoa and helminths
___macrophage	C. recognizes abnormal cells, binds to them, and releases perforin and granzyme molecules, which induce apoptosis
___eosinophil	D. large agranular phagocyte that resides in tissues such as the brain and lungs

Answer

C, A, D, B

Match each cellular defense with the infection it would most likely target.

___natural killer cell	A. virus-infected cell
___neutrophil	B. tapeworm in the intestines
___eosinophil	C. bacteria in a skin lesion

Answer

A, C, B

Fill in the Blank

Platelets are also called _____.

Answer

thrombocytes

The cell in the bone marrow that gives rise to all other blood cell types is the _____.

Answer

pluripotent hematopoietic stem cell (HSC)

PMNs are another name for _____.

Answer

neutrophils

Kupffer cells residing in the liver are a type of _____.

Answer

macrophage

_____ are similar to basophils, but reside in tissues rather than circulating in the blood.

Answer

mast cells

Short Answer

Explain the difference between plasma and the formed elements of the blood.

List three ways that a neutrophil can destroy an infectious bacterium.

Critical Thinking

Neutrophils can sometimes kill human cells along with pathogens when they release the toxic contents of their granules into the surrounding tissue. Likewise, natural killer cells target human cells for destruction. Explain why it is advantageous for the immune system to have cells that can kill human cells as well as pathogens.

Refer to Figure 17.3.2. In a blood smear taken from a healthy patient, which type of leukocyte would you expect to observe in the highest numbers?

17.4: Pathogen Recognition and Phagocytosis

Phagocytes are cells that recognize pathogens and destroy them through phagocytosis. Recognition often takes place by the use of phagocyte receptors that bind molecules commonly found on pathogens, known as pathogen-associated molecular patterns (PAMPs). The receptors that bind PAMPs are called pattern recognition receptors, or PRRs. Toll-like receptors (TLRs) are one type of PRR found on phagocytes.

Multiple Choice

PAMPs would be found on the surface of which of the following?

A. pathogen
B. phagocyte
C. skin cell
D. blood vessel wall

Answer

A

_____ on phagocytes bind to PAMPs on bacteria, which triggers the uptake and destruction of the bacterial pathogens?

A. PRRs
B. AMPs
C. PAMPs
D. PMNs

Answer

A

Which of the following best characterizes the mode of pathogen recognition for opsonin-dependent phagocytosis?

A. Opsonins produced by a pathogen attract phagocytes through chemotaxis.
B. A PAMP on the pathogen's surface is recognized by a phagocyte's toll-like receptors.
C. A pathogen is first coated with a molecule such as a complement protein, which allows it to be recognized by phagocytes.
D. A pathogen is coated with a molecule such as a complement protein that immediately lyses the cell.

Answer

C

Fill in the Blank

_____, also known as diapedesis, refers to the exit from the bloodstream of neutrophils and other circulating leukocytes.

Answer

extravasation

Toll-like receptors are examples of _____.

Answer

pattern-recognition receptors (PRRs)

Short Answer

Briefly summarize the events leading up to and including the process of transendothelial migration.

17.5: Inflammation and Fever

Inflammation results from the collective response of chemical mediators and cellular defenses to an injury or infection. Acute inflammation is short lived and localized to the site of injury or infection. Chronic inflammation occurs when the inflammatory response is unsuccessful, and may result in the formation of granulomas (e.g., with tuberculosis) and scarring (e.g., with hepatitis C viral infections and liver cirrhosis).

Multiple Choice

Which refers to swelling as a result of inflammation?

A. erythema
B. edema
C. granuloma
D. vasodilation

Answer

B

Which type of inflammation occurs at the site of an injury or infection?

A. acute
B. chronic
C. endogenous
D. exogenous

Answer

A

Fill in the Blank

A(n) _____ is a walled-off area of infected tissue that exhibits chronic inflammation.

Answer

granuloma

The _____ is the part of the body responsible for regulating body temperature.

Answer

hypothalamus

Heat and redness, or _____, occur when the small blood vessels in an inflamed area dilate (open up), bringing more blood much closer to the surface of the skin.

Answer

erythema

Short Answer

Differentiate exogenous and endogenous pyrogens, and provide an example of each.

Critical Thinking

If a gram-negative bacterial infection reaches the bloodstream, large quantities of LPS can be released into the blood, resulting in a syndrome called septic shock. Death due to septic shock is a real danger. The overwhelming immune and inflammatory responses that occur with septic shock can cause a perilous drop in blood pressure; intravascular blood clotting; development of thrombi and emboli that block blood vessels, leading to tissue death; failure of multiple organs; and death of the patient. Identify and characterize two to three therapies that might be useful in stopping the dangerous events and outcomes of septic shock once it has begun, given what you have learned about inflammation and innate immunity in this chapter.

In Lubeck, Germany, in 1930, a group of 251 infants was accidentally administered a tainted vaccine for tuberculosis that contained live *Mycobacterium tuberculosis*. This vaccine was administered orally, directly exposing the infants to the deadly bacterium. Many of these infants contracted tuberculosis, and some died. However, 44 of the infants never contracted tuberculosis. Based on your knowledge of the innate immune system, what innate defenses might have inhibited *M. tuberculosis* enough to prevent these infants from contracting the disease?

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SECTION OVERVIEW

6.3: Specific Adaptive Host Defenses

People living in developed nations and born in the 1960s or later may have difficulty understanding the once heavy burden of devastating infectious diseases. For example, smallpox, a deadly viral disease, once destroyed entire civilizations but has since been eradicated. Thanks to the vaccination efforts by multiple groups, including the World Health Organization, Rotary International, and the United Nations Children's Fund (UNICEF), smallpox has not been diagnosed in a patient since 1977. Polio is another excellent example. This crippling viral disease paralyzed patients, who were often kept alive in "iron lung wards" as recently as the 1950s (Figure 6.3.1). Today, vaccination against polio has nearly eradicated the disease. Vaccines have also reduced the prevalence of once-common infectious diseases such as chickenpox, German measles, measles, mumps, and whooping cough. The success of these and other vaccines is due to the very specific and adaptive host defenses that are the focus of this chapter.

Innate Nonspecific Host Defenses described innate immunity against microbial pathogens. Higher animals, such as humans, also possess an adaptive immune defense, which is highly specific for individual microbial pathogens. This specific adaptive immunity is acquired through active infection or vaccination and serves as an important defense against pathogens that evade the defenses of innate immunity.



Figure 6.3.1: Polio was once a common disease with potentially serious consequences, including paralysis. Vaccination has all but eliminated the disease from most countries around the world. An iron-lung ward, such as the one shown in this 1953 photograph, housed patients paralyzed from polio and unable to breathe for themselves.

6.3.1: Architecture of the Immune System

6.3.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes

6.3.3: T Lymphocytes

6.3.4: B Lymphocytes and Antibodies

6.3.5: Vaccines

6.3.E: Specific Adaptive Host Defenses (Exercises)

Thumbnail: From left to right: erythrocyte, platelet and lymphocyte. (Public Domain; The National Cancer Institute at Frederick).

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6.3.1: Architecture of the Immune System

Learning Objectives

- Define memory, primary response, secondary response, and specificity
- Distinguish between humoral and cellular immunity
- Differentiate between antigens, epitopes, and haptens
- Describe the structure and function of antibodies and distinguish between the different classes of antibodies

Clinical Focus: Part 1

Olivia, a one-year old infant, is brought to the emergency room by her parents, who report her symptoms: excessive crying, irritability, sensitivity to light, unusual lethargy, and vomiting. A physician feels swollen lymph nodes in Olivia's throat and armpits. In addition, the area of the abdomen over the spleen is swollen and tender.

Exercise 6.3.1.1

1. What do these symptoms suggest?
2. What tests might be ordered to try to diagnose the problem?

Adaptive immunity is defined by two important characteristics: specificity and memory. Specificity refers to the adaptive immune system's ability to target specific pathogens, and memory refers to its ability to quickly respond to pathogens to which it has previously been exposed. For example, when an individual recovers from chickenpox, the body develops a *memory* of the infection that will *specifically* protect it from the causative agent, the varicella-zoster virus, if it is exposed to the virus again later.

Specificity and memory are achieved by essentially programming certain cells involved in the immune response to respond rapidly to subsequent exposures of the pathogen. This programming occurs as a result of the first exposure to a pathogen or vaccine, which triggers a primary response. Subsequent exposures result in a secondary response that is faster and stronger as a result of the body's memory of the first exposure (Figure 6.3.1.1). This secondary response, however, is specific to the pathogen in question. For example, exposure to one virus (e.g., varicella-zoster virus) will not provide protection against other viral diseases (e.g., measles, mumps, or polio).

Adaptive specific immunity involves the actions of two distinct cell types: B lymphocytes (B cells) and T lymphocytes (T cells). Although B cells and T cells arise from a common hematopoietic stem cell differentiation pathway, their sites of maturation and their roles in adaptive immunity are very different.

B cells mature in the bone marrow and are responsible for the production of glycoproteins called antibodies, or immunoglobulins. Antibodies are involved in the body's defense against pathogens and toxins in the extracellular environment. Mechanisms of adaptive specific immunity that involve B cells and antibody production are referred to as humoral immunity. The maturation of T cells occurs in the thymus. T cells function as the central orchestrator of both innate and adaptive immune responses. They are also responsible for destruction of cells infected with intracellular pathogens. The targeting and destruction of intracellular pathogens by T cells is called cell-mediated immunity, or cellular immunity.

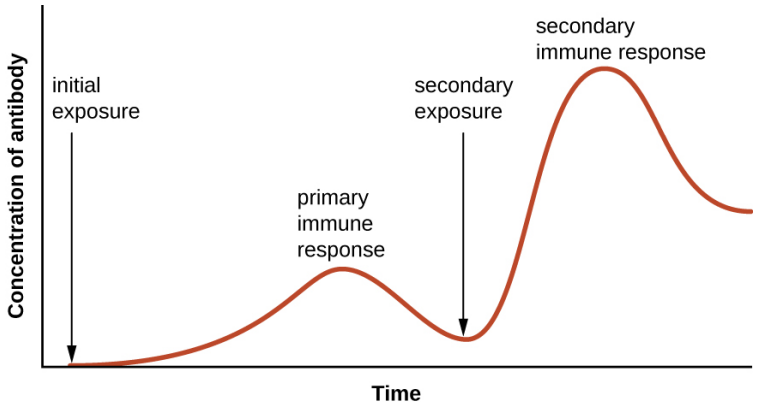


Figure 6.3.1.1: This graph illustrates the primary and secondary immune responses related to antibody production after an initial and secondary exposure to an antigen. Notice that the secondary response is faster and provides a much higher concentration of antibody.

? Exercise 6.3.1.2

1. List the two defining characteristics of adaptive immunity.
2. Explain the difference between a primary and secondary immune response.
3. How do humoral and cellular immunity differ?

Antigens

Activation of the adaptive immune defenses is triggered by pathogen-specific molecular structures called antigens. Antigens are similar to the pathogen-associated molecular patterns (PAMPs) discussed in Pathogen Recognition and Phagocytosis; however, whereas PAMPs are molecular structures found on numerous pathogens, antigens are unique to a specific pathogen. The antigens that stimulate adaptive immunity to chickenpox, for example, are unique to the varicella-zoster virus but significantly different from the antigens associated with other viral pathogens.

The term *antigen* was initially used to describe molecules that stimulate the production of antibodies; in fact, the term comes from a combination of the words antibody and generator, and a molecule that stimulates antibody production is said to be antigenic. However, the role of antigens is not limited to humoral immunity and the production of antibodies; antigens also play an essential role in stimulating cellular immunity, and for this reason antigens are sometimes more accurately referred to as immunogens. In this text, however, we will typically refer to them as antigens.

Pathogens possess a variety of structures that may contain antigens. For example, antigens from bacterial cells may be associated with their capsules, cell walls, fimbriae, flagella, or pili. Bacterial antigens may also be associated with extracellular toxins and enzymes that they secrete. Viruses possess a variety of antigens associated with their capsids, envelopes, and the spike structures they use for attachment to cells.

Antigens may belong to any number of molecular classes, including carbohydrates, lipids, nucleic acids, proteins, and combinations of these molecules. Antigens of different classes vary in their ability to stimulate adaptive immune defenses as well as in the type of response they stimulate (humoral or cellular). The structural complexity of an antigenic molecule is an important factor in its antigenic potential. In general, more complex molecules are more effective as antigens. For example, the three-dimensional complex structure of proteins make them the most effective and potent antigens, capable of stimulating both humoral and cellular immunity. In comparison, carbohydrates are less complex in structure and therefore less effective as antigens; they can only stimulate humoral immune defenses. Lipids and nucleic acids are the least antigenic molecules, and in some cases may only become antigenic when combined with proteins or carbohydrates to form glycolipids, lipoproteins, or nucleoproteins.

One reason the three-dimensional complexity of antigens is so important is that antibodies and T cells do not recognize and interact with an entire antigen but with smaller exposed regions on the surface of antigens called epitopes. A single antigen may possess several different epitopes (Figure 6.3.1.2), and different antibodies may bind to different epitopes on the same antigen (Figure 6.3.1.3). For example, the bacterial flagellum is a large, complex protein structure that can possess hundreds or even thousands of

epitopes with unique three-dimensional structures. Moreover, flagella from different bacterial species (or even strains of the same species) contain unique epitopes that can only be bound by specific antibodies.

An antigen's size is another important factor in its antigenic potential. Whereas large antigenic structures like flagella possess multiple epitopes, some molecules are too small to be antigenic by themselves. Such molecules, called haptens, are essentially free epitopes that are not part of the complex three-dimensional structure of a larger antigen. For a hapten to become antigenic, it must first attach to a larger carrier molecule (usually a protein) to produce a conjugate antigen. The hapten-specific antibodies produced in response to the conjugate antigen are then able to interact with unconjugated free hapten molecules. Haptens are not known to be associated with any specific pathogens, but they are responsible for some allergic responses. For example, the hapten urushiol, a molecule found in the oil of plants that cause poison ivy, causes an immune response that can result in a severe rash (called contact dermatitis). Similarly, the hapten penicillin can cause allergic reactions to drugs in the penicillin class.

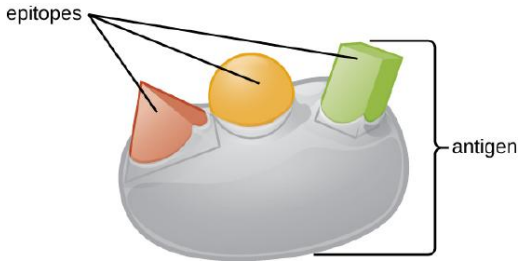


Figure 6.3.1.2: An antigen is a macromolecule that reacts with components of the immune system. A given antigen may contain several motifs that are recognized by immune cells.

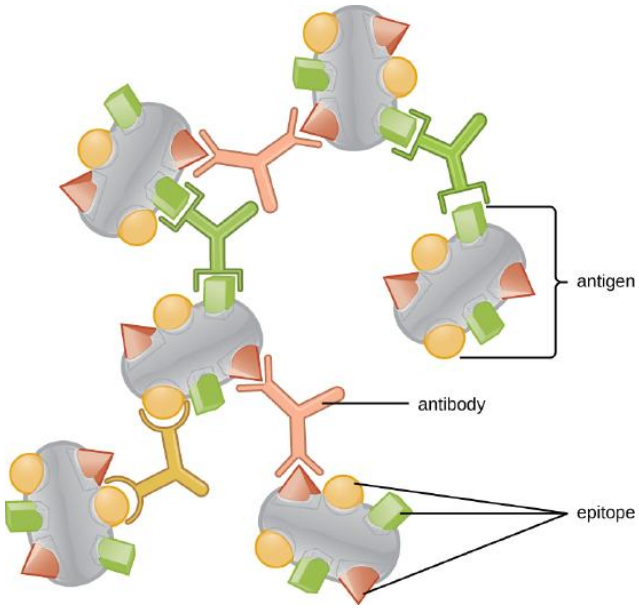


Figure 6.3.1.3: A typical protein antigen has multiple epitopes, shown by the ability of three different antibodies to bind to different epitopes of the same antigen.

? Exercise 6.3.1.3

1. What is the difference between an antigen and an epitope?
2. What factors affect an antigen's antigenic potential?
3. Why are haptens typically not antigenic, and how do they become antigenic?

Antibodies

Antibodies (also called immunoglobulins) are glycoproteins that are present in both the blood and tissue fluids. The basic structure of an antibody monomer consists of four protein chains held together by disulfide bonds (Figure 6.3.1.4). A disulfide bond is a covalent bond between the sulfhydryl *R* groups found on two cysteine amino acids. The two largest chains are identical to each

other and are called the heavy chains. The two smaller chains are also identical to each other and are called the light chains. Joined together, the heavy and light chains form a basic Y-shaped structure.

The two ‘arms’ of the Y-shaped antibody molecule are known as the Fab region, for “fragment of antigen binding.” The far end of the Fab region is the variable region, which serves as the site of antigen binding. The amino acid sequence in the variable region dictates the three-dimensional structure, and thus the specific three-dimensional epitope to which the Fab region is capable of binding. Although the epitope specificity of the Fab regions is identical for each arm of a single antibody molecule, this region displays a high degree of variability between antibodies with different epitope specificities. Binding to the Fab region is necessary for neutralization of pathogens, agglutination or aggregation of pathogens, and antibody-dependent cell-mediated cytotoxicity.

The constant region of the antibody molecule includes the trunk of the Y and lower portion of each arm of the Y. The trunk of the Y is also called the Fc region, for “fragment of crystallization,” and is the site of complement factor binding and binding to phagocytic cells during antibody-mediated opsonization.

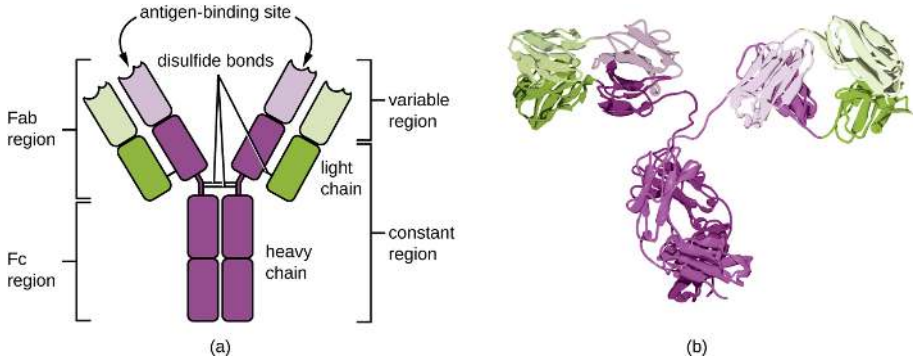


Figure 6.3.1.4: (a) The typical four-chain structure of a generic antibody monomer. (b) The corresponding three-dimensional structure of the antibody IgG. (credit b: modification of work by Tim Vickers)

? Exercise 6.3.1.4

Describe the different functions of the Fab region and the Fc region.

Antibody Classes

The constant region of an antibody molecule determines its class, or isotype. The five classes of antibodies are IgG, IgM, IgA, IgD, and IgE. Each class possesses unique heavy chains designated by Greek letters γ, μ, α, δ, and ε, respectively. Antibody classes also exhibit important differences in abundance in serum, arrangement, body sites of action, functional roles, and size (Figure 6.3.1.5).

IgG is a monomer that is by far the most abundant antibody in human blood, accounting for about 80% of total serum antibody. IgG penetrates efficiently into tissue spaces, and is the only antibody class with the ability to cross the placental barrier, providing passive immunity to the developing fetus during pregnancy. IgG is also the most versatile antibody class in terms of its role in the body’s defense against pathogens.

IgM is initially produced in a monomeric membrane-bound form that serves as an antigen-binding receptor on B cells. The secreted form of IgM assembles into a pentamer with five monomers of IgM bound together by a protein structure called the J chain. Although the location of the J chain relative to the Fc regions of the five monomers prevents IgM from performing some of the functions of IgG, the ten available Fab sites associated with a pentameric IgM make it an important antibody in the body’s arsenal of defenses. IgM is the first antibody produced and secreted by B cells during the primary and secondary immune responses, making pathogen-specific IgM a valuable diagnostic marker during active or recent infections.

IgA accounts for about 13% of total serum antibody, and secretory IgA is the most common and abundant antibody class found in the mucus secretions that protect the mucous membranes. IgA can also be found in other secretions such as breast milk, tears, and saliva. Secretory IgA is assembled into a dimeric form with two monomers joined by a protein structure called the secretory component. One of the important functions of secretory IgA is to trap pathogens in mucus so that they can later be eliminated from the body.

Similar to IgM, IgD is a membrane-bound monomer found on the surface of B cells, where it serves as an antigen-binding receptor. However, IgD is not secreted by B cells, and only trace amounts are detected in serum. These trace amounts most likely come from the degradation of old B cells and the release of IgD molecules from their cytoplasmic membranes.

IgE is the least abundant antibody class in serum. Like IgG, it is secreted as a monomer, but its role in adaptive immunity is restricted to anti-parasitic defenses. The Fc region of IgE binds to basophils and mast cells. The Fab region of the bound IgE then interacts with specific antigen epitopes, causing the cells to release potent pro-inflammatory mediators. The inflammatory reaction resulting from the activation of mast cells and basophils aids in the defense against parasites, but this reaction is also central to allergic reactions (see Diseases of the Immune System.)

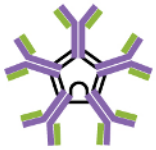
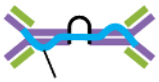
The Five Immunoglobulin (Ig) Classes					
Properties	**IgG monomer**	**IgM pentamer**	**Secretory IgA dimer**	**IgD monomer**	**IgE monomer**
Structure			 Secretory component		
Heavy chains	γ	μ	α	δ	ε
Number of antigen-binding sites	2	10	4	2	2
Molecular weight (Daltons)	150,000	900,000	385,000	180,000	200,000
Percentage of total antibody in serum	80%	6%	13% (monomer)	<1%	<1%
Crosses placenta	yes	no	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to	phagocytes				mast cells and basophils
Function	Neutralization, agglutination, complement activation, opsonization, and antibody-dependent cell-mediated cytotoxicity.	Neutralization, agglutination, and complement activation. The monomer form serves as the B-cell receptor.	Neutralization and trapping of pathogens in mucus.	B-cell receptor.	Activation of basophils and mast cells against parasites and allergens.

Figure 6.3.1.5: The five Immunoglobulin classes

? Exercise 6.3.1.5

1. What part of an antibody molecule determines its class?
2. What class of antibody is involved in protection against parasites?
3. Describe the difference in structure between IgM and IgG.

Antigen-Antibody Interactions

Different classes of antibody play important roles in the body's defense against pathogens. These functions include neutralization of pathogens, opsonization for phagocytosis, agglutination, complement activation, and antibody-dependent cell-mediated cytotoxicity. For most of these functions, antibodies also provide an important link between adaptive specific immunity and innate nonspecific immunity.

Neutralization involves the binding of certain antibodies (IgG, IgM, or IgA) to epitopes on the surface of pathogens or toxins, preventing their attachment to cells. For example, Secretory IgA can bind to specific pathogens and block initial attachment to intestinal mucosal cells. Similarly, specific antibodies can bind to certain toxins, blocking them from attaching to target cells and

thus neutralizing their toxic effects. Viruses can be neutralized and prevented from infecting a cell by the same mechanism (Figure 6.3.1.6).

As described in Chemical Defenses, opsonization is the coating of a pathogen with molecules, such as complementfactors, C-reactive protein, and serum amyloid A, to assist in phagocyte binding to facilitate phagocytosis. IgG antibodies also serve as excellent opsonins, binding their Fab sites to specific epitopes on the surface of pathogens. Phagocytic cells such as macrophages, dendritic cells, and neutrophils have receptors on their surfaces that recognize and bind to the Fc portion of the IgG molecules; thus, IgG helps such phagocytes attach to and engulf the pathogens they have bound (Figure 6.3.1.7).

Agglutination or aggregation involves the cross-linking of pathogens by antibodies to create large aggregates (Figure 6.3.1.8). IgG has two Fab antigen-binding sites, which can bind to two separate pathogen cells, clumping them together. When multiple IgG antibodies are involved, large aggregates can develop; these aggregates are easier for the kidneys and spleen to filter from the blood and easier for phagocytes to ingest for destruction. The pentameric structure of IgMprovides ten Fab binding sites per molecule, making it the most efficient antibody for agglutination.

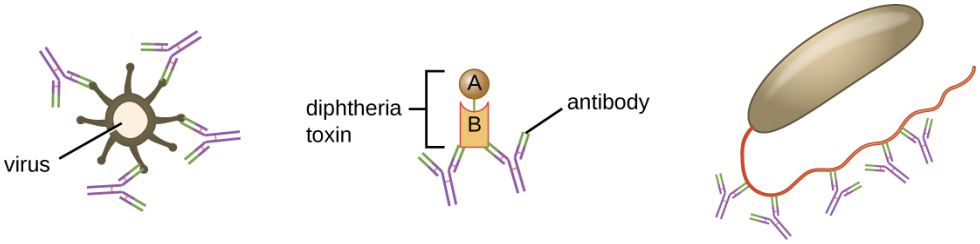


Figure 6.3.1.6: Neutralization involves the binding of specific antibodies to antigens found on bacteria, viruses, and toxins, preventing them from attaching to target cells.

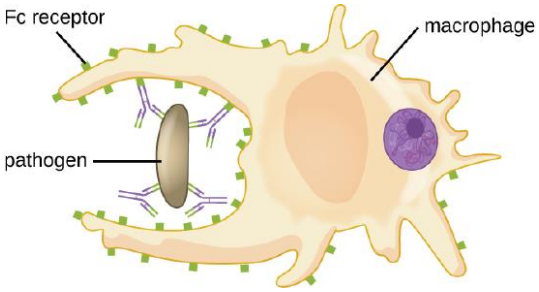


Figure 6.3.1.7: Antibodies serve as opsonins and inhibit infection by tagging pathogens for destruction by macrophages, dendritic cells, and neutrophils. These phagocytic cells use Fc receptors to bind to IgG-opsonized pathogens and initiate the first step of attachment before phagocytosis.

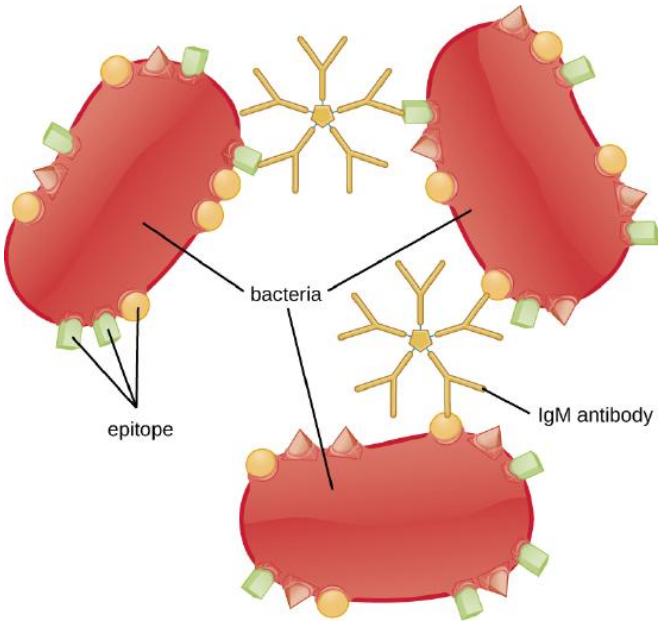


Figure 6.3.1.8: Antibodies, especially IgM antibodies, agglutinate bacteria by binding to epitopes on two or more bacteria simultaneously. When multiple pathogens and antibodies are present, aggregates form when the binding sites of antibodies bind with separate pathogens.

Another important function of antibodies is activation of the complement cascade. As discussed in the previous chapter, the complement system is an important component of the innate defenses, promoting the inflammatory response, recruiting phagocytes to site of infection, enhancing phagocytosis by opsonization, and killing gram-negative bacterial pathogens with the membrane attack complex (MAC). Complement activation can occur through three different pathways (see Figure 17.2.2), but the most efficient is the classical pathway, which requires the initial binding of IgG or IgM antibodies to the surface of a pathogen cell, allowing for recruitment and activation of the C1 complex.

Yet another important function of antibodies is antibody-dependent cell-mediated cytotoxicity (ADCC), which enhances killing of pathogens that are too large to be phagocytosed. This process is best characterized for natural killer cells (NK cells), as shown in Figure 6.3.1.9, but it can also involve macrophages and eosinophils. ADCC occurs when the Fab region of an IgG antibody binds to a large pathogen; Fc receptors on effector cells (e.g., NK cells) then bind to the Fc region of the antibody, bringing them into close proximity with the target pathogen. The effector cell then secretes powerful cytotoxins (e.g., perforin and granzymes) that kill the pathogen.

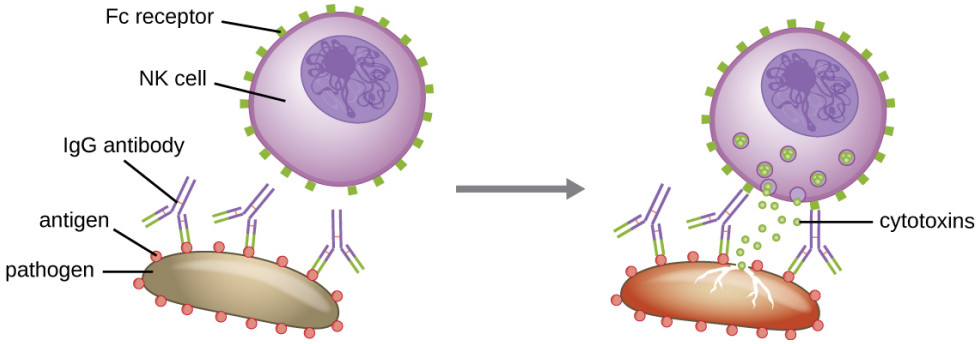


Figure 6.3.1.9: In this example of ADCC, antibodies bind to a large pathogenic cell that is too big for phagocytosis and then bind to Fc receptors on the membrane of a natural killer cell. This interaction brings the NK cell into close proximity, where it can kill the pathogen through release of lethal extracellular cytotoxins.

? Exercise 6.3.1.6

1. Where is IgA normally found?
2. Which class of antibody crosses the placenta, providing protection to the fetus?
3. Compare the mechanisms of opsonization and antibody-dependent cell-mediated cytotoxicity.

Key Concepts and Summary

- **Adaptive immunity** is an acquired defense against foreign pathogens that is characterized by **specificity** and **memory.** The first exposure to an antigen stimulates a **primary response**, and subsequent exposures stimulate a faster and strong **secondary response.**
- Adaptive immunity is a dual system involving **humoral immunity** (antibodies produced by B cells) and **cellular immunity** (T cells directed against intracellular pathogens).
- **Antigens**, also called **immunogens**, are molecules that activate adaptive immunity. A single antigen possesses smaller **epitopes**, each capable of inducing a specific adaptive immune response.
- An antigen's ability to stimulate an immune response depends on several factors, including its molecular class, molecular complexity, and size.
- **Antibodies** (**immunoglobulins**) are Y-shaped glycoproteins with two Fab sites for binding antigens and an Fc portion involved in complement activation and opsonization.
- The five classes of antibody are **IgM**, **IgG**, **IgA**, **IgE**, and **IgD**, each differing in size, arrangement, location within the body, and function. The five primary functions of antibodies are neutralization, opsonization, agglutination, complement activation, and antibody-dependent cell-mediated cytotoxicity (ADCC).

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6.3.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes

Learning Objectives

- Identify cells that express MHC I and/or MHC II molecules and describe the structures and cellular location of MHC I and MHC II molecules
- Identify the cells that are antigen-presenting cells
- Describe the process of antigen processing and presentation with MHC I and MHC II

As discussed in Cellular Defenses, major histocompatibility complex (MHC) molecules are expressed on the surface of healthy cells, identifying them as normal and "self" to natural killer (NK) cells. MHC molecules also play an important role in the presentation of foreign antigens, which is a critical step in the activation of T cells and thus an important mechanism of the adaptive immune system.

Major Histocompatibility Complex Molecules

The major histocompatibility complex (MHC) is a collection of genes coding for MHC molecules found on the surface of all nucleated cells of the body. In humans, the MHC genes are also referred to as human leukocyte antigen (HLA) genes. Mature red blood cells, which lack a nucleus, are the only cells that do not express MHC molecules on their surface.

There are two classes of MHC molecules involved in adaptive immunity, MHC I and MHC II (Figure 6.3.2.1). MHC I molecules are found on all nucleated cells; they present normal self-antigens as well as abnormal or nonself pathogens to the effector T cells involved in cellular immunity. In contrast, MHC II molecules are only found on macrophages, dendritic cells, and B cells; they present abnormal or nonself pathogen antigens for the initial activation of T cells.

Both types of MHC molecules are transmembrane glycoproteins that assemble as dimers in the cytoplasmic membrane of cells, but their structures are quite different. MHC I molecules are composed of a longer α protein chain coupled with a smaller β_2 microglobulin protein, and only the α chain spans the cytoplasmic membrane. The α chain of the MHC I molecule folds into three separate domains: α_1, α_2 and α_3. MHC II molecules are composed of two protein chains (an α and a β chain) that are approximately similar in length. Both chains of the MHC II molecule possess portions that span the plasma membrane, and each chain folds into two separate domains: α_1 and α_2, and β_1, and β_2. In order to present abnormal or non-self-antigens to T cells, MHC molecules have a cleft that serves as the antigen-binding site near the "top" (or outermost) portion of the MHC-I or MHC-II dimer. For MHC I, the antigen-binding cleft is formed by the α_1 and α_2 domains, whereas for MHC II, the cleft is formed by the α_1 and β_1 domains (Figure 6.3.2.1).

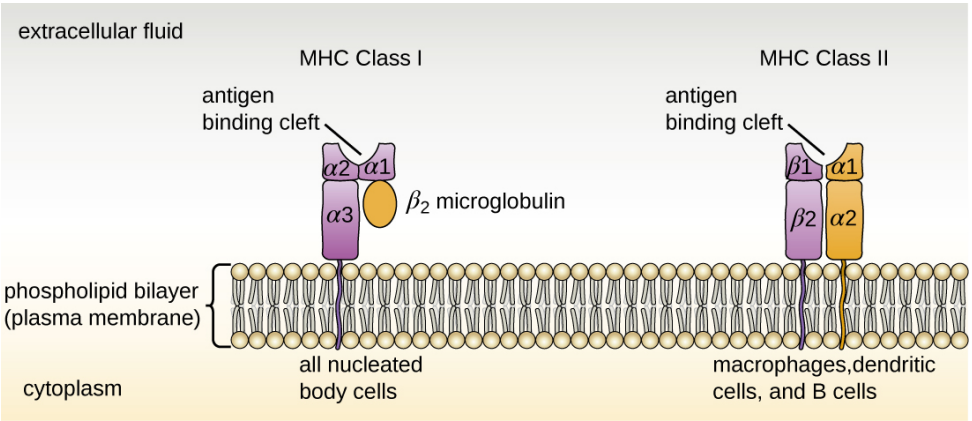


Figure 6.3.2.1: MHC I are found on all nucleated body cells, and MHC II are found on macrophages, dendritic cells, and B cells (along with MHC I). The antigen-binding cleft of MHC I is formed by domains α_1 and α_2. The antigen-binding cleft of MHC II is formed by domains α_1 and β_1.

? Exercise 6.3.2.1

Compare the structures of the MHC I and MHC II molecules.

Antigen-Presenting Cells (APCs)

All nucleated cells in the body have mechanisms for processing and presenting antigens in association with MHC molecules. This signals the immune system, indicating whether the cell is normal and healthy or infected with an intracellular pathogen. However, only macrophages, dendritic cells, and B cells have the ability to present antigens specifically for the purpose of activating T cells; for this reason, these types of cells are sometimes referred to as antigen-presenting cells (APCs).

While all APCs play a similar role in adaptive immunity, there are some important differences to consider. Macrophages and dendritic cells are phagocytes that ingest and kill pathogens that penetrate the first-line barriers (i.e., skin and mucous membranes). B cells, on the other hand, do not function as phagocytes but play a primary role in the production and secretion of antibodies. In addition, whereas macrophages and dendritic cells recognize pathogens through nonspecific receptor interactions (e.g., PAMPs, toll-like receptors, and receptors for opsonizing complement or antibody), B cells interact with foreign pathogens or their free antigens using antigen-specific immunoglobulin as receptors (monomeric IgD and IgM). When the immunoglobulin receptors bind to an antigen, the B cell internalizes the antigen by endocytosis before processing and presentting the antigen to T cells.

Antigen Presentation with MHC II Molecules

MHC II molecules are only found on the surface of APCs. Macrophages and dendritic cells use similar mechanisms for processing and presentation of antigens and their epitopes in association with MHC II; B cells use somewhat different mechanisms that will be described further in B Lymphocytes and Humoral Immunity. For now, we will focus on the steps of the process as they pertain to dendritic cells.

After a dendritic cell recognizes and attaches to a pathogen cell, the pathogen is internalized by phagocytosis and is initially contained within a phagosome. Lysosomes containing antimicrobial enzymes and chemicals fuse with the phagosome to create a phagolysosome, where degradation of the pathogen for antigen processing begins. Proteases (protein-degrading) are especially important in antigen processing because only protein antigen epitopes are presented to T cells by MHC II (Figure 6.3.2.2).

APCs do not present all possible epitopes to T cells; only a selection of the most antigenic or immunodominantepitopes are presented. The mechanism by which epitopes are selected for processing and presentation by an APC is complicated and not well understood; however, once the most antigenic, immunodominant epitopes have been processed, they associate within the antigen-binding cleft of MHC II molecules and are translocated to the cell surface of the dendritic cell for presentation to T cells.

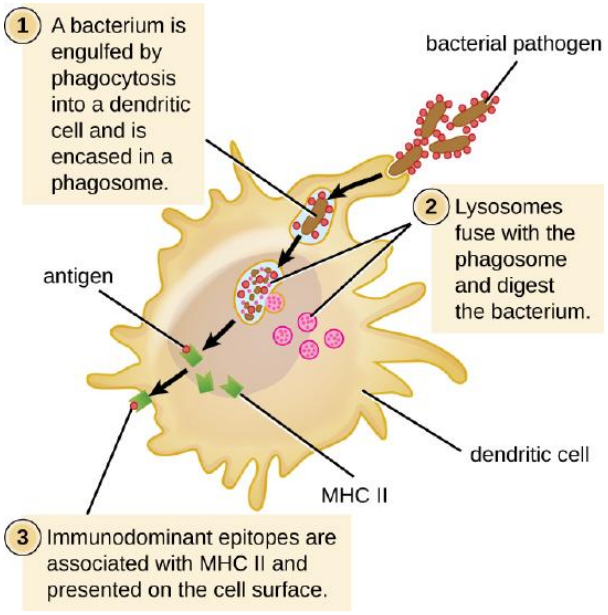


Figure 6.3.2.2: A dendritic cell phagocytoses a bacterial cell and brings it into a phagosome. Lysosomes fuse with the phagosome to create a phagolysosome, where antimicrobial chemicals and enzymes degrade the bacterial cell. Proteases process bacterial antigens, and the most antigenic epitopes are selected and presented on the cell's surface in conjunction with MHC II molecules. T cells recognize the presented antigens and are thus activated.

? Exercise 6.3.2.2

1. What are the three kinds of APCs?
2. What role to MHC II molecules play in antigen presentation?
3. What is the role of antigen presentation in adaptive immunity?

Antigen Presentation with MHC I Molecules

MHC I molecules, found on all normal, healthy, nucleated cells, signal to the immune system that the cell is a normal "self" cell. In a healthy cell, proteins normally found in the cytoplasm are degraded by proteasomes (enzyme complexes responsible for degradation and processing of proteins) and processed into self-antigen epitopes; these self-antigen epitopes bind within the MHC I antigen-binding cleft and are then presented on the cell surface. Immune cells, such as NK cells, recognize these self-antigens and do not target the cell for destruction. However, if a cell becomes infected with an intracellular pathogen (e.g., a virus), protein antigens specific to the pathogen are processed in the proteasomes and bind with MHC I molecules for presentation on the cell surface. This presentation of pathogen-specific antigens with MHC I signals that the infected cell must be targeted for destruction along with the pathogen.

Before elimination of infected cells can begin, APCs must first activate the T cells involved in cellular immunity. If an intracellular pathogen directly infects the cytoplasm of an APC, then the processing and presentation of antigens can occur as described (in proteasomes and on the cell surface with MHC I). However, if the intracellular pathogen does not directly infect APCs, an alternative strategy called cross-presentation is utilized. In cross-presentation, antigens are brought into the APC by mechanisms normally leading to presentation with MHC II (i.e., through phagocytosis), but the antigen is presented on an MHC I molecule for CD8 T cells. The exact mechanisms by which cross-presentation occur are not yet well understood, but it appears that cross-presentation is primarily a function of dendritic cells and not macrophages or B cells.

? Exercise 6.3.2.3

1. Compare and contrast antigen processing and presentation associated with MHC I and MHC II molecules.
2. What is cross-presentation, and when is it likely to occur?

Key Concepts and Summary

- **Major histocompatibility complex (MHC)** is a collection of genes coding for glycoprotein molecules expressed on the surface of all nucleated cells.
- **MHC I** molecules are expressed on all nucleated cells and are essential for presentation of normal “self” antigens. Cells that become infected by intracellular pathogens can present foreign antigens on MHC I as well, marking the infected cell for destruction.
- **MHC II** molecules are expressed only on the surface of **antigen-presenting cells** (macrophages, dendritic cells, and B cells). Antigen presentation with MHC II is essential for the activation of T cells.
- **Antigen-presenting cells (APCs)** primarily ingest pathogens by phagocytosis, destroy them in the phagolysosomes, process the protein antigens, and select the most antigenic/immunodominant epitopes with MHC II for presentation to T cells.
- **Cross-presentation** is a mechanism of antigen presentation and T-cell activation used by dendritic cells not directly infected by the pathogen; it involves phagocytosis of the pathogen but presentation on MHC I rather than MHC II.

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6.3.3: T Lymphocytes

Learning Objectives

- Describe the process of T-cell maturation and thymic selection
- Explain the genetic events that lead to diversity of T-cell receptors
- Compare and contrast the various classes and subtypes of T cells in terms of activation and function
- Explain the mechanism by which superantigens effect unregulated T-cell activation

As explained in Overview of Specific Adaptive Immunity, the antibodies involved in humoral immunity often bind pathogens and toxins before they can attach to and invade host cells. Thus, humoral immunity is primarily concerned with fighting pathogens in extracellular spaces. However, pathogens that have already gained entry to host cells are largely protected from the humoral antibody-mediated defenses. Cellular immunity, on the other hand, targets and eliminates intracellular pathogens through the actions of T lymphocytes, or T cells (Figure 6.3.3.1). T cells also play a more central role in orchestrating the overall adaptive immune response (humoral as well as cellular) along with the cellular defenses of innate immunity.

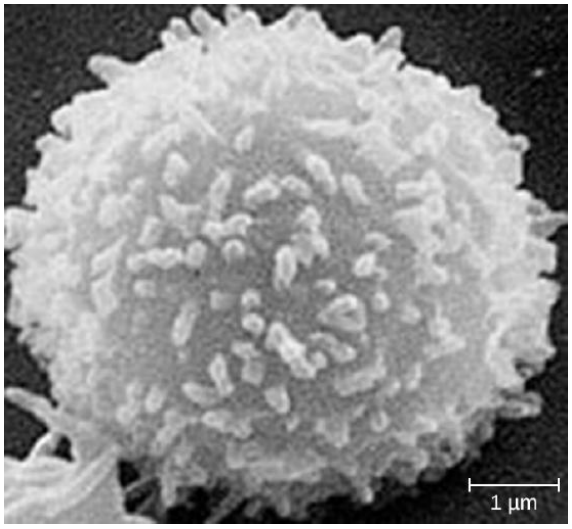


Figure 6.3.3.1: This scanning electron micrograph shows a T lymphocyte, which is responsible for the cell-mediated immune response. The spike-like membrane structures increase surface area, allowing for greater interaction with other cell types and their signals. (credit: modification of work by NCI)

T Cell Production and Maturation

T cells, like all other white blood cells involved in innate and adaptive immunity, are formed from multipotent hematopoietic stem cells (HSCs) in the bone marrow (see Figure 17.3.1). However, unlike the white blood cells of innate immunity, eventual T cells differentiate first into lymphoid stem cells that then become small, immature lymphocytes, sometimes called lymphoblasts. The first steps of differentiation occur in the red marrow of bones (Figure 6.3.3.2), after which immature T lymphocytes enter the bloodstream and travel to the thymus for the final steps of maturation (Figure 6.3.3.3). Once in the thymus, the immature T lymphocytes are referred to as thymocytes.

The maturation of thymocytes within the thymus can be divided into tree critical steps of positive and negative selection, collectively referred to as thymic selection. The first step of thymic selection occurs in the cortex of the thymus and involves the development of a functional T-cell receptor (TCR) that is required for activation by APCs. Thymocytes with defective TCRs are removed by negative selection through the induction of apoptosis (programmed controlled cell death). The second step of thymic selection also occurs in the cortex and involves the positive selection of thymocytes that will interact appropriately with MHC molecules. Thymocytes that can interact appropriately with MHC molecules receive a positive stimulation that moves them further through the process of maturation, whereas thymocytes that do not interact appropriately are not stimulated and are eliminated by apoptosis. The third and final step of thymic selection occurs in both the cortex and medulla and involves negative selection to remove self-reacting thymocytes, those that react to self-antigens, by apoptosis. This final step is sometimes referred to as central

tolerance because it prevents self-reacting T cells from reaching the bloodstream and potentially causing autoimmune disease, which occurs when the immune system attacks healthy “self” cells.

Despite central tolerance, some self-reactive T cells generally escape the thymus and enter the peripheral bloodstream. Therefore, a second line of defense called peripheral tolerance is needed to protect against autoimmune disease. Peripheral tolerance involves mechanisms of anergy and inhibition of self-reactive T cells by regulatory T cells. Anergy refers to a state of nonresponsiveness to antigen stimulation. In the case of self-reactive T cells that escape the thymus, lack of an essential co-stimulatory signal required for activation causes anergy and prevents autoimmune activation. Regulatory T cells participate in peripheral tolerance by inhibiting the activation and function of self-reactive T cells and by secreting anti-inflammatory cytokines.

It is not completely understood what events specifically direct maturation of thymocytes into regulatory T cells. Current theories suggest the critical events may occur during the third step of thymic selection, when most self-reactive T cells are eliminated. Regulatory T cells may receive a unique signal that is below the threshold required to target them for negative selection and apoptosis. Consequently, these cells continue to mature and then exit the thymus, armed to inhibit the activation of self-reactive T cells.

It has been estimated that the three steps of thymic selection eliminate 98% of thymocytes. The remaining 2% that exit the thymus migrate through the bloodstream and lymphatic system to sites of secondary lymphoid organs/tissues, such as the lymph nodes, spleen, and tonsils (Figure 6.3.3.3), where they await activation through the presentation of specific antigens by APCs. Until they are activated, they are known as mature naïve T cells.

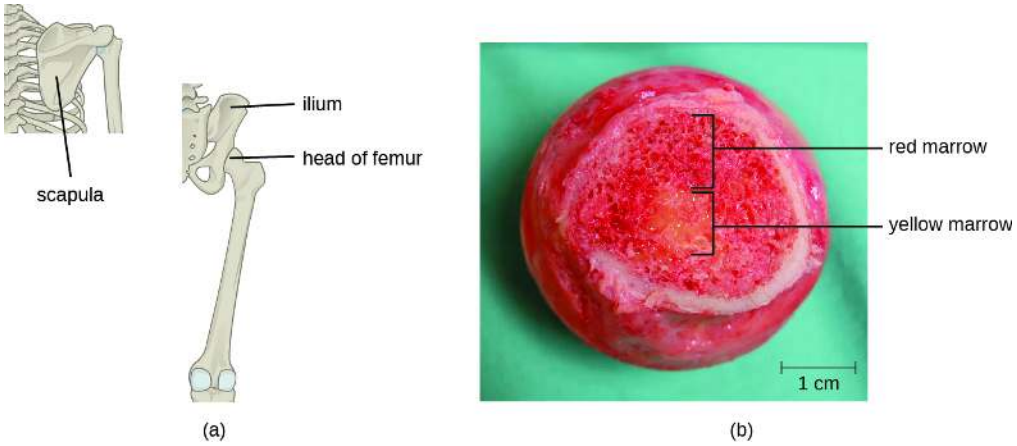


Figure 6.3.3.2: (a) Red bone marrow can be found in the head of the femur (thighbone) and is also present in the flat bones of the body, such as the ilium and the scapula. (b) Red bone marrow is the site of production and differentiation of many formed elements of blood, including erythrocytes, leukocytes, and platelets. The yellow bone marrow is populated primarily with adipose cells.

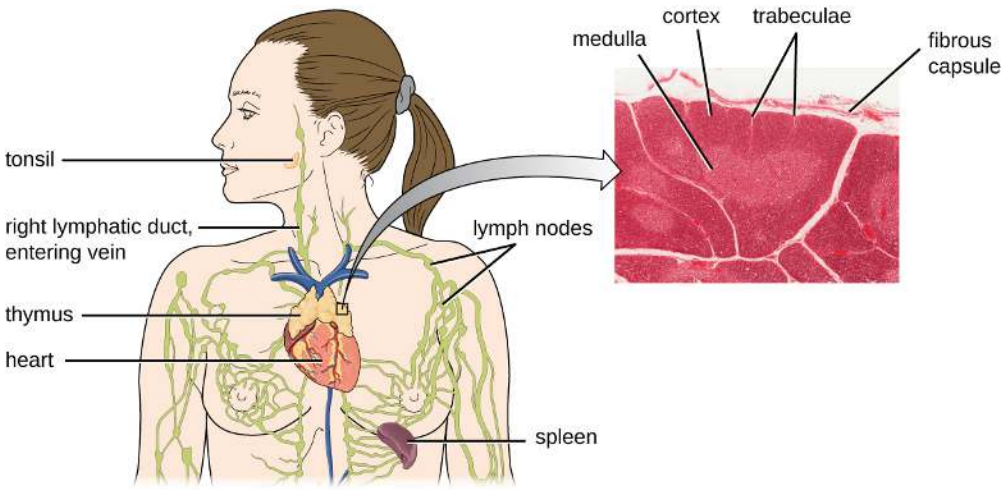


Figure 6.3.3.3: The thymus is a bi-lobed, H-shaped glandular organ that is located just above the heart. It is surrounded by a fibrous capsule of connective tissue. The darkly staining cortex and the lighter staining medulla of individual lobules are clearly visible in the light micrograph of the thymus of a newborn (top right, LM × 100). (credit micrograph: modification of micrograph provided by the Regents of University of Michigan Medical School © 2012)

? Exercise 6.3.3.1

1. What anatomical sites are involved in T cell production and maturation?
2. What are the three steps involved in thymic selection?
3. Why are central tolerance and peripheral tolerance important? What do they prevent?

Classes of T Cells

T cells can be categorized into three distinct classes: helper T cells, regulatory T cells, and cytotoxic T cells. These classes are differentiated based on their expression of certain surface molecules, their mode of activation, and their functional roles in adaptive immunity (Table 6.3.3.1).

All T cells produce cluster of differentiation (CD) molecules, cell surface glycoproteins that can be used to identify and distinguish between the various types of white blood cells. Although T cells can produce a variety of CD molecules, CD4and CD8 are the two most important used for differentiation of the classes. Helper T cells and regulatory T cells are characterized by the expression of CD4 on their surface, whereas cytotoxic T cells are characterized by the expression of CD8.

Classes of T cells can also be distinguished by the specific MHC molecules and APCs with which they interact for activation. Helper T cells and regulatory T cells can only be activated by APCs presenting antigens associated with MHC II. In contrast, cytotoxic T cells recognize antigens presented in association with MHC I, either by APCs or by nucleated cells infected with an intracellular pathogen.

The different classes of T cells also play different functional roles in the immune system. Helper T cells serve as the central orchestrators that help activate and direct functions of humoral and cellular immunity. In addition, helper T cells enhance the pathogen-killing functions of macrophages and NK cells of innate immunity. In contrast, the primary role of regulatory T cells is to prevent undesirable and potentially damaging immune responses. Their role in peripheral tolerance, for example, protects against autoimmune disorders, as discussed earlier. Finally, cytotoxic T cells are the primary effector cells for cellular immunity. They recognize and target cells that have been infected by intracellular pathogens, destroying infected cells along with the pathogens inside.

Table 6.3.3.1: Classes of T Cells

Class	Surface CD Molecules	Activation	Functions
Helper T cells	CD4	APCs presenting antigens associated with MHC II	Orchestrate humoral and cellular immunity
			Involved in the activation of macrophages and NK cells
Regulatory T cells	CD4	APCs presenting antigens associated with MHC II	Involved in peripheral tolerance and prevention of autoimmune responses
Cytotoxic T cells	CD8	APCs or infected nucleated cells presenting antigens associated with MHC I	Destroy cells infected with intracellular pathogens

? Exercise 6.3.3.2

1. What are the unique functions of the three classes of T cells?
2. Which T cells can be activated by antigens presented by cells other than APCs?

T-Cell Receptors

For both helper T cells and cytotoxic T cells, activation is a complex process that requires the interactions of multiple molecules and exposure to cytokines. The T-cell receptor (TCR) is involved in the first step of pathogen epitope recognition during the activation process.

The TCR comes from the same receptor family as the antibodies IgD and IgM, the antigen receptors on the B cell membrane surface, and thus shares common structural elements. Similar to antibodies, the TCR has a variable regionand a constant region, and the variable region provides the antigen-binding site (Figure 6.3.3.4). However, the structure of TCR is smaller and less complex than the immunoglobulin molecules (Figure 18.1.4). Whereas immunoglobulins have four peptide chains and Y-shaped structures, the TCR consists of just two peptide chains (α and β chains), both of which span the cytoplasmic membrane of the T cell.

TCRs are epitope-specific, and it has been estimated that 25 million T cells with unique epitope-binding TCRs are required to protect an individual against a wide range of microbial pathogens. Because the human genome only contains about 25,000 genes, we know that each specific TCR cannot be encoded by its own set of genes. This raises the question of how such a vast population of T cells with millions of specific TCRs can be achieved. The answer is a process called genetic rearrangement, which occurs in the thymus during the first step of thymic selection.

The genes that code for the variable regions of the TCR are divided into distinct gene segments called variable (V), diversity (D), and joining (J) segments. The genes segments associated with the α chain of the TCR consist 70 or more different V_α segments and 61 different J_α segments. The gene segments associated with the β chain of the TCR consist of 52 different V_β segments, two different D_β segments, and 13 different J_β segments. During the development of the functional TCR in the thymus, genetic rearrangement in a T cell brings together one V_α segment and one J_α segment to code for the variable region of the α chain. Similarly, genetic rearrangement brings one of the V_β segments together with one of the D_β segments and one of theJ_β segments to code for the variable region of the β chain. All the possible combinations of rearrangements between different segments of V, D, and J provide the genetic diversity required to produce millions of TCRs with unique epitope-specific variable regions.

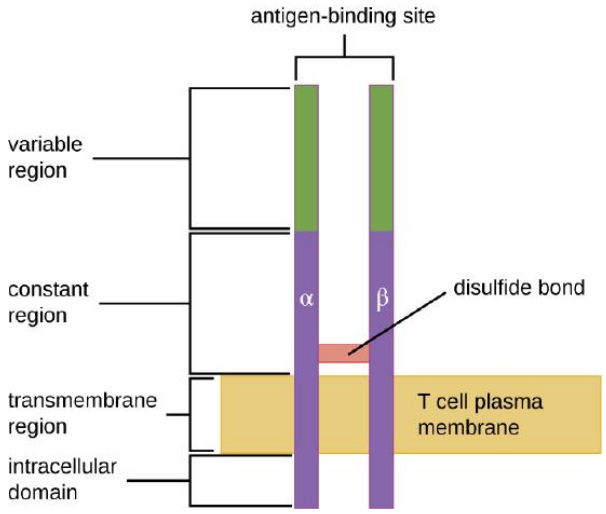


Figure 6.3.3.4: A T-cell receptor spans the cytoplasmic membrane and projects variable binding regions into the extracellular space to bind processed antigens associated with MHC I or MHC II molecules.

? Exercise 6.3.3.3

1. What are the similarities and differences between TCRs and immunoglobulins?
2. What process is used to provide millions of unique TCR binding sites?

Activation and Differentiation of Helper T Cells

Helper T cells can only be activated by APCs presenting processed foreign epitopes in association with MHC II. The first step in the activation process is TCR recognition of the specific foreign epitope presented within the MHC II antigen-binding cleft. The second step involves the interaction of CD4 on the helper T cell with a region of the MHC II molecule separate from the antigen-binding cleft. This second interaction anchors the MHC II-TCR complex and ensures that the helper T cell is recognizing both the foreign ("nonself") epitope and "self" antigen of the APC; both recognitions are required for activation of the cell. In the third step, the APC and T cell secrete cytokines that activate the helper T cell. The activated helper T cell then proliferates, dividing by mitosis to produce clonal naïve helper T cells that differentiate into subtypes with different functions (Figure 6.3.3.5).

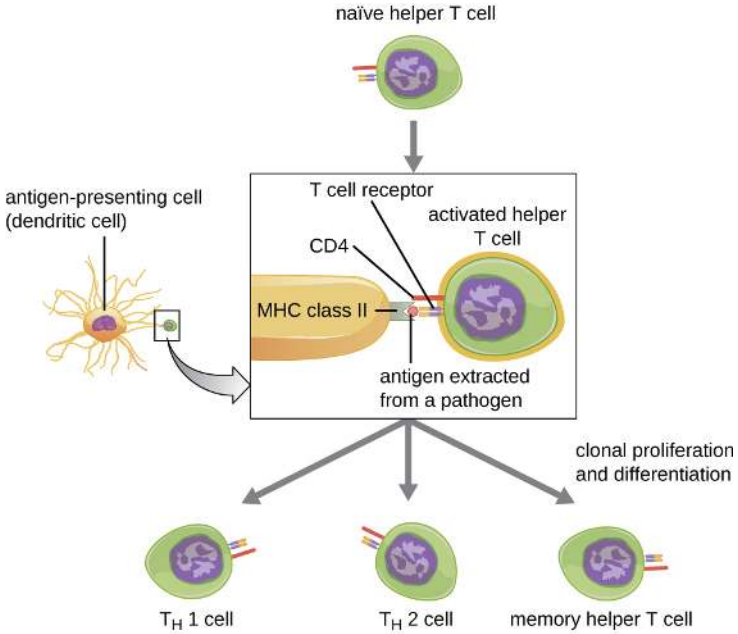


Figure 6.3.3.5: This illustration depicts the activation of a naïve (unactivated) helper T cell by an antigen-presenting cell and the subsequent proliferation and differentiation of the activated T cell into different subtypes.

Activated helper T cells can differentiate into one of four distinct subtypes, summarized in Table 6.3.3.2. The differentiation process is directed by APC-secreted cytokines. Depending on which APC-secreted cytokines interact with an activated helper T cell, the cell may differentiate into a T helper 1 (T_H1) cell, a T helper 2 (T_H2) cell, or a memory helper T cell. The two types of helper T cells are relatively short-lived effector cells, meaning that they perform various functions of the immediate immune response. In contrast, memory helper T cells are relatively long lived; they are programmed to "remember" a specific antigen or epitope in order to mount a rapid, strong, secondary response to subsequent exposures.

T_H1 cells secrete their own cytokines that are involved in stimulating and orchestrating other cells involved in adaptive and innate immunity. For example, they stimulate cytotoxic T cells, enhancing their killing of infected cells and promoting differentiation into memory cytotoxic T cells. T_H1 cells also stimulate macrophages and neutrophils to become more effective in their killing of intracellular bacteria. They can also stimulate NK cells to become more effective at killing target cells.

T_H2 cells play an important role in orchestrating the humoral immune response through their secretion of cytokines that activate B cells and direct B cell differentiation and antibody production. Various cytokines produced by T_H2 cells orchestrate antibody class switching, which allows B cells to switch between the production of IgM, IgG, IgA, and IgE as needed to carry out specific antibody functions and to provide pathogen-specific humoral immune responses.

A third subtype of helper T cells called T_H17 cells was discovered through observations that immunity to some infections is not associated with T_H1 or T_H2 cells. T_H17 cells and the cytokines they produce appear to be specifically responsible for the body's defense against chronic mucocutaneous infections. Patients who lack sufficient T_H17 cells in the mucosa (e.g., HIV patients) may be more susceptible to bacteremia and gastrointestinal infections.[1]

Table 6.3.3.2: Subtypes of Helper T Cells

Subtype	Functions
T_H1 cells	Stimulate cytotoxic T cells and produce memory cytotoxic T cells
	Stimulate macrophages and neutrophils (PMNs) for more effective intracellular killing of pathogens
	Stimulate NK cells to kill more effectively
T_H2 cells	Stimulate B cell activation and differentiation into plasma cells and memory B cells
	Direct antibody class switching in B cells
T_H17 cells	Stimulate immunity to specific infections such as chronic mucocutaneous infections
Memory helper T cells	"Remember" a specific pathogen and mount a strong, rapid secondary response upon re-exposure

Activation and Differentiation of Cytotoxic T Cells

Cytotoxic T cells (also referred to as cytotoxic T lymphocytes, or CTLs) are activated by APCs in a three-step process similar to that of helper T cells. The key difference is that the activation of cytotoxic T cells involves recognition of an antigen presented with MHC I (as opposed to MHC II) and interaction of CD8 (as opposed to CD4) with the receptor complex. After the successful co-recognition of foreign epitope and self-antigen, the production of cytokines by the APC and the cytotoxic T cell activate clonal proliferation and differentiation. Activated cytotoxic T cells can differentiate into effector cytotoxic T cells that target pathogens for destruction or memory cells that are ready to respond to subsequent exposures.

As noted, proliferation and differentiation of cytotoxic T cells is also stimulated by cytokines secreted from T_H1 cells activated by the same foreign epitope. The co-stimulation that comes from these T_H1 cells is provided by secreted cytokines. Although it is possible for activation of cytotoxic T cells to occur without stimulation from T_H1 cells, the activation is not as effective or long-lasting.

Once activated, cytotoxic T cells serve as the effector cells of cellular immunity, recognizing and kill cells infected with intracellular pathogens through a mechanism very similar to that of NK cells. However, whereas NK cells recognize nonspecific

signals of cell stress or abnormality, cytotoxic T cells recognize infected cells through antigen presentation of pathogen-specific epitopes associated with MHC I. Once an infected cell is recognized, the TCR of the cytotoxic T cell binds to the epitope and releases perforin and granzymes that destroy the infected cell (Figure 6.3.3.6). Perforin is a protein that creates pores in the target cell, and granzymes are proteases that enter the pores and induce apoptosis. This mechanism of programmed cell death is a controlled and efficient means of destroying and removing infected cells without releasing the pathogens inside to infect neighboring cells, as might occur if the infected cells were simply lysed.

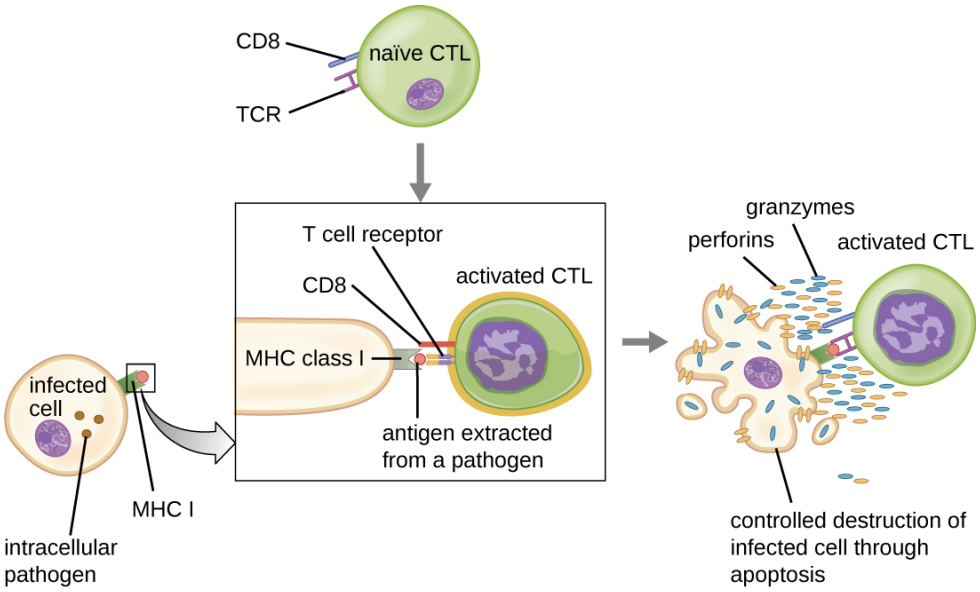


Figure 6.3.3.6: This figure illustrates the activation of a naïve (unactivated) cytotoxic T cell (CTL) by an antigen-presenting MHC I molecule on an infected body cell. Once activated, the CTL releases perforin and granzymes that invade the infected cell and induce controlled cell death, or apoptosis.

Link to Learning

In this video, you can see a cytotoxic T cell inducing apoptosis in a target cell.

Exercise 6.3.3.4

1. Compare and contrast the activation of helper T cells and cytotoxic T cells.
2. What are the different functions of helper T cell subtypes?
3. What is the mechanism of CTL-mediated destruction of infected cells?

Superantigens and Unregulated Activation of T Cells

When T cell activation is controlled and regulated, the result is a protective response that is effective in combating infections. However, if T cell activation is unregulated and excessive, the result can be a life-threatening. Certain bacterial and viral pathogens produce toxins known as superantigens (see Virulence Factors of Bacterial and Viral Pathogens) that can trigger such an unregulated response. Known bacterial superantigens include toxic shock syndrome toxin (TSST), staphylococcal enterotoxins, streptococcal pyrogenic toxins, streptococcal superantigen, and the streptococcal mitogenic exotoxin. Viruses known to produce superantigens include Epstein-Barr virus (human herpesvirus 4), cytomegalovirus (human herpesvirus 5), and others.

The mechanism of T cell activation by superantigens involves their simultaneous binding to MHC II molecules of APCs and the variable region of the TCR β chain. This binding occurs outside of the antigen-binding cleft of MHC II, so the superantigen will bridge together and activate MHC II and TCR without specific foreign epitope recognition (Figure 6.3.3.7). The result is an excessive, uncontrolled release of cytokines, often called a cytokine storm, which stimulates an excessive inflammatory response. This can lead to a dangerous decrease in blood pressure, shock, multi-organ failure, and potentially, death.

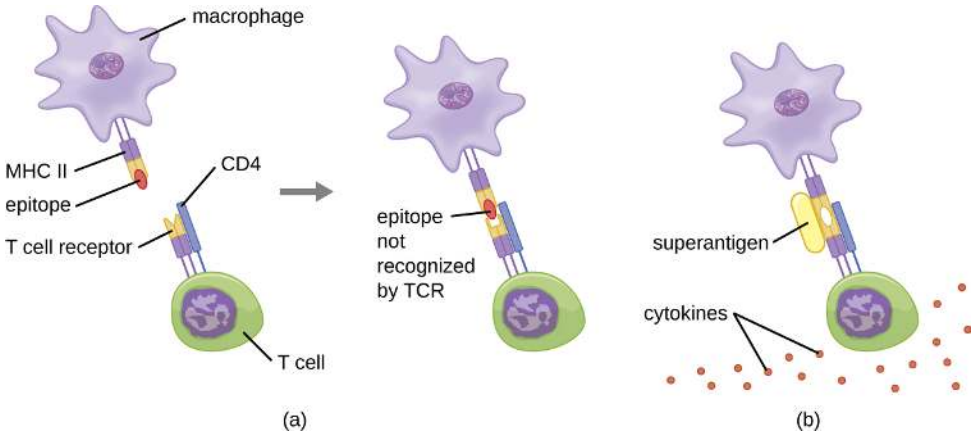


Figure 6.3.3.7: (a) The macrophage in this figure is presenting a foreign epitope that does not match the TCR of the T cell. Because the T cell does not recognize the epitope, it is not activated. (b) The macrophage in this figure is presenting a superantigen that is not recognized by the TCR of the T cell, yet the superantigen still is able to bridge and bind the MHC II and TCR molecules. This nonspecific, uncontrolled activation of the T cell results in an excessive release of cytokines that activate other T cells and cause excessive inflammation. (credit: modification of work by "Microbiotic"/YouTube)

? Exercise 6.3.3.5

1. What are examples of superantigens?
2. How does a superantigen activate a helper T cell?
3. What effect does a superantigen have on a T cell?

Case in Point: Superantigens

Melissa, an otherwise healthy 22-year-old woman, is brought to the emergency room by her concerned boyfriend. She complains of a sudden onset of high fever, vomiting, diarrhea, and muscle aches. In her initial interview, she tells the attending physician that she is on hormonal birth control and also is two days into the menstruation portion of her cycle. She is on no other medications and is not abusing any drugs or alcohol. She is not a smoker. She is not diabetic and does not currently have an infection of any kind to her knowledge.

While waiting in the emergency room, Melissa's blood pressure begins to drop dramatically and her mental state deteriorates to general confusion. The physician believes she is likely suffering from toxic shock syndrome (TSS). TSS is caused by the toxin TSST-1, a superantigen associated with *Staphylococcus aureus*, and improper tampon use is a common cause of infections leading to TSS. The superantigen inappropriately stimulates widespread T cell activation and excessive cytokine release, resulting in a massive and systemic inflammatory response that can be fatal.

Vaginal or cervical swabs may be taken to confirm the presence of the microbe, but these tests are not critical to perform based on Melissa's symptoms and medical history. The physician prescribes rehydration, supportive therapy, and antibiotics to stem the bacterial infection. She also prescribes drugs to increase Melissa's blood pressure. Melissa spends three days in the hospital undergoing treatment; in addition, her kidney function is monitored because of the high risk of kidney failure associated with TSS. After 72 hours, Melissa is well enough to be discharged to continue her recovery at home.

Exercise 6.3.3.6

In what way would antibiotic therapy help to combat a superantigen?

Clinical Focus: Part 2

Olivia's swollen lymph nodes, abdomen, and spleen suggest a strong immune response to a systemic infection in progress. In addition, little Olivia is reluctant to turn her head and appears to be experiencing severe neck pain. The physician orders a complete blood count, blood culture, and lumbar puncture. The cerebrospinal fluid (CSF) obtained appears cloudy and is

further evaluated by Gram stain assessment and culturing for potential bacterial pathogens. The complete blood count indicates elevated numbers of white blood cells in Olivia's bloodstream. The white blood cell increases are recorded at 28.5 K/µL (normal range: 6.0–17.5 K/µL). The neutrophil percentage was recorded as 60% (normal range: 23–45%). Glucose levels in the CSF were registered at 30 mg/100 mL (normal range: 50–80 mg/100 mL). The WBC count in the CSF was 1,163/mm3 (normal range: 5–20/mm^3).

Exercise 6.3.3.7

1. Based on these results, do you have a preliminary diagnosis?
2. What is a recommended treatment based on this preliminary diagnosis?

Key Concepts and Summary

- Immature T lymphocytes are produced in the red bone marrow and travel to the thymus for maturation.
- **Thymic selection** is a three-step process of negative and positive selection that determines which T cells will mature and exit the thymus into the peripheral bloodstream.
- **Central tolerance** involves negative selection of self-reactive T cells in the thymus, and **peripheral tolerance**involves **anergy** and **regulatory T cells** that prevent self-reactive immune responses and autoimmunity.
- The **TCR** is similar in structure to immunoglobulins, but less complex. Millions of unique epitope-binding TCRs are encoded through a process of genetic rearrangement of V, D, and J gene segments.
- T cells can be divided into three classes—**helper T cells, cytotoxic T cells,** and **regulatory T cells—**based on their expression of CD4 or CD8, the MHC molecules with which they interact for activation, and their respective functions.
- Activated helper T cells differentiate into **T_H1, T_H2, T_H17**, or **memory T cell subtypes**. Differentiation is directed by the specific cytokines to which they are exposed. T_H1, T_H2, and T_H17 perform different functions related to stimulation of adaptive and innate immune defenses. Memory T cells are long-lived cells that can respond quickly to secondary exposures.
- Once activated, cytotoxic T cells target and kill cells infected with intracellular pathogens. Killing requires recognition of specific pathogen epitopes presented on the cell surface using MHC I molecules. Killing is mediated by **perforin** and **granzymes** that induce apoptosis.
- **Superantigens** are bacterial or viral proteins that cause a nonspecific activation of helper T cells, leading to an excessive release of cytokines (**cytokine storm**) and a systemic, potentially fatal inflammatory response.

Footnotes

1. 1 Blaschitz C., Raffatellu M. "Th17 cytokines and the gut mucosal barrier." J Clin Immunol. 2010 Mar; 30(2):196-203. doi: 10.1007/s10875-010-9368-7.

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6.3.4: B Lymphocytes and Antibodies

Learning Objectives

- Describe the production and maturation of B cells
- Compare the structure of B-cell receptors and T-cell receptors
- Compare T-dependent and T-independent activation of B cells
- Compare the primary and secondary antibody responses

Humoral immunity refers to mechanisms of the adaptive immune defenses that are mediated by antibodies secreted by B lymphocytes, or B cells. This section will focus on B cells and discuss their production and maturation, receptors, and mechanisms of activation.

B Cell Production and Maturation

Like T cells, B cells are formed from multipotent hematopoietic stem cells (HSCs) in the bone marrow and follow a pathway through lymphoid stem cell and lymphoblast (see Figure 17.3.1). Unlike T cells, however, lymphoblasts destined to become B cells do not leave the bone marrow and travel to the thymus for maturation. Rather, eventual B cells continue to mature in the bone marrow.

The first step of B cell maturation is an assessment of the functionality of their antigen-binding receptors. This occurs through positive selection for B cells with normal functional receptors. A mechanism of negative selection is then used to eliminate self-reacting B cells and minimize the risk of autoimmunity. Negative selection of self-reacting B cells can involve elimination by apoptosis, editing or modification of the receptors so they are no longer self-reactive, or induction of anergy in the B cell. Immature B cells that pass the selection in the bone marrow then travel to the spleenfor their final stages of maturation. There they become naïve mature B cells, i.e., mature B cells that have not yet been activated.

Exercise 6.3.4.1

Compare the maturation of B cells with the maturation of T cells.

B-Cell Receptors

Like T cells, B cells possess antigen-specific receptors with diverse specificities. Although they rely on T cells for optimum function, B cells can be activated without help from T cells. B-cell receptors (BCRs) for naïve mature B cells are membrane-bound monomeric forms of IgD and IgM. They have two identical heavy chains and two identical light chains connected by disulfide bonds into a basic “Y” shape (Figure 6.3.4.1). The trunk of the Y-shaped molecule, the constant region of the two heavy chains, spans the B cell membrane. The two antigen-binding sites exposed to the exterior of the B cell are involved in the binding of specific pathogen epitopes to initiate the activation process. It is estimated that each naïve mature B cell has upwards of 100,000 BCRs on its membrane, and each of these BCRs has an identical epitope-binding specificity.

In order to be prepared to react to a wide range of microbial epitopes, B cells, like T cells, use genetic rearrangementof hundreds of gene segments to provide the necessary diversity of receptor specificities. The variable region of the BCR heavy chain is made up of V, D, and J segments, similar to the β chain of the TCR. The variable region of the BCR light chain is made up of V and J segments, similar to the α chain of the TCR. Genetic rearrangement of all possible combinations of V-J-D (heavy chain) and V-J (light chain) provides for millions of unique antigen-binding sites for the BCR and for the antibodies secreted after activation.

One important difference between BCRs and TCRs is the way they can interact with antigenic epitopes. Whereas TCRs can only interact with antigenic epitopes that are presented within the antigen-binding cleft of MHC I or MHC II, BCRs do not require antigen presentation with MHC; they can interact with epitopes on free antigens or with epitopesdisplayed on the surface of intact pathogens. Another important difference is that TCRs only recognize protein epitopes, whereas BCRs can recognize epitopes associated with different molecular classes (e.g., proteins, polysaccharides, lipopolysaccharides).

Activation of B cells occurs through different mechanisms depending on the molecular class of the antigen. Activation of a B cell by a protein antigen requires the B cell to function as an APC, presenting the protein epitopes with MHC II to helper T cells.

Because of their dependence on T cells for activation of B cells, protein antigens are classified as T-dependent antigens. In contrast, polysaccharides, lipopolysaccharides, and other nonprotein antigens are considered T-independent antigens because they can activate B cells without antigen processing and presentation to T cells.

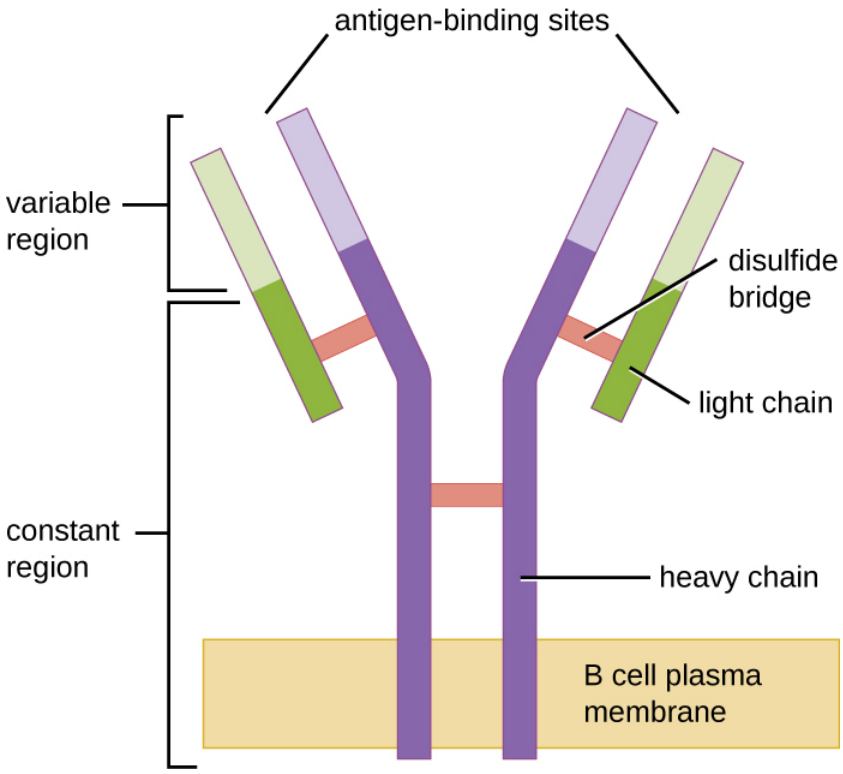


Figure 6.3.4.1: B-cell receptors are embedded in the membranes of B cells. The variable regions of all of the receptors on a single cell bind the same specific antigen.

? Exercise 6.3.4.2

1. What types of molecules serve as the BCR?
2. What are the differences between TCRs and BCRs with respect to antigen recognition?
3. Which molecule classes are T-dependent antigens and which are T-independent antigens?

T Cell-Independent Activation of B cells

Activation of B cells without the cooperation of helper T cells is referred to as T cell-independent activation and occurs when BCRs interact with T-independent antigens. T-independent antigens (e.g., polysaccharide capsules, lipopolysaccharide) have repetitive epitope units within their structure, and this repetition allows for the cross-linkageof multiple BCRs, providing the first signal for activation (Figure 6.3.4.2). Because T cells are not involved, the second signal has to come from other sources, such as interactions of toll-like receptors with PAMPs or interactions with factors from the complement system.

Once a B cell is activated, it undergoes clonal proliferation and daughter cells differentiate into plasma cells. Plasma cells are antibody factories that secrete large quantities of antibodies. After differentiation, the surface BCRs disappear and the plasma cell secretes pentameric IgM molecules that have the same antigen specificity as the BCRs (Figure 6.3.4.2).

The T cell-independent response is short-lived and does not result in the production of memory B cells. Thus it will not result in a secondary response to subsequent exposures to T-independent antigens.

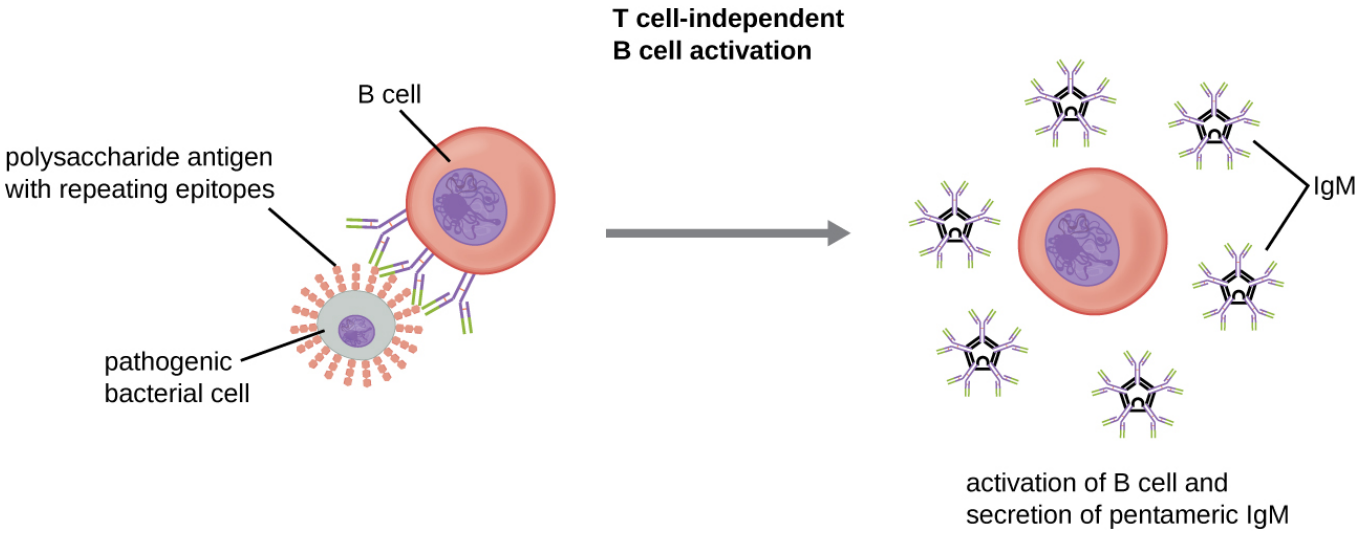


Figure 6.3.4.2: T-independent antigens have repeating epitopes that can induce B cell recognition and activation without involvement from T cells. A second signal, such as interaction of TLRs with PAMPs (not shown), is also required for activation of the B cell. Once activated, the B cell proliferates and differentiates into antibody-secreting plasma cells.

? Exercise 6.3.4.3

1. What are the two signals required for T cell-independent activation of B cells?
2. What is the function of a plasma cell?

T Cell-Dependent Activation of B cells

T cell-dependent activation of B cells is more complex than T cell-independent activation, but the resulting immune response is stronger and develops memory. T cell-dependent activation can occur either in response to free protein antigens or to protein antigens associated with an intact pathogen. Interaction between the BCRs on a naïve mature B cell and a free protein antigen stimulate internalization of the antigen, whereas interaction with antigens associated with an intact pathogen initiates the extraction of the antigen from the pathogen before internalization. Once internalized inside the B cell, the protein antigen is processed and presented with MHC II. The presented antigen is then recognized by helper T cells specific to the same antigen. The TCR of the helper T cell recognizes the foreign antigen, and the T cell's CD4 molecule interacts with MHC II on the B cell. The coordination between B cells and helper T cells that are specific to the same antigen is referred to as linked recognition.

Once activated by linked recognition, T_H2 cells produce and secrete cytokines that activate the B cell and cause proliferation into clonal daughter cells. After several rounds of proliferation, additional cytokines provided by the T_H2 cells stimulate the differentiation of activated B cell clones into memory B cells, which will quickly respond to subsequent exposures to the same protein epitope, and plasma cells that lose their membrane BCRs and initially secrete pentameric IgM (Figure 6.3.4.3).

After initial secretion of IgM, cytokines secreted by T_H2 cells stimulate the plasma cells to switch from IgM production to production of IgG, IgA, or IgE. This process, called class switching or isotype switching, allows plasma cellscloned from the same activated B cell to produce a variety of antibody classes with the same epitope specificity. Class switching is accomplished by genetic rearrangement of gene segments encoding the constant region, which determines an antibody's class. The variable region is not changed, so the new class of antibody retains the original epitope specificity.

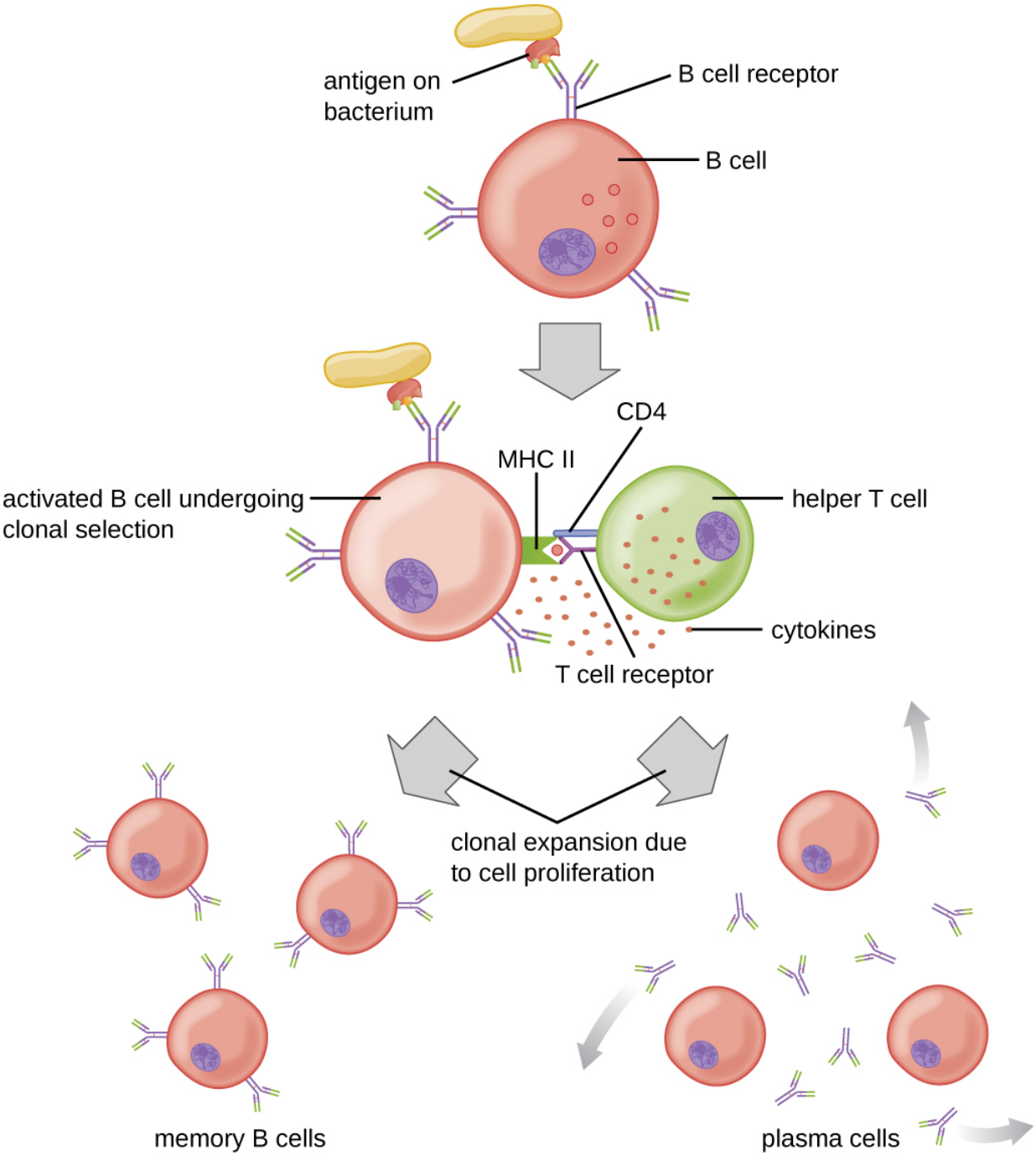


Figure 6.3.4.3: In T cell-dependent activation of B cells, the B cell recognizes and internalizes an antigen and presents it to a helper T cell that is specific to the same antigen. The helper T cell interacts with the antigen presented by the B cell, which activates the T cell and stimulates the release of cytokines that then activate the B cell. Activation of the B cell triggers proliferation and differentiation into B cells and plasma cells.

? Exercise 6.3.4.4

1. What steps are required for T cell-dependent activation of B cells?
2. What is antibody class switching and why is it important?

Primary and Secondary Responses

T cell-dependent activation of B cells plays an important role in both the primary and secondary responses associated with adaptive immunity. With the first exposure to a protein antigen, a T cell-dependent primary antibody responseoccurs. The initial stage of the

primary response is a lag period, or latent period, of approximately 10 days, during which no antibody can be detected in serum. This lag period is the time required for all of the steps of the primary response, including naïve mature B cell binding of antigen with BCRs, antigen processing and presentation, helper T cell activation, B cell activation, and clonal proliferation. The end of the lag period is characterized by a rise in IgM levels in the serum, as T_H2 cells stimulate B cell differentiation into plasma cells. IgM levels reach their peak around 14 days after primary antigen exposure; at about this same time, T_H2 stimulates antibody class switching, and IgM levels in serum begin to decline. Meanwhile, levels of IgG increase until they reach a peak about three weeks into the primary response (Figure 6.3.4.4).

During the primary response, some of the cloned B cells are differentiated into memory B cells programmed to respond to subsequent exposures. This secondary response occurs more quickly and forcefully than the primary response. The lag period is decreased to only a few days and the production of IgG is significantly higher than observed for the primary response (Figure 6.3.4.4). In addition, the antibodies produced during the secondary response are more effective and bind with higher affinity to the targeted epitopes. Plasma cells produced during secondary responses live longer than those produced during the primary response, so levels of specific antibody remain elevated for a longer period of time.

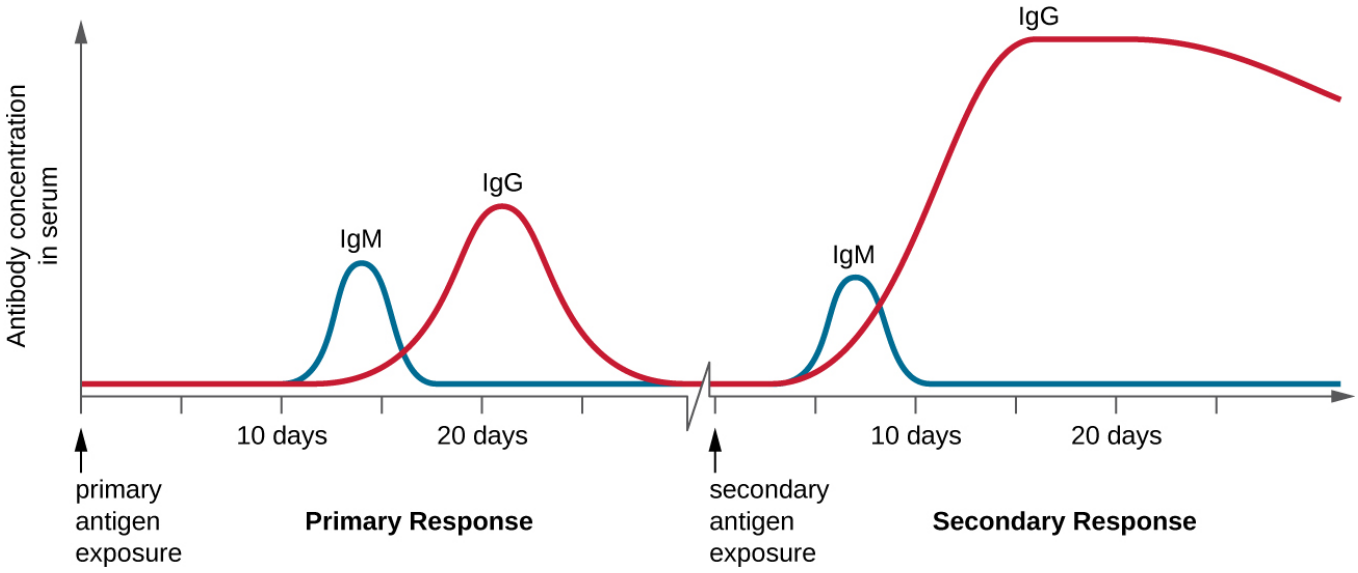


Figure 6.3.4.4: Compared to the primary response, the secondary antibody response occurs more quickly and produces antibody levels that are higher and more sustained. The secondary response mostly involves IgG.

? Exercise 6.3.4.5

1. What events occur during the lag period of the primary antibody response?
2. Why do antibody levels remain elevated longer during the secondary antibody response?

Key Concepts and Summary

- **B lymphocytes** or **B cells** produce antibodies involved in humoral immunity. B cells are produced in the bone marrow, where the initial stages of maturation occur, and travel to the spleen for final steps of maturation into naïve mature B cells.
- **B-cell receptors (BCRs)** are membrane-bound monomeric forms of IgD and IgM that bind specific antigen epitopes with their Fab antigen-binding regions. Diversity of antigen binding specificity is created by genetic rearrangement of V, D, and J segments similar to the mechanism used for TCR diversity.
- Protein antigens are called **T-dependent antigens** because they can only activate B cells with the cooperation of helper T cells. Other molecule classes do not require T cell cooperation and are called **T-independent antigens**.
- **T cell-independent activation** of B cells involves cross-linkage of BCRs by repetitive nonprotein antigen epitopes. It is characterized by the production of IgM by **plasma cells** and does not produce memory B cells.
- **T cell-dependent activation** of B cells involves processing and presentation of protein antigens to helper T cells, activation of the B cells by cytokines secreted from activated T_H2 cells, and plasma cells that produce different classes of antibodies as a result of **class switching**. **Memory B cells** are also produced.

- Secondary exposures to T-dependent antigens result in a secondary antibody response initiated by memory B cells. The secondary response develops more quickly and produces higher and more sustained levels of antibody with higher affinity for the specific antigen.

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6.3.5: Vaccines

Learning Objectives

- Compare the various kinds of artificial immunity
- Differentiate between variolation and vaccination
- Describe different types of vaccines and explain their respective advantages and disadvantages

For many diseases, prevention is the best form of treatment, and few strategies for disease prevention are as effective as vaccination. Vaccination is a form of artificial immunity. By artificially stimulating the adaptive immune defenses, a vaccine triggers memory cell production similar to that which would occur during a primary response. In so doing, the patient is able to mount a strong secondary response upon exposure to the pathogen—but without having to first suffer through an initial infection. In this section, we will explore several different kinds of artificial immunity along with various types of vaccines and the mechanisms by which they induce artificial immunity.

Classifications of Adaptive Immunity

All forms of adaptive immunity can be described as either active or passive. Active immunity refers to the activation of an individual's own adaptive immune defenses, whereas passive immunity refers to the transfer of adaptive immune defenses from another individual or animal. Active and passive immunity can be further subdivided based on whether the protection is acquired naturally or artificially.

Natural active immunity is adaptive immunity that develops after natural exposure to a pathogen (Figure 6.3.5.1). Examples would include the lifelong immunity that develops after recovery from a chickenpox or measles infection (although an acute infection is not always necessary to activate adaptive immunity). The length of time that an individual is protected can vary substantially depending upon the pathogen and antigens involved. For example, activation of adaptive immunity by protein spike structures during an intracellular viral infection can activate lifelong immunity, whereas activation by carbohydrate capsule antigens during an extracellular bacterial infection may activate shorter-term immunity.

Natural passive immunity involves the natural passage of antibodies from a mother to her child before and after birth. IgG is the only antibody class that can cross the placenta from mother's blood to the fetal blood supply. Placental transfer of IgG is an important passive immune defense for the infant, lasting up to six months after birth. Secretory IgA can also be transferred from mother to infant through breast milk.

Artificial passive immunity refers to the transfer of antibodies produced by a donor (human or animal) to another individual. This transfer of antibodies may be done as a prophylactic measure (i.e., to prevent disease after exposure to a pathogen) or as a strategy for treating an active infection. For example, artificial passive immunity is commonly used for post-exposure prophylaxis against rabies, hepatitis A, hepatitis B, and chickenpox (in high risk individuals). Active infections treated by artificial passive immunity include cytomegalovirus infections in immunocompromised patients and Ebola virus infections. In 1995, eight patients in the Democratic Republic of the Congo with active Ebola infections were treated with blood transfusions from patients who were recovering from Ebola. Only one of the eight patients died (a 12.5% mortality rate), which was much lower than the expected 80% mortality rate for Ebola in untreated patients.[1] Artificial passive immunity is also used for the treatment of diseases caused by bacterial toxins, including tetanus, botulism, and diphtheria.

Artificial active immunity is the foundation for vaccination. It involves the activation of adaptive immunity through the deliberate exposure of an individual to weakened or inactivated pathogens, or preparations consisting of key pathogen antigens.

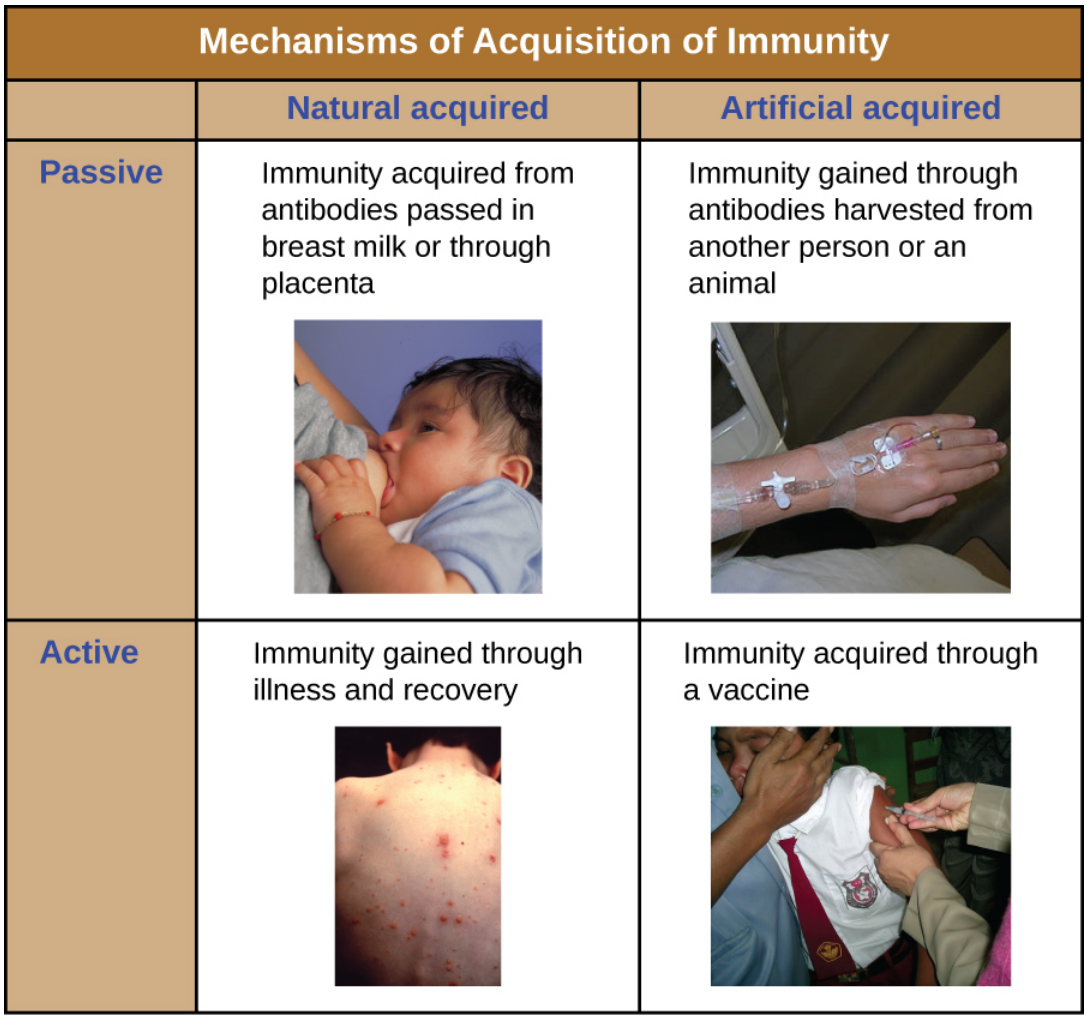


Figure 6.3.5.1: The four classifications of immunity. (credit top left photo: modification of work by USDA; credit top right photo: modification of work by "Michaelberry"/Wikimedia; credit bottom left photo: modification of work by Centers for Disease Control and Prevention; credit bottom right photo: modification of work by Friskila Silitonga, Indonesia, Centers for Disease Control and Prevention)

? Exercise 6.3.5.1

1. What is the difference between active and passive immunity?
2. What kind of immunity is conferred by a vaccine?

Herd Immunity

The four kinds of immunity just described result from an individual's adaptive immune system. For any given disease, an individual may be considered immune or susceptible depending on his or her ability to mount an effective immune response upon exposure. Thus, any given population is likely to have some individuals who are immune and other individuals who are susceptible. If a population has very few susceptible individuals, even those susceptible individuals will be protected by a phenomenon called herd immunity. Herd immunity has nothing to do with an individual's ability to mount an effective immune response; rather, it occurs because there are too few susceptible individuals in a population for the disease to spread effectively.

Vaccination programs create herd immunity by greatly reducing the number of susceptible individuals in a population. Even if some individuals in the population are not vaccinated, as long as a certain percentage is immune (either naturally or artificially), the few susceptible individuals are unlikely to be exposed to the pathogen. However, because new individuals are constantly entering populations (for example, through birth or relocation), vaccination programs are necessary to maintain herd immunity.

Vaccination: Obligation or Choice

A growing number of parents are choosing not to vaccinate their children. They are dubbed “antivaxxers,” and the majority of them believe that vaccines are a cause of autism (or other disease conditions), a link that has now been thoroughly disproven. Others object to vaccines on religious or moral grounds (e.g., the argument that Gardasil vaccination against HPV may promote sexual promiscuity), on personal ethical grounds (e.g., a conscientious objection to any medical intervention), or on political grounds (e.g., the notion that mandatory vaccinations are a violation of individual liberties).[2]

It is believed that this growing number of unvaccinated individuals has led to new outbreaks of whooping cough and measles. We would expect that herd immunity would protect those unvaccinated in our population, but herd immunity can only be maintained if enough individuals are being vaccinated.

Vaccination is clearly beneficial for public health. But from the individual parent’s perspective the view can be murkier. Vaccines, like all medical interventions, have associated risks, and while the risks of vaccination may be extremely low compared to the risks of infection, parents may not always understand or accept the consensus of the medical community. Do such parents have a right to withhold vaccination from their children? Should they be allowed to put their children—and society at large—at risk?

Many governments insist on childhood vaccinations as a condition for entering public school, but it has become easy in most states to opt out of the requirement or to keep children out of the public system. Since the 1970s, West Virginia and Mississippi have had in place a stringent requirement for childhood vaccination, without exceptions, and neither state has had a case of measles since the early 1990s. California lawmakers recently passed a similar law in response to a measles outbreak in 2015, making it much more difficult for parents to opt out of vaccines if their children are attending public schools. Given this track record and renewed legislative efforts, should other states adopt similarly strict requirements?

What role should health-care providers play in promoting or enforcing universal vaccination? Studies have shown that many parents’ minds can be changed in response to information delivered by health-care workers, but is it the place of health-care workers to try to persuade parents to have their children vaccinated? Some health-care providers are understandably reluctant to treat unvaccinated patients. Do they have the right to refuse service to patients who decline vaccines? Do insurance companies have the right to deny coverage to antivaxxers? These are all ethical questions that policymakers may be forced to address as more parents skirt vaccination norms.

Variolation and Vaccination

Thousands of years ago, it was first recognized that individuals who survived a smallpox infection were immune to subsequent infections. The practice of inoculating individuals to actively protect them from smallpox appears to have originated in the 10th century in China, when the practice of variolation was described (Figure 6.3.5.2). Variolation refers to the deliberate inoculation of individuals with infectious material from scabs or pustules of smallpox victims. Infectious materials were either injected into the skin or introduced through the nasal route. The infection that developed was usually milder than naturally acquired smallpox, and recovery from the milder infection provided protection against the more serious disease.

Although the majority of individuals treated by variolation developed only mild infections, the practice was not without risks. More serious and sometimes fatal infections did occur, and because smallpox was contagious, infections resulting from variolation could lead to epidemics. Even so, the practice of variolation for smallpox prevention spread to other regions, including India, Africa, and Europe.



Figure 6.3.5.2: Variolation for smallpox originated in the Far East and the practice later spread to Europe and Africa. This Japanese relief depicts a patient receiving a smallpox variolation from the physician Ogata Shunsaku (1748–1810).

Although variolation had been practiced for centuries, the English physician Edward Jenner (1749–1823) is generally credited with developing the modern process of vaccination. Jenner observed that milkmaids who developed cowpox, a disease similar to smallpox but milder, were immune to the more serious smallpox. This led Jenner to hypothesize that exposure to a less virulent pathogen could provide immune protection against a more virulent pathogen, providing a safer alternative to variolation. In 1796, Jenner tested his hypothesis by obtaining infectious samples from a milkmaid's active cowpox lesion and injecting the materials into a young boy (Figure 6.3.5.3). The boy developed a mild infection that included a low-grade fever, discomfort in his axillae (armpit) and loss of appetite. When the boy was later infected with infectious samples from smallpox lesions, he did not contract smallpox.[3] This new approach was termed vaccination, a name deriving from the use of cowpox (Latin *vacca* meaning "cow") to protect against smallpox. Today, we know that Jenner's vaccine worked because the cowpox virus is genetically and antigenically related to the *Variola* viruses that caused smallpox. Exposure to cowpox antigens resulted in a primary response and the production of memory cells that identical or related epitopes of Variola virus upon a later exposure to smallpox.

The success of Jenner's smallpox vaccination led other scientists to develop vaccines for other diseases. Perhaps the most notable was Louis Pasteur, who developed vaccines for rabies, cholera, and anthrax. During the 20th and 21st centuries, effective vaccines were developed to prevent a wide range of diseases caused by viruses (e.g., chickenpox and shingles, hepatitis, measles, mumps, polio, and yellow fever) and bacteria (e.g., diphtheria, pneumococcal pneumonia, tetanus, and whooping cough).



(a) (b)

Figure 6.3.5.3: (a) A painting of Edward Jenner depicts a cow and a milkmaid in the background. (b) Lesions on a patient infected with cowpox, a zoonotic disease caused by a virus closely related to the one that causes smallpox. (credit b: modification of work by the Centers for Disease Control and Prevention)

? Exercise 6.3.5.2

1. What is the difference between variolation and vaccination for smallpox?
2. Explain why vaccination is less risky than variolation.

Classes of Vaccines

For a vaccine to provide protection against a disease, it must expose an individual to pathogen-specific antigens that will stimulate a protective adaptive immune response. By its very nature, this entails some risk. As with any pharmaceutical drug, vaccines have the potential to cause adverse effects. However, the ideal vaccine causes no severe adverse effects and poses no risk of contracting the disease that it is intended to prevent. Various types of vaccines have been developed with these goals in mind. These different classes of vaccines are described in the next section and summarized in Table 6.3.5.1.

Live Attenuated Vaccines

Live attenuated vaccines expose an individual to a weakened strain of a pathogen with the goal of establishing a subclinical infection that will activate the adaptive immune defenses. Pathogens are attenuated to decrease their virulence using methods such as genetic manipulation (to eliminate key virulence factors) or long-term culturing in an unnatural host or environment (to promote mutations and decrease virulence).

By establishing an active infection, live attenuated vaccines stimulate a more comprehensive immune response than some other types of vaccines. Live attenuated vaccines activate both cellular and humoral immunity and stimulate the development of memory for long-lasting immunity. In some cases, vaccination of one individual with a live attenuated pathogen can even lead to natural transmission of the attenuated pathogen to other individuals. This can cause the other individuals to also develop an active, subclinical infection that activates their adaptive immune defenses.

Disadvantages associated with live attenuated vaccines include the challenges associated with long-term storage and transport as well as the potential for a patient to develop signs and symptoms of disease during the active infection (particularly in immunocompromised patients). There is also a risk of the attenuated pathogen reverting back to full virulence. Table 6.3.5.1 lists examples of live attenuated vaccines.

Inactivated Vaccines

Inactivated vaccines contain whole pathogens that have been killed or inactivated with heat, chemicals, or radiation. For inactivated vaccines to be effective, the inactivation process must not affect the structure of key antigens on the pathogen.

Because the pathogen is killed or inactive, inactivated vaccines do not produce an active infection, and the resulting immune response is weaker and less comprehensive than that provoked by a live attenuated vaccine. Typically the response involves only humoral immunity, and the pathogen cannot be transmitted to other individuals. In addition, inactivated vaccines usually require higher doses and multiple boosters, possibly causing inflammatory reactions at the site of injection.

Despite these disadvantages, inactivated vaccines do have the advantages of long-term storage stability and ease of transport. Also, there is no risk of causing severe active infections. However, inactivated vaccines are not without their side effects. Table 6.3.5.1 lists examples of inactivated vaccines.

Subunit Vaccines

Whereas live attenuated and inactive vaccines expose an individual to a weakened or dead pathogen, subunit vaccines only expose the patient to the key antigens of a pathogen—not whole cells or viruses. Subunit vaccines can be produced either by chemically degrading a pathogen and isolating its key antigens or by producing the antigens through genetic engineering. Because these vaccines contain only the essential antigens of a pathogen, the risk of side effects is relatively low. Table 6.3.5.1 lists examples of subunit vaccines.

Toxoid Vaccines

Like subunit vaccines, toxoid vaccines do not introduce a whole pathogen to the patient; they contain inactivated bacterial toxins, called toxoids. Toxoid vaccines are used to prevent diseases in which bacterial toxins play an important role in pathogenesis. These vaccines activate humoral immunity that neutralizes the toxins. Table 6.3.5.1 lists examples of toxoid vaccines.

Conjugate Vaccines

A conjugate vaccine is a type of subunit vaccine that consists of a protein conjugated to a capsule polysaccharide. Conjugate vaccines have been developed to enhance the efficacy of subunit vaccines against pathogens that have protective polysaccharide capsules that help them evade phagocytosis, causing invasive infections that can lead to meningitis and other serious conditions. The subunit vaccines against these pathogens introduce T-independent capsular polysaccharide antigens that result in the production of antibodies that can opsonize the capsule and thus combat the infection; however, children under the age of two years do not respond effectively to these vaccines. Children do respond effectively when vaccinated with the conjugate vaccine, in which a protein with T-dependent antigens is conjugated to the capsule polysaccharide. The conjugated protein-polysaccharide antigen stimulates production of antibodies against both the protein and the capsule polysaccharide. Table 6.3.5.1 lists examples of conjugate vaccines.

Table 6.3.5.1: Classes of Vaccines

Class	Description	Advantages	Disadvantages	Examples
Live attenuated	Weakened strain of whole pathogen	Cellular and humoral immunity	Difficult to store and transport	Chickenpox, German measles, measles, mumps, tuberculosis, typhoid fever, yellow fever
		Long-lasting immunity	Risk of infection in immunocompromised patients	
		Transmission to contacts	Risk of reversion	
Inactivated	Whole pathogen killed or inactivated with heat, chemicals, or radiation	Ease of storage and transport	Weaker immunity (humoral only)	Cholera, hepatitis A, influenza, plague, rabies
		No risk of severe active infection	Higher doses and more boosters required	
Subunit	Immunogenic antigens	Lower risk of side effects	Limited longevity	Anthrax, hepatitis B, influenza, meningitis, papillomavirus, pneumococcal pneumonia, whooping cough
			Multiple doses required	
			No protection against antigenic variation	
Toxoid	Inactivated bacterial toxin	Humoral immunity to neutralize toxin	Does not prevent infection	Botulism, diphtheria, pertussis, tetanus
Conjugate	Capsule polysaccharide conjugated to protein	T-dependent response to capsule	Costly to produce	Meningitis (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitides*)
			No protection against antigenic variation	
		Better response in young children	May interfere with other vaccines	

? Exercise 6.3.5.3

1. What is the risk associated with a live attenuated vaccine?
2. Why is a conjugated vaccine necessary in some cases?

DNA Vaccines

DNA vaccines represent a relatively new and promising approach to vaccination. A DNA vaccine is produced by incorporating genes for antigens into a recombinant plasmid vaccine. Introduction of the DNA vaccine into a patient leads to uptake of the recombinant plasmid by some of the patient's cells, followed by transcription and translation of antigens and presentation of these antigens with MHC I to activate adaptive immunity. This results in the stimulation of both humoral and cellular immunity without the risk of active disease associated with live attenuated vaccines.

Although most DNA vaccines for humans are still in development, it is likely that they will become more prevalent in the near future as researchers are working on engineering DNA vaccines that will activate adaptive immunity against several different pathogens at once. First-generation DNA vaccines tested in the 1990s looked promising in animal models but were disappointing when tested in human subjects. Poor cellular uptake of the DNA plasmids was one of the major problems impacting their efficacy. Trials of second-generation DNA vaccines have been more promising thanks to new techniques for enhancing cellular uptake and optimizing antigens. DNA vaccines for various cancers and viral pathogens such as HIV, HPV, and hepatitis B and C are currently in development.

Some DNA vaccines are already in use. In 2005, a DNA vaccine against West Nile virus was approved for use in horses in the United States. Canada has also approved a DNA vaccine to protect fish from infectious hematopoietic necrosis virus.[4] A DNA vaccine against Japanese encephalitis virus was approved for use in humans in 2010 in Australia.

Clinical Focus: Resolution

Based on Olivia's symptoms, her physician made a preliminary diagnosis of bacterial meningitis without waiting for positive identification from the blood and CSF samples sent to the lab. Olivia was admitted to the hospital and treated with intravenous broad-spectrum antibiotics and rehydration therapy. Over the next several days, her condition began to improve, and new blood samples and lumbar puncture samples showed an absence of microbes in the blood and CSF with levels of white blood cells returning to normal. During this time, the lab produced a positive identification of *Neisseria meningitidis*, the causative agent of meningococcal meningitis, in her original CSF sample.

N. meningitidis produces a polysaccharide capsule that serves as a virulence factor. *N. meningitidis* tends to affect infants after they begin to lose the natural passive immunity provided by maternal antibodies. At one year of age, Olivia's maternal IgG antibodies would have disappeared, and she would not have developed memory cells capable of recognizing antigens associated with the polysaccharide capsule of the *N. meningitidis*. As a result, her adaptive immune system was unable to produce protective antibodies to combat the infection, and without antibiotics she may not have survived. Olivia's infection likely would have been avoided altogether had she been vaccinated. A conjugate vaccine to prevent meningococcal meningitis is available and approved for infants as young as two months of age. However, current vaccination schedules in the United States recommend that the vaccine be administered at age 11–12 with a booster at age 16.

Link to Learning

In countries with developed public health systems, many vaccines are routinely administered to children and adults. Vaccine schedules are changed periodically, based on new information and research results gathered by public health agencies. In the United States, the CDC publishes schedules and other updated information about vaccines.

Key Concepts and Summary

- Adaptive immunity can be divided into four distinct classifications: **natural active immunity, natural passive immunity, artificial passive immunity,** and **artificial active immunity.**
- Artificial active immunity is the foundation for **vaccination** and vaccine development. Vaccination programs not only confer artificial immunity on individuals, but also foster **herd immunity** in populations.
- **Variolation** against smallpox originated in the 10th century in China, but the procedure was risky because it could cause the disease it was intended to prevent. Modern vaccination was developed by Edward Jenner, who developed the practice of inoculating patients with infectious materials from cowpox lesions to prevent smallpox.
- **Live attenuated vaccines** and **inactivated vaccines** contain whole pathogens that are weak, killed, or inactivated. **Subunit vaccines, toxoid vaccines,** and **conjugate vaccines** contain acellular components with antigens that stimulate an immune response.

Footnotes

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2. 2 Elizabeth Yale. "Why Anti-Vaccination Movements Can Never Be Tamed." *Religion & Politics*, July 22, 2014. religionandpolitics.org/2014/...never-be-tamed.
3. 3 N. J. Willis. "Edward Jenner and the Eradication of Smallpox." *Scottish Medical Journal* 42 (1997): 118–121.
4. 4 M. Alonso and J. C. Leong. "Licensed DNA Vaccines Against Infectious Hematopoietic Necrosis Virus (IHNV)." *Recent Patents on DNA & Gene Sequences (Discontinued)* 7 no. 1 (2013): 62–65, issn 1872-2156/2212-3431. doi 10.2174/1872215611307010009.

5. 5 S.B. Halstead and S. J. Thomas. “New Japanese Encephalitis Vaccines: Alternatives to Production in Mouse Brain.” *Expert Review of Vaccines* 10 no. 3 (2011): 355–64.

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6.3.E: Specific Adaptive Host Defenses (Exercises)

18.1: Architecture of the Immune System

Adaptive immunity is defined by two important characteristics: specificity and memory. Specificity refers to the adaptive immune system's ability to target specific pathogens, and memory refers to its ability to quickly respond to pathogens to which it has previously been exposed. For example, when an individual recovers from chickenpox, the body develops a memory of the infection that will specifically protect it from the causative agent if it is exposed to the virus again later.

Multiple Choice

Antibodies are produced by _____.

A. plasma cells
B. T cells
C. bone marrow
D. B cells

Answer

A

Cellular adaptive immunity is carried out by _____.

A. B cells
B. T cells
C. bone marrow
D. neutrophils

Answer

B

A single antigen molecule may be composed of many individual _____.

A. T-cell receptors
B. B-cell receptors
C. MHC II
D. epitopes

Answer

D

Which class of molecules is the most antigenic?

A. polysaccharides
B. lipids
C. proteins
D. carbohydrates

Answer

C

Matching

Match the antibody class with its description.

___IgA	A. This class of antibody is the only one that can cross the placenta.
___IgD	B. This class of antibody is the first to appear after activation of B cells.
___IgE	C. This class of antibody is involved in the defense against parasitic infections and involved in allergic responses.
___IgG	D. This class of antibody is found in very large amounts in mucus secretions.
___IgM	E. This class of antibody is not secreted by B cells but is expressed on the surface of naïve B cells.

Answer

d, e, c, a, b

Fill in the Blank

There are two critically important aspects of adaptive immunity. The first is specificity, while the second is _____.

Answer

memory

_____ immunity involves the production of antibody molecules that bind to specific antigens.

Answer

Humoral

The heavy chains of an antibody molecule contain _____ region segments, which help to determine its class or isotype.

Answer

constant

The variable regions of the heavy and light chains form the _____ sites of an antibody.

Answer

antigen-binding

Short Answer

What is the difference between humoral and cellular adaptive immunity?

What is the difference between an antigen and a hapten?

Describe the mechanism of antibody-dependent cell-mediated cytotoxicity.

18.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes

Major histocompatibility complex (MHC) molecules are expressed on the surface of healthy cells, identifying them as normal and “self” to natural killer (NK) cells. MHC molecules also play an important role in the presentation of foreign antigens, which is a critical step in the activation of T cells and thus an important mechanism of the adaptive immune system.

Multiple Choice

MHC I molecules present

A. processed foreign antigens from proteasomes.
B. processed self-antigens from phagolysosome.
C. antibodies.
D. T cell antigens.

Answer

A

MHC II molecules present

A. processed self-antigens from proteasomes.
B. processed foreign antigens from phagolysosomes.
C. antibodies.
D. T cell receptors.

Answer

B

Which type of antigen-presenting molecule is found on all nucleated cells?

A. MHC II
B. MHC I
C. antibodies
D. B-cell receptors

Answer

B

Which type of antigen-presenting molecule is found only on macrophages, dendritic cells, and B cells?

A. MHC I
B. MHC II
C. T-cell receptors
D. B-cell receptors

Answer

B

Fill in the Blank

MHC molecules are used for antigen _____ to T cells.

Answer

presentation

MHC II molecules are made up of two subunits (α and β) of approximately equal size, whereas MHC I molecules consist of a larger α subunit and a smaller subunit called _____.

Answer

β_2 microglobulin

Critical Thinking

Which mechanism of antigen presentation would be used to present antigens from a cell infected with a virus?

Which pathway of antigen presentation would be used to present antigens from an extracellular bacterial infection?

18.3: T Lymphocytes

The antibodies involved in humoral immunity often bind pathogens and toxins before they can attach to and invade host cells. Thus, humoral immunity is primarily concerned with fighting pathogens in extracellular spaces. However, pathogens that have already gained entry to host cells are largely protected from the humoral antibody-mediated defenses. Cellular immunity, on the other hand, targets and eliminates intracellular pathogens through the actions of T lymphocytes, or T cells.

Multiple Choice

What is a superantigen?

A. a protein that is highly efficient at stimulating a single type of productive and specific T cell response
B. a protein produced by antigen-presenting cells to enhance their presentation capabilities
C. a protein produced by T cells as a way of increasing the antigen activation they receive from antigen-presenting cells
D. a protein that activates T cells in a nonspecific and uncontrolled manner

Answer

D

To what does the TCR of a helper T cell bind?

A. antigens presented with MHC I molecules
B. antigens presented with MHC II molecules
C. free antigen in a soluble form
D. haptens only

Answer

B

Cytotoxic T cells will bind with their TCR to which of the following?

A. antigens presented with MHC I molecules
B. antigens presented with MHC II molecules
C. free antigen in a soluble form
D. haptens only

Answer

A

A _____ molecule is a glycoprotein used to identify and distinguish white blood cells.

A. T-cell receptor
B. B-cell receptor
C. MHC I
D. cluster of differentiation

Answer

D

Name the T helper cell subset involved in antibody production.

A. T_H1

B. T_H2
C. T_H17
D. CTL

Answer

B

Fill in the Blank

A _____ T cell will become activated by presentation of foreign antigen associated with an MHC I molecule.

Answer

cytotoxic

A _____ T cell will become activated by presentation of foreign antigen in association with an MHC II molecule.

Answer

helper

A TCR is a protein dimer embedded in the plasma membrane of a T cell. The _____ region of each of the two protein chains is what gives it the capability to bind to a presented antigen.

Answer

variable

Peripheral tolerance mechanisms function on T cells after they mature and exit the _____.

Answer

thymus

Both _____ and effector T cells are produced during differentiation of activated T cells.

Answer

memory

Short Answer

What is the basic difference in effector function between helper and cytotoxic T cells?

What necessary interactions are required for activation of helper T cells and activation/effector function of cytotoxic T cells?

18.4: B Lymphocytes and Antibodies

Humoral immunity refers to mechanisms of the adaptive immune defenses that are mediated by antibodies secreted by B lymphocytes, or B cells. This section focuses on B cells and discusses their production and maturation, receptors, and mechanisms of activation.

Multiple Choice

Which of the following would be a T-dependent antigen?

A. lipopolysaccharide
B. glycolipid
C. protein
D. carbohydrate

Answer

C

Which of the following would be a BCR?

A. CD4
B. MHC II
C. MHC I
D. IgD

Answer

D

Which of the following does not occur during the lag period of the primary antibody response?

A. activation of helper T cells
B. class switching to IgG
C. presentation of antigen with MHC II
D. binding of antigen to BCRs

Answer

B

Fill in the Blank

_____ antigens can stimulate B cells to become activated but require cytokine assistance delivered by helper T cells.

Answer

T-dependent

T-independent antigens can stimulate B cells to become activated and secrete antibodies without assistance from helper T cells. These antigens possess _____ antigenic epitopes that cross-link BCRs.

Answer

repetitive

Critical Thinking

A patient lacks the ability to make functioning T cells because of a genetic disorder. Would this patient's B cells be able to produce antibodies in response to an infection? Explain your answer.

18.5: Vaccines

By artificially stimulating the adaptive immune defenses, a vaccine triggers memory cell production similar to that which would occur during a primary response. In so doing, the patient is able to mount a strong secondary response upon exposure to the pathogen—but without having to first suffer through an initial infection. In this section, we explore several different kinds of artificial immunity along with various types of vaccines and their mechanisms for inducing artificial immunity.

Multiple Choice

A patient is bitten by a dog with confirmed rabies infection. After treating the bite wound, the physician injects the patient with antibodies that are specific for the rabies virus to prevent the development of an active infection. This is an example of:

A. Natural active immunity
B. Artificial active immunity
C. Natural passive immunity
D. Artificial passive immunity

Answer

D

A patient gets a cold, and recovers a few days later. The patient's classmates come down with the same cold roughly a week later, but the original patient does not get the same cold again. This is an example of:

A. Natural active immunity
B. Artificial active immunity
C. Natural passive immunity
D. Artificial passive immunity

Answer

A

Matching

Match each type of vaccine with the corresponding example.

___inactivated vaccine	A. Weakened influenza virions that can only replicate in the slightly lower temperatures of the nasal passages are sprayed into the nose. They do not cause serious flu symptoms, but still produce an active infection that induces a protective adaptive immune response.
___live attenuated vaccine	B. Tetanus toxin molecules are harvested and chemically treated to render them harmless. They are then injected into a patient’s arm.
___toxoid vaccine	C. Influenza virus particles grown in chicken eggs are harvested and chemically treated to render them noninfectious. These immunogenic particles are then purified and packaged and administered as an injection.
___subunit vaccine	D. The gene for hepatitis B virus surface antigen is inserted into a yeast genome. The modified yeast is grown and the virus protein is produced, harvested, purified, and used in a vaccine.

Answer

C, A, B, D

Fill in the Blank

A(n) _____ pathogen is in a weakened state; it is still capable of stimulating an immune response but does not cause a disease.

Answer

attenuated

_____ immunity occurs when antibodies from one individual are harvested and given to another to protect against disease or treat active disease.

Answer

Artificial passive

In the practice of _____, scabs from smallpox victims were used to immunize susceptible individuals against smallpox.

Answer

variolation

Short answer

Briefly compare the pros and cons of inactivated versus live attenuated vaccines.

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CHAPTER OVERVIEW

7: Allergies and Autoimmune diseases

Topic hierarchy

7.1: Diseases of the Immune System

7.1.1: Hypersensitivities

7.1.2: Autoimmune Disorders

7.1.3: Organ Transplantation and Rejection

7.1.4: Immunodeficiency

7.1.5: Cancer Immunobiology and Immunotherapy

7.1.E: Diseases of the Immune System (Exercises)

7.2: Disruptions in the Immune System

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SECTION OVERVIEW

7.1: Diseases of the Immune System

An allergic reaction is an immune response to a type of antigen called an allergen. Allergens can be found in many different items, from peanuts and insect stings to latex and some drugs. Unlike other kinds of antigens, allergens are not necessarily associated with pathogenic microbes, and many allergens provoke no immune response at all in most people.

Allergic responses vary in severity. Some are mild and localized, like hay fever or hives, but others can result in systemic, life-threatening reactions. Anaphylaxis, for example, is a rapidly developing allergic reaction that can cause a dangerous drop in blood pressure and severe swelling of the throat that may close off the airway.

Allergies are just one example of how the immune system—the system normally responsible for preventing disease—can actually cause or mediate disease symptoms. In this chapter, we will further explore allergies and other disorders of the immune system, including hypersensitivity reactions, autoimmune diseases, transplant rejection, and diseases associated with immunodeficiency.



Figure 7.1.1: Bee stings and other allergens can cause life-threatening, systemic allergic reactions. Sensitive individuals may need to carry an epinephrine auto-injector (e.g., EpiPen) in case of a sting. A bee-sting allergy is an example of an immune response that is harmful to the host rather than protective; epinephrine counteracts the severe drop in blood pressure that can result from the immune response. (credit right: modification of work by Carol Bleistine)

7.1.1: Hypersensitivities

7.1.2: Autoimmune Disorders

7.1.3: Organ Transplantation and Rejection

7.1.4: Immunodeficiency

7.1.5: Cancer Immunobiology and Immunotherapy

7.1.E: Diseases of the Immune System (Exercises)

Thumbnail: Allergens in plant pollen, shown here in a colorized electron micrograph, may trigger allergic rhinitis or hay fever in sensitive individuals. (Public Domain/modified from original; Dartmouth Electron Microscope Facility, Dartmouth College via

Wikimedia Commons).

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7.1.1: Hypersensitivities

Learning Objectives

- Identify and compare the distinguishing characteristics, mechanisms, and major examples of type I, II, III, and IV hypersensitivities

Clinical Focus: Part 1

Kerry, a 40-year-old airline pilot, has made an appointment with her primary care physician to discuss a rash that develops whenever she spends time in the sun. As she explains to her physician, it does not seem like sunburn. She is careful not to spend too much time in the sun and she uses sunscreen. Despite these precautions, the rash still appears, manifesting as red, raised patches that get slightly scaly. The rash persists for 7 to 10 days each time, and it seems to largely go away on its own. Lately, the rashes have also begun to appear on her cheeks and above her eyes on either side of her forehead.

Exercise 7.1.1.1

1. Is Kerry right to be concerned, or should she simply be more careful about sun exposure?
2. Are there conditions that might be brought on by sun exposure that Kerry's physician should be considering?

In Adaptive Specific Host Defenses, we discussed the mechanisms by which adaptive immune defenses, both humoral and cellular, protect us from infectious diseases. However, these same protective immune defenses can also be responsible for undesirable reactions called hypersensitivity reactions. Hypersensitivity reactions are classified by their immune mechanism.

- Type I hypersensitivity reactions involve immunoglobulin E (IgE) antibody against soluble antigen, triggering mast cell degranulation.
- Type II hypersensitivity reactions involve IgG and IgM antibodies directed against cellular antigens, leading to cell damage mediated by other immune system effectors.
- Type III hypersensitivity reactions involve the interactions of IgG, IgM, and, occasionally, IgA[1] antibodies with antigen to form immune complexes. Accumulation of immune complexes in tissue leads to tissue damage mediated by other immune system effectors.
- Type IV hypersensitivity reactions are T-cell–mediated reactions that can involve tissue damage mediated by activated macrophages and cytotoxic T cells.

Type I Hypersensitivities

When a presensitized individual is exposed to an allergen, it can lead to a rapid immune response that occurs almost immediately. Such a response is called an allergy and is classified as a type I hypersensitivity. Allergens may be seemingly harmless substances such as animal dander, molds, or pollen. Allergens may also be substances considered innately more hazardous, such as insect venom or therapeutic drugs. Food intolerances can also yield allergic reactions as individuals become sensitized to foods such as peanuts or shellfish (Figure 7.1.1.1). Regardless of the allergen, the first exposure activates a primary IgE antibody response that sensitizes an individual to type I hypersensitivity reaction upon subsequent exposure.



Figure 7.1.1.1: (a) Allergens in plant pollen, shown here in a colorized electron micrograph, may trigger allergic rhinitis or hay fever in sensitive individuals. (b) Skin rashes are often associated with allergic reactions. (c) Peanuts can be eaten safely by most people but can provoke severe allergic reactions in sensitive individuals.

For susceptible individuals, a first exposure to an allergen activates a strong T_H2 cell response (Figure 7.1.1.2). Cytokines interleukin (IL)-4 and IL-13 from the T_H2 cells activate B cells specific to the same allergen, resulting in clonal proliferation, differentiation into plasma cells, and antibody-class switch from production of IgM to production of IgE. The fragment crystallizable (Fc) regions of the IgE antibodies bind to specific receptors on the surface of mast cellsthroughout the body. It is estimated that each mast cell can bind up to 500,000 IgE molecules, with each IgE molecule having two allergen-specific fragment antigen-binding (Fab) sites available for binding allergen on subsequent exposures. By the time this occurs, the allergen is often no longer present and there is no allergic reaction, but the mast cells are primed for a subsequent exposure and the individual is sensitized to the allergen.

On subsequent exposure, allergens bind to multiple IgE molecules on mast cells, cross-linking the IgE molecules. Within minutes, this cross-linking of IgE activates the mast cells and triggers degranulation, a reaction in which the contents of the granules in the mast cell are released into the extracellular environment. Preformed components that are released from granules include histamine, serotonin, and bradykinin (Table 7.1.1.1). The activated mast cells also release newly formed lipid mediators (leukotrienes and prostaglandins from membrane arachadonic acid metabolism) and cytokines such as tumor necrosis factor (Table 7.1.1.2).

Table 7.1.1.1: Selected Preformed Components of Mast Cell Granules

Granule Component	Activity
Heparin	Stimulates the generation of bradykinin, which causes increased vascular permeability, vasodilation, bronchiole constriction, and increased mucus secretion
Histamine	Causes smooth-muscle contraction, increases vascular permeability, increases mucus and tear formation
Serotonin	Increases vascular permeability, causes vasodilation and smooth-muscle contraction

The chemical mediators released by mast cells collectively cause the inflammation and signs and symptoms associated with type I hypersensitivity reactions. Histamine stimulates mucus secretion in nasal passages and tear formation from lacrimal glands, promoting the runny nose and watery eyes of allergies. Interaction of histamine with nerve endings causes itching and sneezing. The vasodilation caused by several of the mediators can result in hives, headaches, angioedema (swelling that often affects the lips, throat, and tongue), and hypotension (low blood pressure). Bronchiole constriction caused by some of the chemical mediators leads to wheezing, dyspnea (difficulty breathing), coughing, and, in more severe cases, cyanosis (bluish color to the skin or mucous membranes). Vomiting can result from stimulation of the vomiting center in the cerebellum by histamine and serotonin. Histamine can also cause relaxation of intestinal smooth muscles and diarrhea.

Table 7.1.1.2: Selected Newly Formed Chemical Mediators of Inflammation and Allergic Response

Chemical Mediator	Activity
Leukotriene	Causes smooth-muscle contraction and mucus secretion, increases vascular permeability
Prostaglandin	Causes smooth-muscle contraction and vasodilation
TNF-α (cytokine)	Causes inflammation and stimulates cytokine production by other cell types

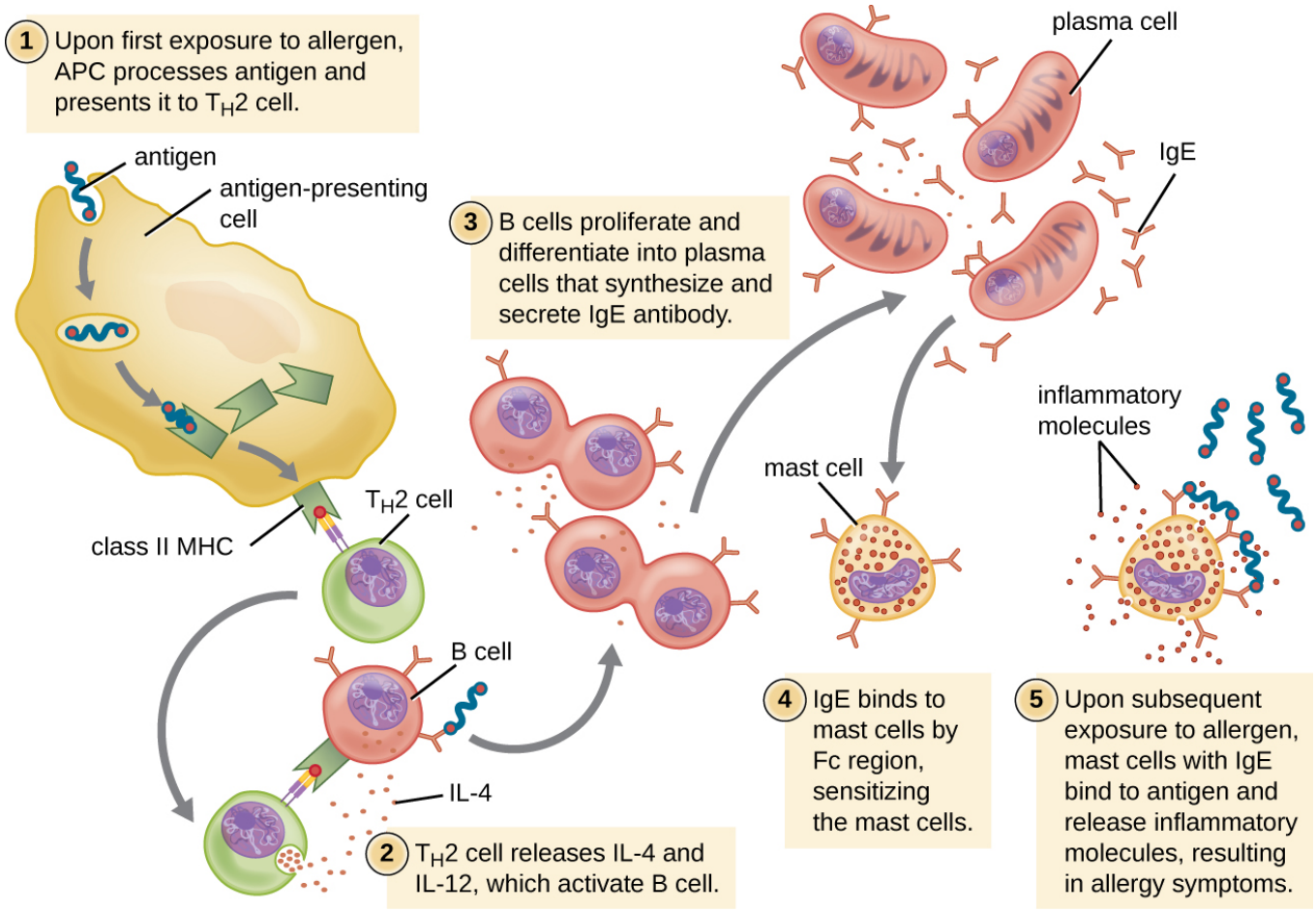


Figure 7.1.1.2: On first exposure to an allergen in a susceptible individual, antigen-presenting cells process and present allergen epitopes with major histocompatibility complex (MHC) II to T helper cells. B cells also process and present the same allergen epitope to T_H2 cells, which release cytokines IL-4 and IL-13 to stimulate proliferation and differentiation into IgE-secreting plasma cells. The IgE molecules bind to mast cells with their Fc region, sensitizing the mast cells for activation with subsequent exposure to the allergen. With each subsequent exposure, the allergen cross-links IgE molecules on the mast cells, activating the mast cells and causing the release of preformed chemical mediators from granules (degranulation), as well as newly formed chemical mediators that collectively cause the signs and symptoms of type I hypersensitivity reactions.

Type I hypersensitivity reactions can be either localized or systemic. Localized type I hypersensitivity reactions include hay fever rhinitis, hives, and asthma (Table 7.1.1.3). Systemic type I hypersensitivity reactions are referred to as anaphylaxisor anaphylactic shock. Although anaphylaxis shares many symptoms common with the localized type I hypersensitivity reactions, the swelling of the tongue and trachea, blockage of airways, dangerous drop in blood pressure, and development of shock can make anaphylaxis especially severe and life-threatening. In fact, death can occur within minutes of onset of signs and symptoms.

Late-phase reactions in type I hypersensitivities may develop 4–12 hours after the early phase and are mediated by eosinophils, neutrophils, and lymphocytes that have been recruited by chemotactic factors released from mast cells. Activation of these recruited cells leads to the release of more chemical mediators that cause tissue damage and late-phase symptoms of swelling and redness of the skin, coughing, wheezing, and nasal discharge.

Individuals who possess genes for maladaptive traits, such as intense type I hypersensitivity reactions to otherwise harmless components of the environment, would be expected to suffer reduced reproductive success. With this kind of evolutionary selective pressure, such traits would not be expected to persist in a population. This suggests that type I hypersensitivities may have an adaptive function. There is evidence that the IgE produced during type I hypersensitivity reactions is actually meant to counter helminth infections[2]. Helminths are one of few organisms that possess proteins that are targeted by IgE. In addition, there is evidence that helminth infections at a young age reduce the likelihood of type I hypersensitivities to innocuous substances later in life. Thus it may be that allergies are an unfortunate consequence of strong selection in the mammalian lineage or earlier for a defense against parasitic worms.

Table 7.1.1.3: Type I Hypersensitivities

Common Name	Cause	Signs and Symptoms
Allergy-induced asthma	Inhalation of allergens	Constriction of bronchi, labored breathing, coughing, chills, body aches
Anaphylaxis	Systemic reaction to allergens	Hives, itching, swelling of tongue and throat, nausea, vomiting, low blood pressure, shock
Hay fever	Inhalation of mold or pollen	Runny nose, watery eyes, sneezing
Hives (urticaria)	Food or drug allergens, insect stings	Raised, bumpy skin rash with itching; bumps may converge into large raised areas

? Exercise 7.1.1.2

1. What are the cells that cause a type I hypersensitivity reaction?
2. Describe the differences between immediate and late-phase type I hypersensitivity reactions.
3. List the signs and symptoms of anaphylaxis.

The Hygiene Hypothesis

In most modern societies, good hygiene is associated with regular bathing, and good health with cleanliness. But some recent studies suggest that the association between health and clean living may be a faulty one. Some go so far as to suggest that children should be encouraged to play in the dirt—or even eat dirt[3]—for the benefit of their health. This recommendation is based on the so-called hygiene hypothesis, which proposes that childhood exposure to antigens from a diverse range of microbes leads to a better-functioning immune system later in life.

The hygiene hypothesis was first suggested in 1989 by David Strachan[4], who observed an inverse relationship between the number of older children in a family and the incidence of hay fever. Although hay fever in children had increased dramatically during the mid-20th century, incidence was significantly lower in families with more children. Strachan proposed that the lower incidence of allergies in large families could be linked to infections acquired from older siblings, suggesting that these infections made children less susceptible to allergies. Strachan also argued that trends toward smaller families and a greater emphasis on cleanliness in the 20th century had decreased exposure to pathogens and thus led to higher overall rates of allergies, asthma, and other immune disorders.

Other researchers have observed an inverse relationship between the incidence of immune disorders and infectious diseases that are now rare in industrialized countries but still common in less industrialized countries.[5] In developed nations, children under the age of 5 years are not exposed to many of the microbes, molecules, and antigens they almost certainly would have encountered a century ago. The lack of early challenges to the immune system by organisms with which humans and their ancestors evolved may result in failures in immune system functioning later in life.

Type II (Cytotoxic) Hypersensitivities

Immune reactions categorized as type II hypersensitivities, or cytotoxic hypersensitivities, are mediated by IgG and IgM antibodies binding to cell-surface antigens or matrix-associated antigens on basement membranes. These antibodies can either activate complement, resulting in an inflammatory response and lysis of the targeted cells, or they can be involved in antibody-dependent cell-mediated cytotoxicity (ADCC) with cytotoxic T cells.

In some cases, the antigen may be a self-antigen, in which case the reaction would also be described as an autoimmune disease. (Autoimmune diseases are described in Autoimmune Disorders). In other cases, antibodies may bind to naturally occurring, but exogenous, cell-surface molecules such as antigens associated with blood typing found on red blood cells (RBCs). This leads to the coating of the RBCs by antibodies, activation of the complement cascade, and complement-mediated lysis of RBCs, as well as opsonization of RBCs for phagocytosis. Two examples of type II hypersensitivity reactions involving RBCs are hemolytic transfusion reaction (HTR) and hemolytic disease of the newborn (HDN). These type II hypersensitivity reactions, which will be discussed in greater detail, are summarized in Table 7.1.1.4.

Immunohematology is the study of blood and blood-forming tissue in relation to the immune response. Antibody-initiated responses against blood cells are type II hypersensitivities, thus falling into the field of immunohematology. For students first learning about immunohematology, understanding the immunological mechanisms involved is made even more challenging by the complex nomenclature system used to identify different blood-group antigens, often called blood types. The first blood-group antigens either used alphabetical names or were named for the first person known to produce antibodies to the red blood cell antigen (e.g., Kell, Duffy, or Diego). However, in 1980, the International Society of Blood Transfusion (ISBT) Working Party on Terminology created a standard for blood-group terminology in an attempt to more consistently identify newly discovered blood group antigens. New antigens are now given a number and assigned to a blood-group system, collection, or series. However, even with this effort, blood-group nomenclature is still inconsistent.

Table 7.1.1.4: Common Type II Hypersensitivities

Common Name	Cause	Signs and Symptoms
Hemolytic disease of the newborn (HDN)	IgG from mother crosses the placenta, targeting the fetus' RBCs for destruction	Anemia, edema, enlarged liver or spleen, hydrops (fluid in body cavity), leading to death of newborn in severe cases
Hemolytic transfusion reactions (HTR)	IgG and IgM bind to antigens on transfused RBCs, targeting donor RBCs for destruction	Fever, jaundice, hypotension, disseminated intravascular coagulation, possibly leading to kidney failure and death

ABO Blood Group Incompatibility

The recognition that individuals have different blood types was first described by Karl Landsteiner (1868–1943) in the early 1900s, based on his observation that serum from one person could cause a clumping of RBCs from another. These studies led Landsteiner to the identification of four distinct blood types. Subsequent research by other scientists determined that the four blood types were based on the presence or absence of surface glycoproteins "A" and "B," and this provided the foundation for the ABO blood group system that is still in use today (Figure 7.1.1.3). The functions of these antigens are unknown, but some have been associated with normal biochemical functions of the cell. Furthermore, ABO blood types are inherited as alleles (one from each parent), and they display patterns of dominant and codominant inheritance. The alleles for A and B blood types are codominant to each other, and both are dominant over blood type O. Therefore, individuals with genotypes of AA or AO have type A blood and express the A glycoprotein antigen on the surface of their RBCs. People with genotypes of BB or BO have type B blood and express the B glycoprotein antigen on the surface of their RBCs. Those with a genotype of AB have type AB blood and express both A and B glycoprotein antigens on the surface of their RBCs. Finally, individuals with a genotype of OO have type O blood and lack A and B glycoproteins on the surface of their RBCs.

It is important to note that the RBCs of all four ABO blood types share a common protein receptor molecule, and it is the addition of specific carbohydrates to the protein receptors that determines A, B, and AB blood types. The genes that are inherited for the A, B, and AB blood types encode enzymes that add the carbohydrate component to the protein receptor. Individuals with O blood type

still have the protein receptor but lack the enzymes that would add carbohydrates that would make their red blood cell type A, B, or AB.

IgM antibodies in plasma that cross-react with blood group antigens not present on an individual's own RBCs are called isohemagglutinins (Figure 7.1.1.3). Isohemagglutinins are produced within the first few weeks after birth and persist throughout life. These antibodies are produced in response to exposure to environmental antigens from food and microorganisms. A person with type A blood has A antigens on the surface of their RBCs and will produce anti-B antibodies to environmental antigens that resemble the carbohydrate component of B antigens. A person with type B blood has B antigens on the surface of their RBCs and will produce anti-A antibodies to environmental antigens that are similar to the carbohydrate component of A antigens. People with blood type O lack both A and B antigens on their RBCs and, therefore, produce both anti-A and anti-B antibodies. Conversely, people with AB blood type have both A and B antigens on their RBCs and, therefore, lack anti-A and anti-B antibodies.

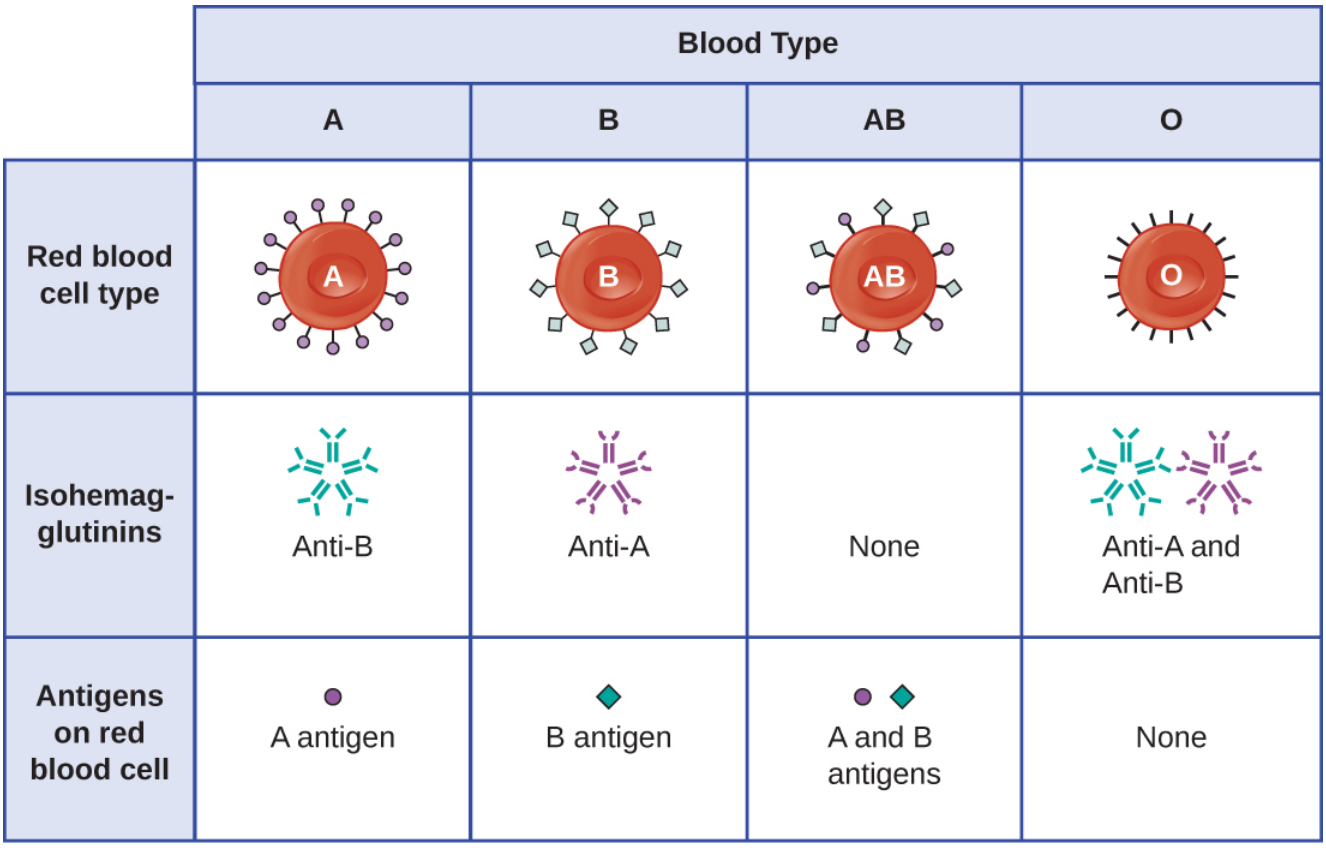


Figure 7.1.1.3: Isohemagglutinins

A patient may require a blood transfusion because they lack sufficient RBCs (anemia) or because they have experienced significant loss of blood volume through trauma or disease. Although the blood transfusion is given to help the patient, it is essential that the patient receive a transfusion with matching ABO blood type. A transfusion with an incompatible ABO blood type may lead to a strong, potentially lethal type II hypersensitivity cytotoxic response called hemolytic transfusion reaction (HTR) (Figure 7.1.1.4).

For instance, if a person with type B blood receives a transfusion of type A blood, their anti-A antibodies will bind to and agglutinate the transfused RBCs. In addition, activation of the classical complement cascade will lead to a strong inflammatory response, and the complement membrane attack complex (MAC) will mediate massive hemolysis of the transfused RBCs. The debris from damaged and destroyed RBCs can occlude blood vessels in the alveoli of the lungs and the glomeruli of the kidneys. Within 1 to 24 hours of an incompatible transfusion, the patient experiences fever, chills, pruritus (itching), urticaria (hives), dyspnea, hemoglobinuria (hemoglobin in the urine), and hypotension (low blood pressure). In the most serious reactions, dangerously low blood pressure can lead to shock, multi-organ failure, and death of the patient.

Hospitals, medical centers, and associated clinical laboratories typically use hemovigilance systems to minimize the risk of HTRs due to clerical error. Hemovigilance systems are procedures that track transfusion information from the donor source and blood

products obtained to the follow-up of recipient patients. Hemovigilance systems used in many countries identify HTRs and their outcomes through mandatory reporting (e.g., to the Food and Drug Administration in the United States), and this information is valuable to help prevent such occurrences in the future. For example, if an HTR is found to be the result of laboratory or clerical error, additional blood products collected from the donor at that time can be located and labeled correctly to avoid additional HTRs. As a result of these measures, HTR-associated deaths in the United States occur in about one per 2 million transfused units.[6]

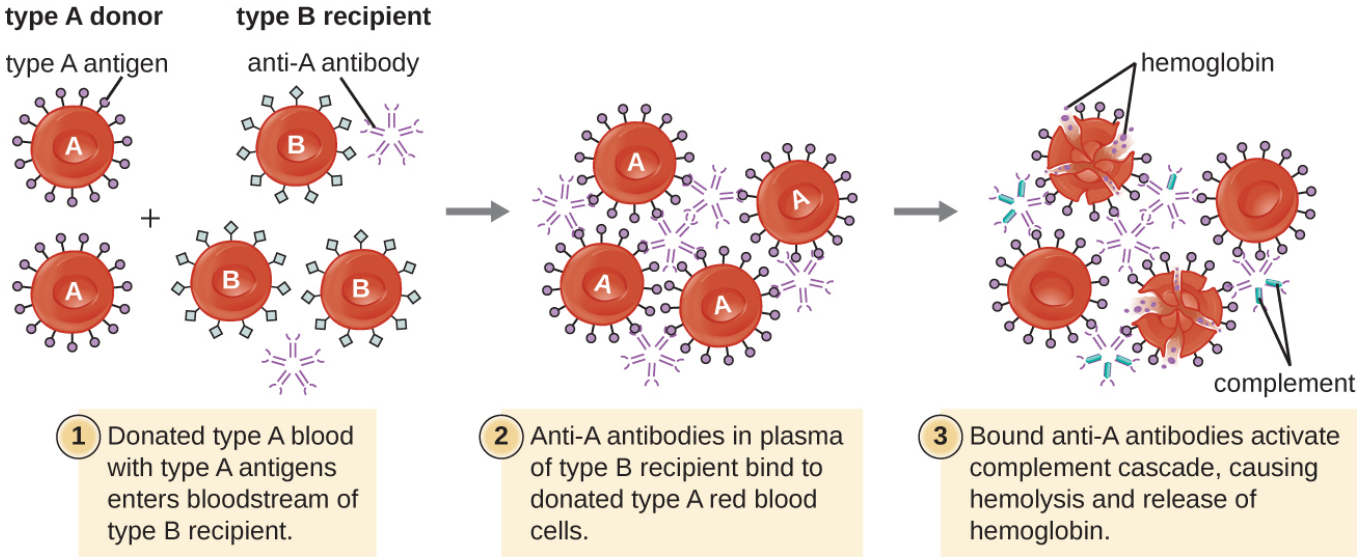


Figure 7.1.1.4: A type II hypersensitivity hemolytic transfusion reaction (HTR) leading to hemolytic anemia. Blood from a type A donor is administered to a patient with type B blood. The anti-A isohemagglutinin IgM antibodies in the recipient bind to and agglutinate the incoming donor type A red blood cells. The bound anti-A antibodies activate the classical complement cascade, resulting in destruction of the donor red blood cells.

Rh Factors

Many different types of erythrocyte antigens have been discovered since the description of the ABO red cell antigens. The second most frequently described RBC antigens are Rh factors, named after the rhesus macaque (*Macaca mulatta*) factors identified by Karl Landsteiner and Alexander Weiner in 1940. The Rh system of RBC antigens is the most complex and immunogenic blood group system, with more than 50 specificities identified to date. Of all the Rh antigens, the one designated Rho (Weiner) or D (Fisher-Race) is the most immunogenic. Cells are classified as Rh positive (Rh+) if the Rho/D antigen is present or as Rh negative (Rh−) if the Rho/D antigen is absent. In contrast to the carbohydrate molecules that distinguish the ABO blood groups and are the targets of IgM isohemagglutinins in HTRs, the Rh factor antigens are proteins. As discussed in B Lymphocytes and Humoral Immunity, protein antigens activate B cells and antibody production through a T-cell–dependent mechanism, and the T_H2 cells stimulate class switching from IgM to other antibody classes. In the case of Rh factor antigens, T_H2 cells stimulate class switching to IgG, and this has important implications for the mechanism of HDN.

Like ABO incompatibilities, blood transfusions from a donor with the wrong Rh factor antigens can cause a type II hypersensitivity HTR. However, in contrast to the IgM isohemagglutinins produced early in life through exposure to environmental antigens, production of anti-Rh factor antibodies requires the exposure of an individual with Rh− blood to Rh+ positive RBCs and activation of a primary antibody response. Although this primary antibody response can cause an HTR in the transfusion patient, the hemolytic reaction would be delayed up to 2 weeks during the extended lag period of a primary antibody response (B Lymphocytes and Humoral Immunity). However, if the patient receives a subsequent transfusion with Rh+ RBCs, a more rapid HTR would occur with anti-Rh factor antibody already present in the blood. Furthermore, the rapid secondary antibody response would provide even more anti-Rh factor antibodies for the HTR.

Rh factor incompatibility between mother and fetus can also cause a type II hypersensitivity hemolytic reaction, referred to as hemolytic disease of the newborn (HDN) (Figure 7.1.1.5). If an Rh− woman carries an Rh+ baby to term, the mother's immune system can be exposed to Rh+ fetal red blood cells. This exposure will usually occur during the last trimester of pregnancy and during the delivery process. If this exposure occurs, the Rh+ fetal RBCs will activate a primary adaptive immune response in the mother, and anti-Rh factor IgG antibodies will be produced. IgG antibodies are the only class of antibody that can cross the

placenta from mother to fetus; however, in most cases, the first Rh+ baby is unaffected by these antibodies because the first exposure typically occurs late enough in the pregnancy that the mother does not have time to mount a sufficient primary antibody response before the baby is born.

If a subsequent pregnancy with an Rh+ fetus occurs, however, the mother's second exposure to the Rh factor antigens causes a strong secondary antibody response that produces larger quantities of anti-Rh factor IgG. These antibodies can cross the placenta from mother to fetus and cause HDN, a potentially lethal condition for the baby (Figure 7.1.1.5).

Prior to the development of techniques for diagnosis and prevention, Rh factor incompatibility was the most common cause of HDN, resulting in thousands of infant deaths each year worldwide.[7] For this reason, the Rh factors of prospective parents are regularly screened, and treatments have been developed to prevent HDN caused by Rh incompatibility. To prevent Rh factor-mediated HDN, human Rho(D) immune globulin (e.g., RhoGAM) is injected intravenously or intramuscularly into the mother during the 28th week of pregnancy and within 72 hours after delivery. Additional doses may be administered after events that may result in transplacental hemorrhage (e.g., umbilical blood sampling, chorionic villus sampling, abdominal trauma, amniocentesis). This treatment is initiated during the first pregnancy with an Rh+ fetus. The anti-Rh antibodies in Rho(D) immune globulin will bind to the Rh factor of any fetal RBCs that gain access to the mother's bloodstream, preventing these Rh+ cells from activating the mother's primary antibody response. Without a primary anti-Rh factor antibody response, the next pregnancy with an Rh+ will have minimal risk of HDN. However, the mother will need to be retreated with Rho(D) immune globulin during that pregnancy to prevent a primary anti-Rh antibody response that could threaten subsequent pregnancies.

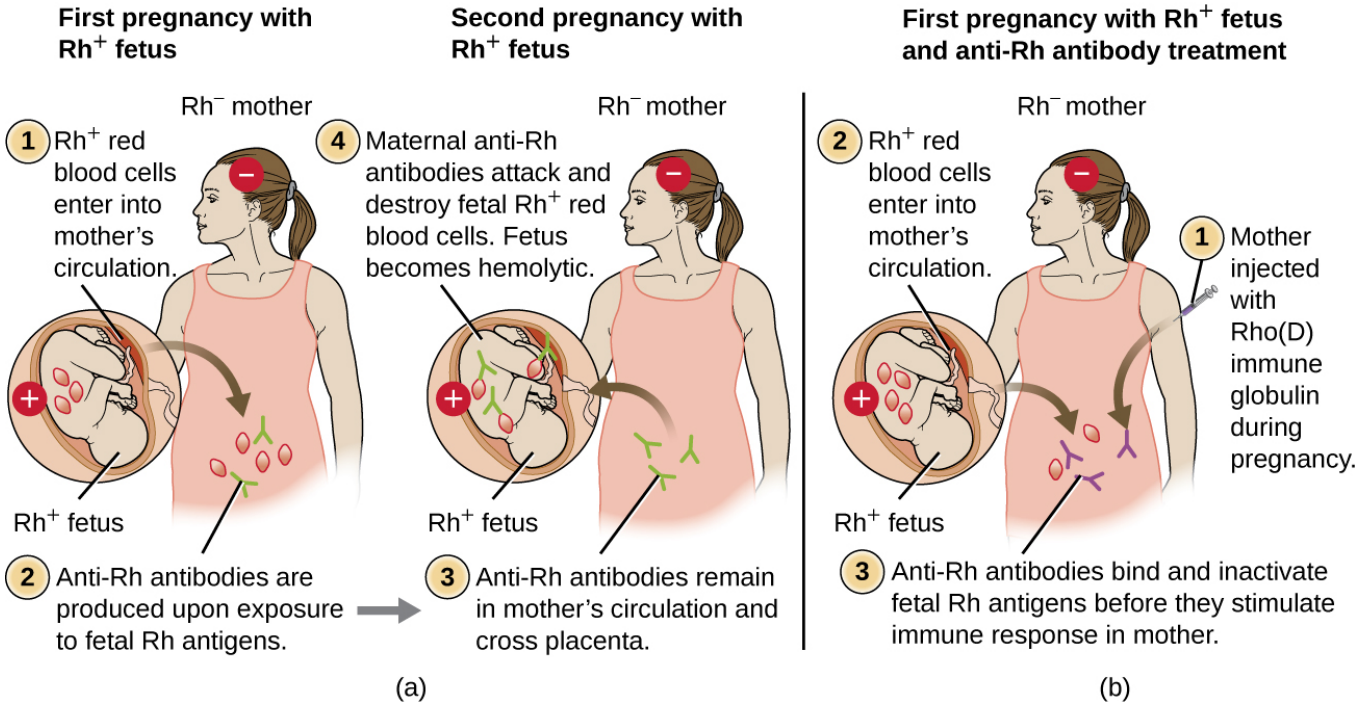


Figure 7.1.1.5: (a) When an Rh− mother has an Rh+ fetus, fetal erythrocytes are introduced into the mother's circulatory system before or during birth, leading to production of anti-Rh IgG antibodies. These antibodies remain in the mother and, if she becomes pregnant with a second Rh+ baby, they can cross the placenta and attach to fetal Rh+ erythrocytes. Complement-mediated hemolysis of fetal erythrocytes results in a lack of sufficient cells for proper oxygenation of the fetus. (b) HDN can be prevented by administering Rho(D) immune globulin during and after each pregnancy with an Rh+ fetus. The immune globulin binds fetal Rh+ RBCs that gain access to the mother's bloodstream, preventing activation of her primary immune response.

Link to Learning

Use this interactive Blood Typing Game to reinforce your knowledge of blood typing.

Exercise 7.1.1.3

1. What happens to cells that possess incompatible antigens in a type II hypersensitivity reaction?
2. Describe hemolytic disease of the newborn and explain how it can be prevented.

Clinical Focus: Part 2

Kerry's primary care physician is not sure why Kerry seems to develop rashes after spending time in the sun, so she orders a urinalysis and basic blood tests. The results reveal that Kerry has proteinuria (abnormal protein levels in the urine), hemoglobinuria (excess hemoglobin in the urine), and a low hematocrit (RBC count). These tests suggest that Kerry is suffering from a mild bout of hemolytic anemia. The physician suspects that the problem might be autoimmune, so she refers Kerry to a rheumatologist for additional testing and diagnosis.

Exercise 7.1.1.4

Rheumatologists specialize in musculoskeletal diseases such as arthritis, osteoporosis, and joint pain. Why might Kerry's physician refer her to this particular type of specialist even though she is exhibiting none of these symptoms?

Type III Hypersensitivities

Type III hypersensitivities are immune-complex reactions that were first characterized by Nicolas Maurice Arthus (1862–1945) in 1903. To produce antibodies for experimental procedures, Arthus immunized rabbits by injecting them with serum from horses. However, while immunizing rabbits repeatedly with horse serum, Arthus noticed a previously unreported and unexpected localized subcutaneous hemorrhage with edema at the site of injection. This reaction developed within 3 to10 hours after injection. This localized reaction to non-self serum proteins was called an Arthus reaction. An Arthus reaction occurs when soluble antigens bind with IgG in a ratio that results in the accumulation of antigen-antibody aggregates called immune complexes.

A unique characteristic of type III hypersensitivity is antibody excess (primarily IgG), coupled with a relatively low concentration of antigen, resulting in the formation of small immune complexes that deposit on the surface of the epithelial cells lining the inner lumen of small blood vessels or on the surfaces of tissues (Figure 7.1.1.6). This immune complex accumulation leads to a cascade of inflammatory events that include the following:

1. IgG binding to antibody receptors on localized mast cells, resulting in mast-cell degranulation
2. Complement activation with production of pro-inflammatory C3a and C5a (see Chemical Defenses)
3. Increased blood-vessel permeability with chemotactic recruitment of neutrophils and macrophages

Because these immune complexes are not an optimal size and are deposited on cell surfaces, they cannot be phagocytosed in the usual way by neutrophils and macrophages, which, in turn, are often described as "frustrated." Although phagocytosis does not occur, neutrophil degranulation results in the release of lysosomal enzymes that cause extracellular destruction of the immune complex, damaging localized cells in the process. Activation of coagulation pathways also occurs, resulting in thrombi (blood clots) that occlude blood vessels and cause ischemia that can lead to vascular necrosis and localized hemorrhage.

Systemic type III hypersensitivity (serum sickness) occurs when immune complexes deposit in various body sites, resulting in a more generalized systemic inflammatory response. These immune complexes involve non-self proteins such as antibodies produced in animals for artificial passive immunity (see Vaccines), certain drugs, or microbial antigens that are continuously released over time during chronic infections (e.g., subacute bacterial endocarditis, chronic viral hepatitis). The mechanisms of serum sickness are similar to those described in localized type III hypersensitivity but involve widespread activation of mast cells, complement, neutrophils, and macrophages, which causes tissue destruction in areas such as the kidneys, joints, and blood vessels. As a result of tissue destruction, symptoms of serum sickness include chills, fever, rash, vasculitis, and arthritis. Development of glomerulonephritis or hepatitis is also possible.

Autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis can also involve damaging type III hypersensitivity reactions when auto-antibodies form immune complexes with self antigens. These conditions are discussed in Autoimmune Disorders.

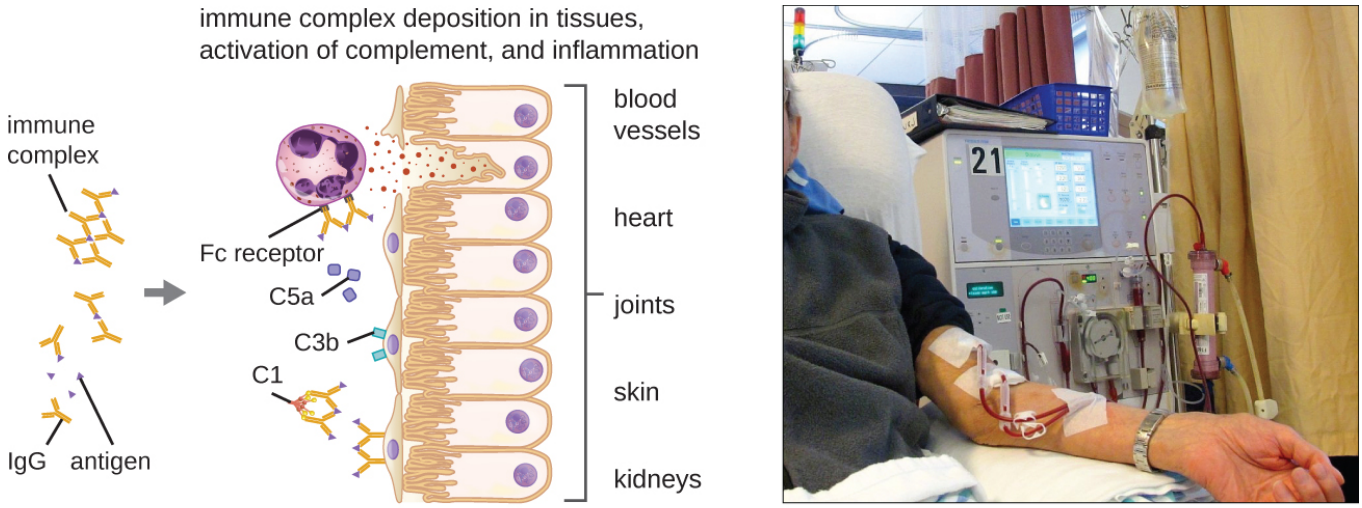


Figure 7.1.1.6: Type III hypersensitivities and the systems they affect. (a) Immune complexes form and deposit in tissue. Complement activation, stimulation of an inflammatory response, and recruitment and activation of neutrophils result in damage to blood vessels, heart tissue, joints, skin, and/or kidneys. (b) If the kidneys are damaged by a type III hypersensitivity reaction, dialysis may be required.

Exercise 7.1.1.5

1. Why is antibody excess important in type III hypersensitivity?
2. Describe the differences between the Arthus reaction and serum sickness.

Diphtheria Antitoxin

Antibacterial sera are much less commonly used now than in the past, having been replaced by toxoid vaccines. However, a diphtheria antitoxin produced in horses is one example of such a treatment that is still used in some parts of the world. Although it is not licensed by the FDA for use in the United States, diphtheria antitoxin can be used to treat cases of diphtheria, which are caused by the bacterium *Corynebacterium diphtheriae*. The treatment is not without risks, however. Serum sickness can occur when the patient develops an immune response to non-self horse proteins. Immune complexes are formed between the horse proteins and circulating antibodies when the two exist in certain proportions. These immune complexes can deposit in organs, causing damage such as arthritis, nephritis, rash, and fever. Serum sickness is usually transient with no permanent damage unless the patient is chronically exposed to the antigen, which can then result in irreversible damage to body sites such as joints and kidneys. Over time, phagocytic cells such as macrophages are able to clear the horse serum antigens, which results in improvement of the patient's condition and a decrease in symptoms as the immune response dissipates.

Clinical Focus: Part 3

Kerry does not make it to the rheumatologist. She has a seizure as she is leaving her primary care physician's office. She is quickly rushed to the emergency department, where her primary care physician relates her medical history and recent test results. The emergency department physician calls in the rheumatologist on staff at the hospital for consultation. Based on the symptoms and test results, the rheumatologist suspects that Kerry has lupus and orders a pair of blood tests: an antinuclear antibody test (ANA) to look for antibodies that bind to DNA and another test that looks for antibodies that bind to a self-antigen called the Smith antigen (Sm).

> **Exercise 7.1.1.6**
>
> Based on the blood tests ordered, what type of reaction does the rheumatologist suspect is causing Kerry's seizure?

Type IV Hypersensitivities

Type IV hypersensitivities are not mediated by antibodies like the other three types of hypersensitivities. Rather, type IV hypersensitivities are regulated by T cells and involve the action of effector cells. These types of hypersensitivities can be organized into three subcategories based on T-cell subtype, type of antigen, and the resulting effector mechanism (Table 7.1.1.5).

In the first type IV subcategory, CD4 T_H1-mediated reactions are described as delayed-type hypersensitivities (DTH). The sensitization step involves the introduction of antigen into the skin and phagocytosis by local antigen presenting cells (APCs). The APCs activate helper T cells, stimulating clonal proliferation and differentiation into memory T_H1 cells. Upon subsequent exposure to the antigen, these sensitized memory T_H1 cells release cytokines that activate macrophages, and activated macrophages are responsible for much of the tissue damage. Examples of this T_H1-mediated hypersensitivity are observed in tuberculin the Mantoux skin test and contact dermatitis, such as occurs in latex allergy reactions.

In the second type IV subcategory, CD4 T_H2-mediated reactions result in chronic asthma or chronic allergic rhinitis. In these cases, the soluble antigen is first inhaled, resulting in eosinophil recruitment and activation with the release of cytokines and inflammatory mediators.

In the third type IV subcategory, CD8 cytotoxic T lymphocyte (CTL)-mediated reactions are associated with tissue transplant rejection and contact dermatitis (Figure 7.1.1.7). For this form of cell-mediated hypersensitivity, APCs process and present the antigen with MHC I to naïve CD8 T cells. When these naïve CD8 T cells are activated, they proliferate and differentiate into CTLs. Activated T_H1 cells can also enhance the activation of the CTLs. The activated CTLs then target and induce granzyme-mediated apoptosis in cells presenting the same antigen with MHC I. These target cells could be "self" cells that have absorbed the foreign antigen (such as with contact dermatitis due to poison ivy), or they could be transplanted tissue cells displaying foreign antigen from the donor.

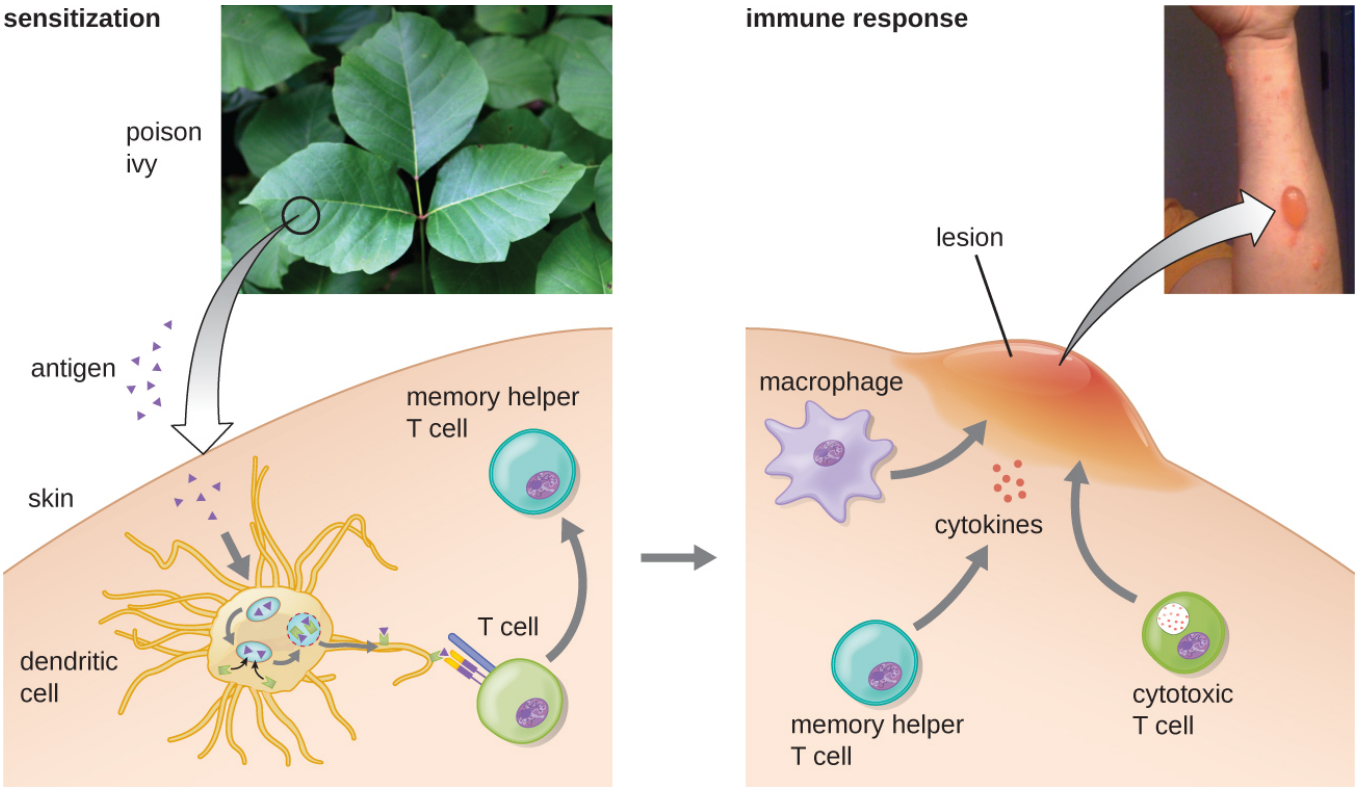


Figure 7.1.1.7: Exposure to hapten antigens in poison ivy can cause contact dermatitis, a type IV hypersensitivity. (a) The first exposure to poison ivy does not result in a reaction. However, sensitization stimulates helper T cells, leading to production of memory helper T cells that can become reactivated on future exposures. (b) Upon secondary exposure, the memory helper T cells become reactivated, producing inflammatory cytokines that stimulate macrophages and cytotoxic T cells to induce an inflammatory lesion at the exposed site. This lesion, which will persist until the allergen is removed, can inflict significant tissue damage if it continues long enough.

Table 7.1.1.5: Type IV Hypersensitivities

Subcategory	Antigen	Effector Mechanism	Examples
1	Soluble antigen	Activated macrophages damage tissue and promote inflammatory response	Contact dermatitis (e.g., exposure to latex) and delayed-type hypersensitivity (e.g., tuberculin reaction)
2	Soluble antigen	Eosinophil recruitment and activation release cytokines and pro-inflammatory chemicals	Chronic asthma and chronic allergic rhinitis
3	Cell-associated antigen	CTL-mediated cytotoxicity	Contact dermatitis (e.g., contact with poison ivy) and tissue-transplant rejection

? Exercise 7.1.1.7

1. Describe the three subtypes of type IV hypersensitivity.
2. Explain how T cells contribute to tissue damage in type IV hypersensitivity.

Using Delayed Hypersensitivity to Test for TB

Austrian pediatrician Clemans von Pirquet (1874–1929) first described allergy mechanisms, including type III serum sickness.[9] His interest led to the development of a test for tuberculosis (TB), using the tuberculin antigen, based on earlier work identifying the TB pathogen performed by Robert Koch. Pirquet's method involved scarification, which results in simultaneous multiple punctures, using a device with an array of needles to break the skin numerous times in a small area. The device Pirquet used was similar to the tine testdevice with four needles seen in Figure 7.1.1.8.

The tips of all the needles in the array are coated with tuberculin, a protein extract of TB bacteria, effectively introducing the tuberculin into the skin. One to 3 days later, the area can be examined for a delayed hypersensitivity reaction, signs of which include swelling and redness.

As you can imagine, scarification was not a pleasant experience,[10] and the numerous skin punctures put the patient at risk of developing bacterial infection of the skin. Mantoux modified Pirquet's test to use a single subcutaneous injection of purified tuberculin material. A positive test, which is indicated by a delayed localized swelling at the injection site, does not necessarily mean that the patient is currently infected with active TB. Because type IV (delayed-type) hypersensitivity is mediated by reactivation of memory T cells, such cells may have been created recently (due to an active current infection) or years prior (if a patient had TB and had spontaneously cleared it, or if it had gone into latency). However, the test can be used to confirm infection in cases in which symptoms in the patient or findings on a radiograph suggest its presence.



Figure 7.1.1.8: The modern version of Pirquet's scarification is the tine test, which uses devices like this to administer tuberculin antigen into the skin, usually on the inside of the forearm. The tine test is considered less reliable than the Mantoux test. (credit: modification of work by the Centers for Disease Control and Prevention)

Hypersensitivity Pneumonitis

Some disease caused by hypersensitivities are not caused exclusively by one type. For example, hypersensitivity pneumonitis (HP), which is often an occupational or environmental disease, occurs when the lungs become inflamed due to an allergic reaction to inhaled dust, endospores, bird feathers, bird droppings, molds, or chemicals. HP goes by many different names associated with various forms of exposure (Figure 7.1.1.9). HP associated with bird droppings is sometimes called pigeon fancier's lung or poultry worker's lung—both common in bird breeders and handlers. Cheese handler's disease, farmer's lung, sauna takers' disease, and hot-tub lung are other names for HP associated with exposure to molds in various environments.

Pathology associated with HP can be due to both type III (mediated by immune complexes) and type IV (mediated by T_H1 cells and macrophages) hypersensitivities. Repeated exposure to allergens can cause alveolitis due to the formation of immune complexes in the alveolar wall of the lung accompanied by fluid accumulation, and the formation of granulomas and other lesions in the lung as a result of T_H1-mediated macrophage activation. Alveolitis with fluid and granuloma formation results in poor oxygen perfusion in the alveoli, which, in turn, can cause symptoms such as coughing, dyspnea, chills, fever, sweating, myalgias, headache, and nausea. Symptoms may occur as quickly as 2 hours after exposure and can persist for weeks if left untreated.



(a) (b)

Figure 7.1.1.9: Occupational exposure to dust, mold, and other allergens can result in hypersensitivity pneumonitis. (a) People exposed daily to large numbers of birds may be susceptible to poultry worker's lung. (b) Workers in a cheese factory may become sensitized to different types of molds and develop cheese handler's disease. (credit a: modification of work by The Global Orphan Project)

? Exercise 7.1.1.8

Explain why hypersensitivity pneumonitis is considered an occupational disease.

Figure 7.1.1.10 summarizes the mechanisms and effects of each type of hypersensitivity discussed in this section.

	Hypersensitivity Types and Their Mechanisms			
	Type I	**Type II**	**Type III**	**Type IV**
Immune reactant	IgE	IgG or IgM	IgG and IgM	T cells
Antigen form	Soluble antigen	Cell-bound antigen	Soluble antigen	Soluble or cell-bound antigen
Mechanism of activation	Allergen-specific IgE antibodies bind to mast cells via their Fc receptor. When the specific allergen binds to the IgE, cross-linking of IgE induces degranulation of mast cells.	IgG or IgM antibody binds to cellular antigen, leading to complement activation and cell lysis. IgG can also mediate ADCC with cytotoxic T cells, natural killer cells, macrophages, and neutrophils.	Antigen-antibody complexes are deposited in tissues. Complement activation provides inflammatory mediators and recruits neutrophils. Enzymes released from neutrophils damage tissue.	T_H1 cells secrete cytokines, which activate macrophages and cytotoxic T cells.
Examples of hypersensitivity reactions	Local and systemic anaphylaxis, seasonal hay fever, food allergies, and drug allergies	Red blood cell destruction after transfusion with mismatched blood types or during hemolytic disease of the newborn.	Post-streptococcal glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Contact dermatitis, type I diabetes mellitus, and multiple sclerosis

Figure 7.1.1.10: Components of the immune system cause four types of hypersensitivities. Notice that types I–III are B-cell/antibody-mediated hypersensitivities, whereas type IV hypersensitivity is exclusively a T-cell phenomenon.

Diagnosis of Hypersensitivities

Diagnosis of type I hypersensitivities is a complex process requiring several diagnostic tests in addition to a well-documented patient history. Serum IgE levels can be measured, but elevated IgE alone does not confirm allergic disease. As part of the process to identify the antigens responsible for a type I reaction allergy, testing through a prick puncture skin test (PPST) or an intradermal test can be performed. PPST is carried out with the introduction of allergens in a series of superficial skin pricks on the patient's back or arms (Figure 7.1.1.11). PPSTs are considered to be the most convenient and least expensive way to diagnose allergies, according to the US Joint Council of Allergy and the European Academy of Allergy and Immunology. The second type of testing, the intradermal test, requires injection into the dermis with a small needle. This needle, also known as a tuberculin needle, is attached to a syringe containing a small amount of allergen. Both the PPST and the intradermal tests are observed for 15–20 minutes for a wheal-flare reaction to the allergens. Measurement of any wheal (a raised, itchy bump) and flare (redness) within minutes indicates a type I hypersensitivity, and the larger the wheal-flare reaction, the greater the patient's sensitivity to the allergen.

Type III hypersensitivities can often be misdiagnosed because of their nonspecific inflammatory nature. The symptoms are easily visible, but they may be associated with any of a number of other diseases. A strong, comprehensive patient history is crucial to proper and accurate diagnosis. Tests used to establish the diagnosis of hypersensitivity pneumonitis (resulting from type III hypersensitivity) include bronchoalveolar lavage (BAL), pulmonary function tests, and high-resolution computed tomography (HRCT).

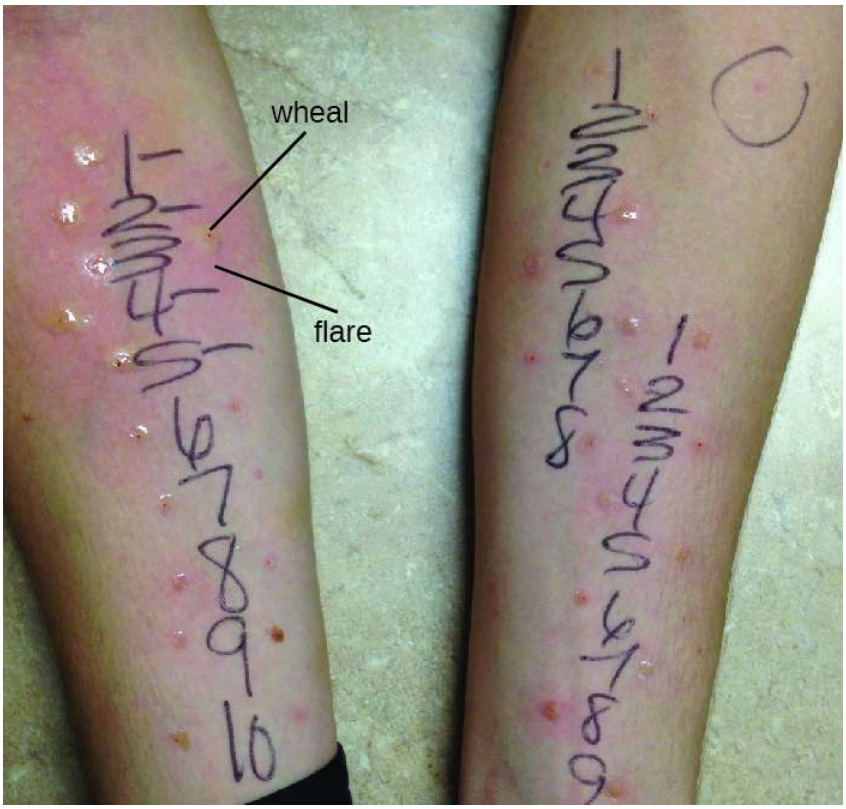


Figure 7.1.1.11: Results of an allergy skin-prick test to test for type I hypersensitivity to a group of potential allergens. A positive result is indicated by a raised area (wheal) and surrounding redness (flare). (credit: modification of work by "OakleyOriginals"/Flickr)

? Exercise 7.1.1.9

1. Describe the prick puncture skin test.
2. Explain why type III hypersensitivities can be difficult to diagnose

Treatments of Hypersensitivities

Allergic reactions can be treated in various ways. Prevention of allergic reactions can be achieved by desensitization(hyposensitization) therapy, which can be used to reduce the hypersensitivity reaction through repeated injections of allergens. Extremely dilute concentrations of known allergens (determined from the allergen tests) are injected into the patient at prescribed intervals (e.g., weekly). The quantity of allergen delivered by the shots is slowly increased over a buildup period until an effective dose is determined and that dose is maintained for the duration of treatment, which can last years. Patients are usually encouraged to remain in the doctor's office for 30 minutes after receiving the injection in case the allergens administered cause a severe systemic reaction. Doctors' offices that administer desensitization therapy must be prepared to provide resuscitation and drug treatment in the case of such an event.

Desensitization therapy is used for insect sting allergies and environmental allergies. The allergy shots elicit the production of different interleukins and IgG antibody responses instead of IgE. When excess allergen-specific IgG antibodies are produced and bind to the allergen, they can act as blocking antibodies to neutralize the allergen before it can bind IgE on mast cells. There are early studies using oral therapy for desensitization of food allergies that are promising.[1112] These studies involve feeding children who have allergies tiny amounts of the allergen (e.g., peanut flour) or related proteins over time. Many of the subjects show reduced severity of reaction to the food allergen after the therapy.

There are also therapies designed to treat severe allergic reactions. Emergency systemic anaphylaxis is treated initially with an epinephrine injection, which can counteract the drop in blood pressure. Individuals with known severe allergies often carry a self-administering auto-injector that can be used in case of exposure to the allergen (e.g., an insect sting or accidental ingestion of a

food that causes a severe reaction). By self-administering an epinephrine shot (or sometimes two), the patient can stem the reaction long enough to seek medical attention. Follow-up treatment generally involves giving the patient antihistamines and slow-acting corticosteroids for several days after the reaction to prevent potential late-phase reactions. However, the effects of antihistamine and corticosteroid treatment are not well studied and are used based on theoretical considerations.

Treatment of milder allergic reactions typically involves antihistamines and other anti-inflammatory drugs. A variety of antihistamine drugs are available, in both prescription and over-the-counter strengths. There are also antileukotriene and antiprostaglandin drugs that can be used in tandem with antihistamine drugs in a combined (and more effective) therapy regime.

Treatments of type III hypersensitivities include preventing further exposure to the antigen and the use of anti-inflammatory drugs. Some conditions can be resolved when exposure to the antigen is prevented. Anti-inflammatory corticosteroid inhalers can also be used to diminish inflammation to allow lung lesions to heal. Systemic corticosteroid treatment, oral or intravenous, is also common for type III hypersensitivities affecting body systems. Treatment of hypersensitivity pneumonitis includes avoiding the allergen, along with the possible addition of prescription steroids such as prednisone to reduce inflammation.

Treatment of type IV hypersensitivities includes antihistamines, anti-inflammatory drugs, analgesics, and, if possible, eliminating further exposure to the antigen.

? Exercise 7.1.1.10

1. Describe desensitization therapy.
2. Explain the role of epinephrine in treatment of hypersensitivity reactions.

Key Concepts and Summary

- An **allergy** is an adaptive immune response, sometimes life-threatening, to an **allergen**.
- **Type I hypersensitivity** requires sensitization of mast cells with IgE, involving an initial IgE antibody response and IgE attachment to mast cells. On second exposure to an allergen, cross-linking of IgE molecules on mast cells triggers degranulation and release of preformed and newly formed chemical mediators of inflammation. Type I hypersensitivity may be localized and relatively minor (hives and hay fever) or system-wide and dangerous (systemic **anaphylaxis**).
- **Type II hypersensitivities** result from antibodies binding to antigens on cells and initiating cytotoxic responses. Examples include **hemolytic transfusion reaction** and **hemolytic disease of the newborn**.
- **Type III hypersensitivities** result from formation and accumulation of **immune complexes** in tissues, stimulating damaging inflammatory responses.
- **Type IV hypersensitivities** are not mediated by antibodies, but by helper T-cell activation of macrophages, eosinophils, and cytotoxic T cells.

Footnotes

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12. 12 P. Varshney et al. “A Randomized Controlled Study of Peanut Oral Immunotherapy: Clinical Desensitization and Modulation of the Allergic Response.” *Journal of Allergy and Clinical Immunology* 127 no. 3 (2011):654–660.

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7.1.2: Autoimmune Disorders

Learning Objectives

- Explain why autoimmune disorders develop
- Provide a few examples of organ-specific and systemic autoimmune diseases

In 1970, artist Walt Kelly developed a poster promoting Earth Day, featuring a character from *Pogo*, his daily newspaper comic strip. In the poster, Pogo looks out across a litter-strewn forest and says wryly, “We have met the enemy and he is us.” Pogo was not talking about the human immune system, but he very well could have been. Although the immune system protects the body by attacking invading “enemies” (pathogens), in some cases, the immune system can mistakenly identify the body’s own cells as the enemy, resulting in autoimmune disease.

Autoimmune diseases are those in which the body is attacked by its own specific adaptive immune response. In normal, healthy states, the immune system induces tolerance, which is a lack of an anti-self immune response. However, with autoimmunity, there is a loss of immune tolerance, and the mechanisms responsible for autoimmune diseases include type II, III, and IV hypersensitivity reactions. Autoimmune diseases can have a variety of mixed symptoms that flare up and disappear, making diagnosis difficult.

The causes of autoimmune disease are a combination of the individual's genetic makeup and the effect of environmental influences, such as sunlight, infections, medications, and environmental chemicals. However, the vagueness of this list reflects our poor understanding of the etiology of these diseases. Except in a very few specific diseases, the initiation event(s) of most autoimmune states has not been fully characterized.

There are several possible causes for the origin of autoimmune diseases and autoimmunity is likely due to several factors. Evidence now suggests that regulatory T and B cells play an essential role in the maintenance of tolerance and prevention of autoimmune responses. The regulatory T cells are especially important for inhibiting autoreactive T cells that are not eliminated during thymic selection and escape the thymus (see T Lymphocytes and Cellular Immunity). In addition, antigen mimicry between pathogen antigens and our own self antigens can lead to cross-reactivity and autoimmunity. Hidden self-antigens may become exposed because of trauma, drug interactions, or disease states, and trigger an autoimmune response. All of these factors could contribute to autoimmunity. Ultimately, damage to tissues and organs in the autoimmune disease state comes as a result of inflammatory responses that are inappropriate; therefore, treatment often includes immunosuppressive drugs and corticosteroids.

Organ-Specific Autoimmune Diseases

Some autoimmune diseases are considered organ specific, meaning that the immune system targets specific organs or tissues. Examples of organ-specific autoimmune diseases include celiac disease, Graves disease, Hashimoto thyroiditis, type I diabetes mellitus, and Addison disease.

Celiac Disease

Celiac disease is largely a disease of the small intestine, although other organs may be affected. People in their 30s and 40s, and children are most commonly affected, but celiac disease can begin at any age. It results from a reaction to proteins, commonly called gluten, found mainly in wheat, barley, rye, and some other grains. The disease has several genetic causes (predispositions) and poorly understood environmental influences. On exposure to gluten, the body produces various autoantibodies and an inflammatory response. The inflammatory response in the small intestine leads to a reduction in the depth of the microvilli of the mucosa, which hinders absorption and can lead to weight loss and anemia. The disease is also characterized by diarrhea and abdominal pain, symptoms that are often misdiagnosed as irritable bowel syndrome.

Diagnosis of celiac disease is accomplished from serological tests for the presence of primarily IgA antibodies to components of gluten, the transglutinaminase enzyme, and autoantibodies to endomysium, a connective tissue surrounding muscle fibers. Serological tests are typically followed up with endoscopy and biopsy of the duodenal mucosa. Serological screening surveys have found about 1% of individuals in the United Kingdom are positive even though they do not all display symptoms.[1] This early recognition allows for more careful monitoring and prevention of severe disease.

Celiac disease is treated with complete removal of gluten-containing foods from the diet, which results in improved symptoms and reduced risk of complications. Other theoretical approaches include breeding grains that do not contain the immunologically reactive components or developing dietary supplements that contain enzymes that break down the protein components that cause the immune response.[2]

Disorders of the Thyroid

Graves disease is the most common cause of hyperthyroidism in the United States. Symptoms of Graves disease result from the production of thyroid-stimulating immunoglobulin (TSI) also called TSH-receptor antibody. TSI targets and binds to the receptor for thyroid stimulating hormone (TSH), which is naturally produced by the pituitary gland. TSI may cause conflicting symptoms because it may stimulate the thyroid to make too much thyroid hormone or block thyroid hormone production entirely, making diagnosis more difficult. Signs and symptoms of Graves disease include heat intolerance, rapid and irregular heartbeat, weight loss, goiter (a swollen thyroid gland, protruding under the skin of the throat [Figure 7.1.2.1]) and exophthalmia (bulging eyes) often referred to as Graves ophthalmopathy (Figure 7.1.2.2).



Figure 7.1.2.1: Goiter, a hypertrophy of the thyroid, is a symptom of Graves disease and Hashimoto thyroiditis.

The most common cause of hypothyroidism in the United States is Hashimoto thyroiditis, also called chronic lymphocytic thyroiditis. Patients with Hashimoto thyroiditis often develop a spectrum of different diseases because they are more likely to develop additional autoimmune diseases such as Addison disease (discussed later in this section), type 1 diabetes, rheumatoid arthritis, and celiac disease. Hashimoto thyroiditis is a T_H1 cell-mediated disease that occurs when the thyroid gland is attacked by cytotoxic lymphocytes, macrophages, and autoantibodies. This autoimmune response leads to numerous symptoms that include goiter (Figure 7.1.2.1), cold intolerance, muscle weakness, painful and stiff joints, depression, and memory loss.

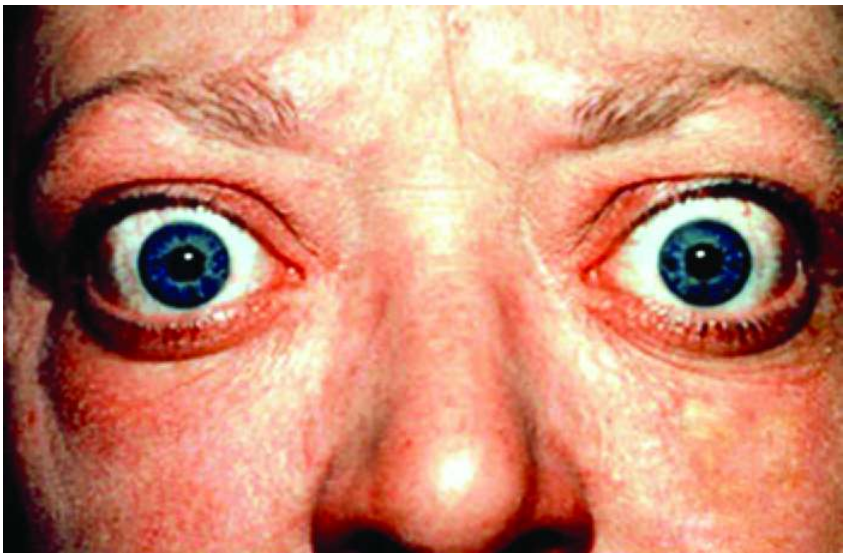


Figure 7.1.2.2: Exophthalmia, or Graves ophthalmopathy, is a sign of Graves disease. (credit: modification of work by Jonathan Trobe, University of Michigan Kellogg Eye Center)

Type 1 Diabetes

Juvenile diabetes, or type 1 diabetes mellitus, is usually diagnosed in children and young adults. It is a T-cell-dependent autoimmune disease characterized by the selective destruction of the β cells of the islets of Langerhans in the pancreas by CD4 T_H1-mediated CD8 T cells, anti-β-cell antibodies, and macrophage activity. There is also evidence that viral infections can have either a potentiating or inhibitory role in the development of type 1 diabetes (T1D) mellitus. The destruction of the β cells causes a lack of insulin production by the pancreas. In T1D, β-cell destruction may take place over several years, but symptoms of hyperglycemia, extreme increase in thirst and urination, weight loss, and extreme fatigue usually have a sudden onset, and diagnosis usually does not occur until most β cells have already been destroyed.

Autoimmune Addison Disease

Destruction of the adrenal glands (the glands lying above the kidneys that produce glucocorticoids, mineralocorticoids, and sex steroids) is the cause of Addison disease, also called primary adrenal insufficiency (PAI). Today, up to 80% of Addison disease cases are diagnosed as autoimmune Addison disease (AAD), which is caused by an autoimmune response to adrenal tissues disrupting adrenal function. Disruption of adrenal function causes impaired metabolic processes that require normal steroid hormone levels, causing signs and symptoms throughout the body. There is evidence that both humoral and CD4 T_H1-driven CD8 T-cell–mediated immune mechanisms are directed at the adrenal cortex in AAD. There is also evidence that the autoimmune response is associated with autoimmune destruction of other endocrine glands as well, such as the pancreas and thyroid, conditions collectively referred to as autoimmune polyendocrine syndromes (APS). In up to 80% of patients with AAD, antibodies are produced to three enzymes involved in steroid synthesis: 21-hydroxylase (21-OH), 17α-hydroxylase, and cholesterol side-chain–cleaving enzyme.[3]The most common autoantibody found in AAD is to 21-OH, and antibodies to any of the key enzymes for steroid production are diagnostic for AAD. The adrenal cortex cells are targeted, destroyed, and replaced with fibrous tissue by immune-mediated inflammation. In some patients, at least 90% of the adrenal cortex is destroyed before symptoms become diagnostic.

Symptoms of AAD include weakness, nausea, decreased appetite, weight loss, hyperpigmentation (Figure 7.1.2.3), hyperkalemia (elevated blood potassium levels), hyponatremia (decreased blood sodium levels), hypoglycemia(decreased levels of blood sugar), hypotension (decreased blood pressure), anemia, lymphocytosis (decreased levels of white blood cells), and fatigue. Under extreme stress, such as surgery, accidental trauma, or infection, patients with AAD may experience an adrenal crisis that causes the patient to vomit, experience abdominal pain, back or leg cramps, and even severe hypotension leading to shock.



Figure 7.1.2.3: Hyperpigmentation is a sign of Addison disease. (credit: modification of work by Petros Perros)

? Exercise 7.1.2.1

1. What are the names of autoimmune diseases that interfere with hormone gland function?
2. Describe how the mechanisms of Graves disease and Hashimoto thyroiditis differ.
3. Name the cells that are destroyed in type 1 diabetes mellitus and describe the result.

Systemic Autoimmune Diseases

Whereas organ-specific autoimmune diseases target specific organs or tissues, systemic autoimmune diseases are more generalized, targeting multiple organs or tissues throughout the body. Examples of systemic autoimmune diseases include multiple sclerosis, myasthenia gravis, psoriasis, rheumatoid arthritis, and systemic lupus erythematosus.

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune central nervous system disease that affects the brain and spinal cord. Lesions in multiple locations within the central nervous system are a hallmark of multiple sclerosis and are caused by infiltration of immune cells across the blood-brain barrier. The immune cells include T cells that promote inflammation, demyelination, and neuron degeneration, all of which disrupt neuronal signaling. Symptoms of MS include visual disturbances; muscle weakness; difficulty with coordination and balance; sensations such as numbness, prickling, or “pins and needles”; and cognitive and memory problems.

Myasthenia Gravis

Autoantibodies directed against acetylcholine receptors (AChRs) in the synaptic cleft of neuromuscular junctions lead to myasthenia gravis (Figure 7.1.2.4). Anti-AChR antibodies are high-affinity IgGs and their synthesis requires activated CD4 T cells to interact with and stimulate B cells. Once produced, the anti-AChR antibodies affect neuromuscular transmission by at least three mechanisms:

- Complement binding and activation at the neuromuscular junction
- Accelerated AChR endocytosis of molecules cross-linked by antibodies
- Functional AChR blocking, which prevents normal acetylcholine attachment to, and activation of, AChR

Regardless of the mechanism, the effect of anti-AChR is extreme muscle weakness and potentially death through respiratory arrest in severe cases.

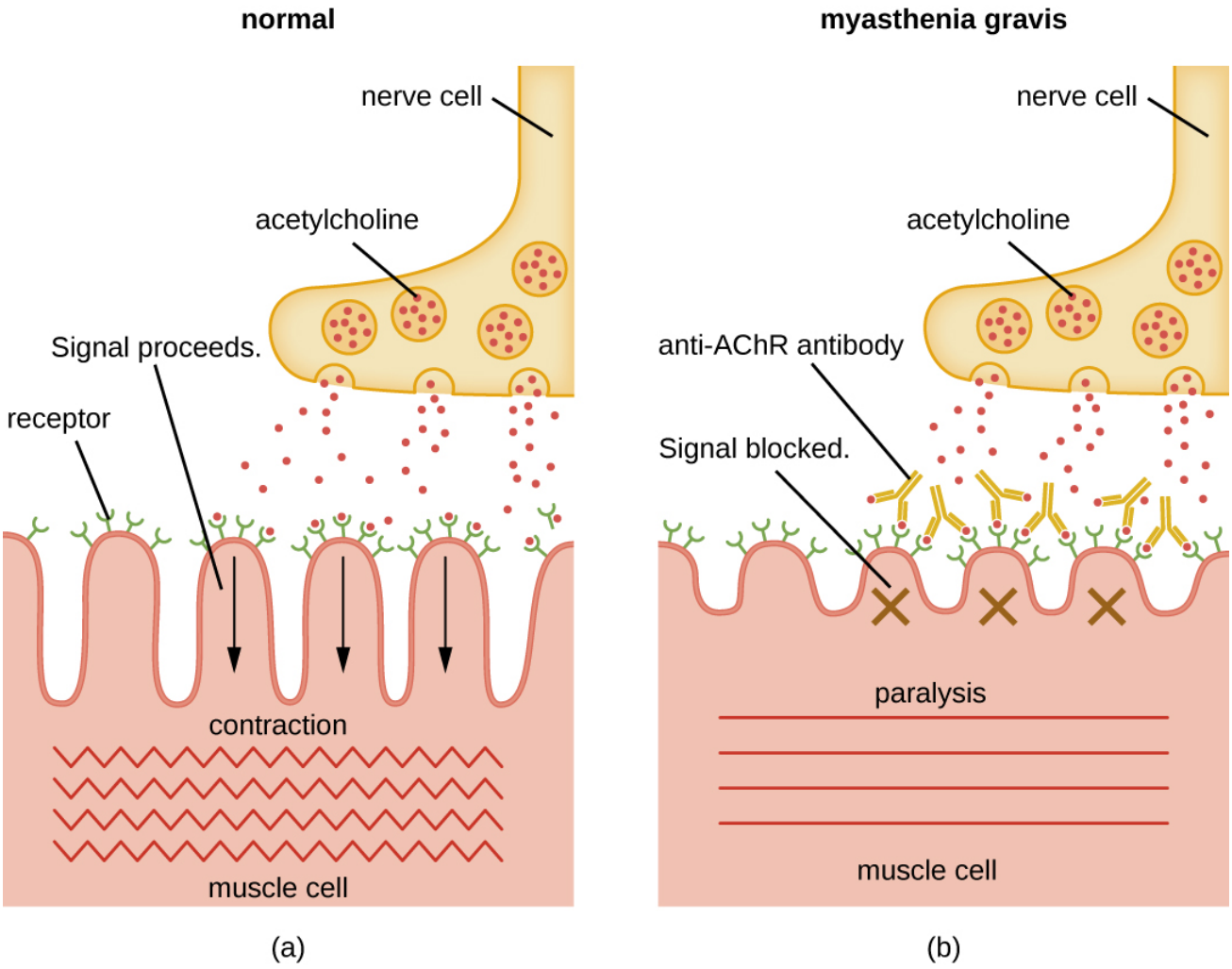


Figure 7.1.2.4: Myasthenia gravis and impaired muscle contraction. (a) Normal release of the neurotransmitter acetylcholine stimulates muscle contraction. (b) In myasthenia gravis, autoantibodies block the receptors for acetylcholine (AChr) on muscle cells, resulting in paralysis.

Psoriasis

Psoriasis is a skin disease that causes itchy or sore patches of thick, red skin with silvery scales on elbows, knees, scalp, back, face, palms, feet, and sometimes other areas. Some individuals with psoriasis also get a form of arthritis called psoriatic arthritis, in which the joints can become inflamed. Psoriasis results from the complex interplay between keratinocytes, dendritic cells, and T cells, and the cytokines produced by these various cells. In a process called cell turnover, skin cells that grow deep in the skin rise to the surface. Normally, this process takes a month. In psoriasis, as a result of cytokine activation, cell turnover happens in just a few days. The thick inflamed patches of skin that are characteristic of psoriasis develop because the skin cells rise too fast.

Rheumatoid Arthritis

The most common chronic inflammatory joint disease is rheumatoid arthritis (RA) (Figure 7.1.2.5) and it is still a major medical challenge because of unsolved questions related to the environmental and genetic causes of the disease. RA involves type III hypersensitivity reactions and the activation of CD4 T cells, resulting in chronic release of the inflammatory cytokines IL-1, IL-6, and tumor necrosis factor-α (TNF-α). The activated CD4 T cells also stimulate the production of rheumatoid factor (RF) antibodies and anticyclic citrullinated peptide antibodies (anti-CCP) that form immune complexes. Increased levels of acute-phase proteins, such as C-reactive protein (CRP), are also produced as part of the inflammatory process and participate in complement fixation with the antibodies on the immune complexes. The formation of immune complexes and reaction to the immune factors cause an inflammatory process in joints, particularly in the hands, feet, and legs. Diagnosis of RA is based on elevated levels of RF, anti-CCP, quantitative CRP, and the erythrocyte sedimentation rate (ESR) (modified Westergren). In addition, radiographs, ultrasound,

or magnetic resonance imaging scans can identify joint damage, such as erosions, a loss of bone within the joint, and narrowing of joint space.



Figure 7.1.2.5: The radiograph (left) and photograph (right) show damage to the hands typical of rheumatoid arthritis. (credit right: modification of work by “handarmdoc”/Flickr)

Systemic Lupus Erythematosus

The damage and pathology of systemic lupus erythematosus (SLE) is caused by type III hypersensitivity reactions. Autoantibodies produced in SLE are directed against nuclear and cytoplasmic proteins. Anti-nuclear antibodies (ANAs) are present in more than 95% of patients with SLE,[4] with additional autoantibodies including anti-double–stranded DNA (ds-DNA) and anti-Sm antibodies (antibodies to small nuclear ribonucleoprotein). Anti-ds-DNA and anti-Sm antibodies are unique to patients with SLE; thus, their presence is included in the classification criteria of SLE. Cellular interaction with autoantibodies leads to nuclear and cellular destruction, with components released after cell death leading to the formation of immune complexes.

Because autoantibodies in SLE can target a wide variety of cells, symptoms of SLE can occur in many body locations. However, the most common symptoms include fatigue, fever with no other cause, hair loss, and a sunlight-sensitive "butterfly" or wolf-mask (lupus) rash that is found in about 50% of people with SLE (Figure 7.1.2.6). The rash is most often seen over the cheeks and bridge of the nose, but can be widespread. Other symptoms may appear depending on affected areas. The joints may be affected, leading to arthritis of the fingers, hands, wrists, and knees. Effects on the brain and nervous system can lead to headaches, numbness, tingling, seizures, vision problems, and personality changes. There may also be abdominal pain, nausea, vomiting, arrhythmias, shortness of breath, and blood in the sputum. Effects on the skin can lead to additional areas of skin lesions, and vasoconstriction can cause color changes in the fingers when they are cold (Raynaud phenomenon). Effects on the kidneys can lead to edema in the legs and weight gain. A diagnosis of SLE depends on identification of four of 11 of the most common symptoms and confirmed production of an array of autoantibodies unique to SLE. A positive test for ANAs alone is not diagnostic.

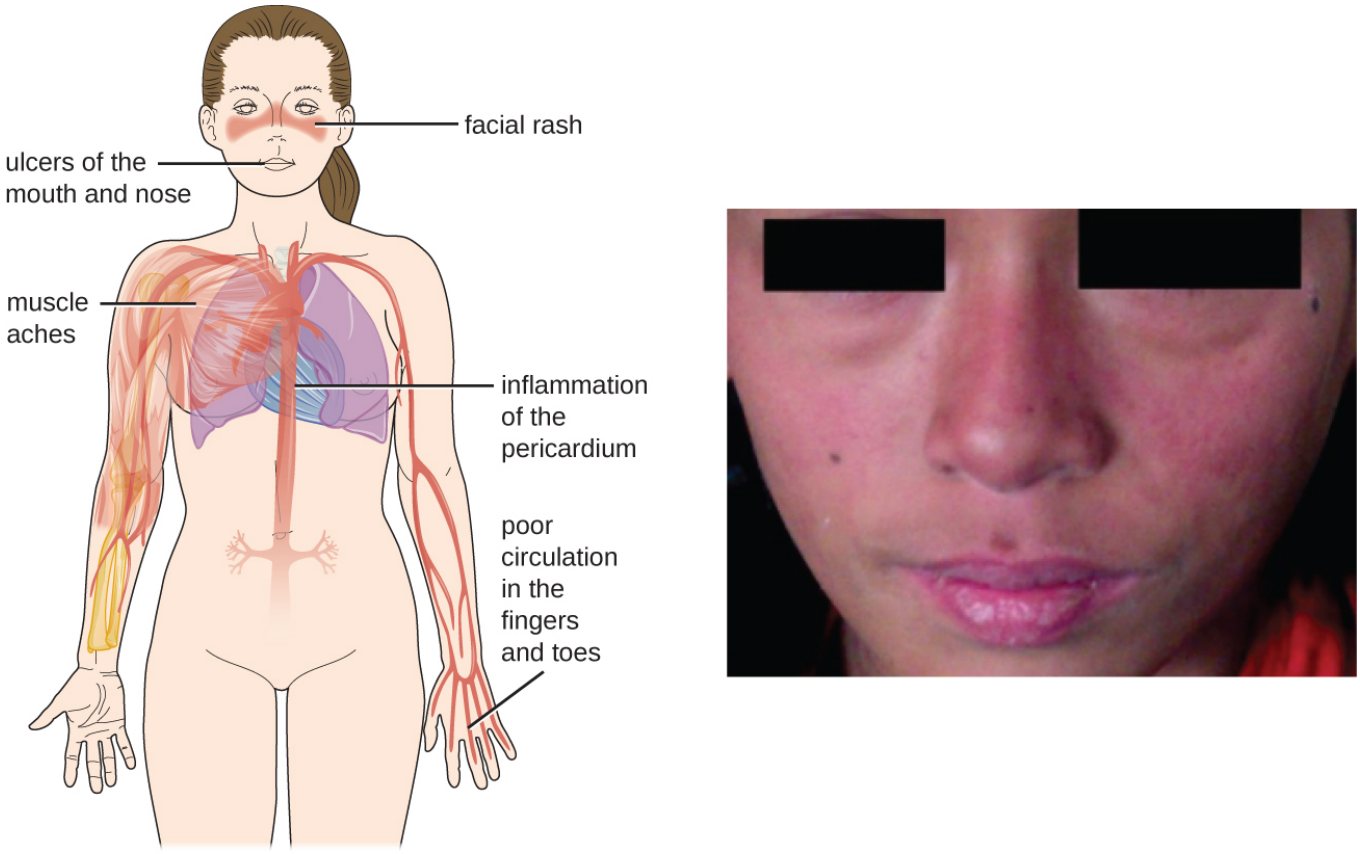


Figure 7.1.2.6: (a) Systemic lupus erythematosus is characterized by autoimmunity to the individual's own DNA and/or proteins. (b) This patient is presenting with a butterfly rash, one of the characteristic signs of lupus. (credit a: modification of work by Mikael Häggström; credit b: modification of work by Shrestha D, Dhakal AK, Shiva RK, Shakya A, Shah SC, Shakya H)

? Exercise 7.1.2.2

1. List the ways antibodies contribute to the pathogenesis of myasthenia gravis.
2. Explain why rheumatoid arthritis is considered a type III hypersensitivity.
3. Describe the symptoms of systemic lupus erythematosus and explain why they affect so many different parts of the body.
4. What is recognized as an antigen in myasthenia gravis?

Table 7.1.2.1 summarizes the causes, signs, and symptoms of select autoimmune diseases.

Table 7.1.2.1: Select Autoimmune Diseases

Disease	Cause	Signs and Symptoms
Addison disease	Destruction of adrenal gland cells by cytotoxic T cells	Weakness, nausea, hypotension, fatigue; adrenal crisis with severe pain in abdomen, lower back, and legs; circulatory system collapse, kidney failure
Celiac disease	Antibodies to gluten become autoantibodies that target cells of the small intestine	Severe diarrhea, abdominal pain, anemia, malnutrition
Diabetes mellitus (type I)	Cytotoxic T-cell destruction of the insulin-producing β cells of the pancreas	Hyperglycemia, extreme increase in thirst and urination, weight loss, extreme fatigue
Graves disease	Autoantibodies target thyroid-stimulating hormone receptors, resulting in overstimulation of the thyroid	Hyperthyroidism with rapid and irregular heartbeat, heat intolerance, weight loss, goiter, exophthalmia
Hashimoto thyroiditis	Thyroid gland is attacked by cytotoxic T cells, lymphocytes, macrophages, and autoantibodies	Thyroiditis with goiter, cold intolerance, muscle weakness, painful and stiff joints, depression, memory loss
Multiple sclerosis (MS)	Cytotoxic T-cell destruction of the myelin sheath surrounding nerve axons in the central nervous system	Visual disturbances, muscle weakness, impaired coordination and balance, numbness, prickling or “pins and needles” sensations, impaired cognitive function and memory
Myasthenia gravis	Autoantibodies directed against acetylcholine receptors within the neuromuscular junction	Extreme muscle weakness eventually leading to fatal respiratory arrest
Psoriasis	Cytokine activation of keratinocytes causes rapid and excessive epidermal cell turnover	Itchy or sore patches of thick, red skin with silvery scales; commonly affects elbows, knees, scalp, back, face, palms, feet
Rheumatoid arthritis	Autoantibodies, immune complexes, complement activation, phagocytes, and T cells damage membranes and bone in joints	Joint inflammation, pain and disfigurement, chronic systemic inflammation
Systemic lupus erythematosus (SLE)	Autoantibodies directed against nuclear and cytoplasmic molecules form immune complexes that deposit in tissues. Phagocytic cells and complement activation cause tissue damage and inflammation	Fatigue, fever, joint pain and swelling, hair loss, anemia, clotting, a sunlight-sensitive "butterfly" rash, skin lesions, photosensitivity, decreased kidney function, memory loss, confusion, depression

Key Concepts and Summary

- **Autoimmune diseases** result from a breakdown in immunological tolerance. The actual induction event(s) for autoimmune states are largely unknown.
- Some autoimmune diseases attack specific organs, whereas others are more systemic.
- Organ-specific autoimmune diseases include **celiac disease**, **Graves disease**, **Hashimoto thyroiditis**, **type I diabetes mellitus,** and **Addison disease**.
- Systemic autoimmune diseases include **multiple sclerosis**, **myasthenia gravis**, **psoriasis**, **rheumatoid arthritis**, and **systemic lupus erythematosus**.
- Treatments for autoimmune diseases generally involve anti-inflammatory and immunosuppressive drugs.

Footnotes

1. 1 D.A. Van Heel, J. West. “Recent Advances in Coeliac Disease.” *Gut* 55 no. 7 (2006):1037—1046.
2. 2 ibid.
3. 3 P. Martorell et al. “Autoimmunity in Addison’s Disease.” *Netherlands Journal of Medicine* 60 no. 7 (2002):269—275.
4. 4 C.C. Mok, C.S. Lau. “Pathogenesis of Systemic Lupus Erythematosus.” *Journal of Clinical Pathology* 56 no. 7 (2003):481—490.

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7.1.3: Organ Transplantation and Rejection

Learning Objectives

- Explain why human leukocyte antigens (HLAs) are important in tissue transplantation
- Explain the types of grafts possible and their potential for interaction with the immune system
- Describe what occurs during graft-versus-host disease (GVHD)

A graft is the transplantation of an organ or tissue to a different location, with the goal of replacing a missing or damaged organ or tissue. Grafts are typically moved without their attachments to the circulatory system and must reestablish these, in addition to the other connections and interactions with their new surrounding tissues. There are different types of grafts depending on the source of the new tissue or organ. Tissues that are transplanted from one genetically distinct individual to another within the same species are called allografts. An interesting variant of the allograft is an isograft, in which tissue from one twin is transplanted to another. As long as the twins are monozygotic(therefore, essentially genetically identical), the transplanted tissue is virtually never rejected. If tissues are transplanted from one area on an individual to another area on the same individual (e.g., a skin graft on a burn patient), it is known as an autograft. If tissues from an animal are transplanted into a human, this is called a xenograft.

Transplant Rejection

The different types of grafts described above have varying risks for rejection (Table 7.1.3.1). Rejection occurs when the recipient's immune system recognizes the donor tissue as foreign (non-self), triggering an immune response. The major histocompatibility complex markers MHC I and MHC II, more specifically identified as human leukocyte antigens (HLAs), play a role in transplant rejection. The HLAs expressed in tissue transplanted from a genetically different individual or species may be recognized as non-self molecules by the host's dendritic cells. If this occurs, the dendritic cells will process and present the foreign HLAs to the host's helper T cells and cytotoxic T cells, thereby activating them. Cytotoxic T cells then target and kill the grafted cells through the same mechanism they use to kill virus-infected cells; helper T cells may also release cytokines that activate macrophages to kill graft cells.

Table 7.1.3.1: Types of Tissue and Organ Grafts and Their Complications

Graft	Procedure	Complications
Autograft	From self to self	No rejection concerns
Isograft	From identical twin to twin	Little concern of rejection
Allograft	From relative or nonrelative to individual	Rejection possible
Xenograft	From animal to human	Rejection possible

With the three highly polymorphic MHC I genes in humans (*HLA-A*, *HLA-B*, and *HLA-C*) determining compatibility, each with many alleles segregating in a population, odds are extremely low that a randomly chosen donor will match a recipient's six-allele genotype (the two alleles at each locus are expressed codominantly). This is why a parent or a sibling may be the best donor in many situations—a genetic match between the MHC genes is much more likely and the organ is much less likely to be rejected.

Although matching all of the MHC genes can lower the risk for rejection, there are a number of additional gene products that also play a role in stimulating responses against grafted tissue. Because of this, no non-self grafted tissue is likely to completely avoid rejection. However, the more similar the MHC gene match, the more likely the graft is to be tolerated for a longer time. Most transplant recipients, even those with tissues well matched to their MHC genes, require treatment with immunosuppressant drugs for the rest of their lives. This can make them more vulnerable than the general population to complications from infectious diseases. It can also result in transplant-related malignancies because the body's normal defenses against cancer cells are being suppressed.

Exercise 7.1.3.1

1. What part of the immune response is responsible for graft rejection?
2. Explain why blood relatives are preferred as organ donors.
3. Describe the role of immunosuppression in transplantation.

Graft-versus-Host Disease

A form of rejection called graft-versus-host disease (GVHD) primarily occurs in recipients of bone marrow transplants and peripheral blood stem cells. GHVD presents a unique situation because the transplanted tissue is capable of producing immune cells; APCs in the donated bone marrow may recognize the host cells as non-self, leading to activation of the donor cytotoxic T cells. Once activated, the donor's T cells attack the recipient cells, causing acute GVHD.

Acute GVHD typically develops within weeks after a bone marrow transplant, causing tissue damage affecting the skin, gastrointestinal tract, liver, and eyes. In addition, acute GVHD may also lead to a cytokine storm, an unregulated secretion of cytokines that may be fatal. In addition to acute GVHD, there is also the risk for chronic GVHD developing months after the bone marrow transplant. The mechanisms responsible for chronic GVHD are not well understood.

To minimize the risk of GVHD, it is critically important to match the HLAs of the host and donor as closely as possible in bone marrow transplants. In addition, the donated bone marrow is processed before grafting to remove as many donor APCs and T cells as possible, leaving mostly *hematopoietic* stem cells.

Exercise Runaway argument for \eatSpaces? 2

1. Why does GVHD occur in specifically in bone marrow transplants?
2. What cells are responsible for GVHD?

The Future of Transplantation

Historically speaking, the practice of transplanting tissues—and the complications that can accompany such procedures—is a relatively recent development. It was not until 1954 that the first successful organ transplantation between two humans was achieved. Yet the field of organ transplantation has progressed rapidly since that time.

Nonetheless, the practice of transplanting non-self tissues may soon become obsolete. Scientists are now attempting to develop methods by which new organs may be grown *in vitro* from an individual's own harvested cells to replace damaged or abnormal ones. Because organs produced in this way would contain the individual's own cells, they could be transplanted into the individual without risk for rejection.

An alternative approach that is gaining renewed research interest is genetic modification of donor animals, such as pigs, to provide transplantable organs that do not elicit an immune response in the recipient. The approach involves excising the genes in the pig (in the embryo) that are most responsible for the rejection reaction after transplantation. Finding these genes and effectively removing them is a challenge, however. So too is identifying and neutralizing risks from viral sequences that might be embedded in the pig genome, posing a risk for infection in the human recipient.

Clinical Focus: Resolution

Kerry's tests come back positive, confirming a diagnosis of lupus, a disease that occurs 10 times more frequently in women than men. SLE cannot be cured, but there are various therapies available for reducing and managing its symptoms. Specific therapies are prescribed based on the particular symptoms presenting in the patient. Kerry's rheumatologist starts her therapy with a low dose of corticosteroids to reduce her rashes. She also prescribes a low dose of hydroxychloroquine, an anti-inflammatory drug that is used to treat inflammation in patients with RA, childhood arthritis, SLE, and other autoimmune diseases. Although the mechanism of action of hydroxychloroquine is not well defined, it appears that this drug interferes with the processes of antigen processing and activation of autoimmunity. Because of its mechanism, the effects of hydroxychloroquine are not as immediate as that of other anti-inflammatory drugs, but it is still considered a good companion

therapy for SLE. Kerry's doctor also advises her to limit her exposure to sunlight, because photosensitivity to sunlight may precipitate rashes.

Over the next 6 months, Kerry follows her treatment plan and her symptoms do not return. However, future flare-ups are likely to occur. She will need to continue her treatment for the rest of her life and seek medical attention whenever new symptoms develop.

Key Concepts and Summary

- Grafts and transplants can be classified as **autografts**, **isografts, allografts**, or **xenografts** based on the genetic differences between the donor's and recipient's tissues.
- Genetic differences, especially among the MHC (HLA) genes, will dictate the likelihood that **rejection** of the transplanted tissue will occur.
- Transplant recipients usually require immunosuppressive therapy to avoid rejection, even with good genetic matching. This can create additional problems when immune responses are needed to fight off infectious agents and prevent cancer.
- **Graft-versus-host disease** can occur in bone marrow transplants, as the mature T cells in the transplant itself recognize the recipient's tissues as foreign.
- Transplantation methods and technology have improved greatly in recent decades and may move into new areas with the use of stem cell technology to avoid the need for genetic matching of MHC molecules.

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7.1.4: Immunodeficiency

Learning Objectives

- Compare the causes of primary and secondary immunodeficiencies
- Describe treatments for primary and secondary immunodeficiencies

Immunodeficiencies are inherited (primary) or acquired (secondary) disorders in which elements of host immune defenses are either absent or functionally defective. In developed countries, most immunodeficiencies are inherited, and they are usually first seen in the clinic as recurrent or overwhelming infections in infants. However, on a global scale, malnutrition is the most common cause of immunodeficiency and would be categorized as an acquired immunodeficiency. Acquired immunodeficiencies are more likely to develop later in life, and the pathogenic mechanisms of many remain obscure.

Primary Immunodeficiency

Primary immunodeficiencies, which number more than 250, are caused by inherited defects of either nonspecific innate or specific adaptive immune defenses. In general, patients born with primary immunodeficiency (PI) commonly have an increased susceptibility to infection. This susceptibility can become apparent shortly after birth or in early childhood for some individuals, whereas other patients develop symptoms later in life. Some primary immunodeficiencies are due to a defect of a single cellular or humoral component of the immune system; others may result from defects of more than one component. Examples of primary immunodeficiencies include chronic granulomatous disease, X-linked agammaglobulinemia, selective IgA deficiency, and severe combined immunodeficiency disease.

Chronic Granulomatous Disease

The causes of chronic granulomatous disease (CGD) are defects in the NADPH oxidase system of phagocytic cells, including neutrophils and macrophages, that prevent the production of superoxide radicals in phagolysosomes. The inability to produce superoxide radicals impairs the antibacterial activity of phagocytes. As a result, infections in patients with CGD persist longer, leading to a chronic local inflammation called a granuloma. Microorganisms that are the most common causes of infections in patients with CGD include *Aspergillus* spp., *Staphylococcus aureus*, *Chromobacterium violaceum*, *Serratia marcescens*, and *Salmonella typhimurium*.

X-Linked Agammaglobulinemia

Deficiencies in B cells due to defective differentiation lead to a lack of specific antibody production known as X-linked agammaglobulinemia. In 1952, Ogden C. Bruton (1908–2003) described the first immunodeficiency in a boy whose immune system failed to produce antibodies. This defect is inherited on the X chromosome and is characterized by the absence of immunoglobulin in the serum; it is called Bruton X-linked agammaglobulinemia (XLA). The defective gene, *BTK*, in XLA is now known to encode a tyrosine kinase called Bruton tyrosine kinase (Btk). In patients whose B cells are unable to produce sufficient amounts of Btk, the B-cell maturation and differentiation halts at the pre-B-cell stage of growth. B-cell maturation and differentiation beyond the pre-B-cell stage of growth is required for immunoglobulin production. Patients who lack antibody production suffer from recurrent infections almost exclusively due to extracellular pathogens that cause pyogenic infections: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *S. pyogenes*, and *S. aureus*. Because cell-mediated immunity is not impaired, these patients are not particularly vulnerable to infections caused by viruses or intracellular pathogens.

Selective IgA Deficiency

The most common inherited form of immunoglobulin deficiency is selective IgA deficiency, affecting about one in 800 people. Individuals with selective IgA deficiency produce normal levels of IgG and IgM, but are not able to produce secretory IgA. IgA deficiency predisposes these individuals to lung and gastrointestinal infections for which secretory IgA is normally an important defense mechanism. Infections in the lungs and gastrointestinal tract can involve a variety of pathogens, including *H. influenzae*, *S. pneumoniae*, *Moraxella catarrhalis*, *S. aureus*, *Giardia lamblia*, or pathogenic strains of *Escherichia coli*.

Severe Combined Immunodeficiency

Patients who suffer from severe combined immunodeficiency (SCID) have B-cell and T-cell defects that impair T-cell dependent antibody responses as well as cell-mediated immune responses. Patients with SCID also cannot develop immunological memory, so vaccines provide them no protection, and live attenuated vaccines (e.g., for varicella-zoster, measles virus, rotavirus, poliovirus) can actually cause the infection they are intended to prevent. The most common form is X-linked SCID, which accounts for nearly 50% of all cases and occurs primarily in males. Patients with SCID are typically diagnosed within the first few months of life after developing severe, often life-threatening, opportunistic infection by *Candida* spp., *Pneumocystis jirovecii*, or pathogenic strains of *E. coli*.

Without treatment, babies with SCID do not typically survive infancy. In some cases, a bone marrow transplant may successfully correct the defects in lymphocyte development that lead to the SCID phenotype, by replacing the defective component. However, this treatment approach is not without risks, as demonstrated by the famous case of David Vetter (1971–1984), better known as "Bubble Boy" (Figure 7.1.4.1). Vetter, a patient with SCID who lived in a protective plastic bubble to prevent exposure to opportunistic microbes, received a bone marrow transplant from his sister. Because of a latent Epstein-Barr virus infection in her bone marrow, however, he developed mononucleosis and died of Burkitt lymphoma at the age of 12 years.



Figure 7.1.4.1: David Vetter, popularly known as "The Bubble Boy," was born with SCID and lived most of his life isolated inside a plastic bubble. Here he is shown outside the bubble in a suit specially built for him by NASA. (credit: NASA Johnson Space Center)

? Exercise 7.1.4.1

1. What is the fundamental cause of a primary immunodeficiency?
2. Explain why patients with chronic granulomatous disease are especially susceptible to bacterial infections.
3. Explain why individuals with selective IgA deficiency are susceptible to respiratory and gastrointestinal infections.

Secondary Immunodeficiency

A secondary immunodeficiency occurs as a result an acquired impairment of function of B cells, T cells, or both. Secondary immunodeficiencies can be caused by:

- Systemic disorders such as diabetes mellitus, malnutrition, hepatitis, or HIV infection
- Immunosuppressive treatments such as cytotoxic chemotherapy, bone marrow ablation before transplantation, or radiation therapy
- Prolonged critical illness due to infection, surgery, or trauma in the very young, elderly, or hospitalized patients

Unlike primary immunodeficiencies, which have a genetic basis, secondary immunodeficiencies are often reversible if the underlying cause is resolved. Patients with secondary immunodeficiencies develop an increased susceptibility to an otherwise benign infection by opportunistic pathogens such as *Candida* spp., *P. jirovecii*, and *Cryptosporidium*.

HIV infection and the associated acquired immunodeficiency syndrome (AIDS) are the best-known secondary immunodeficiencies. AIDS is characterized by profound CD4 T-cell lymphopenia (decrease in lymphocytes). The decrease in CD4 T cells is the result of various mechanisms, including HIV-induced pyroptosis (a type of apoptosis that stimulates an inflammatory response), viral cytopathic effect, and cytotoxicity to HIV-infected cells.

The most common cause of secondary immunodeficiency worldwide is severe malnutrition, which affects both innate and adaptive immunity. More research and information are needed for the more common causes of secondary immunodeficiency; however, the number of new discoveries in AIDS research far exceeds that of any other single cause of secondary immunodeficiency. AIDS research has paid off extremely well in terms of discoveries and treatments; increased research into the most common cause of immunodeficiency, malnutrition, would likely be as beneficial.

Exercise 7.1.4.2

1. What is the most common cause of secondary immunodeficiencies?
2. Explain why secondary immunodeficiencies can sometimes be reversed.

An Immunocompromised Host

Benjamin, a 50-year-old male patient who has been receiving chemotherapy to treat his chronic myelogenous leukemia (CML), a disease characterized by massive overproduction of nonfunctional, malignant myelocytic leukocytes that crowd out other, healthy leukocytes, is seen in the emergency department. He is complaining of a productive, wet cough, dyspnea, and fatigue. On examination, his pulse is 120 beats per minute (bpm) (normal range is 60–100 bpm) and weak, and his blood pressure is 90/60 mm Hg (normal is 120/80 mm Hg). During auscultation, a distinct crackling can be heard in his lungs as he breathes, and his pulse-oximeter level (a measurement of blood-oxygen saturation) is 80% (normal is 95%–100%). He has a fever; his temperature is 38.9 °C (102 °F). Sputum cultures and blood samples are obtained and sent to the lab, but Benjamin goes into respiratory distress and dies before the results can be obtained.

Benjamin's death was a result of a combination of his immune system being compromised by his leukemia and his chemotherapy treatment further weakening his ability to mount an immune response. CML (and leukemia in general) and corresponding chemotherapy cause a decrease in the number of leukocytes capable of normal function, leading to secondary immunodeficiency. This increases the risk for opportunistic bacterial, viral, protozoal, and fungal infections that could include *Staphylococcus*, enteroviruses, *Pneumocystis*, *Giardia*, or *Candida*. Benjamin's symptoms were suggestive of bacterial pneumonia, but his leukemia and chemotherapy likely complicated and contributed to the severity of the pneumonia, resulting in his death. Because his leukemia was overproducing certain white blood cells, and those overproduced white blood cells were largely nonfunctional or abnormal in their function, he did not have the proper immune system blood cells to help him fight off the infection.

Table 7.1.4.1 summarizes primary and secondary immunodeficiencies, their effects on immune function, and typical outcomes.

Table 7.1.4.1: Primary and Secondary Immunodeficiencies

Disease		Effect on Immune Function	Outcomes
Primary immunodeficiencies	Chronic granulomatous disease	Impaired killing of bacteria within the phagolysosome of neutrophils and macrophages	Chronic infections and granulomas
	Selective IgA deficiency	Inability to produce secretory IgA	Predisposition to lung and gastrointestinal infections
	Severe combined immunodeficiency disease (SCID)	Deficient humoral and cell-mediated immune responses	Early development of severe and life-threatening opportunistic infections
	X-linked agammaglobulinemia	Flawed differentiation of B cells and absence of specific antibodies	Recurrent infections almost exclusively due to pathogens that cause pyogenic infections
Secondary immunodeficiencies	Immunosuppressive therapies (e.g., chemotherapy, radiotherapy)	Impaired humoral and/or cell-mediated immune responses	Opportunistic infections, rare cancers
	Malnutrition	Impaired humoral and/or cell-mediated immune responses	Opportunistic infections, rare cancers
	Viral infection (e.g., HIV)	Impaired cell-mediated immune responses due to CD4 T-cell lymphopenia	Opportunistic infections, rare cancers

Key Concepts and Summary

- **Primary immunodeficiencies** are caused by genetic abnormalities; **secondary immunodeficiencies** are acquired through disease, diet, or environmental exposures.
- Primary immunodeficiencies may result from flaws in phagocyte killing of innate immunity, or impairment of T cells and B cells.
- Primary immunodeficiencies include chronic granulomatous disease, X-linked agammaglobulinemia, selective IgA deficiency, and severe combined immunodeficiency disease.
- Secondary immunodeficiencies result from environmentally induced defects in B cells and/or T cells.
- Causes for secondary immunodeficiencies include malnutrition, viral infection, diabetes, prolonged infections, and chemical or radiation exposure.

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7.1.5: Cancer Immunobiology and Immunotherapy

Learning Objectives

- Explain how the adaptive specific immune response responds to tumors
- Discuss the risks and benefits of tumor vaccines

Cancer involves a loss of the ability of cells to control their cell cycle, the stages each eukaryotic cell goes through as it grows and then divides. When this control is lost, the affected cells rapidly divide and often lose the ability to differentiate into the cell type appropriate for their location in the body. In addition, they lose contact inhibition and can start to grow on top of each other. This can result in formation of a tumor. It is important to make a distinction here: The term “cancer” is used to describe the diseases resulting from loss of cell-cycle regulation and subsequent cell proliferation. But the term “tumor” is more general. A “tumor” is an abnormal mass of cells, and a tumor can be benign (not cancerous) or malignant (cancerous).

Traditional cancer treatment uses radiation and/or chemotherapy to destroy cancer cells; however, these treatments can have unwanted side effects because they harm normal cells as well as cancer cells. Newer, promising therapies attempt to enlist the patient’s immune system to target cancer cells specifically. It is known that the immune system can recognize and destroy cancerous cells, and some researchers and immunologists also believe, based on the results of their experiments, that many cancers are eliminated by the body’s own defenses before they can become a health problem. This idea is not universally accepted by researchers, however, and needs further investigation for verification.

Cell-Mediated Response to Tumors

Cell-mediated immune responses can be directed against cancer cells, many of which do not have the normal complement of self-proteins, making them a target for elimination. Abnormal cancer cells may also present tumor antigens. These tumor antigens are not a part of the screening process used to eliminate lymphocytes during development; thus, even though they are self-antigens, they can stimulate and drive adaptive immune responses against abnormal cells.

Presentation of tumor antigens can stimulate naïve helper T cells to become activated by cytokines such as IL-12 and differentiate into T_H1 cells. T_H1 cells release cytokines that can activate natural killer (NK) cells and enhance the killing of activated cytotoxic T cells. Both NK cells and cytotoxic T cells can recognize and target cancer cells, and induce apoptosis through the action of perforins and granzymes. In addition, activated cytotoxic T cells can bind to cell-surface proteins on abnormal cells and induce apoptosis by a second killing mechanism called the CD95 (Fas) cytotoxic pathway.

Despite these mechanisms for removing cancerous cells from the body, cancer remains a common cause of death. Unfortunately, malignant tumors tend to actively suppress the immune response in various ways. In some cancers, the immune cells themselves are cancerous. In leukemia, lymphocytes that would normally facilitate the immune response become abnormal. In other cancers, the cancerous cells can become resistant to induction of apoptosis. This may occur through the expression of membrane proteins that shut off cytotoxic T cells or that induce regulatory T cells that can shut down immune responses.

The mechanisms by which cancer cells alter immune responses are still not yet fully understood, and this is a very active area of research. As scientists’ understanding of adaptive immunity improves, cancer therapies that harness the body’s immune defenses may someday be more successful in treating and eliminating cancer.

Exercise 7.1.5.1

1. How do cancer cells suppress the immune system?
2. Describe how the immune system recognizes and destroys cancer cells.

Cancer Vaccines

There are two types of cancer vaccines: preventive and therapeutic. Preventive vaccines are used to prevent cancer from occurring, whereas therapeutic vaccines are used to treat patients with cancer. Most preventive cancer vaccines target viral infections that are known to lead to cancer. These include vaccines against human papillomavirus (HPV)and hepatitis B, which help prevent cervical and liver cancer, respectively.

Most therapeutic cancer vaccines are in the experimental stage. They exploit tumor-specific antigens to stimulate the immune system to selectively attack cancer cells. Specifically, they aim to enhance T_H1 function and interaction with cytotoxic T cells, which, in turn, results in more effective attack on abnormal tumor cells. In some cases, researchers have used genetic engineering to develop antitumor vaccines in an approach similar to that used for DNA vaccines (see Micro Connections: DNA vaccines). The vaccine contains a recombinant plasmid with genes for tumor antigens; theoretically, the tumor gene would not induce new cancer because it is not functional, but it could trick the immune system into targeting the tumor gene product as a foreign invader.

The first FDA-approved therapeutic cancer vaccine was sipuleucel-T (Provenge), approved in 2010 to treat certain cases of prostate cancer.[1] This unconventional vaccine is custom designed using the patient's own cells. APCs are removed from the patient and cultured with a tumor-specific molecule; the cells are then returned to the patient. This approach appears to enhance the patient's immune response against the cancer cells. Another therapeutic cancer vaccine (talimogene laherparepvec, also called T-VEC or Imlygic) was approved by the FDA in 2015 for treatment of melanoma, a form of skin cancer. This vaccine contains a virus that is injected into tumors, where it infects and lyses the tumor cells. The virus also induces a response in lesions or tumors besides those into which the vaccine is injected, indicating that it is stimulating a more general (as opposed to local) antitumor immune response in the patient.

? Exercise 7.1.5.2

1. Explain the difference between preventative and therapeutic cancer vaccines.
2. Describe at least two different approaches to developing therapeutic anti-cancer vaccines.

Using Viruses to Cure Cancer

Viruses typically destroy the cells they infect—a fact responsible for any number of human diseases. But the cell-killing powers of viruses may yet prove to be the cure for some types of cancer, which is generally treated by attempting to rid the body of cancerous cells. Several clinical trials are studying the effects of viruses targeted at cancer cells. Reolysin, a drug currently in testing phases, uses reoviruses (respiratory enteric orphan viruses) that can infect and kill cells that have an activated Ras-signaling pathway, a common mutation in cancerous cells. Viruses such as rubeola (the measles virus) can also be genetically engineered to aggressively attack tumor cells. These modified viruses not only bind more specifically to receptors overexpressed on cancer cells, they also carry genes driven by promoters that are only turned on within cancer cells. Herpesvirus and others have also been modified in this way.

Key Concepts and Summary

- Cancer results from a loss of control of the cell cycle, resulting in uncontrolled cell proliferation and a loss of the ability to differentiate.
- Adaptive and innate immune responses are engaged by **tumor** antigens, self-molecules only found on abnormal cells. These adaptive responses stimulate helper T cells to activate cytotoxic T cells and NK cells of innate immunity that will seek and destroy cancer cells.
- New anticancer therapies are in development that will exploit natural adaptive immunity anticancer responses. These include external stimulation of cytotoxic T cells and therapeutic vaccines that assist or enhance the immune response.

Footnotes

1. 1 National Institutes of Health, National Cancer Institute. "Cancer Vaccines." www.cancer.gov/about-cancer/c...-fact-sheet#q8. Accessed on May 20, 2016.

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7.1.E: Diseases of the Immune System (Exercises)

19.1: Hypersensitivities

An allergy is an adaptive immune response, sometimes life-threatening, to an allergen. Hypersensitivity reactions are classified by their immune mechanism.

Multiple Choice

Which of the following is the type of cell largely responsible for type I hypersensitivity responses?

A. erythrocyte
B. mast cell
C. T lymphocyte
D. antibody

Answer

B

Type I hypersensitivities require which of the following initial priming events to occur?

A. sensitization
B. secondary immune response
C. cellular trauma
D. degranulation

Answer

A

Which of the following are the main mediators/initiators of type II hypersensitivity reactions?

A. antibodies
B. mast cells
C. erythrocytes
D. histamines

Answer

A

Inflammatory molecules are released by mast cells in type I hypersensitivities; type II hypersensitivities, however, are characterized by which of the following?

A. cell lysis (cytotoxicity)
B. strong antibody reactions against antigens
C. leukotriene release upon stimulation
D. localized tissue reactions, such as hives

Answer

A

An immune complex is an aggregate of which of the following?

A. antibody molecules
B. antigen molecules
C. antibody and antigen molecules
D. histamine molecules

Answer

C

Which of the following is a common treatment for type III hypersensitivity reactions?

A. anti-inflammatory steroid treatments
B. antihistamine treatments
C. hyposensitization injections of allergens
D. RhoGAM injections

Answer

A

Which of the following induces a type III hypersensitivity?

A. release of inflammatory molecules from mast cells
B. accumulation of immune complexes in tissues and small blood vessels
C. destruction of cells bound by antigens
D. destruction of cells bound by antibodies

Answer

B

Which one of the following is not an example of a type IV hypersensitivity?

A. latex allergy
B. Contact dermatitis (e.g., contact with poison ivy)
C. a positive tuberculin skin test
D. hemolytic disease of the newborn

Answer

D

Fill in the Blank

Antibodies involved in type I hypersensitivities are of the _____ class.

Answer

IgE

Allergy shots work by shifting antibody responses to produce _____ antibodies.

Answer

IgG

A person who is blood type A would have IgM hemagglutinin antibodies against type _____ red blood cells in their plasma.

Answer

B

The itchy and blistering rash that develops with contact to poison ivy is caused by a type _____ hypersensitivity reaction.

Answer

IV

Short Answer

Although both type I and type II hypersensitivities involve antibodies as immune effectors, different mechanisms are involved with these different hypersensitivities. Differentiate the two.

What types of antibodies are most common in type III hypersensitivities, and why?

Critical Thinking

Patients are frequently given instructions to avoid allergy medications for a period of time prior to allergy testing. Why would this be important?

In some areas of the world, a tuberculosis vaccine known as bacillus Calmette-Guérin (BCG) is used. It is not used in the United States. Every person who has received this vaccine and mounted a protective response will have a positive reaction in a tuberculin skin test. Why? What does this mean for the usefulness of this skin test in those countries where this vaccine is used?

19.2: Autoimmune Disorders

Autoimmune diseases result from a breakdown in immunological tolerance. The actual induction event(s) for autoimmune states are largely unknown. Some autoimmune diseases attack specific organs, whereas others are more systemic. Organ-specific autoimmune diseases include celiac disease, Graves disease, Hashimoto thyroiditis, type I diabetes mellitus, and Addison disease.

Multiple Choice

Which of the following is an example of an organ-specific autoimmune disease?

A. rheumatoid arthritis
B. psoriasis
C. Addison disease
D. myasthenia gravis

Answer

C

Which of the following is an example of a systemic autoimmune disease?

A. Hashimoto thyroiditis
B. type I diabetes mellitus
C. Graves disease
D. myasthenia gravis

Answer

D

Fill in the Blank

The thyroid-stimulating immunoglobulin that acts like thyroid-stimulating hormone and causes Graves disease is an antibody to the _____.

Answer

thyroid-stimulating hormone receptor

19.3: Organ Transplantation and Rejection

Grafts and transplants can be classified as autografts, isografts, allografts, or xenografts based on the genetic differences between the donor's and recipient's tissues. Genetic differences, especially among the MHC (HLA) genes, will dictate the likelihood that rejection of the transplanted tissue will occur. Transplant recipients usually require immunosuppressive therapy to avoid rejection, even with good genetic matching.

Matching

Match the graft with its description.

___autograft	A. donor is a different species than the recipient
___allograft	B. donor and recipient are the same individual
___xenograft	C. donor is an identical twin of the recipient
___isograft	D. donor is the same species as the recipient, but genetically different

Answer

B, D, A, C

Fill in the Blank

For a transplant to have the best chances of avoiding rejection, the genes coding for the _____ molecules should be closely matched between donor and recipient.

Answer

MHC

Because it is a “transplant” that can include APCs and T cells from the donor, a bone marrow transplant may induce a very specific type of rejection known as _____ disease.

Answer

graft-versus-host

Short Answer

Why is a parent usually a better match for transplanted tissue to a donor than a random individual of the same species?

19.4: Immunodeficiency

Primary immunodeficiencies are caused by genetic abnormalities; secondary immunodeficiencies are acquired through disease, diet, or environmental exposures. Primary immunodeficiencies may result from flaws in phagocyte killing of innate immunity, or impairment of T cells and B cells. Primary immunodeficiencies include chronic granulomatous disease, X-linked agammaglobulinemia, selective IgA deficiency, and severe combined immunodeficiency disease.

Multiple Choice

Which of the following is a genetic disease that results in lack of production of antibodies?

A. agammaglobulinemia
B. myasthenia gravis
C. HIV/AIDS
D. chronic granulomatous disease

Answer

A

Which of the following is a genetic disease that results in almost no adaptive immunity due to lack of B and/ or T cells?

A. agammaglobulinemia
B. severe combined immunodeficiency
C. HIV/AIDS
D. chronic granulomatous disease

Answer

B

All but which one of the following are examples of secondary immunodeficiencies?

A. HIV/AIDS
B. malnutrition
C. chronic granulomatous disease
D. immunosuppression due to measles infection

Answer

C

Fill in the Blank

Diseases due to _____ abnormalities are termed primary immunodeficiencies.

Answer

genetic

A secondary immunodeficiency is _____, rather than genetic.

Answer

acquired

Short Answer

Compare the treatments for primary and secondary immunodeficiencies.

19.5: Cancer Immunobiology and Immunotherapy

When control of the cell cycle is lost, the affected cells rapidly divide and often lose the ability to differentiate into the cell type appropriate for their location in the body. In addition, they lose contact inhibition and can start to grow on top of each other. This can result in formation of a tumor. It is important to make a distinction here: The term “cancer” is used to describe the diseases resulting from loss of cell-cycle regulation and subsequent cell proliferation.

Multiple Choice

Cancer results when a mutation leads to which of the following?

A. cell death
B. apoptosis
C. loss of cell-cycle control
D. shutdown of the cell cycle

Answer

C

Tumor antigens are _____ that are inappropriately expressed and found on abnormal cells.

A. self antigens
B. foreign antigens
C. antibodies
D. T-cell receptors

Answer

A

Fill in the Blank

A _____ cancer vaccine is one that stops the disease from occurring in the first place.

Answer

preventive

A _____ cancer vaccine is one that will help to treat the disease after it has occurred.

Answer

therapeutic

Short Answer

How can tumor antigens be effectively targeted without inducing an autoimmune (anti-self) response?

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7.2: Disruptions in the Immune System

Immune disruptions may involve insufficient immune responses or inappropriate immune targets. Immunodeficiency increases an individual's susceptibility to infections and cancers. Hypersensitivities are misdirected responses either to harmless foreign particles, as in the case of allergies, or to host factors, as in the case of autoimmunity. Reactions to self components may be the result of molecular mimicry.

Immunodeficiency

A functioning immune system is essential for survival, but even the sophisticated cellular and molecular defenses of the mammalian immune response can be defeated by pathogens at virtually every step. In the competition between immune protection and pathogen evasion, pathogens have the advantage of more rapid evolution because of their shorter generation time and other characteristics. For instance, *Streptococcus pneumoniae* (bacterium that cause pneumonia and meningitis) surrounds itself with a capsule that inhibits phagocytes from engulfing it and displaying antigens to the adaptive immune system. *Staphylococcus aureus* (bacterium that can cause skin infections, abscesses, and meningitis) synthesizes a toxin called leukocidin that kills phagocytes after they engulf the bacterium. Other pathogens can also hinder the adaptive immune system. HIV infects T_H cells via their CD4 surface molecules, gradually depleting the number of T_H cells in the body; this inhibits the adaptive immune system's capacity to generate sufficient responses to infection or tumors. As a result, HIV-infected individuals often suffer from infections that would not cause illness in people with healthy immune systems but which can cause devastating illness to immune-compromised individuals. Maladaptive responses of immune cells and molecules themselves can also disrupt the proper functioning of the entire system, leading to host cell damage that could become fatal.

Failures, insufficiencies, or delays at any level of the immune response can allow pathogens or tumor cells to gain a foothold and replicate or proliferate to high enough levels that the immune system becomes overwhelmed. **Immunodeficiency** is the failure, insufficiency, or delay in the response of the immune system, which may be acquired or inherited. Immunodeficiency can be acquired as a result of infection with certain pathogens (such as HIV), chemical exposure (including certain medical treatments), malnutrition, or possibly by extreme stress. For instance, radiation exposure can destroy populations of lymphocytes and elevate an individual's susceptibility to infections and cancer. Dozens of genetic disorders result in immunodeficiencies, including Severe Combined Immunodeficiency (SCID), Bare lymphocyte syndrome, and MHC II deficiencies. Rarely, primary immunodeficiencies that are present from birth may occur. Neutropenia is one form in which the immune system produces a below-average number of neutrophils, the body's most abundant phagocytes. As a result, bacterial infections may go unrestricted in the blood, causing serious complications.

Hypersensitivities

Maladaptive immune responses toward harmless foreign substances or self antigens that occur after tissue sensitization are termed **hypersensitivities**. The types of hypersensitivities include immediate, delayed, and autoimmunity. A large proportion of the population is affected by one or more types of hypersensitivity.

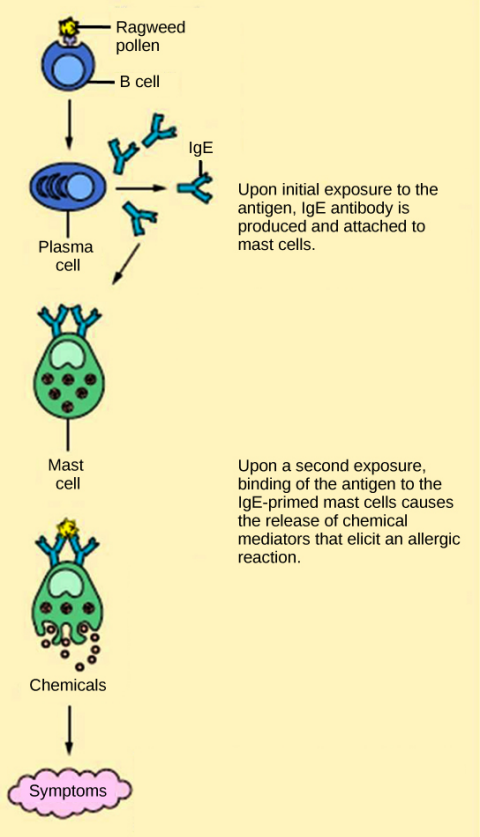


Figure 1. On first exposure to an allergen, an IgE antibody is synthesized by plasma cells in response to a harmless antigen. The IgE molecules bind to mast cells, and on secondary exposure, the mast cells release histamines and other modulators that affect the symptoms of allergy. (credit: modification of work by NIH)

The immune reaction that results from immediate hypersensitivities in which an antibody-mediated immune response occurs within minutes of exposure to a harmless antigen is called an **allergy**. In the United States, 20 percent of the population exhibits symptoms of allergy or asthma, whereas 55 percent test positive against one or more allergens. Upon initial exposure to a potential allergen, an allergic individual synthesizes antibodies of the IgE class via the typical process of APCs presenting processed antigen to T_H cells that stimulate B cells to produce IgE. This class of antibodies also mediates the immune response to parasitic worms. The constant domain of the IgE molecules interact with mast cells embedded in connective tissues. This process primes, or sensitizes, the tissue. Upon subsequent exposure to the same allergen, IgE molecules on mast cells bind the antigen via their variable domains and stimulate the mast cell to release the modified amino acids histamine and serotonin; these chemical mediators then recruit eosinophils which mediate allergic responses.

Figure 1 shows an example of an allergic response to ragweed pollen. The effects of an allergic reaction range from mild symptoms like sneezing and itchy, watery eyes to more severe or even life-threatening reactions involving intensely itchy welts or hives, airway contraction with severe respiratory distress, and plummeting blood pressure. This extreme reaction is known as anaphylactic shock. If not treated with epinephrine to counter the blood pressure and breathing effects, this condition can be fatal.

Delayed hypersensitivity is a cell-mediated immune response that takes approximately one to two days after secondary exposure for a maximal reaction to be observed. This type of hypersensitivity involves the T_H1 cytokine-mediated inflammatory response and may manifest as local tissue lesions or contact dermatitis (rash or skin irritation). Delayed hypersensitivity occurs in some individuals in response to contact with certain types of jewelry or cosmetics. Delayed hypersensitivity facilitates the immune response to poison ivy and is also the reason why the skin test for tuberculosis results in a small region of inflammation on individuals who were previously exposed to *Mycobacterium tuberculosis*. That is also why cortisone is used to treat such responses: it will inhibit cytokine production.

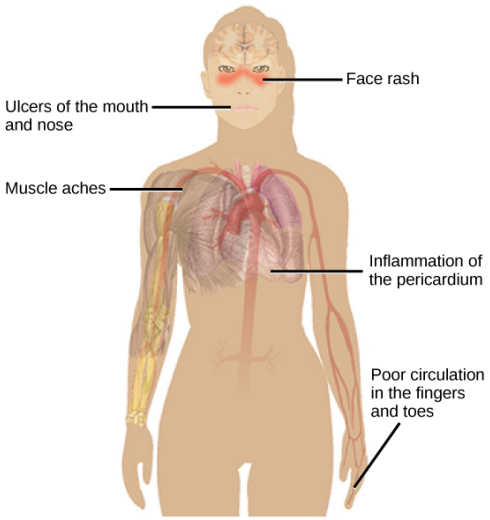


Figure 2. Systemic lupus erythematosus is characterized by autoimmunity to the individual's own DNA and/or proteins, which leads to varied dysfunction of the organs. (credit: modification of work by Mikael Häggström)

Autoimmunity is a type of hypersensitivity to self antigens that affects approximately five percent of the population. Most types of autoimmunity involve the humoral immune response. Antibodies that inappropriately mark self components as foreign are termed **autoantibodies**. In patients with the autoimmune disease myasthenia gravis, muscle cell receptors that induce contraction in response to acetylcholine are targeted by antibodies. The result is muscle weakness that may include marked difficultly with fine and/or gross motor functions. In systemic lupus erythematosus, a diffuse autoantibody response to the individual's own DNA and proteins results in various systemic diseases. As illustrated in Figure 2, systemic lupus erythematosus may affect the heart, joints, lungs, skin, kidneys, central nervous system, or other tissues, causing tissue damage via antibody binding, complement recruitment, lysis, and inflammation.

Autoimmunity can develop with time, and its causes may be rooted in molecular mimicry. Antibodies and TCRs may bind self antigens that are structurally similar to pathogen antigens, which the immune receptors first raised. As an example, infection with *Streptococcus pyogenes* (bacterium that causes strep throat) may generate antibodies or T cells that react with heart muscle, which has a similar structure to the surface of *S. pyogenes*. These antibodies can damage heart muscle with autoimmune attacks, leading to rheumatic fever. Insulin-dependent (Type 1) diabetes mellitus arises from a destructive inflammatory T_H1 response against insulin-producing cells of the pancreas. Patients with this autoimmunity must be injected with insulin that originates from other sources.

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CHAPTER OVERVIEW

8: Infectious diseases of the Skin, Eyes and Nervous System

Topic hierarchy

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8.1.2: Bacterial Infections of the Skin and Eyes

8.1.3: Viral Infections of the Skin and Eyes

8.1.4: Mycoses of the Skin and Eyes

8.1.5: Protozoan and Helminthic Infections of the Eyes

8.1.E: Skin and Eye Infections (Exercises)

8.2: The Nervous System

8.2.1: Prelude to the Nervous System

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8.3.4: Neuromycoses and Parasitic Diseases of the Nervous System

8.3.E: Nervous System Infections (Exercises)

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SECTION OVERVIEW

8.1: Skin and Eye Infections

The human body is covered in skin, and like most coverings, skin is designed to protect what is underneath. One of its primary purposes is to prevent microbes in the surrounding environment from invading underlying tissues and organs. But in spite of its role as a protective covering, skin is not itself immune from infection. Certain pathogens and toxins can cause severe infections or reactions when they come in contact with the skin. Other pathogens are opportunistic, breaching the skin's natural defenses through cuts, wounds, or a disruption of normal microbiota resulting in an infection in the surrounding skin and tissue. Still other pathogens enter the body via different routes—through the respiratory or digestive systems, for example—but cause reactions that manifest as skin rashes or lesions.

Nearly all humans experience skin infections to some degree. Many of these conditions are, as the name suggests, "skin deep," with symptoms that are local and non-life-threatening. At some point, almost everyone must endure conditions like acne, athlete's foot, and minor infections of cuts and abrasions, all of which result from infections of the skin. But not all skin infections are quite so innocuous. Some can become invasive, leading to systemic infection or spreading over large areas of skin, potentially becoming life-threatening.



Figure 8.1.1: The skin is an important barrier to pathogens, but it can also develop infections. These raised lesions (left) are typical of folliculitis, a condition that results from the inflammation of hair follicles. Acne lesions (right) also result from inflammation of hair follicles. In this case, the inflammation results when hair follicles become clogged with complex lipids, fatty acids, and dead skin cells, producing a favorable environment for bacteria.

8.1.1: Anatomy and Normal Microbiota of the Skin and Eyes

8.1.2: Bacterial Infections of the Skin and Eyes

8.1.3: Viral Infections of the Skin and Eyes

8.1.4: Mycoses of the Skin and Eyes

8.1.5: Protozoan and Helminthic Infections of the Eyes

8.1.E: Skin and Eye Infections (Exercises)

Thumbnail: Multiple plantar warts have grown on this toe.

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8.1.1: Anatomy and Normal Microbiota of the Skin and Eyes

Learning Objectives

- Describe the major anatomical features of the skin and eyes
- Compare and contrast the microbiomes of various body sites, such as the hands, back, feet, and eyes
- Explain how microorganisms overcome defenses of skin and eyes in order to cause infection
- Describe general signs and symptoms of disease associated with infections of the skin and eyes

Clinical Focus: Part 1

Sam, a college freshman with a bad habit of oversleeping, nicked himself shaving in a rush to get to class on time. At the time, he didn't think twice about it. But two days later, he noticed the cut was surrounded by a reddish area of skin that was warm to the touch. When the wound started oozing pus, he decided he had better stop by the university's clinic. The doctor took a sample from the lesion and then cleaned the area.

Exercise 8.1.1.1

What type of microbe could be responsible for Sam's infection?

Human skin is an important part of the innate immune system. In addition to serving a wide range of other functions, the skin serves as an important barrier to microbial invasion. Not only is it a physical barrier to penetration of deeper tissues by potential pathogens, but it also provides an inhospitable environment for the growth of many pathogens. In this section, we will provide a brief overview of the anatomy and normal microbiota of the skin and eyes, along with general symptoms associated with skin and eye infections.

Layers of the Skin

Human skin is made up of several layers and sublayers. The two main layers are the epidermis and the dermis. These layers cover a third layer of tissue called the hypodermis, which consists of fibrous and adipose connective tissue (Figure 8.1.1.1).

The epidermis is the outermost layer of the skin, and it is relatively thin. The exterior surface of the epidermis, called the stratum corneum, primarily consists of dead skin cells. This layer of dead cells limits direct contact between the outside world and live cells. The stratum corneum is rich in keratin, a tough, fibrous protein that is also found in hair and nails. Keratin helps make the outer surface of the skin relatively tough and waterproof. It also helps to keep the surface of the skin dry, which reduces microbial growth. However, some microbes are still able to live on the surface of the skin, and some of these can be shed with dead skin cells in the process of desquamation, which is the shedding and peeling of skin that occurs as a normal process but that may be accelerated when infection is present.

Beneath the epidermis lies a thicker skin layer called the dermis. The dermis contains connective tissue and embedded structures such as blood vessels, nerves, and muscles. Structures called hair follicles (from which hair grows) are located within the dermis, even though much of their structure consists of epidermal tissue. The dermis also contains the two major types of glands found in human skin: sweat glands (tubular glands that produce sweat) and sebaceous glands (which are associated with hair follicles and produce sebum, a lipid-rich substance containing proteins and minerals).

Perspiration (sweat) provides some moisture to the epidermis, which can increase the potential for microbial growth. For this reason, more microbes are found on the regions of the skin that produce the most sweat, such as the skin of the underarms and groin. However, in addition to water, sweat also contains substances that inhibit microbial growth, such as salts, lysozyme, and antimicrobial peptides. Sebum also serves to protect the skin and reduce water loss. Although some of the lipids and fatty acids in sebum inhibit microbial growth, sebum contains compounds that provide nutrition for certain microbes.

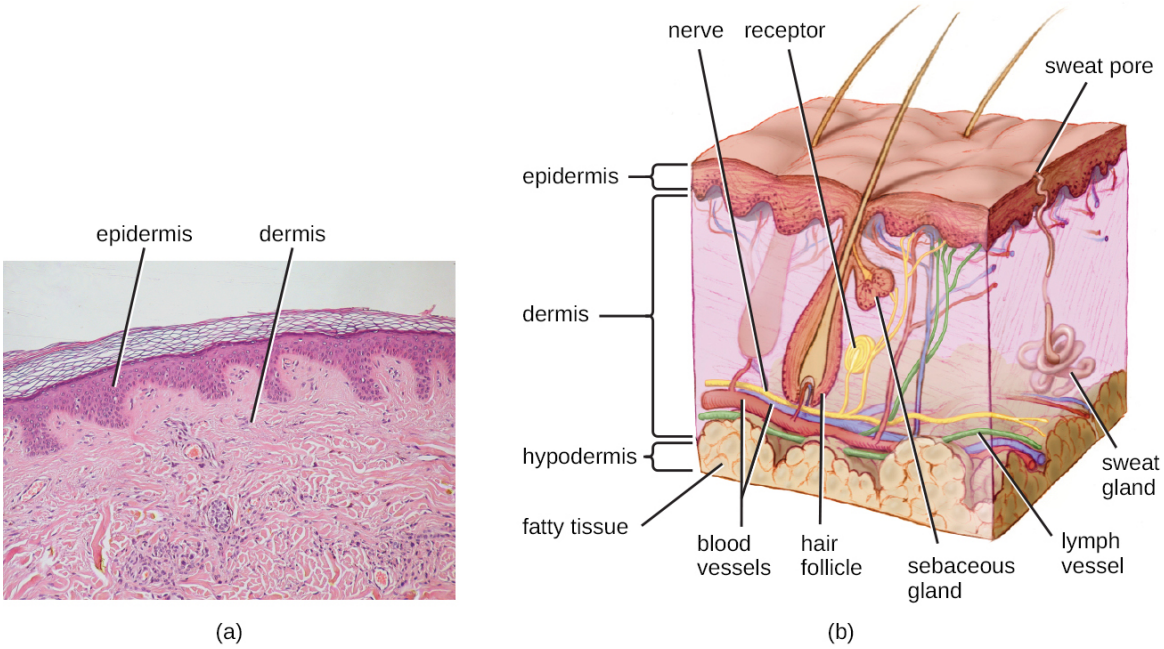


Figure 8.1.1.1: (a) A micrograph of a section through human skin shows the epidermis and dermis. (b) The major layers of human skin are the epidermis, dermis, and hypodermis. (credit b: modification of work by National Cancer Institute)

? Exercise 8.1.1.2

How does desquamation help with preventing infections?

Normal Microbiota of the Skin

The skin is home to a wide variety of normal microbiota, consisting of commensal organisms that derive nutrition from skin cells and secretions such as sweat and sebum. The normal microbiota of skin tends to inhibit transient-microbe colonization by producing antimicrobial substances and outcompeting other microbes that land on the surface of the skin. This helps to protect the skin from pathogenic infection.

The skin's properties differ from one region of the body to another, as does the composition of the skin's microbiota. The availability of nutrients and moisture partly dictates which microorganisms will thrive in a particular region of the skin. Relatively moist skin, such as that of the nares (nostrils) and underarms, has a much different microbiota than the dryer skin on the arms, legs, hands, and top of the feet. Some areas of the skin have higher densities of sebaceous glands. These sebum-rich areas, which include the back, the folds at the side of the nose, and the back of the neck, harbor distinct microbial communities that are less diverse than those found on other parts of the body.

Different types of bacteria dominate the dry, moist, and sebum-rich regions of the skin. The most abundant microbes typically found in the dry and sebaceous regions are Betaproteobacteria and Propionibacteria, respectively. In the moist regions, *Corynebacterium* and *Staphylococcus* are most commonly found (Figure 8.1.1.2). Viruses and fungi are also found on the skin, with *Malassezia* being the most common type of fungus found as part of the normal microbiota. The role and populations of viruses in the microbiota, known as viromes, are still not well understood, and there are limitations to the techniques used to identify them. However, Circoviridae, Papillomaviridae, and Polyomaviridaeappear to be the most common residents in the healthy skin virome.[123]

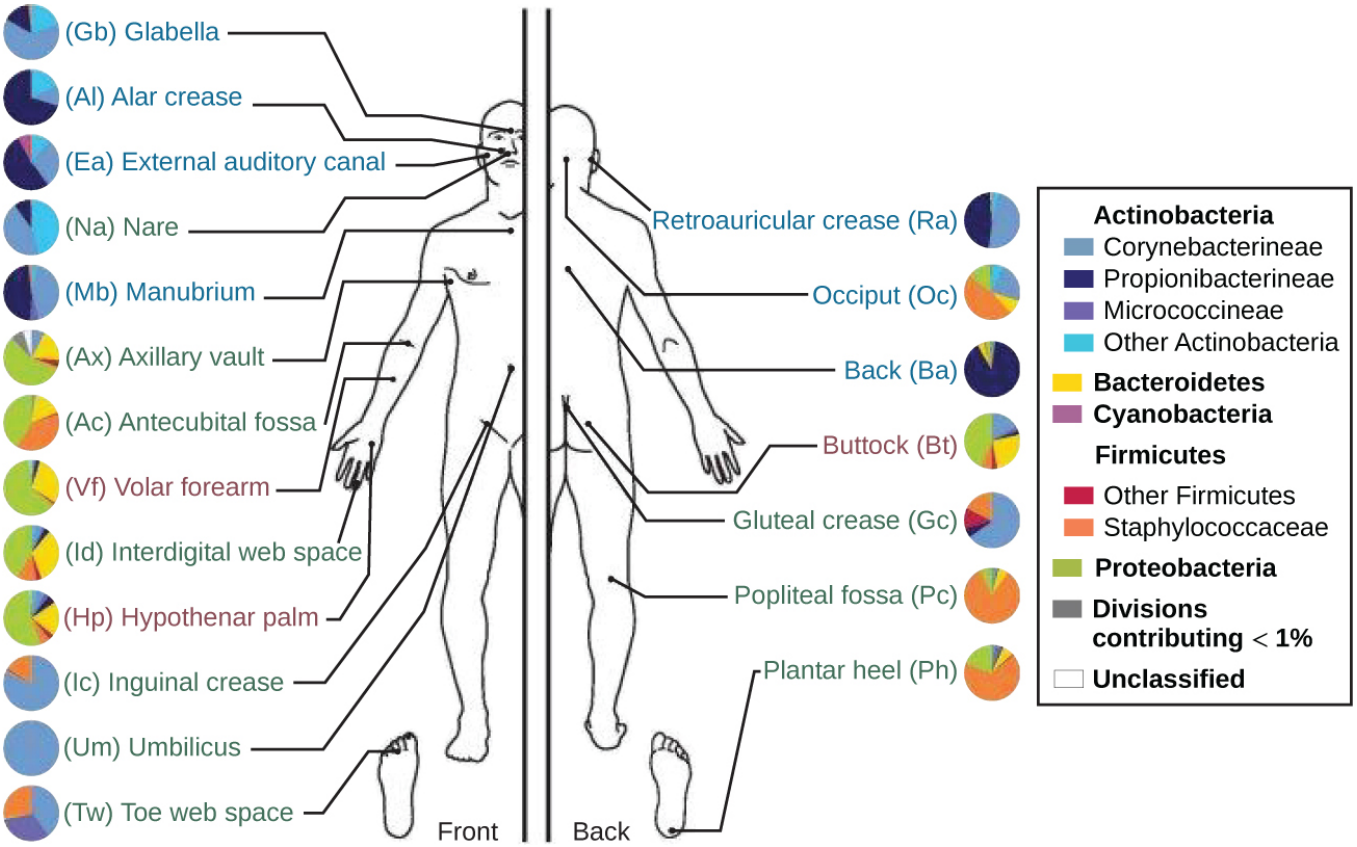


Figure 8.1.1.2: The normal microbiota varies on different regions of the skin, especially in dry versus moist areas. The figure shows the major organisms commonly found in different locations of a healthy individual's skin and external mucosa. Note that there is significant variation among individuals. (credit: modification of work by National Human Genome Research Institute)

? Exercise 8.1.1.3

What are the four most common bacteria that are part of the normal skin microbiota?

Infections of the Skin

While the microbiota of the skin can play a protective role, it can also cause harm in certain cases. Often, an opportunistic pathogen residing in the skin microbiota of one individual may be transmitted to another individual more susceptible to an infection. For example, methicillin-resistant *Staphylococcus aureus* (MRSA) can often take up residence in the nares of health care workers and hospital patients; though harmless on intact, healthy skin, MRSA can cause infections if introduced into other parts of the body, as might occur during surgery or via a post-surgical incision or wound. This is one reason why clean surgical sites are so important.

Injury or damage to the skin can allow microbes to enter deeper tissues, where nutrients are more abundant and the environment is more conducive to bacterial growth. Wound infections are common after a puncture or laceration that damages the physical barrier of the skin. Microbes may infect structures in the dermis, such as hair follicles and glands, causing a localized infection, or they may reach the bloodstream, which can lead to a systemic infection.

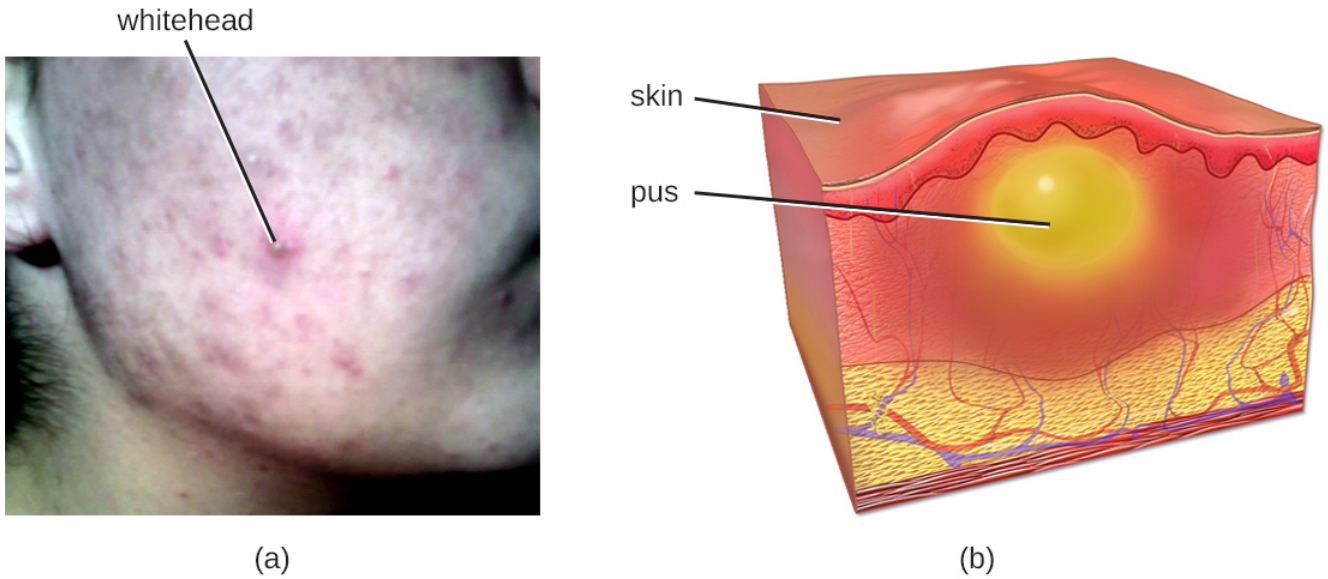


Figure 8.1.1.3: (a) Acne is a bacterial infection of the skin that manifests as a rash of inflamed hair follicles (folliculitis). The large whitehead near the center of the cheek is an infected hair follicle that has become purulent (or suppurative), leading to the formation of a furuncle. (b) An abscess is a pus-filled lesion. (credit b: modification of work by Bruce Blaus)

In some cases, infectious microbes can cause a variety of rashes or lesions that differ in their physical characteristics. These rashes can be the result of inflammation reactions or direct responses to toxins produced by the microbes. Table 8.1.1.1 lists some of the medical terminology used to describe skin lesions and rashes based on their characteristics; Figure 8.1.1.3 and Figure 8.1.1.4 illustrate some of the various types of skin lesions. It is important to note that many different diseases can lead to skin conditions of very similar appearance; thus the terms used in the table are generally not exclusive to a particular type of infection or disease.

Table 8.1.1.1: Some Medical Terms Associated with Skin Lesions and Rashes

Term	Definition
abscess	localized collection of pus
bulla (pl., bullae)	fluid-filled blister no more than 5 mm in diameter
carbuncle	deep, pus-filled abscess generally formed from multiple furuncles
crust	dried fluids from a lesion on the surface of the skin
cyst	encapsulated sac filled with fluid, semi-solid matter, or gas, typically located just below the upper layers of skin
folliculitis	a localized rash due to inflammation of hair follicles
furuncle (boil)	pus-filled abscess due to infection of a hair follicle
macules	smooth spots of discoloration on the skin
papules	small raised bumps on the skin
pseudocyst	lesion that resembles a cyst but with a less defined boundary
purulent	pus-producing; suppurative
pustules	fluid- or pus-filled bumps on the skin
pyoderma	any suppurative (pus-producing) infection of the skin
suppurative	producing pus; purulent
ulcer	break in the skin; open sore
vesicle	small, fluid-filled lesion
wheal	swollen, inflamed skin that itches or burns, such as from an insect bite

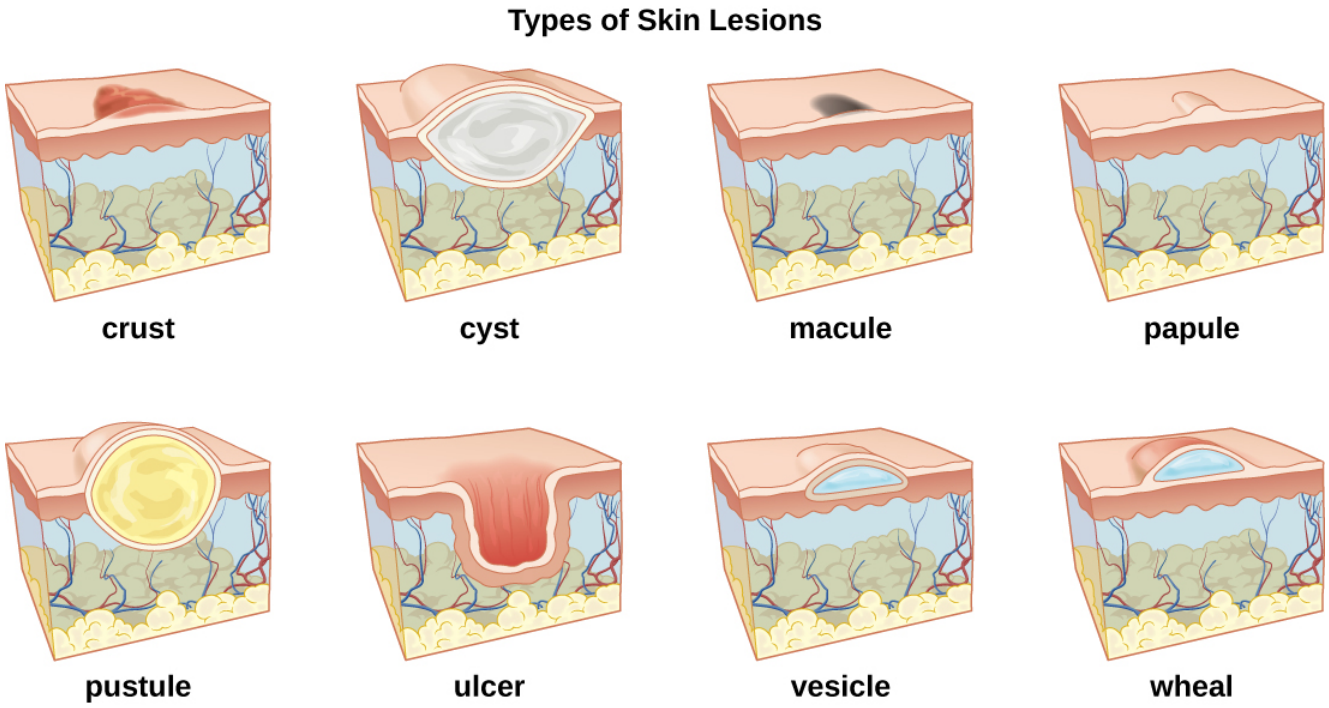


Figure 8.1.1.4: Numerous causes can lead to skin lesions of various types, some of which are very similar in appearance. (credit: modification of work by Bruce Blaus)

? Exercise 8.1.1.4

How can asymptomatic health care workers transmit bacteria such as MRSA to patients?

Anatomy and Microbiota of the Eye

Although the eye and skin have distinct anatomy, they are both in direct contact with the external environment. An important component of the eye is the nasolacrimal drainage system, which serves as a conduit for the fluid of the eye, called tears. Tears flow from the external eye to the nasal cavity by the lacrimal apparatus, which is composed of the structures involved in tear production (Figure 8.1.1.5). The lacrimal gland, above the eye, secretes tears to keep the eye moist. There are two small openings, one on the inside edge of the upper eyelid and one on the inside edge of the lower eyelid, near the nose. Each of these openings is called a lacrimal punctum. Together, these lacrimal puncta collect tears from the eye that are then conveyed through lacrimal ducts to a reservoir for tears called the lacrimal sac**,** also known as the dacrocyst or tear sac.

From the sac, tear fluid flows via a nasolacrimal duct to the inner nose. Each nasolacrimal duct is located underneath the skin and passes through the bones of the face into the nose. Chemicals in tears, such as defensins, lactoferrin, and lysozyme, help to prevent colonization by pathogens. In addition, mucins facilitate removal of microbes from the surface of the eye.

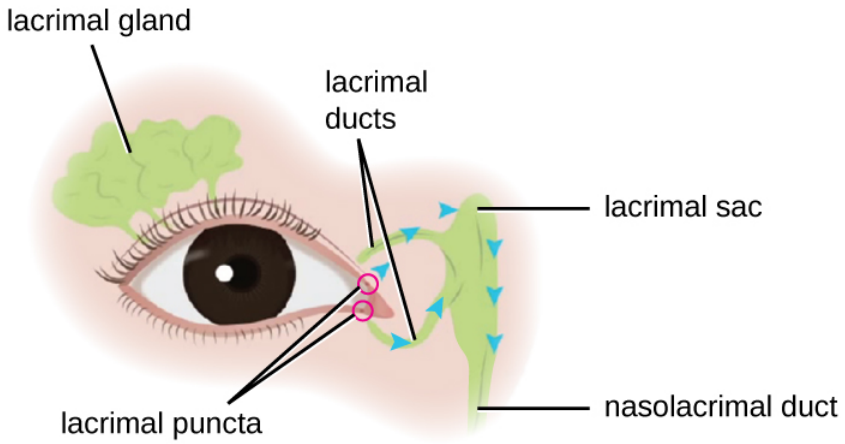


Figure 8.1.1.5: The lacrimal apparatus includes the structures of the eye associated with tear production and drainage. (credit: modification of work by "Evidence Based Medical Educator Inc."/YouTube)

The surfaces of the eyeball and inner eyelid are mucous membranes called conjunctiva. The normal conjunctival microbiota has not been well characterized, but does exist. One small study (part of the Ocular Microbiome project) found twelve genera that were consistently present in the conjunctiva.[4] These microbes are thought to help defend the membranes against pathogens. However, it is still unclear which microbes may be transient and which may form a stable microbiota.[5]

Use of contact lenses can cause changes in the normal microbiota of the conjunctiva by introducing another surface into the natural anatomy of the eye. Research is currently underway to better understand how contact lenses may impact the normal microbiota and contribute to eye disease.

The watery material inside of the eyeball is called the vitreous humor. Unlike the conjunctiva, it is protected from contact with the environment and is almost always sterile, with no normal microbiota (Figure 8.1.1.6).

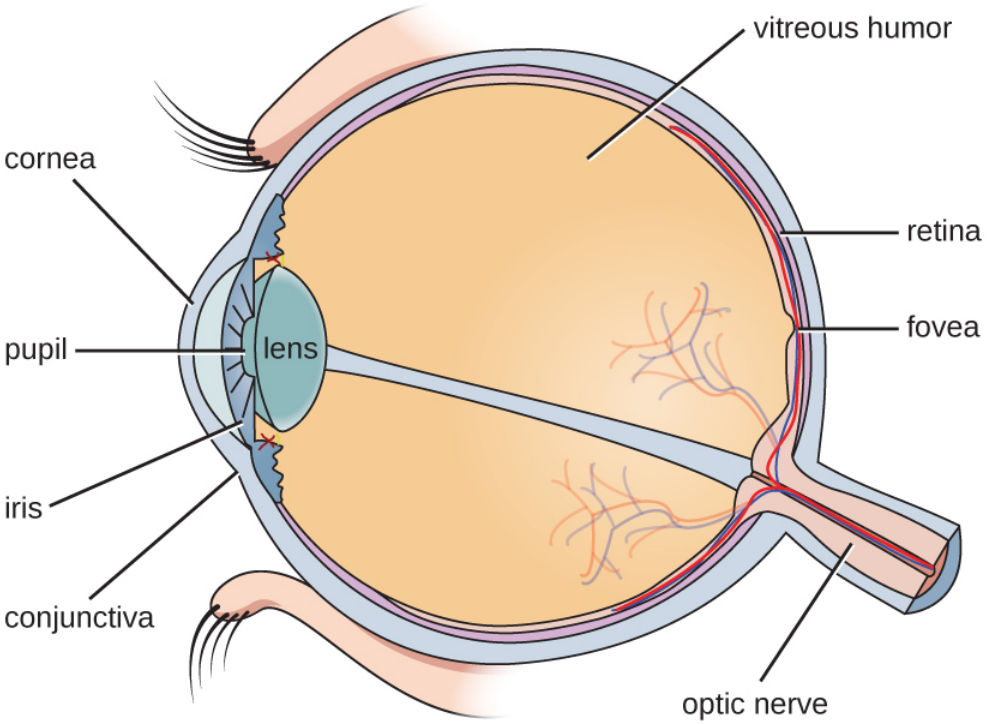


Figure 8.1.1.6: Some microbes live on the conjunctiva of the human eye, but the vitreous humor is sterile.

Infections of the Eye

The conjunctiva is a frequent site of infection of the eye; like other mucous membranes, it is also a common portal of entry for pathogens. Inflammation of the conjunctiva is called conjunctivitis, although it is commonly known as pinkeyebecause of the pink

appearance in the eye. Infections of deeper structures, beneath the cornea, are less common (Figure 8.1.1.7). Conjunctivitis occurs in multiple forms. It may be acute or chronic. Acute purulent conjunctivitis is associated with pus formation, while acute hemorrhagic conjunctivitis is associated with bleeding in the conjunctiva. The term blepharitis refers to an inflammation of the eyelids, while keratitis refers to an inflammation of the cornea (Figure 8.1.1.7); keratoconjunctivitis is an inflammation of both the cornea and the conjunctiva, and dacryocystitis is an inflammation of the lacrimal sac that can often occur when a nasolacrimal duct is blocked.



(a) (b) (c)

Figure 8.1.1.7: (a) Conjunctivitis is inflammation of the conjunctiva. (b) Blepharitis is inflammation of the eyelids. (c) Keratitis is inflammation of the cornea. (credit a: modification of work by Lopez-Prats MJ, Sanz Marco E, Hidalgo-Mora JJ, Garcia-Delpech S, Diaz-Llopis M; credit b, c: modification of work by Centers for Disease Control and Prevention)

Infections leading to conjunctivitis, blepharitis, keratoconjunctivitis, or dacryocystitis may be caused by bacteria or viruses, but allergens, pollutants, or chemicals can also irritate the eye and cause inflammation of various structures. Viral infection is a more likely cause of conjunctivitis in cases with symptoms such as fever and watery discharge that occurs with upper respiratory infection and itchy eyes. Table 8.1.1.2 summarizes some common forms of conjunctivitis and blepharitis.

Table 8.1.1.2: Types of Conjunctivities and Blepharitis

Condition	Description	Causative Agent(s)
Acute purulent conjunctivitis	Conjunctivitis with purulent discharge	Bacterial (*Haemophilus*, *Staphylococcus*)
Acute hemorrhagic conjunctivitis	Involves subconjunctival hemorrhages	Viral (Picornaviradae)
Acute ulcerative blepharitis	Infection involving eyelids; pustules and ulcers may develop	Bacterial (*Staphylococcal*) or viral (herpes simplex, varicella-zoster, etc.)
Follicular conjunctivitis	Inflammation of the conjunctiva with nodules (dome-shaped structures that are red at the base and pale on top)	Viral (adenovirus and others); environmental irritants
Dacryocystitis	Inflammation of the lacrimal sac often associated with a plugged nasolacrimal duct	Bacterial (*Haemophilus*, *Staphylococcus*, *Streptococcus*)
Keratitis	Inflammation of cornea	Bacterial, viral, or protozoal; environmental irritants
Keratoconjunctivitis	Inflammation of cornea and conjunctiva	Bacterial, viral (adenoviruses), or other causes (including dryness of the eye)
Nonulcerative blepharitis	Inflammation, irritation, redness of the eyelids without ulceration	Environmental irritants; allergens
Papillary conjunctivitis	Inflammation of the conjunctiva; nodules and papillae with red tops develop	Environmental irritants; allergens

? Exercise 8.1.1.5

How does the lacrimal apparatus help to prevent eye infections?

Key Concepts and Summary

- Human skin consists of two main layers, the **epidermis** and **dermis**, which are situated on top of the **hypodermis**, a layer of connective tissue.
- The skin is an effective physical barrier against microbial invasion.
- The skin's relatively dry environment and normal microbiota discourage colonization by transient microbes.
- The skin's normal microbiota varies from one region of the body to another.
- The **conjunctiva** of the eye is a frequent site for microbial infection, but deeper eye infections are less common; multiple types of conjunctivitis exist.

Footnotes

1. 1 Belkaid, Y., and J.A. Segre. "Dialogue Between Skin Microbiota and Immunity," *Science* 346 (2014) 6212:954–959.
2. 2 Foulongne, Vincent, et al. "Human Skin Microbiota: High Diversity of DNA Viruses Identified on the Human Skin by High Throughput Sequencing." *PLoS ONE* (2012) 7(6): e38499. doi: 10.1371/journal.pone.0038499.
3. 3 Robinson, C.M., and J.K. Pfeiffer. "Viruses and the Microbiota." *Annual Review of Virology* (2014) 1:55–59. doi: 10.1146/annurev-virology-031413-085550.
4. 4 Abelson, M.B., Lane, K., and Slocum, C.. "The Secrets of Ocular Microbiomes." *Review of Ophthalmology* June 8, 2015. www.reviewofophthalmology.com...isease/c/55178. Accessed Sept 14, 2016.
5. 5 Shaikh-Lesko, R. "Visualizing the Ocular Microbiome." *The Scientist* May 12, 2014. http://www.the-scientist.com/?articl...lar-Microbiome. Accessed Sept 14, 2016.

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8.1.2: Bacterial Infections of the Skin and Eyes

Learning Objectives

- Identify the most common bacterial pathogens that cause infections of the skin and eyes
- Compare the major characteristics of specific bacterial diseases affecting the skin and eyes

Despite the skin's protective functions, infections are common. Gram-positive *Staphylococcus* spp. and *Streptococcus* spp. are responsible for many of the most common skin infections. However, many skin conditions are not strictly associated with a single pathogen. Opportunistic pathogens of many types may infect skin wounds, and individual cases with identical symptoms may result from different pathogens or combinations of pathogens.

In this section, we will examine some of the most important bacterial infections of the skin and eyes and discuss how biofilms can contribute to and exacerbate such infections. Key features of bacterial skin and eye infections are also summarized in the Disease Profile boxes throughout this section.

Staphylococcal Infections of the Skin

Staphylococcus species are commonly found on the skin, with *S. epidermidis* and *S. hominis* being prevalent in the normal microbiota. *S. aureus* is also commonly found in the nasal passages and on healthy skin, but pathogenic strains are often the cause of a broad range of infections of the skin and other body systems.

S. aureus is quite contagious. It is spread easily through skin-to-skin contact, and because many people are chronic nasal carriers (asymptomatic individuals who carry *S. aureus* in their nares), the bacteria can easily be transferred from the nose to the hands and then to fomites or other individuals. Because it is so contagious, *S. aureus* is prevalent in most community settings. This prevalence is particularly problematic in hospitals, where antibiotic-resistant strains of the bacteria may be present, and where immunocompromised patients may be more susceptible to infection. Resistant strains include methicillin-resistant *S. aureus* (MRSA), which can be acquired through health-care settings (hospital-acquired MRSA, or HA-MRSA) or in the community (community-acquired MRSA, or CA-MRSA). Hospital patients often arrive at health-care facilities already colonized with antibiotic-resistant strains of *S. aureus* that can be transferred to health-care providers and other patients. Some hospitals have attempted to detect these individuals in order to institute prophylactic measures, but they have had mixed success (see Eye on Ethics: Screening Patients for MRSA).

When a staphylococcal infection develops, choice of medication is important. As discussed above, many staphylococci (such as MRSA) are resistant to some or many antibiotics. Thus, antibiotic sensitivity is measured to identify the most suitable antibiotic. However, even before receiving the results of sensitivity analysis, suspected *S. aureus* infections are often initially treated with drugs known to be effective against MRSA, such as trimethoprim-sulfamethoxazole(TMP/SMZ), clindamycin, a tetracycline (doxycycline or minocycline), or linezolid.

The pathogenicity of staphylococcal infections is often enhanced by characteristic chemicals secreted by some strains. Staphylococcal virulence factors include hemolysins called staphylolysins, which are cytotoxic for many types of cells, including skin cells and white blood cells. Virulent strains of *S. aureus* are also coagulase-positive, meaning they produce coagulase, a plasma-clotting protein that is involved in abscess formation. They may also produce leukocidins, which kill white blood cells and can contribute to the production of pus and Protein A, which inhibits phagocytosis by binding to the constant region of antibodies. Some virulent strains of *S. aureus* also produce other toxins, such as toxic shock syndrome toxin-1 (see Virulence Factors of Bacterial and Viral Pathogens).

To confirm the causative agent of a suspected staphylococcal skin infection, samples from the wound are cultured. Under the microscope, gram-positive *Staphylococcus* species have cellular arrangements that form grapelike clusters; when grown on blood agar, colonies have a unique pigmentation ranging from opaque white to cream. A catalase testis used to distinguish *Staphylococcus* from *Streptococcus*, which is also a genus of gram-positive cocci and a common cause of skin infections. *Staphylococcus* species are catalase-positive while *Streptococcus* species are catalase-negative.

Other tests are performed on samples from the wound in order to distinguish coagulase-positive species of *Staphylococcus* (CoPS) such as *S. aureus* from common coagulase-negative species (CoNS) such as *S. epidermidis*. Although CoNS are less likely than CoPS to cause human disease, they can cause infections when they enter the body, as can sometimes occur via catheters, indwelling medical devices, and wounds. Passive agglutination testing can be used to distinguish CoPS from CoNS. If the sample is coagulase-positive, the sample is generally presumed to contain *S. aureus*. Additional genetic testing would be necessary to identify the particular strain of *S. aureus*.

Another way to distinguish CoPS from CoNS is by culturing the sample on mannitol salt agar (MSA). *Staphylococcus* species readily grow on this medium because they are tolerant of the high concentration of sodium chloride (7.5% NaCl). However, CoPS such as *S. aureus* ferment mannitol (which will be evident on a MSA plate), whereas CoNS such as *S. epidermidis* do not ferment mannitol but can be distinguished by the fermentation of other sugars such as lactose, malonate, and raffinose (Figure 8.1.2.1).

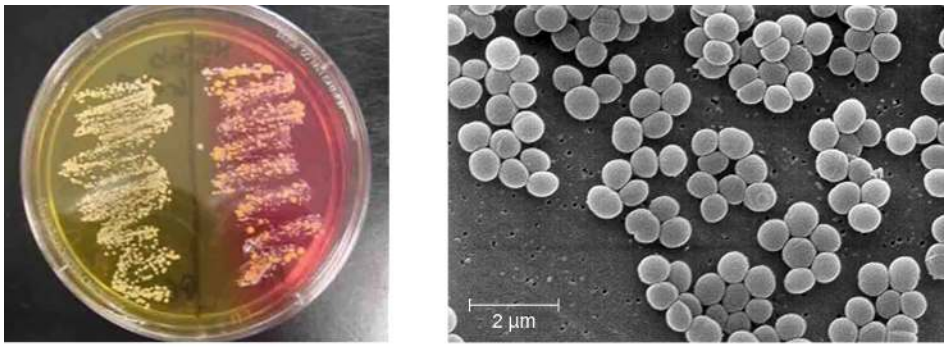


Figure 8.1.2.1: (a) A mannitol salt agar plate is used to distinguish different species of staphylococci. In this plate, *S. aureus* is on the left and *S. epidermidis* is in the right. Because *S. aureus* is capable of fermenting mannitol, it produces acids that cause the color to change to yellow. (b) This scanning electron micrograph shows the characteristic grapelike clusters of *S. aureus*. (credit a: modification of work by "ScienceProfOnline"/YouTube; credit b: modification of work by Centers for Disease Control and Prevention)

Screening Patients for MRSA

According to the CDC, 86% of invasive MRSA infections are associated in some way with healthcare, as opposed to being community-acquired. In hospitals and clinics, asymptomatic patients who harbor MRSA may spread the bacteria to individuals who are more susceptible to serious illness.

In an attempt to control the spread of MRSA, hospitals have tried screening patients for MRSA. If patients test positive following a nasal swab test, they can undergo decolonization using chlorhexidine washes or intranasal mupirocin. Some studies have reported substantial reductions in MRSA disease following implementation of these protocols, while others have not. This is partly because there is no standard protocol for these procedures. Several different MRSA identification tests may be used, some involving slower culturing techniques and others rapid testing. Other factors, such as the effectiveness of general hand-washing protocols, may also play a role in helping to prevent MRSA transmission. There are still other questions that need to be addressed: How frequently should patients be screened? Which individuals should be tested? From where on the body should samples be collected? Will increased resistance develop from the decolonization procedures?

Even if identification and decolonization procedures are perfected, ethical questions will remain. Should patients have the right to decline testing? Should a patient who tests positive for MRSA have the right to decline the decolonization procedure, and if so, should hospitals have the right to refuse treatment to the patient? How do we balance the individual's right to receive care with the rights of other patients who could be exposed to disease as a result?

Superficial Staphylococcal Infections

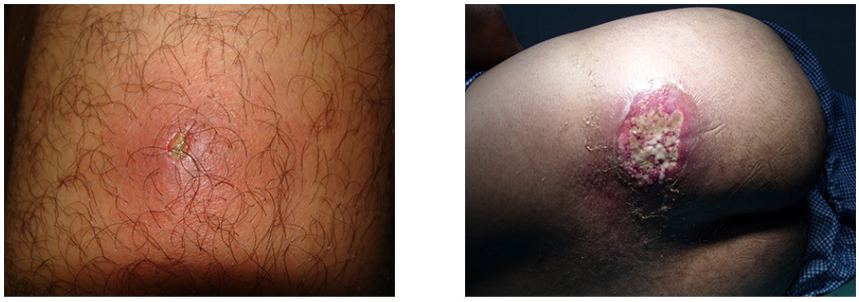
S. aureus is often associated with pyoderma, skin infections that are purulent. Pus formation occurs because many strains of *S. aureus* produce leukocidins, which kill white blood cells. These purulent skin infections may initially manifest as folliculitis, but can lead to furuncles or deeper abscesses called carbuncles.

Folliculitis generally presents as bumps and pimples that may be itchy, red, and/or pus-filled. In some cases, folliculitis is self-limiting, but if it continues for more than a few days, worsens, or returns repeatedly, it may require medical treatment. Sweat, skin injuries, ingrown hairs, tight clothing, irritation from shaving, and skin conditions can all contribute to folliculitis. Avoidance of tight clothing and skin irritation can help to prevent infection, but topical antibiotics (and sometimes other treatments) may also help. Folliculitis can be identified by skin inspection; treatment is generally started without first culturing and identifying the causative agent.

In contrast, furuncles (boils) are deeper infections (Figure 8.1.2.2). They are most common in those individuals (especially young adults and teenagers) who play contact sports, share athletic equipment, have poor nutrition, live in close quarters, or have weakened immune systems. Good hygiene and skin care can often help to prevent furuncles from becoming more infective, and they generally resolve on their own. However, if furuncles spread, increase in number or size, or lead to systemic symptoms such as fever and chills, then medical care is needed. They may sometimes need to be drained (at which time the pathogens can be cultured) and treated with antibiotics.

When multiple boils develop into a deeper lesion, it is called a carbuncle (Figure 8.1.2.2). Because carbuncles are deeper, they are more commonly associated with systemic symptoms and a general feeling of illness. Larger, recurrent, or worsening carbuncles require medical treatment, as do those associated with signs of illness such as fever. Carbuncles generally need to be drained and treated with antibiotics. While carbuncles are relatively easy to identify visually, culturing and laboratory analysis of the wound may be recommended for some infections because antibiotic resistance is relatively common.

Proper hygiene is important to prevent these types of skin infections or to prevent the progression of existing infections.



(a) (b)

Figure 8.1.2.2: Furuncles (boils) and carbuncles are infections of the skin often caused by *Staphylococcus* bacteria. (a) A furuncle contains pus and exhibits swelling. (b) A carbuncle is a pus-filled lesion that is typically deeper than the furuncle. It often forms from multiple furuncles. (credit a: modification of work by “Mahdouch”/Wikimedia Commons; credit b: modification of work by “Drvgaikwad”/Wikimedia Commons)

Staphylococcal scalded skin syndrome (SSSS) is another superficial infection caused by *S. aureus* that is most commonly seen in young children, especially infants. Bacterial exotoxins first produce erythema (redness of the skin) and then severe peeling of the skin, as might occur after scalding (Figure 8.1.2.3). SSSS is diagnosed by examining characteristics of the skin (which may rub off easily), using blood tests to check for elevated white blood cell counts, culturing, and other methods. Intravenous antibiotics and fluid therapy are used as treatment.



Figure 8.1.2.3: A newborn with staphylococcal scalded skin syndrome (SSSS), which results in large regions of peeling, dead skin. (credit: modification of work by D Jeyakumari, R Gopal, M Eswaran, and C MaheshKumar)

Impetigo

The skin infection impetigo causes the formation of vesicles, pustules, and possibly bullae, often around the nose and mouth. Bullae are large, fluid-filled blisters that measure at least 5 mm in diameter. Impetigo can be diagnosed as either nonbullous or bullous. In nonbullous impetigo, vesicles and pustules rupture and become encrusted sores. Typically the crust is yellowish, often with exudate draining from the base of the lesion. In bullous impetigo, the bullae fill and rupture, resulting in larger, draining, encrusted lesions (Figure 8.1.2.4).

Especially common in children, impetigo is particularly concerning because it is highly contagious. Impetigo can be caused by *S. aureus* alone, by *Streptococcus pyogenes* alone, or by coinfection of *S. aureus* and *S. pyogenes*. Impetigo is often diagnosed through observation of its characteristic appearance, although culture and susceptibility testing may also be used.

Topical or oral antibiotic treatment is typically effective in treating most cases of impetigo. However, cases caused by *S. pyogenes* can lead to serious sequelae (pathological conditions resulting from infection, disease, injury, therapy, or other trauma) such as acute glomerulonephritis (AGN), which is severe inflammation in the kidneys.



Figure 8.1.2.4: Impetigo is characterized by vesicles, pustules, or bullae that rupture, producing encrusted sores. (credit: modification of work by FDA)

Nosocomial *S. epidermidis* Infections

Though not as virulent as *S. aureus*, the staphylococcus *S. epidermidis* can cause serious opportunistic infections. Such infections usually occur only in hospital settings. *S. epidermidis* is usually a harmless resident of the normal skin microbiota. However, health-care workers can inadvertently transfer *S. epidermidis* to medical devices that are inserted into the body, such as catheters, prostheses, and indwelling medical devices. Once it has bypassed the skin barrier, *S. epidermidis* can cause infections inside the body that can be difficult to treat. Like *S. aureus*, *S. epidermidis* is resistant to many antibiotics, and localized infections can become systemic if not treated quickly. To reduce the risk of nosocomial (hospital-acquired) *S. epidermidis*, health-care workers must follow strict procedures for handling and sterilizing medical devices before and during surgical procedures.

? Exercise 8.1.2.1

Why are *Staphylococcus aureus* infections often purulent?

Streptococcal Infections of the Skin

Streptococcus are gram-positive cocci with a microscopic morphology that resembles chains of bacteria. Colonies are typically small (1–2 mm in diameter), translucent, entire edge, with a slightly raised elevation that can be either nonhemolytic, alpha-hemolytic, or beta-hemolytic when grown on blood agar (Figure 8.1.2.5). Additionally, they are facultative anaerobes that are catalase-negative.

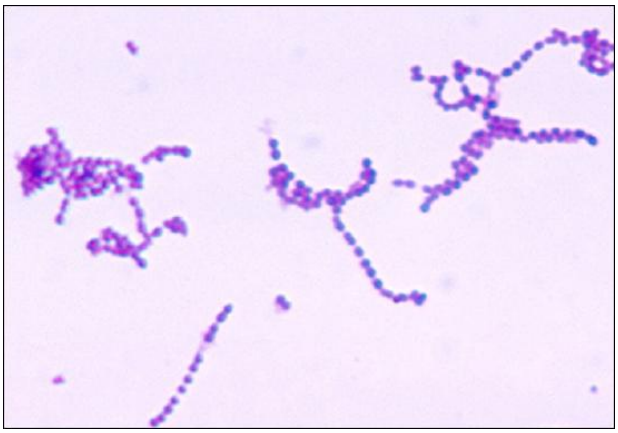


Figure 8.1.2.5: Streptococcus pyogenes forms chains of cocci. (credit: modification of work by Centers for Disease Control and Prevention)

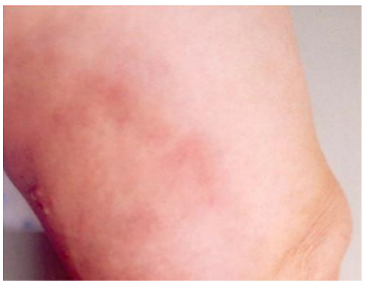
The genus *Streptococcus* includes important pathogens that are categorized in serological Lancefield groups based on the distinguishing characteristics of their surface carbohydrates. The most clinically important streptococcal species in humans is *S. pyogenes*, also known as group A streptococcus (GAS). *S. pyogenes* produces a variety of extracellular enzymes, including streptolysins O and S, hyaluronidase, and streptokinase. These enzymes can aid in transmission and contribute to the inflammatory response.[1] *S. pyogenes* also produces a capsule and M protein, a streptococcal cell wall protein. These virulence factors help the bacteria to avoid phagocytosis while provoking a substantial immune response that contributes to symptoms associated with streptococcal infections.

S. pyogenes causes a wide variety of diseases not only in the skin, but in other organ systems as well. Examples of diseases elsewhere in the body include pharyngitis and scarlet fever, which will be covered in later chapters.

Cellulitis, Erysipelas, and Erythema Nosodum

Common streptococcal conditions of the skin include cellulitis, erysipelas, and erythema nodosum. An infection that develops in the dermis or hypodermis can cause cellulitis, which presents as a reddened area of the skin that is warm to the touch and painful. The causative agent is often *S. pyogenes*, which may breach the epidermis through a cut or abrasion, although cellulitis may also be caused by staphylococci. *S. pyogenes* can also cause erysipelas, a condition that presents as a large, intensely inflamed patch of skin involving the dermis (often on the legs or face). These infections can be suppurative, which results in a bullous form of erysipelas. Streptococcal and other pathogens may also cause a condition called erythema nodosum, characterized by inflammation in the subcutaneous fat cells of the hypodermis. It sometimes results from a streptococcal infection, though other pathogens can also cause the condition. It is not suppurative, but leads to red nodules on the skin, most frequently on the shins (Figure 8.1.2.6).

In general, streptococcal infections are best treated through identification of the specific pathogen followed by treatment based upon that particular pathogen's susceptibility to different antibiotics. Many immunological tests, including agglutination reactions and ELISAs, can be used to detect streptococci. Penicillin is commonly prescribed for treatment of cellulitis and erysipelas because resistance is not widespread in streptococci at this time. In most patients, erythema nodosum is self-limiting and is not treated with antimicrobial drugs. Recommended treatments may include nonsteroidal anti-inflammatory drugs (NSAIDs), cool wet compresses, elevation, and bed rest.


(a)


(b)


(c)

Figure 8.1.2.6: S. pyogenes can cause a variety of skin conditions once it breaches the skin barrier through a cut or wound. (a) Cellulitis presents as a painful, red rash. (b) Erysipelas presents as a raised rash, usually with clear borders. (c) Erythema nodosum is characterized by red lumps or nodules, typically on the lower legs. (credit a: modification of work by "Bassukas ID, Gaitanis G, Zioga A, Boboyianni C, Stergiopoulou C; credit b: modification of work by Centers for Disease Control and Prevention; credit c: modification of work by Dean C, Crow WT)

Necrotizing Fasciitis

Streptococcal infections that start in the skin can sometimes spread elsewhere, resulting in a rare but potentially life-threatening condition called necrotizing fasciitis, sometimes referred to as flesh-eating bacterial syndrome. *S. pyogenes* is one of several species that can cause this rare but potentially-fatal condition; others include *Klebsiella*, *Clostridium*, *Escherichia coli*, *S. aureus*, and *Aeromonas hydrophila*.

Necrotizing fasciitis occurs when the fascia, a thin layer of connective tissue between the skin and muscle, becomes infected. Severe invasive necrotizing fasciitis due to *Streptococcus pyogenes* occurs when virulence factors that are responsible for adhesion and invasion overcome host defenses. *S. pyogenes* invasins allow bacterial cells to adhere to tissues and establish infection. Bacterial proteases unique to *S. pyogenes* aggressively infiltrate and destroy host tissues, inactivate complement, and prevent neutrophil migration to the site of infection. The infection and resulting tissue death can spread very rapidly, as large areas of skin become detached and die. Treatment generally requires debridement (surgical removal of dead or infected tissue) or amputation of infected limbs to stop the spread of the infection; surgical treatment is supplemented with intravenous antibiotics and other therapies (Figure 8.1.2.7).

Necrotizing fasciitis does not always originate from a skin infection; in some cases there is no known portal of entry. Some studies have suggested that experiencing a blunt force trauma can increase the risk of developing streptococcal necrotizing fasciitis.[2]


(a)

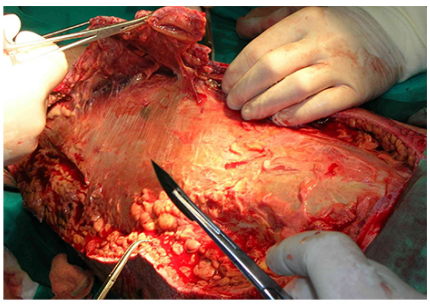

(b)

Figure 8.1.2.7: (a) The left leg of this patient shows the clinical features of necrotizing fasciitis. (b) The same patient's leg is surgically debrided to remove the infection. (credit a, b: modification of work by Piotr Smuszkiewicz, Iwona Trojanowska, and Hanna Tomczak)

? Exercise 8.1.2.2

How do staphylococcal infections differ in general presentation from streptococcal infections?

Clinical Focus: Part 2

Observing that Sam's wound is purulent, the doctor tells him that he probably has a bacterial infection. She takes a sample from the lesion to send for laboratory analysis, but because it is Friday, she does not expect to receive the results until the following Monday. In the meantime, she prescribes an over-the-counter topical antibiotic ointment. She tells Sam to keep the wound clean and apply a new bandage with the ointment at least twice per day.

Exercise 8.1.2.3

1. How would the lab technician determine if the infection is staphylococcal or streptococcal? Suggest several specific methods.
2. What tests might the lab perform to determine the best course of antibiotic treatment?

Pseudomonas Infections of the Skin

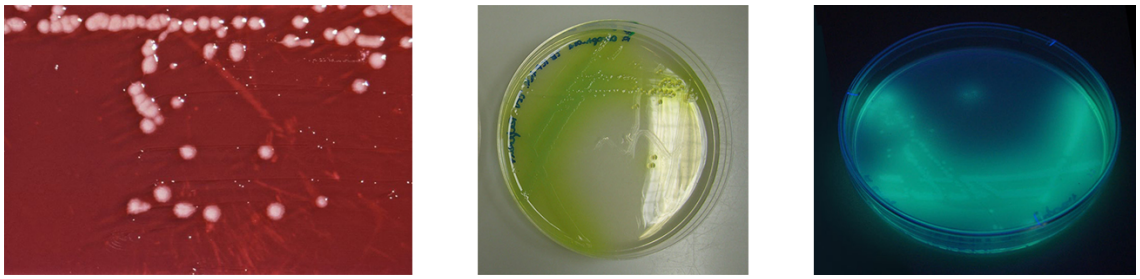
Another important skin pathogen is *Pseudomonas aeruginosa*, a gram-negative, oxidase-positive, aerobic bacillus that is commonly found in water and soil as well as on human skin. *P. aeruginosa* is a common cause of opportunistic infections of wounds and burns. It can also cause hot tub rash, a condition characterized by folliculitis that frequently afflicts users of pools and hot tubs (recall the Clinical Focus case in Microbial Biochemistry). *P. aeruginosa* is also the cause of otitis externa (swimmer's ear), an infection of the ear canal that causes itching, redness, and discomfort, and can progress to fever, pain, and swelling (Figure 8.1.2.8).



(a) (b)

Figure 8.1.2.8: (a) Hot tub folliculitis presents as an itchy red rash. It is typically caused by *P. aeruginosa*, a bacterium that thrives in wet, warm environments such as hot tubs. (b) Otitis externa (swimmer's ear) may also be caused by *P. aeruginosa* or other bacteria commonly found in water. Inflammation of the outer ear and ear canal can lead to painful swelling. (credit b: modification of work by Klaus D. Peter)

Wounds infected with *P. aeruginosa* have a distinctive odor resembling grape soda or fresh corn tortillas. This odor is caused by the 2-aminoacetophenone that is used by *P. aeruginosa* in quorum sensing and contributes to its pathogenicity. Wounds infected with certain strains of *P. aeruginosa* also produce a blue-green pus due to the pigments pyocyanin and pyoverdin, which also contribute to its virulence. Pyocyanin and pyoverdin are siderophores that help *P. aeruginosa* survive in low-iron environments by enhancing iron uptake. *P. aeruginosa* also produces several other virulence factors, including phospholipase C (a hemolysin capable of breaking down red blood cells), exoenzyme S(involved in adherence to epithelial cells), and exotoxin A (capable of causing tissue necrosis). Other virulence factors include a slime that allows the bacterium to avoid being phagocytized, fimbriae for adherence, and proteases that cause tissue damage. *P. aeruginosa* can be detected through the use of cetrimide agar, which is selective for *Pseudomonas* species (Figure 8.1.2.9).



(a) (b) (c)

Figure 8.1.2.9: (a) These *P. aeruginosa* colonies are growing on xylose lysine sodium deoxycholate (XLD) agar. (b) *Pseudomonas* spp. can produce a variety of blue-green pigments. (c) *Pseudomonas* spp. may produce fluorescein, which fluoresces green under ultraviolet light under the right conditions. (credit a: modification of work by Centers for Disease Control and Prevention)

Pseudomonas spp. tend to be resistant to most antibiotics. They often produce β-lactamases, may have mutations affecting porins (small cell wall channels) that affect antibiotic uptake, and may pump some antibiotics out of the cell, contributing to this resistance. Polymyxin B and gentamicin are effective, as are some fluoroquinolones. Otitis externa is typically treated with ear drops containing acetic acid, antibacterials, and/or steroids to reduce inflammation; ear drops may also include antifungals because fungi can sometimes cause or contribute to otitis externa. Wound infections caused by *Pseudomonas* spp. may be treated with topical antibiofilm agents that disrupt the formation of biofilms.

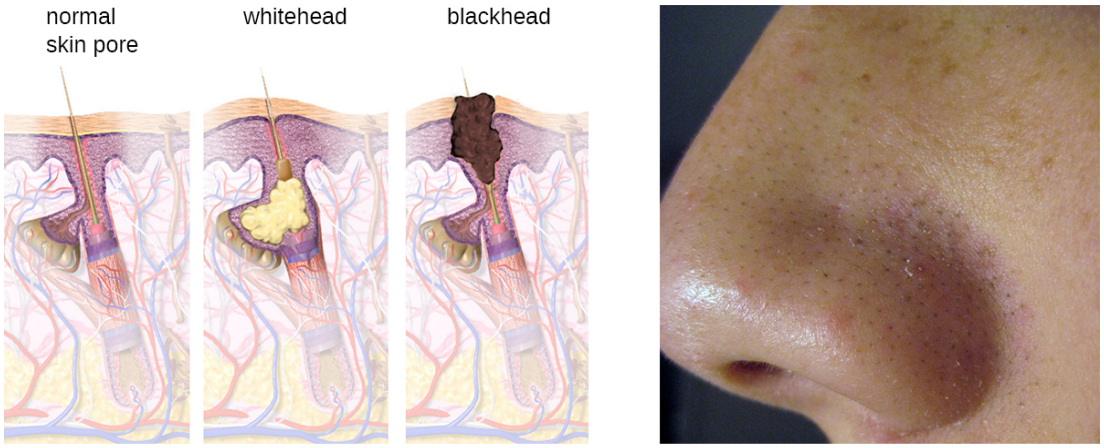
? Exercise 8.1.2.4

Name at least two types of skin infections commonly caused by *Pseudomonas* spp.

Acne

One of the most ubiquitous skin conditions is acne. Acne afflicts nearly 80% of teenagers and young adults, but it can be found in individuals of all ages. Higher incidence among adolescents is due to hormonal changes that can result in overproduction of sebum.

Acne occurs when hair follicles become clogged by shed skin cells and sebum, causing non-inflammatory lesions called comedones. Comedones (singular “comedo”) can take the form of whitehead and blackhead pimples. Whiteheads are covered by skin, whereas blackhead pimples are not; the black color occurs when lipids in the clogged follicle become exposed to the air and oxidize (Figure 8.1.2.10).



(a) (b)

Figure 8.1.2.10: (a) Acne is characterized by whitehead and blackhead comedones that result from clogged hair follicles. (b) Blackheads, visible as black spots on the skin, have a dark appearance due to the oxidation of lipids in sebum via exposure to the air. (credit a: modification of work by Bruce Blaus)

Often comedones lead to infection by *Propionibacterium acnes*, a gram-positive, non-spore-forming, aerotolerant anaerobic bacillus found on skin that consumes components of sebum. *P. acnes* secretes enzymes that damage the hair follicle, causing inflammatory lesions that may include papules, pustules, nodules, or pseudocysts, depending on their size and severity.

Treatment of acne depends on the severity of the case. There are multiple ways to grade acne severity, but three levels are usually considered based on the number of comedones, the number of inflammatory lesions, and the types of lesions. Mild acne is treated with topical agents that may include salicylic acid (which helps to remove old skin cells) or retinoids (which have multiple mechanisms, including the reduction of inflammation). Moderate acne may be treated with antibiotics (erythromycin, clindamycin), acne creams (e.g., benzoyl peroxide), and hormones. Severe acne may require treatment using strong medications such as isotretinoin (a retinoid that reduces oil buildup, among other effects, but that also has serious side effects such as photosensitivity). Other treatments, such as phototherapy and laser therapy to kill bacteria and possibly reduce oil production, are also sometimes used.

? Exercise 8.1.2.5

What is the role of *Propionibacterium acnes* in causing acne?

Clinical Focus: Resolution

Sam uses the topical antibiotic over the weekend to treat his wound, but he does not see any improvement. On Monday, the doctor calls to inform him that the results from his laboratory tests are in. The tests show evidence of both *Staphylococcus* and *Streptococcus* in his wound. The bacterial species were confirmed using several tests. A passive agglutination test confirmed the presence of *S. aureus*. In this type of test, latex beads with antibodies cause agglutination when *S. aureus* is present. *Streptococcus pyogenes* was confirmed in the wound based on bacitracin (0.04 units) susceptibility as well as latex agglutination tests specific for *S. pyogenes*.

Because many strains of *S. aureus* are resistant to antibiotics, the doctor had also requested an antimicrobial susceptibility test (AST) at the same time the specimen was submitted for identification. The results of the AST indicated no drug resistance for the *Streptococcus* spp.; the *Staphylococcus* spp. showed resistance to several common antibiotics, but were susceptible to cefoxitin and oxacillin. Once Sam began to use these new antibiotics, the infection resolved within a week and the lesion healed.

Anthrax

The zoonotic disease anthrax is caused by *Bacillus anthracis*, a gram-positive, endospore-forming, facultative anaerobe. Anthrax mainly affects animals such as sheep, goats, cattle, and deer, but can be found in humans as well. Sometimes called wool sorter's disease, it is often transmitted to humans through contact with infected animals or animal products, such as wool or hides. However, exposure to *B. anthracis* can occur by other means, as the endospores are widespread in soils and can survive for long periods of time, sometimes for hundreds of years.

The vast majority of anthrax cases (95–99%) occur when anthrax endospores enter the body through abrasions of the skin.[3] This form of the disease is called cutaneous anthrax. It is characterized by the formation of a nodule on the skin; the cells within the nodule die, forming a black eschar, a mass of dead skin tissue (Figure 8.1.2.11). The localized infection can eventually lead to bacteremia and septicemia. If untreated, cutaneous anthrax can cause death in 20% of patients.[4] Once in the skin tissues, *B. anthracis* endospores germinate and produce a capsule, which prevents the bacteria from being phagocytized, and two binary exotoxins that cause edema and tissue damage. The first of the two exotoxins consists of a combination of protective antigen (PA) and an enzymatic lethal factor (LF), forming lethal toxin (LeTX). The second consists of protective antigen (PA) and an edema factor (EF), forming edema toxin (EdTX).



(a)



(b)

Figure 8.1.2.11: (a) Cutaneous anthrax is an infection of the skin by *B. anthracis*, which produces tissue-damaging exotoxins. Dead tissues accumulating in this nodule have produced a small black eschar. (b) Colonies of *B. anthracis* grown on sheep's blood agar. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Less commonly, anthrax infections can be initiated through other portals of entry such as the digestive tract (gastrointestinal anthrax) or respiratory tract (pulmonary anthrax or inhalation anthrax). Typically, cases of noncutaneous anthrax are more difficult to treat than the cutaneous form. The mortality rate for gastrointestinal anthrax can be up to 40%, even with treatment. Inhalation anthrax, which occurs when anthrax spores are inhaled, initially causes influenza-like symptoms, but mortality rates are approximately 45% in treated individuals and 85% in those not treated. A relatively new form of the disease, injection anthrax, has been reported in Europe in intravenous drug users; it occurs when drugs are contaminated with *B. anthracis*. Patients with injection anthrax show signs and symptoms of severe soft tissue infection that differ clinically from cutaneous anthrax. This often delays diagnosis and treatment, and leads to a high mortality rate.[5]

B. anthracis colonies on blood agar have a rough texture and serrated edges that eventually form an undulating band (Figure 8.1.2.11). Broad spectrum antibiotics such as penicillin, erythromycin, and tetracycline are often effective treatments.

Unfortunately, *B. anthracis* has been used as a biological weapon and remains on the United Nations' list of potential agents of bioterrorism.[6] Over a period of several months in 2001, a number of letters were mailed to members of the news media and the United States Congress. As a result, 11 individuals developed cutaneous anthrax and another 11 developed inhalation anthrax. Those infected included recipients of the letters, postal workers, and two other individuals. Five of those infected with pulmonary anthrax died. The anthrax spores had been carefully prepared to aerosolize, showing that the perpetrator had a high level of expertise in microbiology.[7]

A vaccine is available to protect individuals from anthrax. However, unlike most routine vaccines, the current anthrax vaccine is unique in both its formulation and the protocols dictating who receives it.[8] The vaccine is administered through five intramuscular injections over a period of 18 months, followed by annual boosters. The US Food and Drug Administration (FDA) has only approved administration of the vaccine prior to exposure for at-risk adults, such as individuals who work with anthrax in a laboratory, some individuals who handle animals or animal products (e.g., some veterinarians), and some members of the United States military. The vaccine protects against cutaneous and inhalation anthrax using cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *B. anthracis*.[9] The FDA has not approved the vaccine for routine use *after* exposure to anthrax, but if there were ever an anthrax emergency in the United States, patients could be given anthrax vaccine after exposure to help prevent disease.

? Exercise 8.1.2.6

What is the characteristic feature of a cutaneous anthrax infection?

Bacterial Infections of the Skin

Bacterial infections of the skin can cause a wide range of symptoms and syndromes, ranging from the superficial and relatively harmless to the severe and even fatal. Most bacterial skin infections can be diagnosed by culturing the bacteria and treated with

antibiotics. Antimicrobial susceptibility testing is also often necessary because many strains of bacteria have developed antibiotic resistance. Figure 8.1.2.12 summarizes the characteristics of some common bacterial skin infections.

Bacterial Infections of the Skin				
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Antimicrobial Drugs**
Acne	*Propionibacterium acnes*	Comedones (whiteheads, blackheads); papules, pustules, nodules, or pseudocysts	Not transmissible; clogged pores become infected by normal skin microbiota (*P. acnes*)	Erythromycin, clindamycin
Anthrax (cutaneous)	*Bacillus anthracis*	Eschar at site of infection; may lead to septicemia and can be fatal	Entry of *B. anthracis* endospores through cut or abrasion	Penicillin, erythromycin, or tetracycline
Cellulitis	*Streptococcus pyogenes*	Localized inflammation of dermis and hypodermis; skin red, warm, and painful to the touch	Entry of *S. pyogenes* through cut or abrasion	Oral or intravenous antibiotics (e.g., penicillin)
Erysipelas	*S. pyogenes*	Inflamed, swollen patch of skin, often on face; may be suppurative	Entry of *S. pyogenes* through cut or abrasion	Oral or intravenous antibiotics (e.g., penicillin)
Erythema nodosum	*S. pyogenes*	Small red nodules, often on shins	Associated with other streptococcal infection	None or anti-inflammatory drugs for severe cases
Impetigo	*Staphylococcus aureus*, *S. pyogenes*	Vesicles, pustules, and sometimes bullae around nose and mouth	Highly contagious, especially via contact	Topical or oral antibiotics
Necrotizing fasciitis	*S. pyogenes*, *Klebsiella*, *Clostridium*, others	Infection of fascia and rapidly spreading tissue death; can lead to septic shock and death	Entry of bacteria through cut or abrasion	Intravenous broad-spectrum antibiotics
Otitis externa	*Pseudomonas aeruginosa*	Itching, redness, discomfort of ear canal, progressing to fever, pain, swelling	*P. aeruginosa* enters ear canal via pool or other water	Acidic ear drops with antibiotics, antifungals, steroids
Staphylococcal scalded skin syndrome (SSSS)	*S. aureus*	Erythema and severe peeling of skin	Infection of skin and mucous membranes, especially in children	Intravenous antibiotics, fluid therapy
Wound infections	*P. aeruginosa*, others	Formation of biofilm in or on wound	Exposure of wound to microbes in environment; poor wound hygiene	Polymyxin B, gentamicin, fluoroquinolones, topical anti-biofilm agents

Figure 8.1.2.12: Bacterial infections of the skin

Bacterial Conjunctivitis

Like the skin, the surface of the eye comes in contact with the outside world and is somewhat prone to infection by bacteria in the environment. Bacterial conjunctivitis (pinkeye) is a condition characterized by inflammation of the conjunctiva, often accompanied by a discharge of sticky fluid (described as acute purulent conjunctivitis) (Figure 8.1.2.13). Conjunctivitis can affect one eye or both, and it usually does not affect vision permanently. Bacterial conjunctivitis is most commonly caused by *Haemophilus influenzae*, but can also be caused by other species such as *Moraxella catarrhalis*, *S. pneumoniae*, and *S. aureus*. The causative agent may be identified using bacterial cultures, Gram stain, and diagnostic biochemical, antigenic, or nucleic acid profile tests of the isolated pathogen. Bacterial conjunctivitis is very contagious, being transmitted via secretions from infected individuals, but it is also self-limiting. Bacterial conjunctivitis usually resolves in a few days, but topical antibiotics are sometimes prescribed. Because this condition is so contagious, medical attention is recommended whenever it is suspected. Individuals who use contact lenses should discontinue their use when conjunctivitis is suspected. Certain symptoms, such as blurred vision, eye pain, and light sensitivity, can be associated with serious conditions and require medical attention.

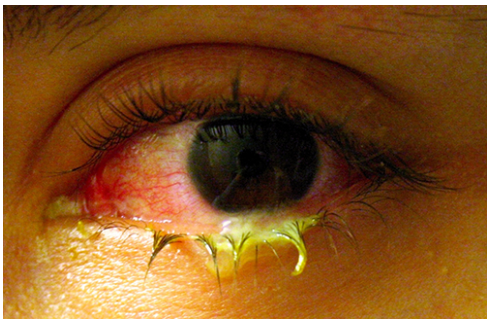


Figure 8.1.2.13: Acute, purulent, bacterial conjunctivitis causes swelling and redness in the conjunctiva, the membrane lining the whites of the eyes and the inner eyelids. It is often accompanied by a yellow, green, or white discharge, which can dry and become encrusted on the eyelashes. (credit: “Tanalai”/Wikimedia Commons)

Neonatal Conjunctivitis

Newborns whose mothers have certain sexually transmitted infections are at risk of contracting ophthalmia neonatorum or inclusion conjunctivitis, which are two forms of neonatal conjunctivitis contracted through exposure to pathogens during passage through the birth canal. Gonococcal ophthalmia neonatorum is caused by *Neisseria gonorrhoeae*, the bacterium that causes the STD gonorrhea (Figure 8.1.2.14). Inclusion (chlamydial) conjunctivitis is caused by *Chlamydia trachomatis*, the anaerobic, obligate, intracellular parasite that causes the STD chlamydia.

To prevent gonoccocal ophthalmia neonatorum, silver nitrate ointments were once routinely applied to all infants’ eyes shortly after birth; however, it is now more common to apply antibacterial creams or drops, such as erythromycin. Most hospitals are required by law to provide this preventative treatment to all infants, because conjunctivitis caused by *N. gonorrhoeae*, *C. trachomatis*, or other bacteria acquired during a vaginal delivery can have serious complications. If untreated, the infection can spread to the cornea, resulting in ulceration or perforation that can cause vision loss or even permanent blindness. As such, neonatal conjunctivitis is treated aggressively with oral or intravenous antibiotics to stop the spread of the infection. Causative agents of inclusion conjunctivitis may be identified using bacterial cultures, Gram stain, and diagnostic biochemical, antigenic, or nucleic acid profile tests.

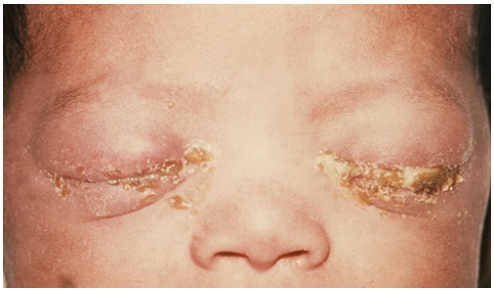


Figure 8.1.2.14: A newborn suffering from gonoccocal opthalmia neonatorum. Left untreated, purulent discharge can scar the cornea, causing loss of vision or permanent blindness. (credit: Centers for Disease Control and Prevention)

? Exercise 8.1.2.7

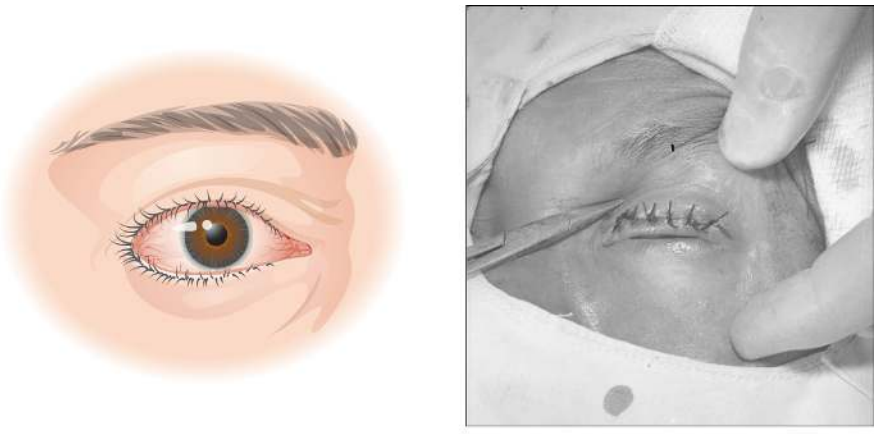
Compare and contrast bacterial conjunctivitis with neonatal conjunctivitis.

Trachoma

Trachoma, or granular conjunctivitis, is a common cause of preventable blindness that is rare in the United States but widespread in developing countries, especially in Africa and Asia. The condition is caused by the same species that causes neonatal inclusion conjunctivitis in infants, *Chlamydia trachomatis*. *C. trachomatis* can be transmitted easily through fomites such as contaminated towels, bed linens, and clothing and also by direct contact with infected individuals. *C. trachomatis* can also be spread by flies that transfer infected mucous containing *C. trachomatis* from one human to another.

Infection by *C. trachomatis* causes chronic conjunctivitis, which leads to the formation of necrotic follicles and scarring in the upper eyelid. The scars turn the eyelashes inward (a condition known as trichiasis) and mechanical abrasion of the cornea leads to

blindness (Figure 8.1.2.15). Antibiotics such as azithromycin are effective in treating trachoma, and outcomes are good when the disease is treated promptly. In areas where this disease is common, large public health efforts are focused on reducing transmission by teaching people how to avoid the risks of the infection.



(a) (b)

Figure 8.1.2.15: (a) If trachoma is not treated early with antibiotics, scarring on the eyelid can lead to trichiasis, a condition in which the eyelashes turn inward. (b) Trichiasis leads to blindness if not corrected by surgery, as shown here. (credit b: modification of work by Otis Historical Archives National Museum of Health & Medicine)

? Exercise 8.1.2.8

Why is trachoma rare in the United States?

SAFE Eradication of Trachoma

Though uncommon in the United States and other developed nations, trachoma is the leading cause of preventable blindness worldwide, with more than 4 million people at immediate risk of blindness from trichiasis. The vast majority of those affected by trachoma live in Africa and the Middle East in isolated rural or desert communities with limited access to clean water and sanitation. These conditions provide an environment conducive to the growth and spread of *Chlamydia trachomatis*, the bacterium that causes trachoma, via wastewater and eye-seeking flies.

In response to this crisis, recent years have seen major public health efforts aimed at treating and preventing trachoma. The Alliance for Global Elimination of Trachoma by 2020 (GET 2020), coordinated by the World Health Organization (WHO), promotes an initiative dubbed “SAFE,” which stands for “Surgery, Antibiotics, Facial cleanliness, and Environmental improvement.” The Carter Center, a charitable, nongovernment organization led by former US President Jimmy Carter, has partnered with the WHO to promote the SAFE initiative in six of the most critically impacted nations in Africa. Through its Trachoma Control Program, the Carter Center trains and equips local surgeons to correct trichiasis and distributes antibiotics to treat trachoma. The program also promotes better personal hygiene through health education and improves sanitation by funding the construction of household latrines. This reduces the prevalence of open sewage, which provides breeding grounds for the flies that spread trachoma.

Bacterial Keratitis

Keratitis can have many causes, but bacterial keratitis is most frequently caused by *Staphylococcus epidermidis*and/or *Pseudomonas aeruginosa*. Contact lens users are particularly at risk for such an infection because *S. epidermidis* and *P. aeruginosa* both adhere well to the surface of the lenses. Risk of infection can be greatly reduced by proper care of contact lenses and avoiding wearing lenses overnight. Because the infection can quickly lead to blindness, prompt and aggressive treatment with antibiotics is important. The causative agent may be identified using bacterial cultures, Gram stain, and diagnostic biochemical, antigenic, or nucleic acid profile tests of the isolated pathogen.

Exercise 8.1.2.9

Why are contact lens wearers at greater risk for developing keratitis?

Biofilms and Infections of the Skin and Eyes

When treating bacterial infections of the skin and eyes, it is important to consider that few such infections can be attributed to a single pathogen. While biofilms may develop in other parts of the body, they are especially relevant to skin infections (such as those caused by *S. aureus* or *P. aeruginosa*) because of their prevalence in chronic skin wounds. Biofilms develop when bacteria (and sometimes fungi) attach to a surface and produce extracellular polymeric substances (EPS) in which cells of multiple organisms may be embedded. When a biofilm develops on a wound, it may interfere with the natural healing process as well as diagnosis and treatment.

Because biofilms vary in composition and are difficult to replicate in the lab, they are still not thoroughly understood. The extracellular matrix of a biofilm consists of polymers such as polysaccharides, extracellular DNA, proteins, and lipids, but the exact makeup varies. The organisms living within the extracellular matrix may include familiar pathogens as well as other bacteria that do not grow well in cultures (such as numerous obligate anaerobes). This presents challenges when culturing samples from infections that involve a biofilm. Because only some species grow *in vitro*, the culture may contain only a subset of the bacterial species involved in the infection.

Biofilms confer many advantages to the resident bacteria. For example, biofilms can facilitate attachment to surfaces on or in the host organism (such as wounds), inhibit phagocytosis, prevent the invasion of neutrophils, and sequester host antibodies. Additionally, biofilms can provide a level of antibiotic resistance not found in the isolated cells and colonies that are typical of laboratory cultures. The extracellular matrix provides a physical barrier to antibiotics, shielding the target cells from exposure. Moreover, cells within a biofilm may differentiate to create subpopulations of dormant cells called persister cells. Nutrient limitations deep within a biofilm add another level of resistance, as stress responses can slow metabolism and increase drug resistance.

Bacterial Infections of the Eyes

A number of bacteria are able to cause infection when introduced to the mucosa of the eye. In general, bacterial eye infections can lead to inflammation, irritation, and discharge, but they vary in severity. Some are typically short-lived, and others can become chronic and lead to permanent eye damage. Prevention requires limiting exposure to contagious pathogens. When infections do occur, prompt treatment with antibiotics can often limit or prevent permanent damage. Figure 8.1.2.16summarizes the characteristics of some common bacterial infections of the eyes.

Bacterial Infections of the Eyes				
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Antimicrobial Drugs**
Acute bacterial conjunctivitis	*Haemophilus influenzae*	Inflammation of conjunctiva with purulent discharge	Exposure to secretions from infected individuals	Broad-spectrum topical antibiotics
Bacterial keratitis	*Staphylococcus epidermidis, Pseudomonas aeruginosa*	Redness and irritation of eye, blurred vision, sensitivity to light; progressive corneal scarring, which can lead to blindness	Exposure to pathogens on contaminated contact lenses	Antibiotic eye drops (e.g., with fluoroquinolones)
Neonatal conjunctivitis	*Chlamydia trachomatis, Neisseria gonorrhoeae*	Inflammation of conjunctiva, purulent discharge, scarring and perforation of cornea; may lead to blindness	Neonate exposed to pathogens in birth canal of mother with chlamydia or gonorrhea	Erythromycin
Trachoma (granular conjunctivitis)	*C. trachomatis*	Chronic conjunctivitis, trichiasis, scarring, blindness	Contact with infected individuals or contaminated fomites; transmission by eye-seeking flies	Azithromycin

Figure 8.1.2.16: Bacterial infections of the eyes

Key Concepts and Summary

- *Staphylococcus* and *Streptococcus* cause many different types of skin infections, many of which occur when bacteria breach the skin barrier through a cut or wound.
- *S. aureus* are frequently associated with purulent skin infections that manifest as **folliculitis**, **furuncles**, or **carbuncles**. *S. aureus* is also a leading cause of staphylococcal scalded skin syndrome (SSSS).
- *S. aureus* is generally drug resistant and current MRSA strains are resistant to a wide range of antibiotics.
- Community-acquired and hospital-acquired staphyloccocal infections are an ongoing problem because many people are asymptomatic carriers.
- **Group A streptococci (GAS)**, *S. pyogenes*, is often responsible for cases of **cellulitis**, **erysipelas**, and **erythema nosodum**. GAS are also one of many possible causes of **necrotizing fasciitis**.
- *P. aeruginosa* is often responsible for infections of the skin and eyes, including wound and burn infections, **hot tub rash**, **otitis externa**, and bacterial **keratitis**.
- **Acne** is a common skin condition that can become more inflammatory when *Propionibacterium acnes* infects hair follicles and pores clogged with dead skin cells and sebum.
- Cutaneous **anthrax** occurs when *Bacillus anthracis* breaches the skin barrier. The infection results in a localized black **eschar** on skin. Anthrax can be fatal if *B. anthracis* spreads to the bloodstream.
- Common bacterial **conjunctivitis** is often caused by *Haemophilus influenzae* and usually resolves on its own in a few days. More serious forms of conjunctivitis include gonococcal **ophthalmia neonatorum**, **inclusion conjunctivitis** (chlamydial), and **trachoma**, all of which can lead to blindness if untreated.
- **Keratitis** is frequently caused by *Staphylococcus epidermidis* and/or *Pseudomonas aeruginosa*, especially among contact lens users, and can lead to blindness.
- Biofilms complicate the treatment of wound and eye infections because pathogens living in biofilms can be difficult to treat and eliminate.

Footnotes

1. 1 Starr, C.R. and Engelberg N.C. “Role of Hyaluronidase in Subcutaneous Spread and Growth of Group A Streptococcus.” *Infection and Immunity* 2006(7:1): 40–48. doi: 10.1128/IAI.74.1.40-48.2006.
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3. 3 Shadomy, S.V., Traxler, R.M., and Marston, C.K. “Infectious Diseases Related to Travel: Anthrax” 2015. Centers for Disease Control and Prevention. wwwnc.cdc.gov/travel/yellowbo...travel/anthrax. Accessed Sept 14, 2016.
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7. 7 Federal Bureau of Investigation. “Famous Cases and Criminals: Amerithrax or Anthrax Investigation.” www.fbi.gov/history/famous-c...-investigation. Accessed Sept 14, 2016.
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9. 9 Emergent Biosolutions. AVA (BioThrax) vaccine package insert (Draft). Nov 2015. www.fda.gov/downloads/biologi...ductsblas/ucm0

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8.1.3: Viral Infections of the Skin and Eyes

Learning Objectives

- Identify the most common viruses associated with infections of the skin and eyes
- Compare the major characteristics of specific viral diseases affecting the skin and eyes

Until recently, it was thought that the normal microbiota of the body consisted primarily of bacteria and some fungi. However, in addition to bacteria, the skin is colonized by viruses, and recent studies suggest that Papillomaviridae, Polyomaviridae and Circoviridae also contribute to the normal skin microbiota. However, some viruses associated with skin are pathogenic, and these viruses can cause diseases with a wide variety of presentations.

Numerous types of viral infections cause rashes or lesions on the skin; however, in many cases these skin conditions result from infections that originate in other body systems. In this chapter, we will limit the discussion to viral skin infections that use the skin as a portal of entry. Later chapters will discuss viral infections such as chickenpox, measles, and rubella—diseases that cause skin rashes but invade the body through portals of entry other than the skin.

Papillomas

Papillomas (warts) are the expression of common skin infections by human papillomavirus (HPV) and are transmitted by direct contact. There are many types of HPV, and they lead to a variety of different presentations, such as common warts, plantar warts, flat warts, and filiform warts. HPV can also cause sexually-transmitted genital warts, which will be discussed in Urogenital System Infections. Vaccination is available for some strains of HPV.

Common warts tend to develop on fingers, the backs of hands, and around nails in areas with broken skin. In contrast, plantar warts (also called foot warts) develop on the sole of the foot and can grow inwards, causing pain and pressure during walking. Flat warts can develop anywhere on the body, are often numerous, and are relatively smooth and small compared with other wart types. Filiform warts are long, threadlike warts that grow quickly.

In some cases, the immune system may be strong enough to prevent warts from forming or to eradicate established warts. However, treatment of established warts is typically required. There are many available treatments for warts, and their effectiveness varies. Common warts can be frozen off with liquid nitrogen. Topical applications of salicylic acidmay also be effective. Other options are electrosurgery (burning), curettage (cutting), excision, painting with cantharidin (which causes the wart to die so it can more easily be removed), laser treatments, treatment with bleomycin, chemical peels, and immunotherapy (Figure 8.1.3.1).



(a) (b)

Figure 8.1.3.1: Warts can vary in shape and in location. (a) Multiple plantar warts have grown on this toe. (b) A filiform wart has grown on this eyelid.

Oral Herpes

Another common skin virus is herpes simplex virus (HSV). HSV has historically been divided into two types, HSV-1 and HSV-2. HSV-1 is typically transmitted by direct oral contact between individuals, and is usually associated with oral herpes. HSV-2 is

usually transmitted sexually and is typically associated with genital herpes. However, both HSV-1 and HSV-2 are capable of infecting any mucous membrane, and the incidence of genital HSV-1 and oral HSV-2 infections has been increasing in recent years. In this chapter, we will limit our discussion to infections caused by HSV-1; HSV-2 and genital herpes will be discussed in Urogenital System Infections.

Infection by HSV-1 commonly manifests as cold sores or fever blisters, usually on or around the lips (Figure 8.1.3.2). HSV-1 is highly contagious, with some studies suggesting that up to 65% of the US population is infected; however, many infected individuals are asymptomatic.[1] Moreover, the virus can be latent for long periods, residing in the trigeminal nerve ganglia between recurring bouts of symptoms. Recurrence can be triggered by stress or environmental conditions (systemic or affecting the skin). When lesions are present, they may blister, break open, and crust. The virus can be spread through direct contact, even when a patient is asymptomatic.

While the lips, mouth, and face are the most common sites for HSV-1 infections, lesions can spread to other areas of the body. Wrestlers and other athletes involved in contact sports may develop lesions on the neck, shoulders, and trunk. This condition is often called herpes gladiatorum. Herpes lesions that develop on the fingers are often called herpetic whitlow.

HSV-1 infections are commonly diagnosed from their appearance, although laboratory testing can confirm the diagnosis. There is no cure, but antiviral medications such as acyclovir, penciclovir, famciclovir, and valacyclovir are used to reduce symptoms and risk of transmission. Topical medications, such as creams with *n*-docosanol and penciclovir, can also be used to reduce symptoms such as itching, burning, and tingling.

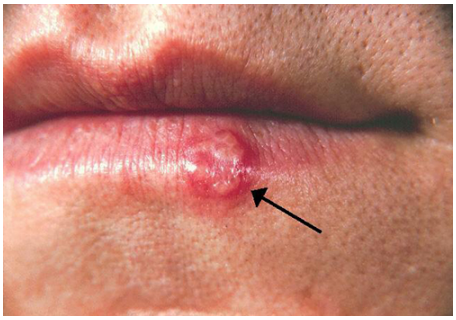


Figure 8.1.3.2: This cold sore was caused by HSV-1. (credit: Centers for Disease Control and Prevention)

? Exercise 8.1.3.1

What are the most common sites for the appearance of herpetic lesions?

Roseola and Fifth Disease

The viral diseases roseola and fifth disease are somewhat similar in terms of their presentation, but they are caused by different viruses. Roseola, sometimes called roseola infantum or exanthem subitum (“sudden rash”), is a mild viral infection usually caused by human herpesvirus-6 (HHV-6) and occasionally by HHV-7. It is spread via direct contact with the saliva or respiratory secretions of an infected individual, often through droplet aerosols. Roseola is very common in children, with symptoms including a runny nose, a sore throat, and a cough, along with (or followed by) a high fever (39.4 ºC). About three to five days after the fever subsides, a rash may begin to appear on the chest and abdomen. The rash, which does not cause discomfort, initially forms characteristic macules that are flat or papules that are firm and slightly raised; some macules or papules may be surrounded by a white ring. The rash may eventually spread to the neck and arms, and sometimes continues to spread to the face and legs. The diagnosis is generally made based upon observation of the symptoms. However, it is possible to perform serological tests to confirm the diagnosis. While treatment may be recommended to control the fever, the disease usually resolves without treatment within a week after the fever develops. For individuals at particular risk, such as those who are immunocompromised, the antiviral medication ganciclovir may be used.

Fifth disease (also known as erythema infectiosum) is another common, highly contagious illness that causes a distinct rash that is critical to diagnosis. Fifth disease is caused by parvovirus B19, and is transmitted by contact with respiratory secretions from an infected individual. Infection is more common in children than adults. While approximately 20% of individuals will be

asymptomatic during infection,[2] others will exhibit cold-like symptoms (headache, fever, and upset stomach) during the early stages when the illness is most infectious. Several days later, a distinct red facial rash appears, often called “slapped cheek” rash (Figure 8.1.3.3). Within a few days, a second rash may appear on the arms, legs, chest, back, or buttocks. The rash may come and go for several weeks, but usually disappears within seven to twenty-one days, gradually becoming lacy in appearance as it recedes.

In children, the disease usually resolves on its own without medical treatment beyond symptom relief as needed. Adults may experience different and possibly more serious symptoms. Many adults with fifth disease do not develop any rash, but may experience joint pain and swelling that lasts several weeks or months. Immunocompromised individuals can develop severe anemia and may need blood transfusions or immune globulin injections. While the rash is the most important component of diagnosis (especially in children), the symptoms of fifth disease are not always consistent. Serological testing can be conducted for confirmation.



(a) (b)

Figure 8.1.3.3: (a) Roseola, a mild viral infection common in young children, generally begins with symptoms similar to a cold, followed by a pink, patchy rash that starts on the trunk and spreads outward. (b) Fifth disease exhibits similar symptoms in children, except for the distinctive “slapped cheek” rash that originates on the face.

? Exercise 8.1.3.2

Identify at least one similarity and one difference between roseola and fifth disease.

Viral Conjunctivitis

Like bacterial conjunctivitis viral infections of the eye can cause inflammation of the conjunctiva and discharge from the eye. However, viral conjunctivitis tends to produce a discharge that is more watery than the thick discharge associated with bacterial conjunctivitis. The infection is contagious and can easily spread from one eye to the other or to other individuals through contact with eye discharge.

Viral conjunctivitis is commonly associated with colds caused by adenoviruses; however, other viruses can also cause conjunctivitis. If the causative agent is uncertain, eye discharge can be tested to aid in diagnosis. Antibiotic treatment of viral conjunctivitis is ineffective, and symptoms usually resolve without treatment within a week or two.

Herpes Keratitis

Herpes infections caused by HSV-1 can sometimes spread to the eye from other areas of the body, which may result in keratoconjunctivitis. This condition, generally called herpes keratitis or herpetic keratitis, affects the conjunctiva and cornea, causing irritation, excess tears, and sensitivity to light. Deep lesions in the cornea may eventually form, leading to blindness. Because keratitis can have numerous causes, laboratory testing is necessary to confirm the diagnosis when HSV-1 is suspected; once confirmed, antiviral medications may be prescribed.

Viral Infections of the Skin and Eyes

A number of viruses can cause infections via direct contact with skin and eyes, causing signs and symptoms ranging from rashes and lesions to warts and conjunctivitis. All of these viral diseases are contagious, and while some are more common in children (fifth disease and roseola), others are prevalent in people of all ages (oral herpes, viral conjunctivitis, papillomas). In general, the best means of prevention is avoiding contact with infected individuals. Treatment may require antiviral medications; however, several of these conditions are mild and typically resolve without treatment. Figure 8.1.3.4 summarizes the characteristics of some common viral infections of the skin and eyes.

Viral Infections of the Skin and Eyes				
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Antimicrobial Drugs**
Fifth disease	Parvovirus B19	May have initial cold-like symptoms; “slapped cheek” rash	Highly contagious via respiratory secretions of infected individuals	None
Herpes keratitis	Herpes simplex virus 1 (HSV-1)	Inflammation of conjunctiva and cornea; irritation, excess tears, sensitivity to light; lesions in cornea leading to blindness	Direct eye contact with discharge from herpes lesions elsewhere in the body or from another infected individual	Acyclovir, ganciclovir, famiclovir, valacyclovir
Oral herpes	Herpes simplex virus 1 (HSV-1)	May cause initial systemic symptoms; cold sores	Highly contagious via direct contact with infected individuals	Acyclovir, penciclovir, famiclovir, valacyclovir
Papillomas	Human papillomavirus (HPV)	Common warts, plantar warts, flat warts, filiform warts, and others	Contact with infected individuals	Topical salicylic acid, cantharidin
Roseola (roseola infantum, exanthem subitum)	Human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7)	Initial cold-like symptoms with high fever, followed by a macular or papular rash three to five days later	Spread by viral and respiratory secretions of infected individuals	Typically none; ganciclovir for immunocompromised patients
Viral conjunctivitis	Adenoviruses and others	Inflammation of the conjunctiva; watery, nonpurulent discharge	Associated with common cold; contagious via contact with eye discharge	None

Figure 8.1.3.4: Viral infections of the skin and eyes

Key Concepts and Summary

- **Papillomas** (warts) are caused by human papillomaviruses.
- **Herpes simplex virus** (especially HSV-1) mainly causes **oral herpes**, but lesions can appear on other areas of the skin and mucous membranes.
- **Roseola** and **fifth disease** are common viral illnesses that cause skin rashes; roseola is caused by HHV-6 and HHV-7 while fifth disease is caused by parvovirus 19.
- **Viral conjunctivitis** is often caused by adenoviruses and may be associated with the common cold. **Herpes keratitis** is caused by herpesviruses that spread to the eye.

Footnotes

1. 1 Wald, A., and Corey, L. “Persistence in the Population: Epidemiology, Transmission.” In: A. Arvin, G. Campadelli-Fiume, E. Mocarski et al. *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*. Cambridge: Cambridge University Press, 2007. www.ncbi.nlm.nih.gov/books/NBK47447/. Accessed Sept 14, 2016.

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8.1.4: Mycoses of the Skin and Eyes

Learning Objectives

- Identify the most common fungal pathogens associated with cutaneous and subcutaneous mycoses
- Compare the major characteristics of specific fungal diseases affecting the skin

Many fungal infections of the skin involve fungi that are found in the normal skin microbiota. Some of these fungi can cause infection when they gain entry through a wound; others mainly cause opportunistic infections in immunocompromised patients. Other fungal pathogens primarily cause infection in unusually moist environments that promote fungal growth; for example, sweaty shoes, communal showers, and locker rooms provide excellent breeding grounds that promote the growth and transmission of fungal pathogens.

Fungal infections, also called mycoses, can be divided into classes based on their invasiveness. Mycoses that cause superficial infections of the epidermis, hair, and nails, are called cutaneous mycoses. Mycoses that penetrate the epidermis and the dermis to infect deeper tissues are called subcutaneous mycoses. Mycoses that spread throughout the body are called systemic mycoses.

Tineas

A group of cutaneous mycoses called tineas are caused by dermatophytes, fungal molds that require keratin, a protein found in skin, hair, and nails, for growth. There are three genera of dermatophytes, all of which can cause cutaneous mycoses: *Trichophyton*, *Epidermophyton*, and *Microsporum*. Tineas on most areas of the body are generally called ringworm, but tineas in specific locations may have distinctive names and symptoms (see Table 8.1.4.1 and Figure 8.1.4.1). Keep in mind that these names—even though they are Latinized—refer to locations on the body, not causative organisms. Tineas can be caused by different dermatophytes in most areas of the body.

Table 8.1.4.1: Tineas and locations

Some Common Tineas and Location on the Body	
Tinea corporis (ringworm)	Body
Tinea capitis (ringworm)	Scalp
Tinea pedis (athlete's foot)	Feet
Tinea barbae (barber's itch)	Beard
Tinea cruris (jock itch)	Groin
Tinea unguium (onychomycosis)	Toenails, fingernails



(a) (b) (c)

Figure 8.1.4.1: Tineas are superficial cutaneous mycoses and are common. (a) Tinea barbae (barber's itch) occurs on the lower face. (b) Tinea pedis (athlete's foot) occurs on the feet, causing itching, burning, and dry, cracked skin between the toes. (c) A close-up view of tinea corporis (ringworm) caused by *Trichophyton mentagrophytes*. (credit a, c: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Al Hasan M, Fitzgerald SM, Saoudian M, Krishnaswamy G)

Dermatophytes are commonly found in the environment and in soils and are frequently transferred to the skin via contact with other humans and animals. Fungal spores can also spread on hair. Many dermatophytes grow well in moist, dark environments. For example, tinea pedis (athlete's foot) commonly spreads in public showers, and the causative fungi grow well in the dark, moist confines of sweaty shoes and socks. Likewise, tinea cruris (jock itch) often spreads in communal living environments and thrives in warm, moist undergarments.

Tineas on the body (tinea corporis) often produce lesions that grow radially and heal towards the center. This causes the formation of a red ring, leading to the misleading name of ringworm recall the Clinical Focus case in The Eukaryotes of Microbiology.

Several approaches may be used to diagnose tineas. A Wood's lamp (also called a black lamp) with a wavelength of 365 nm is often used. When directed on a tinea, the ultraviolet light emitted from the Wood's lamp causes the fungal elements (spores and hyphae) to fluoresce. Direct microscopic evaluation of specimens from skin scrapings, hair, or nails can also be used to detect fungi. Generally, these specimens are prepared in a wet mount using a potassium hydroxide solution (10%–20% aqueous KOH), which dissolves the keratin in hair, nails, and skin cells to allow for visualization of the hyphae and fungal spores. The specimens may be grown on Sabouraud dextrose CC (chloramphenicol/cyclohexamide), a selective agar that supports dermatophyte growth while inhibiting the growth of bacteria and saprophytic fungi (Figure 8.1.4.2). Macroscopic colony morphology is often used to initially identify the genus of the dermatophyte; identification can be further confirmed by visualizing the microscopic morphology using either a slide culture or a sticky tape prep stained with lactophenol cotton blue.

Various antifungal treatments can be effective against tineas. Allylamine ointments that include terbinafine are commonly used; miconazole and clotrimazole are also available for topical treatment, and griseofulvin is used orally.

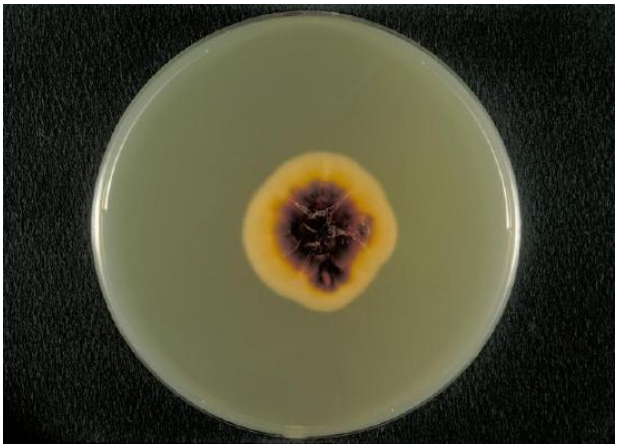


Figure 8.1.4.2: To diagnose tineas, the dermatophytes may be grown on a Sabouraud dextrose CC agar plate. This culture contains a strain of *Trichophyton rubrum*, one of the most common causes of tineas on various parts of the body. (credit: Centers for Disease Control and Prevention)

? Exercise 8.1.4.1

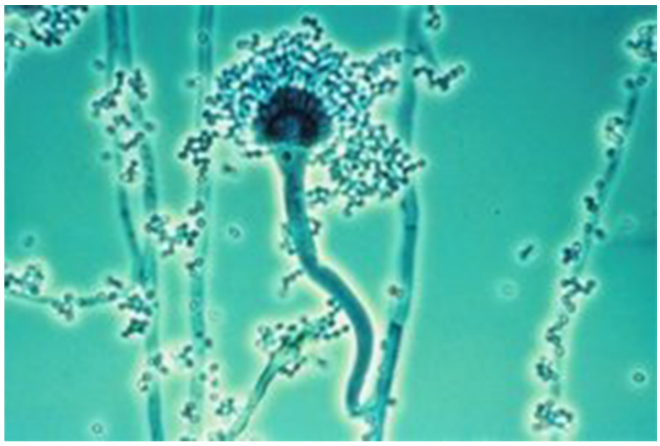
Why are tineas, caused by fungal molds, often called ringworm?

Cutaneous Aspergillosis

Another cause of cutaneous mycoses is *Aspergillus*, a genus consisting of molds of many different species, some of which cause a condition called aspergillosis. Primary cutaneous aspergillosis, in which the infection begins in the skin, is rare but does occur. More common is secondary cutaneous aspergillosis, in which the infection begins in the respiratory system and disseminates systemically. Both primary and secondary cutaneous aspergillosis result in distinctive eschars that form at the site or sites of infection (Figure 8.1.4.3). Pulmonary aspergillosis will be discussed more thoroughly in Respiratory Mycoses).



(a)



(b)

Figure 8.1.4.3: (a) Eschar on a patient with secondary cutaneous aspergillosis. (b) Micrograph showing a conidiophore of *Aspergillus*. (credit a: modification of work by Santiago M, Martinez JH, Palermo C, Figueroa C, Torres O, Trinidad R, Gonzalez E, Miranda Mde L, Garcia M, Villamarzo G; credit b: modification of work by U.S. Department of Health and Human Services)

Primary cutaneous aspergillosis usually occurs at the site of an injury and is most often caused by *Aspergillus fumigatus* or *Aspergillus flavus*. It is usually reported in patients who have had an injury while working in an agricultural or outdoor environment. However, opportunistic infections can also occur in health-care settings, often at the site of intravenous catheters, venipuncture wounds, or in association with burns, surgical wounds, or occlusive dressing. After candidiasis, aspergillosis is the second most common hospital-acquired fungal infection and often occurs in immunocompromised patients, who are more vulnerable to opportunistic infections.

Cutaneous aspergillosis is diagnosed using patient history, culturing, histopathology using a skin biopsy. Treatment involves the use of antifungal medications such as voriconazole (preferred for invasive aspergillosis), itraconazole, and amphotericin B if itraconazole is not effective. For immunosuppressed individuals or burn patients, medication may be used and surgical or immunotherapy treatments may be needed.

? Exercise 8.1.4.2

Identify the sources of infection for primary and secondary cutaneous aspergillosis.

Candidiasis of the Skin and Nails

Candida albicans and other yeasts in the genus *Candida* can cause skin infections referred to as cutaneous candidiasis. *Candida* spp. are sometimes responsible for intertrigo, a general term for a rash that occurs in a skin fold, or other localized rashes on the skin. *Candida* can also infect the nails, causing them to become yellow and harden (Figure 8.1.4.4).



(a)



(b)



(c)

Figure 8.1.4.4: (a) This red, itchy rash is the result of cutaneous candidiasis, an opportunistic infection of the skin caused by the yeast *Candida albicans*. (b) Fungal infections of the nail (tinea unguium) can be caused by dermatophytes or *Candida* spp. The nail becomes yellow, brittle, and prone to breaking. This condition is relatively common among adults. (c) *C. albicans* growing on Sabouraud dextrose agar. (credit a: modification of work by U.S. Department of Veterans Affairs; credit c: modification of work by Centers for Disease Control and Prevention)

Candidiasis of the skin and nails is diagnosed through clinical observation and through culture, Gram stain, and KOH wet mounts. Susceptibility testing for anti-fungal agents can also be done. Cutaneous candidiasis can be treated with topical or systemic azole antifungal medications. Because candidiasis can become invasive, patients suffering from HIV/AIDS, cancer, or other conditions that compromise the immune system may benefit from preventive treatment. Azoles, such as clotrimazole, econazole, fluconazole, ketoconazole, and miconazole; nystatin; terbinafine; and naftifine may be used for treatment. Long-term treatment with medications such as itraconazole or ketoconazole may be used for chronic infections. Repeat infections often occur, but this risk can be reduced by carefully following treatment recommendations, avoiding excessive moisture, maintaining good health, practicing good hygiene, and having appropriate clothing (including footwear).

Candida also causes infections in other parts of the body besides the skin. These include vaginal yeast infections (see Fungal Infections of the Reproductive System) and oral thrush (see Microbial Diseases of the Mouth and Oral Cavity).

? Exercise 8.1.4.3

What are the signs and symptoms of candidiasis of the skin and nails?

Sporotrichosis

Whereas cutaneous mycoses are superficial, subcutaneous mycoses can spread from the skin to deeper tissues. In temperate regions, the most common subcutaneous mycosis is a condition called sporotrichosis, caused by the fungus *Sporothrix schenkii* and commonly known as rose gardener's disease or rose thorn disease (recall Case in Point: Every Rose Has Its Thorn). Sporotrichosis is often contracted after working with soil, plants, or timber, as the fungus can gain entry through a small wound such as a thorn-prick or splinter. Sporotrichosis can generally be avoided by wearing gloves and protective clothing while gardening and promptly cleaning and disinfecting any wounds sustained during outdoor activities.

Sporothrix infections initially present as small ulcers in the skin, but the fungus can spread to the lymphatic system and sometimes beyond. When the infection spreads, nodules appear, become necrotic, and may ulcerate. As more lymph nodes become affected, abscesses and ulceration may develop over a larger area (often on one arm or hand). In severe cases, the infection may spread more widely throughout the body, although this is relatively uncommon.

Sporothrix infection can be diagnosed based upon histologic examination of the affected tissue. Its macroscopic morphology can be observed by culturing the mold on potato dextrose agar, and its microscopic morphology can be observed by staining a slide culture with lactophenol cotton blue. Treatment with itraconazole is generally recommended.

? Exercise 8.1.4.4

Describe the progression of a *Sporothrix schenkii* infection.

Mycoses of the Skin

Cutaneous mycoses are typically opportunistic, only able to cause infection when the skin barrier is breached through a wound. Tineas are the exception, as the dermatophytes responsible for tineas are able to grow on skin, hair, and nails, especially in moist conditions. Most mycoses of the skin can be avoided through good hygiene and proper wound care. Treatment requires antifungal medications. Figure 8.1.4.5 summarizes the characteristics of some common fungal infections of the skin.

Mycoses of the Skin				
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Antimicrobial Drugs**
Aspergillosis (cutaneous)	*Aspergillus fumigatus, Aspergillus flavus*	Distinctive eschars at site(s) of infection	Entry via wound (primary cutaneous aspergillosis) or via the respiratory system (secondary cutaneous aspergillosis); commonly a hospital-acquired infection	Itraconazole, voriconazole, amphotericin B
Candidiasis (cutaneous)	*Candida albicans*	Intertrigo, localized rash, yellowing of nails	Overgrowth of normal skin microbiota, especially in moist, dark areas	Azoles
Sporotrichosis (rose gardener's disease)	*Sporothrix schenkii*	Subcutaneous ulcers and abscesses; may spread to a large area, e.g., hand or arm	Entry via thorn prick or other wound	Itraconazole
Tineas	*Trichophyton* spp., *Epidermophyton* spp., *Microsporum* spp.	Itchy, ring-like lesions (ringworm) at sites of infection	Contact with dermatophytic fungi, especially in warm, moist environments conducive to fungal growth	Terbinafine, miconazole, clotrimazole, griseofulvin

Figure 8.1.4.5: Mycoses of the skin

Key Concepts and Summary

- Mycoses can be cutaneous, subcutaneous, or systemic.
- Common cutaneous mycoses include tineas caused by dermatophytes of the genera Trichophyton, Epidermophyton, and Microsporum. Tinea corporis is called ringworm. Tineas on other parts of the body have names associated with the affected body part.
- Aspergillosis is a fungal disease caused by molds of the genus Aspergillus. Primary cutaneous aspergillosis enters through a break in the skin, such as the site of an injury or a surgical wound; it is a common hospital-acquired infection. In secondary cutaneous aspergillosis, the fungus enters via the respiratory system and disseminates systemically, manifesting in lesions on the skin.
- The most common subcutaneous mycosis is sporotrichosis (rose gardener's disease), caused by Sporothrix schenkii.
- Yeasts of the genus Candida can cause opportunistic infections of the skin called candidiasis, producing intertrigo, localized rashes, or yellowing of the nails.

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8.1.5: Protozoan and Helminthic Infections of the Eyes

Learning Objectives

- Identify two parasites that commonly cause infections of the skin and eyes
- Identify the major characteristics of specific parasitic diseases affecting the skin and eyes

Many parasitic protozoans and helminths use the skin or eyes as a portal of entry. Some may physically burrow into the skin or the mucosa of the eye; others breach the skin barrier by means of an insect bite. Still others take advantage of a wound to bypass the skin barrier and enter the body, much like other opportunistic pathogens. Although many parasites enter the body through the skin, in this chapter we will limit our discussion to those for which the skin or eyes are the primary site of infection. Parasites that enter through the skin but travel to a different site of infection will be covered in other chapters. In addition, we will limit our discussion to microscopic parasitic infections of the skin and eyes. Macroscopic parasites such as lice, scabies, mites, and ticks are beyond the scope of this text.

Acanthamoeba Infections

Acanthamoeba is a genus of free-living protozoan amoebae that are common in soils and unchlorinated bodies of fresh water. (This is one reason why some swimming pools are treated with chlorine.) The genus contains a few parasitic species, some of which can cause infections of the eyes, skin, and nervous system. Such infections can sometimes travel and affect other body systems. Skin infections may manifest as abscesses, ulcers, and nodules. When acanthamoebae infect the eye, causing inflammation of the cornea, the condition is called *Acanthamoeba* keratitis. Figure 8.1.5.1 illustrates the *Acanthamoeba* life cycle and various modes of infection.

While *Acanthamoeba* keratitis is initially mild, it can lead to severe corneal damage, vision impairment, or even blindness if left untreated. Similar to eye infections involving *P. aeruginosa*, *Acanthamoeba* poses a much greater risk to wearers of contact lenses because the amoeba can thrive in the space between contact lenses and the cornea. Prevention through proper contact lens care is important. Lenses should always be properly disinfected prior to use, and should never be worn while swimming or using a hot tub.

Acanthamoeba can also enter the body through other pathways, including skin wounds and the respiratory tract. It usually does not cause disease except in immunocompromised individuals; however, in rare cases, the infection can spread to the nervous system, resulting in a usually fatal condition called granulomatous amoebic encephalitis (GAE) (see Fungal and Parasitic Diseases of the Nervous System). Disseminated infections, lesions, and *Acanthamoeba* keratitis can be diagnosed by observing symptoms and examining patient samples under the microscope to view the parasite. Skin biopsies may be used.

Acanthamoeba keratitis is difficult to treat, and prompt treatment is necessary to prevent the condition from progressing. The condition generally requires three to four weeks of intensive treatment to resolve. Common treatments include topical antiseptics (e.g., polyhexamethylene biguanide, chlorhexidine, or both), sometimes with painkillers or corticosteroids (although the latter are controversial because they suppress the immune system, which can worsen the infection). Azoles are sometimes prescribed as well. Advanced cases of keratitis may require a corneal transplant to prevent blindness.

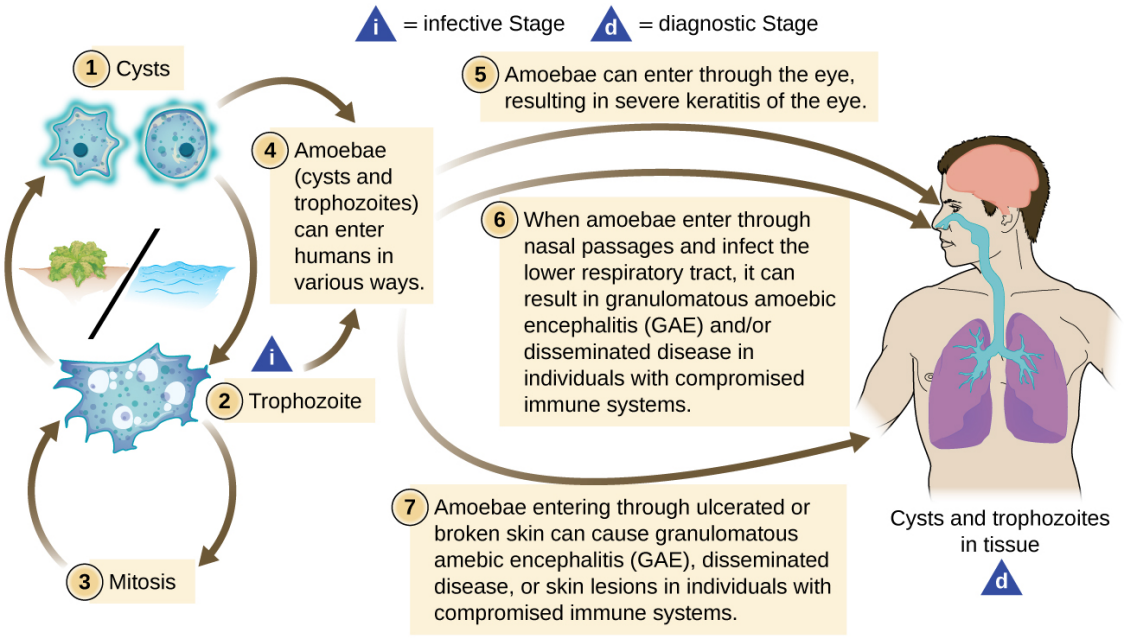
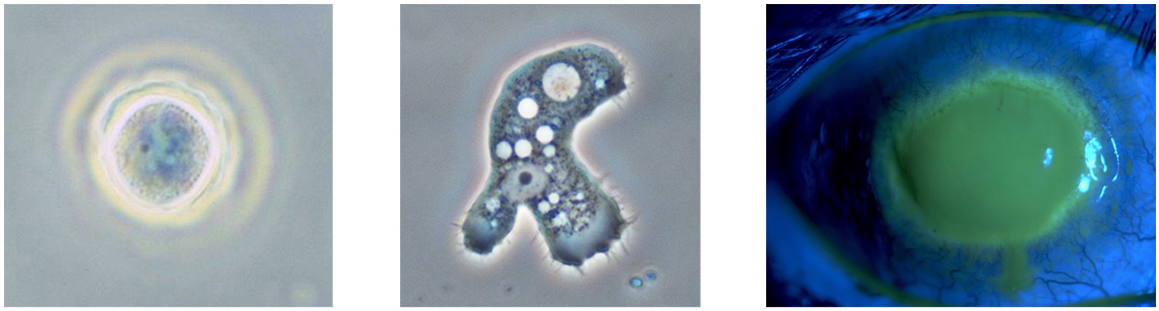


Figure 8.1.5.1: Acanthamoeba spp. are waterborne parasites very common in unchlorinated aqueous environments. As shown in this life cycle, *Acanthamoeba* cysts and trophozoites are both capable of entering the body through various routes, causing infections of the eye, skin, and central nervous system. (credit: modification of work by Centers for Disease Control and Prevention)



Acanthamoeba cyst (a) | *Acanthamoeba* trophozoite (b) | (c)

Figure 8.1.5.2: (a) An *Acanthamoeba* cyst. (b) An *Acanthamoeba* trophozoite (c) The eye of a patient with *Acanthamoeba* keratitis. The fluorescent color, which is due to sodium fluorescein application, highlights significant damage to the cornea and vascularization of the surrounding conjunctiva. (credit a: modification of work by Centers for Disease Control and Prevention; credit b, c: modification of work by Jacob Lorenzo-Morales, Naveed A Kahn and Julia Walochnik)

? Exercise 8.1.5.1

How are *Acanthamoeba* infections acquired?

Loiasis

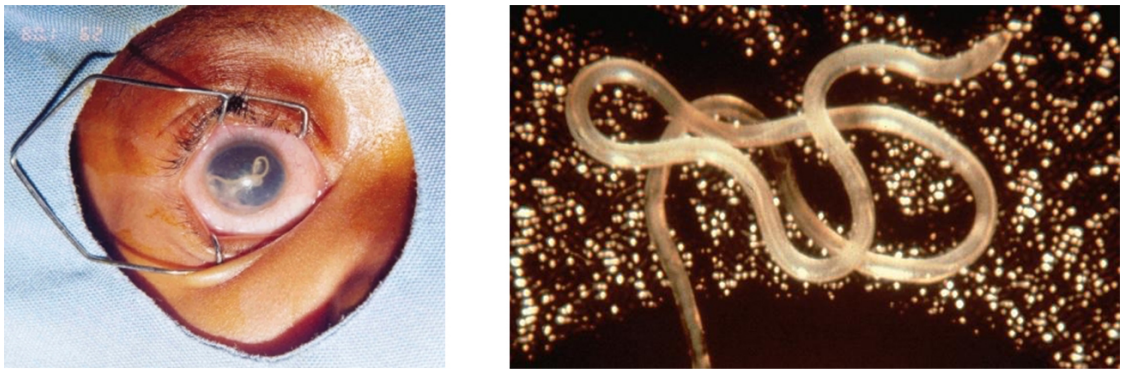
The helminth *Loa loa*, also known as the African eye worm, is a nematode that can cause loiasis, a disease endemic to West and Central Africa (Figure 8.1.5.3). The disease does not occur outside that region except when carried by travelers. There is evidence that individual genetic differences affect susceptibility to developing loiasis after infection by the *Loa loa* worm. Even in areas in which *Loa loa* worms are common, the disease is generally found in less than 30% of the population.[1] It has been suggested that travelers who spend time in the region may be somewhat more susceptible to developing symptoms than the native population, and the presentation of infection may differ.[2]

The parasite is spread by deerflies (genus *Chrysops*), which can ingest the larvae from an infected human via a blood meal (Figure 8.1.5.3). When the deerfly bites other humans, it deposits the larvae into their bloodstreams. After about five months in the human

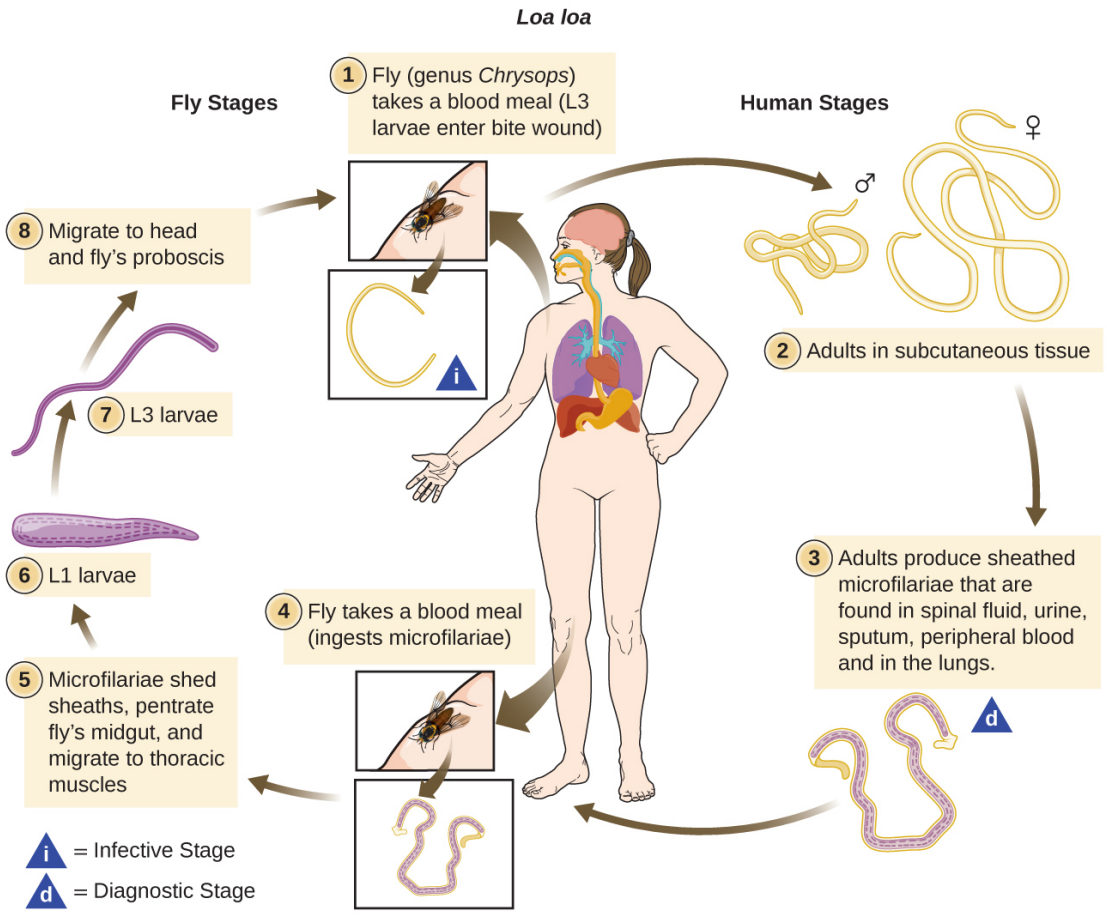
body, some larvae develop into adult worms, which can grow to several centimeters in length and live for years in the subcutaneous tissue of the host.

The name “eye worm” alludes to the visible migration of worms across the conjunctiva of the eye. Adult worms live in the subcutaneous tissues and can travel at about 1 cm per hour. They can often be observed when migrating through the eye, and sometimes under the skin; in fact, this is generally how the disease is diagnosed. It is also possible to test for antibodies, but the presence of antibodies does not necessarily indicate a current infection; it only means that the individual was exposed at some time. Some patients are asymptomatic, but in others the migrating worms can cause fever and areas of allergic inflammation known as Calabar swellings. Worms migrating through the conjunctiva can cause temporary eye pain and itching, but generally there is no lasting damage to the eye. Some patients experience a range of other symptoms, such as widespread itching, hives, and joint and muscle pain.

Worms can be surgically removed from the eye or the skin, but this treatment only relieves discomfort; it does not cure the infection, which involves many worms. The preferred treatment is diethylcarbamazine, but this medication produces severe side effects in some individuals, such as brain inflammation and possible death in patients with heavy infections. Albendazole is also sometimes used if diethylcarbamazine is not appropriate or not successful. If left untreated for many years, loiasis can damage the kidneys, heart, and lungs, though these symptoms are rare.



(a) (b)



(c)

Figure 8.1.5.3: This *Loa loa* worm, measuring about 55 mm long, was extracted from the conjunctiva of a patient with loiasis. The *Loa loa* has a complex life cycle. Biting deerflies native to the rain forests of Central and West Africa transmit the larvae between humans. (credit a: modification of work by Eballe AO, Epée E, Koki G, Owono D, Mvogo CE, Bella AL; credit b: modification of work by NIAID; credit c: modification of work by Centers for Disease Control and Prevention)

? Exercise 8.1.5.2

Describe the most common way to diagnose loiasis.

Link to Learning

See a video of a live *Loa loa* microfilaria under the microscope.

Parasitic Skin and Eye Infections

The protozoan *Acanthamoeba* and the helminth *Loa loa* are two parasites capable of causing infections of the skin and eyes. Figure 8.1.5.4 summarizes the characteristics of some common fungal infections of the skin.

Parasitic Skin and Eye Infections

Disease	Pathogen	Signs and Symptoms	Transmission	Antimicrobial Drugs
Acanthamoeba keratitis	*Acanthamoeba*	Inflammation and damage to cornea; vision impairment or blindness	Exposure to pathogens in contaminated water or on contact lenses	Polyhexamethylene biguanide, chlorhexidine, azoles
Loiasis	*Loa loa*	Recurring fever and localized Calabar swelling, itching, and skin or eye pain during subcutaneous migration of worms	Larvae transmitted between humans by deerfly vector	Diethylcarbamazine, albendazole

Figure 8.1.5.4: Parasitic skin and eye infections

Key Concepts and Summary

The protozoan *Acanthamoeba* and the helminth *Loa loa* are two parasites that can breach the skin barrier, causing infections of the skin and eyes. ***Acanthamoeba* keratitis** is a parasitic infection of the eye that often results from improper disinfection of contact lenses or swimming while wearing contact lenses. **Loiasis**, or eye worm, is a disease endemic to Africa that is caused by parasitic worms that infect the subcutaneous tissue of the skin and eyes. It is transmitted by deerfly vectors.

Footnotes

1. 1 Garcia, A.. et al. “Genetic Epidemiology of Host Predisposition Microfilaraemia in Human Loiasis.” *Tropical Medicine and International Health* 4 (1999) 8:565–74. http://www.ncbi.nlm.nih.gov/pubmed/10499080. Accessed Sept 14, 2016.
2. 2 Spinello, A., et al. “Imported *Loa loa* Filariasis: Three Cases and a Review of Cases Reported in Non-Endemic Countries in the Past 25 Years.” *International Journal of Infectious Disease* 16 (2012) 9: e649–e662. DOI: http://dx.doi.org/10.1016/j.ijid.2012.05.1023.

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8.1.E: Skin and Eye Infections (Exercises)

21.1: Anatomy and Normal Microbiota of the Skin and Eyes

Human skin consists of two main layers, the epidermis and dermis, which are situated on top of the hypodermis, a layer of connective tissue. The skin is an effective physical barrier against microbial invasion. The skin's relatively dry environment and normal microbiota discourage colonization by transient microbes. The skin's normal microbiota varies from one region of the body to another. The conjunctiva of the eye is a frequent site for microbial infection; deeper infections are less common.

Multiple Choice

_____ glands produce a lipid-rich substance that contains proteins and minerals and protects the skin.

A. Sweat
B. Mammary
C. Sebaceous
D. Endocrine

Answer

C

Which layer of skin contains living cells, is vascularized, and lies directly above the hypodermis?

A. the stratum corneum
B. the dermis
C. the epidermis
D. the conjunctiva

Answer

B

Fill in the Blank

The _____ is the outermost layer of the epidermis.

Answer

stratum corneum

The mucous membrane that covers the surface of the eyeball and inner eyelid is called the _____.

Answer

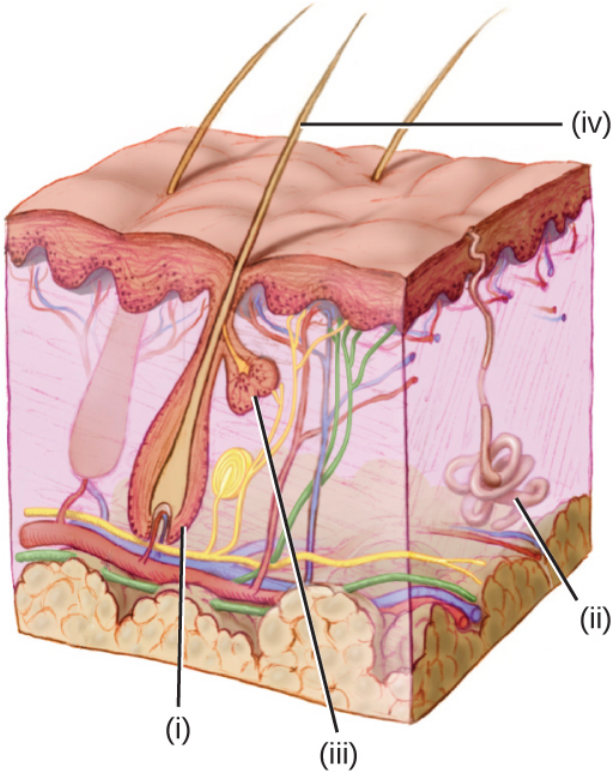
conjunctiva

Short Answer

What is the role of keratin in the skin?

What are two ways in which tears help to prevent microbial colonization?

Which label indicates a sweat gland?



(credit: modification of work by National Cancer Institute)

Critical Thinking

Explain why it is important to understand the normal microbiota of the skin.

Besides the presence or absence of ulceration, how do acute ulcerative and nonulcerative blepharitis differ?

21.2: Bacterial Infections of the Skin and Eyes

Staphylococcus and *Streptococcus* cause many different types of skin infections, many of which occur when bacteria breach the skin barrier through a cut or wound. *S. aureus* are frequently associated with purulent skin infections that manifest as folliculitis, furuncles, or carbuncles. *S. aureus* is also a leading cause of staphylococcal scalded skin syndrome (SSSS). *S. aureus* is generally drug resistant and current MRSA strains are resistant to a wide range of antibiotics.

Multiple Choice

Staphylococcus aureus is most often associated with being

A. coagulase-positive.
B. coagulase-negative.
C. catalase-negative.
D. gram-negative

Answer

A

M protein is produced by

A. *Pseudomonas aeruginosa*
B. *Staphylococcus aureus*
C. *Propionibacterium acnes*
D. *Streptococcus pyogenes*

Answer

D

_____ is a major cause of preventable blindness that can be reduced through improved sanitation.

A. Ophthalmia neonatorum
B. Keratitis
C. Trachoma
D. Cutaneous anthrax

Answer

C

Which species is frequently associated with nosocomial infections transmitted via medical devices inserted into the body?

A. *Staphylococcus epidermidis*
B. *Streptococcus pyogenes*
C. *Proproniobacterium acnes*
D. *Bacillus anthracis*

Answer

A

Fill in the Blank

A purulent wound produces _____.

Answer

pus

Short Answer

How are leukocidins associated with pus production?

What is a good first test to distinguish streptococcal infections from staphylococcal infections?

21.3: Viral Infections of the Skin and Eyes

Papillomas (warts) are caused by human papillomaviruses. Herpes simplex virus (especially HSV-1) mainly causes oral herpes, but lesions can appear on other areas of the skin and mucous membranes. Roseola and fifth disease are common viral illnesses that cause skin rashes; roseola is caused by HHV-6 and HHV-7 while fifth disease is caused by parvovirus 19. Viral conjunctivitis is often caused by adenoviruses and may be associated with the common cold. Herpes keratitis is caused by herpesviruses.

Multiple Choice

Warts are caused by

A. human papillomavirus.
B. herpes simplex virus.
C. adenoviruses.
D. parvovirus B19.

Answer

A

Which of these viruses can spread to the eye to cause a form of keratitis?

A. human papillomavirus

B. herpes simplex virus 1
C. parvovirus 19
D. circoviruses

Answer

B

Cold sores are associated with:

A. human papillomavirus
B. roseola
C. herpes simplex viruses
D. human herpesvirus 6

Answer

C

Which disease is usually self-limiting but is most commonly treated with ganciclovir if medical treatment is needed?

A. roseola
B. oral herpes
C. papillomas
D. viral conjunctivitis

Answer

A

Adenoviruses can cause:

A. viral conjunctivitis
B. herpetic conjunctivitis
C. papillomas
D. oral herpes

Answer

A

Fill in the Blank

Human herpesvirus 6 is the causative agent of _____.

Answer

roseola

Short Answer

Compare and contrast bacterial and viral conjunctivitis.

21.4: Mycoses of the Skin and Eyes

Mycoses can be cutaneous, subcutaneous, or systemic. Common cutaneous mycoses include tineas caused by dermatophytes of the genera *Trichophyton*, *Epidermophyton*, and *Microsporum*. Tinea corporis is called ringworm. Tineas on other parts of the body have names associated with the affected body part. Aspergillosis is a fungal disease caused by molds of the genus *Aspergillus*. Primary cutaneous aspergillosis enters through a break in the skin, such as the site of an injury or a surgical wound.

Multiple Choice

_____ is a superficial fungal infection found on the head.

A. Tinea cruris
B. Tinea capitis
C. Tinea pedis
D. Tinea corporis

Answer

B

For what purpose would a health-care professional use a Wood's lamp for a suspected case of ringworm?

A. to prevent the rash from spreading
B. to kill the fungus
C. to visualize the fungus
D. to examine the fungus microscopically

Answer

C

Sabouraud dextrose agar CC is selective for:

A. all fungi
B. non-saprophytic fungi
C. bacteria
D. viruses

Answer

B

The first-line recommended treatment for sporotrichosis is:

A. itraconazole
B. clindamycin
C. amphotericin
D. nystatin

Answer

A

Fill in the Blank

The most common subcutaneous mycosis in temperate regions is _____.

Answer

sporotrichosis

Short Answer

What yeasts commonly cause opportunistic infections?

Critical Thinking

What steps might you recommend to a patient for reducing the risk of developing a fungal infection of the toenails?

21.5: Protozoan and Helminthic Infections of the Eyes

The protozoan *Acanthamoeba* and the helminth *Loa loa* are two parasites that can breach the skin barrier, causing infections of the skin and eyes. *Acanthamoeba* keratitis is a parasitic infection of the eye that often results from improper disinfection of contact lenses or swimming while wearing contact lenses. Loiasis, or eye worm, is a disease endemic to Africa that is caused by parasitic worms that infect the subcutaneous tissue of the skin and eyes. It is transmitted by deerfly vectors.

Multiple Choice

Which of the following is most likely to cause an *Acanthamoeba* infection?

A. swimming in a lake while wearing contact lenses
B. being bitten by deerflies in Central Africa
C. living environments in a college dormitory with communal showers
D. participating in a contact sport such as wrestling

Answer

A

The parasitic *Loa loa* worm can cause great pain when it:

A. moves through the bloodstream
B. exits through the skin of the foot
C. travels through the conjunctiva
D. enters the digestive tract

Answer

C

A patient tests positive for *Loa loa* antibodies. What does this test indicate?

A. The individual was exposed to *Loa loa* at some point.
B. The individual is currently suffering from loiasis.
C. The individual has never been exposed to *Loa loa*.
D. The individual is immunosuppressed.

Answer

A

_____ is commonly treated with a combination of chlorhexidine and polyhexamethylene biguanide.

A. *Acanthamoeba* keratitis
B. Sporotrichosis
C. Candidiasis
D. Loiasis

Answer

A

Fill in the Blank

Eye worm is another name for _____.

Answer

loiasis

The _____ is the part of the eye that is damaged due to *Acanthamoeba* keratitis.

Answer

cornea

Critical Thinking

Why might a traveler to a region with *Loa loa* worm have a greater risk of serious infection compared with people who live in the region?

What preventative actions might you recommend to a patient traveling to a region where loiasis is endemic?

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SECTION OVERVIEW

8.2: The Nervous System

A nervous system is an organism's control center: it processes sensory information from outside (and inside) the body and controls all behaviors—from eating to sleeping to finding a mate.

8.2.1: Prelude to the Nervous System

8.2.2: Video - The Nervous System

8.2.3: Neurons and Glial Cells

8.2.4: How Neurons Communicate

8.2.5: The Central Nervous System

8.2.6: The Peripheral Nervous System

8.2.7: Nervous System Disorders

8.2.E: The Nervous System (Exercises)

Thumbnail: Human brain toy. (Photo by Robina Weermeijer on Unsplash)

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8.2.1: Prelude to the Nervous System



Figure 8.2.1.1: An athlete's nervous system is hard at work during the planning and execution of a movement as precise as a high jump. Parts of the nervous system are involved in determining how hard to push off and when to turn, as well as controlling the muscles throughout the body that make this complicated movement possible without knocking the bar down—all in just a few seconds. (credit: modification of work by Shane T. McCoy, U.S. Navy)

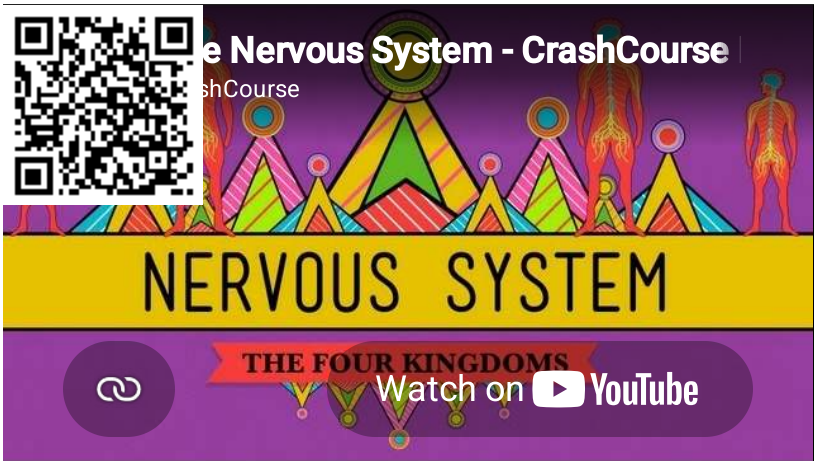
When you're reading this book, your nervous system is performing several functions simultaneously. The visual system is processing what is seen on the page; the motor system controls the turn of the pages (or click of the mouse); the prefrontal cortex maintains attention. Even fundamental functions, like breathing and regulation of body temperature, are controlled by the nervous system. A nervous system is an organism's control center: it processes sensory information from outside (and inside) the body and controls all behaviors—from eating to sleeping to finding a mate.

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8.2.2: Video - The Nervous System

This video takes a look at the nervous system and all of the things that it is responsible for in the body.



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8.2.3: Neurons and Glial Cells

Skills to Develop

- List and describe the functions of the structural components of a neuron
- List and describe the four main types of neurons
- Compare the functions of different types of glial cells

Nervous systems throughout the animal kingdom vary in structure and complexity, as illustrated by the variety of animals shown in Figure 8.2.3.1. Some organisms, like sea sponges, lack a true nervous system. Others, like jellyfish, lack a true brain and instead have a system of separate but connected nerve cells (neurons) called a "nerve net." Echinoderms such as sea stars have nerve cells that are bundled into fibers called nerves. Flatworms of the phylum Platyhelminthes have both a central nervous system (CNS), made up of a small "brain" and two nerve cords, and a peripheral nervous system (PNS) containing a system of nerves that extend throughout the body. The insect nervous system is more complex but also fairly decentralized. It contains a brain, ventral nerve cord, and ganglia (clusters of connected neurons). These ganglia can control movements and behaviors without input from the brain. Octopi may have the most complicated of invertebrate nervous systems—they have neurons that are organized in specialized lobes and eyes that are structurally similar to vertebrate species.

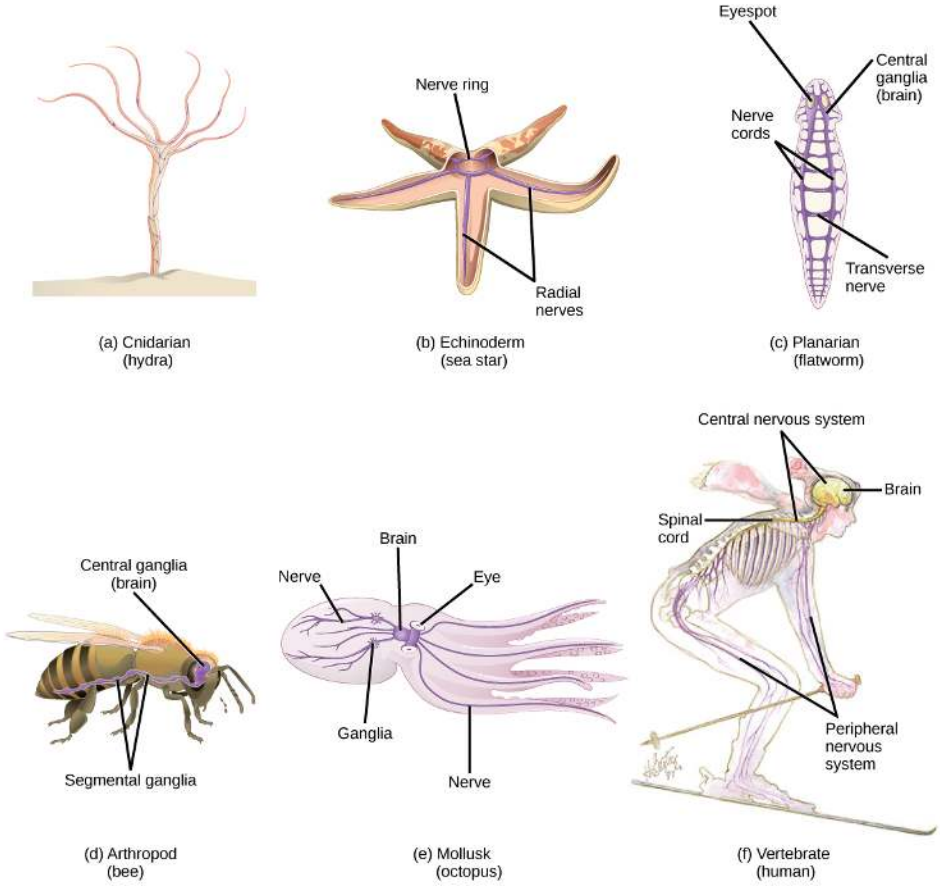
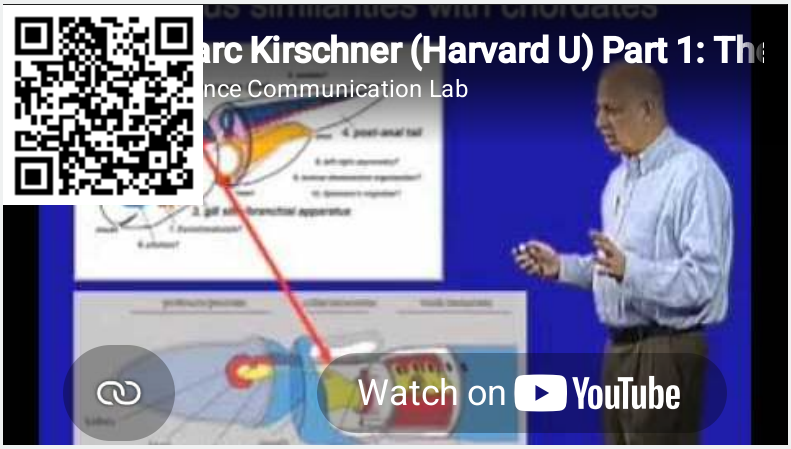


Figure 8.2.3.1: Nervous systems vary in structure and complexity. In (a) cnidarians, nerve cells form a decentralized nerve net. In (b) echinoderms, nerve cells are bundled into fibers called nerves. In animals exhibiting bilateral symmetry such as (c) planarians, neurons cluster into an anterior brain that processes information. In addition to a brain, (d) arthropods have clusters of nerve cell bodies, called peripheral ganglia, located along the ventral nerve cord. Mollusks such as squid and (e) octopi, which must hunt to survive, have complex brains containing millions of neurons. In (f) vertebrates, the brain and spinal cord comprise the central nervous system, while neurons extending into the rest of the body comprise the peripheral nervous system. (credit e: modification of work by Michael Vecchione, Clyde F.E. Roper, and Michael J. Sweeney, NOAA; credit f: modification of work by NIH).

Compared to invertebrates, vertebrate nervous systems are more complex, centralized, and specialized. While there is great diversity among different vertebrate nervous systems, they all share a basic structure: a CNS that contains a brain and spinal cord

and a PNS made up of peripheral sensory and motor nerves. One interesting difference between the nervous systems of invertebrates and vertebrates is that the nerve cords of many invertebrates are located ventrally whereas the vertebrate spinal cords are located dorsally. There is debate among evolutionary biologists as to whether these different nervous system plans evolved separately or whether the invertebrate body plan arrangement somehow "flipped" during the evolution of vertebrates.

Link to Learning



Watch this video of biologist Mark Kirschner discussing the "flipping" phenomenon of vertebrate evolution.

The nervous system is made up of neurons, specialized cells that can receive and transmit chemical or electrical signals, and glia, cells that provide support functions for the neurons by playing an information processing role that is complementary to neurons. A neuron can be compared to an electrical wire—it transmits a signal from one place to another. Glia can be compared to the workers at the electric company who make sure wires go to the right places, maintain the wires, and take down wires that are broken. Although glia have been compared to workers, recent evidence suggests that also usurp some of the signaling functions of neurons.

There is great diversity in the types of neurons and glia that are present in different parts of the nervous system. There are four major types of neurons, and they share several important cellular components.

Neurons

The nervous system of the common laboratory fly, *Drosophila melanogaster*, contains around 100,000 neurons, the same number as a lobster. This number compares to 75 million in the mouse and 300 million in the octopus. A human brain contains around 86 billion neurons. Despite these very different numbers, the nervous systems of these animals control many of the same behaviors—from basic reflexes to more complicated behaviors like finding food and courting mates. The ability of neurons to communicate with each other as well as with other types of cells underlies all of these behaviors.

Most neurons share the same cellular components. But neurons are also highly specialized—different types of neurons have different sizes and shapes that relate to their functional roles.

Parts of a Neuron

Like other cells, each neuron has a cell body (or soma) that contains a nucleus, smooth and rough endoplasmic reticulum, Golgi apparatus, mitochondria, and other cellular components. Neurons also contain unique structures, illustrated in Figure 8.2.3.2 for receiving and sending the electrical signals that make neuronal communication possible. Dendrites are tree-like structures that extend away from the cell body to receive messages from other neurons at specialized junctions called synapses. Although some neurons do not have any dendrites, some types of neurons have multiple dendrites. Dendrites can have small protrusions called dendritic spines, which further increase surface area for possible synaptic connections.

Once a signal is received by the dendrite, it then travels passively to the cell body. The cell body contains a specialized structure, the axon hillock that integrates signals from multiple synapses and serves as a junction between the cell body and an axon. An axon is a tube-like structure that propagates the integrated signal to specialized endings called axon terminals. These terminals in turn synapse on other neurons, muscle, or target organs. Chemicals released at axon terminals allow signals to be communicated to

these other cells. Neurons usually have one or two axons, but some neurons, like amacrine cells in the retina, do not contain any axons. Some axons are covered with myelin, which acts as an insulator to minimize dissipation of the electrical signal as it travels down the axon, greatly increasing the speed on conduction. This insulation is important as the axon from a human motor neuron can be as long as a meter—from the base of the spine to the toes. The myelin sheath is not actually part of the neuron. Myelin is produced by glial cells. Along the axon there are periodic gaps in the myelin sheath. These gaps are called nodes of Ranvier and are sites where the signal is “recharged” as it travels along the axon.

It is important to note that a single neuron does not act alone—neuronal communication depends on the connections that neurons make with one another (as well as with other cells, like muscle cells). Dendrites from a single neuron may receive synaptic contact from many other neurons. For example, dendrites from a Purkinje cell in the cerebellum are thought to receive contact from as many as 200,000 other neurons.

Art Connection

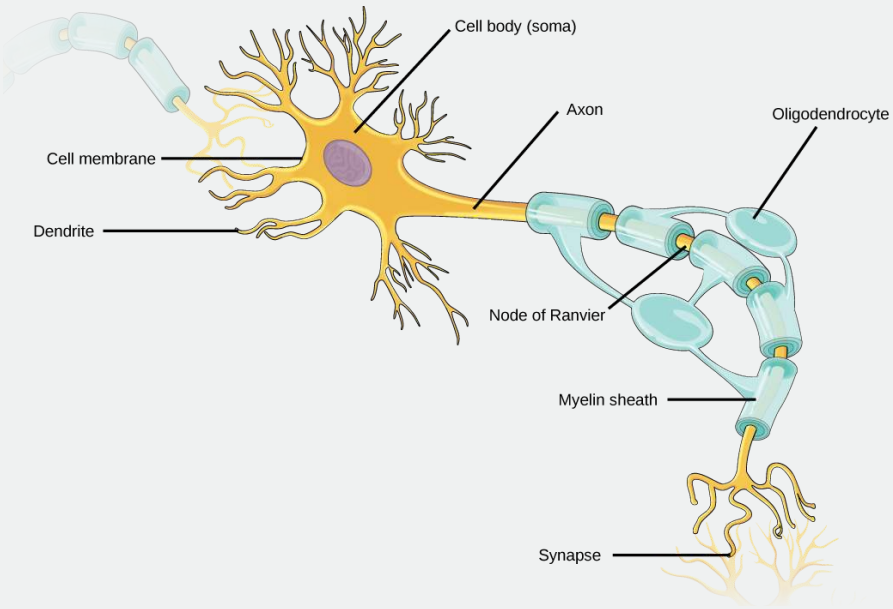


Figure 8.2.3.2: Neurons contain organelles common to many other cells, such as a nucleus and mitochondria. They also have more specialized structures, including dendrites and axons.

Which of the following statements is false?

A. The soma is the cell body of a nerve cell.
B. Myelin sheath provides an insulating layer to the dendrites.
C. Axons carry the signal from the soma to the target.
D. Dendrites carry the signal to the soma.

Types of Neurons

There are different types of neurons, and the functional role of a given neuron is intimately dependent on its structure. There is an amazing diversity of neuron shapes and sizes found in different parts of the nervous system (and across species), as illustrated by the neurons shown in Figure 8.2.3.3.

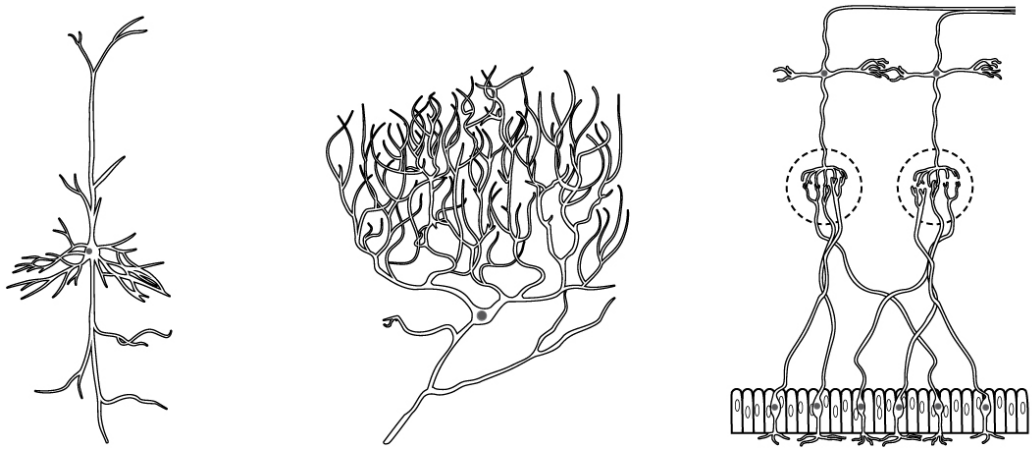


Figure 8.2.3.3: There is great diversity in the size and shape of neurons throughout the nervous system. Examples include (a) a pyramidal cell from the cerebral cortex, (b) a Purkinje cell from the cerebellar cortex, and (c) olfactory cells from the olfactory epithelium and olfactory bulb.

While there are many defined neuron cell subtypes, neurons are broadly divided into four basic types: unipolar, bipolar, multipolar, and pseudounipolar. Figure 8.2.3.4 illustrates these four basic neuron types. Unipolar neurons have only one structure that extends away from the soma. These neurons are not found in vertebrates but are found in insects where they stimulate muscles or glands. A bipolar neuron has one axon and one dendrite extending from the soma. An example of a bipolar neuron is a retinal bipolar cell, which receives signals from photoreceptor cells that are sensitive to light and transmits these signals to ganglion cells that carry the signal to the brain. Multipolar neurons are the most common type of neuron. Each multipolar neuron contains one axon and multiple dendrites. Multipolar neurons can be found in the central nervous system (brain and spinal cord). An example of a multipolar neuron is a Purkinje cell in the cerebellum, which has many branching dendrites but only one axon. Pseudounipolar cells share characteristics with both unipolar and bipolar cells. A pseudounipolar cell has a single process that extends from the soma, like a unipolar cell, but this process later branches into two distinct structures, like a bipolar cell. Most sensory neurons are pseudounipolar and have an axon that branches into two extensions: one connected to dendrites that receive sensory information and another that transmits this information to the spinal cord.

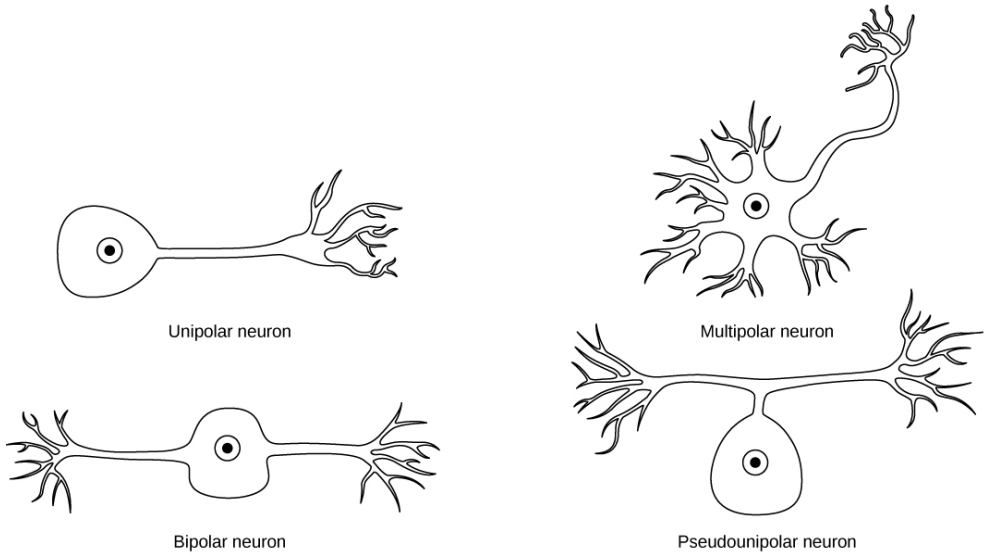


Figure 8.2.3.4: Neurons are broadly divided into four main types based on the number and placement of axons: (1) unipolar, (2) bipolar, (3) multipolar, and (4) pseudounipolar.

Everyday Connection: Neurogenesis

At one time, scientists believed that people were born with all the neurons they would ever have. Research performed during the last few decades indicates that neurogenesis, the birth of new neurons, continues into adulthood. Neurogenesis was first discovered in songbirds that produce new neurons while learning songs. For mammals, new neurons also play an important role in learning: about 1000 new neurons develop in the hippocampus (a brain structure involved in learning and memory) each day. While most of the new neurons will die, researchers found that an increase in the number of surviving new neurons in the hippocampus correlated with how well rats learned a new task. Interestingly, both exercise and some antidepressant medications also promote neurogenesis in the hippocampus. Stress has the opposite effect. While neurogenesis is quite limited compared to regeneration in other tissues, research in this area may lead to new treatments for disorders such as Alzheimer's, stroke, and epilepsy.

How do scientists identify new neurons? A researcher can inject a compound called bromodeoxyuridine (BrdU) into the brain of an animal. While all cells will be exposed to BrdU, BrdU will only be incorporated into the DNA of newly generated cells that are in S phase. A technique called immunohistochemistry can be used to attach a fluorescent label to the incorporated BrdU, and a researcher can use fluorescent microscopy to visualize the presence of BrdU, and thus new neurons, in brain tissue. Figure 8.2.3.5 is a micrograph which shows fluorescently labeled neurons in the hippocampus of a rat.

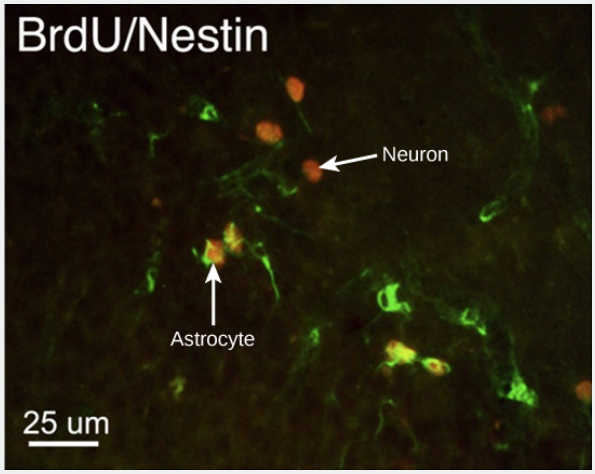


Figure 8.2.3.5: This micrograph shows fluorescently labeled new neurons in a rat hippocampus. Cells that are actively dividing have bromodoxyuridine (BrdU) incorporated into their DNA and are labeled in red. Cells that express glial fibrillary acidic protein (GFAP) are labeled in green. Astrocytes, but not neurons, express GFAP. Thus, cells that are labeled both red and green are actively dividing astrocytes, whereas cells labeled red only are actively dividing neurons. (credit: modification of work by Dr. Maryam Faiz, et. al., University of Barcelona; scale-bar data from Matt Russell)

Link to Learning

This site contains more information about neurogenesis, including an interactive laboratory simulation and a video that explains how BrdU labels new cells.

Glia

While glia are often thought of as the supporting cast of the nervous system, the number of glial cells in the brain actually outnumbers the number of neurons by a factor of ten. Neurons would be unable to function without the vital roles that are fulfilled by these glial cells. Glia guide developing neurons to their destinations, buffer ions and chemicals that would otherwise harm neurons, and provide myelin sheaths around axons. Scientists have recently discovered that they also play a role in responding to nerve activity and modulating communication between nerve cells. When glia do not function properly, the result can be disastrous—most brain tumors are caused by mutations in glia.

Types of Glia

There are several different types of glia with different functions, two of which are shown in Figure 8.2.3.6. Astrocytes, shown in Figure 8.2.3.7 make contact with both capillaries and neurons in the CNS. They provide nutrients and other substances to neurons, regulate the concentrations of ions and chemicals in the extracellular fluid, and provide structural support for synapses. Astrocytes also form the blood-brain barrier—a structure that blocks entrance of toxic substances into the brain. Astrocytes, in particular, have been shown through calcium imaging experiments to become active in response to nerve activity, transmit calcium waves between astrocytes, and modulate the activity of surrounding synapses.

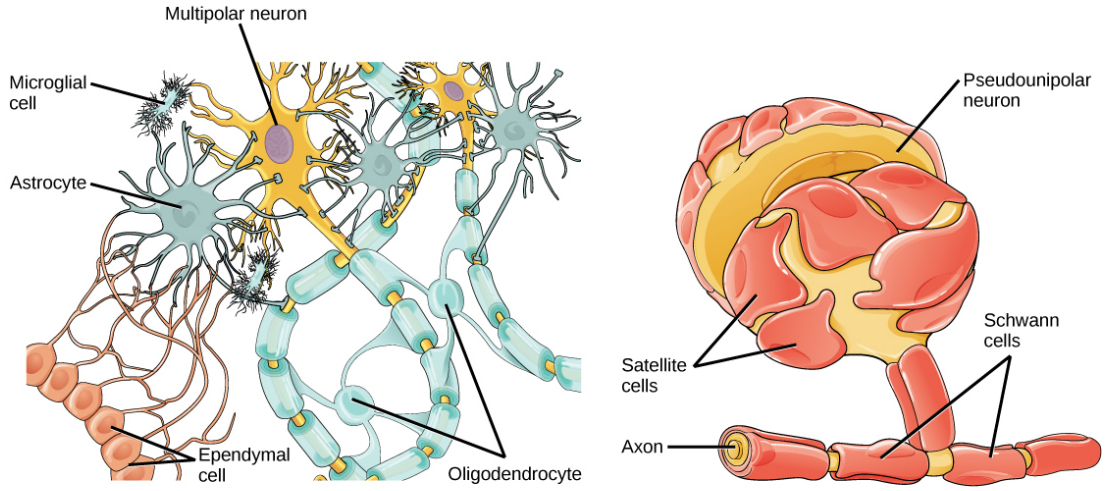
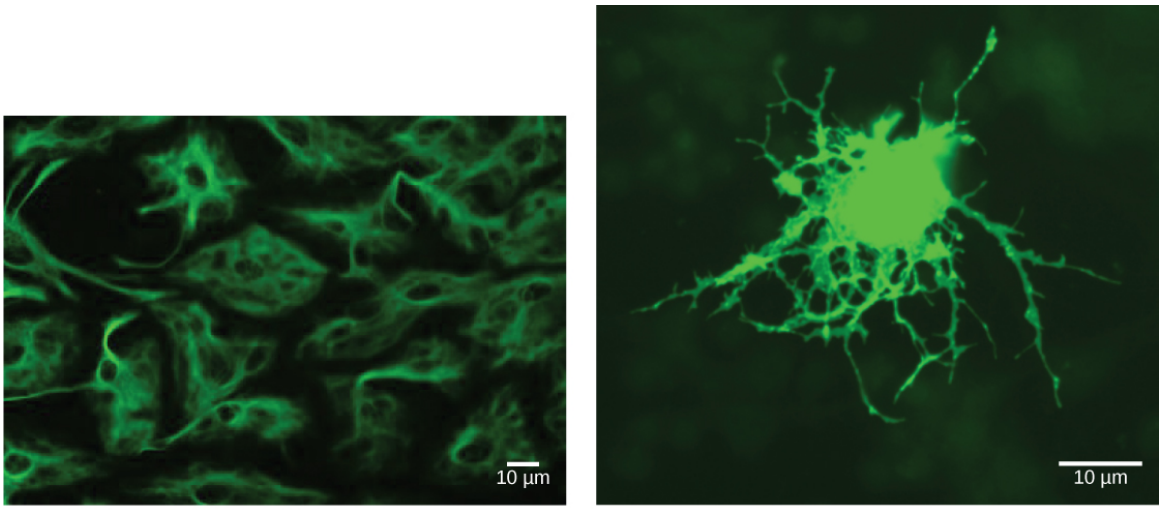


Figure 8.2.3.6: Glial cells support neurons and maintain their environment. Glial cells of the (a) central nervous system include oligodendrocytes, astrocytes, ependymal cells, and microglial cells. Oligodendrocytes form the myelin sheath around axons. Astrocytes provide nutrients to neurons, maintain their extracellular environment, and provide structural support. Microglia scavenge pathogens and dead cells. Ependymal cells produce cerebrospinal fluid that cushions the neurons. Glial cells of the (b) peripheral nervous system include Schwann cells, which form the myelin sheath, and satellite cells, which provide nutrients and structural support to neurons.

Satellite glia provide nutrients and structural support for neurons in the PNS. Microglia scavenge and degrade dead cells and protect the brain from invading microorganisms. Oligodendrocytes, shown in Figure 8.2.3.7 form myelin sheaths around axons in the CNS. One axon can be myelinated by several oligodendrocytes, and one oligodendrocyte can provide myelin for multiple neurons. This is distinctive from the PNS where a single Schwann cell provides myelin for only one axon as the entire Schwann cell surrounds the axon. Radial glia serve as scaffolds for developing neurons as they migrate to their end destinations. Ependymal cells line fluid-filled ventricles of the brain and the central canal of the spinal cord. They are involved in the production of cerebrospinal fluid, which serves as a cushion for the brain, moves the fluid between the spinal cord and the brain, and is a component for the choroid plexus.



(a) Astrocyte (b) Oligodendrocyte

Figure 8.2.3.7: (a) Astrocytes and (b) oligodendrocytes are glial cells of the central nervous system. (credit a: modification of work by Uniformed Services University; credit b: modification of work by Jurjen Broeke; scale-bar data from Matt Russell)

Summary

The nervous system is made up of neurons and glia. Neurons are specialized cells that are capable of sending electrical as well as chemical signals. Most neurons contain dendrites, which receive these signals, and axons that send signals to other neurons or tissues. There are four main types of neurons: unipolar, bipolar, multipolar, and pseudounipolar neurons. Glia are non-neuronal cells in the nervous system that support neuronal development and signaling. There are several types of glia that serve different functions.

Art Connections

Figure 8.2.3.2: Which of the following statements is false?

A. The soma is the cell body of a nerve cell.
B. Myelin sheath provides an insulating layer to the dendrites.
C. Axons carry the signal from the soma to the target.
D. Dendrites carry the signal to the soma.

Answer

B

Glossary

astrocyte
glial cell in the central nervous system that provide nutrients, extracellular buffering, and structural support for neurons; also makes up the blood-brain barrier

axon
tube-like structure that propagates a signal from a neuron’s cell body to axon terminals

axon hillock
electrically sensitive structure on the cell body of a neuron that integrates signals from multiple neuronal connections

axon terminal
structure on the end of an axon that can form a synapse with another neuron

dendrite
structure that extends away from the cell body to receive messages from other neurons

ependymal
cell that lines fluid-filled ventricles of the brain and the central canal of the spinal cord; involved in production of cerebrospinal fluid

glia
(also, glial cells) cells that provide support functions for neurons

microglia
glia that scavenge and degrade dead cells and protect the brain from invading microorganisms

myelin
fatty substance produced by glia that insulates axons

neuron
specialized cell that can receive and transmit electrical and chemical signals

nodes of Ranvier
gaps in the myelin sheath where the signal is recharged

oligodendrocyte
glial cell that myelinates central nervous system neuron axons

radial glia
glia that serve as scaffolds for developing neurons as they migrate to their final destinations

satellite glia
glial cell that provides nutrients and structural support for neurons in the peripheral nervous system

Schwann cell
glial cell that creates myelin sheath around a peripheral nervous system neuron axon

synapse
junction between two neurons where neuronal signals are communicated

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8.2.4: How Neurons Communicate

Skills to Develop

- Describe the basis of the resting membrane potential
- Explain the stages of an action potential and how action potentials are propagated
- Explain the similarities and differences between chemical and electrical synapses
- Describe long-term potentiation and long-term depression

All functions performed by the nervous system—from a simple motor reflex to more advanced functions like making a memory or a decision—require neurons to communicate with one another. While humans use words and body language to communicate, neurons use electrical and chemical signals. Just like a person in a committee, one neuron usually receives and synthesizes messages from multiple other neurons before "making the decision" to send the message on to other neurons.

Nerve Impulse Transmission within a Neuron

For the nervous system to function, neurons must be able to send and receive signals. These signals are possible because each neuron has a charged cellular membrane (a voltage difference between the inside and the outside), and the charge of this membrane can change in response to neurotransmitter molecules released from other neurons and environmental stimuli. To understand how neurons communicate, one must first understand the basis of the baseline or 'resting' membrane charge.

Neuronal Charged Membranes

The lipid bilayer membrane that surrounds a neuron is impermeable to charged molecules or ions. To enter or exit the neuron, ions must pass through special proteins called ion channels that span the membrane. Ion channels have different configurations: open, closed, and inactive, as illustrated in Figure 8.2.4.1. Some ion channels need to be activated in order to open and allow ions to pass into or out of the cell. These ion channels are sensitive to the environment and can change their shape accordingly. Ion channels that change their structure in response to voltage changes are called voltage-gated ion channels. Voltage-gated ion channels regulate the relative concentrations of different ions inside and outside the cell. The difference in total charge between the inside and outside of the cell is called the membrane potential.

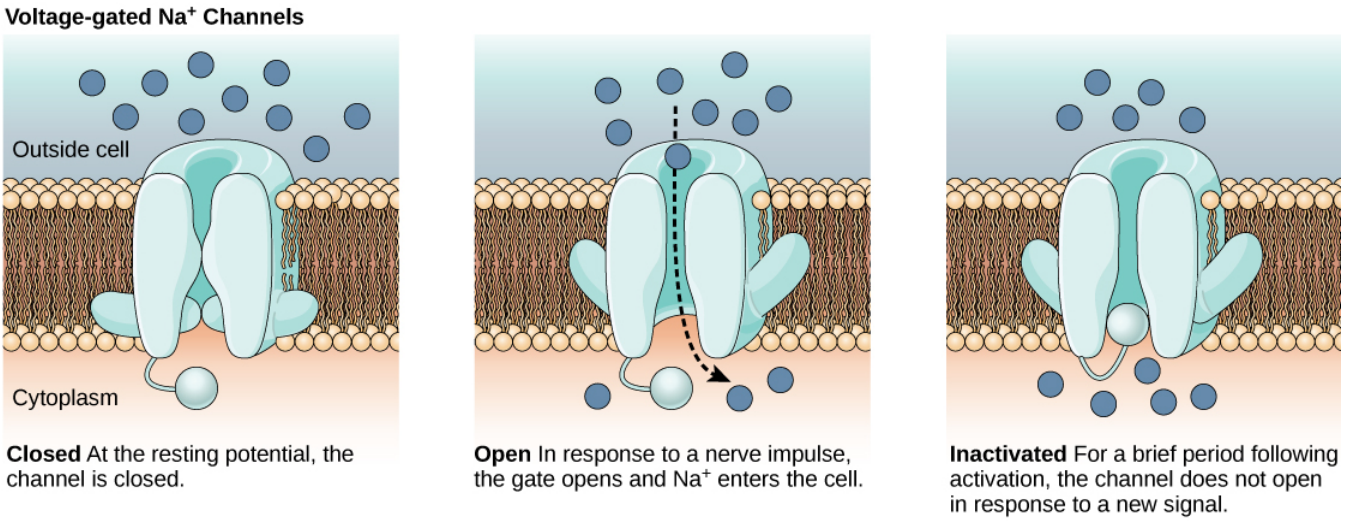


Figure 8.2.4.1: Voltage-gated ion channels open in response to changes in membrane voltage. After activation, they become inactivated for a brief period and will no longer open in response to a signal.

Link to Learning



This video discusses the basis of the resting membrane potential.

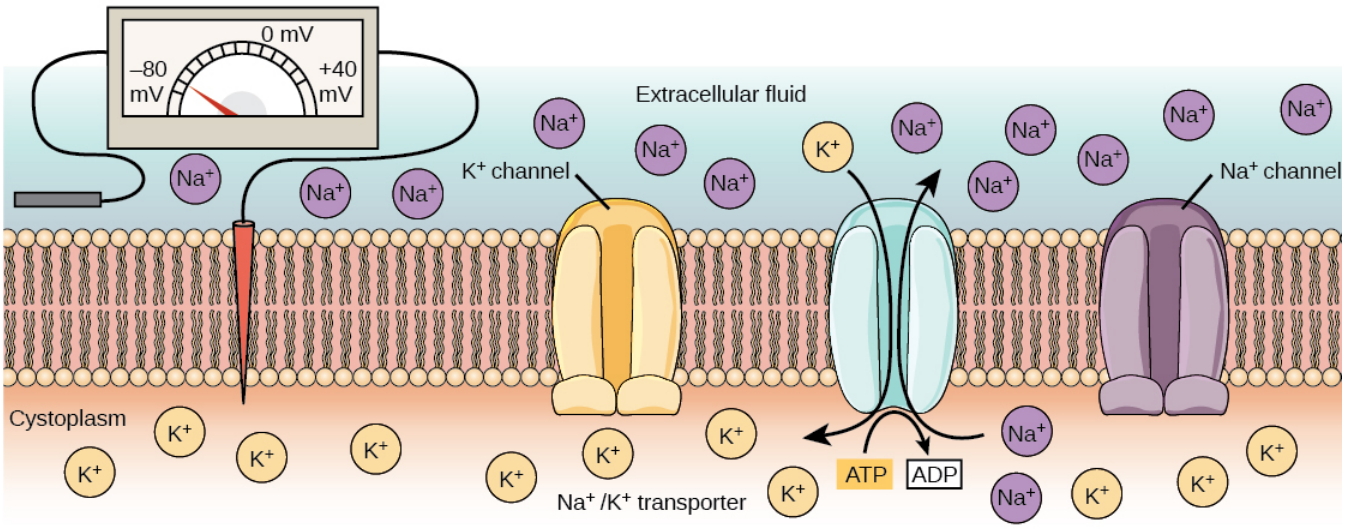
Resting Membrane Potential

A neuron at rest is negatively charged: the inside of a cell is approximately 70 millivolts more negative than the outside (−70 mV, note that this number varies by neuron type and by species). This voltage is called the resting membrane potential; it is caused by differences in the concentrations of ions inside and outside the cell. If the membrane were equally permeable to all ions, each type of ion would flow across the membrane and the system would reach equilibrium. Because ions cannot simply cross the membrane at will, there are different concentrations of several ions inside and outside the cell, as shown in the table below. The difference in the number of positively charged potassium ions (K^+) inside and outside the cell dominates the resting membrane potential (Figure 8.2.4.2). When the membrane is at rest, K^+ ions accumulate inside the cell due to a net movement with the concentration gradient. The negative resting membrane potential is created and maintained by increasing the concentration of cations outside the cell (in the extracellular fluid) relative to inside the cell (in the cytoplasm). The negative charge within the cell is created by the cell membrane being more permeable to potassium ion movement than sodium ion movement. In neurons, potassium ions are maintained at high concentrations within the cell while sodium ions are maintained at high concentrations outside of the cell. The cell possesses potassium and sodium leakage channels that allow the two cations to diffuse down their concentration gradient. However, the neurons have far more potassium leakage channels than sodium leakage channels. Therefore, potassium diffuses out of the cell at a much faster rate than sodium leaks in. Because more cations are leaving the cell than are entering, this causes the interior of the cell to be negatively charged relative to the outside of the cell. The actions of the sodium potassium pump help to maintain the resting potential, once established. Recall that sodium potassium pumps brings two K^+ ions into the cell while removing three Na^+ ions per ATP consumed. As more cations are expelled from the cell than taken in, the inside of the cell remains negatively charged relative to the extracellular fluid. It should be noted that calcium ions (Cl^-) tend to accumulate outside of the cell because they are repelled by negatively-charged proteins within the cytoplasm.

Table 8.2.4.1**:** Ion Concentration Inside and Outside Neurons. The resting membrane potential is a result of different concentrations inside and outside the cell.

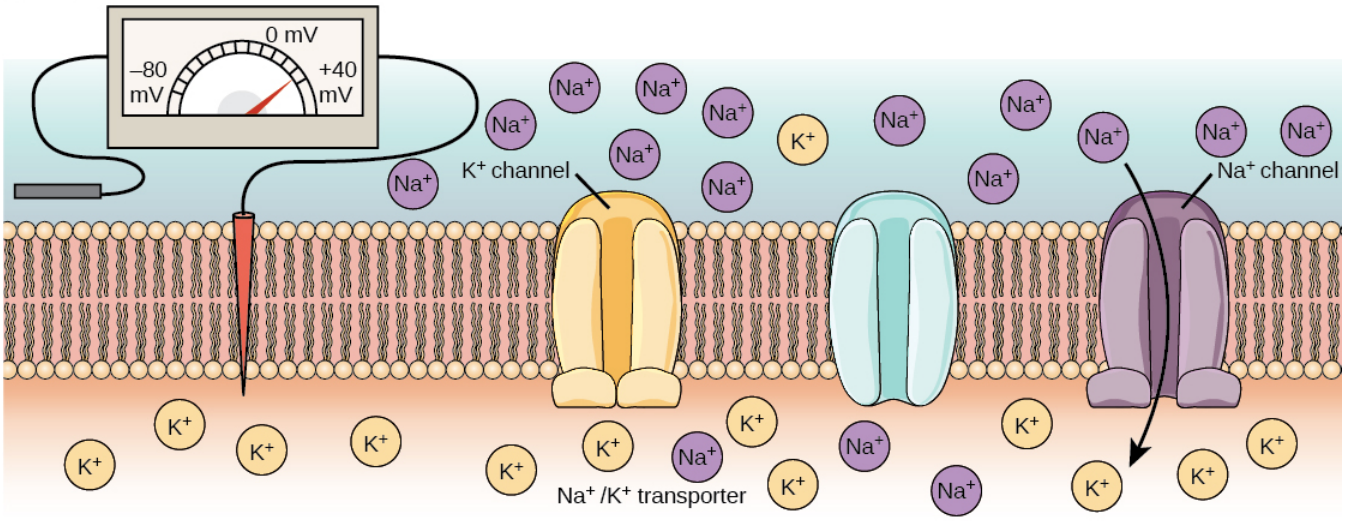
Ion	Extracellular concentration (mM)	Intracellular concentration (mM)	Ratio outside/inside
Na^+	145	12	12
K^+	4	155	0.026
Cl^-	120	4	30
Organic anions (A−)	—	100	

(a) Resting potential



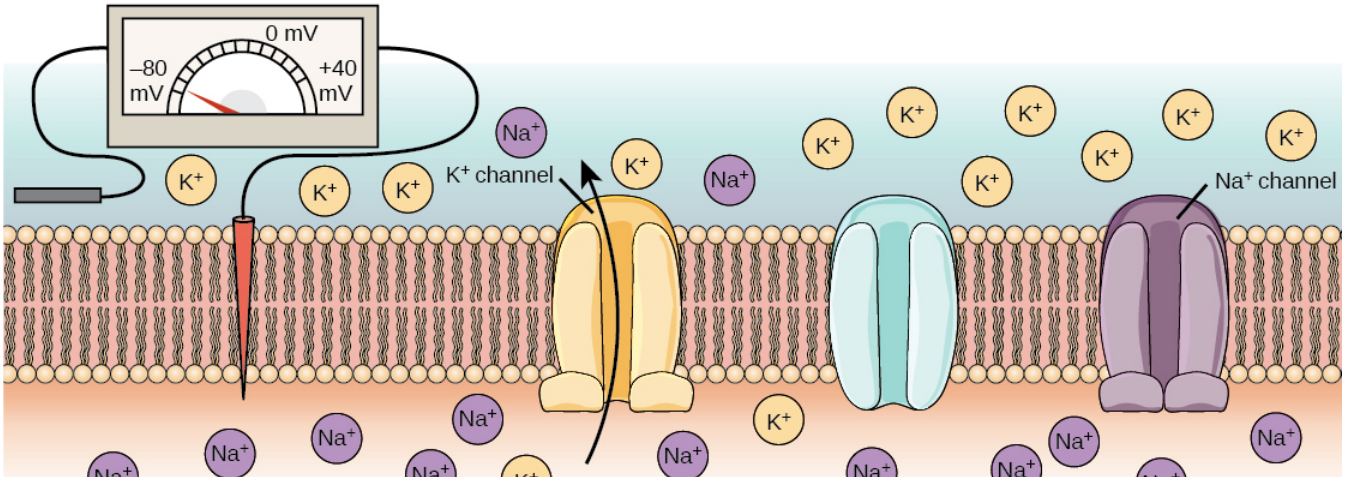
At the resting potential, all voltage-gated Na^+ channels and most voltage-gated K^+ channels are closed. The Na^+/K^+ transporter pumps K^+ ions into the cell and Na^+ ions out.

(b) Depolarization



In response to a depolarization, some Na^+ channels open, allowing Na^+ ions to enter the cell. The membrane starts to depolarize (the charge across the membrane lessens). If the threshold of excitation is reached, all the Na^+ channels open.

(c) Hyperpolarization



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Figure 8.2.4.2: The (a) resting membrane potential is a result of different concentrations of Na^+ and K^+ ions inside and outside the cell. A nerve impulse causes Na^+ to enter the cell, resulting in (b) depolarization. At the peak action potential, K^+ channels open and the cell becomes (c) hyperpolarized.

At the peak action potential, Na^+ channels close while K^+ channels open. K^+ leaves the cell, and the membrane eventually becomes hyperpolarized.

Action Potential

A neuron can receive input from other neurons and, if this input is strong enough, send the signal to downstream neurons. Transmission of a signal between neurons is generally carried by a chemical called a neurotransmitter. Transmission of a signal within a neuron (from dendrite to axon terminal) is carried by a brief reversal of the resting membrane potential called an action potential. When neurotransmitter molecules bind to receptors located on a neuron's dendrites, ion channels open. At excitatory synapses, this opening allows positive ions to enter the neuron and results in depolarization of the membrane—a decrease in the difference in voltage between the inside and outside of the neuron. A stimulus from a sensory cell or another neuron depolarizes the target neuron to its threshold potential (-55 mV). Na^+ channels in the axon hillock open, allowing positive ions to enter the cell (Figure 8.2.4.3 and Figure 8.2.4.4). Once the sodium channels open, the neuron completely depolarizes to a membrane potential of about +40 mV. Action potentials are considered an "all-or nothing" event, in that, once the threshold potential is reached, the neuron always completely depolarizes. Once depolarization is complete, the cell must now "reset" its membrane voltage back to the resting potential. To accomplish this, the Na^+ channels close and cannot be opened. This begins the neuron's refractory period, in which it cannot produce another action potential because its sodium channels will not open. At the same time, voltage-gated K^+ channels open, allowing K^+ to leave the cell. As K^+ ions leave the cell, the membrane potential once again becomes negative. The diffusion of K^+ out of the cell actually hyperpolarizes the cell, in that the membrane potential becomes more negative than the cell's normal resting potential. At this point, the sodium channels will return to their resting state, meaning they are ready to open again if the membrane potential again exceeds the threshold potential. Eventually the extra K^+ ions diffuse out of the cell through the potassium leakage channels, bringing the cell from its hyperpolarized state, back to its resting membrane potential.

Art Connection

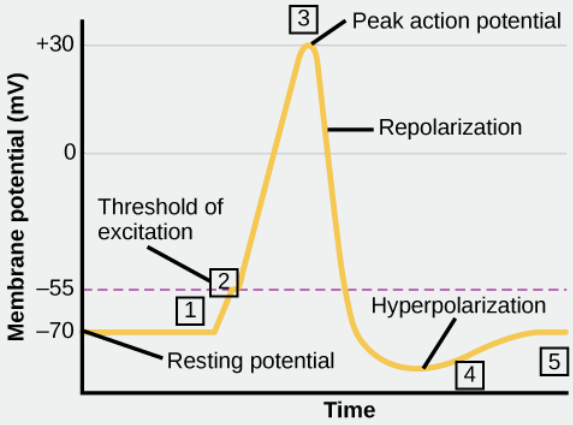


Figure 8.2.4.3: The formation of an action potential can be divided into five steps: (1) A stimulus from a sensory cell or another neuron causes the target cell to depolarize toward the threshold potential. (2) If the threshold of excitation is reached, all Na^+ channels open and the membrane depolarizes. (3) At the peak action potential, K^+ channels open and K^+ begins to leave the cell. At the same time, Na^+ channels close. (4) The membrane becomes hyperpolarized as K^+ ions continue to leave the cell. The hyperpolarized membrane is in a refractory period and cannot fire. (5) The K^+ channels close and the Na^+/K^+ transporter restores the resting potential.

Potassium channel blockers, such as amiodarone and procainamide, which are used to treat abnormal electrical activity in the heart, called cardiac dysrhythmia, impede the movement of K^+ through voltage-gated K^+ channels. Which part of the action potential would you expect potassium channels to affect?

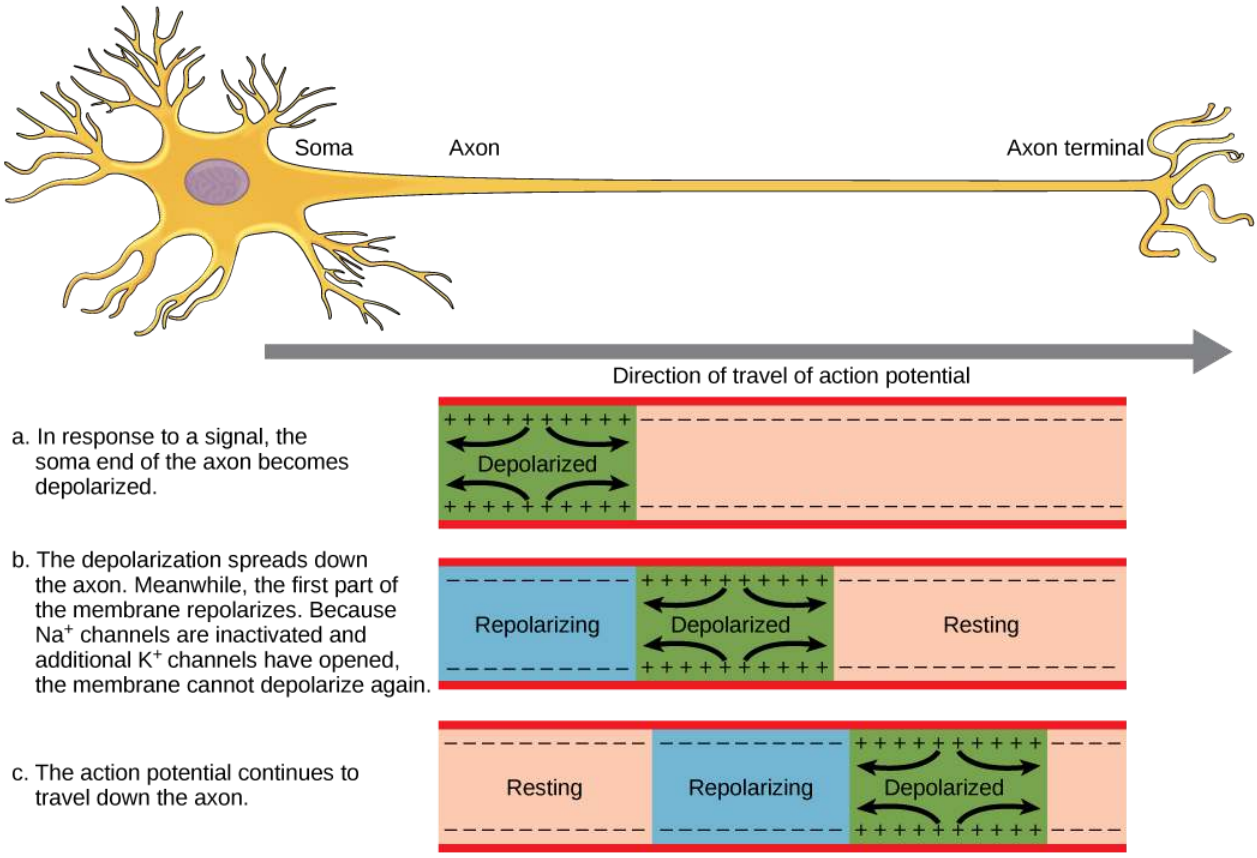
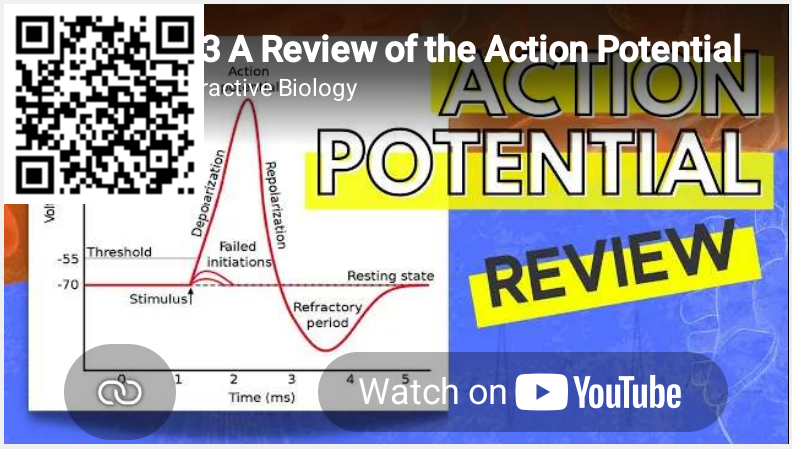


Figure 8.2.4.4: The action potential is conducted down the axon as the axon membrane depolarizes, then repolarizes.

Link to Learning



This video presents an overview of action potential.

Myelin and the Propagation of the Action Potential

For an action potential to communicate information to another neuron, it must travel along the axon and reach the axon terminals where it can initiate neurotransmitter release. The speed of conduction of an action potential along an axon is influenced by both the diameter of the axon and the axon's resistance to current leak. Myelin acts as an insulator that prevents current from leaving the axon; this increases the speed of action potential conduction. In demyelinating diseases like multiple sclerosis, action potential conduction slows because current leaks from previously insulated axon areas. The nodes of Ranvier, illustrated in Figure 8.2.4.5 are gaps in the myelin sheath along the axon. These unmyelinated spaces are about one micrometer long and contain voltage gated Na^+

and K^+ channels. Flow of ions through these channels, particularly the Na^+ channels, regenerates the action potential over and over again along the axon. This 'jumping' of the action potential from one node to the next is called saltatory conduction. If nodes of Ranvier were not present along an axon, the action potential would propagate very slowly since Na^+ and K^+ channels would have to continuously regenerate action potentials at every point along the axon instead of at specific points. Nodes of Ranvier also save energy for the neuron since the channels only need to be present at the nodes and not along the entire axon.

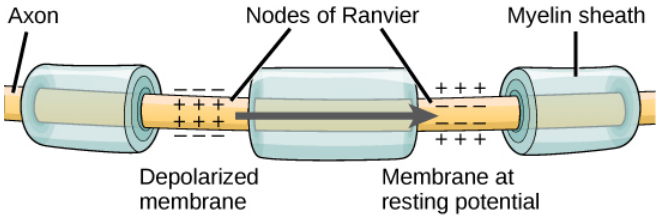


Figure 8.2.4.5: Nodes of Ranvier are gaps in myelin coverage along axons. Nodes contain voltage-gated K^+ and Na^+ channels. Action potentials travel down the axon by jumping from one node to the next.

Synaptic Transmission

The synapse or "gap" is the place where information is transmitted from one neuron to another. Synapses usually form between axon terminals and dendritic spines, but this is not universally true. There are also axon-to-axon, dendrite-to-dendrite, and axon-to-cell body synapses. The neuron transmitting the signal is called the presynaptic neuron, and the neuron receiving the signal is called the postsynaptic neuron. Note that these designations are relative to a particular synapse—most neurons are both presynaptic and postsynaptic. There are two types of synapses: chemical and electrical.

Chemical Synapse

When an action potential reaches the axon terminal it depolarizes the membrane and opens voltage-gated Na^+ channels. Na^+ ions enter the cell, further depolarizing the presynaptic membrane. This depolarization causes voltage-gated Ca^{2+} channels to open. Calcium ions entering the cell initiate a signaling cascade that causes small membrane-bound vesicles, called synaptic vesicles, containing neurotransmitter molecules to fuse with the presynaptic membrane. Synaptic vesicles are shown in Figure 8.2.4.6, which is an image from a scanning electron microscope.

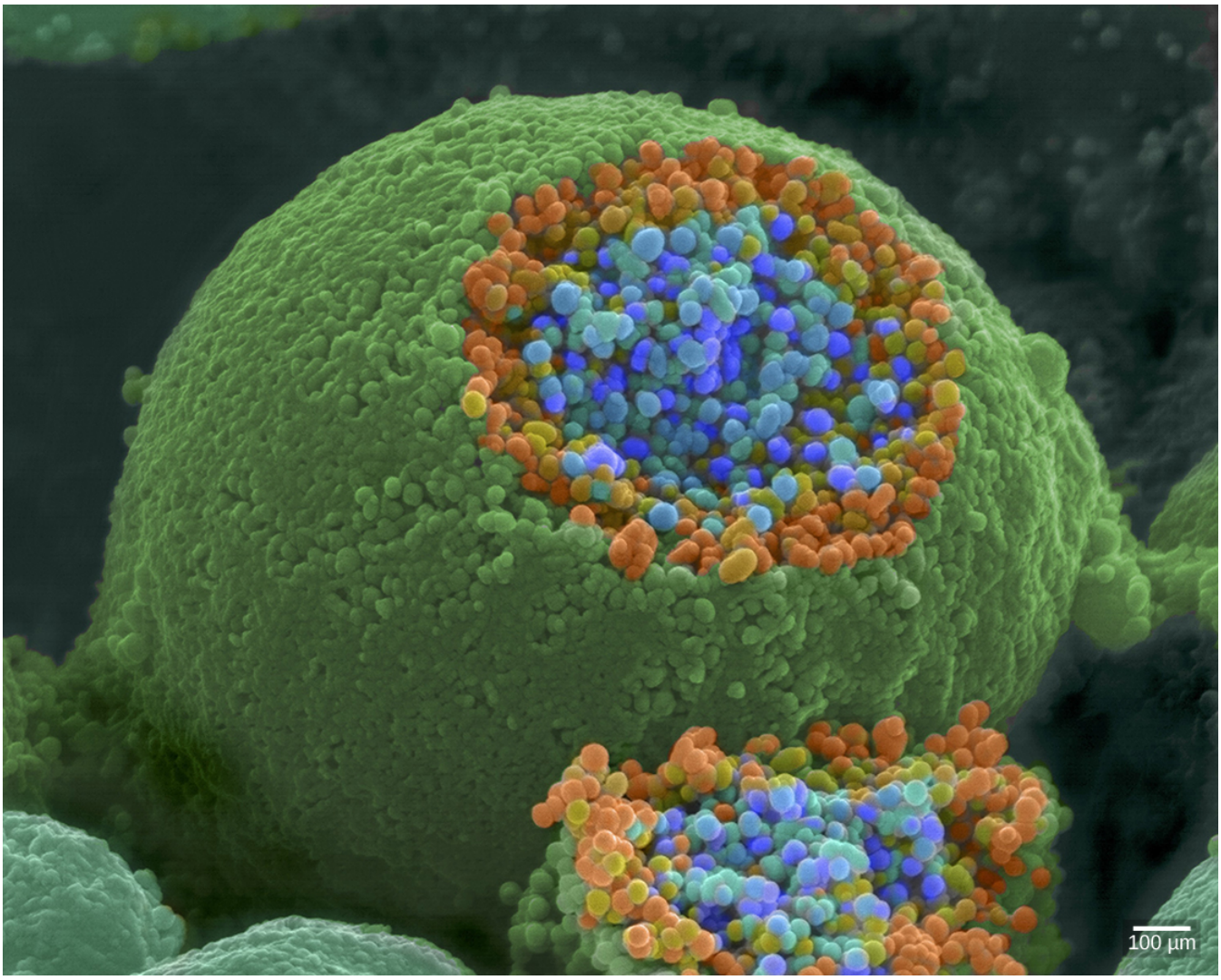
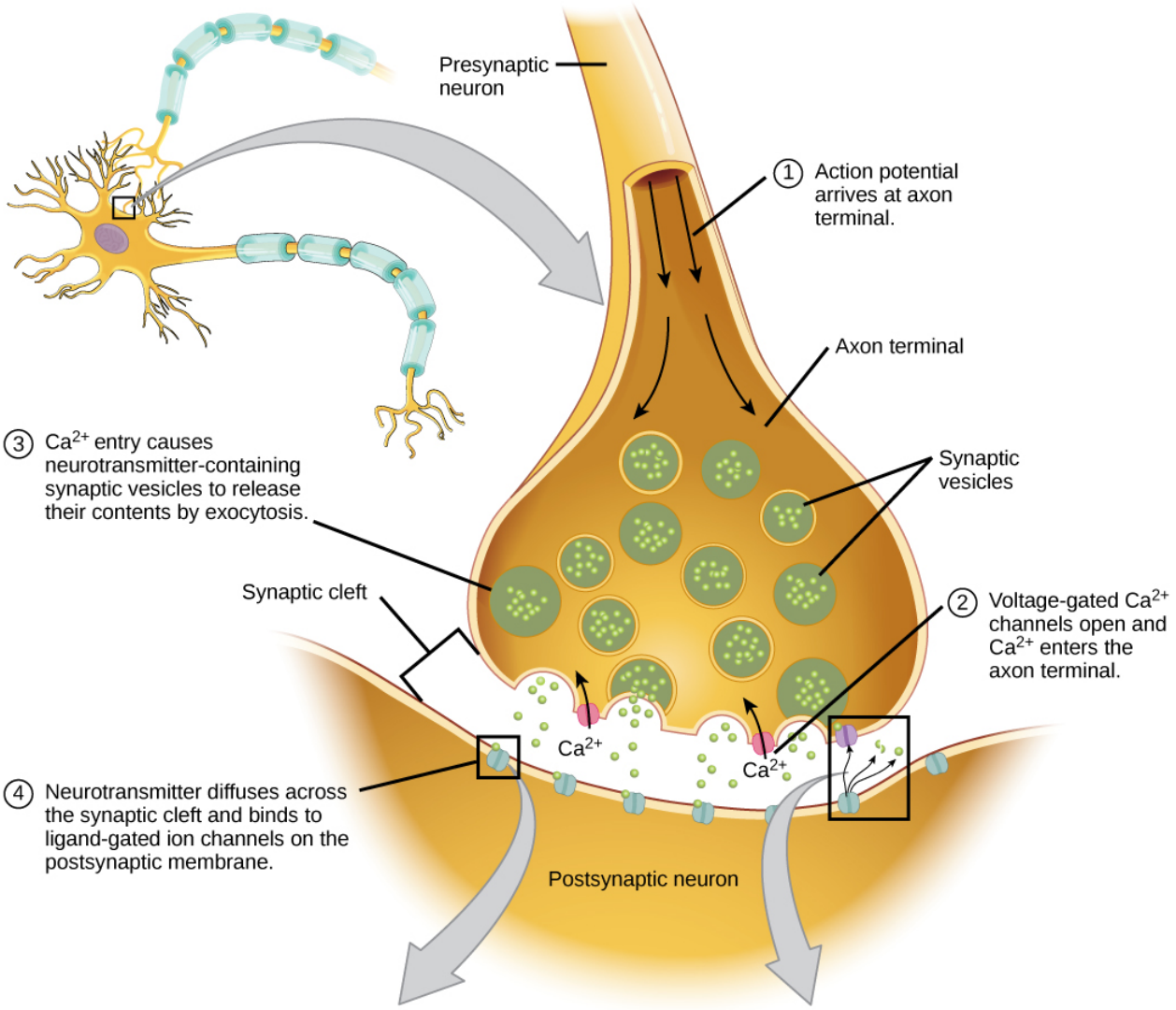
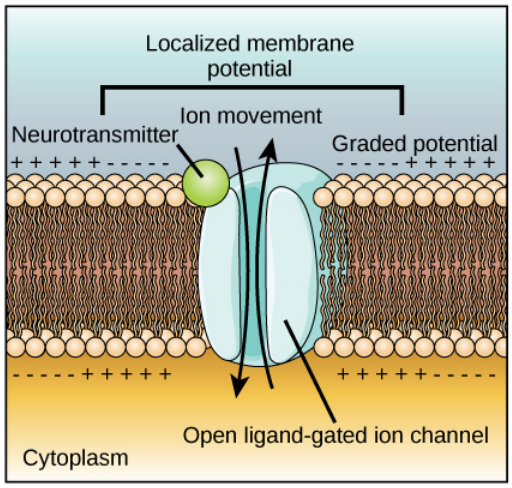


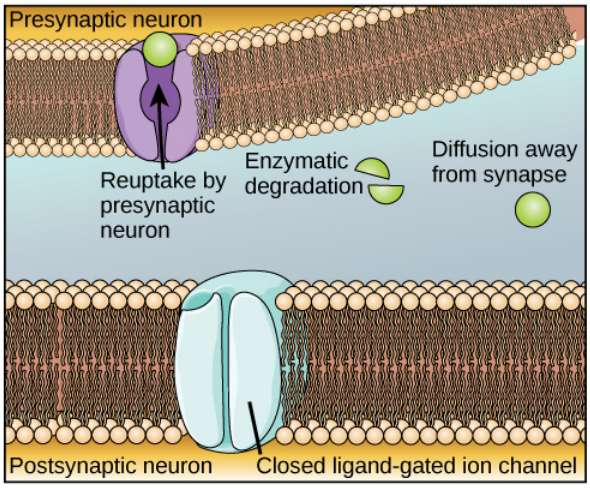
Figure 8.2.4.6: This pseudocolored image taken with a scanning electron microscope shows an axon terminal that was broken open to reveal synaptic vesicles (blue and orange) inside the neuron. (credit: modification of work by Tina Carvalho, NIH-NIGMS; scale-bar data from Matt Russell)

Fusion of a vesicle with the presynaptic membrane causes neurotransmitter to be released into the synaptic cleft, the extracellular space between the presynaptic and postsynaptic membranes, as illustrated in Figure 8.2.4.7. The neurotransmitter diffuses across the synaptic cleft and binds to receptor proteins on the postsynaptic membrane.





5 Binding of neurotransmitter opens ligand-gated ion channels, resulting in graded potentials.



6 Reuptake by the presynapic neuron, enzymatic degradation, and diffusion reduce neurotransmitter levels, terminating the signal.

Figure 8.2.4.7: Communication at chemical synapses requires release of neurotransmitters. When the presynaptic membrane is depolarized, voltage-gated Ca^{2+} channels open and allow Ca^{2+} to enter the cell. The calcium entry causes synaptic vesicles to fuse with the membrane and release neurotransmitter molecules into the synaptic cleft. The neurotransmitter diffuses across the synaptic cleft and binds to ligand-gated ion channels in the postsynaptic membrane, resulting in a localized depolarization or hyperpolarization of the postsynaptic neuron.

The binding of a specific neurotransmitter causes particular ion channels, in this case ligand-gated channels, on the postsynaptic membrane to open. Neurotransmitters can either have excitatory or inhibitory effects on the postsynaptic membrane, as detailed in the table below. For example, when acetylcholine is released at the synapse between a nerve and muscle (called the neuromuscular junction) by a presynaptic neuron, it causes postsynaptic Na^+ channels to open. Na^+ enters the postsynaptic cell and causes the postsynaptic membrane to depolarize. This depolarization is called an excitatory postsynaptic potential (EPSP) and makes the postsynaptic neuron more likely to fire an action potential. Release of neurotransmitter at inhibitory synapses causes inhibitory postsynaptic potentials (IPSPs), a hyperpolarization of the presynaptic membrane. For example, when the neurotransmitter GABA (gamma-aminobutyric acid) is released from a presynaptic neuron, it binds to and opens Cl^- channels. Cl^- ions enter the cell and hyperpolarizes the membrane, making the neuron less likely to fire an action potential.

Once neurotransmission has occurred, the neurotransmitter must be removed from the synaptic cleft so the postsynaptic membrane can “reset” and be ready to receive another signal. This can be accomplished in three ways: the neurotransmitter can diffuse away from the synaptic cleft, it can be degraded by enzymes in the synaptic cleft, or it can be recycled (sometimes called reuptake) by the presynaptic neuron. Several drugs act at this step of neurotransmission. For example, some drugs that are given to Alzheimer’s patients work by inhibiting acetylcholinesterase, the enzyme that degrades acetylcholine. This inhibition of the enzyme essentially increases neurotransmission at synapses that release acetylcholine. Once released, the acetylcholine stays in the cleft and can continually bind and unbind to postsynaptic receptors.

Table 8.2.4.2**:** Neurotransmitter Function and Location

Neurotransmitter	Example	Location
Acetylcholine	—	CNS and/or PNS
Biogenic amine	Dopamine, serotonin, norepinephrine	CNS and/or PNS
Amino acid	Glycine, glutamate, aspartate, gamma aminobutyric acid	CNS
Neuropeptide	Substance P, endorphins	CNS and/or PNS

Electrical Synapse

While electrical synapses are fewer in number than chemical synapses, they are found in all nervous systems and play important and unique roles. The mode of neurotransmission in electrical synapses is quite different from that in chemical synapses. In an electrical synapse, the presynaptic and postsynaptic membranes are very close together and are actually physically connected by channel proteins forming gap junctions. Gap junctions allow current to pass directly from one cell to the next. In addition to the ions that carry this current, other molecules, such as ATP, can diffuse through the large gap junction pores.

There are key differences between chemical and electrical synapses. Because chemical synapses depend on the release of neurotransmitter molecules from synaptic vesicles to pass on their signal, there is an approximately one millisecond delay between when the axon potential reaches the presynaptic terminal and when the neurotransmitter leads to opening of postsynaptic ion channels. Additionally, this signaling is unidirectional. Signaling in electrical synapses, in contrast, is virtually instantaneous (which is important for synapses involved in key reflexes), and some electrical synapses are bidirectional. Electrical synapses are also more reliable as they are less likely to be blocked, and they are important for synchronizing the electrical activity of a group of neurons. For example, electrical synapses in the thalamus are thought to regulate slow-wave sleep, and disruption of these synapses can cause seizures.

Signal Summation

Sometimes a single EPSP is strong enough to induce an action potential in the postsynaptic neuron, but often multiple presynaptic inputs must create EPSPs around the same time for the postsynaptic neuron to be sufficiently depolarized to fire an action potential.

This process is called summation and occurs at the axon hillock, as illustrated in Figure 8.2.4.8. Additionally, one neuron often has inputs from many presynaptic neurons—some excitatory and some inhibitory—so IPSPs can cancel out EPSPs and vice versa. It is the net change in postsynaptic membrane voltage that determines whether the postsynaptic cell has reached its threshold of excitation needed to fire an action potential. Together, synaptic summation and the threshold for excitation act as a filter so that random "noise" in the system is not transmitted as important information.

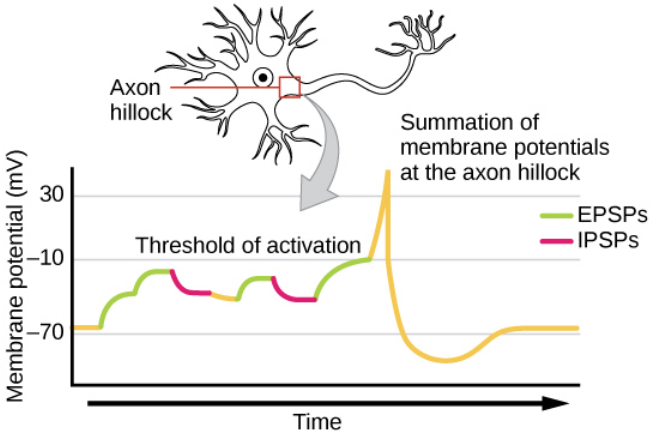


Figure 8.2.4.8: A single neuron can receive both excitatory and inhibitory inputs from multiple neurons, resulting in local membrane depolarization (EPSP input) and hyperpolarization (IPSP input). All these inputs are added together at the axon hillock. If the EPSPs are strong enough to overcome the IPSPs and reach the threshold of excitation, the neuron will fire.

Everyday Connection: Brain-computer interface

Amyotrophic lateral sclerosis (ALS, also called Lou Gehrig's Disease) is a neurological disease characterized by the degeneration of the motor neurons that control voluntary movements. The disease begins with muscle weakening and lack of coordination and eventually destroys the neurons that control speech, breathing, and swallowing; in the end, the disease can lead to paralysis. At that point, patients require assistance from machines to be able to breathe and to communicate. Several special technologies have been developed to allow "locked-in" patients to communicate with the rest of the world. One technology, for example, allows patients to type out sentences by twitching their cheek. These sentences can then be read aloud by a computer.

A relatively new line of research for helping paralyzed patients, including those with ALS, to communicate and retain a degree of self-sufficiency is called brain-computer interface (BCI) technology and is illustrated in Figure 8.2.4.9. This technology sounds like something out of science fiction: it allows paralyzed patients to control a computer using only their thoughts. There are several forms of BCI. Some forms use EEG recordings from electrodes taped onto the skull. These recordings contain information from large populations of neurons that can be decoded by a computer. Other forms of BCI require the implantation of an array of electrodes smaller than a postage stamp in the arm and hand area of the motor cortex. This form of BCI, while more invasive, is very powerful as each electrode can record actual action potentials from one or more neurons. These signals are then sent to a computer, which has been trained to decode the signal and feed it to a tool—such as a cursor on a computer screen. This means that a patient with ALS can use e-mail, read the Internet, and communicate with others by thinking of moving his or her hand or arm (even though the paralyzed patient cannot make that bodily movement). Recent advances have allowed a paralyzed locked-in patient who suffered a stroke 15 years ago to control a robotic arm and even to feed herself coffee using BCI technology.

Despite the amazing advancements in BCI technology, it also has limitations. The technology can require many hours of training and long periods of intense concentration for the patient; it can also require brain surgery to implant the devices.

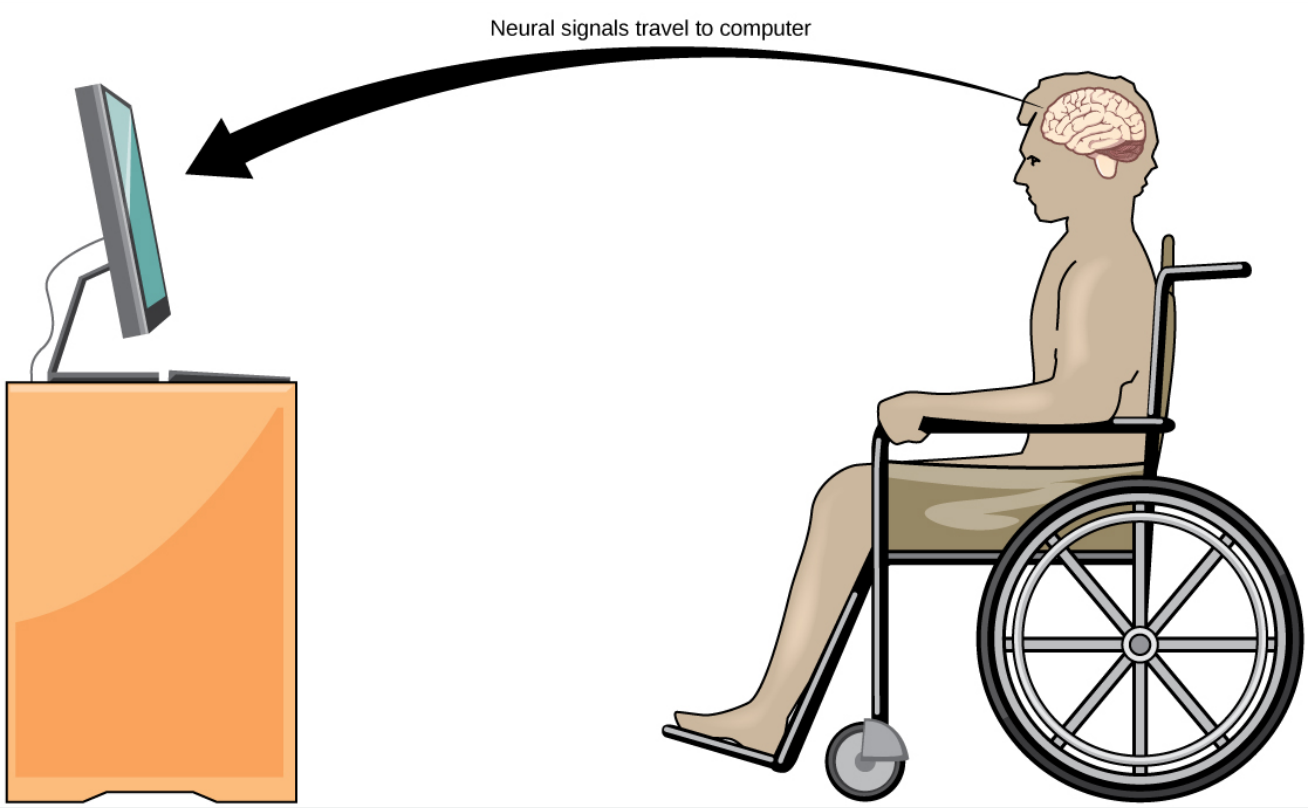
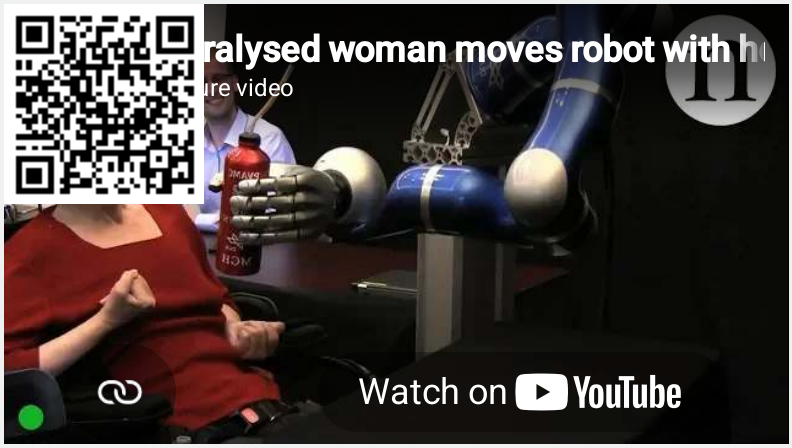


Figure 8.2.4.9: With brain-computer interface technology, neural signals from a paralyzed patient are collected, decoded, and then fed to a tool, such as a computer, a wheelchair, or a robotic arm.

Link to Learning



Watch this video in which a paralyzed woman use a brain-controlled robotic arm to bring a drink to her mouth, among other images of brain-computer interface technology in action.

Synaptic Plasticity

Synapses are not static structures. They can be weakened or strengthened. They can be broken, and new synapses can be made. Synaptic plasticity allows for these changes, which are all needed for a functioning nervous system. In fact, synaptic plasticity is the basis of learning and memory. Two processes in particular, long-term potentiation (LTP) and long-term depression (LTD) are

important forms of synaptic plasticity that occur in synapses in the hippocampus, a brain region that is involved in storing memories.

Long-term Potentiation (LTP)

Long-term potentiation (LTP) is a persistent strengthening of a synaptic connection. LTP is based on the Hebbian principle: cells that fire together wire together. There are various mechanisms, none fully understood, behind the synaptic strengthening seen with LTP. One known mechanism involves a type of postsynaptic glutamate receptor, called NMDA (N-Methyl-D-aspartate) receptors, shown in Figure 8.2.4.10. These receptors are normally blocked by magnesium ions; however, when the postsynaptic neuron is depolarized by multiple presynaptic inputs in quick succession (either from one neuron or multiple neurons), the magnesium ions are forced out allowing Ca ions to pass into the postsynaptic cell. Next, Ca^{2+} ions entering the cell initiate a signaling cascade that causes a different type of glutamate receptor, called AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, to be inserted into the postsynaptic membrane, since activated AMPA receptors allow positive ions to enter the cell. So, the next time glutamate is released from the presynaptic membrane, it will have a larger excitatory effect (EPSP) on the postsynaptic cell because the binding of glutamate to these AMPA receptors will allow more positive ions into the cell. The insertion of additional AMPA receptors strengthens the synapse and means that the postsynaptic neuron is more likely to fire in response to presynaptic neurotransmitter release. Some drugs of abuse co-opt the LTP pathway, and this synaptic strengthening can lead to addiction.

Long-term Depression (LTD)

Long-term depression (LTD) is essentially the reverse of LTP: it is a long-term weakening of a synaptic connection. One mechanism known to cause LTD also involves AMPA receptors. In this situation, calcium that enters through NMDA receptors initiates a different signaling cascade, which results in the removal of AMPA receptors from the postsynaptic membrane, as illustrated in Figure 8.2.4.10. The decrease in AMPA receptors in the membrane makes the postsynaptic neuron less responsive to glutamate released from the presynaptic neuron. While it may seem counterintuitive, LTD may be just as important for learning and memory as LTP. The weakening and pruning of unused synapses allows for unimportant connections to be lost and makes the synapses that have undergone LTP that much stronger by comparison.

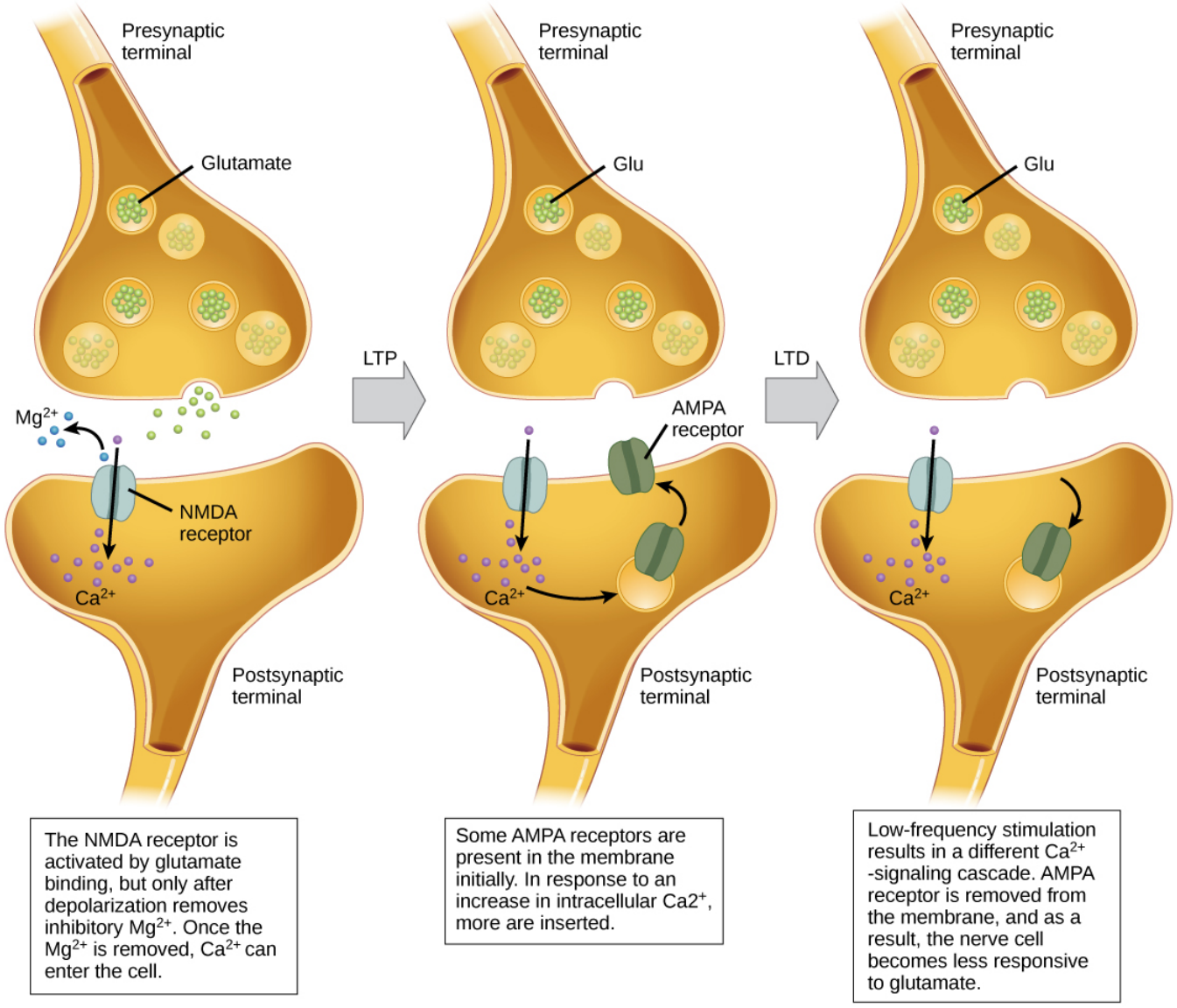


Figure 8.2.4.10: Calcium entry through postsynaptic NMDA receptors can initiate two different forms of synaptic plasticity: long-term potentiation (LTP) and long-term depression (LTD). LTP arises when a single synapse is repeatedly stimulated. This stimulation causes a calcium- and CaMKII-dependent cellular cascade, which results in the insertion of more AMPA receptors into the postsynaptic membrane. The next time glutamate is released from the presynaptic cell, it will bind to both NMDA and the newly inserted AMPA receptors, thus depolarizing the membrane more efficiently. LTD occurs when few glutamate molecules bind to NMDA receptors at a synapse (due to a low firing rate of the presynaptic neuron). The calcium that does flow through NMDA receptors initiates a different calcineurin and protein phosphatase 1-dependent cascade, which results in the endocytosis of AMPA receptors. This makes the postsynaptic neuron less responsive to glutamate released from the presynaptic neuron.

Summary

Neurons have charged membranes because there are different concentrations of ions inside and outside of the cell. Voltage-gated ion channels control the movement of ions into and out of a neuron. When a neuronal membrane is depolarized to at least the threshold of excitation, an action potential is fired. The action potential is then propagated along a myelinated axon to the axon terminals. In a chemical synapse, the action potential causes release of neurotransmitter molecules into the synaptic cleft. Through binding to postsynaptic receptors, the neurotransmitter can cause excitatory or inhibitory postsynaptic potentials by depolarizing or hyperpolarizing, respectively, the postsynaptic membrane. In electrical synapses, the action potential is directly communicated to the postsynaptic cell through gap junctions—large channel proteins that connect the pre-and postsynaptic membranes. Synapses are not static structures and can be strengthened and weakened. Two mechanisms of synaptic plasticity are long-term potentiation and long-term depression.

Art Connections

Figure 8.2.4.3: Potassium channel blockers, such as amiodarone and procainamide, which are used to treat abnormal electrical activity in the heart, called cardiac dysrhythmia, impede the movement of K^+ through voltage-gated K^+ channels. Which part of the action potential would you expect potassium channels to affect?

Answer

Potassium channel blockers slow the repolarization phase, but have no effect on depolarization.

Glossary

action potential
self-propagating momentary change in the electrical potential of a neuron (or muscle) membrane

depolarization
change in the membrane potential to a less negative value

excitatory postsynaptic potential (EPSP)
depolarization of a postsynaptic membrane caused by neurotransmitter molecules released from a presynaptic cell

hyperpolarization
change in the membrane potential to a more negative value

inhibitory postsynaptic potential (IPSP)
hyperpolarization of a postsynaptic membrane caused by neurotransmitter molecules released from a presynaptic cell

long-term depression (LTD)
prolonged decrease in synaptic coupling between a pre- and postsynaptic cell

long-term potentiation (LTP)
prolonged increase in synaptic coupling between a pre-and postsynaptic cell

membrane potential
difference in electrical potential between the inside and outside of a cell

refractory period
period after an action potential when it is more difficult or impossible for an action potential to be fired; caused by inactivation of sodium channels and activation of additional potassium channels of the membrane

saltatory conduction
“jumping” of an action potential along an axon from one node of Ranvier to the next

summation
process of multiple presynaptic inputs creating EPSPs around the same time for the postsynaptic neuron to be sufficiently depolarized to fire an action potential

synaptic cleft
space between the presynaptic and postsynaptic membranes

synaptic vesicle
spherical structure that contains a neurotransmitter

threshold of excitation

level of depolarization needed for an action potential to fire

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8.2.5: The Central Nervous System

Skills to Develop

- Identify the spinal cord, cerebral lobes, and other brain areas on a diagram of the brain
- Describe the basic functions of the spinal cord, cerebral lobes, and other brain areas

The central nervous system (CNS) is made up of the brain, a part of which is shown in Figure 8.2.5.1 and spinal cord and is covered with three layers of protective coverings called meninges (from the Greek word for membrane). The outermost layer is the dura mater (Latin for “hard mother”). As the Latin suggests, the primary function for this thick layer is to protect the brain and spinal cord. The dura mater also contains vein-like structures that carry blood from the brain back to the heart. The middle layer is the web-like arachnoid mater. The last layer is the pia mater (Latin for “soft mother”), which directly contacts and covers the brain and spinal cord like plastic wrap. The space between the arachnoid and pia maters is filled with cerebrospinal fluid (CSF). CSF is produced by a tissue called choroid plexus in fluid-filled compartments in the CNS called ventricles. The brain floats in CSF, which acts as a cushion and shock absorber and makes the brain neutrally buoyant. CSF also functions to circulate chemical substances throughout the brain and into the spinal cord.

The entire brain contains only about 8.5 tablespoons of CSF, but CSF is constantly produced in the ventricles. This creates a problem when a ventricle is blocked—the CSF builds up and creates swelling and the brain is pushed against the skull. This swelling condition is called hydrocephalus (“water head”) and can cause seizures, cognitive problems, and even death if a shunt is not inserted to remove the fluid and pressure.

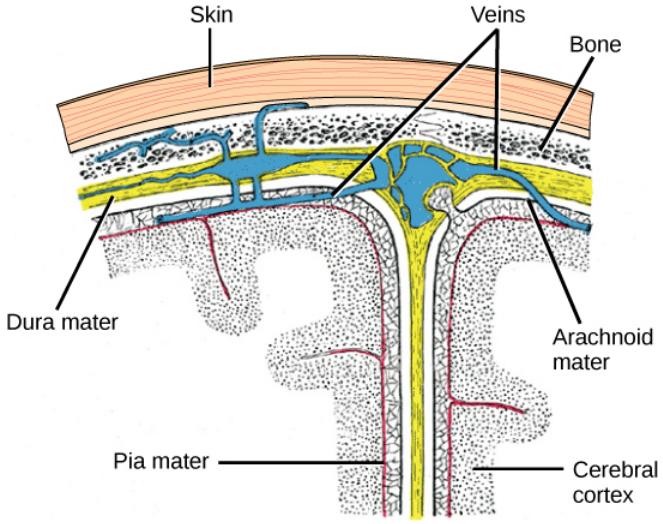


Figure 8.2.5.1: The cerebral cortex is covered by three layers of meninges: the dura, arachnoid, and pia maters. (credit: modification of work by Gray’s Anatomy)

Brain

The brain is the part of the central nervous system that is contained in the cranial cavity of the skull. It includes the cerebral cortex, limbic system, basal ganglia, thalamus, hypothalamus, and cerebellum. There are three different ways that a brain can be sectioned in order to view internal structures: a sagittal section cuts the brain left to right, as shown in Figure 8.2.5.2**b**, a coronal section cuts the brain front to back, as shown in Figure 8.2.5.2**a**, and a horizontal section cuts the brain top to bottom.

Cerebral Cortex

The outermost part of the brain is a thick piece of nervous system tissue called the cerebral cortex, which is folded into hills called gyri (singular: gyrus) and valleys called sulci (singular: sulcus). The cortex is made up of two hemispheres—right and left—which are separated by a large sulcus. A thick fiber bundle called the corpus callosum (Latin: “tough body”) connects the two hemispheres and allows information to be passed from one side to the other. Although there are some brain functions that are localized more to one hemisphere than the other, the functions of the two hemispheres are largely redundant. In fact, sometimes (very rarely) an

entire hemisphere is removed to treat severe epilepsy. While patients do suffer some deficits following the surgery, they can have surprisingly few problems, especially when the surgery is performed on children who have very immature nervous systems.

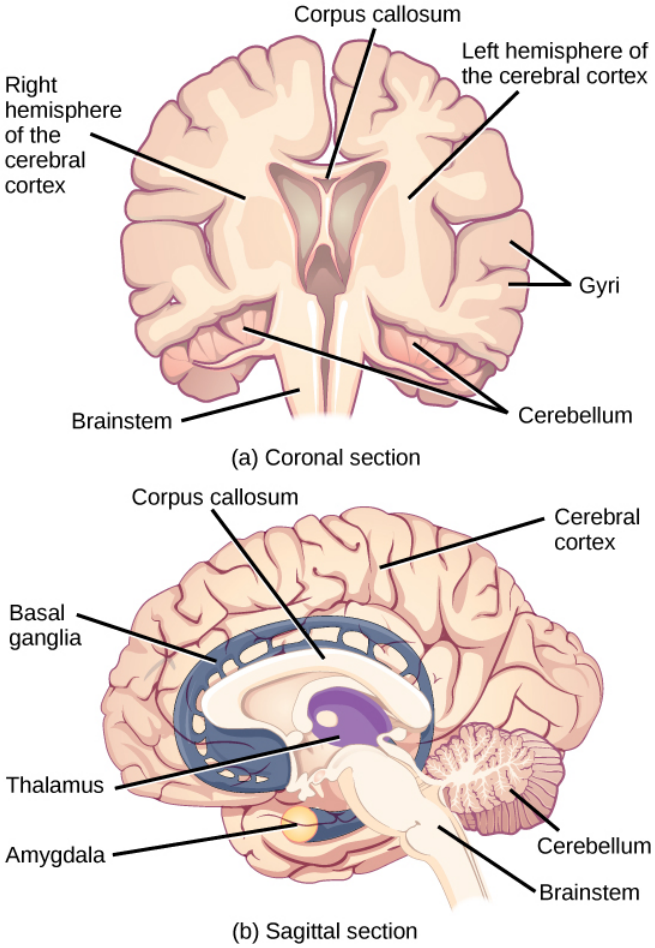


Figure 8.2.5.2: These illustrations show the (a) coronal and (b) sagittal sections of the human brain.

In other surgeries to treat severe epilepsy, the corpus callosum is cut instead of removing an entire hemisphere. This causes a condition called split-brain, which gives insights into unique functions of the two hemispheres. For example, when an object is presented to patients' left visual field, they may be unable to verbally name the object (and may claim to not have seen an object at all). This is because the visual input from the left visual field crosses and enters the right hemisphere and cannot then signal to the speech center, which generally is found in the left side of the brain. Remarkably, if a split-brain patient is asked to pick up a specific object out of a group of objects with the left hand, the patient will be able to do so but will still be unable to vocally identify it.

Link to Learning

See this website to learn more about split-brain patients and to play a game where you can model the split-brain experiments yourself.

Each cortical hemisphere contains regions called lobes that are involved in different functions. Scientists use various techniques to determine what brain areas are involved in different functions: they examine patients who have had injuries or diseases that affect specific areas and see how those areas are related to functional deficits. They also conduct animal studies where they stimulate brain areas and see if there are any behavioral changes. They use a technique called transmagnetic stimulation (TMS) to temporarily deactivate specific parts of the cortex using strong magnets placed outside the head; and they use functional magnetic resonance imaging (fMRI) to look at changes in oxygenated blood flow in particular brain regions that correlate with specific behavioral tasks. These techniques, and others, have given great insight into the functions of different brain regions but have also showed that any given brain area can be involved in more than one behavior or process, and any given behavior or process generally involves neurons in multiple brain areas. That being said, each hemisphere of the mammalian cerebral cortex can be broken down into four functionally and spatially defined lobes: frontal, parietal, temporal, and occipital. Figure 8.2.5.3 illustrates these four lobes of the human cerebral cortex.

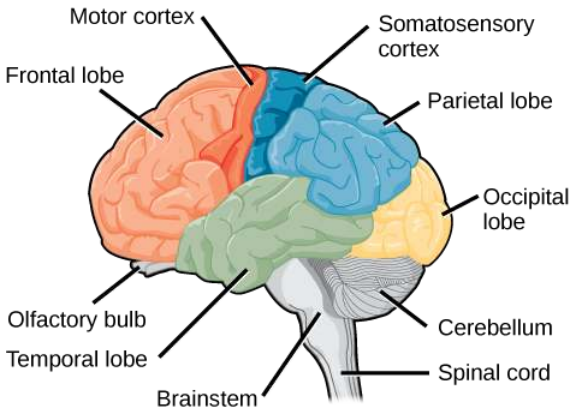


Figure 8.2.5.3: The human cerebral cortex includes the frontal, parietal, temporal, and occipital lobes.

The frontal lobe is located at the front of the brain, over the eyes. This lobe contains the olfactory bulb, which processes smells. The frontal lobe also contains the motor cortex, which is important for planning and implementing movement. Areas within the motor cortex map to different muscle groups, and there is some organization to this map, as shown in Figure 8.2.5.4. For example, the neurons that control movement of the fingers are next to the neurons that control movement of the hand. Neurons in the frontal lobe also control cognitive functions like maintaining attention, speech, and decision-making. Studies of humans who have damaged their frontal lobes show that parts of this area are involved in personality, socialization, and assessing risk.

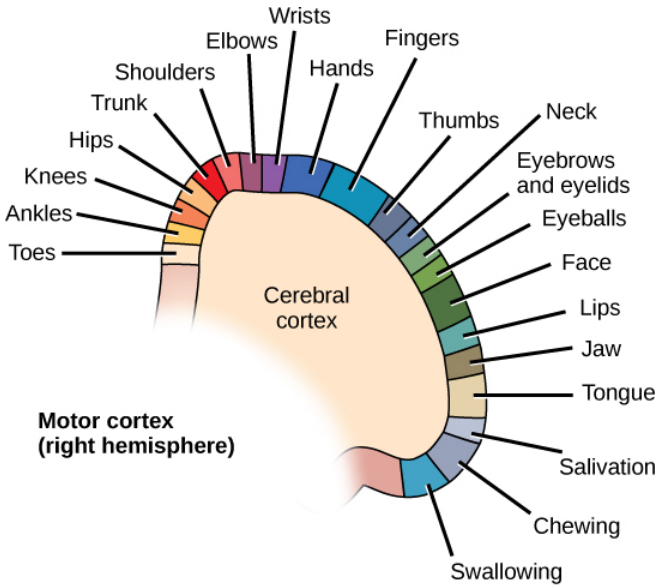


Figure 8.2.5.4: Different parts of the motor cortex control different muscle groups. Muscle groups that are neighbors in the body are generally controlled by neighboring regions of the motor cortex as well. For example, the neurons that control finger movement are near the neurons that control hand movement.

The parietal lobe is located at the top of the brain. Neurons in the parietal lobe are involved in speech and also reading. Two of the parietal lobe's main functions are processing somatosensation—touch sensations like pressure, pain, heat, cold—and processing proprioception—the sense of how parts of the body are oriented in space. The parietal lobe contains a somatosensory map of the body similar to the motor cortex.

The occipital lobe is located at the back of the brain. It is primarily involved in vision—seeing, recognizing, and identifying the visual world.

The temporal lobe is located at the base of the brain by your ears and is primarily involved in processing and interpreting sounds. It also contains the hippocampus (Greek for "seahorse")—a structure that processes memory formation. The hippocampus is illustrated in Figure 8.2.5.6. The role of the hippocampus in memory was partially determined by studying one famous epileptic patient, HM, who had both sides of his hippocampus removed in an attempt to cure his epilepsy. His seizures went away, but he could no longer form new memories (although he could remember some facts from before his surgery and could learn new motor tasks).

Evolution Connection: Cerebral Cortex

Compared to other vertebrates, mammals have exceptionally large brains for their body size. An entire alligator's brain, for example, would fill about one and a half teaspoons. This increase in brain to body size ratio is especially pronounced in apes, whales, and dolphins. While this increase in overall brain size doubtlessly played a role in the evolution of complex behaviors unique to mammals, it does not tell the whole story. Scientists have found a relationship between the relatively high surface area of the cortex and the intelligence and complex social behaviors exhibited by some mammals. This increased surface area is due, in part, to increased folding of the cortical sheet (more sulci and gyri). For example, a rat cortex is very smooth with very few sulci and gyri. Cat and sheep cortices have more sulci and gyri. Chimps, humans, and dolphins have even more.

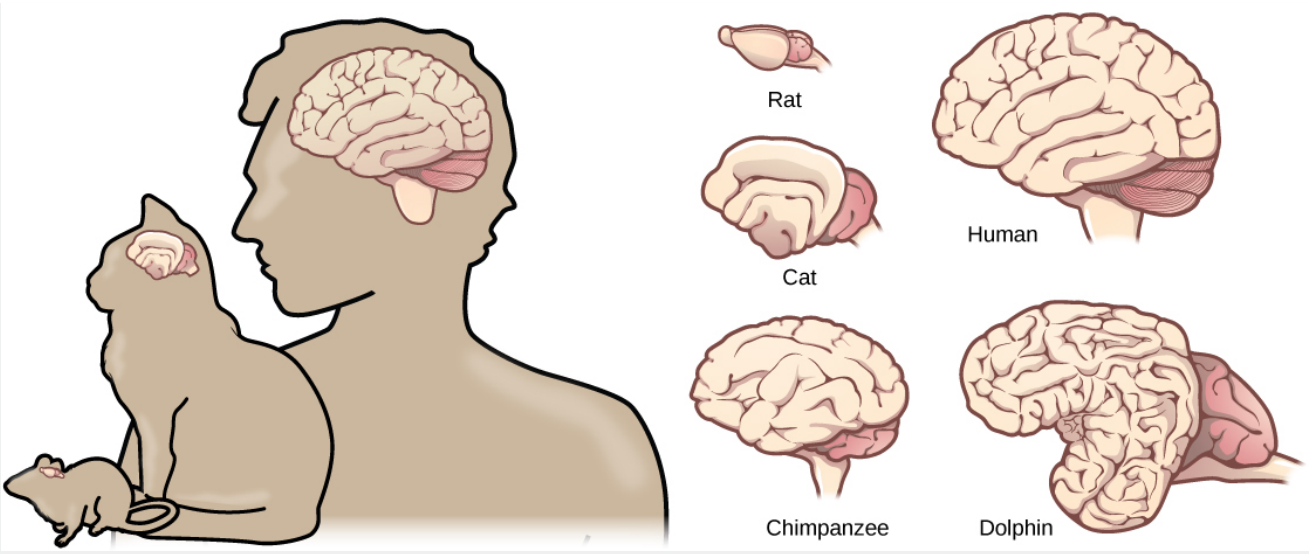


Figure 8.2.5.5: Mammals have larger brain-to-body ratios than other vertebrates. Within mammals, increased cortical folding and surface area is correlated with complex behavior.

Basal Ganglia

Interconnected brain areas called the basal ganglia (or basal nuclei) play important roles in movement control and posture. Damage to the basal ganglia, as in Parkinson's disease, leads to motor impairments like a shuffling gait when walking. The basal ganglia also regulate motivation. For example, when a wasp sting led to bilateral basal ganglia damage in a 25-year-old businessman, he began to spend all his days in bed and showed no interest in anything or anybody. But when he was externally stimulated—as when someone asked to play a card game with him—he was able to function normally. Interestingly, he and other similar patients do not report feeling bored or frustrated by their state.

Thalamus

The thalamus (Greek for "inner chamber"), illustrated in Figure 8.2.5.6, acts as a gateway to and from the cortex. It receives sensory and motor inputs from the body and also receives feedback from the cortex. This feedback mechanism can modulate conscious awareness of sensory and motor inputs depending on the attention and arousal state of the animal. The thalamus helps regulate consciousness, arousal, and sleep states. A rare genetic disorder called fatal familial insomnia causes the degeneration of thalamic neurons and glia. This disorder prevents affected patients from being able to sleep, among other symptoms, and is eventually fatal.

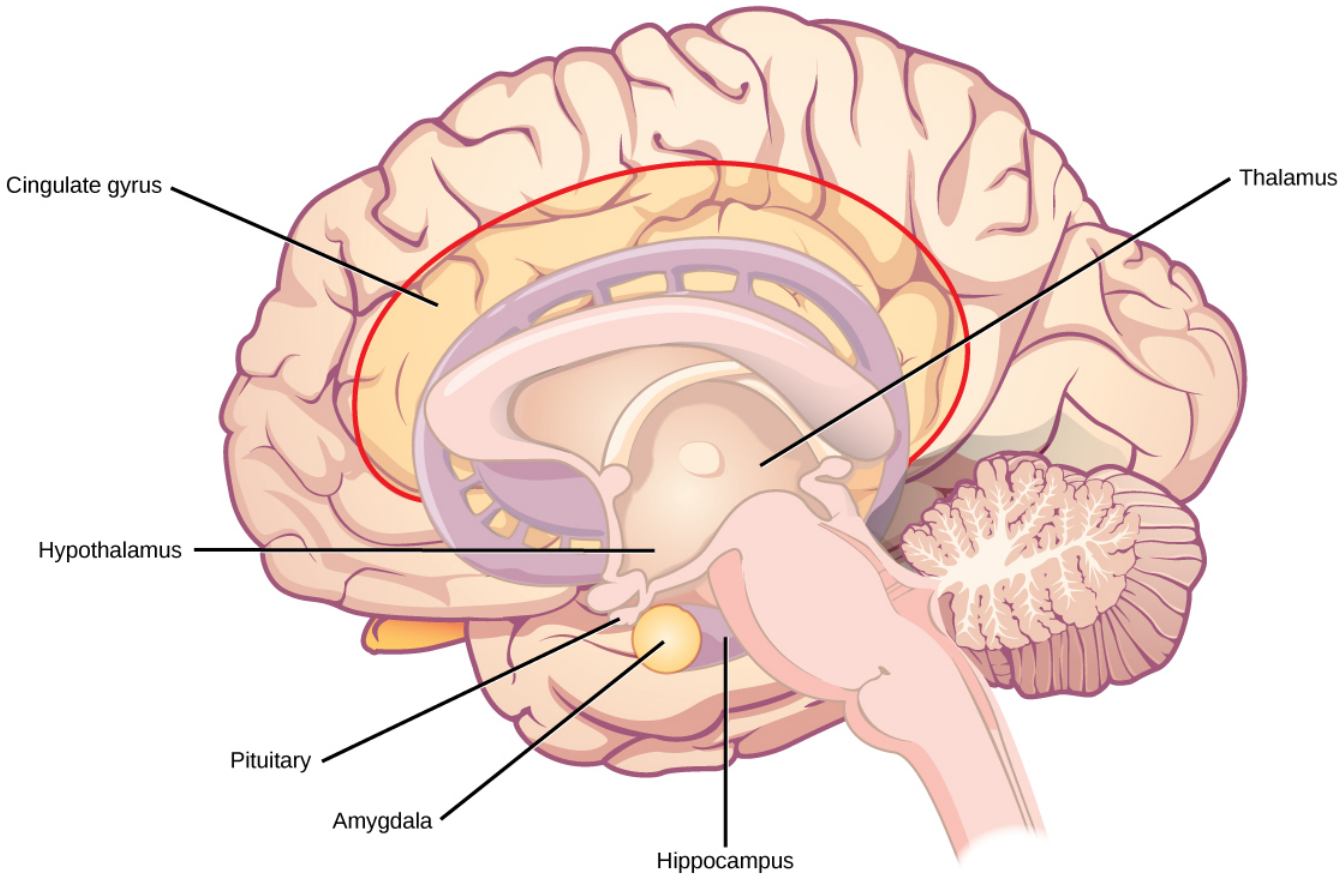


Figure 8.2.5.6: The limbic system regulates emotion and other behaviors. It includes parts of the cerebral cortex located near the center of the brain, including the cingulate gyrus and the hippocampus as well as the thalamus, hypothalamus and amygdala.

Hypothalamus

Below the thalamus is the hypothalamus, shown in Figure 8.2.5.6. The hypothalamus controls the endocrine system by sending signals to the pituitary gland, a pea-sized endocrine gland that releases several different hormones that affect other glands as well as other cells. This relationship means that the hypothalamus regulates important behaviors that are controlled by these hormones. The hypothalamus is the body's thermostat—it makes sure key functions like food and water intake, energy expenditure, and body temperature are kept at appropriate levels. Neurons within the hypothalamus also regulate circadian rhythms, sometimes called sleep cycles.

Limbic System

The limbic system is a connected set of structures that regulates emotion, as well as behaviors related to fear and motivation. It plays a role in memory formation and includes parts of the thalamus and hypothalamus as well as the hippocampus. One important structure within the limbic system is a temporal lobe structure called the amygdala (Greek for "almond"), illustrated in Figure 8.2.5.6. The two amygdala are important both for the sensation of fear and for recognizing fearful faces. The cingulate gyrus helps regulate emotions and pain.

Cerebellum

The cerebellum (Latin for "little brain"), shown in Figure 8.2.5.3, sits at the base of the brain on top of the brainstem. The cerebellum controls balance and aids in coordinating movement and learning new motor tasks.

Brainstem

The brainstem, illustrated in Figure 8.2.5.3, connects the rest of the brain with the spinal cord. It consists of the midbrain, medulla oblongata, and the pons. Motor and sensory neurons extend through the brainstem allowing for the relay of signals between the brain and spinal cord. Ascending neural pathways cross in this section of the brain allowing the left hemisphere of the cerebrum to

control the right side of the body and vice versa. The brainstem coordinates motor control signals sent from the brain to the body. The brainstem controls several important functions of the body including alertness, arousal, breathing, blood pressure, digestion, heart rate, swallowing, walking, and sensory and motor information integration.

Spinal Cord

Connecting to the brainstem and extending down the body through the spinal column is the spinal cord, shown in Figure 8.2.5.3. The spinal cord is a thick bundle of nerve tissue that carries information about the body to the brain and from the brain to the body. The spinal cord is contained within the bones of the vertebrate column but is able to communicate signals to and from the body through its connections with spinal nerves (part of the peripheral nervous system). A cross-section of the spinal cord looks like a white oval containing a gray butterfly-shape, as illustrated in Figure 8.2.5.7. Myelinated axons make up the "white matter" and neuron and glial cell bodies make up the "gray matter." Gray matter is also composed of interneurons, which connect two neurons each located in different parts of the body. Axons and cell bodies in the dorsal (facing the back of the animal) spinal cord convey mostly sensory information from the body to the brain. Axons and cell bodies in the ventral (facing the front of the animal) spinal cord primarily transmit signals controlling movement from the brain to the body.

The spinal cord also controls motor reflexes. These reflexes are quick, unconscious movements—like automatically removing a hand from a hot object. Reflexes are so fast because they involve local synaptic connections. For example, the knee reflex that a doctor tests during a routine physical is controlled by a single synapse between a sensory neuron and a motor neuron. While a reflex may only require the involvement of one or two synapses, synapses with interneurons in the spinal column transmit information to the brain to convey what happened (the knee jerked, or the hand was hot).

In the United States, there around 10,000 spinal cord injuries each year. Because the spinal cord is the information superhighway connecting the brain with the body, damage to the spinal cord can lead to paralysis. The extent of the paralysis depends on the location of the injury along the spinal cord and whether the spinal cord was completely severed. For example, if the spinal cord is damaged at the level of the neck, it can cause paralysis from the neck down, whereas damage to the spinal column further down may limit paralysis to the legs. Spinal cord injuries are notoriously difficult to treat because spinal nerves do not regenerate, although ongoing research suggests that stem cell transplants may be able to act as a bridge to reconnect severed nerves. Researchers are also looking at ways to prevent the inflammation that worsens nerve damage after injury. One such treatment is to pump the body with cold saline to induce hypothermia. This cooling can prevent swelling and other processes that are thought to worsen spinal cord injuries.

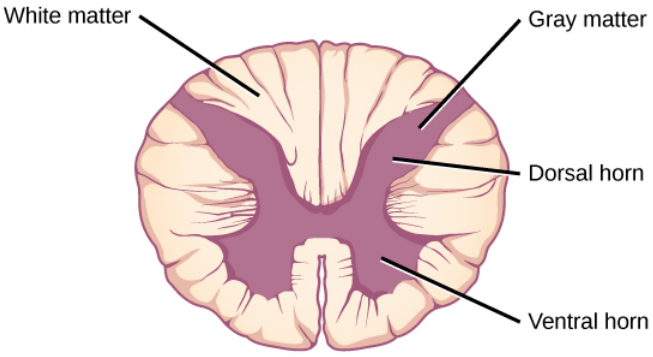


Figure 8.2.5.7: A cross-section of the spinal cord shows gray matter (containing cell bodies and interneurons) and white matter (containing axons).

Summary

The vertebrate central nervous system contains the brain and the spinal cord, which are covered and protected by three meninges. The brain contains structurally and functionally defined regions. In mammals, these include the cortex (which can be broken down into four primary functional lobes: frontal, temporal, occipital, and parietal), basal ganglia, thalamus, hypothalamus, limbic system, cerebellum, and brainstem—although structures in some of these designations overlap. While functions may be primarily localized to one structure in the brain, most complex functions, like language and sleep, involve neurons in multiple brain regions. The spinal cord is the information superhighway that connects the brain with the rest of the body through its connections with peripheral nerves. It transmits sensory and motor input and also controls motor reflexes.

Glossary

amygdala
structure within the limbic system that processes fear

arachnoid mater
spiderweb-like middle layer of the meninges that cover the central nervous system

basal ganglia
interconnected collections of cells in the brain that are involved in movement and motivation; also known as basal nuclei

basal nuclei
see basal ganglia

brainstem
portion of the brain that connects with the spinal cord; controls basic nervous system functions like breathing, heart rate, and swallowing

cerebellum
brain structure involved in posture, motor coordination, and learning new motor actions

cerebral cortex
outermost sheet of brain tissue; involved in many higher-order functions

choroid plexus
spongy tissue within ventricles that produces cerebrospinal fluid

cingulate gyrus
helps regulate emotions and pain; thought to directly drive the body's conscious response to unpleasant experiences

corpus callosum
thick fiber bundle that connects the cerebral hemispheres

cerebrospinal fluid (CSF)
clear liquid that surrounds the brain and spinal cord and fills the ventricles and central canal; acts as a shock absorber and circulates material throughout the brain and spinal cord.

dura mater
tough outermost layer that covers the central nervous system

frontal lobe
part of the cerebral cortex that contains the motor cortex and areas involved in planning, attention, and language

gyrus
(plural: gyri) ridged protrusions in the cortex

hippocampus
brain structure in the temporal lobe involved in processing memories

hypothalamus
brain structure that controls hormone release and body homeostasis

limbic system

connected brain areas that process emotion and motivation

meninge
membrane that covers and protects the central nervous system

occipital lobe
part of the cerebral cortex that contains visual cortex and processes visual stimuli

parietal lobe
part of the cerebral cortex involved in processing touch and the sense of the body in space

pia mater
thin membrane layer directly covering the brain and spinal cord

proprioception
sense about how parts of the body are oriented in space

somatosensation
sense of touch

spinal cord
thick fiber bundle that connects the brain with peripheral nerves; transmits sensory and motor information; contains neurons that control motor reflexes

sulcus
(plural: sulci) indents or “valleys” in the cortex

temporal lobe
part of the cerebral cortex that processes auditory input; parts of the temporal lobe are involved in speech, memory, and emotion processing

thalamus
brain area that relays sensory information to the cortex

ventricle
cavity within brain that contains cerebrospinal fluid

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8.2.6: The Peripheral Nervous System

Skills to Develop

- Describe the organization and functions of the sympathetic and parasympathetic nervous systems
- Describe the organization and function of the sensory-somatic nervous system

The peripheral nervous system (PNS) is the connection between the central nervous system and the rest of the body. The CNS is like the power plant of the nervous system. It creates the signals that control the functions of the body. The PNS is like the wires that go to individual houses. Without those “wires,” the signals produced by the CNS could not control the body (and the CNS would not be able to receive sensory information from the body either).

The PNS can be broken down into the autonomic nervous system, which controls bodily functions without conscious control, and the sensory-somatic nervous system, which transmits sensory information from the skin, muscles, and sensory organs to the CNS and sends motor commands from the CNS to the muscles.

Autonomic Nervous System

Art Connection

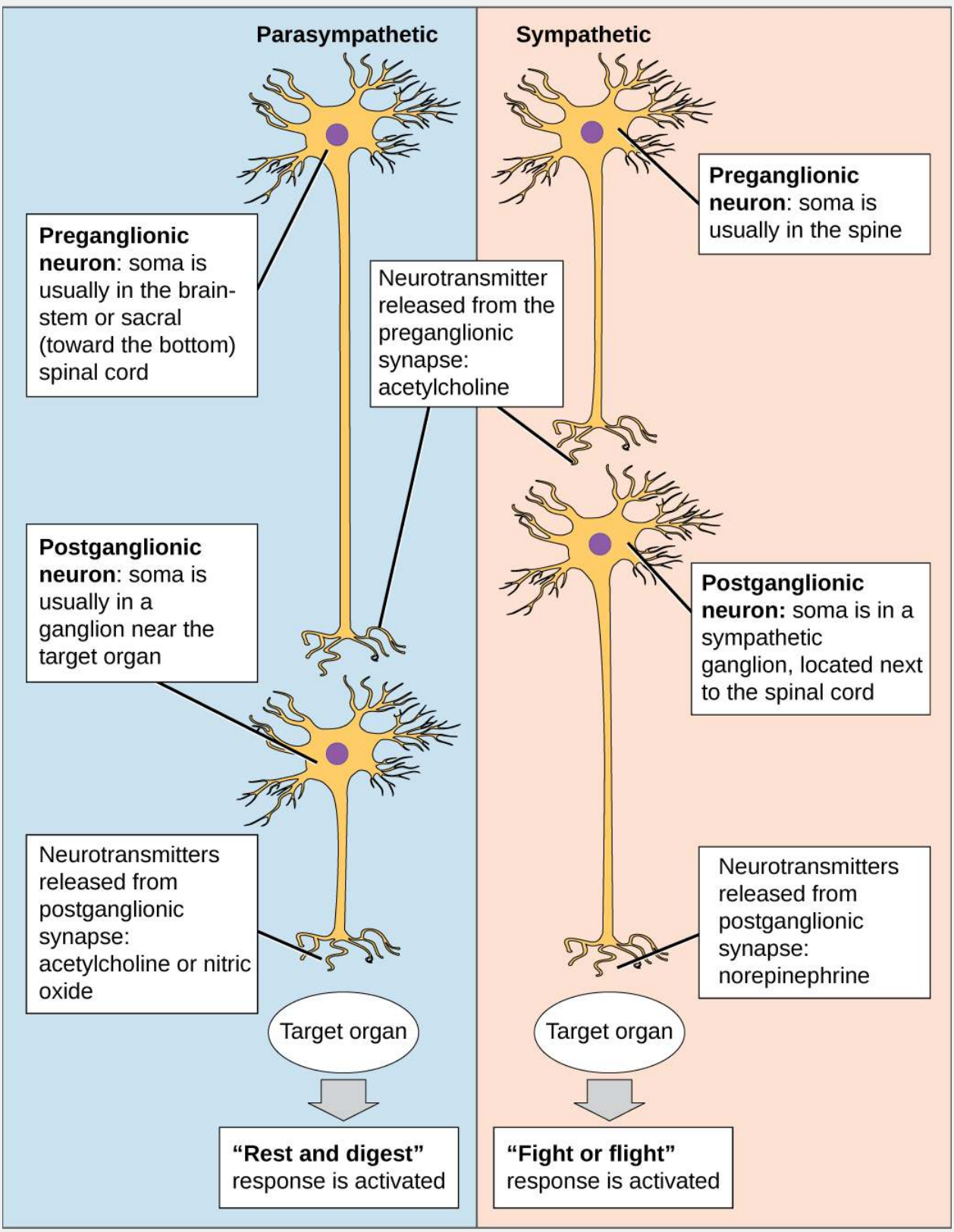


Figure 8.2.6.1: In the autonomic nervous system, a preganglionic neuron of the CNS synapses with a postganglionic neuron of the PNS. The postganglionic neuron, in turn, acts on a target organ. Autonomic responses are mediated by the sympathetic and the parasympathetic systems, which are antagonistic to one another. The sympathetic system activates the "fight or flight" response, while the parasympathetic system activates the "rest and digest" response.

Which of the following statements is false?

A. The parasympathetic pathway is responsible for resting the body, while the sympathetic pathway is responsible for preparing for an emergency.
B. Most preganglionic neurons in the sympathetic pathway originate in the spinal cord.
C. Slowing of the heartbeat is a parasympathetic response.
D. Parasympathetic neurons are responsible for releasing norepinephrine on the target organ, while sympathetic neurons are responsible for releasing acetylcholine.

The autonomic nervous system serves as the relay between the CNS and the internal organs. It controls the lungs, the heart, smooth muscle, and exocrine and endocrine glands. The autonomic nervous system controls these organs largely without conscious control; it can continuously monitor the conditions of these different systems and implement changes as needed. Signaling to the target tissue usually involves two synapses: a preganglionic neuron (originating in the CNS) synapses to a neuron in a ganglion that, in turn, synapses on the target organ, as illustrated in Figure 8.2.6.1. There are two divisions of the autonomic nervous system that often have opposing effects: the sympathetic nervous system and the parasympathetic nervous system.

Sympathetic Nervous System

The sympathetic nervous system is responsible for the “fight or flight” response that occurs when an animal encounters a dangerous situation. One way to remember this is to think of the surprise a person feels when encountering a snake (“snake” and “sympathetic” both begin with “s”). Examples of functions controlled by the sympathetic nervous system include an accelerated heart rate and inhibited digestion. These functions help prepare an organism’s body for the physical strain required to escape a potentially dangerous situation or to fend off a predator.

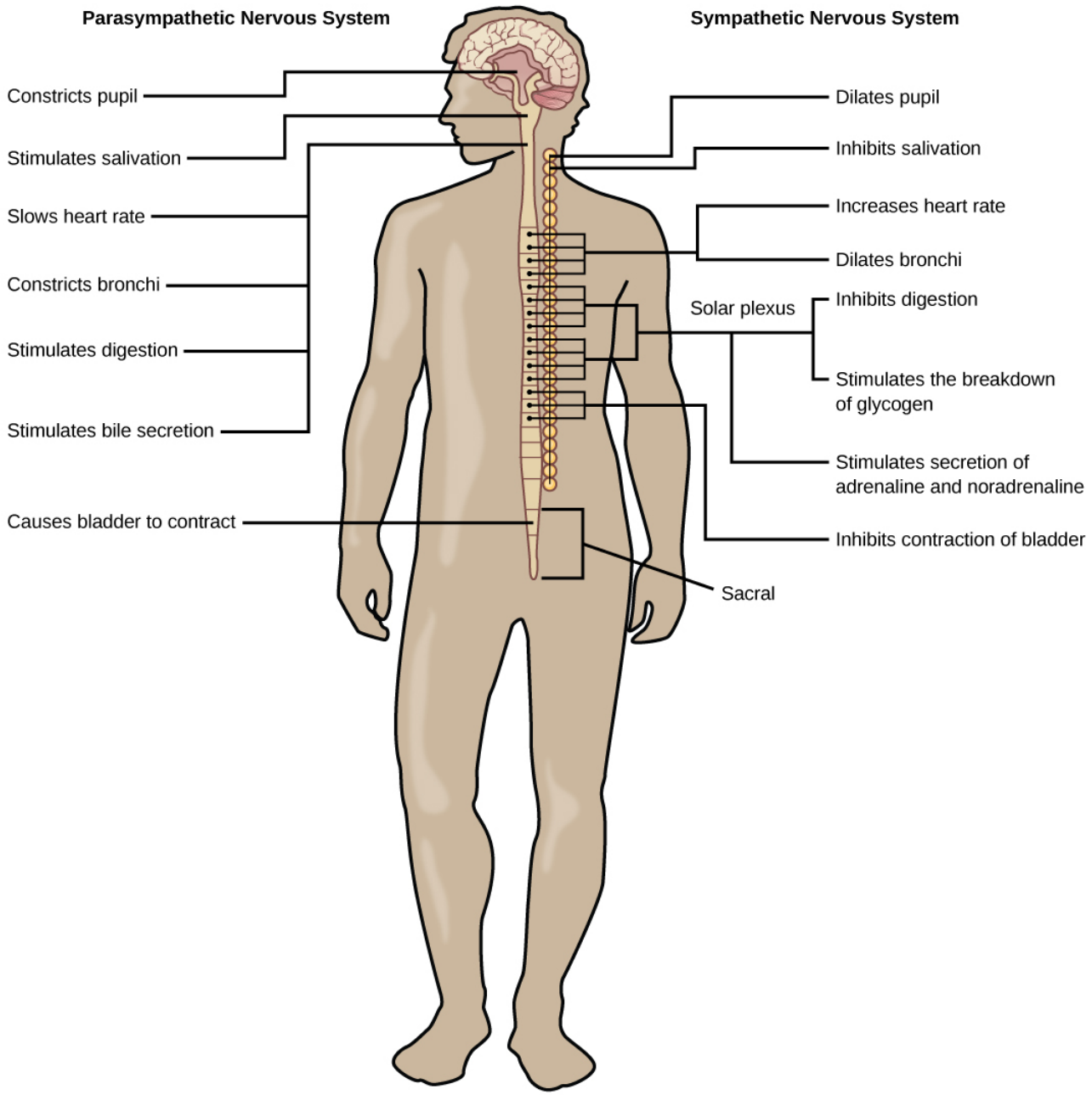


Figure 8.2.6.2: The sympathetic and parasympathetic nervous systems often have opposing effects on target organs.

Most preganglionic neurons in the sympathetic nervous system originate in the spinal cord, as illustrated in Figure 8.2.6.2. The axons of these neurons release acetylcholine on postganglionic neurons within sympathetic ganglia (the sympathetic ganglia form a chain that extends alongside the spinal cord). The acetylcholine activates the postganglionic neurons. Postganglionic neurons then release norepinephrine onto target organs. As anyone who has ever felt a rush before a big test, speech, or athletic event can attest, the effects of the sympathetic nervous system are quite pervasive. This is both because one preganglionic neuron synapses on multiple postganglionic neurons, amplifying the effect of the original synapse, and because the adrenal gland also releases norepinephrine (and the closely related hormone epinephrine) into the blood stream. The physiological effects of this norepinephrine release include dilating the trachea and bronchi (making it easier for the animal to breathe), increasing heart rate, and moving blood from the skin to the heart, muscles, and brain (so the animal can think and run). The strength and speed of the sympathetic response helps an organism avoid danger, and scientists have found evidence that it may also increase LTP—allowing the animal to remember the dangerous situation and avoid it in the future.

Parasympathetic Nervous System

While the sympathetic nervous system is activated in stressful situations, the parasympathetic nervous system allows an animal to "rest and digest." One way to remember this is to think that during a restful situation like a picnic, the parasympathetic nervous system is in control ("picnic" and "parasympathetic" both start with "p"). Parasympathetic preganglionic neurons have cell bodies located in the brainstem and in the sacral (toward the bottom) spinal cord, as shown in Figure 8.2.6.2. The axons of the preganglionic neurons release acetylcholine on the postganglionic neurons, which are generally located very near the target organs. Most postganglionic neurons release acetylcholine onto target organs, although some release nitric oxide.

The parasympathetic nervous system resets organ function after the sympathetic nervous system is activated (the common adrenaline dump you feel after a 'fight-or-flight' event). Effects of acetylcholine release on target organs include slowing of heart rate, lowered blood pressure, and stimulation of digestion.

Sensory-Somatic Nervous System

The sensory-somatic nervous system is made up of cranial and spinal nerves and contains both sensory and motor neurons. Sensory neurons transmit sensory information from the skin, skeletal muscle, and sensory organs to the CNS. Motor neurons transmit messages about desired movement from the CNS to the muscles to make them contract. Without its sensory-somatic nervous system, an animal would be unable to process any information about its environment (what it sees, feels, hears, and so on) and could not control motor movements. Unlike the autonomic nervous system, which has two synapses between the CNS and the target organ, sensory and motor neurons have only one synapse—one ending of the neuron is at the organ and the other directly contacts a CNS neuron. Acetylcholine is the main neurotransmitter released at these synapses.

Humans have 12 cranial nerves, nerves that emerge from or enter the skull (cranium), as opposed to the spinal nerves, which emerge from the vertebral column. Each cranial nerve is accorded a name, which are detailed in Figure 8.2.6.3. Some cranial nerves transmit only sensory information. For example, the olfactory nerve transmits information about smells from the nose to the brainstem. Other cranial nerves transmit almost solely motor information. For example, the oculomotor nerve controls the opening and closing of the eyelid and some eye movements. Other cranial nerves contain a mix of sensory and motor fibers. For example, the glossopharyngeal nerve has a role in both taste (sensory) and swallowing (motor).

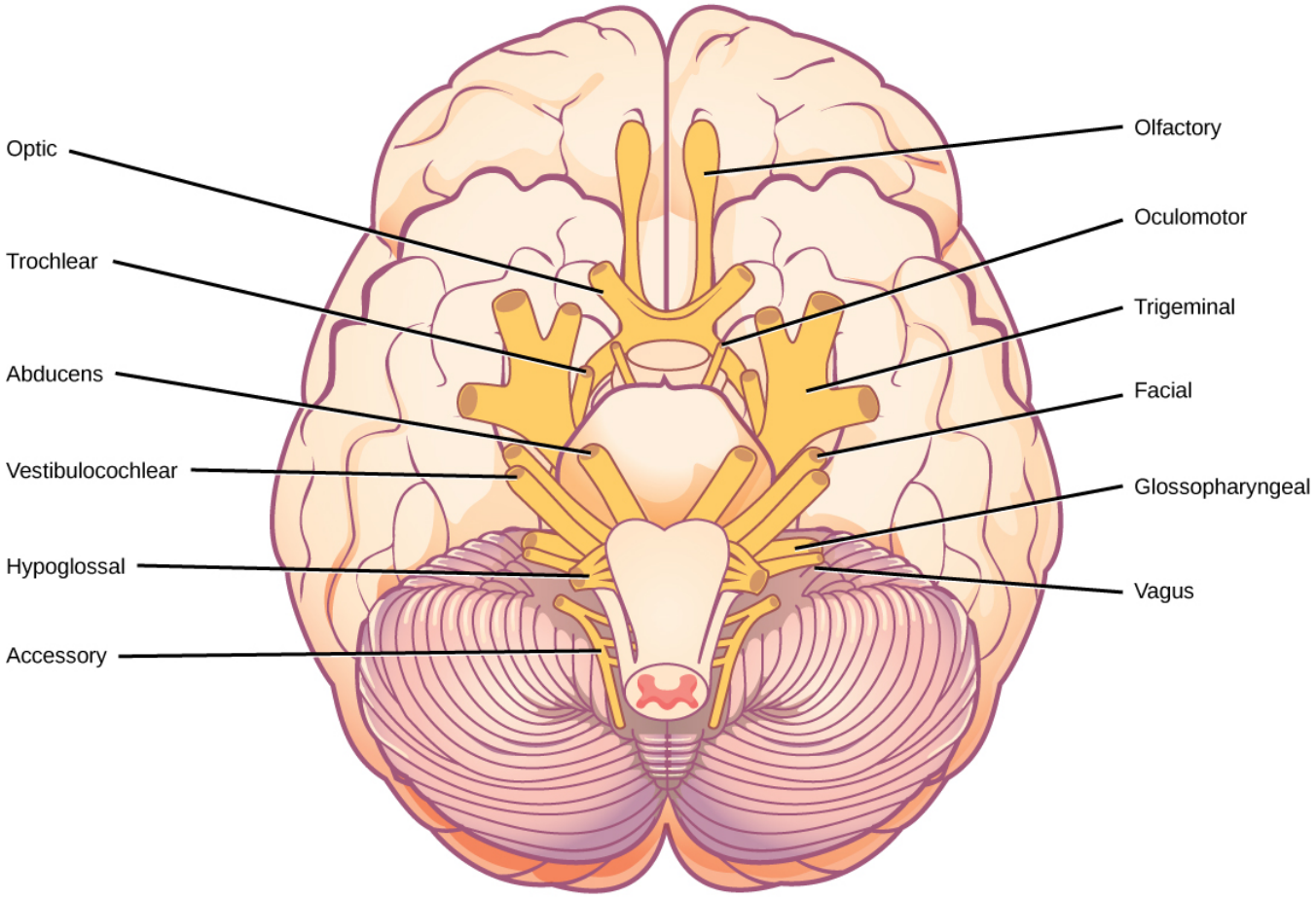


Figure 8.2.6.3: The human brain contains 12 cranial nerves that receive sensory input and control motor output for the head and neck.

Spinal nerves transmit sensory and motor information between the spinal cord and the rest of the body. Each of the 31 spinal nerves (in humans) contains both sensory and motor axons. The sensory neuron cell bodies are grouped in structures called dorsal root ganglia and are shown in Figure 8.2.6.4. Each sensory neuron has one projection—with a sensory receptor ending in skin, muscle, or sensory organs—and another that synapses with a neuron in the dorsal spinal cord. Motor neurons have cell bodies in the ventral gray matter of the spinal cord that project to muscle through the ventral root. These neurons are usually stimulated by interneurons within the spinal cord but are sometimes directly stimulated by sensory neurons.

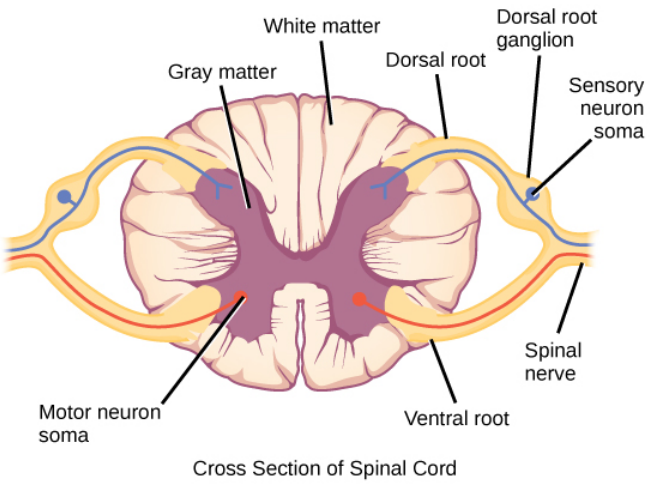


Figure 8.2.6.4: Spinal nerves contain both sensory and motor axons. The somas of sensory neurons are located in dorsal root ganglia. The somas of motor neurons are found in the ventral portion of the gray matter of the spinal cord.

Summary

The peripheral nervous system contains both the autonomic and sensory-somatic nervous systems. The autonomic nervous system provides unconscious control over visceral functions and has two divisions: the sympathetic and parasympathetic nervous systems. The sympathetic nervous system is activated in stressful situations to prepare the animal for a “fight or flight” response. The parasympathetic nervous system is active during restful periods. The sensory-somatic nervous system is made of cranial and spinal nerves that transmit sensory information from skin and muscle to the CNS and motor commands from the CNS to the muscles.

Art Connections

Figure 8.2.6.1: Which of the following statements is false?

A. The parasympathetic pathway is responsible for relaxing the body, while the sympathetic pathway is responsible for preparing for an emergency.
B. Most preganglionic neurons in the sympathetic pathway originate in the spinal cord.
C. Slowing of the heartbeat is a parasympathetic response.
D. Parasympathetic neurons are responsible for releasing norepinephrine on the target organ, while sympathetic neurons are responsible for releasing acetylcholine.

Answer

D

Glossary

acetylcholine
neurotransmitter released by neurons in the central nervous system and peripheral nervous system

autonomic nervous system
part of the peripheral nervous system that controls bodily functions

cranial nerve
sensory and/or motor nerve that emanates from the brain

norepinephrine
neurotransmitter and hormone released by activation of the sympathetic nervous system

parasympathetic nervous system

division of autonomic nervous system that regulates visceral functions during rest and digestion

sensory-somatic nervous system

system of sensory and motor nerves

spinal nerve

nerve projecting between skin or muscle and spinal cord

sympathetic nervous system

division of autonomic nervous system activated during stressful “fight or flight” situations

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8.2.7: Nervous System Disorders

Skills to Develop

- Describe the symptoms, potential causes, and treatment of several examples of nervous system disorders

A nervous system that functions correctly is a fantastically complex, well-oiled machine—synapses fire appropriately, muscles move when needed, memories are formed and stored, and emotions are well regulated. Unfortunately, each year millions of people in the United States deal with some sort of nervous system disorder. While scientists have discovered potential causes of many of these diseases, and viable treatments for some, ongoing research seeks to find ways to better prevent and treat all of these disorders.

Neurodegenerative Disorders

Neurodegenerative disorders are illnesses characterized by a loss of nervous system functioning that are usually caused by neuronal death. These diseases generally worsen over time as more and more neurons die. The symptoms of a particular neurodegenerative disease are related to where in the nervous system the death of neurons occurs. Spinocerebellar ataxia, for example, leads to neuronal death in the cerebellum. The death of these neurons causes problems in balance and walking. Neurodegenerative disorders include Huntington's disease, amyotrophic lateral sclerosis, Alzheimer's disease and other types of dementia disorders, and Parkinson's disease. Here, Alzheimer's and Parkinson's disease will be discussed in more depth.

Alzheimer's Disease

Alzheimer's disease is the most common cause of dementia in the elderly. In 2012, an estimated 5.4 million Americans suffered from Alzheimer's disease, and payments for their care are estimated at $200 billion. Roughly one in every eight people age 65 or older has the disease. Due to the aging of the baby-boomer generation, there are projected to be as many as 13 million Alzheimer's patients in the United States in the year 2050.

Symptoms of Alzheimer's disease include disruptive memory loss, confusion about time or place, difficulty planning or executing tasks, poor judgment, and personality changes. Problems smelling certain scents can also be indicative of Alzheimer's disease and may serve as an early warning sign. Many of these symptoms are also common in people who are aging normally, so it is the severity and longevity of the symptoms that determine whether a person is suffering from Alzheimer's.

Alzheimer's disease was named for Alois Alzheimer, a German psychiatrist who published a report in 1911 about a woman who showed severe dementia symptoms. Along with his colleagues, he examined the woman's brain following her death and reported the presence of abnormal clumps, which are now called amyloid plaques, along with tangled brain fibers called neurofibrillary tangles. Amyloid plaques, neurofibrillary tangles, and an overall shrinking of brain volume are commonly seen in the brains of Alzheimer's patients. Loss of neurons in the hippocampus is especially severe in advanced Alzheimer's patients. Figure 8.2.7.1 compares a normal brain to the brain of an Alzheimer's patient. Many research groups are examining the causes of these hallmarks of the disease.

One form of the disease is usually caused by mutations in one of three known genes. This rare form of early onset Alzheimer's disease affects fewer than five percent of patients with the disease and causes dementia beginning between the ages of 30 and 60. The more prevalent, late-onset form of the disease likely also has a genetic component. One particular gene, apolipoprotein E (APOE) has a variant (E4) that increases a carrier's likelihood of getting the disease. Many other genes have been identified that might be involved in the pathology.

Link to Learning

Visit this website for video links discussing genetics and Alzheimer's disease.

Unfortunately, there is no cure for Alzheimer's disease. Current treatments focus on managing the symptoms of the disease. Because decrease in the activity of cholinergic neurons (neurons that use the neurotransmitter acetylcholine) is common in Alzheimer's disease, several drugs used to treat the disease work by increasing acetylcholine neurotransmission, often by inhibiting the enzyme that breaks down acetylcholine in the synaptic cleft. Other clinical interventions focus on behavioral therapies like psychotherapy, sensory therapy, and cognitive exercises. Since Alzheimer's disease appears to hijack the normal aging process,

research into prevention is prevalent. Smoking, obesity, and cardiovascular problems may be risk factors for the disease, so treatments for those may also help to prevent Alzheimer's disease. Some studies have shown that people who remain intellectually active by playing games, reading, playing musical instruments, and being socially active in later life have a reduced risk of developing the disease.

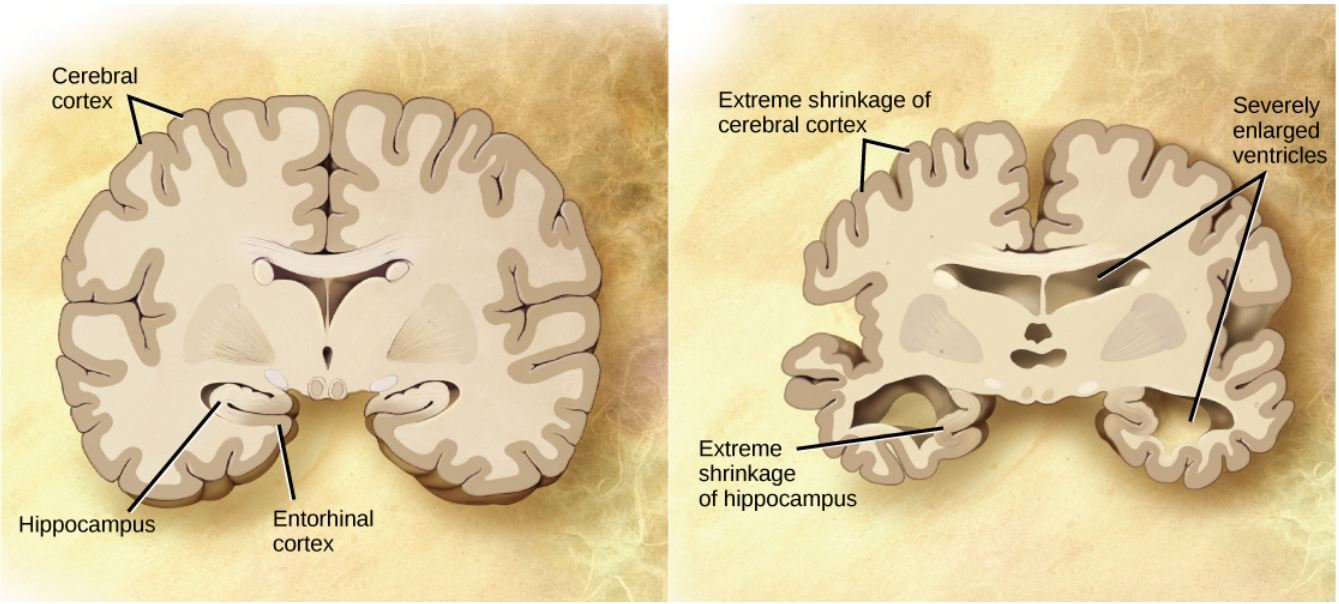


Figure 8.2.7.1: Compared to a normal brain (left), the brain from a patient with Alzheimer's disease (right) shows a dramatic neurodegeneration, particularly within the ventricles and hippocampus. (credit: modification of work by "Garrando"/Wikimedia Commons based on original images by ADEAR: "Alzheimer's Disease Education and Referral Center, a service of the National Institute on Aging")

Parkinson's Disease

Like Alzheimer's disease, Parkinson's disease is a neurodegenerative disease. It was first characterized by James Parkinson in 1817. Each year, 50,000-60,000 people in the United States are diagnosed with the disease. Parkinson's disease causes the loss of dopamine neurons in the substantia nigra, a midbrain structure that regulates movement. Loss of these neurons causes many symptoms including tremor (shaking of fingers or a limb), slowed movement, speech changes, balance and posture problems, and rigid muscles. The combination of these symptoms often causes a characteristic slow hunched shuffling walk, illustrated in Figure 8.2.7.2. Patients with Parkinson's disease can also exhibit psychological symptoms, such as dementia or emotional problems.

Although some patients have a form of the disease known to be caused by a single mutation, for most patients the exact causes of Parkinson's disease remain unknown: the disease likely results from a combination of genetic and environmental factors (similar to Alzheimer's disease). Post-mortem analysis of brains from Parkinson's patients shows the presence of Lewy bodies—abnormal protein clumps—in dopaminergic neurons. The prevalence of these Lewy bodies often correlates with the severity of the disease.

There is no cure for Parkinson's disease, and treatment is focused on easing symptoms. One of the most commonly prescribed drugs for Parkinson's is L-DOPA, which is a chemical that is converted into dopamine by neurons in the brain. This conversion increases the overall level of dopamine neurotransmission and can help compensate for the loss of dopaminergic neurons in the substantia nigra. Other drugs work by inhibiting the enzyme that breaks down dopamine.



Figure 8.2.7.2: Parkinson's patients often have a characteristic hunched walk.

Neurodevelopmental Disorders

Neurodevelopmental disorders occur when the development of the nervous system is disturbed. There are several different classes of neurodevelopmental disorders. Some, like Down Syndrome, cause intellectual deficits. Others specifically affect communication, learning, or the motor system. Some disorders like autism spectrum disorder and attention deficit/hyperactivity disorder have complex symptoms.

Autism

Autism spectrum disorder (ASD) is a neurodevelopmental disorder. Its severity differs from person to person. Estimates for the prevalence of the disorder have changed rapidly in the past few decades. Current estimates suggest that one in 88 children will develop the disorder. ASD is four times more prevalent in males than females.

A characteristic symptom of ASD is impaired social skills. Children with autism may have difficulty making and maintaining eye contact and reading social cues. They also may have problems feeling empathy for others. Other symptoms of ASD include repetitive motor behaviors (such as rocking back and forth), preoccupation with specific subjects, strict adherence to certain rituals, and unusual language use. Up to 30 percent of patients with ASD develop epilepsy, and patients with some forms of the disorder (like Fragile X) also have intellectual disability. Because it is a spectrum disorder, other ASD patients are very functional and have good-to-excellent language skills. Many of these patients do not feel that they suffer from a disorder and instead think that their brains just process information differently.

Except for some well-characterized, clearly genetic forms of autism (like Fragile X and Rett's Syndrome), the causes of ASD are largely unknown. Variants of several genes correlate with the presence of ASD, but for any given patient, many different mutations in different genes may be required for the disease to develop. At a general level, ASD is thought to be a disease of "incorrect" wiring. Accordingly, brains of some ASD patients lack the same level of synaptic pruning that occurs in non-affected people. In the 1990s, a research paper linked autism to a common vaccine given to children. This paper was retracted when it was discovered that the author falsified data, and follow-up studies showed no connection between vaccines and autism.

Treatment for autism usually combines behavioral therapies and interventions, along with medications to treat other disorders common to people with autism (depression, anxiety, obsessive compulsive disorder). Although early interventions can help mitigate the effects of the disease, there is currently no cure for ASD.

Attention Deficit Hyperactivity Disorder (ADHD)

Approximately three to five percent of children and adults are affected by attention deficit/hyperactivity disorder (ADHD). Like ASD, ADHD is more prevalent in males than females. Symptoms of the disorder include inattention (lack of focus), executive functioning difficulties, impulsivity, and hyperactivity beyond what is characteristic of the normal developmental stage. Some patients do not have the hyperactive component of symptoms and are diagnosed with a subtype of ADHD: attention deficit disorder (ADD). Many people with ADHD also show comorbitity, in that they develop secondary disorders in addition to ADHD. Examples include depression or obsessive compulsive disorder (OCD). Figure 8.2.7.3 provides some statistics concerning comorbidity with ADHD.

The cause of ADHD is unknown, although research points to a delay and dysfunction in the development of the prefrontal cortex and disturbances in neurotransmission. According to studies of twins, the disorder has a strong genetic component. There are several candidate genes that may contribute to the disorder, but no definitive links have been discovered. Environmental factors, including exposure to certain pesticides, may also contribute to the development of ADHD in some patients. Treatment for ADHD often involves behavioral therapies and the prescription of stimulant medications, which paradoxically cause a calming effect in these patients.



Figure 8.2.7.3: Many people with ADHD have one or more other neurological disorders. (credit “chart design and illustration”: modification of work by Leigh Coriale; credit “data”: Drs. Biederman and Faraone, Massachusetts General Hospital).

Career Connection: Neurologist

Neurologists are physicians who specialize in disorders of the nervous system. They diagnose and treat disorders such as epilepsy, stroke, dementia, nervous system injuries, Parkinson’s disease, sleep disorders, and multiple sclerosis. Neurologists are medical doctors who have attended college, medical school, and completed three to four years of neurology residency.

When examining a new patient, a neurologist takes a full medical history and performs a complete physical exam. The physical exam contains specific tasks that are used to determine what areas of the brain, spinal cord, or peripheral nervous system may be damaged. For example, to check whether the hypoglossal nerve is functioning correctly, the neurologist will ask the patient to move his or her tongue in different ways. If the patient does not have full control over tongue movements, then the hypoglossal nerve may be damaged or there may be a lesion in the brainstem where the cell bodies of these neurons reside (or there could be damage to the tongue muscle itself).

Neurologists have other tools besides a physical exam they can use to diagnose particular problems in the nervous system. If the patient has had a seizure, for example, the neurologist can use electroencephalography (EEG), which involves taping electrodes to the scalp to record brain activity, to try to determine which brain regions are involved in the seizure. In suspected stroke patients, a neurologist can use a computerized tomography (CT) scan, which is a type of X-ray, to look for bleeding in the brain or a possible brain tumor. To treat patients with neurological problems, neurologists can prescribe medications or refer the patient to a neurosurgeon for surgery.

Link to Learning

This website allows you to see the different tests a neurologist might use to see what regions of the nervous system may be damaged in a patient.

Mental Illnesses

Mental illnesses are nervous system disorders that result in problems with thinking, mood, or relating with other people. These disorders are severe enough to affect a person's quality of life and often make it difficult for people to perform the routine tasks of daily living. Debilitating mental disorders plague approximately 12.5 million Americans (about 1 in 17 people) at an annual cost of more than $300 billion. There are several types of mental disorders including schizophrenia, major depression, bipolar disorder, anxiety disorders and phobias, post-traumatic stress disorders, and obsessive-compulsive disorder (OCD), among others. The American Psychiatric Association publishes the Diagnostic and Statistical Manual of Mental Disorders (or DSM), which describes the symptoms required for a patient to be diagnosed with a particular mental disorder. Each newly released version of the DSM contains different symptoms and classifications as scientists learn more about these disorders, their causes, and how they relate to each other. A more detailed discussion of two mental illnesses—schizophrenia and major depression—is given below.

Schizophrenia

Schizophrenia is a serious and often debilitating mental illness affecting one percent of people in the United States. Symptoms of the disease include the inability to differentiate between reality and imagination, inappropriate and unregulated emotional responses, difficulty thinking, and problems with social situations. People with schizophrenia can suffer from hallucinations and hear voices; they may also suffer from delusions. Patients also have so-called "negative" symptoms like a flattened emotional state, loss of pleasure, and loss of basic drives. Many schizophrenic patients are diagnosed in their late adolescence or early 20s. The development of schizophrenia is thought to involve malfunctioning dopaminergic neurons and may also involve problems with glutamate signaling. Treatment for the disease usually requires antipsychotic medications that work by blocking dopamine receptors and decreasing dopamine neurotransmission in the brain. This decrease in dopamine can cause Parkinson's disease-like symptoms in some patients. While some classes of antipsychotics can be quite effective at treating the disease, they are not a cure, and most patients must remain medicated for the rest of their lives.

Depression

Major depression affects approximately 6.7 percent of the adults in the United States each year and is one of the most common mental disorders. To be diagnosed with major depressive disorder, a person must have experienced a severely depressed mood lasting longer than two weeks along with other symptoms including a loss of enjoyment in activities that were previously enjoyed, changes in appetite and sleep schedules, difficulty concentrating, feelings of worthlessness, and suicidal thoughts. The exact causes of major depression are unknown and likely include both genetic and environmental risk factors. Some research supports the "classic monoamine hypothesis," which suggests that depression is caused by a decrease in norepinephrine and serotonin neurotransmission. One argument against this hypothesis is the fact that some antidepressant medications cause an increase in norepinephrine and serotonin release within a few hours of beginning treatment—but clinical results of these medications are not seen until weeks later. This has led to alternative hypotheses: for example, dopamine may also be decreased in depressed patients, or it may actually be an increase in norepinephrine and serotonin that causes the disease, and antidepressants force a feedback loop that decreases this release. Treatments for depression include psychotherapy, electroconvulsive therapy, deep-brain stimulation, and prescription medications. There are several classes of antidepressant medications that work through different mechanisms. For example, monoamine oxidase inhibitors (MAO inhibitors) block the enzyme that degrades many neurotransmitters (including dopamine, serotonin, norepinephrine), resulting in increased neurotransmitter in the synaptic cleft. Selective serotonin reuptake inhibitors (SSRIs) block the reuptake of serotonin into the presynaptic neuron. This blockage results in an increase in serotonin in the synaptic cleft. Other types of drugs such as norepinephrine-dopamine reuptake inhibitors and norepinephrine-serotonin reuptake inhibitors are also used to treat depression.

Other Neurological Disorders

There are several other neurological disorders that cannot be easily placed in the above categories. These include chronic pain conditions, cancers of the nervous system, epilepsy disorders, and stroke. Epilepsy and stroke are discussed below.

Epilepsy

Estimates suggest that up to three percent of people in the United States will be diagnosed with epilepsy in their lifetime. While there are several different types of epilepsy, all are characterized by recurrent seizures. Epilepsy itself can be a symptom of a brain injury, disease, or other illness. For example, people who have intellectual disability or ASD can experience seizures, presumably because the developmental wiring malfunctions that caused their disorders also put them at risk for epilepsy. For many patients, however, the cause of their epilepsy is never identified and is likely to be a combination of genetic and environmental factors. Often, seizures can be controlled with anticonvulsant medications. However, for very severe cases, patients may undergo brain surgery to remove the brain area where seizures originate.

Stroke

A stroke results when blood fails to reach a portion of the brain for a long enough time to cause damage. Without the oxygen supplied by blood flow, neurons in this brain region die. This neuronal death can cause many different symptoms—depending on the brain area affected— including headache, muscle weakness or paralysis, speech disturbances, sensory problems, memory loss, and confusion. Stroke is often caused by blood clots and can also be caused by the bursting of a weak blood vessel. Strokes are extremely common and are the third most common cause of death in the United States. On average one person experiences a stroke every 40 seconds in the United States. Approximately 75 percent of strokes occur in people older than 65. Risk factors for stroke include high blood pressure, diabetes, high cholesterol, and a family history of stroke. Smoking doubles the risk of stroke. Because a stroke is a medical emergency, patients with symptoms of a stroke should immediately go to the emergency room, where they can receive drugs that will dissolve any clot that may have formed. These drugs will not work if the stroke was caused by a burst blood vessel or if the stroke occurred more than three hours before arriving at the hospital. Treatment following a stroke can include blood pressure medication (to prevent future strokes) and (sometimes intense) physical therapy.

Summary

Some general themes emerge from the sampling of nervous system disorders presented above. The causes for most disorders are not fully understood—at least not for all patients—and likely involve a combination of nature (genetic mutations that become risk factors) and nurture (emotional trauma, stress, hazardous chemical exposure). Because the causes have yet to be fully determined, treatment options are often lacking and only address symptoms.

Glossary

Alzheimer's disease
: neurodegenerative disorder characterized by problems with memory and thinking

attention deficit hyperactivity disorder (ADHD)
: neurodevelopmental disorder characterized by difficulty maintaining attention and controlling impulses

autism spectrum disorder (ASD)
: neurodevelopmental disorder characterized by impaired social interaction and communication abilities

epilepsy
: neurological disorder characterized by recurrent seizures

major depression
: mental illness characterized by prolonged periods of sadness

neurodegenerative disorder
: nervous system disorder characterized by the progressive loss of neurological functioning, usually caused by neuron death

Parkinson’s disease

neurodegenerative disorder that affects the control of movement

schizophrenia

mental disorder characterized by the inability to accurately perceive reality; patients often have difficulty thinking clearly and can suffer from delusions

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8.2.E: The Nervous System (Exercises)

35.1: Neurons and Glial Cells

Nervous systems throughout the animal kingdom vary in structure and complexity, as illustrated by the variety of animals shown in Figure 35.1.1. Some organisms, like sea sponges, lack a true nervous system. Others, like jellyfish, lack a true brain and instead have a system of separate but connected nerve cells (neurons) called a “nerve net.” Echinoderms such as sea stars have nerve cells that are bundled into fibers called nerves.

Review Questions

Neurons contain _____, which can receive signals from other neurons.

A. axons
B. mitochondria
C. dendrites
D. Golgi bodies

Answer

C

A(n) _____ neuron has one axon and one dendrite extending directly from the cell body.

A. unipolar
B. bipolar
C. multipolar
D. pseudounipolar

Answer

B

Glia that provide myelin for neurons in the brain are called _____.

A. Schwann cells
B. oligodendrocytes
C. microglia
D. astrocytes

Answer

B

Free Response

How are neurons similar to other cells? How are they unique?

Answer

Neurons contain organelles common to all cells, such as a nucleus and mitochondria. They are unique because they contain dendrites, which can receive signals from other neurons, and axons that can send these signals to other cells.

Multiple sclerosis causes demyelination of axons in the brain and spinal cord. Why is this problematic?

Answer

Myelin provides insulation for signals traveling along axons. Without myelin, signal transmission can slow down and degrade over time. This would slow down neuronal communication across the nervous system and affect all downstream functions.

35.2: How Neurons Communicate

All functions performed by the nervous system—from a simple motor reflex to more advanced functions like making a memory or a decision—require neurons to communicate with one another. While humans use words and body language to communicate, neurons use electrical and chemical signals. Just like a person in a committee, one neuron usually receives and synthesizes messages from multiple other neurons before "making the decision" to send the message on to other neurons.

Review Questions

For a neuron to fire an action potential, its membrane must reach _____.

A. hyperpolarization
B. the threshold of excitation
C. the refractory period
D. inhibitory postsynaptic potential

Answer

B

After an action potential, the opening of additional voltage-gated _____ channels and the inactivation of sodium channels, cause the membrane to return to its resting membrane potential.

A. sodium
B. potassium
C. calcium
D. chloride

Answer

B

What is the term for protein channels that connect two neurons at an electrical synapse?

A. synaptic vesicles
B. voltage-gated ion channels
C. gap junction protein
D. sodium-potassium exchange pumps

Answer

C

Free Response

How does myelin aid propagation of an action potential along an axon? How do the nodes of Ranvier help this process?

Answer

Myelin prevents the leak of current from the axon. Nodes of Ranvier allow the action potential to be regenerated at specific points along the axon. They also save energy for the cell since voltage-gated ion channels and sodium-potassium transporters are not needed along myelinated portions of the axon.

What are the main steps in chemical neurotransmission?

Answer

An action potential travels along an axon until it depolarizes the membrane at an axon terminal. Depolarization of the membrane causes voltage-gated Ca^{2+} channels to open and Ca^{2+} to enter the cell. The intracellular calcium influx causes synaptic vesicles containing neurotransmitter to fuse with the presynaptic membrane. The neurotransmitter diffuses across the synaptic cleft and binds to receptors on the postsynaptic membrane. Depending on the specific neurotransmitter and postsynaptic receptor, this action can cause positive (excitatory postsynaptic potential) or negative (inhibitory postsynaptic potential) ions to enter the cell.

35.3: The Central Nervous System

The central nervous system is made up of the brain and spinal cord and is covered with three layers of protective coverings called meninges (from the Greek word for membrane). The outermost layer is the dura mater with the primary function for this thick layer is to protect the brain and spinal cord. The dura mater also contains vein-like structures that carry blood from the brain back to the heart. The middle layer is the web-like arachnoid mater. The last layer is the pia mater.

Review Questions

The _____ lobe contains the visual cortex.

A. frontal
B. parietal
C. temporal
D. occipital

Answer

D

The _____ connects the two cerebral hemispheres.

A. limbic system
B. corpus callosum
C. cerebellum
D. pituitary

Answer

B

Neurons in the _____ control motor reflexes.

A. thalamus
B. spinal cord
C. parietal lobe
D. hippocampus

Answer

B

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Free Response

What methods can be used to determine the function of a particular brain region?

Answer

To determine the function of a specific brain area, scientists can look at patients who have damage in that brain area and see what symptoms they exhibit. Researchers can disable the brain structure temporarily using transcranial magnetic stimulation. They can disable or remove the area in an animal model. fMRI can be used to correlate specific functions with increased blood flow to brain regions.

What are the main functions of the spinal cord?

Answer

The spinal cord transmits sensory information from the body to the brain and motor commands from the brain to the body through its connections with peripheral nerves. It also controls motor reflexes.

35.4: The Peripheral Nervous System

The peripheral nervous system (PNS) is the connection between the central nervous system and the rest of the body. The central nervious system (CNS) is like the power plant of the nervous system. It creates the signals that control the functions of the body. The PNS is like the wires that go to individual houses. Without those “wires,” the signals produced by the CNS could not control the body (and the CNS would not be able to receive sensory information from the body either).

Review Questions

Activation of the sympathetic nervous system causes:

A. increased blood flow into the skin
B. a decreased heart rate
C. an increased heart rate
D. increased digestion

Answer

C

Where are parasympathetic preganglionic cell bodies located?

A. cerebellum
B. brainstem
C. dorsal root ganglia
D. skin

Answer

B

_____ is released by motor nerve endings onto muscle.

A. Acetylcholine
B. Norepinephrine
C. Dopamine
D. Serotonin

Answer

A

Free Response

What are the main differences between the sympathetic and parasympathetic branches of the autonomic nervous system?

Answer

The sympathetic nervous system prepares the body for “fight or flight,” whereas the parasympathetic nervous system allows the body to “rest and digest.” Sympathetic neurons release norepinephrine onto target organs; parasympathetic neurons release acetylcholine. Sympathetic neuron cell bodies are located in sympathetic ganglia. Parasympathetic neuron cell bodies are located in the brainstem and sacral spinal cord. Activation of the sympathetic nervous system increases heart rate and blood pressure and decreases digestion and blood flow to the skin. Activation of the parasympathetic nervous system decreases heart rate and blood pressure and increases digestion and blood flow to the skin.

What are the main functions of the sensory-somatic nervous system?

Answer

The sensory-somatic nervous system transmits sensory information from the skin, muscles, and sensory organs to the CNS. It also sends motor commands from the CNS to the muscles, causing them to contract.

35.5: Nervous System Disorders

A nervous system that functions correctly is a fantastically complex, well-oiled machine—synapses fire appropriately, muscles move when needed, memories are formed and stored, and emotions are well regulated. Unfortunately, each year millions of people in the United States deal with some sort of nervous system disorder.

Review Questions

Parkinson’s disease is a caused by the degeneration of neurons that release _____.

A. serotonin
B. dopamine
C. glutamate
D. norepinephrine

Answer

B

_____ medications are often used to treat patients with ADHD.

A. Tranquilizer
B. Antibiotic
C. Stimulant
D. Anti-seizure

Answer

C

Strokes are often caused by _____.

A. neurodegeneration
B. blood clots or burst blood vessels

C. seizures
D. viruses

Answer

B

Free Response

What are the main symptoms of Alzheimer’s disease?

Answer

Symptoms of Alzheimer’s disease include disruptive memory loss, confusion about time or place, difficulties planning or executing tasks, poor judgment, and personality changes.

What are possible treatments for patients with major depression?

Answer

Possible treatments for patients with major depression include psychotherapy and prescription medications. MAO inhibitor drugs inhibit the breakdown of certain neurotransmitters (including dopamine, serotonin, norepinephrine) in the synaptic cleft. SSRI medications inhibit the reuptake of serotonin into the presynaptic neuron.

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SECTION OVERVIEW

8.3: Nervous System Infections

Few diseases inspire the kind of fear that rabies does. The name is derived from the Latin word for “madness” or “fury,” most likely because animals infected with rabies may behave with uncharacteristic rage and aggression. And while the thought of being attacked by a rabid animal is terrifying enough, the disease itself is even more frightful. Once symptoms appear, the disease is almost always fatal, even when treated.



Figure 8.3.1: This dog is exhibiting the restlessness and aggression associated with rabies, a neurological disease that frequently affects mammals and can be transmitted to humans. (credit: modification of work by the Centers for Disease Control and Prevention)

Rabies is an example of a neurological disease caused by an acellular pathogen. The rabies virus enters nervous tissue shortly after transmission and makes its way to the central nervous system, where its presence leads to changes in behavior and motor function. Well-known symptoms associated with rabid animals include foaming at the mouth, hydrophobia (fear of water), and unusually aggressive behavior. Rabies claims tens of thousands of human lives worldwide, mainly in Africa and Asia. Most human cases result from dog bites, although many mammal species can become infected and transmit the disease. Human infection rates are low in the United States and many other countries as a result of control measures in animal populations. However, rabies is not the only disease with serious or fatal neurological effects. In this chapter, we examine the important microbial diseases of the nervous system.

8.3.1: Anatomy of the Nervous System

8.3.2: Bacterial Diseases of the Nervous System

8.3.3: Acellular Pathogenic Diseases of the Nervous System

8.3.4: Neuromycoses and Parasitic Diseases of the Nervous System

8.3.E: Nervous System Infections (Exercises)

Thumbnail: Sir Charles Bell’s portrait of a soldier dying of tetanus.

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8.3.1: Anatomy of the Nervous System

Learning Objectives

- Describe the major anatomical features of the nervous system
- Explain why there is no normal microbiota of the nervous system
- Explain how microorganisms overcome defenses of the nervous system to cause infection
- Identify and describe general symptoms associated with various infections of the nervous system

Clinical Focus: Part 1

David is a 35-year-old carpenter from New Jersey. A year ago, he was diagnosed with Crohn's disease, a chronic inflammatory bowel disease that has no known cause. He has been taking a prescription corticosteroid to manage the condition, and the drug has been highly effective in keeping his symptoms at bay. However, David recently fell ill and decided to visit his primary care physician. His symptoms included a fever, a persistent cough, and shortness of breath. His physician ordered a chest X-ray, which revealed consolidation of the right lung. The doctor prescribed a course of levofloxacin and told David to come back in a week if he did not feel better.

Exercise 8.3.1.1

1. What type of drug is levofloxacin?
2. What type of microbes would this drug be effective against?
3. What type of infection is consistent with David's symptoms?

The human nervous system can be divided into two interacting subsystems: the peripheral nervous system (PNS) and the central nervous system (CNS). The CNS consists of the brain and spinal cord. The peripheral nervous system is an extensive network of nerves connecting the CNS to the muscles and sensory structures. The relationship of these systems is illustrated in Figure 8.3.1.1.

The Central Nervous System

The brain is the most complex and sensitive organ in the body. It is responsible for all functions of the body, including serving as the coordinating center for all sensations, mobility, emotions, and intellect. Protection for the brain is provided by the bones of the skull, which in turn are covered by the scalp, as shown in Figure 8.3.1.2. The scalp is composed of an outer layer of skin, which is loosely attached to the aponeurosis, a flat, broad tendon layer that anchors the superficial layers of the skin. The periosteum, below the aponeurosis, firmly encases the bones of the skull and provides protection, nutrition to the bone, and the capacity for bone repair. Below the boney layer of the skull are three layers of membranes called meninges that surround the brain. The relative positions of these meninges are shown in Figure 8.3.1.2. The meningeal layer closest to the bones of the skull is called the dura mater (literally meaning *tough mother*). Below the dura mater lies the arachnoid mater (literally *spider-like mother*). The innermost meningeal layer is a delicate membrane called the pia mater (literally *tender mother*). Unlike the other meningeal layers, the pia mater firmly adheres to the convoluted surface of the brain. Between the arachnoid mater and pia mater is the subarachnoid space. The subarachnoid space within this region is filled with cerebrospinal fluid (CSF). This watery fluid is produced by cells of the choroid plexus—areas in each ventricle of the brain that consist of cuboidal epithelial cells surrounding dense capillary beds. The CSF serves to deliver nutrients and remove waste from neural tissues.

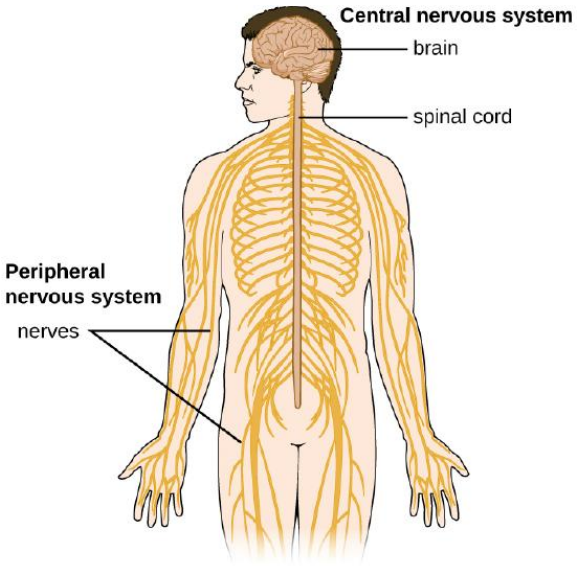


Figure 8.3.1.1: The essential components of the human nervous system are shown in this illustration. The central nervous system (CNS) consists of the brain and spinal cord. It connects to the peripheral nervous system (PNS), a network of nerves that extends throughout the body.

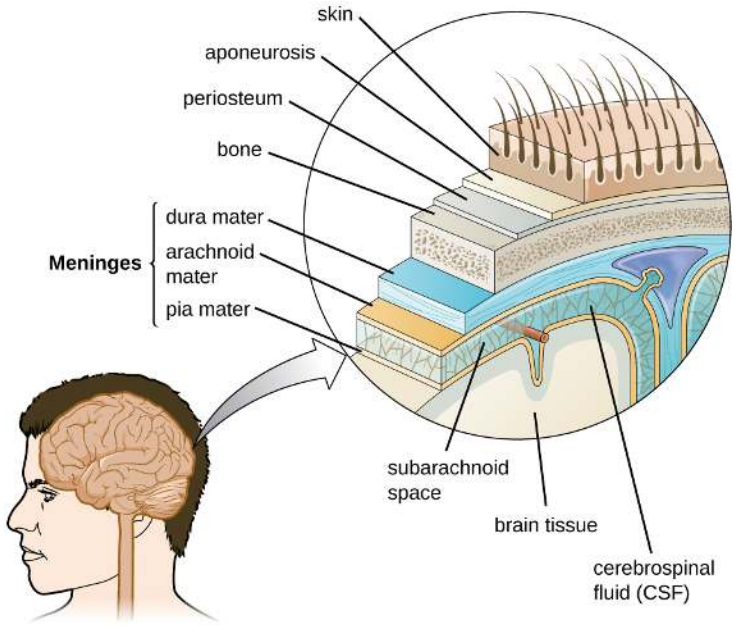


Figure 8.3.1.2: The layers of tissue surrounding the human brain include three meningeal membranes: the dura mater, arachnoid mater, and pia mater. (credit: modification of work by National Institutes of Health)

The Blood-Brain Barrier

The tissues of the CNS have extra protection in that they are not exposed to blood or the immune system in the same way as other tissues. The blood vessels that supply the brain with nutrients and other chemical substances lie on top of the pia mater. The capillaries associated with these blood vessels in the brain are less permeable than those in other locations in the body. The capillary endothelial cells form tight junctions that control the transfer of blood components to the brain. In addition, cranial capillaries have far fewer fenestra (pore-like structures that are sealed by a membrane) and pinocytotic vesicles than other capillaries. As a result, materials in the circulatory system have a very limited ability to interact with the CNS directly. This phenomenon is referred to as the blood-brain barrier.

The blood-brain barrier protects the cerebrospinal fluid from contamination, and can be quite effective at excluding potential microbial pathogens. As a consequence of these defenses, there is no normal microbiota in the cerebrospinal fluid. The blood-brain barrier also inhibits the movement of many drugs into the brain, particularly compounds that are not lipid soluble. This has

profound ramifications for treatments involving infections of the CNS, because it is difficult for drugs to cross the blood-brain barrier to interact with pathogens that cause infections.

The spinal cord also has protective structures similar to those surrounding the brain. Within the bones of the vertebrae are meninges of dura mater (sometimes called the dural sheath), arachnoid mater, pia mater, and a blood-spinal cord barrier that controls the transfer of blood components from blood vessels associated with the spinal cord.

To cause an infection in the CNS, pathogens must successfully breach the blood-brain barrier or blood-spinal cord barrier. Various pathogens employ different virulence factors and mechanisms to achieve this, but they can generally be grouped into four categories: intercellular (also called paracellular), transcellular, leukocyte facilitated, and nonhematogenous. Intercellular entry involves the use of microbial virulence factors, toxins, or inflammation-mediated processes to pass between the cells of the blood-brain barrier. In transcellular entry, the pathogen passes through the cells of the blood-brain barrier using virulence factors that allow it to adhere to and trigger uptake by vacuole- or receptor-mediated mechanisms. Leukocyte-facilitated entry is a Trojan-horse mechanism that occurs when a pathogen infects peripheral blood leukocytes to directly enter the CNS. Nonhematogenous entry allows pathogens to enter the brain without encountering the blood-brain barrier; it occurs when pathogens travel along either the olfactory or trigeminal cranial nerves that lead directly into the CNS.

Link to Learning

View this video about the blood-brain barrier

Exercise 8.3.1.2

What is the primary function of the blood-brain barrier?

The Peripheral Nervous System

The PNS is formed of the nerves that connect organs, limbs, and other anatomic structures of the body to the brain and spinal cord. Unlike the brain and spinal cord, the PNS is not protected by bone, meninges, or a blood barrier, and, as a consequence, the nerves of the PNS are much more susceptible to injury and infection. Microbial damage to peripheral nerves can lead to tingling or numbness known as neuropathy. These symptoms can also be produced by trauma and noninfectious causes such as drugs or chronic diseases like diabetes.

The Cells of the Nervous System

Tissues of the PNS and CNS are formed of cells called glial cells (neuroglial cells) and neurons (nerve cells). Glial cells assist in the organization of neurons, provide a scaffold for some aspects of neuronal function, and aid in recovery from neural injury.

Neurons are specialized cells found throughout the nervous system that transmit signals through the nervous system using electrochemical processes. The basic structure of a neuron is shown in Figure 8.3.1.3. The cell body (or soma) is the metabolic center of the neuron and contains the nucleus and most of the cell's organelles. The many finely branched extensions from the soma are called dendrites. The soma also produces an elongated extension, called the axon, which is responsible for the transmission of electrochemical signals through elaborate ion transport processes. Axons of some types of neurons can extend up to one meter in length in the human body. To facilitate electrochemical signal transmission, some neurons have a myelin sheath surrounding the axon. Myelin, formed from the cell membranes of glial cells like the Schwann cells in the PNS and oligodendrocytes in the CNS, surrounds and insulates the axon, significantly increasing the speed of electrochemical signal transmission along the axon. The end of an axon forms numerous branches that end in bulbs called synaptic terminals. Neurons form junctions with other cells, such as another neuron, with which they exchange signals. The junctions, which are actually gaps between neurons, are referred to as synapses. At each synapse, there is a presynaptic neuron and a postsynaptic neuron (or other cell). The synaptic terminals of the axon of the presynaptic terminal form the synapse with the dendrites, soma, or sometimes the axon of the postsynaptic neuron, or a part of another type of cell such as a muscle cell. The synaptic terminals contain vesicles filled with chemicals called neurotransmitters. When the electrochemical signal moving down the axon reaches the synapse, the vesicles fuse with the membrane, and neurotransmitters are released, which diffuse across the synapse and bind to receptors on the membrane of the

postsynaptic cell, potentially initiating a response in that cell. That response in the postsynaptic cell might include further propagation of an electrochemical signal to transmit information or contraction of a muscle fiber.

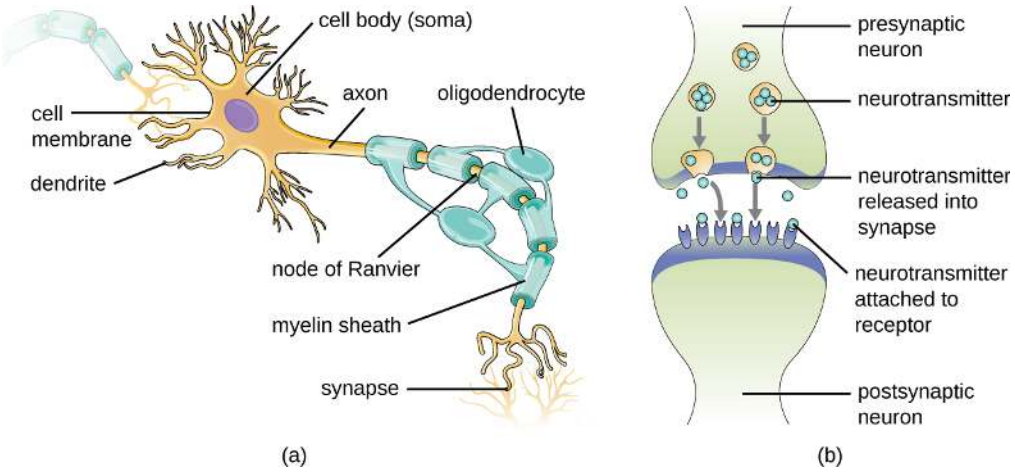


Figure 8.3.1.3: (a) A myelinated neuron is associated with oligodendrocytes. Oligodendrocytes are a type of glial cell that forms the myelin sheath in the CNS that insulates the axon so that electrochemical nerve impulses are transferred more efficiently. (b) A synapse consists of the axonal end of the presynaptic neuron (top) that releases neurotransmitters that cross the synaptic space (or cleft) and bind to receptors on dendrites of the postsynaptic neuron (bottom).

? Exercise 8.3.1.3

1. What cells are associated with neurons, and what is their function?
2. What is the structure and function of a synapse?

Meningitis and Encephalitis

Although the skull provides the brain with an excellent defense, it can also become problematic during infections. Any swelling of the brain or meninges that results from inflammation can cause intracranial pressure, leading to severe damage of the brain tissues, which have limited space to expand within the inflexible bones of the skull. The term meningitis is used to describe an inflammation of the meninges. Typical symptoms can include severe headache, fever, photophobia (increased sensitivity to light), stiff neck, convulsions, and confusion. An inflammation of brain tissue is called encephalitis, and patients exhibit signs and symptoms similar to those of meningitis in addition to lethargy, seizures, and personality changes. When inflammation affects both the meninges and the brain tissue, the condition is called meningoencephalitis. All three forms of inflammation are serious and can lead to blindness, deafness, coma, and death.

Meningitis and encephalitis can be caused by many different types of microbial pathogens. However, these conditions can also arise from noninfectious causes such as head trauma, some cancers, and certain drugs that trigger inflammation. To determine whether the inflammation is caused by a pathogen, a lumbar puncture is performed to obtain a sample of CSF. If the CSF contains increased levels of white blood cells and abnormal glucose and protein levels, this indicates that the inflammation is a response to an infectioninflinin.

? Exercise 8.3.1.4

1. What are the two types of inflammation that can impact the CNS?
2. Why do both forms of inflammation have such serious consequences?

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is a rare condition that can be preceded by a viral or bacterial infection that results in an autoimmune reaction against myelinated nerve cells. The destruction of the myelin sheath around these neurons results in a loss of sensation and function. The first symptoms of this condition are tingling and weakness in the affected tissues. The symptoms intensify over a period of several weeks and can culminate in complete paralysis. Severe cases can be life-

threatening. Infections by several different microbial pathogens, including *Campylobacter jejuni* (the most common risk factor), cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, *Mycoplasma pneumoniae*,[1] and Zika virus[2] have been identified as triggers for GBS. Anti-myelin antibodies from patients with GBS have been demonstrated to also recognize *C. jejuni*. It is possible that cross-reactive antibodies, antibodies that react with similar antigenic sites on different proteins, might be formed during an infection and may lead to this autoimmune response.

GBS is solely identified by the appearance of clinical symptoms. There are no other diagnostic tests available. Fortunately, most cases spontaneously resolve within a few months with few permanent effects, as there is no available vaccine. GBS can be treated by plasmapheresis. In this procedure, the patient's plasma is filtered from their blood, removing autoantibodies.

Key Concepts and Summary

- The nervous system consists of two subsystems: the **central nervous system** and **peripheral nervous system**.
- The skull and three **meninges** (the **dura mater**, **arachnoid mater**, and **pia mater**) protect the brain.
- Tissues of the PNS and CNS are formed of cells called **glial cells** and **neurons**.
- Since the **blood-brain barrier** excludes most microbes, there is no normal microbiota in the CNS.
- Some pathogens have specific virulence factors that allow them to breach the blood-brain barrier. Inflammation of the brain or **meninges** caused by infection is called **encephalitis** or **meningitis**, respectively. These conditions can lead to blindness, deafness, coma, and death.

Footnotes

1. Yuki, Nobuhiro and Hans-Peter Hartung, "Guillain–Barré Syndrome," *New England Journal of Medicine* 366, no. 24 (2012): 2294-304.
2. Cao-Lormeau, Van-Mai, Alexandre Blake, Sandrine Mons, Stéphane Lastère, Claudine Roche, Jessica Vanhomwegen, Timothée Dub et al., "Guillain-Barré Syndrome Outbreak Associated with Zika Virus Infection in French Polynesia: A Case-Control Study," *The Lancet* 387, no. 10027 (2016): 1531-9.

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8.3.2: Bacterial Diseases of the Nervous System

Learning Objectives

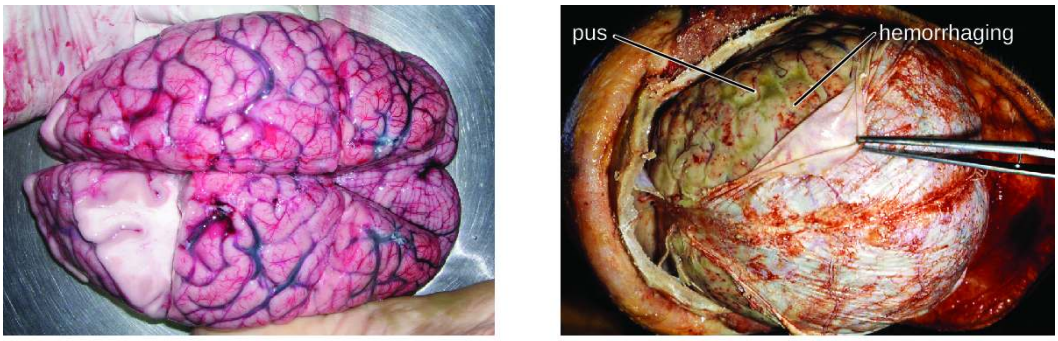
- Identify the most common bacteria that can cause infections of the nervous system
- Compare the major characteristics of specific bacterial diseases affecting the nervous system

Bacterial infections that affect the nervous system are serious and can be life-threatening. Fortunately, there are only a few bacterial species commonly associated with neurological infections.

Bacterial Meningitis

Bacterial meningitis is one of the most serious forms of meningitis. Bacteria that cause meningitis often gain access to the CNS through the bloodstream after trauma or as a result of the action of bacterial toxins. Bacteria may also spread from structures in the upper respiratory tract, such as the oropharynx, nasopharynx, sinuses, and middle ear. Patients with head wounds or cochlear implants (an electronic device placed in the inner ear) are also at risk for developing meningitis.

Many of the bacteria that can cause meningitis are commonly found in healthy people. The most common causes of non-neonatal bacterial meningitis are *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. All three of these bacterial pathogens are spread from person to person by respiratory secretions. Each can colonize and cross through the mucous membranes of the oropharynx and nasopharynx, and enter the blood. Once in the blood, these pathogens can disseminate throughout the body and are capable of both establishing an infection and triggering inflammation in any body site, including the meninges (Figure 8.3.2.1). Without appropriate systemic antibacterial therapy, the case-fatality rate can be as high as 70%, and 20% of those survivors may be left with irreversible nerve damage or tissue destruction, resulting in hearing loss, neurologic disability, or loss of a limb. Mortality rates are much lower (as low as 15%) in populations where appropriate therapeutic drugs and preventive vaccines are available.[1]



(a) (b)

Figure 8.3.2.1: (a) A normal human brain removed during an autopsy. (b) The brain of a patient who died from bacterial meningitis. Note the pus under the dura mater (being retracted by the forceps) and the red hemorrhagic foci on the meninges. (credit b: modification of work by the Centers for Disease Control and Prevention)

A variety of other bacteria, including *Listeria monocytogenes* and *Escherichia coli*, are also capable of causing meningitis. These bacteria cause infections of the arachnoid mater and CSF after spreading through the circulation in blood or by spreading from an infection of the sinuses or nasopharynx. *Streptococcus agalactiae*, commonly found in the microbiota of the vagina and gastrointestinal tract, can also cause bacterial meningitis in newborns after transmission from the mother either before or during birth.

The profound inflammation caused by these microbes can result in early symptoms that include severe headache, fever, confusion, nausea, vomiting, photophobia, and stiff neck. Systemic inflammatory responses associated with some types of bacterial meningitis can lead to hemorrhaging and purpuric lesions on skin, followed by even more severe conditions that include shock, convulsions, coma, and death—in some cases, in the span of just a few hours.

Diagnosis of bacterial meningitis is best confirmed by analysis of CSF obtained by a lumbar puncture. Abnormal levels of polymorphonuclear neutrophils (PMNs) (> 10 PMNs/mm^3), glucose (< 45 mg/dL), and protein (> 45 mg/dL) in the CSF are

suggestive of bacterial meningitis.[2] Characteristics of specific forms of bacterial meningitis are detailed in the subsections that follow.

Meningococcal Meningitis

Meningococcal meningitis is a serious infection caused by the gram-negative coccus *N. meningitidis*. In some cases, death can occur within a few hours of the onset of symptoms. Nonfatal cases can result in irreversible nerve damage, resulting in hearing loss and brain damage, or amputation of extremities because of tissue necrosis.

Meningococcal meningitis can infect people of any age, but its prevalence is highest among infants, adolescents, and young adults.[3] Meningococcal meningitis was once the most common cause of meningitis epidemics in human populations. This is still the case in a swath of sub-Saharan Africa known as the meningitis belt, but meningococcal meningitis epidemics have become rare in most other regions, thanks to meningococcal vaccines. However, outbreaks can still occur in communities, schools, colleges, prisons, and other populations where people are in close direct contact.

N. meningitidis has a high affinity for mucosal membranes in the oropharynx and nasopharynx. Contact with respiratory secretions containing *N. meningitidis* is an effective mode of transmission. The pathogenicity of *N. meningitidis* is enhanced by virulence factors that contribute to the rapid progression of the disease. These include lipooligosaccharide (LOS) endotoxin, type IV pili for attachment to host tissues, and polysaccharide capsules that help the cells avoid phagocytosis and complement-mediated killing. Additional virulence factors include IgA protease(which breaks down IgA antibodies), the invasion factors Opa, Opc, and porin (which facilitate transcellular entry through the blood-brain barrier), iron-uptake factors (which strip heme units from hemoglobin in host cells and use them for growth), and stress proteins that protect bacteria from reactive oxygen molecules.

A unique sign of meningococcal meningitis is the formation of a petechial rash on the skin or mucous membranes, characterized by tiny, red, flat, hemorrhagic lesions. This rash, which appears soon after disease onset, is a response to LOS endotoxin and adherence virulence factors that disrupt the endothelial cells of capillaries and small veins in the skin. The blood vessel disruption triggers the formation of tiny blood clots, causing blood to leak into the surrounding tissue. As the infection progresses, the levels of virulence factors increase, and the hemorrhagic lesions can increase in size as blood continues to leak into tissues. Lesions larger than 1.0 cm usually occur in patients developing shock, as virulence factors cause increased hemorrhage and clot formation. Sepsis, as a result of systemic damage from meningococcal virulence factors, can lead to rapid multiple organ failure, shock, disseminated intravascular coagulation, and death.

Because meningococcoal meningitis progresses so rapidly, a greater variety of clinical specimens are required for the timely detection of *N. meningitidis*. Required specimens can include blood, CSF, naso- and oropharyngeal swabs, urethral and endocervical swabs, petechial aspirates, and biopsies. Safety protocols for handling and transport of specimens suspected of containing *N. meningitidis* should always be followed, since cases of fatal meningococcal disease have occurred in healthcare workers exposed to droplets or aerosols from patient specimens. Prompt presumptive diagnosis of meningococcal meningitis can occur when CSF is directly evaluated by Gram stain, revealing extra- and intracellular gram-negative diplococci with a distinctive coffee-bean microscopic morphology associated with PMNs (Figure 8.3.2.2). Identification can also be made directly from CSF using latex agglutination and immunochromatographic rapid diagnostic tests specific for *N. meningitidis*. Species identification can also be performed using DNA sequence-based typing schemes for hypervariable outer membrane proteins of *N. meningitidis*, which has replaced sero(sub)typing.

Meningococcal infections can be treated with antibiotic therapy, and third-generation cephalosporins are most often employed. However, because outcomes can be negative even with treatment, preventive vaccination is the best form of treatment. In 2010, countries in Africa's meningitis belt began using a new serogroup A meningococcal conjugate vaccine. This program has dramatically reduced the number of cases of meningococcal meningitis by conferring individual and herd immunity.

Twelve different capsular serotypes of *N. meningitidis* are known to exist. Serotypes A, B, C, W, X, and Y are the most prevalent worldwide. The CDC recommends that children between 11–12 years of age be vaccinated with a single dose of a quadrivalent vaccine that protects against serotypes A, C, W, and Y, with a booster at age 16.[4] An additional booster or injections of serogroup B meningococcal vaccine may be given to individuals in high-risk settings (such as epidemic outbreaks on college campuses).

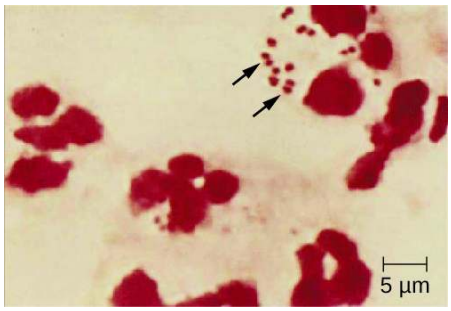


Figure 8.3.2.2: N. meningitidis (arrows) associated with neutrophils (the larger stained cells) in a gram-stained CSF sample. (credit: modification of work by the Centers for Disease Control and Prevention)

Meningitis on Campus

College students living in dorms or communal housing are at increased risk for contracting epidemic meningitis. From 2011 to 2015, there have been at least nine meningococcal outbreaks on college campuses in the United States. These incidents involved a total of 43 students (of whom four died).[5] In spite of rapid diagnosis and aggressive antimicrobial treatment, several of the survivors suffered from amputations or serious neurological problems.

Prophylactic vaccination of first-year college students living in dorms is recommended by the CDC, and insurance companies now cover meningococcal vaccination for students in college dorms. Some colleges have mandated vaccination with meningococcal conjugate vaccine for certain students entering college (Figure 8.3.2.3).



Figure 8.3.2.3: To prevent campus outbreaks, some colleges now require students to be vaccinated against meningogoccal meningitis. (credit: modification of work by James Gathany, Centers for Disease Control and Prevention)

Pneumococcal Meningitis

Pneumococcal meningitis is caused by the encapsulated gram-positive bacterium *S. pneumoniae* (pneumococcus, also called strep pneumo). This organism is commonly found in the microbiota of the pharynx of 30–70% of young children, depending on the sampling method, while *S. pneumoniae* can be found in fewer than 5% of healthy adults. Although it is often present without disease symptoms, this microbe can cross the blood-brain barrier in susceptible individuals. In some cases, it may also result in septicemia. Since the introduction of the Hib vaccine, *S. pneumoniae* has become the leading cause of meningitis in humans aged 2 months through adulthood.

S. pneumoniae can be identified in CSF samples using gram-stained specimens, latex agglutination, and immunochromatographic RDT specific for *S. pneumoniae*. In gram-stained samples, *S. pneumoniae* appears as gram-positive, lancet-shaped diplococci (Figure 8.3.2.4). Identification of *S. pneumoniae* can also be achieved using cultures of CSF and blood, and at least 93 distinct serotypes can be identified based on the quellung reaction to unique capsular polysaccharides. PCR and RT-PCR assays are also available to confirm identification.

Major virulence factors produced by *S. pneumoniae* include PI-1 pilin for adherence to host cells (pneumococcal adherence) and virulence factor B (PavB) for attachment to cells of the respiratory tract; choline-binding proteins(cbpA) that bind to epithelial cells

and interfere with immune factors IgA and C3; and the cytoplasmic bacterial toxin pneumolysin that triggers an inflammatory response.

With the emergence of drug-resistant strains of *S. pneumoniae*, pneumococcal meningitis is typically treated with broad-spectrum antibiotics, such as levofloxacin, cefotaxime, penicillin, or other β-lactam antibiotics. The two available pneumococcal vaccines are described in Bacterial Infections of the Respiratory Tract.

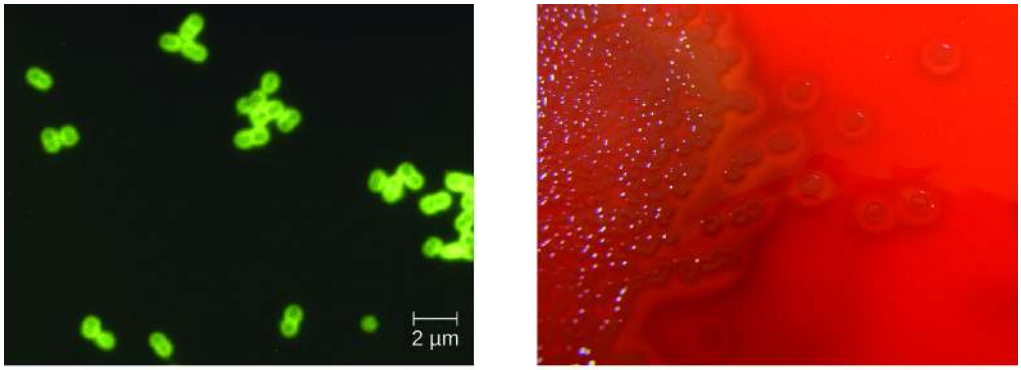


Figure 8.3.2.4: (a) Digitally colorized fluorescent antibody stained micrograph of *Streptococcus pneumoniae* in CSF. (b) *S. pneumoniae* growing on blood agar. (credit a: modification of work by the Centers for Disease Control and Prevention; credit b: modification of work by Nathan Reading)

Haemophilus influenzae Type b

Meningitis due to *H. influenzae* serotype b (Hib), an encapsulated pleomorphic gram-negative coccobacilli, is now uncommon in most countries, because of the use of the effective Hib vaccine. Without the use of the Hib vaccine, *H. influenzae* can be the primary cause of meningitis in children 2 months thru 5 years of age. *H. influenzae* can be found in the throats of healthy individuals, including infants and young children. By five years of age, most children have developed immunity to this microbe. Infants older than 2 months of age, however, do not produce a sufficient protective antibody response and are susceptible to serious disease. The intracranial pressure caused by this infection leads to a 5% mortality rate and 20% incidence of deafness or brain damage in survivors.[6]

H. influenzae produces at least 16 different virulence factors, including LOS, which triggers inflammation, and *Haemophilus* adhesion and penetration factor (Hap), which aids in attachment and invasion into respiratory epithelial cells. The bacterium also has a polysaccharide capsule that helps it avoid phagocytosis, as well as factors such as IgA1 protease and P2 protein that allow it to evade antibodies secreted from mucous membranes. In addition, factors such as hemoglobin-binding protein (Hgp) and transferrin-binding protein (Tbp) acquire iron from hemoglobin and transferrin, respectively, for bacterial growth.

Preliminary diagnosis of *H. influenzae* infections can be made by direct PCR and a smear of CSF. Stained smears will reveal intracellular and extracellular PMNs with small, pleomorphic, gram-negative coccobacilli or filamentous forms that are characteristic of *H. influenzae*. Initial confirmation of this genus can be based on its fastidious growth on chocolate agar. Identification is confirmed with requirements for exogenous biochemical growth cofactors NAD and heme (by MALDI-TOF), latex agglutination, and RT-PCR.

Meningitis caused by *H. influenzae* is usually treated with doxycycline, fluoroquinolones, second- and third-generation cephalosporins, and carbapenems. The best means of preventing *H. influenza* infection is with the use of the Hib polysaccharide conjugate vaccine. It is recommended that all children receive this vaccine at 2, 4, and 6 months of age, with a final booster dose at 12 to 15 months of age.[7]

Neonatal Meningitis

S. agalactiae, Group B streptococcus (GBS), is an encapsulated gram-positive bacterium that is the most common cause of neonatal meningitis, a term that refers to meningitis occurring in babies up to 3 months of age.[8] *S. agalactiae* can also cause meningitis in people of all ages and can be found in the urogenital and gastrointestinal microbiota of about 10–30% of humans.

Neonatal infection occurs as either early onset or late-onset disease. Early onset disease is defined as occurring in infants up to 7 days old. The infant initially becomes infected by *S. agalactiae* during childbirth, when the bacteria may be transferred from the mother's vagina. Incidence of early onset neonatal meningitis can be greatly reduced by giving intravenous antibiotics to the mother during labor.

Late-onset neonatal meningitis occurs in infants between 1 week and 3 months of age. Infants born to mothers with *S. agalactiae* in the urogenital tract have a higher risk of late-onset menigitis, but late-onset infections can be transmitted from sources other than the mother; often, the source of infection is unknown. Infants who are born prematurely (before 37 weeks of pregnancy) or to mothers who develop a fever also have a greater risk of contracting late-onset neonatal meningitis.

Signs and symptoms of early onset disease include temperature instability, apnea (cessation of breathing), bradycardia(slow heart rate), hypotension, difficulty feeding, irritability, and limpness. When asleep, the baby may be difficult to wake up. Symptoms of late-onset disease are more likely to include seizures, bulging fontanel (soft spot), stiff neck, hemiparesis (weakness on one side of the body), and opisthotonos (rigid body with arched back and head thrown backward).

S. agalactiae produces at least 12 virulence factors that include FbsA that attaches to host cell surface proteins, PI-1 pilithat promotes the invasion of human endothelial cells, a polysaccharide capsule that prevents the activation of the alternative complement pathway and inhibits phagocytosis, and the toxin CAMP factor, which forms pores in host cell membranes and binds to IgG and IgM antibodies.

Diagnosis of neonatal meningitis is often, but not uniformly, confirmed by positive results from cultures of CSF or blood. Tests include routine culture, antigen detection by enzyme immunoassay, serotyping of different capsule types, PCR, and RT-PCR. It is typically treated with β-lactam antibiotics such as intravenous penicillin or ampicillin plus gentamicin. Even with treatment, roughly 10% mortality is seen in infected neonates.[9]

? Exercise 8.3.2.1

1. Which groups are most vulnerable to each of the bacterial meningitis diseases?
2. For which of the bacterial meningitis diseases are there vaccines presently available?
3. Which organism can cause epidemic meningitis?

Clostridium-Associated Diseases

Species in the genus *Clostridium* are gram-positive, endospore-forming rods that are obligate anaerobes. Endospores of *Clostridium* spp. are widespread in nature, commonly found in soil, water, feces, sewage, and marine sediments. *Clostridium* spp. produce more types of protein exotoxins than any other bacterial genus, including two exotoxins with protease activity that are the most potent known biological toxins: botulinum neurotoxin (BoNT) and tetanus neurotoxin (TeNT). These two toxins have lethal doses of 0.2–10 ng per kg body weight.

BoNT can be produced by unique strains of *C. butyricum*, and *C. baratii*; however, it is primarily associated with *C. botulinum* and the condition of botulism. TeNT, which causes tetanus, is only produced by *C. tetani*. These powerful neural exotoxins are the primary virulence factors for these pathogens. The mode of action for these toxins was described in Virulence Factors of Bacterial and Viral Pathogens and illustrated in Figure 15.3.7.

Diagnosis of tetanus or botulism typically involves bioassays that detect the presence of BoNT and TeNT in fecal specimens, blood (serum), or suspect foods. In addition, both *C. botulinum* and *C. tetani* can be isolated and cultured using commercially available media for anaerobes. ELISA and RT-PCR tests are also available.

Tetanus

Tetanus is a noncommunicable disease characterized by uncontrollable muscle spasms (contractions) caused by the action of TeNT. It generally occurs when *C. tetani* infects a wound and produces TeNT, which rapidly binds to neural tissue, resulting in an intoxication (poisoning) of neurons. Depending on the site and extent of infection, cases of tetanus can be described as localized, cephalic, or generalized. Generalized tetanus that occurs in a newborn is called neonatal tetanus.

Localized tetanus occurs when TeNT only affects the muscle groups close to the injury site. There is no CNS involvement, and the symptoms are usually mild, with localized muscle spasms caused by a dysfunction in the surrounding neurons. Individuals with

partial immunity—especially previously vaccinated individuals who neglect to get the recommended booster shots—are most likely to develop localized tetanus as a result of *C. tetani* infecting a puncture wound.

Cephalic tetanus is a rare, localized form of tetanus generally associated with wounds on the head or face. In rare cases, it has occurred in cases of otitis media (middle ear infection). Cephalic tetanus often results in patients seeing double images, because of the spasms affecting the muscles that control eye movement.

Both localized and cephalic tetanus may progress to generalized tetanus—a much more serious condition—if TeNT is able to spread further into body tissues. In generalized tetanus, TeNT enters neurons of the PNS. From there, TeNT travels from the site of the wound, usually on an extremity of the body, retrograde (back up) to inhibitory neurons in the CNS. There, it prevents the release of gamma aminobutyric acid (GABA), the neurotransmitter responsible for muscle relaxation. The resulting muscle spasms often first occur in the jaw muscles, leading to the characteristic symptom of lockjaw (inability to open the mouth). As the toxin progressively continues to block neurotransmitter release, other muscles become involved, resulting in uncontrollable, sudden muscle spasms that are powerful enough to cause tendons to rupture and bones to fracture. Spasms in the muscles in the neck, back, and legs may cause the body to form a rigid, stiff arch, a posture called opisthotonos (Figure 8.3.2.5). Spasms in the larynx, diaphragm, and muscles of the chest restrict the patient's ability to swallow and breathe, eventually leading to death by asphyxiation (insufficient supply of oxygen).

Neonatal tetanus typically occurs when the stump of the umbilical cord is contaminated with spores of *C. tetani* after delivery. Although this condition is rare in the United States, neonatal tetanus is a major cause of infant mortality in countries that lack maternal immunization for tetanus and where birth often occurs in unsanitary conditions. At the end of the first week of life, infected infants become irritable, feed poorly, and develop rigidity with spasms. Neonatal tetanus has a very poor prognosis with a mortality rate of 70%–100%.[10]

Treatment for patients with tetanus includes assisted breathing through the use of a ventilator, wound debridement, fluid balance, and antibiotic therapy with metronidazole or penicillin to halt the growth of *C. tetani*. In addition, patients are treated with TeNT antitoxin, preferably in the form of human immunoglobulin to neutralize nonfixed toxin and benzodiazepines to enhance the effect of GABA for muscle relaxation and anxiety.

A tetanus toxoid (TT) vaccine is available for protection and prevention of tetanus. It is the T component of vaccines such as DTaP, Tdap, and Td. The CDC recommends children receive doses of the DTaP vaccine at 2, 4, 6, and 15–18 months of age and another at 4–6 years of age. One dose of Td is recommended for adolescents and adults as a TT booster every 10 years.[11]



Figure 8.3.2.5: A tetanus patient exhibiting the rigid body posture known as opisthotonos. (credit: Centers for Disease Control and Prevention)

Botulism

Botulism is a rare but frequently fatal illness caused by intoxication by BoNT. It can occur either as the result of an infection by *C. botulinum*, in which case the bacteria produce BoNT *in vivo*, or as the result of a direct introduction of BoNT into tissues.

Infection and production of BoNT *in vivo* can result in wound botulism, infant botulism, and adult intestinal toxemia. Wound botulism typically occurs when *C. botulinum* is introduced directly into a wound after a traumatic injury, deep puncture wound, or injection site. Infant botulism, which occurs in infants younger than 1 year of age, and adult intestinal toxemia, which occurs in

immunocompromised adults, results from ingesting *C. botulinum* endospores in food. The endospores germinate in the body, resulting in the production of BoNT in the intestinal tract.

Intoxications occur when BoNT is produced outside the body and then introduced directly into the body through food (foodborne botulism), air (inhalation botulism), or a clinical procedure (iatrogenic botulism). Foodborne botulism, the most common of these forms, occurs when BoNT is produced in contaminated food and then ingested along with the food (recall Case in Point: A Streak of Bad Potluck). Inhalation botulism is rare because BoNT is unstable as an aerosol and does not occur in nature; however, it can be produced in the laboratory and was used (unsuccessfully) as a bioweapon by terrorists in Japan in the 1990s. A few cases of accidental inhalation botulism have also occurred. Iatrogenic botulism is also rare; it is associated with injections of BoNT used for cosmetic purposes (see Micro Connections: Medicinal Uses of Botulinum Toxin).

When BoNT enters the bloodstream in the gastrointestinal tract, wound, or lungs, it is transferred to the neuromuscular junctions of motor neurons where it binds irreversibly to presynaptic membranes and prevents the release of acetylcholine from the presynaptic terminal of motor neurons into the neuromuscular junction. The consequence of preventing acetylcholine release is the loss of muscle activity, leading to muscle relaxation and eventually paralysis.

If BoNT is absorbed through the gastrointestinal tract, early symptoms of botulism include blurred vision, drooping eyelids, difficulty swallowing, abdominal cramps, nausea, vomiting, constipation, or possibly diarrhea. This is followed by progressive flaccid paralysis, a gradual weakening and loss of control over the muscles. A patient's experience can be particularly terrifying, because hearing remains normal, consciousness is not lost, and he or she is fully aware of the progression of his or her condition. In infants, notable signs of botulism include weak cry, decreased ability to suckle, and hypotonia (limpness of head or body). Eventually, botulism ends in death from respiratory failure caused by the progressive paralysis of the muscles of the upper airway, diaphragm, and chest.

Botulism is treated with an antitoxin specific for BoNT. If administered in time, the antitoxin stops the progression of paralysis but does not reverse it. Once the antitoxin has been administered, the patient will slowly regain neurological function, but this may take several weeks or months, depending on the severity of the case. During recovery, patients generally must remain hospitalized and receive breathing assistance through a ventilator.

? Exercise 8.3.2.2

1. How frequently should the tetanus vaccination be updated in adults?
2. What are the most common causes of botulism?
3. Why is botulism not treated with an antibiotic?

Medicinal Uses of Botulinum Toxin

Although it is the most toxic biological material known to man, botulinum toxin is often intentionally injected into people to treat other conditions. Type A botulinum toxin is used cosmetically to reduce wrinkles. The injection of minute quantities of this toxin into the face causes the relaxation of facial muscles, thereby giving the skin a smoother appearance. Eyelid twitching and crossed eyes can also be treated with botulinum toxin injections. Other uses of this toxin include the treatment of hyperhidrosis (excessive sweating). In fact, botulinum toxin can be used to moderate the effects of several other apparently nonmicrobial diseases involving inappropriate nerve function. Such diseases include cerebral palsy, multiple sclerosis, and Parkinson's disease. Each of these diseases is characterized by a loss of control over muscle contractions; treatment with botulinum toxin serves to relax contracted muscles.

Listeriosis

Listeria monocytogenes is a nonencapsulated, nonsporulating, gram-positive rod and a foodborne pathogen that causes listeriosis. At-risk groups include pregnant women, neonates, the elderly, and the immunocompromised (recall the Clinical Focus case studies in Microbial Growth and Microbial Mechanisms of Pathogenicity). Listeriosis leads to meningitis in about 20% of cases, particularly neonates and patients over the age of 60. The CDC identifies listeriosis as the third leading cause of death due to

foodborne illness, with overall mortality rates reaching 16%.[12] In pregnant women, listeriosis can cause also cause spontaneous abortion in pregnant women because of the pathogen's unique ability to cross the placenta.

L. monocytogenes is generally introduced into food items by contamination with soil or animal manure used as fertilizer. Foods commonly associated with listeriosis include fresh fruits and vegetables, frozen vegetables, processed meats, soft cheeses, and raw milk.[13] Unlike most other foodborne pathogens, *Listeria* is able to grow at temperatures between 0 °C and 50 °C, and can therefore continue to grow, even in refrigerated foods.

Ingestion of contaminated food leads initially to infection of the gastrointestinal tract. However, *L. monocytogenes* produces several unique virulence factors that allow it to cross the intestinal barrier and spread to other body systems. Surface proteins called internalins (InlA and InlB) help *L. monocytogenes* invade nonphagocytic cells and tissues, penetrating the intestinal wall and becoming disseminating through the circulatory and lymphatic systems. Internalins also enable *L. monocytogenes* to breach other important barriers, including the blood-brain barrier and the placenta. Within tissues, *L. monocytogenes* uses other proteins called listeriolysin O and ActA to facilitate intercellular movement, allowing the infection to spread from cell to cell (Figure 8.3.2.6).

L. monocytogenes is usually identified by cultivation of samples from a normally sterile site (e.g., blood or CSF). Recovery of viable organisms can be enhanced using cold enrichment by incubating samples in a broth at 4 °C for a week or more. Distinguishing types and subtypes of *L. monocytogenes*—an important step for diagnosis and epidemiology—is typically done using pulsed-field gel electrophoresis. Identification can also be achieved using chemiluminescence DNA probe assays and MALDI-TOF.

Treatment for listeriosis involves antibiotic therapy, most commonly with ampicillin and gentamicin. There is no vaccine available.

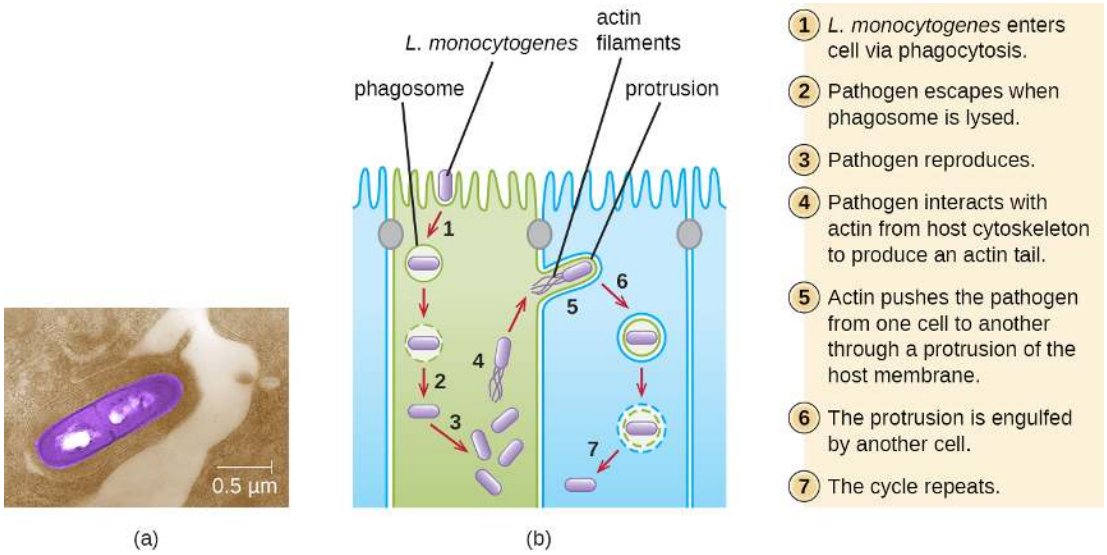


Figure 8.3.2.6: (a) An electron micrograph of *Listeria monocytogenes* infecting a host cell. (b) *Listeria* is able to use host cell components to cause infection. For example, phagocytosis allows it to enter host cells, and the host's cytoskeleton provides the materials to help the pathogen move to other cells. (credit a: modification of work by the Centers for Disease Control and Prevention; credit b: modification of work by Keith Ireton)

? Exercise 8.3.2.3

How does *Listeria* enter the nervous system?

Hansen's Disease (Leprosy)

Hansen's disease (also known as leprosy) is caused by a long, thin, filamentous rod-shaped bacterium *Mycobacterium leprae*, an obligate intracellular pathogen. *M. leprae* is classified as gram-positive bacteria, but it is best visualized microscopically with an acid-fast stain and is generally referred to as an acid-fast bacterium. Hansen's disease affects the PNS, leading to permanent damage and loss of appendages or other body parts.

Hansen's disease is communicable but not highly contagious; approximately 95% of the human population cannot be easily infected because they have a natural immunity to *M. leprae*. Person-to-person transmission occurs by inhalation into nasal mucosa or prolonged and repeated contact with infected skin. Armadillos, one of only five mammals susceptible to Hansen's disease, have also been implicated in transmission of some cases.[14]

In the human body, *M. leprae* grows best at the cooler temperatures found in peripheral tissues like the nose, toes, fingers, and ears. Some of the virulence factors that contribute to *M. leprae*'s pathogenicity are located on the capsule and cell wall of the bacterium. These virulence factors enable it to bind to and invade Schwann cells, resulting in progressive demyelination that gradually destroys neurons of the PNS. The loss of neuronal function leads to hypoesthesia (numbness) in infected lesions. *M. leprae* is readily phagocytized by macrophages but is able to survive within macrophages in part by neutralizing reactive oxygen species produced in the oxidative burst of the phagolysosome. Like *L. monocytogenes*, *M. leprae* also can move directly between macrophages to avoid clearance by immune factors.

The extent of the disease is related to the immune response of the patient. Initial symptoms may not appear for as long as 2 to 5 years after infection. These often begin with small, blanched, numb areas of the skin. In most individuals, these will resolve spontaneously, but some cases may progress to a more serious form of the disease. Tuberculoid (paucibacillary) Hansen's disease is marked by the presence of relatively few (three or less) flat, blanched skin lesions with small nodules at the edges and few bacteria present in the lesion. Although these lesions can persist for years or decades, the bacteria are held in check by an effective immune response including cell-mediated cytotoxicity. Individuals who are unable to contain the infection may later develop lepromatous (multibacillary) Hansen's disease. This is a progressive form of the disease characterized by nodules filled with acid-fast bacilli and macrophages. Impaired function of infected Schwann cells leads to peripheral nerve damage, resulting in sensory loss that leads to ulcers, deformities, and fractures. Damage to the ulnar nerve (in the wrist) by *M. leprae* is one of the most common causes of crippling of the hand. In some cases, chronic tissue damage can ultimately lead to loss of fingers or toes. When mucosal tissues are also involved, disfiguring lesions of the nose and face can also occur (Figure 8.3.2.7).

Hansen's disease is diagnosed on the basis of clinical signs and symptoms of the disease, and confirmed by the presence of acid-fast bacilli on skin smears or in skin biopsy specimens (Figure 8.3.2.7). *M. leprae* does not grow *in vitro* on any known laboratory media, but it can be identified by culturing *in vivo* in the footpads of laboratory mice or armadillos. Where needed, PCR and genotyping of *M. leprae* DNA in infected human tissue may be performed for diagnosis and epidemiology.

Hansen's disease responds well to treatment and, if diagnosed and treated early, does not cause disability. In the United States, most patients with Hansen's disease are treated in ambulatory care clinics in major cities by the National Hansen's Disease program, the only institution in the United States exclusively devoted to Hansen's disease. Since 1995, WHO has made multidrug therapy for Hansen's disease available free of charge to all patients worldwide. As a result, global prevalence of Hansen's disease has declined from about 5.2 million cases in 1985 to roughly 176,000 in 2014.[15] Multidrug therapy consists of dapsone and rifampicin for all patients and a third drug, clofazimin, for patients with multibacillary disease.

Currently, there is no universally accepted vaccine for Hansen's disease. India and Brazil use a tuberculosis vaccineagainst Hansen's disease because both diseases are caused by species of *Mycobacterium*. The effectiveness of this method is questionable, however, since it appears that the vaccine works in some populations but not in others.

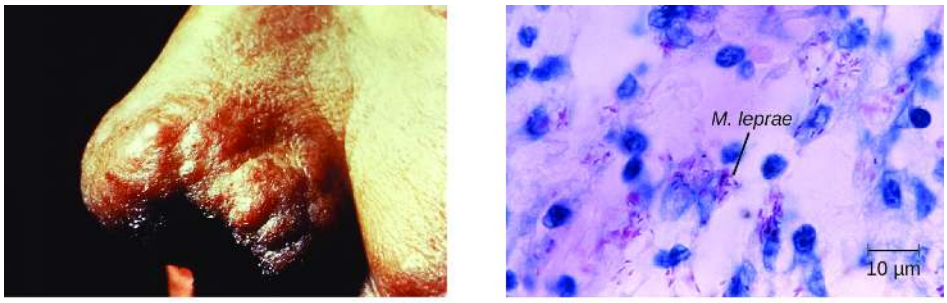


Figure 8.3.2.7: (a) The nose of a patient with Hansen's disease. Note the lepromatous/multibacillary lesions around the nostril. (b) Hansen's disease is caused by *Mycobacterium leprae*, a gram-positive bacillus. (credit a, b: modifications of work by the Centers for Disease Control and Prevention)

Exercise 8.3.2.4

1. What prevents the progression from tuberculoid to lepromatus leprosy?
2. Why does Hansen's disease typically affect the nerves of the extremities?

Leper Colonies

Disfiguring, deadly diseases like leprosy have historically been stigmatized in many cultures. Before leprosy was understood, victims were often isolated in leper colonies, a practice mentioned frequently in ancient texts, including the Bible. But leper colonies are not just an artifact of the ancient world. In Hawaii, a leper colony established in the late nineteenth century persisted until the mid-twentieth century, its residents forced to live in deplorable conditions.[16] Although leprosy is a communicable disease, it is not considered contagious (easily communicable), and it certainly does not pose enough of a threat to justify the permanent isolation of its victims. Today, we reserve the practices of isolation and quarantine to patients with more dangerous diseases, such as Ebola or multiple-drug-resistant bacteria like *Mycobacterium tuberculosis* and *Staphylococcus aureus*. The ethical argument for this practice is that isolating infected patients is necessary to prevent the transmission and spread of highly contagious diseases—even when it goes against the wishes of the patient.

Of course, it is much easier to justify the practice of temporary, clinical quarantining than permanent social segregation, as occurred in leper colonies. In the 1980s, there were calls by some groups to establish camps for people infected with AIDS. Although this idea was never actually implemented, it begs the question—where do we draw the line? Are permanent isolation camps or colonies ever medically or socially justifiable? Suppose there were an outbreak of a fatal, contagious disease for which there is no treatment. Would it be justifiable to impose social isolation on those afflicted with the disease? How would we balance the rights of the infected with the risk they pose to others? To what extent should society expect individuals to put their own health at risk for the sake of treating others humanely?

Bacterial Infections of the Nervous System

Despite the formidable defenses protecting the nervous system, a number of bacterial pathogens are known to cause serious infections of the CNS or PNS. Unfortunately, these infections are often serious and life threatening. Figure 8.3.2.8 summarizes some important infections of the nervous system.

Bacterial Infections of the Nervous System					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Antimicrobial Drugs**	**Vaccine**
Botulism	*Clostridium botulinum*	Blurred vision, drooping eyelids, difficulty swallowing and breathing, nausea, vomiting, often fatal	Ingestion of preformed toxin in food, ingestion of endospores in food by infants or immuno-compromised adults, bacterium introduced via wound or injection	Antitoxin; penicillin (for wound botulism)	None
Hansen's disease (leprosy)	*Mycobacterium leprae*	Hypopigmented skin, skin lesions, and nodules, loss of peripheral nerve function, loss of fingers, toes, and extremities	Inhalation, possible transmissible from armadillos to humans	Dapsone, rifampin, clofazimin	None
Haemophilus influenzae type b meningitis	*Haemophilus influenzae*	Nausea, vomiting, photophobia, stiff neck, confusion	Direct contact, inhalation of aerosols	Doxycycline, fluoroquinolones, second- and third-generation cephalosporins, and carbapenems	Hib vaccine
Listeriosis	*Listeria monocytogenes*	Initial flu-like symptoms, sepsis and potentially fatal meningitis in susceptible individu-als, miscarriage in pregnant women	Bacterium ingested with contaminated food or water	Ampicillin, gentamicin	None
Meningococcal meningitis	*Neisseria meningitidis*	Nausea, vomiting, photophobia, stiff neck, confusion; often fatal	Direct contact	Cephalosporins or penicillins	Meningococcal conjugate
Neonatal meningitis	*Streptococcus agalactiae*	Temperature instability, apnea, bradycardia, hypotension, feeding difficulty, irritability, limpness, seizures, bulging fontanel, stiff neck, opisthotonos, hemiparesis, often fatal	Direct contact in birth canal	Ampicillin plus gentamicin, cefotaxime, or both	None
Pneumococcal meningitis	*Streptococcus pneumoniae*	Nausea, vomiting, photophobia, stiff neck, confusion, often fatal	Direct contact, aerosols	Cephalosporins, penicillin	Pneumococcal vaccines
Tetanus	*Clostridium tetani*	Progressive spasmatic paralysis starting with the jaw, often fatal	Bacterium introduced in puncture wound	Penicillin, antitoxin	DTaP, Tdap

Figure 8.3.2.8: Bacterial infections of the Nervous system.

Key Concepts and Summary

- **Bacterial meningitis** can be caused by several species of encapsulated bacteria, including *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Streptococcus agalactiae* (group B streptococci). *H. influenzae* affects primarily young children and neonates, *N. meningitidis* is the only communicable pathogen and mostly affects children and young adults, *S. pneumoniae* affects mostly young children, and *S. agalactiae* affects newborns during or shortly after birth.
- Symptoms of bacterial meningitis include fever, neck stiffness, headache, confusion, convulsions, coma, and death.
- Diagnosis of bacterial meningitis is made through observations and culture of organisms in CSF. Bacterial meningitis is treated with antibiotics. *H. influenzae* and *N. meningitidis* have vaccines available.
- *Clostridium* species cause neurological diseases, including **botulism** and **tetanus**, by producing potent neurotoxins that interfere with neurotransmitter release. The PNS is typically affected. Treatment of *Clostridium* infection is effective only

through early diagnosis with administration of antibiotics to control the infection and antitoxins to neutralize the endotoxin before they enter cells.

- *Listeria monocytogenes* is a foodborne pathogen that can infect the CNS, causing meningitis. The infection can be spread through the placenta to a fetus. Diagnosis is through culture of blood or CSF. Treatment is with antibiotics and there is no vaccine.
- **Hansen's disease** (**leprosy**) is caused by the intracellular parasite *Mycobacterium leprae*. Infections cause demylenation of neurons, resulting in decreased sensation in peripheral appendages and body sites. Treatment is with multi-drug antibiotic therapy, and there is no universally recognized vaccine.

Footnotes

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8.3.3: Acellular Pathogenic Diseases of the Nervous System

Learning Objectives

- Identify the most common acellular pathogens that can cause infections of the nervous system
- Compare the major characteristics of specific viral diseases affecting the nervous system

A number of different viruses and subviral particles can cause diseases that affect the nervous system. Viral diseases tend to be more common than bacterial infections of the nervous system today. Fortunately, viral infections are generally milder than their bacterial counterparts and often spontaneously resolve. Some of the more important acellular pathogens of the nervous system are described in this section.

Viral Meningitis

Although it is much more common than bacterial meningitis, viral meningitis is typically less severe. Many different viruses can lead to meningitis as a sequela of the primary infection, including those that cause herpes, influenza, measles, and mumps. Most cases of viral meningitis spontaneously resolve, but severe cases do occur.

Arboviral Encephalitis

Several types of insect-borne viruses can cause encephalitis. Collectively, these viruses are referred to as arboviruses (because they are arthropod-borne), and the diseases they cause are described as arboviral encephalitis. Most arboviruses are endemic to specific geographical regions. Arborviral encephalitis diseases found in the United States include eastern equine encephalitis (EEE), western equine encephalitis (WEE), St. Louis encephalitis, and West Nile encephalitis (WNE). Expansion of arboviruses beyond their endemic regions sometimes occurs, generally as a result of environmental changes that are favorable to the virus or its vector. Increased travel of infected humans, animals, or vectors has also allowed arboviruses to spread into new regions.

In most cases, arboviral infections are asymptomatic or lead to a mild disease. However, when symptoms do occur, they include high fever, chills, headaches, vomiting, diarrhea, and restlessness. In elderly patients, severe arboviral encephalitis can rapidly lead to convulsions, coma, and death.

Mosquitoes are the most common biological vectors for arboviruses, which tend to be enveloped ssRNA viruses. Thus, prevention of arboviral infections is best achieved by avoiding mosquitoes—using insect repellent, wearing long pants and sleeves, sleeping in well-screened rooms, using bed nets, etc.

Diagnosis of arboviral encephalitis is based on clinical symptoms and serologic testing of serum or CSF. There are no antiviral drugs to treat any of these arboviral diseases, so treatment consists of supportive care and management of symptoms.

Eastern equine encephalitis (EEE) is caused by eastern equine encephalitis virus (EEEV), which can cause severe disease in horses and humans. Birds are reservoirs for EEEV with accidental transmission to horses and humans by *Aedes*, *Coquillettidia*, and *Culex* species of mosquitoes. Neither horses nor humans serve as reservoirs. EEE is most common in US Gulf Coast and Atlantic states. EEE is one of the more severe mosquito-transmitted diseases in the United States, but fortunately, it is a very rare disease in the United States (Figure 8.3.3.1).[12]

Western equine encephalitis (WEE) is caused by western equine encephalitis virus (WEEV). WEEV is usually transmitted to horses and humans by the *Culex tarsalis* mosquitoes and, in the past decade, has caused very few cases of encephalitis in humans in the United States. In humans, WEE symptoms are less severe than EEE and include fever, chills, and vomiting, with a mortality rate of 3–4%. Like EEEV, birds are the natural reservoir for WEEV. Periodically, for indeterminate reasons, epidemics in human cases have occurred in North America in the past. The largest on record was in 1941, with more than 3400 cases.[3]

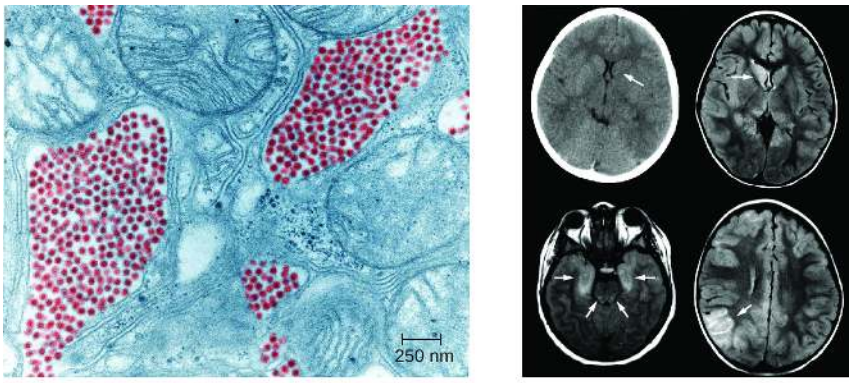


Figure 8.3.3.1: (a) A false color TEM of a mosquito salivary gland cell shows an infection of the eastern equine encephalitis virus (red). (b) CT (left) and MRI (right) scans of the brains of children with eastern equine encephalitis infections, showing abnormalities (arrows) resulting from the infection. (credit a, b: modifications of work by the Centers for Disease Control and Prevention)

St. Louis encephalitis (SLE), caused by St. Louis encephalitis virus (SLEV), is a rare form of encephalitis with symptoms occurring in fewer than 1% of infected patients. The natural reservoirs for SLEV are birds. SLEV is most often found in the Ohio-Mississippi River basin of the central United States and was named after a severe outbreak in Missouri in 1934. The worst outbreak of St. Louis encephalitis occurred in 1975, with over 2000 cases reported.[4]Humans become infected when bitten by *C. tarsalis*, *C. quinquefasciatus*, or *C. pipiens* mosquitoes carrying SLEV. Most patients are asymptomatic, but in a small number of individuals, symptoms range from mild flu-like syndromes to fatal encephalitis. The overall mortality rate for symptomatic patients is 5–15%.[5]

Japanese encephalitis, caused by Japanese encephalitis virus (JEV), is the leading cause of vaccine-preventable encephalitis in humans and is endemic to some of the most populous countries in the world, including China, India, Japan, and all of Southeast Asia. JEV is transmitted to humans by *Culex* mosquitoes, usually the species *C. tritaeniorhynchus*. The biological reservoirs for JEV include pigs and wading birds. Most patients with JEV infections are asymptomatic, with symptoms occurring in fewer than 1% of infected individuals. However, about 25% of those who do develop encephalitis die, and among those who recover, 30–50% have psychiatric, neurologic, or cognitive impairment.[6] Fortunately, there is an effective vaccine that can prevent infection with JEV. The CDC recommends this vaccine for travelers who expect to spend more than one month in endemic areas.

As the name suggests, West Nile virus (WNV) and its associated disease, West Nile encephalitis (WNE), did not originate in North America. Until 1999, it was endemic in the Middle East, Africa, and Asia; however, the first US cases were identified in New York in 1999, and by 2004, the virus had spread across the entire continental United States. Over 35,000 cases, including 1400 deaths, were confirmed in the five-year period between 1999 and 2004. WNV infection remains reportable to the CDC.

WNV is transmitted to humans by *Culex* mosquitoes from its natural reservoir, infected birds, with 70–80% of infected patients experiencing no symptoms. Most symptomatic cases involve only mild, flu-like symptoms, but fewer than 1% of infected people develop severe and sometimes fatal encephalitis or meningitis. The mortality rate in WNV patients who develop neurological disease is about 10%. More information about West Nile virus can be found in Modes of Disease Transmission.

Link to Learning

This interactive map identifies cases of several arboviral diseases in humans and reservoir species by state and year for the United States.

Exercise 8.3.3.1

1. Why is it unlikely that arboviral encephalitis viruses will be eradicated in the future?
2. Which is the most common form of viral encephalitis in the United States?

Clinical Focus: Part 2

Levofloxacin is a quinolone antibiotic that is often prescribed to treat bacterial infections of the respiratory tract, including pneumonia and bronchitis. But after taking the medication for a week, David returned to his physician sicker than before. He claimed that the antibiotic had no effect on his earlier symptoms. In addition, he now was experiencing headaches, a stiff neck, and difficulty focusing at work. He also showed the doctor a rash that had developed on his arms over the past week. His doctor, more concerned now, began to ask about David's activities over the past two weeks.

David explained that he had been recently working on a project to disassemble an old barn. His doctor collected sputum samples and scrapings from David's rash for cultures. A spinal tap was also performed to examine David's CSF. Microscopic examination of his CSF revealed encapsulated yeast cells. Based on this result, the doctor prescribed a new antimicrobial therapy using amphotericin B and flucytosine.

Exercise 8.3.3.2

1. Why was the original treatment ineffective?
2. Why is the presence of a capsule clinically important?

Zika Virus Infection

Zika virus infection is an emerging arboviral disease associated with human illness in Africa, Southeast Asia, and South and Central America; however, its range is expanding as a result of the widespread range of its mosquito vector. The first cases originating in the United States were reported in 2016.The Zika virus was initially described in 1947 from monkeys in the Zika Forest of Uganda through a network that monitored yellow fever. It was not considered a serious human pathogen until the first large-scale outbreaks occurred in Micronesia in 2007;[7] however, the virus has gained notoriety over the past decade, as it has emerged as a cause of symptoms similar to other arboviral infections that include fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache. Mosquitoes of the *Aedes* genus are the primary vectors, although the virus can also be transmitted sexually, from mother to baby during pregnancy, or through a blood transfusion.

Most Zika virus infections result in mild symptoms such as fever, a slight rash, or conjunctivitis. However, infections in pregnant women can adversely affect the developing fetus. Reports in 2015 indicate fetal infections can result in brain damage, including a serious birth defect called microcephaly, in which the infant is born with an abnormally small head (Figure 8.3.3.2).[8]

Diagnosis of Zika is primarily based on clinical symptoms. However, the FDA recently authorized the use of a Zika virus RNA assay, Trioplex RT-PCR, and Zika MAC-ELISA to test patient blood and urine to confirm Zika virus disease. There are currently no antiviral treatments or vaccines for Zika virus, and treatment is limited to supportive care.

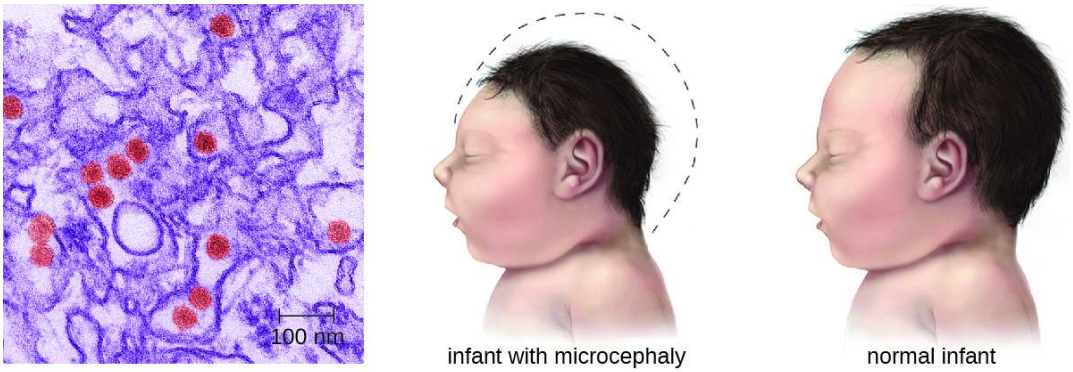


Figure 8.3.3.2: (a) This colorized electron micrograph shows Zika virus particles (red). (b) Women infected by the Zika virus during pregnancy may give birth to children with microcephaly, a deformity characterized by an abnormally small head and brain. (credit a, b: modifications of work by the Centers for Disease Control and Prevention)

? Exercise 8.3.3.3

1. What are the signs and symptoms of Zika virus infection in adults?
2. Why is Zika virus infection considered a serious public health threat?

Rabies

Rabies is a deadly zoonotic disease that has been known since antiquity. The disease is caused by rabies virus (RV), a member of the family Rhabdoviridae, and is primarily transmitted through the bite of an infected mammal. Rhabdoviridae are enveloped RNA viruses that have a distinctive bullet shape (Figure 8.3.3.3); they were first studied by Louis Pasteur, who obtained rabies virus from rabid dogs and cultivated the virus in rabbits. He successfully prepared a rabies vaccine using dried nerve tissues from infected animals. This vaccine was used to first treat an infected human in 1885.

The most common reservoirs in the United States are wild animals such as raccoons (30.2% of all animal cases during 2014), bats (29.1%), skunks (26.3%), and foxes (4.1%); collectively, these animals were responsible for a total of 92.6% of animal rabies cases in the United States in 2014. The remaining 7.4% of cases that year were in domesticated animals such as dogs, cats, horses, mules, sheep, goats, and llamas.[9] While there are typically only one or two human cases per year in the United States, rabies still causes tens of thousands of human deaths per year worldwide, primarily in Asia and Africa.

The low incidence of rabies in the United States is primarily a result of the widespread vaccination of dogs and cats. An oral vaccine is also used to protect wild animals, such as raccoons and foxes, from infection. Oral vaccine programs tend to focus on geographic areas where rabies is endemic.[10] The oral vaccine is usually delivered in a package of bait that is dropped by airplane, although baiting in urban areas is done by hand to maximize safety.[11] Many countries require a quarantine or proof of rabies vaccination for domestic pets being brought into the country. These procedures are especially strict in island nations where rabies is not yet present, such as Australia.

The incubation period for rabies can be lengthy, ranging from several weeks or months to over a year. As the virus replicates, it moves from the site of the bite into motor and sensory axons of peripheral nerves and spreads from nerve to nerve using a process called retrograde transport, eventually making its way to the CNS through the spinal ganglia. Once rabies virus reaches the brain, the infection leads to encephalitis caused by the disruption of normal neurotransmitter function, resulting in the symptoms associated with rabies. The virions act in the synaptic spaces as competitors with a variety of neurotransmitters for acetylcholine, GABA, and glycine receptors. Thus, the action of rabies virus is neurotoxic rather than cytotoxic. After the rabies virus infects the brain, it can continue to spread through other neuronal pathways, traveling out of the CNS to tissues such as the salivary glands, where the virus can be released. As a result, as the disease progresses the virus can be found in many other tissues, including the salivary glands, taste buds, nasal cavity, and tears.

The early symptoms of rabies include discomfort at the site of the bite, fever, and headache. Once the virus reaches the brain and later symptoms appear, the disease is always fatal. Terminal rabies cases can end in one of two ways: either furious or paralytic rabies. Individuals with furious rabies become very agitated and hyperactive. Hydrophobia (a fear of water) is common in patients with furious rabies, which is caused by muscular spasms in the throat when swallowing or thinking about water. Excess salivation and a desire to bite can lead to foaming of the mouth. These behaviors serve to enhance the likelihood of viral transmission, although contact with infected secretions like saliva or tears alone is sufficient for infection. The disease culminates after just a few days with terror and confusion, followed by cardiovascular and respiratory arrest. In contrast, individuals with paralytic rabies generally follow a longer course of disease. The muscles at the site of infection become paralyzed. Over a period of time, the paralysis slowly spreads throughout the body. This paralytic form of disease culminates in coma and death.

Before present-day diagnostic methods were available, rabies diagnosis was made using a clinical case history and histopathological examination of biopsy or autopsy tissues, looking for the presence of Negri bodies. We now know these histologic changes *cannot* be used to confirm a rabies diagnosis. There are no tests that can detect rabies virus in humans at the time of the bite or shortly thereafter. Once the virus has begun to replicate (but before clinical symptoms occur), the virus can be detected using an immunofluorescence test on cutaneous nerves found at the base of hair follicles. Saliva can also be tested for viral genetic material by reverse transcription followed by polymerase chain reaction (RT-PCR). Even when these tests are performed, most suspected infections are treated as positive in the absence of contravening evidence. It is better that patients undergo unnecessary therapy because of a false-positiveresult, rather than die as the result of a false-negative result.

Human rabies infections are treated by immunization with multiple doses of an attenuated vaccine to develop active immunity in the patient (see the Clinical Focus feature in the chapter on Acellular Pathogens). Vaccination of an already-infected individual has the potential to work because of the slow progress of the disease, which allows time for the patient's immune system to develop antibodies against the virus. Patients may also be treated with human rabies immune globulin (antibodies to the rabies virus) to encourage passive immunity. These antibodies will neutralize any free viral particles. Although the rabies infection progresses slowly in peripheral tissues, patients are not normally able to mount a protective immune response on their own.



Figure 8.3.3.3: Virions of the rabies virus have a characteristic bullet-like shape. (credit: modification of work by the Centers for Disease Control and Prevention)

? Exercise 8.3.3.4

1. How does the bite from an infected animal transmit rabies?
2. What is the goal of wildlife vaccination programs for rabies?
3. How is rabies treated in a human?

Poliomyelitis

Poliomyelitis (polio), caused by poliovirus, is a primarily intestinal disease that, in a small percentage of cases, proceeds to the nervous system, causing paralysis and, potentially, death. Poliovirus is highly contagious, with transmission occurring by the fecal-oral route or by aerosol or droplet transmission. Approximately 72% of all poliovirus infections are asymptomatic; another 25% result only in mild intestinal disease, producing nausea, fever, and headache.[12] However, even in the absence of symptoms, patients infected with the virus can shed it in feces and oral secretions, potentially transmitting the virus to others. In about one case in every 200, the poliovirus affects cells in the CNS.[13]

After it enters through the mouth, initial replication of poliovirus occurs at the site of implantation in the pharynx and gastrointestinal tract. As the infection progresses, poliovirus is usually present in the throat and in the stool before the onset of symptoms. One week after the onset of symptoms, there is less poliovirus in the throat, but for several weeks, poliovirus continues to be excreted in the stool. Poliovirus invades local lymphoid tissue, enters the bloodstream, and then may infect cells of the CNS. Replication of poliovirus in motor neurons of the anterior horn cells in the spinal cord, brain stem, or motor cortex results in cell destruction and leads to flaccid paralysis. In severe cases, this can involve the respiratory system, leading to death. Patients with impaired respiratory function are treated using positive-pressure ventilation systems. In the past, patients were sometimes confined to Emerson respirators, also known as iron lungs (Figure 8.3.3.4).

Direct detection of the poliovirus from the throat or feces can be achieved using reverse transcriptase PCR (RT-PCR) or genomic sequencing to identify the genotype of the poliovirus infecting the patient. Serological tests can be used to determine whether the patient has been previously vaccinated. There are no therapeutic measures for polio; treatment is limited to various supportive measures. These include pain relievers, rest, heat therapy to ease muscle spasms, physical therapy and corrective braces if necessary to help with walking, and mechanical ventilation to assist with breathing if necessary.



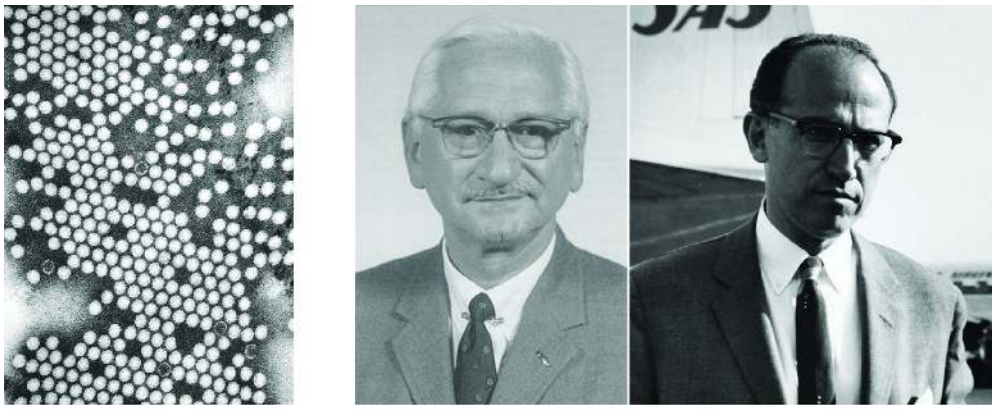
(a) (b)

Figure 8.3.3.4: (a) An Emerson respiratory (or iron lung) that was used to help some polio victims to breathe. (b) Polio can also result in impaired motor function. (credit b: modification of work by the Centers for Disease Control and Prevention)

Two different vaccines were introduced in the 1950s that have led to the dramatic decrease in polio worldwide (Figure 8.3.3.5). The Salk vaccine is an inactivated polio virus that was first introduced in 1955. This vaccine is delivered by intramuscular injection. The Sabin vaccine is an oral polio vaccine that contains an attenuated virus; it was licensed for use in 1962. There are three serotypes of poliovirus that cause disease in humans; both the Salk and the Sabin vaccines are effective against all three.

Attenuated viruses from the Sabin vaccine are shed in the feces of immunized individuals and thus have the potential to infect nonimmunized individuals. By the late 1990s, the few polio cases originating in the United States could be traced back to the Sabin vaccine. In these cases, mutations of the attenuated virus following vaccination likely allowed the microbe to revert to a virulent form. For this reason, the United States switched exclusively to the Salk vaccine in 2000. Because the Salk vaccine contains an inactivated virus, there is no risk of transmission to others (see Vaccines). Currently four doses of the vaccine are recommended for children: at 2, 4, and 6–18 months of age, and at 4–6 years of age.

In 1988, WHO launched the Global Polio Eradication Initiative with the goal of eradicating polio worldwide through immunization. That goal is now close to being realized. Polio is now endemic in only a few countries, including Afghanistan, Pakistan, and Nigeria, where vaccination efforts have been disrupted by military conflict or political instability.



(a) (b)

Figure 8.3.3.5: (a) Polio is caused by the poliovirus. (b) Two American virologists developed the first polio vaccines: Albert Sabin (left) and Jonas Salk (right). (credit a: modification of work by the Centers for Disease Control and Prevention)

The Terror of Polio

In the years after World War II, the United States and the Soviet Union entered a period known as the Cold War. Although there was no armed conflict, the two super powers were diplomatically and economically isolated from each other, as represented by the so-called Iron Curtain between the Soviet Union and the rest of the world. After 1950, migration or travel outside of the Soviet Union was exceedingly difficult, and it was equally difficult for foreigners to enter the Soviet Union. The United States

also placed strict limits on Soviets entering the country. During the Eisenhower administration, only 20 graduate students from the Soviet Union were allowed to come to study in the United States per year.

Yet even the Iron Curtain was no match for polio. The Salk vaccine became widely available in the West in 1955, and by the time the Sabin vaccine was ready for clinical trials, most of the susceptible population in the United States and Canada had already been vaccinated against polio. Sabin needed to look elsewhere for study participants. At the height of the Cold War, Mikhail Chumakov was allowed to come to the United States to study Sabin's work. Likewise, Sabin, an American microbiologist, was allowed to travel to the Soviet Union to begin clinical trials. Chumakov organized Soviet-based production and managed the experimental trials to test the new vaccine in the Soviet Union. By 1959, over ten million Soviet children had been safely treated with Sabin's vaccine.

As a result of a global vaccination campaign with the Sabin vaccine, the overall incidence of polio has dropped dramatically. Today, polio has been nearly eliminated around the world and is only rarely seen in the United States. Perhaps one day soon, polio will become the third microbial disease to be eradicated from the general population [small pox and rinderpest (the cause of cattle plague) being the first two].

Exercise 8.3.3.5

1. How is poliovirus transmitted?
2. Compare the pros and cons of each of the two polio vaccines.

Transmissible Spongiform Encephalopathies

Acellular infectious agents called prions are responsible for a group of related diseases known as transmissible spongiform encephalopathies (TSEs) that occurs in humans and other animals (see Viroids, Virusoids, and Prions). All TSEs are degenerative, fatal neurological diseases that occur when brain tissue becomes infected by prions. These diseases have a slow onset; symptoms may not become apparent until after an incubation period of years and perhaps decades, but death usually occurs within months to a few years after the first symptoms appear.

TSEs in animals include scrapie, a disease in sheep that has been known since the 1700s, and chronic wasting disease, a disease of deer and elk in the United States and Canada. Mad cow disease is seen in cattle and can be transmitted to humans through the consumption of infected nerve tissues. Human prion diseases include Creutzfeldt-Jakob disease and kuru, a rare disease endemic to Papua New Guinea.

Prions are infectious proteinaceous particles that are not viruses and do not contain nucleic acid. They are typically transmitted by exposure to and ingestion of infected nervous system tissues, tissue transplants, blood transfusions, or contaminated fomites. Prion proteins are normally found in a healthy brain tissue in a form called PrP^{C}. However, if this protein is misfolded into a denatured form (PrP^{Sc}), it can cause disease. Although the exact function of PrP^{C} is not currently understood, the protein folds into mostly alpha helices and binds copper. The rogue protein, on the other hand, folds predominantly into beta-pleated sheets and is resistant to proteolysis. In addition, PrP^{Sc} can induce PrP^{C} to become misfolded and produce more rogue protein (Figure 8.3.3.6).

As PrP^{Sc} accumulates, it aggregates and forms fibrils within nerve cells. These protein complexes ultimately cause the cells to die. As a consequence, brain tissues of infected individuals form masses of neurofibrillary tangles and amyloid plaques that give the brain a spongy appearance, which is why these diseases are called spongiform encephalopathy (Figure 6.4.3). Damage to brain tissue results in a variety of neurological symptoms. Most commonly, affected individuals suffer from memory loss, personality changes, blurred vision, uncoordinated movements, and insomnia. These symptoms gradually worsen over time and culminate in coma and death.

The gold standard for diagnosing TSE is the histological examination of brain biopsies for the presence of characteristic amyloid plaques, vacuoles, and prion proteins. Great care must be taken by clinicians when handling suspected prion-infected materials to avoid becoming infected themselves. Other tissue assays search for the presence of the 14-3-3 protein, a marker for prion diseases like Creutzfeldt-Jakob disease. New assays, like RT-QuIC (real-time quaking-induced conversion), offer new hope to effectively detect the abnormal prion proteins in tissues earlier in the course of infection. Prion diseases cannot be cured. However, some medications may help slow their progress. Medical support is focused on keeping patients as comfortable as possible despite progressive and debilitating symptoms.

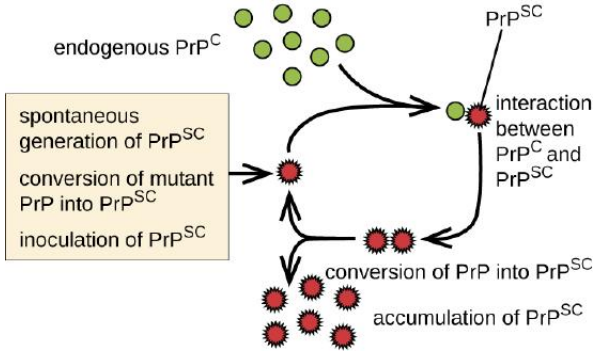


Figure 8.3.3.6: The replicative cycle of misfolded prion proteins.

Link to Learning

Because prion-contaminated materials are potential sources of infection for clinical scientists and physicians, both the World Health Organization and CDC provide information to inform, educate and minimize the risk of infections due to prions.

Exercise 8.3.3.6

1. Do prions reproduce in the conventional sense?
2. What is the connection between prions and the removal of animal byproducts from the food of farm animals?

Acellular Infections of the Nervous System

Serious consequences are the common thread among these neurological diseases. Several cause debilitating paralysis, and some, such as Creutzfeldt-Jakob disease and rabies, are always or nearly always fatal. Since few drugs are available to combat these infections, vector control and vaccination are critical for prevention and containment. Figure 8.3.3.7 summarizes some important viral and prion infections of the nervous system.

Acellular Infections of the Nervous System						
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**	**Vaccine**
Arboviral encephalitis (eastern equine, western equine, St. Louis, West Nile, Japanese)	EEEV, WEEV, SLEV, WNV, JEV	In mild cases, fever, chills, headaches, and restlessness; in serious cases, encephalitis leading to convulsions, coma, and death	From bird reservoirs to humans (and horses) by mosquito vectors of various species	Serologic testing of serum or CSF	None	Human vaccine available for JEV only; no vaccines available for other arboviruses
Creutzfeldt-Jacob Disease and other TSEs	Prions	Memory loss, confusion, blurred vision, uncoordi-nated movement, insomnia, coma, death	Exposure to infected nerve tissue via consumption or transplant, inherited	Tissue biopsy	None	None
Poliomyelitis	Poliovirus	Asymptomatic or mild nausea, fever, headache in most cases; in neurological infections, flaccid paralysis and potentially fatal respiratory paralysis	Fecal-oral route or contact with droplets or aerosols	Culture of poliovirus, PCR	None	Attenuated vaccine (Sabin), killed vaccine (Salk)
Rabies	Rabies virus (RV)	Fever, headaches, hyperactivity, hydrophobia, excessive salivation, terrors, confusion, spreading paralysis, coma, always fatal if not promptly treated	From bite of infected mammal	Viral antigen in tissue, antibodies to virus	Attenuated vaccine, rabies immunoglobulin	Attenuated vaccine
Viral meningitis	HSV-1, HSV-2, varicella zoster virus, mumps virus, influenza virus, measles virus	Nausea, vomiting, photophobia, stiff neck, confusion, symptoms generally resolve within 7–10 days	Sequela of primary viral infection	Testing of oral, fecal, blood, or CSF samples	Varies depending on cause	Varies depending on cause
Zika virus infection	Zika virus	Fever, rash, conjunctivitis; in pregnant women, can cause fetal brain damage and microcephaly	Between humans by *Aedes* spp. mosquito vectors, also may be transmitted sexually or via blood transfusion	Zika virus RNA assay, Trioplex RT-PCR, Zika MAC-ELISA test	None	None

Figure 8.3.3.7: Acellular infections of the Nervous system.

Key Concepts and Summary

- **Viral meningitis** is more common and generally less severe than bacterial menigitis. It can result from secondary sequelae of many viruses or be caused by infections of arboviruses.
- Various types of **arboviral encephalitis** are concentrated in particular geographic locations throughout the world. These mosquito-borne viral infections of the nervous system are typically mild, but they can be life-threatening in some cases.
- **Zika virus** is an emerging arboviral infection with generally mild symptoms in most individuals, but infections of pregnant women can cause the birth defect microcephaly.
- **Polio** is typically a mild intestinal infection but can be damaging or fatal if it progresses to a neurological disease.

- **Rabies** is nearly always fatal when untreated and remains a significant problem worldwide.
- **Transmissible spongiform encephalopathies** such as **Creutzfeldt-Jakob disease** and **kuru** are caused by prions. These diseases are untreatable and ultimately fatal. Similar prion diseases are found in animals.

Footnotes

1. 1 US Centers for Disease Control and Prevention, “Eastern Equine Encephalitis Virus Disease Cases and Deaths Reported to CDC by Year and Clinical Presentation, 2004–2013,” 2014. www.cdc.gov/EasternEquineEnce..._2004-2013.pdf.
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4. 4 US Centers for Disease Control and Prevention, “Saint Louis encephalitis, Epidemiology & Geographic Distribution,” Accessed June 30, 2016. http://www.cdc.gov/sle/technical/epi.html.
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9. 9 US Centers for Disease Control and Prevention, “Rabies, Wild Animals,” 2016. Accessed September 13, 2016. www.cdc.gov/rabies/location/u...d_animals.html.
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11. 11 Finnegan, Christopher J., Sharon M. Brookes, Nicholas Johnson, Jemma Smith, Karen L. Mansfield, Victoria L. Keene, Lorraine M. McElhinney, and Anthony R. Fooks, “Rabies in North America and Europe,” *Journal of the Royal Society of Medicine* 95, no. 1 (2002): 9-13. www.ncbi.nlm.nih.gov/pmc/articles/PMC1279140/.
12. 12 US Centers for Disease Control and Prevention, “Global Health – Polio,” 2014. Accessed June 30, 2016. http://www.cdc.gov/polio/about/index.htm.
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8.3.4: Neuromycoses and Parasitic Diseases of the Nervous System

Learning Objectives

- Identify the most common fungi that can cause infections of the nervous system
- Compare the major characteristics of specific fungal diseases affecting the nervous system

Fungal infections of the nervous system, called neuromycoses, are rare in healthy individuals. However, neuromycoses can be devastating in immunocompromised or elderly patients. Several eukaryotic parasites are also capable of infecting the nervous system of human hosts. Although relatively uncommon, these infections can also be life-threatening in immunocompromised individuals. In this section, we will first discuss neuromycoses, followed by parasitic infections of the nervous system.

Cryptococcocal Meningitis

Cryptococcus neoformans is a fungal pathogen that can cause meningitis. This yeast is commonly found in soils and is particularly associated with pigeon droppings. It has a thick capsule that serves as an important virulence factor, inhibiting clearance by phagocytosis. Most *C. neoformans* cases result in subclinical respiratory infections that, in healthy individuals, generally resolve spontaneously with no long-term consequences (see Respiratory Mycoses). In immunocompromised patients or those with other underlying illnesses, the infection can progress to cause meningitisand granuloma formation in brain tissues. *Cryptococcus* antigens can also serve to inhibit cell-mediated immunity and delayed-type hypersensitivity.

Cryptococcus can be easily cultured in the laboratory and identified based on its extensive capsule (Figure 8.3.4.1). *C. neoformans* is frequently cultured from urine samples of patients with disseminated infections.

Prolonged treatment with antifungal drugs is required to treat cryptococcal infections. Combined therapy is required with amphotericin B plus flucytosine for at least 10 weeks. Many antifungal drugs have difficulty crossing the blood-brain barrier and have strong side effects that necessitate low doses; these factors contribute to the lengthy time of treatment. Patients with AIDS are particularly susceptible to *Cryptococcus* infections because of their compromised immune state. AIDS patients with cryptococcosis can also be treated with antifungal drugs, but they often have relapses; lifelong doses of fluconazole may be necessary to prevent reinfection.

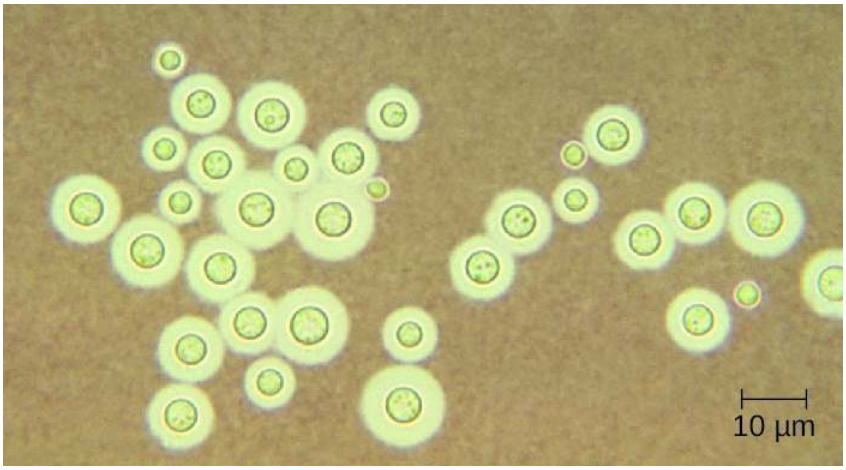


Figure 8.3.4.1: An India ink-negative stain of *C. neoformans* showing the thick capsules around the spherical yeast cells. (credit: modification of work by Centers for Disease Control and Prevention)

Exercise 8.3.4.1

1. Why are neuromycoses infections rare in the general population?
2. How is a cryptococcal infection acquired?

Neuromycoses

Neuromycoses typically occur only in immunocompromised individuals and usually only invade the nervous system after first infecting a different body system. As such, many diseases that sometimes affect the nervous system have already been discussed in previous chapters. Figure 8.3.4.2 presents some of the most common fungal infections associated with neurological disease. This table includes only the neurological aspects associated with these diseases; it does not include characteristics associated with other body systems.

Neuromycoses					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Aspergillosis	*Aspergillus fumigatus*	Meningitis, brain abscesses	Dissemination from respiratory infection	CSF, routine culture	Amphotericin B, voriconazole
Candidiasis	*Candida albicans*	Meningitis	Oropharynx or urogenital	CSF, routine culture	Amphotericin B, flucytosine
Coccidioido-mycosis (Valley fever)	*Coccidioides immitis*	Meningitis (in about 1% of infections)	Dissemination from respiratory infection	CSF, routine culture	Amphotericin B, azoles
Cryptococcosis	*Cryptococcus neoformans*	Meningitis, granuloma formation in brain	Inhalation	Negative stain of CSF, routine culture	Amphotericin B, flucytosine
Histoplasmosis	*Histoplasma capsulatum*	Meningitis, granulomas in the brain	Dissemination from respiratory infection	CSF, routine culture	Amphotericin B, itraconazole
Mucormycosis	*Rhizopus arrhizus*	Brain abscess	Nasopharynx	CSF, routine culture	Amphotericin B, azoles

Figure 8.3.4.2: Neuromycoses.

Clinical Focus: Resolution

David's new prescription for two antifungal drugs, amphotericin B and flucytosine, proved effective, and his condition began to improve. Culture results from David's sputum, skin, and CSF samples confirmed a fungal infection. All were positive for *C. neoformans*. Serological tests of his tissues were also positive for the *C. neoformans* capsular polysaccharide antigen.

Since *C. neoformans* is known to occur in bird droppings, it is likely that David had been exposed to the fungus while working on the barn. Despite this exposure, David's doctor explained to him that immunocompetent people rarely contract cryptococcal meningitis and that his immune system had likely been compromised by the anti-inflammatory medication he was taking to treat his Crohn's disease. However, to rule out other possible causes of immunodeficiency, David's doctor recommended that he be tested for HIV.

After David tested negative for HIV, his doctor took him off the corticosteroid he was using to manage his Crohn's disease, replacing it with a different class of drug. After several weeks of antifungal treatments, David managed a full recovery.

Amoebic Meningitis

Primary amoebic meningoencephalitis (PAM) is caused by *Naegleria fowleri*. This amoeboflagellate is commonly found free-living in soils and water. It can exist in one of three forms—the infective amoebic trophozoite form, a motile flagellate form, and a resting cyst form. PAM is a rare disease that has been associated with young and otherwise healthy individuals. Individuals are typically infected by the amoeba while swimming in warm bodies of freshwater such as rivers, lakes, and hot springs. The pathogenic trophozoite infects the brain by initially entering through nasal passages to the sinuses; it then moves down olfactory nerve fibers to penetrate the submucosal nervous plexus, invades the cribriform plate, and reaches the subarachnoid space. The subarachnoid space is highly vascularized and is a route of dissemination of trophozoites to other areas of the CNS, including the brain (Figure 8.3.4.3). Inflammation and destruction of gray matter leads to severe headaches and fever. Within days, confusion and convulsions

occur and quickly progress to seizures, coma, and death. The progression can be very rapid, and the disease is often not diagnosed until autopsy.

N. fowleri infections can be confirmed by direct observation of CSF; the amoebae can often be seen moving while viewing a fresh CSF wet mount through a microscope. Flagellated forms can occasionally also be found in CSF. The amoebae can be stained with several stains for identification, including Giemsa-Wright or a modified trichrome stain. Detection of antigens with indirect immunofluorescence, or genetic analysis with PCR, can be used to confirm an initial diagnosis. *N. fowleri* infections are nearly always fatal; only 3 of 138 patients with PAM in the United States have survived.[1] A new experimental drug called miltefosine shows some promise for treating these infections. This drug is a phosphotidylcholine derivative that is thought to inhibit membrane function in *N. fowleri*, triggering apoptosis and disturbance of lipid-dependent cell signaling pathways.[2] When administered early in infection and coupled with therapeutic hypothermia (lowering the body's core temperature to reduce the cerebral edema associated with infection), this drug has been successfully used to treat primary amoebic encephalitis.

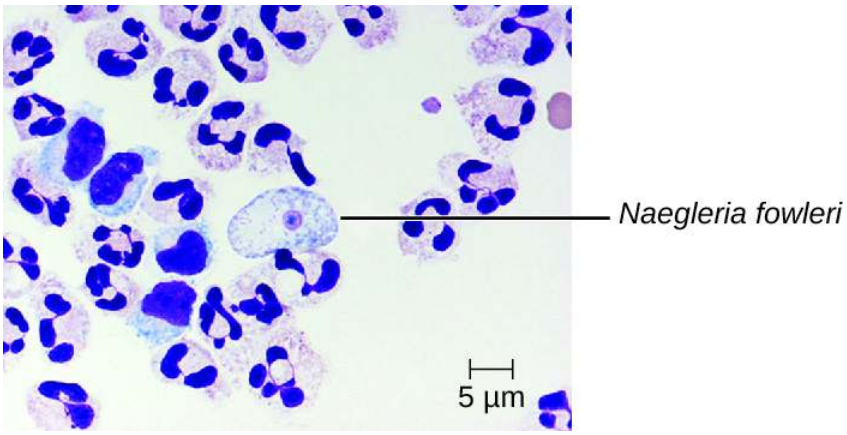
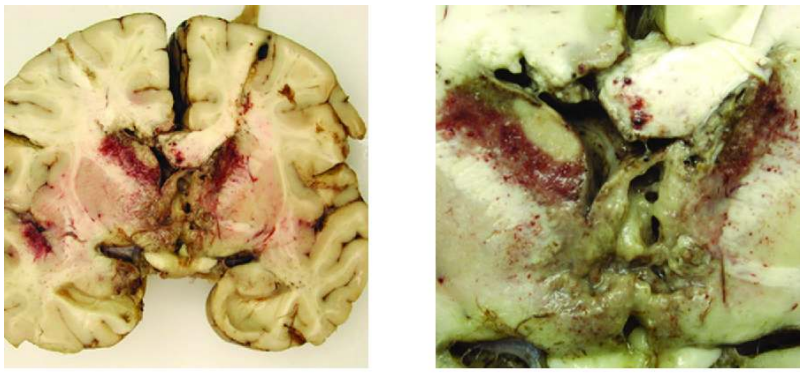


Figure 8.3.4.3: Free-living amoeba in human brain tissue from a patient suffering from PAM. (credit: modification of work by the Centers for Disease Control and Prevention)

Granulomatous Amoebic Encephalitis

Acanthamoeba and *Balamuthia* species are free-living amoebae found in many bodies of fresh water. Human infections by these amoebae are rare. However, they can cause amoebic keratitis in contact lens wearers (see Protozoan and Helminthic Infections of the Eyes), disseminated infections in immunocompromised patients, and granulomatous amoebic encephalitis (GAE) in severe cases. Compared to PAM, GAE tend to be subacute infections. The microbe is thought to enter through either the nasal sinuses or breaks in the skin. It is disseminated hematogenously and can invade the CNS. There, the infections lead to inflammation, formation of lesions, and development of typical neurological symptoms of encephalitis (Figure 8.3.4.4). GAE is nearly always fatal.

GAE is often not diagnosed until late in the infection. Lesions caused by the infection can be detected using CT or MRI. The live amoebae can be directly detected in CSF or tissue biopsies. Serological tests are available but generally are not necessary to make a correct diagnosis, since the presence of the organism in CSF is definitive. Some antifungal drugs, like fluconazole, have been used to treat acanthamoebal infections. In addition, a combination of miltefosine and voriconazole (an inhibitor of ergosterol biosynthesis) has recently been used to successfully treat GAE. Even with treatment, however, the mortality rate for patients with these infections is high.



(a) (b)

Figure 8.3.4.4: (a) Brain tissue from a patient who died of granulomatous amebic encephalitis (GAE) caused by *Balamuthia mandrillaris*. (b) A close-up of the necrosis in the center of the brain section. (credit a, b: modifications of work by the Centers for Disease Control and Prevention)

? Exercise 8.3.4.2

How is granulomatous amoebic encephalitis diagnosed?

Human African Trypanosomiasis

Human African trypanosomiasis (also known as African sleeping sickness) is a serious disease endemic to two distinct regions in sub-Saharan Africa. It is caused by the insect-borne hemoflagellate *Trypanosoma brucei*. The subspecies *Trypanosoma brucei rhodesiense* causes East African trypanosomiasis (EAT), and another subspecies, *Trypanosoma brucei gambiense* causes West African trypanosomiasis (WAT). A few hundred cases of EAT are currently reported each year.[3] WAT is more commonly reported and tends to be a more chronic disease. Around 7000 to 10,000 new cases of WAT are identified each year.[4]

T. brucei is primarily transmitted to humans by the bite of the tsetse fly (*Glossina* spp.). Soon after the bite of a tsetse fly, a chancre forms at the site of infection. The flagellates then spread, moving into the circulatory system (Figure 8.3.4.5). These systemic infections result in an undulating fever, during which symptoms persist for two or three days with remissions of about a week between bouts. As the disease enters its final phase, the pathogens move from the lymphatics into the CNS. Neurological symptoms include daytime sleepiness, insomnia, and mental deterioration. In EAT, the disease runs its course over a span of weeks to months. In contrast, WAT often occurs over a span of months to years.

Although a strong immune response is mounted against the trypanosome, it is not sufficient to eliminate the pathogen. Through antigenic variation, *Trypanosoma* can change their surface proteins into over 100 serological types. This variation leads to the undulating form of the initial disease. The initial septicemia caused by the infection leads to high fevers. As the immune system responds to the infection, the number of organisms decrease, and the clinical symptoms abate. However, a subpopulation of the pathogen then alters its surface coat antigens by antigenic variation and evades the immune response. These flagellates rapidly proliferate and cause another bout of disease. If untreated, these infections are usually fatal.

Clinical symptoms can be used to recognize the early signs of African trypanosomiasis. These include the formation of a chancre at the site of infection and Winterbottom's sign. Winterbottom's sign refers to the enlargement of lymph nodes on the back of the neck —often indicative of cerebral infections. *Trypanosoma* can be directly observed in stained samples including blood, lymph, CSF, and skin biopsies of chancres from patients. Antibodies against the parasite are found in most patients with acute or chronic disease. Serologic testing is generally not used for diagnosis, however, since the microscopic detection of the parasite is sufficient. Early diagnosis is important for treatment. Before the nervous system is involved, drugs like pentamidine (an inhibitor of nuclear metabolism) and suramin (mechanism unclear) can be used. These drugs have fewer side effects than the drugs needed to treat the second stage of the disease. Once the sleeping sickness phase has begun, harsher drugs including melarsoprol (an arsenic derivative) and eflornithine can be effective. Following successful treatment, patients still need to have follow-up examinations of their CSF for two years to detect possible relapses of the disease. The most effective means of preventing these diseases is to control the insect vector populations.

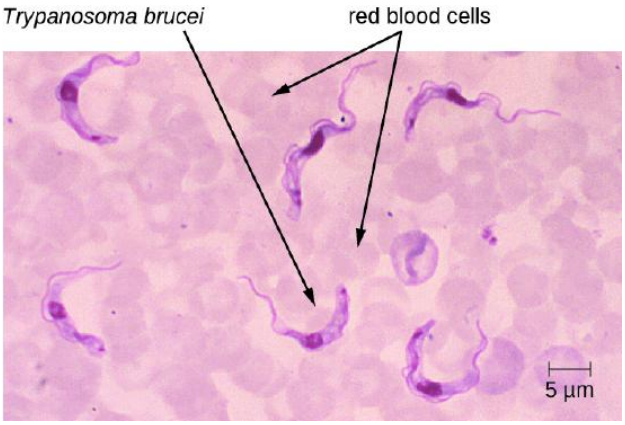


Figure 8.3.4.5: Trypanosoma brucei, the causative agent of African sleeping sickness, in a human blood smear. (credit: modification of work by the Centers for Disease Control and Prevention)

? Exercise 8.3.4.3

1. What is the symptom of a systemic *Trypanosoma* infection?
2. What are the symptoms of a neurological *Trypanosoma* infection*?*
3. Why are trypanosome infections so difficult to eradicate?

Neurotoxoplasmosis

Toxoplasma gondii is an ubiquitous intracellular parasite that can cause neonatal infections. Cats are the definitive host, and humans can become infected after eating infected meat or, more commonly, by ingesting oocysts shed in the feces of cats (see Parasitic Infections of the Circulatory and Lymphatic Systems). *T. gondii* enters the circulatory system by passing between the endothelial cells of blood vessels.[5] Most cases of toxoplasmosis are asymptomatic. However, in immunocompromised patients, neurotoxoplasmosis caused by *T. gondii* infections are one of the most common causes of brain abscesses.[6] The organism is able to cross the blood-brain barrier by infecting the endothelial cells of capillaries in the brain. The parasite reproduces within these cells, a step that appears to be necessary for entry to the brain, and then causes the endothelial cell to lyse, releasing the progeny into brain tissues. This mechanism is quite different than the method it uses to enter the bloodstream in the first place.[7]

The brain lesions associated with neurotoxoplasmosis can be detected radiographically using MRI or CAT scans (Figure 8.3.4.6). Diagnosis can be confirmed by direct observation of the organism in CSF. RT-PCR assays can also be used to detect *T. gondii* through genetic markers.

Treatment of neurotoxoplasmosis caused by *T. gondii* infections requires six weeks of multi-drug therapy with pyrimethamine, sulfadiazine, and folinic acid. Long-term maintenance doses are often required to prevent recurrence.

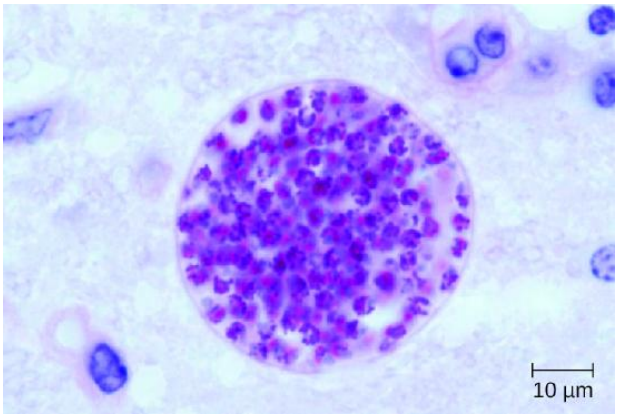


Figure 8.3.4.6: This *Toxoplasma gondii* cyst, observed in mouse brain tissue, contains thousands of inactive parasites. (credit: modification of work by USDA)

Exercise 8.3.4.4

1. Under what conditions is *Toxoplasma* infection serious?
2. How does *Toxoplasma* circumvent the blood-brain barrier?

Neurocysticercosis

Cysticercosis is a parasitic infection caused by the larval form of the pork tapeworm, *Taenia solium*. When the larvae invade the brain and spinal cord, the condition is referred to as neurocysticercosis. This condition affects millions of people worldwide and is the leading cause of adult onset epilepsy in the developing world.[8]

The life cycle of *T. solium* is discussed in Helminthic Infections of the Gastrointestinal Tract. Following ingestion, the eggs hatch in the intestine to form larvae called cysticerci. Adult tapeworms form in the small intestine and produce eggs that are shed in the feces. These eggs can infect other individuals through fecal contamination of food or other surfaces. Eggs can also hatch within the intestine of the original patient and lead to an ongoing autoinfection. The cystercerci, can migrate to the blood and invade many tissues in the body, including the CNS.

Neurocysticercosis is usually diagnosed through noninvasive techniques. Epidemiological information can be used as an initial screen; cysticercosis is endemic in Central and South America, Africa, and Asia. Radiological imaging (MRI and CT scans) is the primary method used to diagnose neurocysticercosis; imaging can be used to detect the one- to two-centimeter cysts that form around the parasites (Figure 8.3.4.7). Elevated levels of eosinophils in the blood can also indicate a parasitic infection. EIA and ELISA are also used to detect antigens associated with the pathogen.

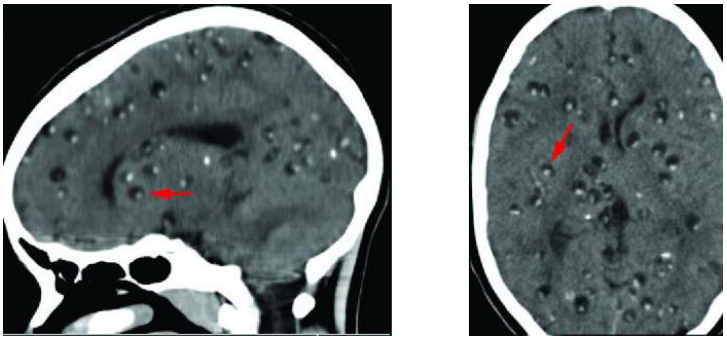


Figure 8.3.4.7: Brain CT scans of sagittal (left) and axial (right) sections of a brain with neurocysticercosis. Numerous cysts are visible in both images, as indicated by the arrows. (credit: modification of work by Segamwenge IL, Kioko NP)

The treatment for neurocysticercosis depends on the location, number, size, and stage of cysticerci present. Antihelminthic chemotherapy includes albendazole and praziquantel. Because these drugs kill viable cysts, they may acutely increase symptoms by provoking an inflammatory response caused by the release of *Taenia* cysticerci antigens, as the cysts are destroyed by the drugs. To alleviate this response, corticosteroids that cross the blood-brain barrier(e.g., dexamethasone) can be used to mitigate these effects. Surgical intervention may be required to remove intraventricular cysts.

Parasitic Diseases of the Nervous System

Parasites that successfully invade the nervous system can cause a wide range of neurological signs and symptoms. Often, they inflict lesions that can be visualized through radiologic imaging. A number of these infections are fatal, but some can be treated (with varying levels of success) by antimicrobial drugs (Figure 8.3.4.8).

Parasitic Diseases of the Nervous System					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Granulomatous amoebic encephalitis (GAE)	*Acantham-oeba* spp., *Balamuthia mandrillaris*	Inflammation, lesions in CNS, almost always fatal	Freshwater ameobae invade CNS via breaks in skin or sinuses	CT scan, MRI, CSF	Fluconazole, miltefosine, voriconazole
Human African trypanosomiasis	*Trypanosoma brucei gambiense, T. brucei rhodesiense*	Chancre, Winterbottom's sign, undulating fever, lethargy, insomnia, usually fatal if untreated	Protozoan transmitted via bite of tsetse fly	Blood smear	Pentamidine and suramine (initial phase); melarsoprol and eflornithine (final phase)
Neurocysticer-cosis	*Taenia solium*	Brain cysts, epilepsy	Ingestion of tapeworm eggs in fecally contaminated food or surfaces	CT scan, MRI	Albendazole, praziquantel, dexamethasone
Neurotoxoplas-mosis	*Toxoplasma gondii*	Brain abscesses, chronic encephalitis	Protozoan transmitted via contact with oocytes in cat feces	CT scan, MRI, CSF	Pyrimethamine, sulfadiazine, folinic acid
Primary amoebic meningoencepha-litis (PAM)	*Naegleria fowleri*	Headache, seizures, coma, almost always fatal	Freshwater ameobae invade brain via nasal passages	CSF, IFA, PCR	Miltefosine (experimental)

Figure 8.3.4.8: Parasitic diseases of the Nervous system.

? Exercise 8.3.4.5

1. What neurological condition is associated with neurocysticercosis?
2. How is neurocysticercosis diagnosed?

Key Concepts and Summary

- **Neuromycoses** are uncommon in immunocompetent people, but immunocompromised individuals with fungal infections have high mortality rates. Treatment of neuromycoses require prolonged therapy with antifungal drugs at low doses to avoid side effects and overcome the effect of the blood-brain barrier.
- Some protist infections of the nervous systems are fatal if not treated, including **primary amoebic meningitis**, **granulomatous amoebic encephalitis**, **human African trypanosomiasis**, and **neurotoxoplasmosis**.
- The various forms of ameobic encephalitis caused by the different amoebic infections are typically fatal even with treatment, but they are rare.
- **African trypanosomiasis** is a serious but treatable disease endemic to two distinct regions in sub-Saharan Africa caused by the insect-borne hemoflagellate *Trypanosoma brucei*.
- **Neurocysticercosis** is treated using antihelminthic drugs or surgery to remove the large cysts from the CNS.

Footnotes

1. 1 US Centers for Disease Control and Prevention, "*Naegleria fowleri*—Primary Amoebic Meningoencephalitis (PAM)—Amebic Encephalitis," 2016. Accessed June 30, 2016. http://www.cdc.gov/parasites/naegleria/treatment.html.
2. 2 Dorlo, Thomas PC, Manica Balasegaram, Jos H. Beijnen, and Peter J. de Vries, "Miltefosine: A Review of Its Pharmacology and Therapeutic Efficacy in the Treatment of Leishmaniasis," *Journal of Antimicrobial Chemotherapy* 67, no. 11 (2012): 2576-97.
3. 3 US Centers for Disease Control and Prevention, "Parasites – African Trypanosomiasis (also known as Sleeping Sickness), East African Trypanosomiasis FAQs," 2012. Accessed June 30, 2016. www.cdc.gov/parasites/sleepin...faqs-east.html.

4. 4 US Centers for Disease Control and Prevention, “Parasites – African Trypanosomiasis (also known as Sleeping Sickness), Epidemiology & Risk Factors,” 2012. Accessed June 30, 2016. www.cdc.gov/parasites/sleepin...kness/epi.html.
5. 5 Carruthers, Vern B., and Yasuhiro Suzuki, “Effects of *Toxoplasma gondii* Infection on the Brain,” *Schizophrenia Bulletin* 33, no. 3 (2007): 745-51.
6. 6 Uppal, Gulshan, “CNS Toxoplasmosis in HIV,” 2015. Accessed June 30, 2016. emedicine.medscape.com/articl...98-overview#a3.
7. 7 Konradt, Christoph, Norikiyo Ueno, David A. Christian, Jonathan H. Delong, Gretchen Harms Pritchard, Jasmin Herz, David J. Bzik et al., “Endothelial Cells Are a Replicative Niche for Entry of *Toxoplasma gondii* to the Central Nervous System,” *Nature Microbiology* 1 (2016): 16001.
8. 8 DeGiorgio, Christopher M., Marco T. Medina, Reyna Durón, Chi Zee, and Susan Pietsch Escueta, “Neurocysticercosis,” *Epilepsy Currents* 4, no. 3 (2004): 107-11.

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8.3.E: Nervous System Infections (Exercises)

26.1: Anatomy of the Nervous System

The human nervous system can be divided into two interacting subsystems: the peripheral nervous system (PNS) and the central nervous system (CNS). The CNS consists of the brain and spinal cord. The peripheral nervous system is an extensive network of nerves connecting the CNS to the muscles and sensory structures.

Multiple Choice

What is the outermost membrane surrounding the brain called?

A. pia mater
B. arachnoid mater
C. dura mater
D. alma mater

Answer

C

What term refers to an inflammation of brain tissues?

A. encephalitis
B. meningitis
C. sinusitis
D. meningoencephalitis

Answer

A

Nerve cells form long projections called _____.

A. soma
B. axons
C. dendrites
D. synapses

Answer

B

Chemicals called _____ are stored in neurons and released when the cell is stimulated by a signal.

A. toxins
B. cytokines
C. chemokines
D. neurotransmitters

Answer

D

The central nervous system is made up of

A. sensory organs and muscles.
B. the brain and muscles.
C. the sensory organs and spinal cord.
D. the brain and spinal column.

Answer

D

Matching

Match each strategy for microbial invasion of the CNS with its description.

___intercellular entry	A. pathogen gains entry by infecting peripheral white blood cells
___transcellular entry	B. pathogen bypasses the blood-brain barrier by travel along the olfactory or trigeminal cranial nerves
___leukocyte-facilitated entry	C. pathogen passes through the cells of the blood-brain barrier
___nonhematogenous entry	D. pathogen passes between the cells of the blood-brain barrier

Answer

D, C, A, B

Fill in the Blank

The cell body of a neuron is called the _____.

Answer

soma

A signal is transmitted down the _____ of a nerve cell.

Answer

axon

The _____ is filled with cerebrospinal fluid.

Answer

subarachnoid space

The _____ _____ prevents access of microbes in the blood from gaining access to the central nervous system.

Answer

blood-brain barrier

The _____ are a set of membranes that cover and protect the brain.

Answer

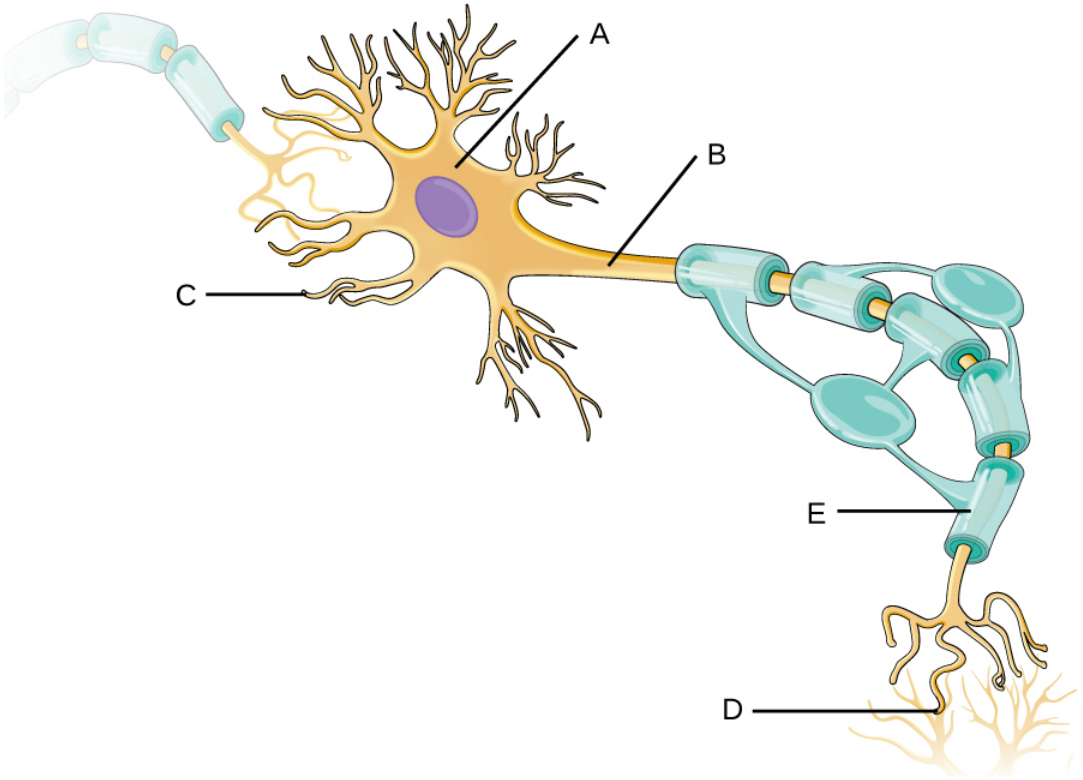
meninges

Short Answer

Briefly describe the defenses of the brain against trauma and infection.

Describe how the blood-brain barrier is formed.

Identify the type of cell shown, as well as the following structures: axon, dendrite, myelin sheath, soma, and synapse.



Critical Thinking

What important function does the blood-brain barrier serve? How might this barrier be problematic at times?

26.2: Bacterial Diseases of the Nervous System

Bacterial infections that affect the nervous system are serious and can be life-threatening. Fortunately, there are only a few bacterial species commonly associated with neurological infections.

Multiple Choice

Which of the following organisms causes epidemic meningitis cases at college campuses?

A. *Haemophilus influenzae* type b
B. *Neisseria meningitidis*
C. *Streptococcus pneumoniae*
D. *Listeria monocytogenes*

Answer

B

Which of the following is the most common cause of neonatal meningitis?

A. *Haemophilus influenzae b*
B. *Streptococcus agalactiae*
C. *Neisseria meningitidis*
D. *Streptococcus pneumoniae*

Answer

B

What sign/symptom would NOT be associated with infant botulism?

A. difficulty suckling
B. limp body
C. stiff neck
D. weak cry

Answer

C

Which of the following can NOT be prevented with a vaccine?

A. tetanus
B. pneumococcal meningitis
C. meningococcal meningitis
D. listeriosis

Answer

D

How is leprosy primarily transmitted from person to person?

A. contaminated toilet seats
B. shaking hands
C. blowing nose
D. sexual intercourse

Answer

C

Fill in the Blank

The form of meningitis that can cause epidemics is caused by the pathogen _____.

Answer

Neisseria meningitidis

The symptoms of tetanus are caused by the neurotoxin _____.

Answer

tetanospasmin

_____ is another name for leprosy.

Answer

Hansen's disease

Botulism prevents the release of the neurotransmitter _____.

Answer

acetylcholine

_____ is a neurological disease that can be prevented with the DTaP vaccine.

Answer

Tetanus

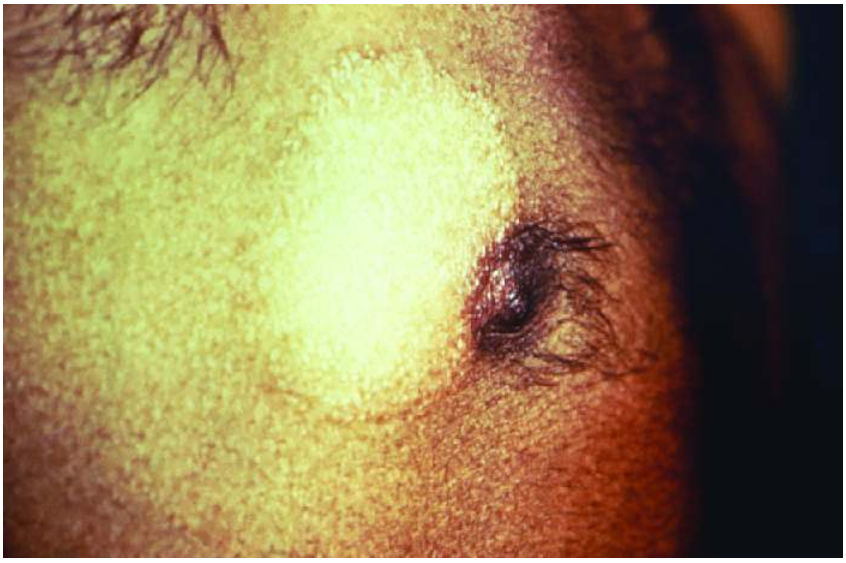
Tetanus patients exhibit _____ when muscle spasms causes them to arch their backs.

Answer

opisthotonos

Short Answer

A physician suspects the lesion and pustule pictured here are indicative of tuberculoid leprosy. If the diagnosis is correct, what microorganism would be found in a skin biopsy?



(credit: Centers for Disease Control and Prevention)

Critical Thinking

Explain how tetanospasmin functions to cause disease.

The most common causes of bacterial meningitis can be the result of infection by three very different bacteria. Which bacteria are they and how are these microbes similar to each other?

Explain how infant botulism is different than foodborne botulism.

26.3: Acellular Pathogenic Diseases of the Nervous System

A number of different viruses and subviral particles can cause diseases that affect the nervous system. Viral diseases tend to be more common than bacterial infections of the nervous system today. Fortunately, viral infections are generally milder than their bacterial counterparts and often spontaneously resolve. Some of the more important acellular pathogens of the nervous system are described in this section.

Multiple Choice

Which of these diseases can be prevented with a vaccine for humans?

A. eastern equine encephalitis
B. western equine encephalitis
C. West Nile encephalitis
D. Japanese encephalitis

Answer

D

Which of these diseases does NOT require the introduction of foreign nucleic acid?

A. kuru
B. polio
C. rabies
D. St. Louis encephalitis

Answer

A

Which of these is true of the Sabin but NOT the Salk polio vaccine?

A. requires four injections
B. currently administered in the United States
C. mimics the normal route of infection
D. is an inactivated vaccine

Answer

C

Which of the following animals is NOT a typical reservoir for the spread of rabies?

A. dog
B. bat
C. skunk
D. chicken

Answer

D

Fill in the Blank

The rogue form of the prion protein is called _____.

Answer

PrP^{Sc}

_____ are the most common reservoir for the rabies virus worldwide.

Answer

Dogs

_____ was the scientist who developed the inactivated polio vaccine.

Answer

Jonas Salk

_____ is a prion disease of deer and elk.

Answer

Chronic wasting disease

The rogue form of prion protein exists primarily in the _____ conformation.

Answer

beta sheet

Short Answer

Explain how a person could contract variant Creutzfeldt-Jakob disease by consuming products from a cow with bovine spongiform encephalopathy (mad cow disease).

Critical Thinking

If the Sabin vaccine is being used to eliminate polio worldwide, explain why a country with a near zero infection rate would opt to use the Salk vaccine but not the Sabin vaccine?

26.4: Neuromycoses and Parasitic Diseases of the Nervous System

Fungal infections of the nervous system, called neuromycoses, are rare in healthy individuals. However, neuromycoses can be devastating in immunocompromised or elderly patients. Several eukaryotic parasites are also capable of infecting the nervous system of human hosts. Although relatively uncommon, these infections can also be life-threatening in immunocompromised individuals. In this section, we first discuss neuromycoses, followed by parasitic infections of the nervous system.

Multiple Choice

Which of these diseases results in meningitis caused by an encapsulated yeast?

A. cryptococcosis
B. histoplasmosis
C. candidiasis
D. coccidiomycosis

Answer

A

What kind of stain is most commonly used to visualize the capsule of cryptococcus?

A. Gram stain
B. simple stain
C. negative stain
D. fluorescent stain

Answer

C

Which of the following is the causative agent of East African trypanosomiasis?

A. *Trypanosoma cruzi*
B. *Trypanosoma vivax*
C. *Trypanosoma brucei rhodanese*
D. *Trypanosoma brucei gambiense*

Answer

C

Which of the following is the causative agent of primary amoebic meningoencephalitis?

A. *Naegleria fowleri*
B. *Entameba histolyticum*
C. *Amoeba proteus*
D. *Acanthamoeba polyphaga*

Answer

A

What is the biological vector for African sleeping sickness?

A. mosquito
B. tsetse fly
C. deer tick
D. sand fly

Answer

B

How do humans usually contract neurocysticercosis?

A. the bite of an infected arthropod
B. exposure to contaminated cat feces
C. swimming in contaminated water
D. ingestion of undercooked pork

Answer

D

Which of these is the most important cause of adult onset epilepsy?

A. neurocysticercosis
B. neurotoxoplasmosis
C. primary amoebic meningoencephalitis
D. African trypanosomiasis

Answer

A

Fill in the Blank

The _____ is the main virulence factor of *Cryptococcus neoformans*.

Answer

capsule

The drug of choice for fungal infections of the nervous system is _____.

Answer

Amphotericin B

The larval forms of a tapeworm are known as _____.

Answer

cysticerci

_____ sign appears as swollen lymph nodes at the back of the neck in early African trypanosomiasis.

Answer

Winterbottom’s

_____ African trypanosomiasis causes a chronic form of sleeping sickness.

Answer

West

The definitive host for *Toxoplasma gondii* is _____.

Answer

cats

Trypanosomes can evade the immune response through _____ variation.

Answer

antigenic

Short Answer

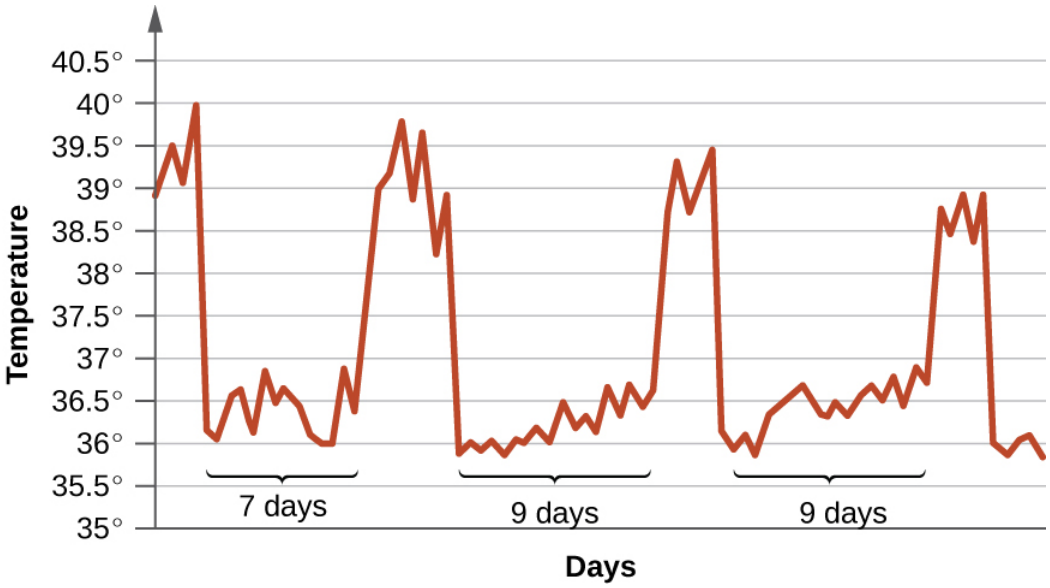
Why do nervous system infections by fungi require such long treatment times?

Briefly describe how humans are infected by *Naegleria fowleri*.

Briefly describe how humans can develop neurocysticercosis.

Critical Thinking

The graph shown tracks the body temperature of a patient infected with *Trypanosoma brucei*. How would you describe this pattern, and why does it occur?



(credit: modification of work by Wellcome Images)

Fungal meningoencephalitis is often the ultimate cause of death for AIDS patients. What factors make these infections more problematic than those of bacterial origin?

Compare East African trypanosomiasis with West African trypanosomiasis.

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CHAPTER OVERVIEW

9: Infectious diseases of the Lymphatic and Cardiovascular systems

Topic hierarchy

9.1: The Circulatory System

9.1.1: Prelude to the Circulatory System

9.1.2: Video - The Circulatory and Respiratory Systems

9.1.3: Overview of the Circulatory System

9.1.4: Components of the Blood

9.1.5: Mammalian Heart and Blood Vessels

9.1.6: Blood Flow and Blood Pressure Regulation

9.1.E: The Circulatory System (Exercises)

9.2: Circulatory and Lymphatic System Infections

9.2.1: Anatomy of the Circulatory and Lymphatic Systems

9.2.2: Bacterial Infections of the Circulatory and Lymphatic Systems

9.2.3: Viral Infections of the Circulatory and Lymphatic Systems

9.2.4: Parasitic Infections of the Circulatory and Lymphatic Systems

9.2.E: Circulatory and Lymphatic System Infections (Exercises)

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SECTION OVERVIEW

9.1: The Circulatory System

Most animals are complex multicellular organisms that require a mechanism for transporting nutrients throughout their bodies and removing waste products. The circulatory system has evolved over time from simple diffusion through cells in the early evolution of animals to a complex network of blood vessels that reach all parts of the human body. This extensive network supplies the cells, tissues, and organs with oxygen and nutrients, and removes carbon dioxide and waste, which are byproducts of respiration.

9.1.1: Prelude to the Circulatory System

9.1.2: Video - The Circulatory and Respiratory Systems

9.1.3: Overview of the Circulatory System

9.1.4: Components of the Blood

9.1.5: Mammalian Heart and Blood Vessels

9.1.6: Blood Flow and Blood Pressure Regulation

9.1.E: The Circulatory System (Exercises)

Thumbnail: The human heart. (CC-BY 4.0 / modified from original; OpenStax).

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9.1.1: Prelude to the Circulatory System

Most animals are complex multicellular organisms that require a mechanism for transporting nutrients throughout their bodies and removing waste products. The circulatory system has evolved over time from simple diffusion through cells in the early evolution of animals to a complex network of blood vessels that reach all parts of the human body. This extensive network supplies the cells, tissues, and organs with oxygen and nutrients, and removes carbon dioxide and waste, which are byproducts of respiration.



Figure 9.1.1.1: Just as highway systems transport people and goods through a complex network, the circulatory system transports nutrients, gases, and wastes throughout the animal body. (credit: modification of work by Andrey Belenko)

At the core of the human circulatory system is the heart. The size of a clenched fist, the human heart is protected beneath the rib cage. Made of specialized and unique cardiac muscle, it pumps blood throughout the body and to the heart itself. Heart contractions are driven by intrinsic electrical impulses that the brain and endocrine hormones help to regulate. Understanding the heart's basic anatomy and function is important to understanding the body's circulatory and respiratory systems.

Gas exchange is one essential function of the circulatory system. A circulatory system is not needed in organisms with no specialized respiratory organs because oxygen and carbon dioxide diffuse directly between their body tissues and the external environment. However, in organisms that possess lungs and gills, oxygen must be transported from these specialized respiratory organs to the body tissues via a circulatory system. Therefore, circulatory systems have had to evolve to accommodate the great diversity of body sizes and body types present among animals.

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9.1.2: Video - The Circulatory and Respiratory Systems

This video takes us on a trip around the body—we follow the circulatory and respiratory systems as they deliver oxygen and remove carbon dioxide from cells, and help make it possible for our bodies to function.



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9.1.3: Overview of the Circulatory System

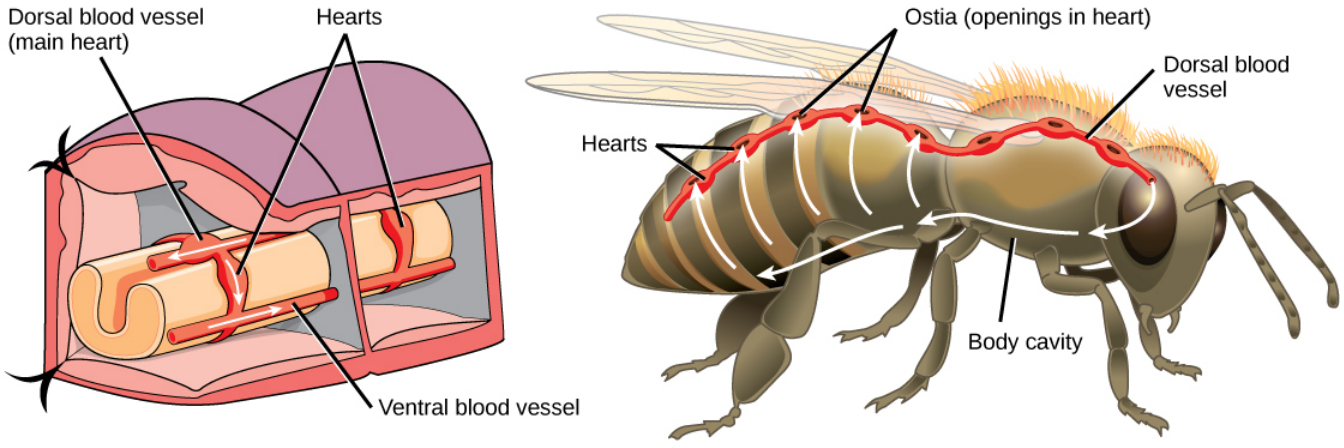
Skills to Develop

- Describe an open and closed circulatory system
- Describe interstitial fluid and hemolymph
- Compare and contrast the organization and evolution of the vertebrate circulatory system.

In all animals, except a few simple types, the circulatory system is used to transport nutrients and gases through the body. Simple diffusion allows some water, nutrient, waste, and gas exchange into primitive animals that are only a few cell layers thick; however, bulk flow is the only method by which the entire body of larger more complex organisms is accessed.

Circulatory System Architecture

The circulatory system is effectively a network of cylindrical vessels: the arteries, veins, and capillaries that emanate from a pump, the heart. In all vertebrate organisms, as well as some invertebrates, this is a closed-loop system, in which the blood is not free in a cavity. In a closed circulatory system, blood is contained inside blood vessels and circulates unidirectionally from the heart around the systemic circulatory route, then returns to the heart again, as illustrated in Figure 9.1.3.1a. As opposed to a closed system, arthropods—including insects, crustaceans, and most mollusks—have an open circulatory system, as illustrated in Figure 9.1.3.1b. In an open circulatory system, the blood is not enclosed in the blood vessels but is pumped into a cavity called a hemocoel and is called hemolymph because the blood mixes with the interstitial fluid. As the heart beats and the animal moves, the hemolymph circulates around the organs within the body cavity and then reenters the hearts through openings called ostia. This movement allows for gas and nutrient exchange. An open circulatory system does not use as much energy as a closed system to operate or to maintain; however, there is a trade-off with the amount of blood that can be moved to metabolically active organs and tissues that require high levels of oxygen. In fact, one reason that insects with wing spans of up to two feet wide (70 cm) are not around today is probably because they were outcompeted by the arrival of birds 150 million years ago. Birds, having a closed circulatory system, are thought to have moved more agilely, allowing them to get food faster and possibly to prey on the insects.



(a) Closed circulatory system (b) Open circulatory system

Figure 9.1.3.1: In (a) closed circulatory systems, the heart pumps blood through vessels that are separate from the interstitial fluid of the body. Most vertebrates and some invertebrates, like this annelid earthworm, have a closed circulatory system. In (b) open circulatory systems, a fluid called hemolymph is pumped through a blood vessel that empties into the body cavity. Hemolymph returns to the blood vessel through openings called ostia. Arthropods like this bee and most mollusks have open circulatory systems.

Circulatory System Variation in Animals

The circulatory system varies from simple systems in invertebrates to more complex systems in vertebrates. The simplest animals, such as the sponges (Porifera) and rotifers (Rotifera), do not need a circulatory system because diffusion allows adequate exchange of water, nutrients, and waste, as well as dissolved gases, as shown in Figure 9.1.3.2a. Organisms that are more complex but still only have two layers of cells in their body plan, such as jellies (Cnidaria) and comb jellies (Ctenophora) also use diffusion through

their epidermis and internally through the gastrovascular compartment. Both their internal and external tissues are bathed in an aqueous environment and exchange fluids by diffusion on both sides, as illustrated in Figure 9.1.3.2b. Exchange of fluids is assisted by the pulsing of the jellyfish body.

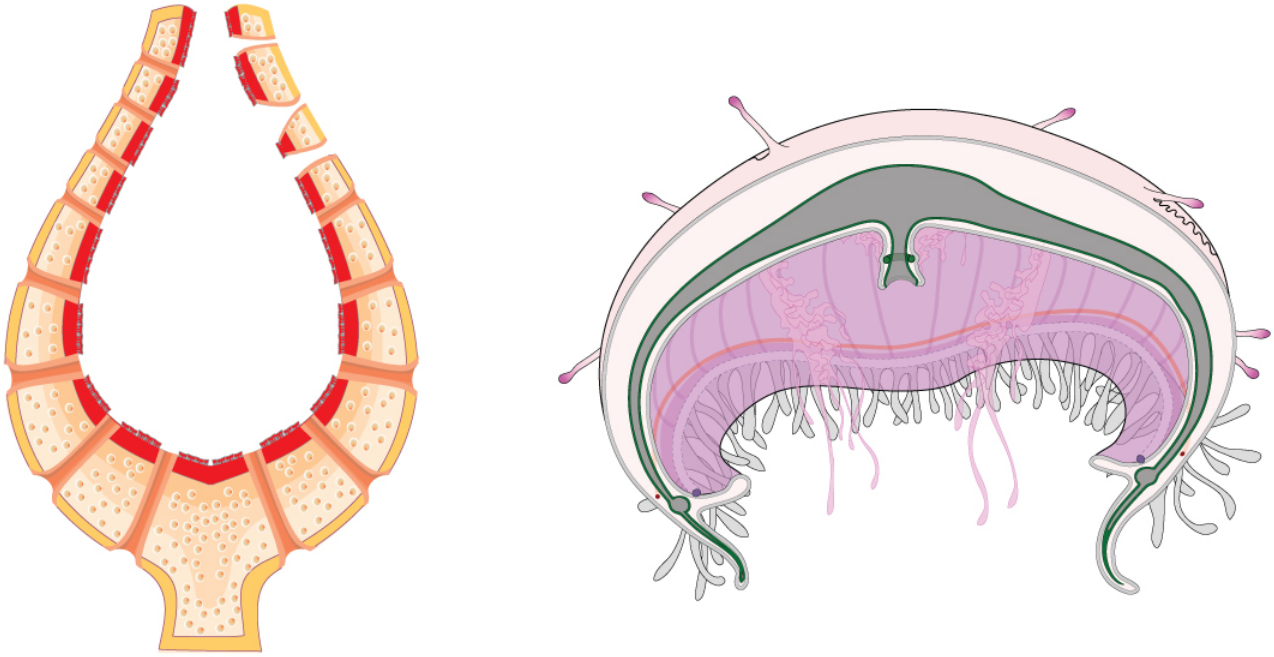
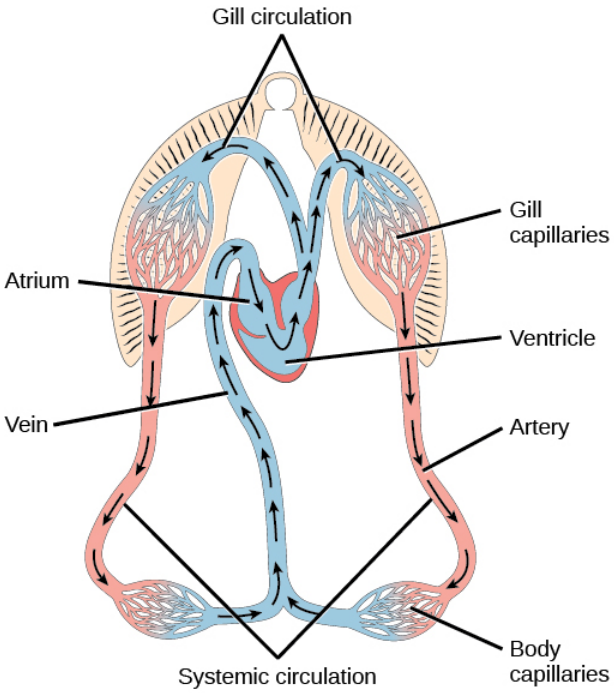
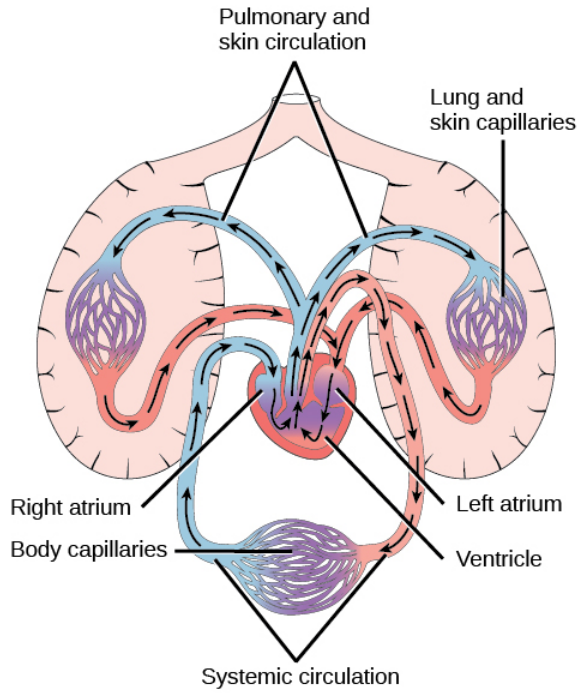


Figure 9.1.3.2: Simple animals consisting of a single cell layer such as the (a) sponge or only a few cell layers such as the (b) jellyfish do not have a circulatory system. Instead, gases, nutrients, and wastes are exchanged by diffusion.

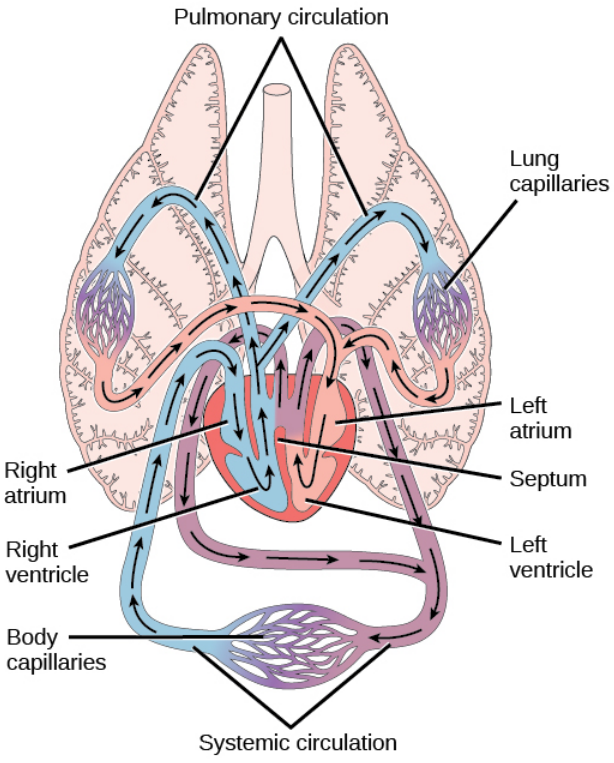
For more complex organisms, diffusion is not efficient for cycling gases, nutrients, and waste effectively through the body; therefore, more complex circulatory systems evolved. Most arthropods and many mollusks have open circulatory systems. In an open system, an elongated beating heart pushes the hemolymph through the body and muscle contractions help to move fluids. The larger more complex crustaceans, including lobsters, have developed arterial-like vessels to push blood through their bodies, and the most active mollusks, such as squids, have evolved a closed circulatory system and are able to move rapidly to catch prey. Closed circulatory systems are a characteristic of vertebrates; however, there are significant differences in the structure of the heart and the circulation of blood between the different vertebrate groups due to adaptation during evolution and associated differences in anatomy. Figure 9.1.3.3 illustrates the basic circulatory systems of some vertebrates: fish, amphibians, reptiles, and mammals.



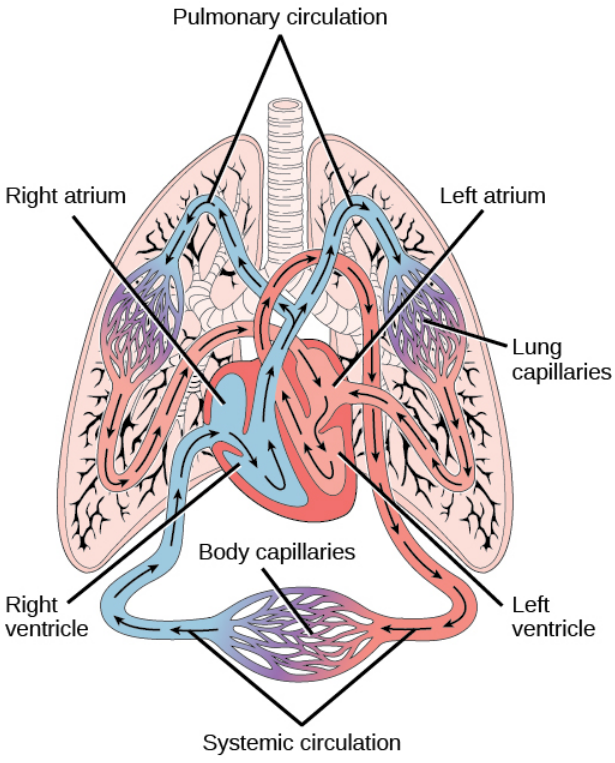
(a) Fish



(b) Amphibians



(c) Reptile



(d) Mammals

Figure 9.1.3.3: (a) Fish have the simplest circulatory systems of the vertebrates: blood flows unidirectionally from the two-chambered heart through the gills and then the rest of the body. (b) Amphibians have two circulatory routes: one for oxygenation of the blood through the lungs and skin, and the other to take oxygen to the rest of the body. The blood is pumped from a three-chambered heart with two atria and a single ventricle. (c) Reptiles also have two circulatory routes; however, blood is only oxygenated through the lungs. The heart is three chambered, but the ventricles are partially separated so some mixing of oxygenated and deoxygenated blood occurs except in crocodilians and birds. (d) Mammals and birds have the most efficient heart with four chambers that completely separate the oxygenated and deoxygenated blood; it pumps only oxygenated blood through the body and deoxygenated blood to the lungs.

As illustrated in Figure 9.1.3.3a Fish have a single circuit for blood flow and a two-chambered heart that has only a single atrium and a single ventricle. The atrium collects blood that has returned from the body and the ventricle pumps the blood to the gills where gas exchange occurs and the blood is re-oxygenated; this is called gill circulation. The blood then continues through the rest of the body before arriving back at the atrium; this is called systemic circulation. This unidirectional flow of blood produces a gradient of oxygenated to deoxygenated blood around the fish's systemic circuit. The result is a limit in the amount of oxygen that can reach some of the organs and tissues of the body, reducing the overall metabolic capacity of fish.

In amphibians, reptiles, birds, and mammals, blood flow is directed in two circuits: one through the lungs and back to the heart, which is called pulmonary circulation, and the other throughout the rest of the body and its organs including the brain (systemic circulation). In amphibians, gas exchange also occurs through the skin during pulmonary circulation and is referred to as pulmocutaneous circulation.

As shown in Figure 9.1.3.3b, amphibians have a three-chambered heart that has two atria and one ventricle rather than the two-chambered heart of fish. The two atria (superior heart chambers) receive blood from the two different circuits (the lungs and the systems), and then there is some mixing of the blood in the heart's ventricle (inferior heart chamber), which reduces the efficiency of oxygenation. The advantage to this arrangement is that high pressure in the vessels pushes blood to the lungs and body. The mixing is mitigated by a ridge within the ventricle that diverts oxygen-rich blood through the systemic circulatory system and deoxygenated blood to the pulmocutaneous circuit. For this reason, amphibians are often described as having double circulation.

Most reptiles also have a three-chambered heart similar to the amphibian heart that directs blood to the pulmonary and systemic circuits, as shown in Figure 9.1.3.3c. The ventricle is divided more effectively by a partial septum, which results in less mixing of oxygenated and deoxygenated blood. Some reptiles (alligators and crocodiles) are the most primitive animals to exhibit a four-chambered heart. Crocodilians have a unique circulatory mechanism where the heart shunts blood from the lungs toward the stomach and other organs during long periods of submergence, for instance, while the animal waits for prey or stays underwater waiting for prey to rot. One adaptation includes two main arteries that leave the same part of the heart: one takes blood to the lungs and the other provides an alternate route to the stomach and other parts of the body. Two other adaptations include a hole in the heart between the two ventricles, called the foramen of Panizza, which allows blood to move from one side of the heart to the other, and specialized connective tissue that slows the blood flow to the lungs. Together these adaptations have made crocodiles and alligators one of the most evolutionarily successful animal groups on earth.

In mammals and birds, the heart is also divided into four chambers: two atria and two ventricles, as illustrated in Figure 40.1.3d. The oxygenated blood is separated from the deoxygenated blood, which improves the efficiency of double circulation and is probably required for the warm-blooded lifestyle of mammals and birds. The four-chambered heart of birds and mammals evolved independently from a three-chambered heart. The independent evolution of the same or a similar biological trait is referred to as convergent evolution.

Summary

In most animals, the circulatory system is used to transport blood through the body. Some primitive animals use diffusion for the exchange of water, nutrients, and gases. However, complex organisms use the circulatory system to carry gases, nutrients, and waste through the body. Circulatory systems may be open (mixed with the interstitial fluid) or closed (separated from the interstitial fluid). Closed circulatory systems are a characteristic of vertebrates; however, there are significant differences in the structure of the heart and the circulation of blood between the different vertebrate groups due to adaptions during evolution and associated differences in anatomy. Fish have a two-chambered heart with unidirectional circulation. Amphibians have a three-chambered heart, which has some mixing of the blood, and they have double circulation. Most non-avian reptiles have a three-chambered heart, but have little mixing of the blood; they have double circulation. Mammals and birds have a four-chambered heart with no mixing of the blood and double circulation.

Glossary

atrium
(plural: atria) chamber of the heart that receives blood from the veins and sends blood to the ventricles

closed circulatory system
system in which the blood is separated from the bodily interstitial fluid and contained in blood vessels

double circulation
flow of blood in two circuits: the pulmonary circuit through the lungs and the systemic circuit through the organs and body

gill circulation
circulatory system that is specific to animals with gills for gas exchange; the blood flows through the gills for oxygenation

hemocoel
cavity into which blood is pumped in an open circulatory system

hemolymph
mixture of blood and interstitial fluid that is found in insects and other arthropods as well as most mollusks

interstitial fluid
fluid between cells

open circulatory system
system in which the blood is mixed with interstitial fluid and directly covers the organs

ostium
(plural: ostia) holes between blood vessels that allow the movement of hemolymph through the body of insects, arthropods, and mollusks with open circulatory systems

pulmocutaneous circulation
circulatory system in amphibians; the flow of blood to the lungs and the moist skin for gas exchange

pulmonary circulation
flow of blood away from the heart through the lungs where oxygenation occurs and then returns to the heart again

systemic circulation
flow of blood away from the heart to the brain, liver, kidneys, stomach, and other organs, the limbs, and the muscles of the body, and then the return of this blood to the heart

unidirectional circulation
flow of blood in a single circuit; occurs in fish where the blood flows through the gills, then past the organs and the rest of the body, before returning to the heart

ventricle
(heart) large inferior chamber of the heart that pumps blood into arteries

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9.1.4: Components of the Blood

Skills to Develop

- List the basic components of the blood
- Compare red and white blood cells
- Describe blood plasma and serum

Hemoglobin is responsible for distributing oxygen, and to a lesser extent, carbon dioxide, throughout the circulatory systems of humans, vertebrates, and many invertebrates. The blood is more than the proteins, though. Blood is actually a term used to describe the liquid that moves through the vessels and includes plasma (the liquid portion, which contains water, proteins, salts, lipids, and glucose) and the cells (red and white cells) and cell fragments called platelets. Blood plasma is actually the dominant component of blood and contains the water, proteins, electrolytes, lipids, and glucose. The cells are responsible for carrying the gases (red cells) and immune the response (white). The platelets are responsible for blood clotting. Interstitial fluid that surrounds cells is separate from the blood, but in hemolymph, they are combined. In humans, cellular components make up approximately 45 percent of the blood and the liquid plasma 55 percent. Blood is 20 percent of a person's extracellular fluid and eight percent of weight.

The Role of Blood in the Body

Blood, like the human blood illustrated in Figure 9.1.4.1 is important for regulation of the body's systems and homeostasis. Blood helps maintain homeostasis by stabilizing pH, temperature, osmotic pressure, and by eliminating excess heat. Blood supports growth by distributing nutrients and hormones, and by removing waste. Blood plays a protective role by transporting clotting factors and platelets to prevent blood loss and transporting the disease-fighting agents or white blood cells to sites of infection.

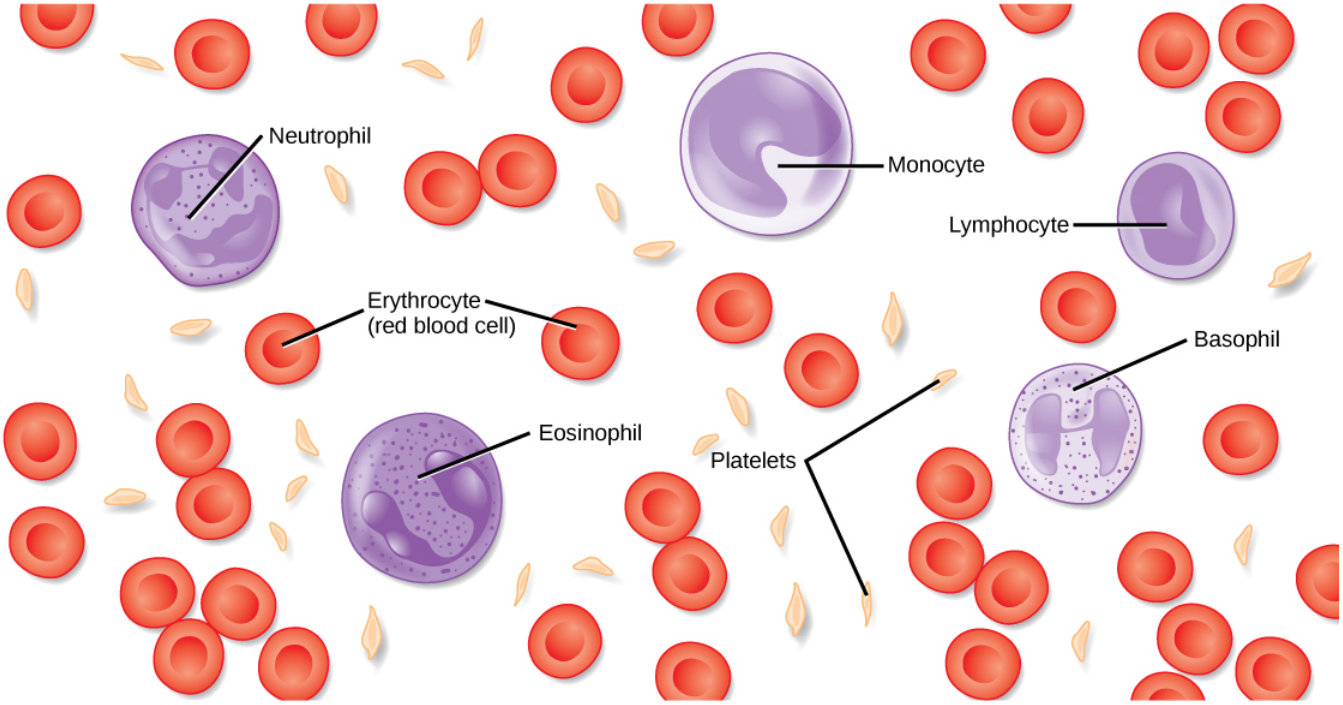


Figure 9.1.4.1: The cells and cellular components of human blood are shown. Red blood cells deliver oxygen to the cells and remove carbon dioxide. White blood cells—including neutrophils, monocytes, lymphocytes, eosinophils, and basophils—are involved in the immune response. Platelets form clots that prevent blood loss after injury.

Red Blood Cells

Red blood cells, or erythrocytes (erythro- = "red"; -cyte = "cell"), are specialized cells that circulate through the body delivering oxygen to cells; they are formed from stem cells in the bone marrow. In mammals, red blood cells are small biconcave cells that at maturity do not contain a nucleus or mitochondria and are only 7–8 µm in size. In birds and non-avian reptiles, a nucleus is still maintained in red blood cells.

The red coloring of blood comes from the iron-containing protein hemoglobin, illustrated in Figure 9.1.4.2a. The principal job of this protein is to carry oxygen, but it also transports carbon dioxide as well. Hemoglobin is packed into red blood cells at a rate of about 250 million molecules of hemoglobin per cell. Each hemoglobin molecule binds four oxygen molecules so that each red blood cell carries one billion molecules of oxygen. There are approximately 25 trillion red blood cells in the five liters of blood in the human body, which could carry up to 25 sextillion (25×10^{21}) molecules of oxygen in the body at any time. In mammals, the lack of organelles in erythrocytes leaves more room for the hemoglobin molecules, and the lack of mitochondria also prevents use of the oxygen for metabolic respiration. Only mammals have anucleated red blood cells, and some mammals (camels, for instance) even have nucleated red blood cells. The advantage of nucleated red blood cells is that these cells can undergo mitosis. Anucleated red blood cells metabolize anaerobically (without oxygen), making use of a primitive metabolic pathway to produce ATP and increase the efficiency of oxygen transport.

Not all organisms use hemoglobin as the method of oxygen transport. Invertebrates that utilize hemolymph rather than blood use different pigments to bind to the oxygen. These pigments use copper or iron to the oxygen. Invertebrates have a variety of other respiratory pigments. Hemocyanin, a blue-green, copper-containing protein, illustrated in Figure 9.1.4.2b is found in mollusks, crustaceans, and some of the arthropods. Chlorocruorin, a green-colored, iron-containing pigment is found in four families of polychaete tubeworms. Hemerythrin, a red, iron-containing protein is found in some polychaete worms and annelids and is illustrated in Figure 9.1.4.2c. Despite the name, hemerythrin does not contain a heme group and its oxygen-carrying capacity is poor compared to hemoglobin.

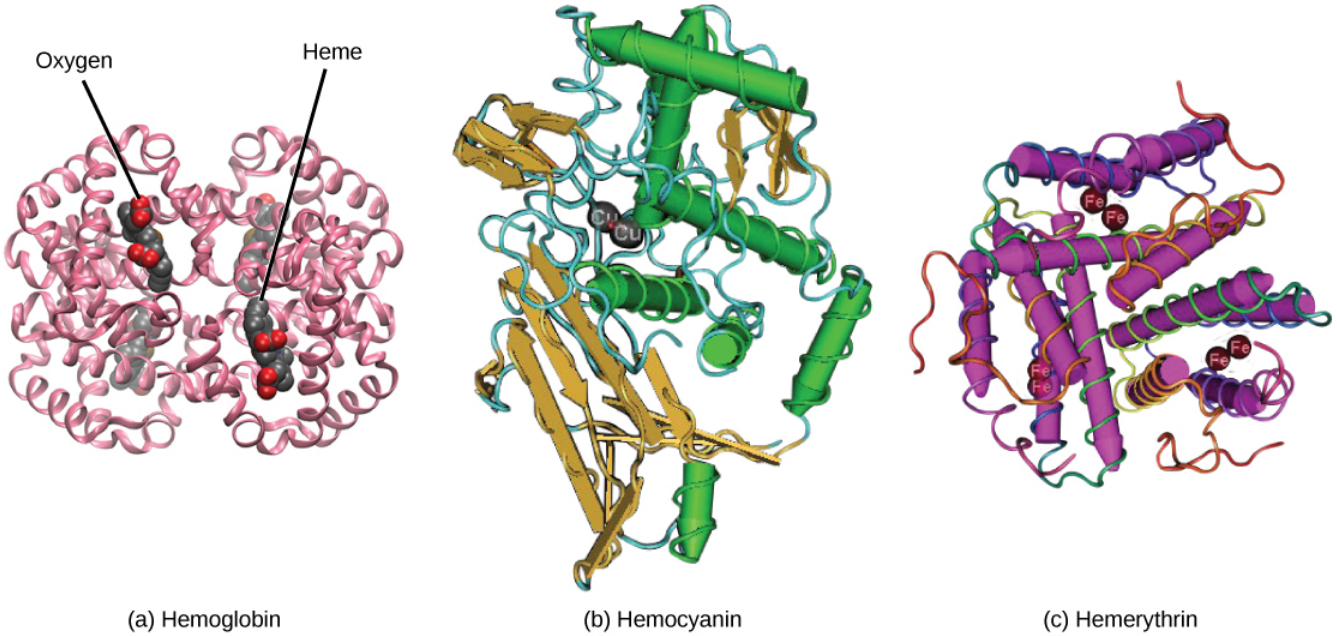


Figure 9.1.4.2: In most vertebrates, (a) hemoglobin delivers oxygen to the body and removes some carbon dioxide. Hemoglobin is composed of four protein subunits, two alpha chains and two beta chains, and a heme group that has iron associated with it. The iron reversibly associates with oxygen, and in so doing is oxidized from Fe^{2+} to Fe^{3+}. In most mollusks and some arthropods, (b) hemocyanin delivers oxygen. Unlike hemoglobin, hemolymph is not carried in blood cells, but floats free in the hemolymph. Copper instead of iron binds the oxygen, giving the hemolymph a blue-green color. In annelids, such as the earthworm, and some other invertebrates, (c) hemerythrin carries oxygen. Like hemoglobin, hemerythrin is carried in blood cells and has iron associated with it, but despite its name, hemerythrin does not contain heme.

The small size and large surface area of red blood cells allows for rapid diffusion of oxygen and carbon dioxide across the plasma membrane. In the lungs, carbon dioxide is released and oxygen is taken in by the blood. In the tissues, oxygen is released from the blood and carbon dioxide is bound for transport back to the lungs. Studies have found that hemoglobin also binds nitrous oxide (NO). NO is a vasodilator that relaxes the blood vessels and capillaries and may help with gas exchange and the passage of red blood cells through narrow vessels. Nitroglycerin, a heart medication for angina and heart attacks, is converted to NO to help relax the blood vessels and increase oxygen flow through the body.

A characteristic of red blood cells is their glycolipid and glycoprotein coating; these are lipids and proteins that have carbohydrate molecules attached. In humans, the surface glycoproteins and glycolipids on red blood cells vary between individuals, producing

the different blood types, such as A, B, and O. Red blood cells have an average life span of 120 days, at which time they are broken down and recycled in the liver and spleen by phagocytic macrophages, a type of white blood cell.

White Blood Cells

White blood cells, also called leukocytes (leuko = white), make up approximately one percent by volume of the cells in blood. The role of white blood cells is very different than that of red blood cells: they are primarily involved in the immune response to identify and target pathogens, such as invading bacteria, viruses, and other foreign organisms. White blood cells are formed continually; some only live for hours or days, but some live for years.

The morphology of white blood cells differs significantly from red blood cells. They have nuclei and do not contain hemoglobin. The different types of white blood cells are identified by their microscopic appearance after histologic staining, and each has a different specialized function. The two main groups, both illustrated in Figure 9.1.4.3 are the granulocytes, which include the neutrophils, eosinophils, and basophils, and the agranulocytes, which include the monocytes and lymphocytes.

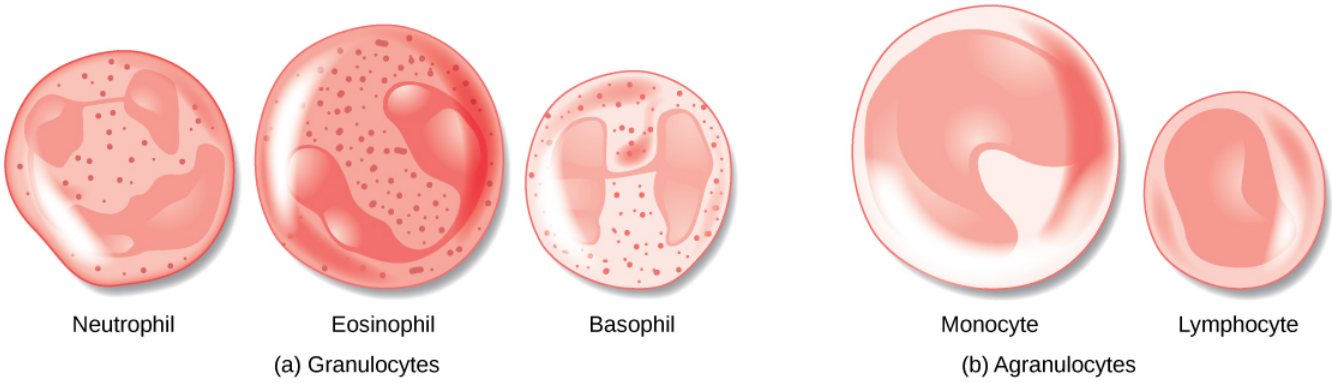


Figure 9.1.4.3: (a) Granulocytes—including neutrophils, eosinophils and basophils—are characterized by a lobed nucleus and granular inclusions in the cytoplasm. Granulocytes are typically first-responders during injury or infection. (b) Agranulocytes include lymphocytes and monocytes. Lymphocytes, including B and T cells, are responsible for adaptive immune response. Monocytes differentiate into macrophages and dendritic cells, which in turn respond to infection or injury.

Granulocytes contain granules in their cytoplasm; the agranulocytes are so named because of the lack of granules in their cytoplasm. Some leukocytes become macrophages that either stay at the same site or move through the blood stream and gather at sites of infection or inflammation where they are attracted by chemical signals from foreign particles and damaged cells. Lymphocytes are the primary cells of the immune system and include B cells, T cells, and natural killer cells. B cells destroy bacteria and inactivate their toxins. They also produce antibodies. T cells attack viruses, fungi, some bacteria, transplanted cells, and cancer cells. T cells attack viruses by releasing toxins that kill the viruses. Natural killer cells attack a variety of infectious microbes and certain tumor cells.

One reason that HIV poses significant management challenges is because the virus directly targets T cells by gaining entry through a receptor. Once inside the cell, HIV then multiplies using the T cell's own genetic machinery. After the HIV virus replicates, it is transmitted directly from the infected T cell to macrophages. The presence of HIV can remain unrecognized for an extensive period of time before full disease symptoms develop.

Platelets and Coagulation Factors

Blood must clot to heal wounds and prevent excess blood loss. Small cell fragments called platelets (thrombocytes) are attracted to the wound site where they adhere by extending many projections and releasing their contents. These contents activate other platelets and also interact with other coagulation factors, which convert fibrinogen, a water-soluble protein present in blood serum into fibrin (a non-water soluble protein), causing the blood to clot. Many of the clotting factors require vitamin K to work, and vitamin K deficiency can lead to problems with blood clotting. Many platelets converge and stick together at the wound site forming a platelet plug (also called a fibrin clot), as illustrated in Figure 9.1.4.4b. The plug or clot lasts for a number of days and stops the loss of blood. Platelets are formed from the disintegration of larger cells called megakaryocytes, like that shown in Figure 9.1.4.4a. For each megakaryocyte, 2000–3000 platelets are formed with 150,000 to 400,000 platelets present in each cubic millimeter of blood. Each platelet is disc shaped and 2–4 μm in diameter. They contain many small vesicles but do not contain a nucleus.

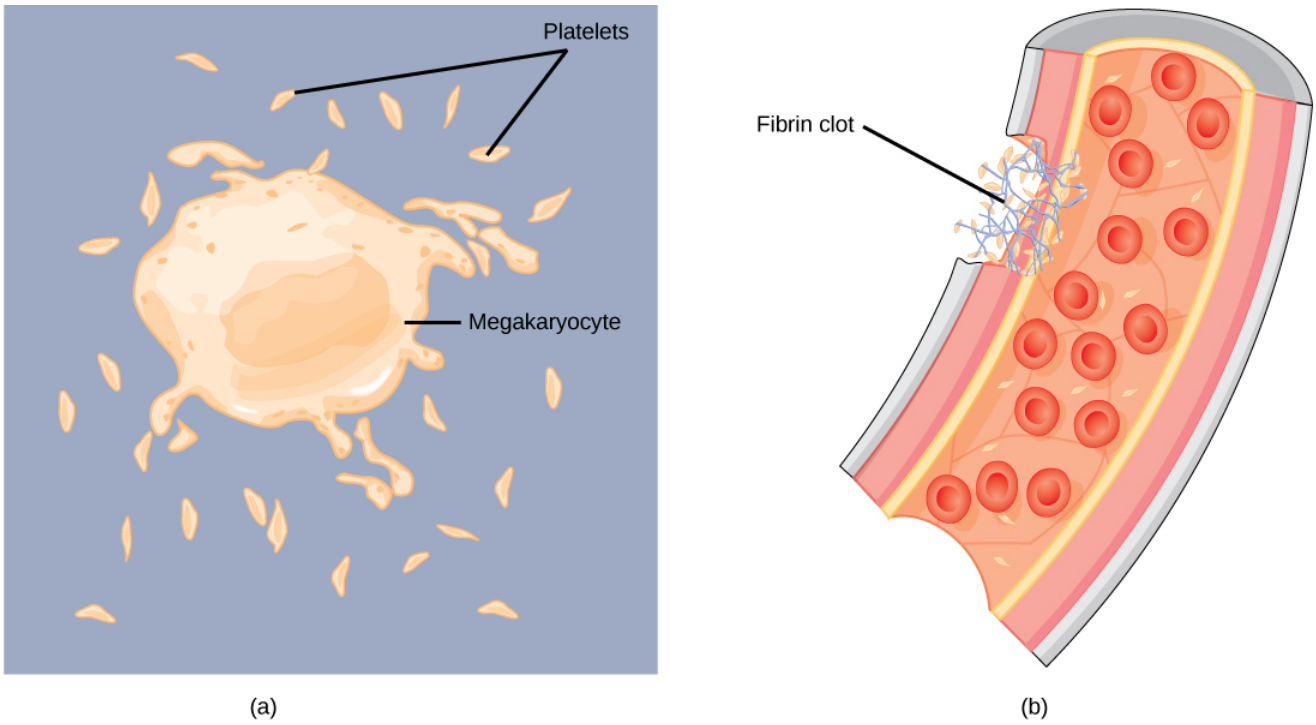


Figure 9.1.4.4: (a) Platelets are formed from large cells called megakaryocytes. The megakaryocyte breaks up into thousands of fragments that become platelets. (b) Platelets are required for clotting of the blood. The platelets collect at a wound site in conjunction with other clotting factors, such as fibrinogen, to form a fibrin clot that prevents blood loss and allows the wound to heal.

Plasma and Serum

The liquid component of blood is called plasma, and it is separated by spinning or centrifuging the blood at high rotations (3000 rpm or higher). The blood cells and platelets are separated by centrifugal forces to the bottom of a specimen tube. The upper liquid layer, the plasma, consists of 90 percent water along with various substances required for maintaining the body's pH, osmotic load, and for protecting the body. The plasma also contains the coagulation factors and antibodies.

The plasma component of blood without the coagulation factors is called the serum. Serum is similar to interstitial fluid in which the correct composition of key ions acting as electrolytes is essential for normal functioning of muscles and nerves. Other components in the serum include proteins that assist with maintaining pH and osmotic balance while giving viscosity to the blood. The serum also contains antibodies, specialized proteins that are important for defense against viruses and bacteria. Lipids, including cholesterol, are also transported in the serum, along with various other substances including nutrients, hormones, metabolic waste, plus external substances, such as, drugs, viruses, and bacteria.

Human serum albumin is the most abundant protein in human blood plasma and is synthesized in the liver. Albumin, which constitutes about half of the blood serum protein, transports hormones and fatty acids, buffers pH, and maintains osmotic pressures. Immunoglobin is a protein antibody produced in the mucosal lining and plays an important role in antibody mediated immunity.

Evolution Connection: Blood Types

Related to Proteins on the Surface of the Red Blood Cells Red blood cells are coated in antigens made of glycolipids and glycoproteins. The composition of these molecules is determined by genetics, which have evolved over time. In humans, the different surface antigens are grouped into 24 different blood groups with more than 100 different antigens on each red blood cell. The two most well known blood groups are the ABO, shown in Figure 9.1.4.5, and Rh systems. The surface antigens in the ABO blood group are glycolipids, called antigen A and antigen B. People with blood type A have antigen A, those with blood type B have antigen B, those with blood type AB have both antigens, and people with blood type O have neither antigen. Antibodies called agglutinougens are found in the blood plasma and react with the A or B antigens, if the two are mixed. When type A and type B blood are combined, agglutination (clumping) of the blood occurs because of antibodies in the plasma that bind with the opposing antigen; this causes clots that coagulate in the kidney causing kidney failure. Type O blood has neither

A or B antigens, and therefore, type O blood can be given to all blood types. Type O negative blood is the universal donor. Type AB positive blood is the universal acceptor because it has both A and B antigen. The ABO blood groups were discovered in 1900 and 1901 by Karl Landsteiner at the University of Vienna.

The Rh blood group was first discovered in Rhesus monkeys. Most people have the Rh antigen (Rh+) and do not have anti-Rh antibodies in their blood. The few people who do not have the Rh antigen and are Rh– can develop anti-Rh antibodies if exposed to Rh+ blood. This can happen after a blood transfusion or after an Rh– woman has an Rh+ baby. The first exposure does not usually cause a reaction; however, at the second exposure, enough antibodies have built up in the blood to produce a reaction that causes agglutination and breakdown of red blood cells. An injection can prevent this reaction.

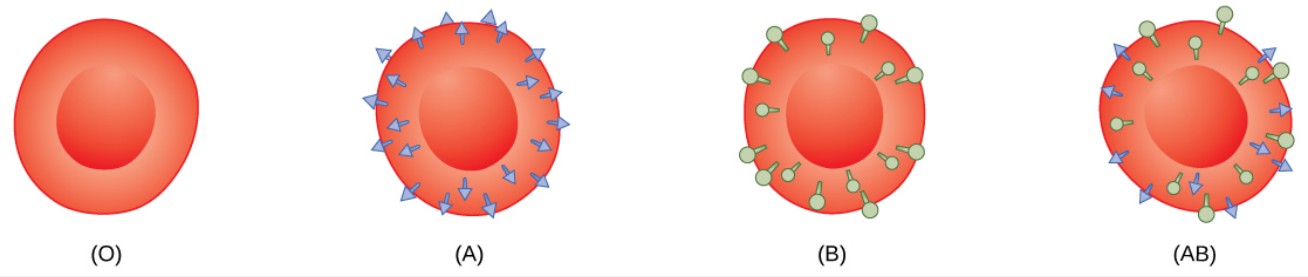


Figure 9.1.4.5: Human red blood cells may have either type A or B glycoproteins on their surface, both glycoproteins combined (AB), or neither (O). The glycoproteins serve as antigens and can elicit an immune response in a person who receives a transfusion containing unfamiliar antigens. Type O blood, which has no A or B antigens, does not elicit an immune response when injected into a person of any blood type. Thus, O is considered the universal donor. Persons with type AB blood can accept blood from any blood type, and type AB is considered the universal acceptor.

Summary

Specific components of the blood include red blood cells, white blood cells, platelets, and the plasma, which contains coagulation factors and serum. Blood is important for regulation of the body's pH, temperature, osmotic pressure, the circulation of nutrients and removal of waste, the distribution of hormones from endocrine glands, and the elimination of excess heat; it also contains components for blood clotting. Red blood cells are specialized cells that contain hemoglobin and circulate through the body delivering oxygen to cells. White blood cells are involved in the immune response to identify and target invading bacteria, viruses, and other foreign organisms; they also recycle waste components, such as old red blood cells. Platelets and blood clotting factors cause the change of the soluble protein fibrinogen to the insoluble protein fibrin at a wound site forming a plug. Plasma consists of 90 percent water along with various substances, such as coagulation factors and antibodies. The serum is the plasma component of the blood without the coagulation factors.

Glossary

plasma
: liquid component of blood that is left after the cells are removed

platelet
: (also, thrombocyte) small cellular fragment that collects at wounds, cross-reacts with clotting factors, and forms a plug to prevent blood loss

red blood cell
: small (7–8 µm) biconcave cell without mitochondria (and in mammals without nuclei) that is packed with hemoglobin, giving the cell its red color; transports oxygen through the body

serum
: plasma without the coagulation factors

white blood cell

large (30 μm) cell with nuclei of which there are many types with different roles including the protection of the body from viruses and bacteria, and cleaning up dead cells and other waste

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9.1.5: Mammalian Heart and Blood Vessels

Skills to Develop

- Describe the structure of the heart and explain how cardiac muscle is different from other muscles
- Describe the cardiac cycle
- Explain the structure of arteries, veins, and capillaries, and how blood flows through the body

The heart is a complex muscle that pumps blood through the three divisions of the circulatory system: the coronary (vessels that serve the heart), pulmonary (heart and lungs), and systemic (systems of the body), as shown in Figure 9.1.5.1. Coronary circulation intrinsic to the heart takes blood directly from the main artery (aorta) coming from the heart. For pulmonary and systemic circulation, the heart has to pump blood to the lungs or the rest of the body, respectively. In vertebrates, the lungs are relatively close to the heart in the thoracic cavity. The shorter distance to pump means that the muscle wall on the right side of the heart is not as thick as the left side which must have enough pressure to pump blood all the way to your big toe.

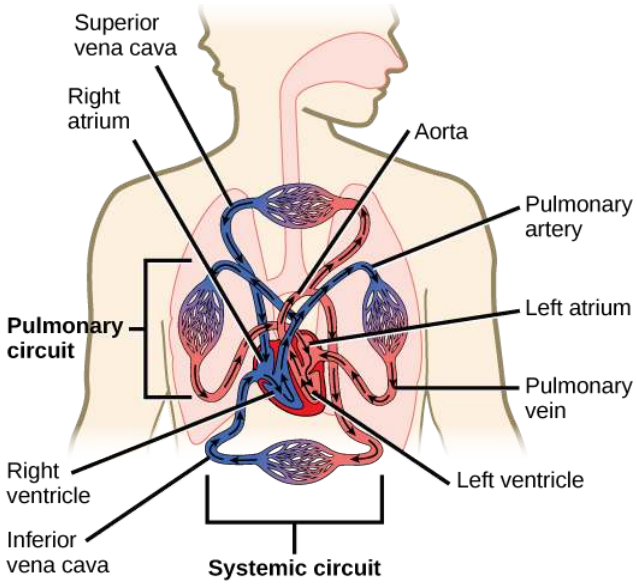


Figure 9.1.5.1: The mammalian circulatory system is divided into three circuits: the systemic circuit, the pulmonary circuit, and the coronary circuit. Blood is pumped from veins of the systemic circuit into the right atrium of the heart, then into the right ventricle. Blood then enters the pulmonary circuit, and is oxygenated by the lungs. From the pulmonary circuit, blood re-enters the heart through the left atrium. From the left ventricle, blood re-enters the systemic circuit through the aorta and is distributed to the rest of the body. The coronary circuit, which provides blood to the heart, is not shown.

Exercise

Which of the following statements about the circulatory system is false?

A. Blood in the pulmonary vein is deoxygenated.
B. Blood in the inferior vena cava is deoxygenated.
C. Blood in the pulmonary artery is deoxygenated.
D. Blood in the aorta is oxygenated.

Answer

C

Structure of the Heart

The heart muscle is asymmetrical as a result of the distance blood must travel in the pulmonary and systemic circuits. Since the right side of the heart sends blood to the pulmonary circuit it is smaller than the left side which must send blood out to the whole

body in the systemic circuit, as shown in Figure 9.1.5.2. In humans, the heart is about the size of a clenched fist; it is divided into four chambers: two atria and two ventricles. There is one atrium and one ventricle on the right side and one atrium and one ventricle on the left side. The atria are the chambers that receive blood, and the ventricles are the chambers that pump blood. The right atrium receives deoxygenated blood from the superior vena cava, which drains blood from the jugular vein that comes from the brain and from the veins that come from the arms, as well as from the inferior vena cava which drains blood from the veins that come from the lower organs and the legs. In addition, the right atrium receives blood from the coronary sinus which drains deoxygenated blood from the heart itself. This deoxygenated blood then passes to the right ventricle through the atrioventricular valve or the tricuspid valve, a flap of connective tissue that opens in only one direction to prevent the backflow of blood.

The valve separating the chambers on the left side of the heart valve is called the biscuspid or mitral valve. After it is filled, the right ventricle pumps the blood through the pulmonary arteries, by-passing the semilunar valve (or pulmonic valve) to the lungs for re-oxygenation. After blood passes through the pulmonary arteries, the right semilunar valves close preventing the blood from flowing backwards into the right ventricle. The left atrium then receives the oxygen-rich blood from the lungs via the pulmonary veins. This blood passes through the bicuspid valve or mitral valve (the atrioventricular valve on the left side of the heart) to the left ventricle where the blood is pumped out through aorta, the major artery of the body, taking oxygenated blood to the organs and muscles of the body. Once blood is pumped out of the left ventricle and into the aorta, the aortic semilunar valve (or aortic valve) closes preventing blood from flowing backward into the left ventricle. This pattern of pumping is referred to as double circulation and is found in all mammals.

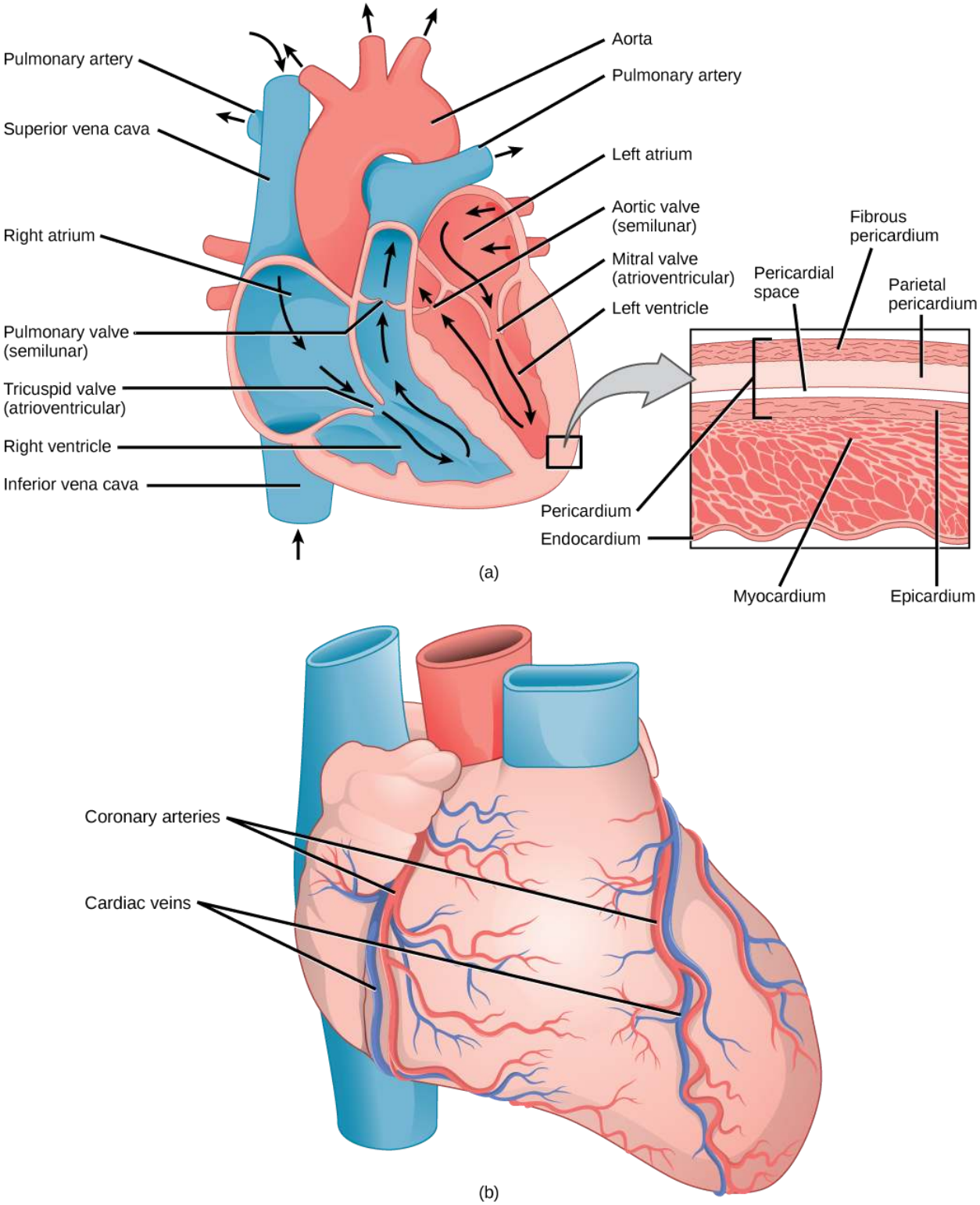


Figure 9.1.5.2: (a) The heart is primarily made of a thick muscle layer, called the myocardium, surrounded by membranes. One-way valves separate the four chambers. (b) Blood vessels of the coronary system, including the coronary arteries and veins, keep the heart musculature oxygenated.

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Exercise

Which of the following statements about the heart is false?

A. The mitral valve separates the left ventricle from the left atrium.
B. Blood travels through the bicuspid valve to the left atrium.
C. Both the aortic and the pulmonary valves are semilunar valves.
D. The mitral valve is an atrioventricular valve.

Answer

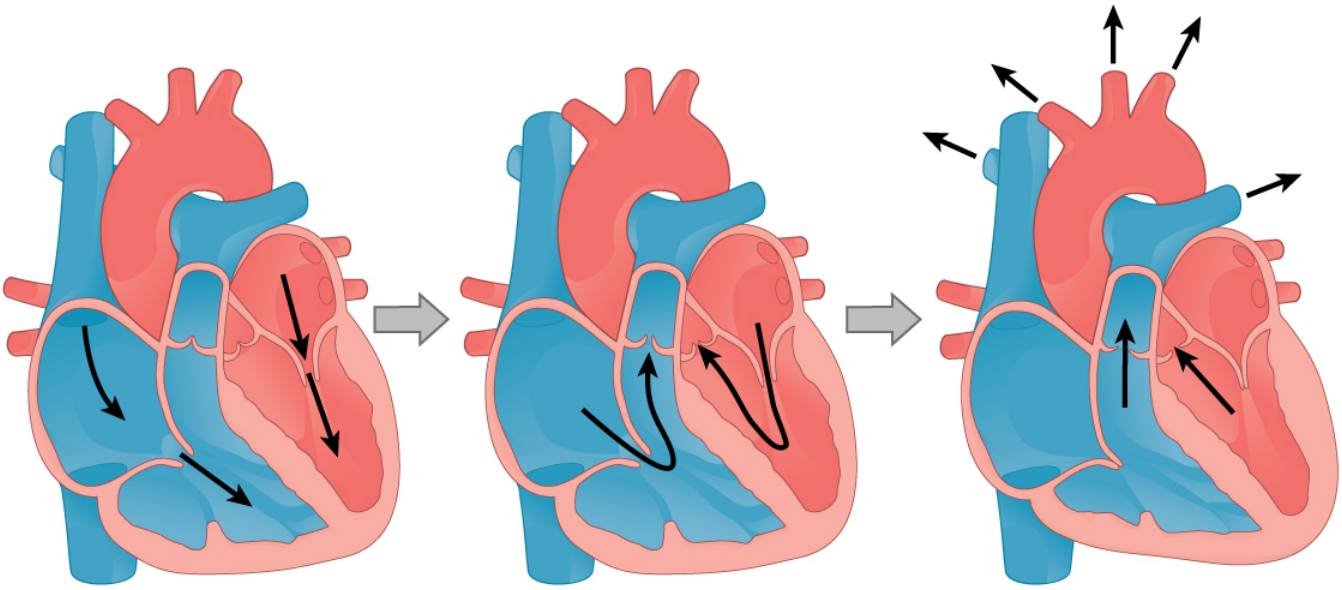
B

The heart is composed of three layers; the epicardium, the myocardium, and the endocardium, illustrated in Figure 9.1.5.2. The inner wall of the heart has a lining called the endocardium. The myocardium consists of the heart muscle cells that make up the middle layer and the bulk of the heart wall. The outer layer of cells is called the epicardium, of which the second layer is a membranous layered structure called the pericardium that surrounds and protects the heart; it allows enough room for vigorous pumping but also keeps the heart in place to reduce friction between the heart and other structures.

The heart has its own blood vessels that supply the heart muscle with blood. The coronary arteries branch from the aorta and surround the outer surface of the heart like a crown. They diverge into capillaries where the heart muscle is supplied with oxygen before converging again into the coronary veins to take the deoxygenated blood back to the right atrium where the blood will be re-oxygenated through the pulmonary circuit. The heart muscle will die without a steady supply of blood. Atherosclerosis is the blockage of an artery by the buildup of fatty plaques. Because of the size (narrow) of the coronary arteries and their function in serving the heart itself, atherosclerosis can be deadly in these arteries. The slowdown of blood flow and subsequent oxygen deprivation that results from atherosclerosis causes severe pain, known as angina, and complete blockage of the arteries will cause myocardial infarction: the death of cardiac muscle tissue, commonly known as a heart attack.

The Cardiac Cycle

The main purpose of the heart is to pump blood through the body; it does so in a repeating sequence called the cardiac cycle. The cardiac cycle is the coordination of the filling and emptying of the heart of blood by electrical signals that cause the heart muscles to contract and relax. The human heart beats over 100,000 times per day. In each cardiac cycle, the heart contracts (systole), pushing out the blood and pumping it through the body; this is followed by a relaxation phase (diastole), where the heart fills with blood, as illustrated in Figure 9.1.5.3. The atria contract at the same time, forcing blood through the atrioventricular valves into the ventricles. Closing of the atrioventricular valves produces a monosyllabic “lup” sound. Following a brief delay, the ventricles contract at the same time forcing blood through the semilunar valves into the aorta and the artery transporting blood to the lungs (via the pulmonary artery). Closing of the semilunar valves produces a monosyllabic “dup” sound.



(a) Cardiac diastole: all chambers are relaxed, and blood flows into the heart.

(b) Atrial systole, ventricular diastole: atria contract, pushing blood into the ventricles.

(c) Atrial diastole, ventricular systole: after the atria relax, the ventricles contract, pushing blood out of the heart.

Figure 9.1.5.3: During (a) cardiac diastole, the heart muscle is relaxed and blood flows into the heart. During (b) atrial systole, the atria contract, pushing blood into the ventricles. During (c) atrial diastole, the ventricles contract, forcing blood out of the heart.

The pumping of the heart is a function of the cardiac muscle cells, or cardiomyocytes, that make up the heart muscle. Cardiomyocytes, shown in Figure 9.1.5.4, are distinctive muscle cells that are striated like skeletal muscle but pump rhythmically and involuntarily like smooth muscle; they are connected by intercalated disks exclusive to cardiac muscle. They are self-stimulated for a period of time and isolated cardiomyocytes will beat if given the correct balance of nutrients and electrolytes.

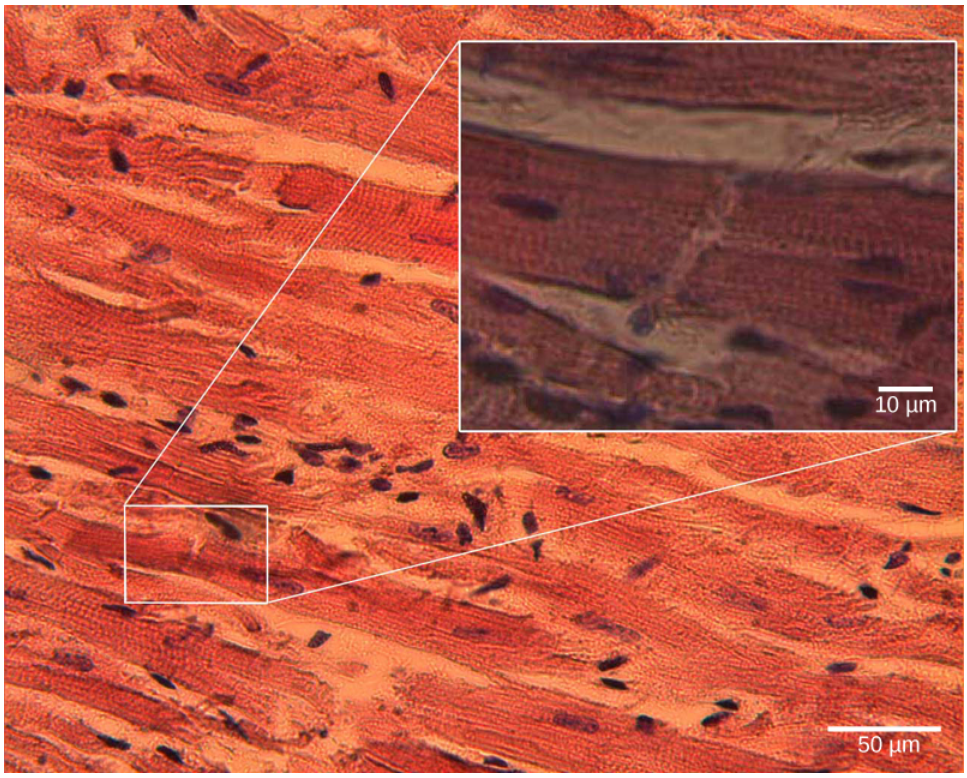


Figure 9.1.5.4: Cardiomyocytes are striated muscle cells found in cardiac tissue. (credit: modification of work by Dr. S. Girod, Anton Becker; scale-bar data from Matt Russell)

The autonomous beating of cardiac muscle cells is regulated by the heart's internal pacemaker that uses electrical signals to time the beating of the heart. The electrical signals and mechanical actions, illustrated in Figure 9.1.5.5, are intimately intertwined. The internal pacemaker starts at the sinoatrial (SA) node, which is located near the wall of the right atrium. Electrical charges spontaneously pulse from the SA node causing the two atria to contract in unison. The pulse reaches a second node, called the atrioventricular (AV) node, between the right atrium and right ventricle where it pauses for approximately 0.1 second before spreading to the walls of the ventricles. From the AV node, the electrical impulse enters the bundle of His, then to the left and right bundle branches extending through the interventricular septum. Finally, the Purkinje fibers conduct the impulse from the apex of the heart up the ventricular myocardium, and then the ventricles contract. This pause allows the atria to empty completely into the ventricles before the ventricles pump out the blood. The electrical impulses in the heart produce electrical currents that flow through the body and can be measured on the skin using electrodes. This information can be observed as an electrocardiogram (ECG)—a recording of the electrical impulses of the cardiac muscle.

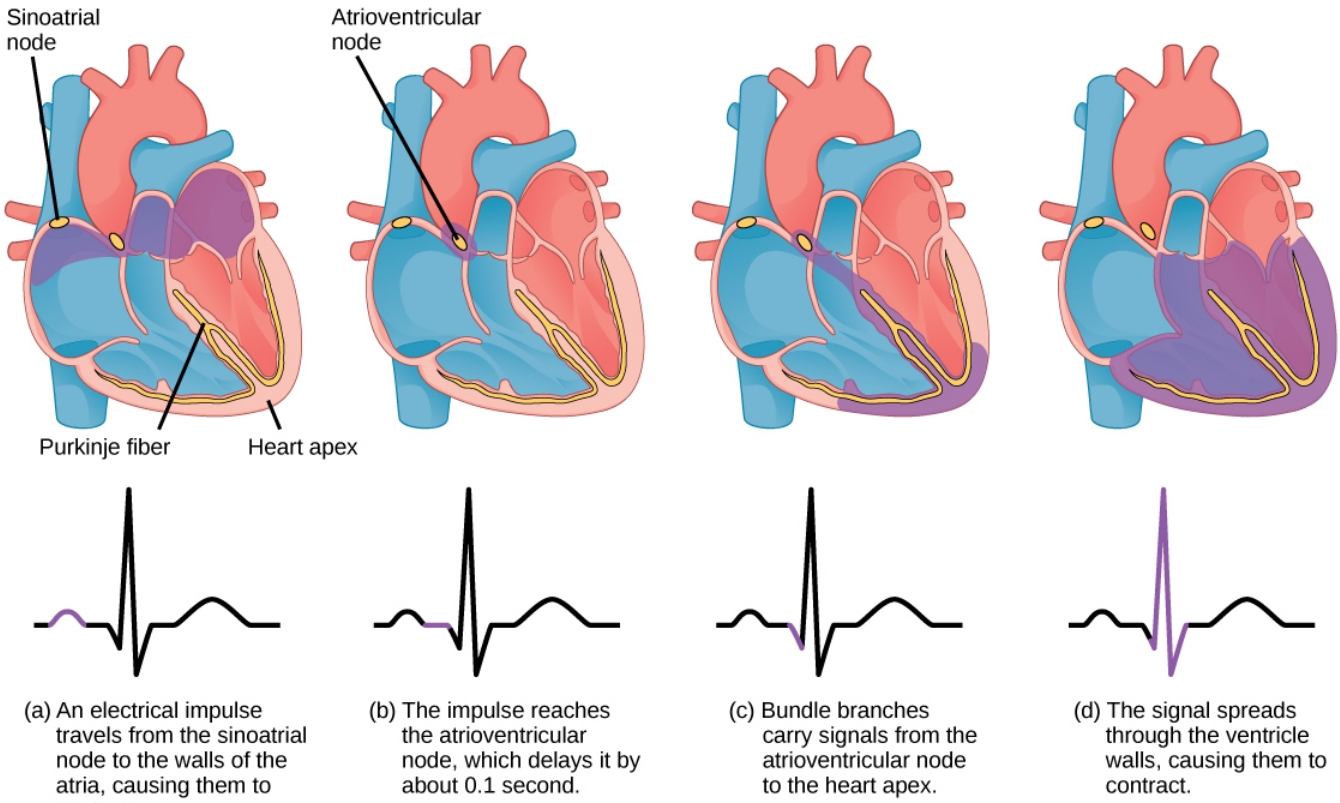
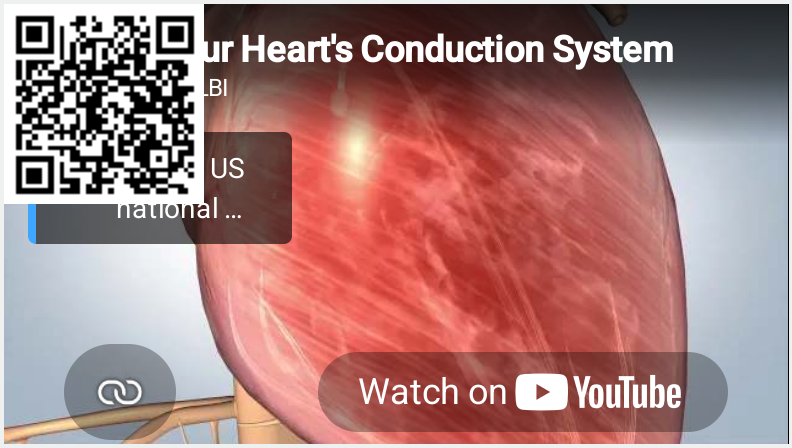


Figure 9.1.5.5: The beating of the heart is regulated by an electrical impulse that causes the characteristic reading of an ECG. The signal is initiated at the sinoatrial valve. The signal then (a) spreads to the atria, causing them to contract. The signal is (b) delayed at the atrioventricular node before it is passed on to the (c) heart apex. The delay allows the atria to relax before the (d) ventricles contract. The final part of the ECG cycle prepares the heart for the next beat.

Link to Learning



Visit this site and select the dropdown "Your Heart's Electrical System" to see the heart's "pacemaker" in action.

Arteries, Veins, and Capillaries

The blood from the heart is carried through the body by a complex network of blood vessels (Figure 9.1.5.6). Arteries take blood away from the heart. The main artery is the aorta that branches into major arteries that take blood to different limbs and organs. These major arteries include the carotid artery that takes blood to the brain, the brachial arteries that take blood to the arms, and the thoracic artery that takes blood to the thorax and then into the hepatic, renal, and gastric arteries for the liver, kidney, and stomach, respectively. The iliac artery takes blood to the lower limbs. The major arteries diverge into minor arteries, and then smaller vessels called arterioles, to reach more deeply into the muscles and organs of the body.

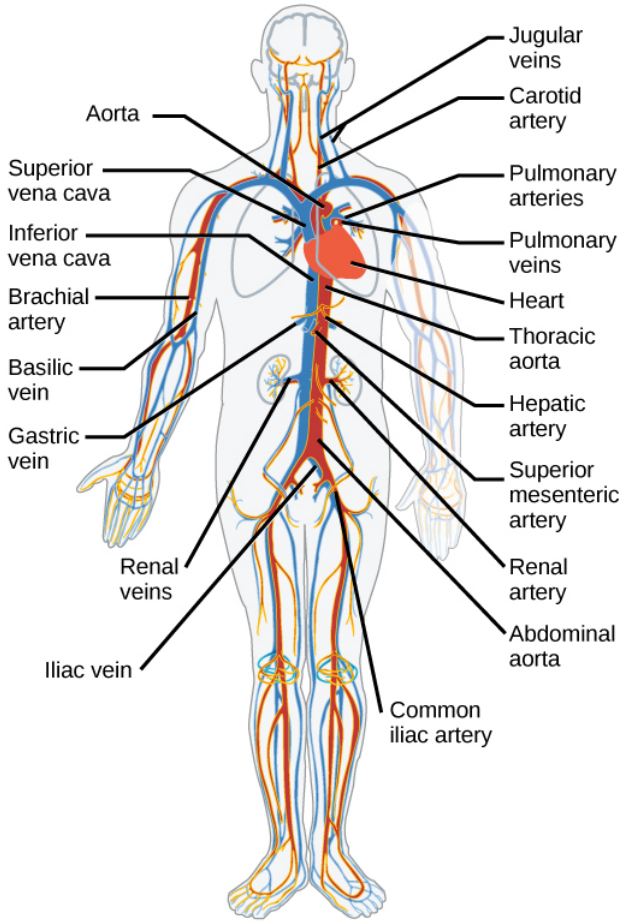


Figure 9.1.5.6: The major human arteries and veins are shown. (credit: modification of work by Mariana Ruiz Villareal)

Arterioles diverge into capillary beds. Capillary beds contain a large number (10 to 100) of capillaries that branch among the cells and tissues of the body. Capillaries are narrow-diameter tubes that can fit red blood cells through in single file and are the sites for the exchange of nutrients, waste, and oxygen with tissues at the cellular level. Fluid also crosses into the interstitial space from the capillaries. The capillaries converge again into venules that connect to minor veins that finally connect to major veins that take blood high in carbon dioxide back to the heart. Veins are blood vessels that bring blood back to the heart. The major veins drain blood from the same organs and limbs that the major arteries supply. Fluid is also brought back to the heart via the lymphatic system.

The structure of the different types of blood vessels reflects their function or layers. There are three distinct layers, or tunics, that form the walls of blood vessels (Figure 9.1.5.7). The first tunic is a smooth, inner lining of endothelial cells that are in contact with the red blood cells. The endothelial tunic is continuous with the endocardium of the heart. In capillaries, this single layer of cells is the location of diffusion of oxygen and carbon dioxide between the endothelial cells and red blood cells, as well as the exchange site via endocytosis and exocytosis. The movement of materials at the site of capillaries is regulated by vasoconstriction, narrowing of the blood vessels, and vasodilation, widening of the blood vessels; this is important in the overall regulation of blood pressure.

Veins and arteries both have two further tunics that surround the endothelium: the middle tunic is composed of smooth muscle and the outermost layer is connective tissue (collagen and elastic fibers). The elastic connective tissue stretches and supports the blood vessels, and the smooth muscle layer helps regulate blood flow by altering vascular resistance through vasoconstriction and vasodilation. The arteries have thicker smooth muscle and connective tissue than the veins to accommodate the higher pressure and speed of freshly pumped blood. The veins are thinner walled as the pressure and rate of flow are much lower. In addition, veins are structurally different than arteries in that veins have valves to prevent the backflow of blood. Because veins have to work against gravity to get blood back to the heart, contraction of skeletal muscle assists with the flow of blood back to the heart.

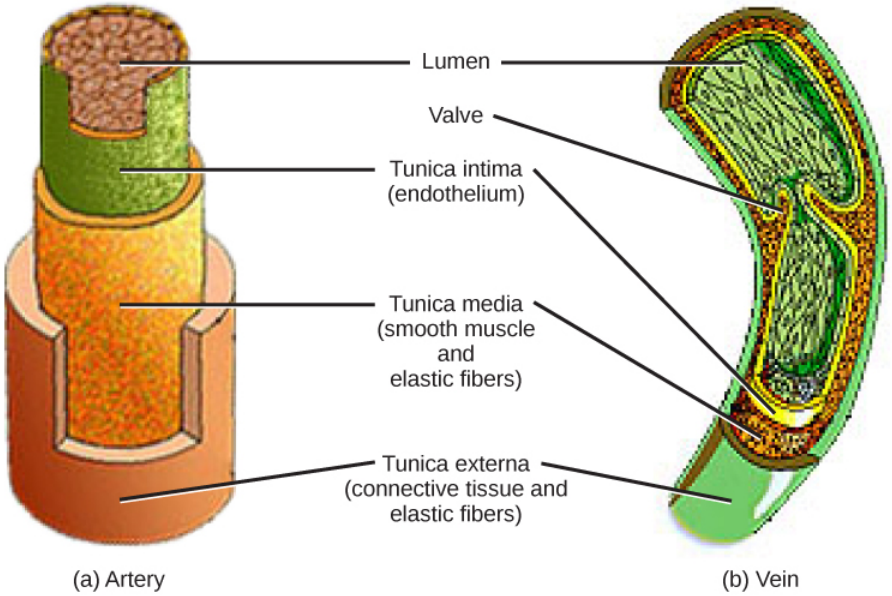


Figure 9.1.5.7: Arteries and veins consist of three layers: an outer tunica externa, a middle tunica media, and an inner tunica intima. Capillaries consist of a single layer of epithelial cells, the tunica intima. (credit: modification of work by NCI, NIH)

Summary

The heart muscle pumps blood through three divisions of the circulatory system: coronary, pulmonary, and systemic. There is one atrium and one ventricle on the right side and one atrium and one ventricle on the left side. The pumping of the heart is a function of cardiomyocytes, distinctive muscle cells that are striated like skeletal muscle but pump rhythmically and involuntarily like smooth muscle. The internal pacemaker starts at the sinoatrial node, which is located near the wall of the right atrium. Electrical charges pulse from the SA node causing the two atria to contract in unison; then the pulse reaches the atrioventricular node between the right atrium and right ventricle. A pause in the electric signal allows the atria to empty completely into the ventricles before the ventricles pump out the blood. The blood from the heart is carried through the body by a complex network of blood vessels; arteries take blood away from the heart, and veins bring blood back to the heart.

Glossary

angina
pain caused by partial blockage of the coronary arteries by the buildup of plaque and lack of oxygen to the heart muscle

aorta
major artery of the body that takes blood away from the heart

arteriole
small vessel that connects an artery to a capillary bed

artery
blood vessel that takes blood away from the heart

atherosclerosis
buildup of fatty plaques in the coronary arteries in the heart

atrioventricular valve
one-way membranous flap of connective tissue between the atrium and the ventricle in the right side of the heart; also known as tricuspid valve

bicuspid valve

(also, mitral valve; left atrioventricular valve) one-way membranous flap between the atrium and the ventricle in the left side of the heart

capillary
smallest blood vessel that allows the passage of individual blood cells and the site of diffusion of oxygen and nutrient exchange

capillary bed
large number of capillaries that converge to take blood to a particular organ or tissue

cardiac cycle
filling and emptying the heart of blood by electrical signals that cause the heart muscles to contract and relax

cardiomyocyte
specialized heart muscle cell that is striated but contracts involuntarily like smooth muscle

coronary artery
vessel that supplies the heart tissue with blood

coronary vein
vessel that takes blood away from the heart tissue back to the chambers in the heart

diastole
relaxation phase of the cardiac cycle when the heart is relaxed and the ventricles are filling with blood

electrocardiogram (ECG)
recording of the electrical impulses of the cardiac muscle

endocardium
innermost layer of tissue in the heart

epicardium
outermost tissue layer of the heart

inferior vena cava
drains blood from the veins that come from the lower organs and the legs

myocardial infarction
(also, heart attack) complete blockage of the coronary arteries and death of the cardiac muscle tissue

myocardium
heart muscle cells that make up the middle layer and the bulk of the heart wall

pericardium
membrane layer protecting the heart; also part of the epicardium

semilunar valve
membranous flap of connective tissue between the aorta and a ventricle of the heart (the aortic or pulmonary semilunar valves)

sinoatrial (SA) node
the heart’s internal pacemaker; located near the wall of the right atrium

superior vena cava
drains blood from the jugular vein that comes from the brain and from the veins that come from the arms

systole

contraction phase of cardiac cycle when the ventricles are pumping blood into the arteries

tricuspid valve

one-way membranous flap of connective tissue between the atrium and the ventricle in the right side of the heart; also known as atrioventricular valve

vasoconstriction

narrowing of a blood vessel

vasodilation

widening of a blood vessel

vein

blood vessel that brings blood back to the heart

vena cava

major vein of the body returning blood from the upper and lower parts of the body; see the superior vena cava and inferior vena cava

venule

blood vessel that connects a capillary bed to a vein

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9.1.6: Blood Flow and Blood Pressure Regulation

Skills to Develop

- Describe the system of blood flow through the body
- Describe how blood pressure is regulated

Blood pressure (BP) is the pressure exerted by blood on the walls of a blood vessel that helps to push blood through the body. Systolic blood pressure measures the amount of pressure that blood exerts on vessels while the heart is beating. The optimal systolic blood pressure is 120 mmHg. Diastolic blood pressure measures the pressure in the vessels between heartbeats. The optimal diastolic blood pressure is 80 mmHg. Many factors can affect blood pressure, such as hormones, stress, exercise, eating, sitting, and standing. Blood flow through the body is regulated by the size of blood vessels, by the action of smooth muscle, by one-way valves, and by the fluid pressure of the blood itself.

How Blood Flows Through the Body

Blood is pushed through the body by the action of the pumping heart. With each rhythmic pump, blood is pushed under high pressure and velocity away from the heart, initially along the main artery, the aorta. In the aorta, the blood travels at 30 cm/sec. As blood moves into the arteries, arterioles, and ultimately to the capillary beds, the rate of movement slows dramatically to about 0.026 cm/sec, one-thousand times slower than the rate of movement in the aorta. While the diameter of each individual arteriole and capillary is far narrower than the diameter of the aorta, and according to the law of continuity, fluid should travel faster through a narrower diameter tube, the rate is actually slower due to the overall diameter of all the combined capillaries being far greater than the diameter of the individual aorta.

The slow rate of travel through the capillary beds, which reach almost every cell in the body, assists with gas and nutrient exchange and also promotes the diffusion of fluid into the interstitial space. After the blood has passed through the capillary beds to the venules, veins, and finally to the main venae cavae, the rate of flow increases again but is still much slower than the initial rate in the aorta. Blood primarily moves in the veins by the rhythmic movement of smooth muscle in the vessel wall and by the action of the skeletal muscle as the body moves. Because most veins must move blood against the pull of gravity, blood is prevented from flowing backward in the veins by one-way valves. Because skeletal muscle contraction aids in venous blood flow, it is important to get up and move frequently after long periods of sitting so that blood will not pool in the extremities.

Blood flow through the capillary beds is regulated depending on the body's needs and is directed by nerve and hormone signals. For example, after a large meal, most of the blood is diverted to the stomach by vasodilation of vessels of the digestive system and vasoconstriction of other vessels. During exercise, blood is diverted to the skeletal muscles through vasodilation while blood to the digestive system would be lessened through vasoconstriction. The blood entering some capillary beds is controlled by small muscles, called precapillary sphincters, illustrated in Figure 9.1.6.1. If the sphincters are open, the blood will flow into the associated branches of the capillary blood. If all of the sphincters are closed, then the blood will flow directly from the arteriole to the venule through the thoroughfare channel (see Figure 9.1.6.1). These muscles allow the body to precisely control when capillary beds receive blood flow. At any given moment only about 5-10% of our capillary beds actually have blood flowing through them.

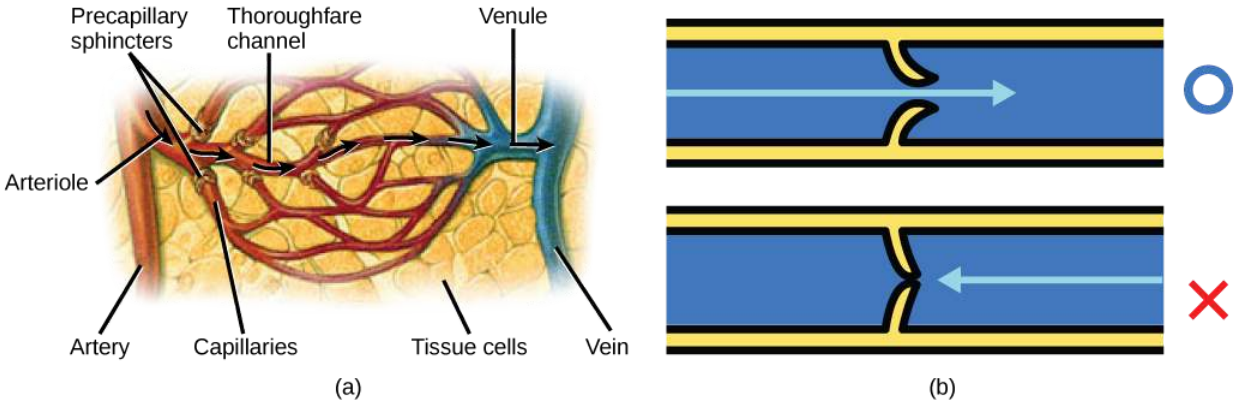


Figure 9.1.6.1: (a) Precapillary sphincters are rings of smooth muscle that regulate the flow of blood through capillaries; they help control the location of blood flow to where it is needed. (b) Valves in the veins prevent blood from moving backward. (credit a: modification of work by NCI)

Exercise

Varicose veins are veins that become enlarged because the valves no longer close properly, allowing blood to flow backward. Varicose veins are often most prominent on the legs. Why do you think this is the case?

Answer

Blood in the legs is farthest away from the heart and has to flow up to reach it.

Link to Learning



The circulatory system consisting of the heart, arteries, capillaries, and veins, is the pumping mechanism that transports blood throughout the body. Watch this video to see the circulatory system's blood flow.

Proteins and other large solutes cannot leave the capillaries. The loss of the watery plasma creates a hyperosmotic solution within the capillaries, especially near the venules. This causes about 85% of the plasma that leaves the capillaries to eventually diffuses back into the capillaries near the venules. The remaining 15% of blood plasma drains out from the interstitial fluid into nearby lymphatic vessels (Figure 9.1.6.2). The fluid in the lymph is similar in composition to the interstitial fluid. The lymph fluid passes through lymph nodes before it returns to the heart via the vena cava. Lymph nodes are specialized organs that filter the lymph by percolation through a maze of connective tissue filled with white blood cells. The white blood cells remove infectious agents, such as bacteria and viruses, to clean the lymph before it returns to the bloodstream. After it is cleaned, the lymph returns to the heart by the action of smooth muscle pumping, skeletal muscle action, and one-way valves joining the returning blood near the junction of the venae cavae entering the right atrium of the heart.

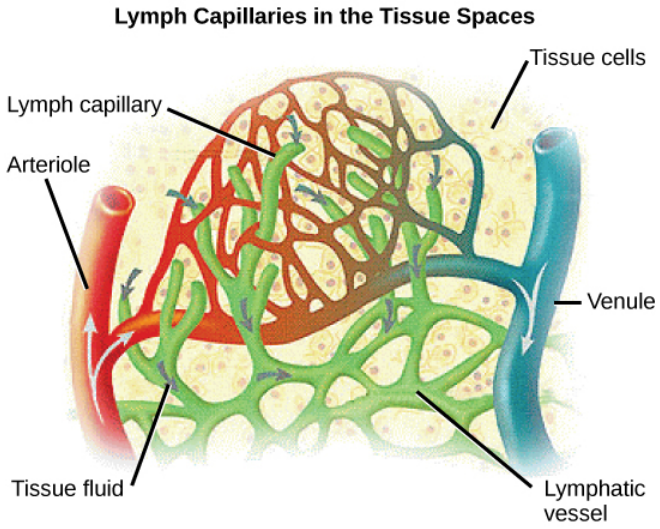


Figure 9.1.6.2: Fluid from the capillaries moves into the interstitial space and lymph capillaries by diffusion down a pressure gradient and also by osmosis. Out of 7,200 liters of fluid pumped by the average heart in a day, over 1,500 liters is filtered. (credit: modification of work by NCI, NIH)

Evolution Connection: Vertebrate Diversity in Blood Circulation

Blood circulation has evolved differently in vertebrates and may show variation in different animals for the required amount of pressure, organ and vessel location, and organ size. Animals with longs necks and those that live in cold environments have distinct blood pressure adaptations.

Long necked animals, such as giraffes, need to pump blood upward from the heart against gravity. The blood pressure required from the pumping of the left ventricle would be equivalent to 250 mm Hg (mm Hg = millimeters of mercury, a unit of pressure) to reach the height of a giraffe's head, which is 2.5 meters higher than the heart. However, if checks and balances were not in place, this blood pressure would damage the giraffe's brain, particularly if it was bending down to drink. These checks and balances include valves and feedback mechanisms that reduce the rate of cardiac output. Long-necked dinosaurs such as the sauropods had to pump blood even higher, up to ten meters above the heart. This would have required a blood pressure of more than 600 mm Hg, which could only have been achieved by an enormous heart. Evidence for such an enormous heart does not exist and mechanisms to reduce the blood pressure required include the slowing of metabolism as these animals grew larger. It is likely that they did not routinely feed on tree tops but grazed on the ground.

Living in cold water, whales need to maintain the temperature in their blood. This is achieved by the veins and arteries being close together so that heat exchange can occur. This mechanism is called a countercurrent heat exchanger. The blood vessels and the whole body are also protected by thick layers of blubber to prevent heat loss. In land animals that live in cold environments, thick fur and hibernation are used to retain heat and slow metabolism.

Blood Pressure

The pressure of the blood flow in the body is produced by the hydrostatic pressure of the fluid (blood) against the walls of the blood vessels. Fluid will move from areas of high to low hydrostatic pressures. In the arteries, the hydrostatic pressure near the heart is very high and blood flows to the arterioles where the rate of flow is slowed by the narrow openings of the arterioles. During systole, when new blood is entering the arteries, the artery walls stretch to accommodate the increase of pressure of the extra blood; during diastole, the walls return to normal because of their elastic properties. The blood pressure of the systole phase and the diastole phase, graphed in Figure 9.1.6.3, gives the two pressure readings for blood pressure. For example, 120/80 indicates a reading of 120 mm Hg during the systole and 80 mm Hg during diastole. Throughout the cardiac cycle, the blood continues to empty into the arterioles at a relatively even rate. This resistance to blood flow is called peripheral resistance.

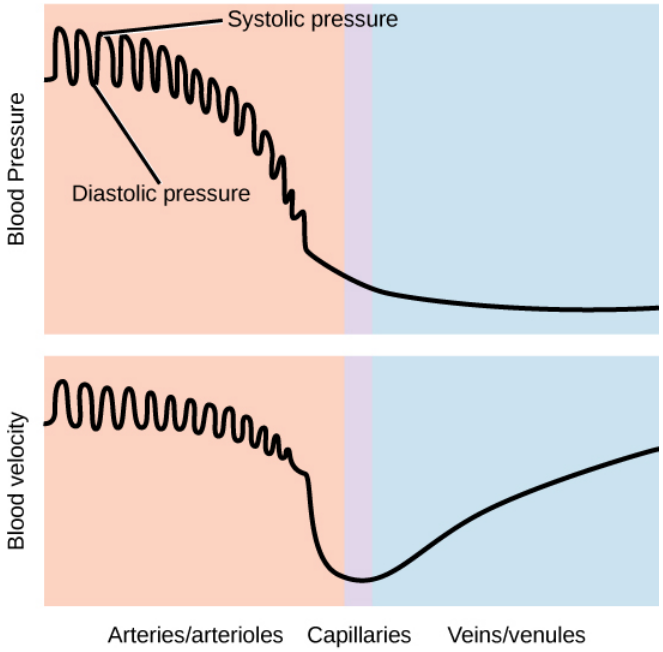


Figure 9.1.6.3: Blood pressure is related to the blood velocity in the arteries and arterioles. In the capillaries and veins, the blood pressure continues to decease but velocity increases.

Blood Pressure Regulation

Cardiac output is the volume of blood pumped by the heart in one minute. It is calculated by multiplying the number of heart contractions that occur per minute (heart rate) times the stroke volume (the volume of blood pumped into the aorta per contraction of the left ventricle). Therefore, cardiac output can be increased by increasing heart rate, as when exercising. However, cardiac output can also be increased by increasing stroke volume, such as if the heart contracts with greater strength. Stroke volume can also be increased by speeding blood circulation through the body so that more blood enters the heart between contractions. During heavy exertion, the blood vessels relax and increase in diameter, offsetting the increased heart rate and ensuring adequate oxygenated blood gets to the muscles. Stress triggers a decrease in the diameter of the blood vessels, consequently increasing blood pressure. These changes can also be caused by nerve signals or hormones, and even standing up or lying down can have a great effect on blood pressure.

Summary

Blood primarily moves through the body by the rhythmic movement of smooth muscle in the vessel wall and by the action of the skeletal muscle as the body moves. Blood is prevented from flowing backward in the veins by one-way valves. Blood flow through the capillary beds is controlled by precapillary sphincters to increase and decrease flow depending on the body's needs and is directed by nerve and hormone signals. Lymph vessels take fluid that has leaked out of the blood to the lymph nodes where it is cleaned before returning to the heart. During systole, blood enters the arteries, and the artery walls stretch to accommodate the extra blood. During diastole, the artery walls return to normal. The blood pressure of the systole phase and the diastole phase gives the two pressure readings for blood pressure.

Glossary

blood pressure (BP)
pressure of blood in the arteries that helps to push blood through the body

cardiac output
the volume of blood pumped by the heart in one minute as a product of heart rate multiplied by stroke volume

lymph node
specialized organ that contains a large number of macrophages that clean the lymph before the fluid is returned to the heart

peripheral resistance

resistance of the artery and blood vessel walls to the pressure placed on them by the force of the heart pumping

precapillary sphincter

small muscle that controls blood circulation in the capillary beds

stroke volume

the volume of blood pumped into the aorta per contraction of the left ventricle

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9.1.E: The Circulatory System (Exercises)

40.1: Overview of the Circulatory System

In all animals, except a few simple types, the circulatory system is used to transport nutrients and gases through the body. Simple diffusion allows some water, nutrient, waste, and gas exchange into primitive animals that are only a few cell layers thick; however, bulk flow is the only method by which the entire body of larger more complex organisms is accessed.

Review Questions

Why are open circulatory systems advantageous to some animals?

A. They use less metabolic energy.
B. They help the animal move faster.
C. They do not need a heart.
D. They help large insects develop.

Answer

A

Some animals use diffusion instead of a circulatory system. Examples include:

A. birds and jellyfish
B. flatworms and arthropods
C. mollusks and jellyfish
D. None of the above

Answer

D

Blood flow that is directed through the lungs and back to the heart is called _____.

A. unidirectional circulation
B. gill circulation
C. pulmonary circulation
D. pulmocutaneous circulation

Answer

C

Free Response

Describe a closed circulatory system.

Answer

A closed circulatory system is a closed-loop system, in which blood is not free in a cavity. Blood is separate from the bodily interstitial fluid and contained within blood vessels. In this type of system, blood circulates unidirectionally from the heart around the systemic circulatory route, and then returns to the heart.

Describe systemic circulation.

Answer

Systemic circulation flows through the systems of the body. The blood flows away from the heart to the brain, liver, kidneys, stomach, and other organs, the limbs, and the muscles of the body; it then returns to the heart.

40.2: Components of the Blood

Blood is the liquid that moves through the vessels and includes plasma (the liquid portion, which contains water, proteins, salts, lipids, and glucose) and the cells (red and white cells) and cell fragments called platelets. Blood plasma is actually the dominant component of blood and contains the water, proteins, electrolytes, lipids, and glucose. The cells are responsible for carrying the gases (red cells) and immune the response (white). The platelets are responsible for blood clotting.

Review Questions

White blood cells:

A. can be classified as granulocytes or agranulocytes
B. defend the body against bacteria and viruses
C. are also called leucocytes
D. All of the above

Answer

D

Platelet plug formation occurs at which point?

A. when large megakaryocytes break up into thousands of smaller fragments
B. when platelets are dispersed through the blood stream
C. when platelets are attracted to a site of blood vessel damage
D. none of the above

Answer

C

In humans, the plasma comprises what percentage of the blood?

A. 45 percent
B. 55 percent
C. 25 percent
D. 90 percent

Answer

B

The red blood cells of birds differ from mammalian red blood cells because:

A. they are white and have nuclei
B. they do not have nuclei
C. they have nuclei
D. they fight disease

Answer

C

Free Response

Describe the cause of different blood type groups.

Answer

Red blood cells are coated with proteins called antigens made of glycolipids and glycoproteins. When type A and type B blood are mixed, the blood agglutinates because of antibodies in the plasma that bind with the opposing antigen. Type O blood has no antigens. The Rh blood group has either the Rh antigen (Rh+) or no Rh antigen (Rh–).

List some of the functions of blood in the body.

Answer

Blood is important for regulation of the body's pH, temperature, and osmotic pressure, the circulation of nutrients and removal of wastes, the distribution of hormones from endocrine glands, the elimination of excess heat; it also contains components for the clotting of blood to prevent blood loss. Blood also transports clotting factors and disease-fighting agents.

How does the lymphatic system work with blood flow?

Answer

Lymph capillaries take fluid from the blood to the lymph nodes. The lymph nodes filter the lymph by percolation through connective tissue filled with white blood cells. The white blood cells remove infectious agents, such as bacteria and viruses, to clean the lymph before it returns to the bloodstream.

40.3: Mammalian Heart and Blood Vessels

The heart is a complex muscle that pumps blood through the three divisions of the circulatory system: the coronary (vessels that serve the heart), pulmonary (heart and lungs), and systemic (systems of the body). Coronary circulation intrinsic to the heart takes blood directly from the main artery (aorta) coming from the heart.

Review Questions

The heart's internal pacemaker beats by:

A. an internal implant that sends an electrical impulse through the heart
B. the excitation of cardiac muscle cells at the sinoatrial node followed by the atrioventricular node
C. the excitation of cardiac muscle cells at the atrioventricular node followed by the sinoatrial node
D. the action of the sinus

Answer

B

During the systolic phase of the cardiac cycle, the heart is _____.

A. contracting
B. relaxing
C. contracting and relaxing
D. filling with blood

Answer

A

Cardiomyocytes are similar to skeletal muscle because:

A. they beat involuntarily
B. they are used for weight lifting
C. they pulse rhythmically
D. they are striated

Answer

D

How do arteries differ from veins?

A. Arteries have thicker smooth muscle layers to accommodate the changes in pressure from the heart.
B. Arteries carry blood.
C. Arteries have thinner smooth muscle layers and valves and move blood by the action of skeletal muscle.
D. Arteries are thin walled and are used for gas exchange.

Answer

A

Free Response

Describe the cardiac cycle.

Answer

The heart receives an electrical signal from the sinoatrial node triggering the cardiac muscle cells in the atria to contract. The signal pauses at the atrioventricular node before spreading to the walls of the ventricles so the blood is pumped through the body. This is the systolic phase. The heart then relaxes in the diastole and fills again with blood.

What happens in capillaries?

Answer

The capillaries basically exchange materials with their surroundings. Their walls are very thin and are made of one or two layers of cells, where gases, nutrients, and waste are diffused. They are distributed as beds, complex networks that link arteries as well as veins.

40.4: Blood Flow and Blood Pressure Regulation

Blood pressure is the pressure exerted by blood on the walls of a blood vessel that helps to push blood through the body. Systolic blood pressure measures the amount of pressure that blood exerts on vessels while the heart is beating. The optimal systolic blood pressure is 120 mmHg. Diastolic blood pressure measures the pressure in the vessels between heartbeats. The optimal diastolic blood pressure is 80 mmHg.

Review Questions

High blood pressure would be a result of _____.

A. a high cardiac output and high peripheral resistance
B. a high cardiac output and low peripheral resistance
C. a low cardiac output and high peripheral resistance
D. a low cardiac output and low peripheral resistance

Answer

A

Free Response

How does blood pressure change during heavy exercise?

Answer

The heart rate increases, which increases the hydrostatic pressure against the artery walls. At the same time, the arterioles dilate in response to the increased exercise, which reduces peripheral resistance.

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SECTION OVERVIEW

9.2: Circulatory and Lymphatic System Infections

Yellow fever was once common in the southeastern US, with annual outbreaks of more than 25,000 infections in New Orleans in the mid-1800s.[1] In the early 20th century, efforts to eradicate the virus that causes yellow fever were successful thanks to vaccination programs and effective control (mainly through the insecticide dichlorodiphenyltrichloroethane [DDT]) of *Aedes aegypti*, the mosquito that serves as a vector. Today, the virus has been largely eradicated in North America.

Elsewhere, efforts to contain yellow fever have been less successful. Despite mass vaccination campaigns in some regions, the risk for yellow fever epidemics is rising in dense urban cities in Africa and South America.[2] In an increasingly globalized society, yellow fever could easily make a comeback in North America, where *A. aegypti* is still present. If these mosquitoes were exposed to infected individuals, new outbreaks would be possible.

Like yellow fever, many of the circulatory and lymphatic diseases discussed in this chapter are emerging or re-emerging worldwide. Despite medical advances, diseases like malaria, Ebola, and others could become endemic in the US given the right circumstances.



Figure 9.2.1: Yellow fever is a viral hemorrhagic disease that can cause liver damage, resulting in jaundice (left) as well as serious and sometimes fatal complications. The virus that causes yellow fever is transmitted through the bite of a biological vector, the *Aedes aegypti* mosquito (right). (credit left: modification of work by Centers for Disease Control and Prevention; credit right: modification of work by James Gathany, Centers for Disease Control and Prevention)

9.2.1: Anatomy of the Circulatory and Lymphatic Systems

9.2.2: Bacterial Infections of the Circulatory and Lymphatic Systems

9.2.3: Viral Infections of the Circulatory and Lymphatic Systems

9.2.4: Parasitic Infections of the Circulatory and Lymphatic Systems

9.2.E: Circulatory and Lymphatic System Infections (Exercises)

Footnotes

1. 1 Centers for Disease Control and Prevention. “The History of Yellow Fever.” http://www.cdc.gov/travel-training/local/HistoryEpidemiologyandVaccination/page27568.html
2. 2 C.L. Gardner, K.D. Ryman. “Yellow Fever: A Reemerging Threat.” *Clinical Laboratory Medicine* 30 no. 1 (2010):237–260.

Thumbnail: This "classic" bull's-eye rash is also called erythema migrans. A rash caused by Lyme does not always look like this and approximately 25% of those infected with Lyme disease may have no rash. (Public Domain; CDC/ James Gathany).

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9.2.1: Anatomy of the Circulatory and Lymphatic Systems

Learning Objectives

- Describe the major anatomical features of the circulatory and lymphatic systems
- Explain why the circulatory and lymphatic systems lack normal microbiota
- Explain how microorganisms overcome defenses of the circulatory and lymphatic systems to cause infection
- Describe general signs and symptoms of disease associated with infections of the circulatory and lymphatic systems

Clinical Focus: Part 1

Barbara is a 43-year-old patient who has been diagnosed with metastatic inflammatory breast cancer. To facilitate her ongoing chemotherapy, her physician implanted a port attached to a central venous catheter. At a recent checkup, she reported feeling restless and complained that the site of the catheter had become uncomfortable. After removing the dressing, the physician observed that the surgical site appeared red and was warm to the touch, suggesting a localized infection. Barbara was also running a fever of 38.2 °C (100.8 °F). Her physician treated the affected area with a topical antiseptic and applied a fresh dressing. She also prescribed a course of the antibiotic oxacillin.

Exercise 9.2.1.1

1. Based on this information, what factors likely contributed to Barbara's condition?
2. What is the most likely source of the microbes involved?

The circulatory and lymphatic systems are networks of vessels and a pump that transport blood and lymph, respectively, throughout the body. When these systems are infected with a microorganism, the network of vessels can facilitate the rapid dissemination of the microorganism to other regions of the body, sometimes with serious results. In this section, we will examine some of the key anatomical features of the circulatory and lymphatic systems, as well as general signs and symptoms of infection.

The Circulatory System

The circulatory (or cardiovascular) system is a closed network of organs and vessels that moves blood around the body (Figure 9.2.1.1). The primary purposes of the circulatory system are to deliver nutrients, immune factors, and oxygen to tissues and to carry away waste products for elimination. The heart is a four-chambered pump that propels the blood throughout the body. Deoxygenated blood enters the right atrium through the superior vena cava and the inferior vena cava after returning from the body. The blood next passes through the tricuspid valve to enter the right ventricle. When the heart contracts, the blood from the right ventricle is pumped through the pulmonary arteries to the lungs. There, the blood is oxygenated at the alveoli and returns to the heart through the pulmonary veins. The oxygenated blood is received at the left atrium and proceeds through the mitral valve to the left ventricle. When the heart contracts, the oxygenated blood is pumped throughout the body via a series of thick-walled vessels called arteries. The first and largest artery is called the aorta. The arteries sequentially branch and decrease in size (and are called arterioles) until they end in a network of smaller vessels called capillaries. The capillary beds are located in the interstitial spaces within tissues and release nutrients, immune factors, and oxygen to those tissues. The capillaries connect to a series of vessels called venules, which increase in size to form the veins. The veins join together into larger vessels as they transfer blood back to the heart. The largest veins, the superior and inferior vena cava, return the blood to the right atrium.

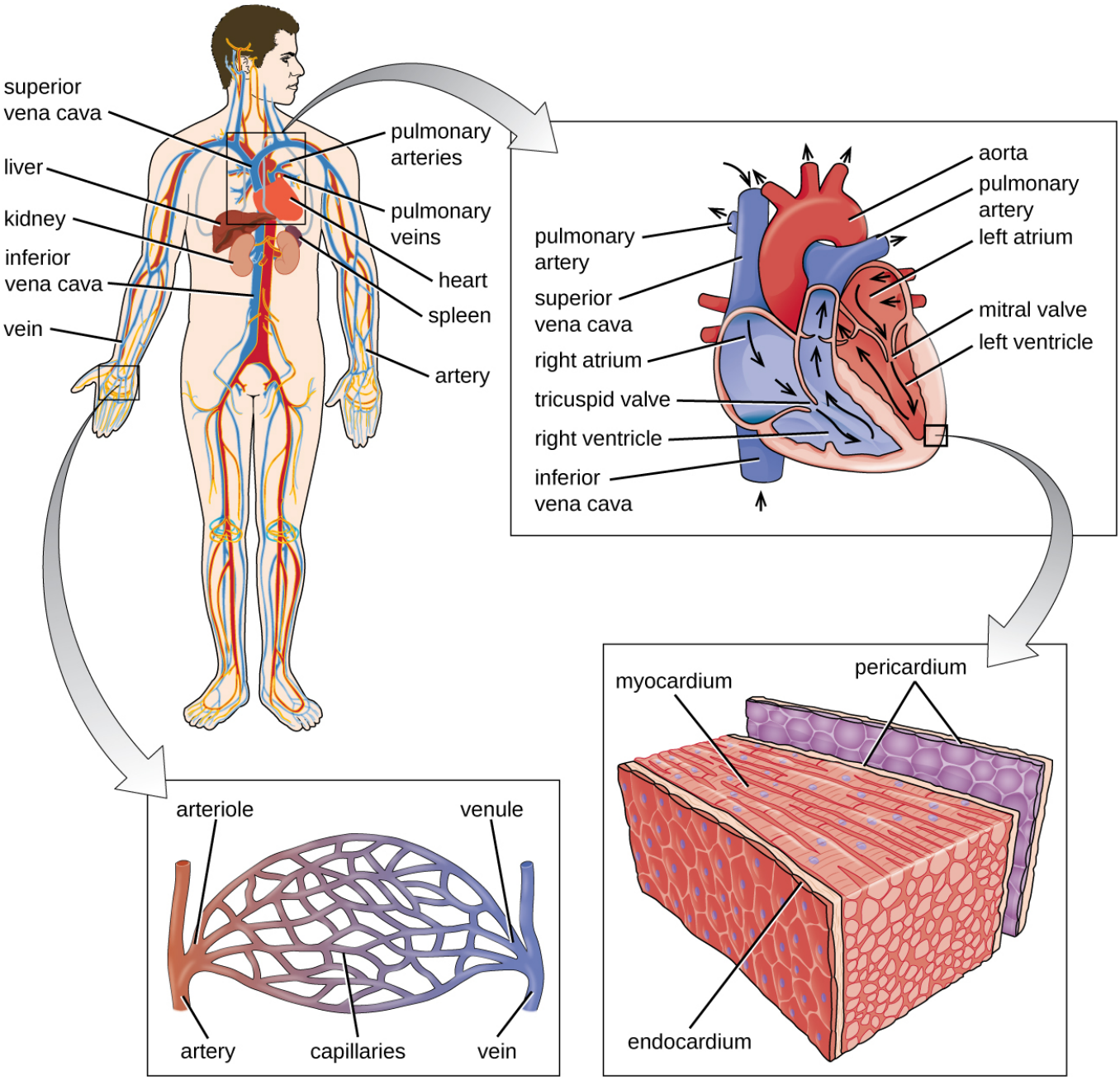


Figure 9.2.1.1: The major components of the human circulatory system include the heart, arteries, veins, and capillaries. This network delivers blood to the body's organs and tissues. (credit top left: modification of work by Mariana Ruiz Villareal; credit bottom right: modification of work by Bruce Blaus)

Other organs play important roles in the circulatory system as well. The kidneys filter the blood, removing waste products and eliminating them in the urine. The liver also filters the blood and removes damaged or defective red blood cells. The spleen filters and stores blood, removes damaged red blood cells, and is a reservoir for immune factors. All of these filtering structures serve as sites for entrapment of microorganisms and help maintain an environment free of microorganisms in the blood.

The Lymphatic System

The lymphatic system is also a network of vessels that run throughout the body (Figure 9.2.1.2). However, these vessels do not form a full circulating system and are not pressurized by the heart. Rather, the lymphatic system is an open system with the fluid moving in one direction from the extremities toward two drainage points into veins just above the heart. Lymphatic fluids move more slowly than blood because they are not pressurized. Small lymph capillaries interact with blood capillaries in the interstitial spaces

in tissues. Fluids from the tissues enter the lymph capillaries and are drained away (Figure 9.2.1.3). These fluids, termed lymph, also contain large numbers of white blood cells.

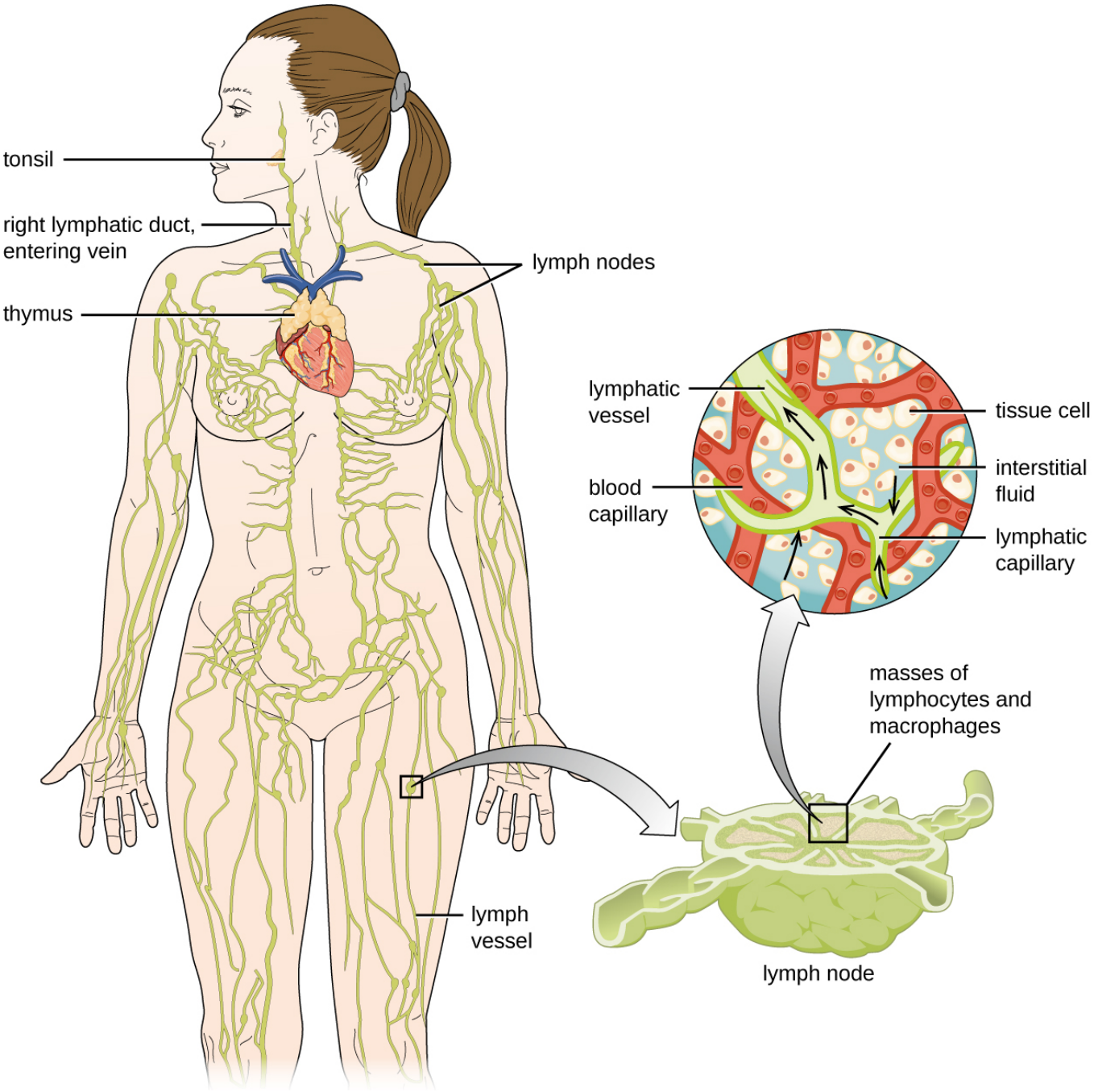


Figure 9.2.1.2: The essential components of the human lymphatic system drain fluid away from tissues.

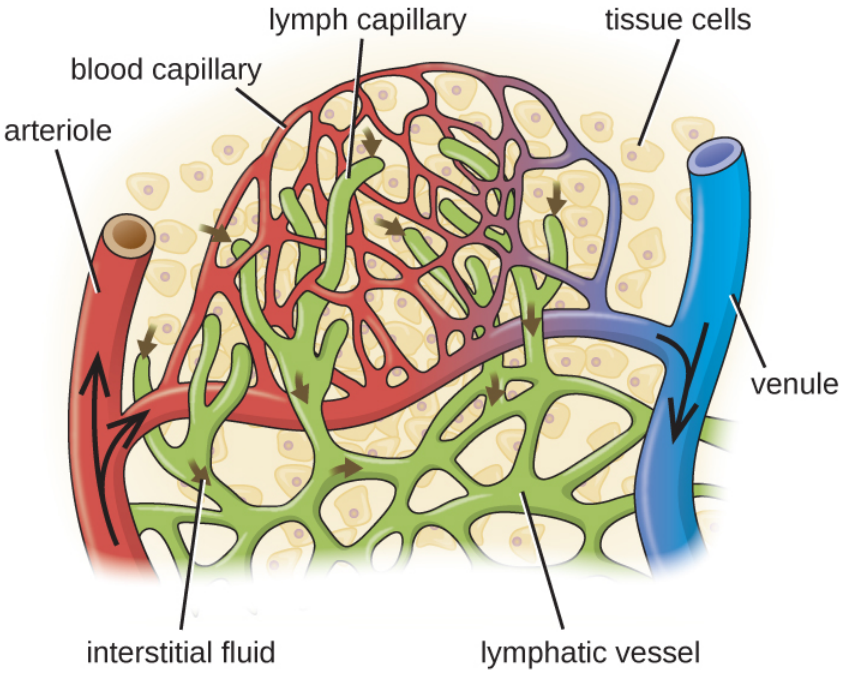


Figure 9.2.1.3: Blood enters the capillaries from an arteriole (red) and leaves through venules (blue). Interstitial fluids may drain into the lymph capillaries (green) and proceed to lymph nodes. (credit: modification of work by National Cancer Institute, National Institutes of Health)

The lymphatic system contains two types of lymphoid tissues. The primary lymphoid tissue includes bone marrow and the thymus. Bone marrow contains the hematopoietic stem cells (HSC) that differentiate and mature into the various types of blood cells and lymphocytes (see Figure 17.3.1). The secondary lymphoid tissues include the spleen, lymph nodes, and several areas of diffuse lymphoid tissues underlying epithelial membranes. The spleen, an encapsulated structure, filters blood and captures pathogens and antigens that pass into it (Figure 9.2.1.4). The spleen contains specialized macrophages and dendritic cells that are crucial for antigen presentation, a mechanism critical for activation of T lymphocytes and B lymphocytes (see Major Histocompatibility Complexes and Antigen-Presenting Cells). Lymph nodes are bean-shaped organs situated throughout the body. These structures contain areas called germinal centers that are rich in B and T lymphocytes. The lymph nodes also contain macrophages and dendritic cells for antigen presentation. Lymph from nearby tissues enters the lymph node through afferent lymphatic vessels and encounters these lymphocytes as it passes through; the lymph exits the lymph node through the efferent lymphatic vessels (Figure 9.2.1.4).

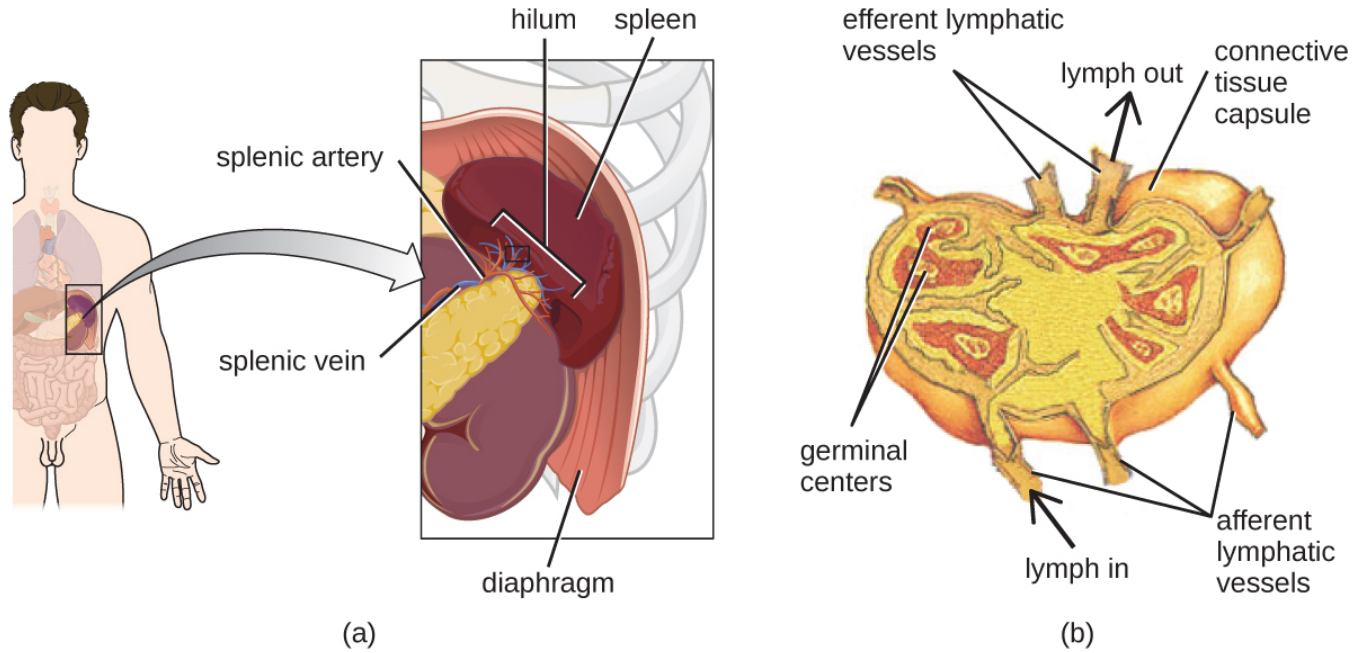


Figure 9.2.1.4: (a) The spleen is a lymphatic organ located in the upper left quadrant of the abdomen near the stomach and left kidney. It contains numerous phagocytes and lymphocytes that combat and prevent circulatory infections by killing and removing pathogens from the blood. (b) Lymph nodes are masses of lymphatic tissue located along the larger lymph vessels. They contain numerous lymphocytes that kill and remove pathogens from lymphatic fluid that drains from surrounding tissues.

Link to Learning

The lymphatic system filters fluids that have accumulated in tissues before they are returned to the blood. A brief overview of this process is provided at this website.

Exercise 9.2.1.2

What is the main function of the lymphatic system?

Infections of the Circulatory System

Under normal circumstances, the circulatory system and the blood should be sterile; the circulatory system has no normal microbiota. Because the system is closed, there are no easy portals of entry into the circulatory system for microbes. Those that are able to breach the body's physical barriers and enter the bloodstream encounter a host of circulating immune defenses, such as antibodies, complement proteins, phagocytes, and other immune cells. Microbes often gain access to the circulatory system through a break in the skin (e.g., wounds, needles, intravenous catheters, insect bites) or spread to the circulatory system from infections in other body sites. For example, microorganisms causing pneumonia or renal infection may enter the local circulation of the lung or kidney and spread from there throughout the circulatory network.

If microbes in the bloodstream are not quickly eliminated, they can spread rapidly throughout the body, leading to serious, even life-threatening infections. Various terms are used to describe conditions involving microbes in the circulatory system. The term bacteremia refers to bacteria in the blood. If bacteria are reproducing in the blood as they spread, this condition is called septicemia. The presence of viruses in the blood is called viremia. Microbial toxins can also be spread through the circulatory system, causing a condition termed toxemia.

Microbes and microbial toxins in the blood can trigger an inflammatory response so severe that the inflammation damages host tissues and organs more than the infection itself. This counterproductive immune response is called systemic inflammatory response syndrome (SIRS), and it can lead to the life-threatening condition known as sepsis. Sepsis is characterized by the production of excess cytokines that leads to classic signs of inflammation such as fever, vasodilation, and edema (see Inflammation and Fever). In a patient with sepsis, the inflammatory response becomes dysregulated and disproportionate to the threat of

infection. Critical organs such as the heart, lungs, liver, and kidneys become dysfunctional, resulting in increased heart and respiratory rates, and disorientation. If not treated promptly and effectively, patients with sepsis can go into shock and die.

Certain infections can cause inflammation in the heart and blood vessels. Inflammation of the endocardium, the inner lining of the heart, is called endocarditis and can result in damage to the heart valves severe enough to require surgical replacement. Inflammation of the pericardium, the sac surrounding the heart, is called pericarditis. The term myocarditis refers to the inflammation of the heart's muscle tissue. Pericarditis and myocarditis can cause fluid to accumulate around the heart, resulting in congestive heart failure. Inflammation of blood vessels is called vasculitis. Although somewhat rare, vasculitis can cause blood vessels to become damaged and rupture; as blood is released, small red or purple spots called petechiae appear on the skin. If the damage of tissues or blood vessels is severe, it can result in reduced blood flow to the surrounding tissues. This condition is called ischemia, and it can be very serious. In severe cases, the affected tissues can die and become necrotic; these situations may require surgical debridement or amputation.

? Exercise 9.2.1.3

1. Why does the circulatory system have no normal microbiota?
2. Explain why the presence of microbes in the circulatory system can lead to serious consequences.

Infections of the Lymphatic System

Like the circulatory system, the lymphatic system does not have a normal microbiota, and the large numbers of immune cells typically eliminate transient microbes before they can establish an infection. Only microbes with an array of virulence factors are able to overcome these defenses and establish infection in the lymphatic system. However, when a localized infection begins to spread, the lymphatic system is often the first place the invading microbes can be detected.

Infections in the lymphatic system also trigger an inflammatory response. Inflammation of lymphatic vessels, called lymphangitis, can produce visible red streaks under the skin. Inflammation in the lymph nodes can cause them to swell. A swollen lymph node is referred to as a bubo, and the condition is referred to as lymphadenitis.

Key Concepts and Summary

- The **circulatory system** moves blood throughout the body and has no normal microbiota.
- The **lymphatic system** moves fluids from the interstitial spaces of tissues toward the circulatory system and filters the lymph. It also has no normal microbiota.
- The circulatory and lymphatic systems are home to many components of the host immune defenses.
- Infections of the circulatory system may occur after a break in the skin barrier or they may enter the bloodstream at the site of a localized infection. Pathogens or toxins in the bloodstream can spread rapidly throughout the body and can provoke systemic and sometimes fatal inflammatory responses such as **SIRS**, **sepsis**, and **endocarditis**.
- Infections of the lymphatic system can cause **lymphangitis** and **lymphadenitis**.

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9.2.2: Bacterial Infections of the Circulatory and Lymphatic Systems

Learning Objectives

- Identify and compare bacteria that most commonly cause infections of the circulatory and lymphatic systems
- Compare the major characteristics of specific bacterial diseases affecting the circulatory and lymphatic systems

Bacteria can enter the circulatory and lymphatic systems through acute infections or breaches of the skin barrier or mucosa. Breaches may occur through fairly common occurrences, such as insect bites or small wounds. Even the act of tooth brushing, which can cause small ruptures in the gums, may introduce bacteria into the circulatory system. In most cases, the bacteremia that results from such common exposures is transient and remains below the threshold of detection. In severe cases, bacteremia can lead to septicemia with dangerous complications such as toxemia, sepsis, and septic shock. In these situations, it is often the immune response to the infection that results in the clinical signs and symptoms rather than the microbes themselves.

Bacterial Sepsis, Septic and Toxic Shock

At low concentrations, pro-inflammatory cytokines such as interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α) play important roles in the host's immune defenses. When they circulate systemically in larger amounts, however, the resulting immune response can be life threatening. IL-1 induces vasodilation (widening of blood vessels) and reduces the tight junctions between vascular endothelial cells, leading to widespread edema. As fluids move out of circulation into tissues, blood pressure begins to drop. If left unchecked, the blood pressure can fall below the level necessary to maintain proper kidney and respiratory functions, a condition known as septic shock. In addition, the excessive release of cytokines during the inflammatory response can lead to the formation of blood clots. The loss of blood pressure and occurrence of blood clots can result in multiple organ failure and death.

Bacteria are the most common pathogens associated with the development of sepsis, and septic shock.[1] The most common infection associated with sepsis is bacterial pneumonia (see Bacterial Infections of the Respiratory Tract), accounting for about half of all cases, followed by intra-abdominal infections (Bacterial Infections of the Gastrointestinal Tract) and urinary tract infections (Bacterial Infections of the Urinary System).[2] Infections associated with superficial wounds, animal bites, and indwelling catheters may also lead to sepsis and septic shock.

These initially minor, localized infections can be caused by a wide range of different bacteria, including *Staphylococcus*, *Streptococcus*, *Pseudomonas*, *Pasteurella*, *Acinetobacter*, and members of the Enterobacteriaceae. However, if left untreated, infections by these gram-positive and gram-negative pathogens can potentially progress to sepsis, shock, and death.

Toxic Shock Syndrome and Streptococcal Toxic Shock-Like Syndrome

Toxemia associated with infections caused by *Staphylococcus aureus* can cause staphylococcal toxic shock syndrome (TSS). Some strains of *S. aureus* produce a superantigen called toxic shock syndrome toxin-1 (TSST-1). TSS may occur as a complication of other localized or systemic infections such as pneumonia, osteomyelitis, sinusitis, and skin wounds (surgical, traumatic, or burns). Those at highest risk for staphylococcal TSS are women with preexisting *S. aureus* colonization of the vagina who leave tampons, contraceptive sponges, diaphragms, or other devices in the vagina for longer than the recommended time.

Staphylococcal TSS is characterized by sudden onset of vomiting, diarrhea, myalgia, body temperature higher than 38.9 °C (102.0 °F), and rapid-onset hypotension with a systolic blood pressure less than 90 mm Hg for adults; a diffuse erythematous rash that leads to peeling and shedding skin 1 to 2 weeks after onset; and additional involvement of three or more organ systems.[3] The mortality rate associated with staphylococcal TSS is less than 3% of cases.

Diagnosis of staphylococcal TSS is based on clinical signs, symptoms, serologic tests to confirm bacterial species, and the detection of toxin production from staphylococcal isolates. Cultures of skin and blood are often negative; less than 5% are positive in cases of staphylococcal TSS. Treatment for staphylococcal TSS includes decontamination, debridement, vasopressors to elevate blood pressure, and antibiotic therapy with clindamycin plus vancomycin or daptomycin pending susceptibility results.

A syndrome with signs and symptoms similar to staphylococcal TSS can be caused by *Streptococcus pyogenes*. This condition, called streptococcal toxic shock-like syndrome (STSS), is characterized by more severe pathophysiology than staphylococcal TSS,[4] with about 50% of patients developing *S. pyogenes* bacteremia and necrotizing fasciitis. In contrast to staphylococcal TSS, STSS is

more likely to cause acute respiratory distress syndrome (ARDS), a rapidly progressive disease characterized by fluid accumulation in the lungs that inhibits breathing and causes hypoxemia (low oxygen levels in the blood). STSS is associated with a higher mortality rate (20%–60%), even with aggressive therapy. STSS usually develops in patients with a streptococcal soft-tissue infection such as bacterial cellulitis, necrotizing fasciitis, pyomyositis (pus formation in muscle caused by infection), a recent influenza A infection, or chickenpox.

Exercise 9.2.2.1

How can large amounts of pro-inflammatory cytokines lead to septic shock?

Clinical Focus: Part 2

Despite oxacillin therapy, Barbara's condition continued to worsen over the next several days. Her fever increased to 40.1 °C (104.2 °F) and she began to experience chills, rapid breathing, and confusion. Her doctor suspected bacteremia by a drug-resistant bacterium and admitted Barbara to the hospital. Cultures of the surgical site and blood revealed *Staphylococcus aureus*. Antibiotic susceptibility testing confirmed that the isolate was methicillin-resistant *S. aureus* (MRSA). In response, Barbara's doctor changed her antibiotic therapy to vancomycin and arranged to have the port and venous catheter removed.

Exercise 9.2.2.2

1. Why did Barbara's infection not respond to oxacillin therapy?
2. Why did the physician have the port and catheter removed?
3. Based on the signs and symptoms described, what are some possible diagnoses for Barbara's condition?

Puerperal Sepsis

A type of sepsis called puerperal sepsis, also known as puerperal infection, puerperal fever, or childbed fever, is a nosocomial infection associated with the period of puerperium—the time following childbirth during which the mother's reproductive system returns to a nonpregnant state. Such infections may originate in the genital tract, breast, urinary tract, or a surgical wound. Initially the infection may be limited to the uterus or other local site of infection, but it can quickly spread, resulting in peritonitis, septicemia, and death. Before the 19th century work of Ignaz Semmelweis and the widespread acceptance of germ theory (see Modern Foundations of Cell Theory), puerperal sepsis was a major cause of mortality among new mothers in the first few days following childbirth.

Puerperal sepsis is often associated with *Streptococcus pyogenes*, but numerous other bacteria can also be responsible. Examples include gram-positive bacterial (e.g. *Streptococcus* spp., *Staphylococcus* spp., and *Enterococcus* spp.), gram-negative bacteria (e.g. *Chlamydia* spp., *Escherichia coli*, *Klebsiella* spp., and *Proteus* spp.), as well as anaerobes such as *Peptostreptococcus* spp., *Bacteroides* spp., and *Clostridium* spp. In cases caused by *S. pyogenes*, the bacteria attach to host tissues using M protein and produce a carbohydrate capsule to avoid phagocytosis. *S. pyogenes* also produces a variety of exotoxins, like streptococcal pyrogenic exotoxins A and B, that are associated with virulence and may function as superantigens.

Diagnosis of puerperal fever is based on the timing and extent of fever and isolation, and identification of the etiologic agent in blood, wound, or urine specimens. Because there are numerous possible causes, antimicrobial susceptibility testing must be used to determine the best antibiotic for treatment. Nosocomial incidence of puerperal fever can be greatly reduced through the use of antiseptics during delivery and strict adherence to handwashing protocols by doctors, midwives, and nurses.

Infectious Arthritis

Also called septic arthritis, infectious arthritis can be either an acute or a chronic condition. Infectious arthritis is characterized by inflammation of joint tissues and is most often caused by bacterial pathogens. Most cases of acute infectious arthritis are secondary to bacteremia, with a rapid onset of moderate to severe joint pain and swelling that limits the motion of the affected joint. In adults and young children, the infective pathogen is most often introduced directly through injury, such as a wound or a surgical site, and brought to the joint through the circulatory system. Acute infections may also occur after joint replacement surgery. Acute

infectious arthritis often occurs in patients with an immune system impaired by other viral and bacterial infections. *S. aureus* is the most common cause of acute septic arthritis in the general population of adults and young children. *Neisseria gonorrhoeae* is an important cause of acute infectious arthritis in sexually active individuals.

Chronic infectious arthritis is responsible for 5% of all infectious arthritis cases and is more likely to occur in patients with other illnesses or conditions. Patients at risk include those who have an HIV infection, a bacterial or fungal infection, prosthetic joints, rheumatoid arthritis (RA), or who are undergoing immunosuppressive chemotherapy. Onset is often in a single joint; there may be little or no pain, aching pain that may be mild, gradual swelling, mild warmth, and minimal or no redness of the joint area.

Diagnosis of infectious arthritis requires the aspiration of a small quantity of synovial fluid from the afflicted joint. Direct microscopic evaluation, culture, antimicrobial susceptibility testing, and polymerase chain reaction (PCR) analyses of the synovial fluid are used to identify the potential pathogen. Typical treatment includes administration of appropriate antimicrobial drugs based on antimicrobial susceptibility testing. For nondrug-resistant bacterial strains, β-lactams such as oxacillin and cefazolin are often prescribed for staphylococcal infections. Third-generation cephalosporins (e.g., ceftriaxone) are used for increasingly prevalent β-lactam-resistant *Neisseria* infections. Infections by *Mycobacterium* spp. or fungi are treated with appropriate long-term antimicrobial therapy. Even with treatment, the prognosis is often poor for those infected. About 40% of patients with nongonnococcal infectious arthritis will suffer permanent joint damage and mortality rates range from 5% to 20%.[5] Mortality rates are higher among the elderly.[6]

Osteomyelitis

Osteomyelitis is an inflammation of bone tissues most commonly caused by infection. These infections can either be acute or chronic and can involve a variety of different bacteria. The most common causative agent of osteomyelitis is *S. aureus*. However, *M. tuberculosis*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *S. agalactiae*, species in the Enterobacteriaceae, and other microorganisms can also cause osteomyelitis, depending on which bones are involved. In adults, bacteria usually gain direct access to the bone tissues through trauma or a surgical procedure involving prosthetic joints. In children, the bacteria are often introduced from the bloodstream, possibly spreading from focal infections. The long bones, such as the femur, are more commonly affected in children because of the more extensive vascularization of bones in the young.[7]

The signs and symptoms of osteomyelitis include fever, localized pain, swelling due to edema, and ulcers in soft tissues near the site of infection. The resulting inflammation can lead to tissue damage and bone loss. In addition, the infection may spread to joints, resulting in infectious arthritis, or disseminate into the blood, resulting in sepsis and thrombosis(formation of blood clots). Like septic arthritis, osteomyelitis is usually diagnosed using a combination of radiography, imaging, and identification of bacteria from blood cultures, or from bone cultures if blood cultures are negative. Parenteral antibiotic therapy is typically used to treat osteomyelitis. Because of the number of different possible etiologic agents, however, a variety of drugs might be used. Broad-spectrum antibacterial drugs such as nafcillin, oxacillin, or cephalosporin are typically prescribed for acute osteomyelitis, and ampicillin and piperacillin/tazobactam for chronic osteomyelitis. In cases of antibiotic resistance, vancomycin treatment is sometimes required to control the infection. In serious cases, surgery to remove the site of infection may be required. Other forms of treatment include hyperbaric oxygen therapy (see Using Physical Methods to Control Microorganisms) and implantation of antibiotic beads or pumps.

? Exercise 9.2.2.3

What bacterium the most common cause of both septic arthritis and osteomyelitis?

Rheumatic Fever

Infections with *S. pyogenes* have a variety of manifestations and complications generally called sequelae. As mentioned, the bacterium can cause suppurative infections like puerperal fever. However, this microbe can also cause nonsuppurative sequelae in the form of acute rheumatic fever (ARF), which can lead to rheumatic heart disease, thus impacting the circulatory system. Rheumatic fever occurs primarily in children a minimum of 2–3 weeks after an episode of untreated or inadequately treated pharyngitis (see Bacterial Infections of the Respiratory Tract). At one time, rheumatic fever was a major killer of children in the US; today, however, it is rare in the US because of early diagnosis and treatment of streptococcal pharyngitis with antibiotics. In

parts of the world where diagnosis and treatment are not readily available, acute rheumatic fever and rheumatic heart disease are still major causes of mortality in children.[8]

Rheumatic fever is characterized by a variety of diagnostic signs and symptoms caused by nonsuppurative, immune-mediated damage resulting from a cross-reaction between patient antibodies to bacterial surface proteins and similar proteins found on cardiac, neuronal, and synovial tissues. Damage to the nervous tissue or joints, which leads to joint pain and swelling, is reversible. However, damage to heart valves can be irreversible and is worsened by repeated episodes of acute rheumatic fever, particularly during the first 3–5 years after the first rheumatic fever attack. The inflammation of the heart valves caused by cross-reacting antibodies leads to scarring and stiffness of the valve leaflets. This, in turn, produces a characteristic heart murmur. Patients who have previously developed rheumatic fever and who subsequently develop recurrent pharyngitis due to *S. pyogenes* are at high risk for a recurrent attacks of rheumatic fever.

The American Heart Association recommends[9] a treatment regimen consisting of benzathine benzylpenicillin every 3 or 4 weeks, depending on the patient's risk for reinfection. Additional prophylactic antibiotic treatment may be recommended depending on the age of the patient and risk for reinfection.

Bacterial Endocarditis and Pericarditis

The endocardium is a tissue layer that lines the muscles and valves of the heart. This tissue can become infected by a variety of bacteria, including gram-positive cocci such as *Staphylococcus aureus*, viridans streptococci, and *Enterococcus faecalis*, and the gram-negative so-called HACEK bacilli: *Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*. The resulting inflammation is called endocarditis, which can be described as either acute or subacute. Causative agents typically enter the bloodstream during accidental or intentional breaches in the normal barrier defenses (e.g., dental procedures, body piercings, catheterization, wounds). Individuals with preexisting heart damage, prosthetic valves and other cardiac devices, and those with a history of rheumatic fever have a higher risk for endocarditis. This disease can rapidly destroy the heart valves and, if untreated, lead to death in just a few days.

In subacute bacterial endocarditis, heart valve damage occurs slowly over a period of months. During this time, blood clots form in the heart, and these protect the bacteria from phagocytes. These patches of tissue-associated bacteria are called vegetations. The resulting damage to the heart, in part resulting from the immune response causing fibrosis of heart valves, can necessitate heart valve replacement (Figure 9.2.2.1). Outward signs of subacute endocarditis may include a fever.

Diagnosis of infective endocarditis is determined using the combination of blood cultures, echocardiogram, and clinical symptoms. In both acute and subacute endocarditis, treatment typically involves relatively high doses of intravenous antibiotics as determined by antimicrobial susceptibility testing. Acute endocarditis is often treated with a combination of ampicillin, nafcillin, and gentamicin for synergistic coverage of *Staphylococcus* spp. and *Streptococcus* spp. Prosthetic-valve endocarditis is often treated with a combination of vancomycin, rifampin, and gentamicin. Rifampin is necessary to treat individuals with infection of prosthetic valves or other foreign bodies because rifampin can penetrate the biofilm of most of the pathogens that infect these devices.

Staphylcoccus spp. and *Streptococcus* spp. can also infect and cause inflammation in the tissues surrounding the heart, a condition called acute pericarditis. Pericarditis is marked by chest pain, difficulty breathing, and a dry cough. In most cases, pericarditis is self-limiting and clinical intervention is not necessary. Diagnosis is made with the aid of a chest radiograph, electrocardiogram, echocardiogram, aspirate of pericardial fluid, or biopsy of pericardium. Antibacterial medications may be prescribed for infections associated with pericarditis; however, pericarditis can also be caused other pathogens, including viruses (e.g., echovirus, influenza virus), fungi (e.g., *Histoplasma* spp., *Coccidioides* spp.), and eukaryotic parasites (e.g., *Toxoplasma* spp.).

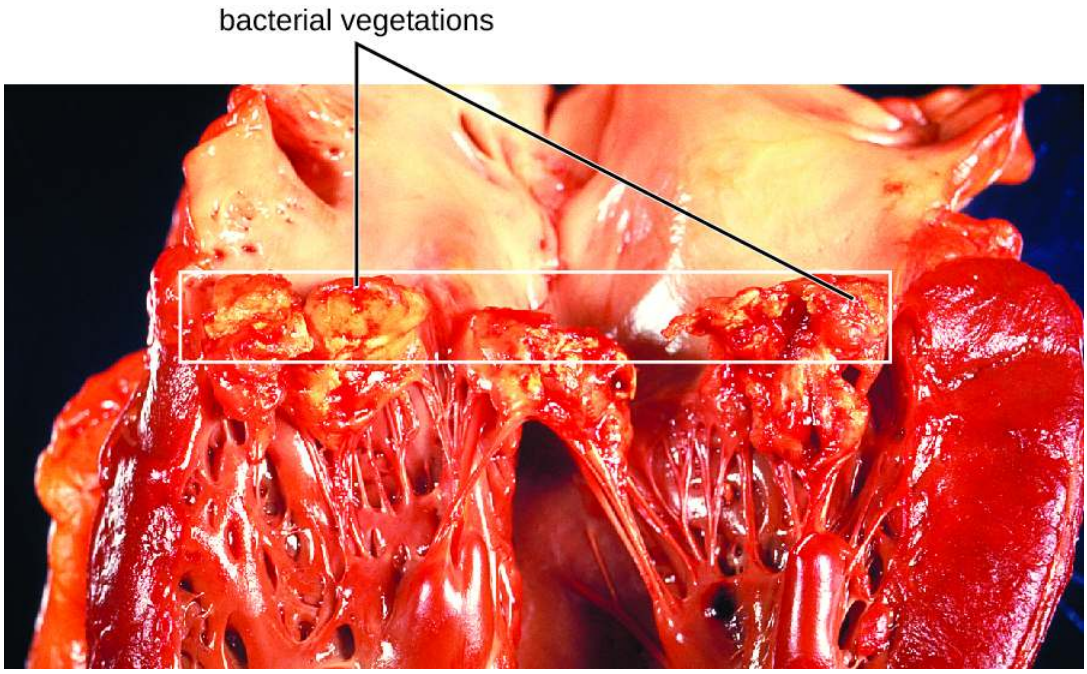


Figure 9.2.2.1: The heart of an individual who had subacute bacterial endocarditis of the mitral valve. Bacterial vegetations are visible on the valve tissues. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 9.2.2.4

Compare acute and subacute bacterial endocarditis.

Gas Gangrene

Traumatic injuries or certain medical conditions, such as diabetes, can cause damage to blood vessels that interrupts blood flow to a region of the body. When blood flow is interrupted, tissues begin to die, creating an anaerobic environment in which anaerobic bacteria can thrive. This condition is called ischemia. Endospores of the anaerobic bacterium *Clostridium perfringens* (along with a number of other *Clostridium* spp. from the gut) can readily germinate in ischemic tissues and colonize the anaerobic tissues.

The resulting infection, called gas gangrene, is characterized by rapidly spreading myonecrosis (death of muscle tissue). The patient experiences a sudden onset of excruciating pain at the infection site and the rapid development of a foul-smelling wound containing gas bubbles and a thin, yellowish discharge tinged with a small amount of blood. As the infection progresses, edema and cutaneous blisters containing bluish-purple fluid form. The infected tissue becomes liquefied and begins sloughing off. The margin between necrotic and healthy tissue often advances several inches per hour even with antibiotic therapy. Septic shock and organ failure frequently accompany gas gangrene; when patients develop sepsis, the mortality rate is greater than 50%.

α-Toxin and theta (θ) toxin are the major virulence factors of *C. perfringens* implicated in gas gangrene. α-Toxin is a lipase responsible for breaking down cell membranes; it also causes the formation of thrombi (blood clots) in blood vessels, contributing to the spread of ischemia. θ-Toxin forms pores in the patient's cell membranes, causing cell lysis. The gas associated with gas gangrene is produced by *Clostridium*'s fermentation of butyric acid, which produces hydrogen and carbon dioxide that are released as the bacteria multiply, forming pockets of gas in tissues (Figure 9.2.2.2).

Gas gangrene is initially diagnosed based on the presence of the clinical signs and symptoms described earlier in this section. Diagnosis can be confirmed through Gram stain and anaerobic cultivation of wound exudate (drainage) and tissue samples on blood agar. Treatment typically involves surgical debridement of any necrotic tissue; advanced cases may require amputation. Surgeons may also use vacuum-assisted closure (VAC), a surgical technique in which vacuum-assisted drainage is used to remove blood or serous fluid from a wound or surgical site to speed recovery. The most common antibiotic treatments include penicillin G and clindamycin. Some cases are also treated with hyperbaric oxygen therapy because *Clostridium* spp. are incapable of surviving in oxygen-rich environments.



Figure 9.2.2.2: (a) In this image of a patient with gas gangrene, note the bluish-purple discoloration around the bicep and the irregular margin of the discolored tissue indicating the spread of infection. (b) A radiograph of the arm shows a darkening in the tissue, which indicates the presence of gas. (credit a, b: modification of work by Aggelidakis J, Lasithiotakis K, Topalidou A, Koutroumpas J, Kouvidis G, and Katonis P)

Tularemia

Infection with the gram-negative bacterium *Francisella tularensis* causes tularemia (or rabbit fever), a zoonotic infection in humans. *F. tularensis* is a facultative intracellular parasite that primarily causes illness in rabbits, although a wide variety of domesticated animals are also susceptible to infection. Humans can be infected through ingestion of contaminated meat or, more typically, handling of infected animal tissues (e.g., skinning an infected rabbit). Tularemia can also be transmitted by the bites of infected arthropods, including the dog tick (*Dermacentor variabilis*), the lone star tick (*Amblyomma americanum*), the wood tick (*Dermacentor andersoni*), and deer flies (*Chrysops* spp.). Although the disease is not directly communicable between humans, exposure to aerosols of *F. tularensis* can result in life-threatening infections. *F. tularensis* is highly contagious, with an infectious dose of as few as 10 bacterial cells. In addition, pulmonary infections have a 30%–60% fatality rate if untreated.[10] For these reasons, *F. tularensis* is currently classified and must be handled as a biosafety level-3 (BSL-3) organism and as a potential biological warfare agent.

Following introduction through a break in the skin, the bacteria initially move to the lymph nodes, where they are ingested by phagocytes. After escaping from the phagosome, the bacteria grow and multiply intracellularly in the cytoplasm of phagocytes. They can later become disseminated through the blood to other organs such as the liver, lungs, and spleen, where they produce masses of tissue called granulomas (Figure 9.2.2.3). After an incubation period of about 3 days, skin lesions develop at the site of infection. Other signs and symptoms include fever, chills, headache, and swollen and painful lymph nodes.



(a) (b)

Figure 9.2.2.3: (a) A skin lesion appears at the site of infection on the hand of an individual infected with *Francisella tularensis*. (b) A scanning electron micrograph shows the coccobacilli cells (blue) of *F. tularensis*. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by NIAID)

A direct diagnosis of tularemia is challenging because it is so contagious. Once a presumptive diagnosis of tularemia is made, special handling is required to collect and process patients' specimens to prevent the infection of health-care workers. Specimens suspected of containing *F. tularensis* can only be handled by BSL-2 or BSL-3 laboratories registered with the Federal Select Agent Program, and individuals handling the specimen must wear protective equipment and use a class II biological safety cabinet.

Tularemia is relatively rare in the US, and its signs and symptoms are similar to a variety of other infections that may need to be ruled out before a diagnosis can be made. Direct fluorescent-antibody (DFA) microscopic examination using antibodies specific for *F. tularensis* can rapidly confirm the presence of this pathogen. Culturing this microbe is difficult because of its requirement for the amino acid cysteine, which must be supplied as an extra nutrient in culturing media. Serological tests are available to detect an immune response against the bacterial pathogen. In patients with suspected infection, acute- and convalescent-phase serum samples are required to confirm an active infection. PCR-based tests can also be used for clinical identification of direct specimens from body fluids or tissues as well as cultured specimens. In most cases, diagnosis is based on clinical findings and likely incidents of exposure to the bacterium. The antibiotics streptomycin, gentamycin, doxycycline, and ciprofloxacin are effective in treating tularemia.

Brucellosis

Species in the genus *Brucella* are gram-negative facultative intracellular pathogens that appear as coccobacilli. Several species cause zoonotic infections in animals and humans, four of which have significant human pathogenicity: *B. abortus* from cattle and buffalo, *B. canis* from dogs, *B. suis* from swine, and *B. melitensis* from goats, sheep, and camels. Infections by these pathogens are called brucellosis, also known as undulant fever, "Mediterranean fever," or "Malta fever." Vaccination of animals has made brucellosis a rare disease in the US, but it is still common in the Mediterranean, south and central Asia, Central and South America, and the Caribbean. Human infections are primarily associated with the ingestion of meat or unpasteurized dairy products from infected animals. Infection can also occur through inhalation of bacteria in aerosols when handling animal products, or through direct contact with skin wounds. In the US, most cases of brucellosis are found in individuals with extensive exposure to potentially infected animals (e.g., slaughterhouse workers, veterinarians).

Two important virulence factors produced by *Brucella* spp. are urease, which allows ingested bacteria to avoid destruction by stomach acid, and lipopolysaccharide (LPS), which allows the bacteria to survive within phagocytes. After gaining entry to tissues, the bacteria are phagocytized by host neutrophils and macrophages. The bacteria then escape from the phagosome and grow within the cytoplasm of the cell. Bacteria phagocytized by macrophages are disseminated throughout the body. This results in the formation of granulomas within many body sites, including bone, liver, spleen, lung, genitourinary tract, brain, heart, eye, and skin. Acute infections can result in undulant (relapsing) fever, but untreated infections develop into chronic disease that usually manifests as acute febrile illness (fever of 40–41 °C [104–105.8 °F]) with recurring flu-like signs and symptoms.

Brucella is only reliably found in the blood during the acute fever stage; it is difficult to diagnose by cultivation. In addition, *Brucella* is considered a BSL-3 pathogen and is hazardous to handle in the clinical laboratory without protective clothing and at least a class II biological safety cabinet. Agglutination tests are most often used for serodiagnosis. In addition, enzyme-linked immunosorbent assays (ELISAs) are available to determine exposure to the organism. The antibiotics doxycycline or ciprofloxacin are typically prescribed in combination with rifampin; gentamicin, streptomycin, and trimethoprim-sulfamethoxazole (TMP-SMZ) are also effective against *Brucella* infections and can be used if needed.

? Exercise 9.2.2.5

Compare the pathogenesis of tularemia and brucellosis.

Cat-Scratch Disease

The zoonosis cat-scratch disease (CSD) (or cat-scratch fever) is a bacterial infection that can be introduced to the lymph nodes when a human is bitten or scratched by a cat. It is caused by the facultative intracellular gram-negative bacterium *Bartonella henselae*. Cats can become infected from flea feces containing *B. henselae* that they ingest while grooming. Humans become infected when flea feces or cat saliva (from claws or licking) containing *B. henselae* are introduced at the site of a bite or scratch. Once introduced into a wound, *B. henselae* infects red blood cells.

B. henselae invasion of red blood cells is facilitated by adhesins associated with outer membrane proteins and a secretion system that mediates transport of virulence factors into the host cell. Evidence of infection is indicated if a small nodule with pus forms in the location of the scratch 1 to 3 weeks after the initial injury. The bacteria then migrate to the nearest lymph nodes, where they cause swelling and pain. Signs and symptoms may also include fever, chills, and fatigue. Most infections are mild and tend to be self-limiting. However, immunocompromised patients may develop bacillary angiomatosis (BA), characterized by the proliferation of blood vessels, resulting in the formation of tumor-like masses in the skin and internal organs; or bacillary peliosis (BP), characterized by multiple cyst-like, blood-filled cavities in the liver and spleen. Most cases of CSD can be prevented by keeping cats free of fleas and promptly cleaning a cat scratch with soap and warm water.

The diagnosis of CSD is difficult because the bacterium does not grow readily in the laboratory. When necessary, immunofluorescence, serological tests, PCR, and gene sequencing can be performed to identify the bacterial species. Given the limited nature of these infections, antibiotics are not normally prescribed. For immunocompromised patients, rifampin, azithromycin, ciprofloxacin, gentamicin (intramuscularly), or TMP-SMZ are generally the most effective options.

Rat-Bite Fever

The zoonotic infection rat-bite fever can be caused by two different gram-negative bacteria: *Streptobacillus moniliformis*, which is more common in North America, and *Spirillum minor*, which is more common in Asia. Because of modern sanitation efforts, rat bites are rare in the US. However, contact with fomites, food, or water contaminated by rat feces or body fluids can also cause infections. Signs and symptoms of rat-bite fever include fever, vomiting, myalgia (muscle pain), arthralgia (joint pain), and a maculopapular rash on the hands and feet. An ulcer may also form at the site of a bite, along with some swelling of nearby lymph nodes. In most cases, the infection is self-limiting. Little is known about the virulence factors that contribute to these signs and symptoms of disease.

Cell culture, MALDI-TOF mass spectrometry, PCR, or ELISA can be used in the identification of *Streptobacillus moniliformis*. The diagnosis *Spirillum minor* may be confirmed by direct microscopic observation of the pathogens in blood using Giemsa or Wright stains, or darkfield microscopy. Serological tests can be used to detect a host immune response to the pathogens after about 10 days. The most commonly used antibiotics to treat these infections are penicillin or doxycycline.

Plague

The gram-negative bacillus *Yersinia pestis* causes the zoonotic infection plague. This bacterium causes acute febrile disease in animals, usually rodents or other small mammals, and humans. The disease is associated with a high mortality rate if left untreated. Historically, *Y. pestis* has been responsible for several devastating pandemics, resulting in millions of deaths (see Micro Connections: The History of the Plague). There are three forms of plague: bubonic plague (the most common form, accounting for

about 80% of cases), pneumonic plague, and septicemic plague. These forms are differentiated by the mode of transmission and the initial site of infection. Figure 9.2.2.4 illustrates these various modes of transmission and infection between animals and humans.

In bubonic plague, *Y. pestis* is transferred by the bite of infected fleas. Since most flea bites occur on the legs and ankles, *Y. pestis* is often introduced into the tissues and blood circulation in the lower extremities. After a 2- to 6-day incubation period, patients experience an abrupt onset fever (39.5–41 °C [103.1–105.8 °F]), headache, hypotension, and chills. The pathogen localizes in lymph nodes, where it causes inflammation, swelling, and hemorrhaging that results in purple buboes (Figure 9.2.2.5). Buboes often form in lymph nodes of the groin first because these are the nodes associated with the lower limbs; eventually, through circulation in the blood and lymph, lymph nodes throughout the body become infected and form buboes. The average mortality rate for bubonic plague is about 55% if untreated and about 10% with antibiotic treatment.

Septicemic plague occurs when *Y. pestis* is directly introduced into the bloodstream through a cut or wound and circulates through the body. The incubation period for septicemic plague is 1 to 3 days, after which patients develop fever, chills, extreme weakness, abdominal pain, and shock. Disseminated intravascular coagulation (DIC) can also occur, resulting in the formation of thrombi that obstruct blood vessels and promote ischemia and necrosis in surrounding tissues (Figure 9.2.2.5). Necrosis occurs most commonly in extremities such as fingers and toes, which become blackened. Septicemic plague can quickly lead to death, with a mortality rate near 100% when it is untreated. Even with antibiotic treatment, the mortality rate is about 50%.

Pneumonic plague occurs when *Y. pestis* causes an infection of the lungs. This can occur through inhalation of aerosolized droplets from an infected individual or when the infection spreads to the lungs from elsewhere in the body in patients with bubonic or septicemic plague. After an incubation period of 1 to 3 days, signs and symptoms include fever, headache, weakness, and a rapidly developing pneumonia with shortness of breath, chest pain, and cough producing bloody or watery mucus. The pneumonia may result in rapid respiratory failure and shock. Pneumonic plague is the only form of plague that can be spread from person to person by infectious aerosol droplet. If untreated, the mortality rate is near 100%; with antibiotic treatment, the mortality rate is about 50%.

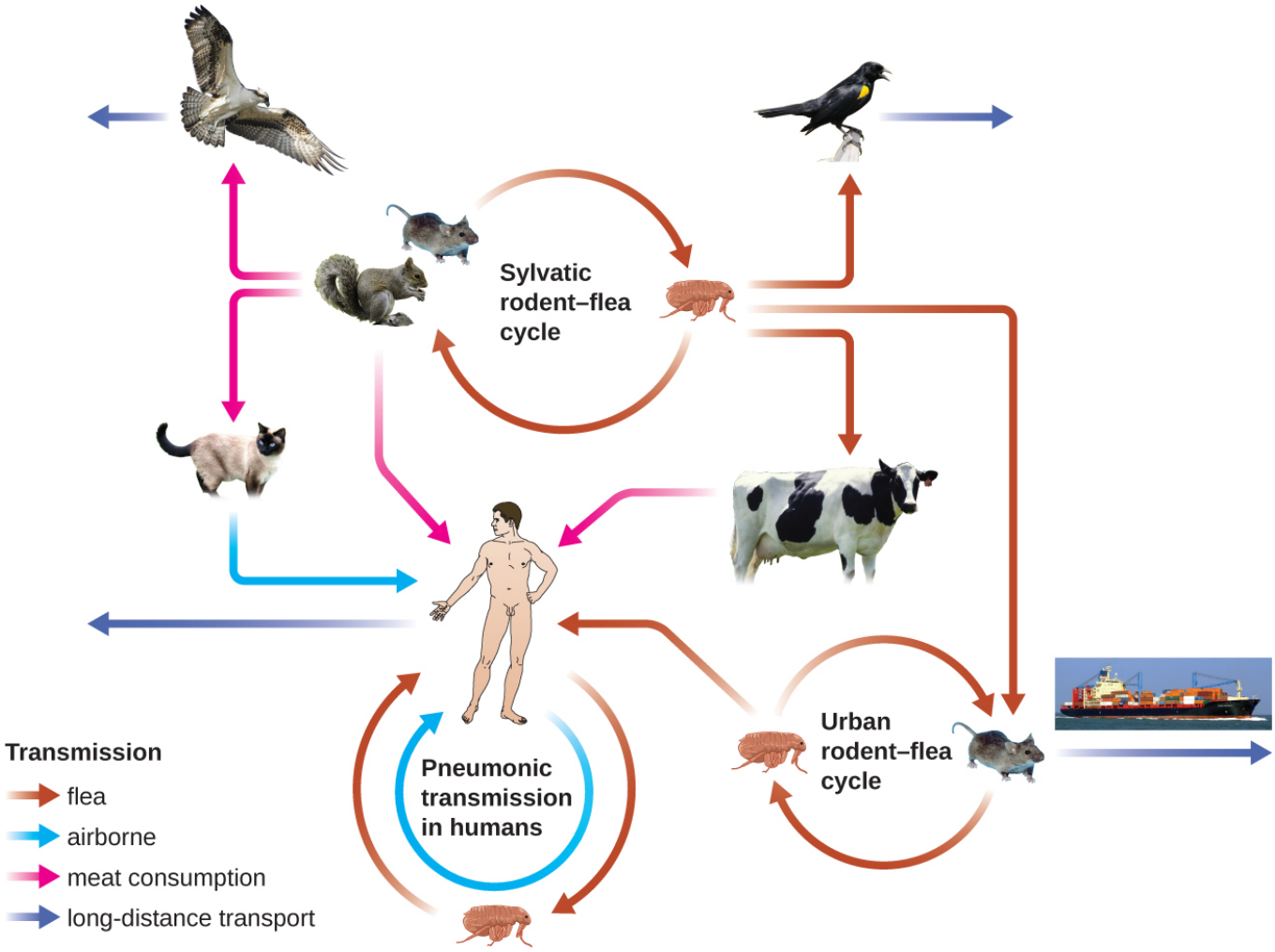


Figure 9.2.2.4: Yersinia pestis, the causative agent of plague, has numerous modes of transmission. The modes are divided into two ecological classes: urban and sylvatic (i.e., forest or rural). The urban cycle primarily involves transmission from infected urban mammals (rats) to humans by flea vectors (brown arrows). The disease may travel between urban centers (purple arrow) if infected rats find their way onto ships or trains. The sylvatic cycle involves mammals more common in nonurban environments. Sylvatic birds and mammals (including humans) may become infected after eating infected mammals (pink arrows) or by flea vectors. Pneumonic transmission occurs between humans or between humans and infected animals through the inhalation of *Y. pestis* in aerosols. (credit “diagram”: modification of work by Stenseth NC, Atshabar BB, Begon M, Belmain SR, Bertherat E, Carniel E, Gage KL, Leirs H, and Rahalison L; credit “cat”: modification of work by “KaCey97078”/Flickr)



(a) (b)

Figure 9.2.2.5: (a) *Yersinia pestis* infection can cause inflamed and swollen lymph nodes (buboes), like these in the groin of an infected patient. (b) Septicemic plague caused necrotic toes in this patient. Vascular damage at the extremities causes ischemia and tissue death. (credit a: modification of work by American Society for Microbiology; credit b: modification of work by Centers for Disease Control and Prevention)

The high mortality rate for the plague is, in part, a consequence of it being unusually well equipped with virulence factors. To date, there are at least 15 different major virulence factors that have been identified from *Y. pestis* and, of these, eight are involved with adherence to host cells. In addition, the F1 component of the *Y. pestis* capsule is a virulence factor that allows the bacterium to avoid phagocytosis. F1 is produced in large quantities during mammalian infection and is the most immunogenic component.[11] Successful use of virulence factors allows the bacilli to disseminate from the area of the bite to regional lymph nodes and eventually the entire blood and lymphatic systems.

Culturing and direct microscopic examination of a sample of fluid from a bubo, blood, or sputum is the best way to identify *Y. pestis* and confirm a presumptive diagnosis of plague. Specimens may be stained using either a Gram, Giemsa, Wright, or Wayson's staining technique (Figure 9.2.2.6). The bacteria show a characteristic bipolar staining pattern, resembling safety pins, that facilitates presumptive identification. Direct fluorescent antibody tests (rapid test of outer-membrane antigens) and serological tests like ELISA can be used to confirm the diagnosis. The confirmatory method for identifying *Y. pestis* isolates in the US is bacteriophage lysis.

Prompt antibiotic therapy can resolve most cases of bubonic plague, but septicemic and pneumonic plague are more difficult to treat because of their shorter incubation stages. Survival often depends on an early and accurate diagnosis and an appropriate choice of antibiotic therapy. In the US, the most common antibiotics used to treat patients with plague are gentamicin, fluoroquinolones, streptomycin, levofloxacin, ciprofloxacin, and doxycycline.

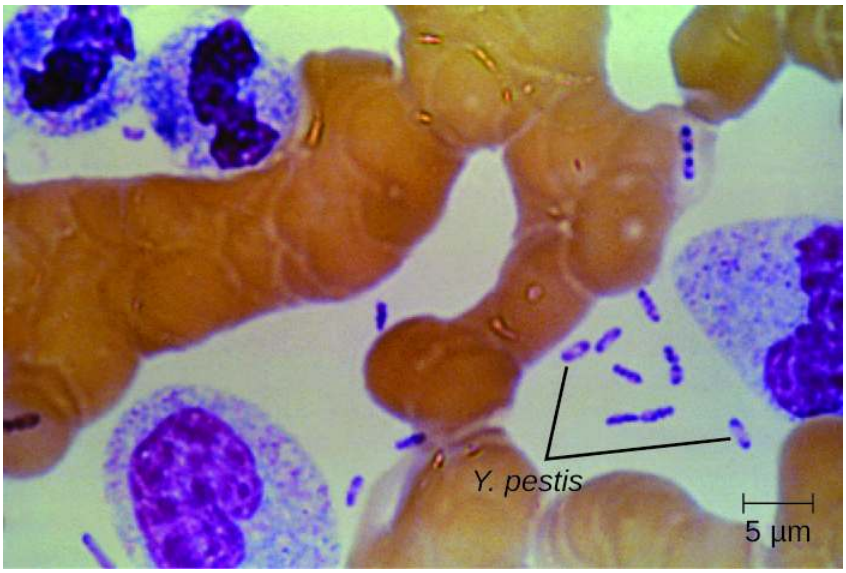


Figure 9.2.2.6: This Wright's stain of a blood sample from a patient with plague shows the characteristic "safety pin" appearance of *Yersinia pestis*. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 9.2.2.6

Compare bubonic plague, septicemic plague, and pneumonic plague.

Micro Connections: The History of the Plague

The first recorded pandemic of plague, the Justinian plague, occurred in the sixth century CE. It is thought to have originated in central Africa and spread to the Mediterranean through trade routes. At its peak, more than 5,000 people died per day in Constantinople alone. Ultimately, one-third of that city's population succumbed to plague.[12] The impact of this outbreak probably contributed to the later fall of Emperor Justinian.

The second major pandemic, dubbed the Black Death, occurred during the 14th century. This time, the infections are thought to have originated somewhere in Asia before being transported to Europe by trade, soldiers, and war refugees. This outbreak killed an estimated one-quarter of the population of Europe (25 million, primarily in major cities). In addition, at least another 25 million are thought to have been killed in Asia and Africa.[13] This second pandemic, associated with strain *Yersinia pestis* biovar Medievalis, cycled for another 300 years in Europe and Great Britain, and was called the Great Plague in the 1660s.

The most recent pandemic occurred in the 1890s with *Yersinia pestis* biovar Orientalis. This outbreak originated in the Yunnan province of China and spread worldwide through trade. It is at this time that plague made its way to the US. The etiologic agent of plague was discovered by Alexandre Yersin (1863–1943) during this outbreak as well. The overall number of deaths was lower than in prior outbreaks, perhaps because of improved sanitation and medical support.[14] Most of the deaths attributed to this final pandemic occurred in India.

Link to Learning

Visit this link to see an article describing how similar the genome of the Black Death bacterium is to today's strains of bubonic plague.

Zoonotic Febrile Diseases

A wide variety of zoonotic febrile diseases (diseases that cause fever) are caused by pathogenic bacteria that require arthropod vectors. These pathogens are either obligate intracellular species of *Anaplasma*, *Bartonella*, *Ehrlichia*, *Orientia*, and *Rickettsia*, or spirochetes in the genus *Borrelia*. Isolation and identification of pathogens in this group are best performed in BSL-3 laboratories because of the low infective dose associated with the diseases.

Anaplasmosis

The zoonotic tickborne disease human granulocytic anaplasmosis (HGA) is caused by the obligate intracellular pathogen *Anaplasma phagocytophilum*. HGA is endemic primarily in the central and northeastern US and in countries in Europe and Asia.

HGA is usually a mild febrile disease that causes flu-like symptoms in immunocompetent patients; however, symptoms are severe enough to require hospitalization in at least 50% of infections and, of those patients, less than 1% will die of HGA.[15] Small mammals such as white-footed mice, chipmunks, and voles have been identified as reservoirs of *A. phagocytophilum*, which is transmitted by the bite of an *Ixodes* tick. Five major virulence factors[16] have been reported in *Anaplasma*; three are adherence factors and two are factors that allow the pathogen to avoid the human immune response. Diagnostic approaches include locating intracellular microcolonies of *Anaplasma* through microscopic examination of neutrophils or eosinophils stained with Giemsa or Wright stain, PCR for detection of *A. phagocytophilum*, and serological tests to detect antibody titers against the pathogens. The primary antibiotic used for treatment is doxycycline.

Ehrlichiosis

Human monocytotropic ehrlichiosis (HME) is a zoonotic tickborne disease caused by the BSL-2, obligate intracellular pathogen *Ehrlichia chaffeensis*. Currently, the geographic distribution of HME is primarily the eastern half of the US, with a few cases reported in the West, which corresponds with the known geographic distribution of the primary vector, the lone star tick (*Amblyomma americanum*). Symptoms of HME are similar to the flu-like symptoms observed in anaplasmosis, but a rash is more common, with 60% of children and less than 30% of adults developing petechial, macula, and maculopapular rashes.[17] Virulence factors allow *E. chaffeensis* to adhere to and infect monocytes, forming intracellular microcolonies in monocytes that are diagnostic for the HME. Diagnosis of HME can be confirmed with PCR and serologic tests. The first-line treatment for adults and children of all ages with HME is doxycycline.

Epidemic Typhus

The disease epidemic typhus is caused by *Rickettsia prowazekii* and is transmitted by body lice, *Pediculus humanus*. Flying squirrels are animal reservoirs of *R. prowazekii* in North America and can also be sources of lice capable of transmitting the pathogen. Epidemic typhus is characterized by a high fever and body aches that last for about 2 weeks. A rash develops on the abdomen and chest and radiates to the extremities. Severe cases can result in death from shock or damage to heart and brain tissues. Infected humans are an important reservoir for this bacterium because *R. prowazekii* is the only *Rickettsia* that can establish a chronic carrier state in humans.

Epidemic typhus has played an important role in human history, causing large outbreaks with high mortality rates during times of war or adversity. During World War I, epidemic typhus killed more than 3 million people on the Eastern front.[18]With the advent of effective insecticides and improved personal hygiene, epidemic typhus is now quite rare in the US. In the developing world, however, epidemics can lead to mortality rates of up to 40% in the absence of treatment.[19] In recent years, most outbreaks have taken place in Burundi, Ethiopia, and Rwanda. For example, an outbreak in Burundi refugee camps in 1997 resulted in 45,000 illnesses in a population of about 760,000 people.[20]

A rapid diagnosis is difficult because of the similarity of the primary symptoms with those of many other diseases. Molecular and immunohistochemical diagnostic tests are the most useful methods for establishing a diagnosis during the acute stage of illness when therapeutic decisions are critical. PCR to detect distinctive genes from *R. prowazekii* can be used to confirm the diagnosis of epidemic typhus, along with immunofluorescent staining of tissue biopsy specimens. Serology is usually used to identify rickettsial infections. However, adequate antibody titers take up to 10 days to develop. Antibiotic therapy is typically begun before the diagnosis is complete. The most common drugs used to treat patients with epidemic typhus are doxycycline or chloramphenicol.

Murine (Endemic) Typhus

Murine typhus (also known as endemic typhus) is caused by *Rickettsia typhi* and is transmitted by the bite of the rat flea, *Xenopsylla cheopis*, with infected rats as the main reservoir. Clinical signs and symptoms of murine typhusinclude a rash and chills accompanied by headache and fever that last about 12 days. Some patients also exhibit a cough and pneumonia-like symptoms. Severe illness can develop in immunocompromised patients, with seizures, coma, and renal and respiratory failure.

Clinical diagnosis of murine typhus can be confirmed from a biopsy specimen from the rash. Diagnostic tests include indirect immunofluorescent antibody (IFA) staining, PCR for *R. typhi*, and acute and convalescent serologic testing. Primary treatment is

doxycycline, with chloramphenicol as the second choice.

Rocky Mountain Spotted Fever

The disease Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii* and is transmitted by the bite of a hard-bodied tick such as the American dog tick (*Dermacentor variabilis*), Rocky Mountain wood tick (*D. andersoni*), or brown dog tick (*Rhipicephalus sanguineus*).

This disease is endemic in North and South America and its incidence is coincident with the arthropod vector range. Despite its name, most cases in the US do not occur in the Rocky Mountain region but in the Southeast; North Carolina, Oklahoma, Arkansas, Tennessee, and Missouri account for greater than 60% of all cases.[21] The map in Figure 9.2.2.7 shows the distribution of prevalence in the US in 2010.

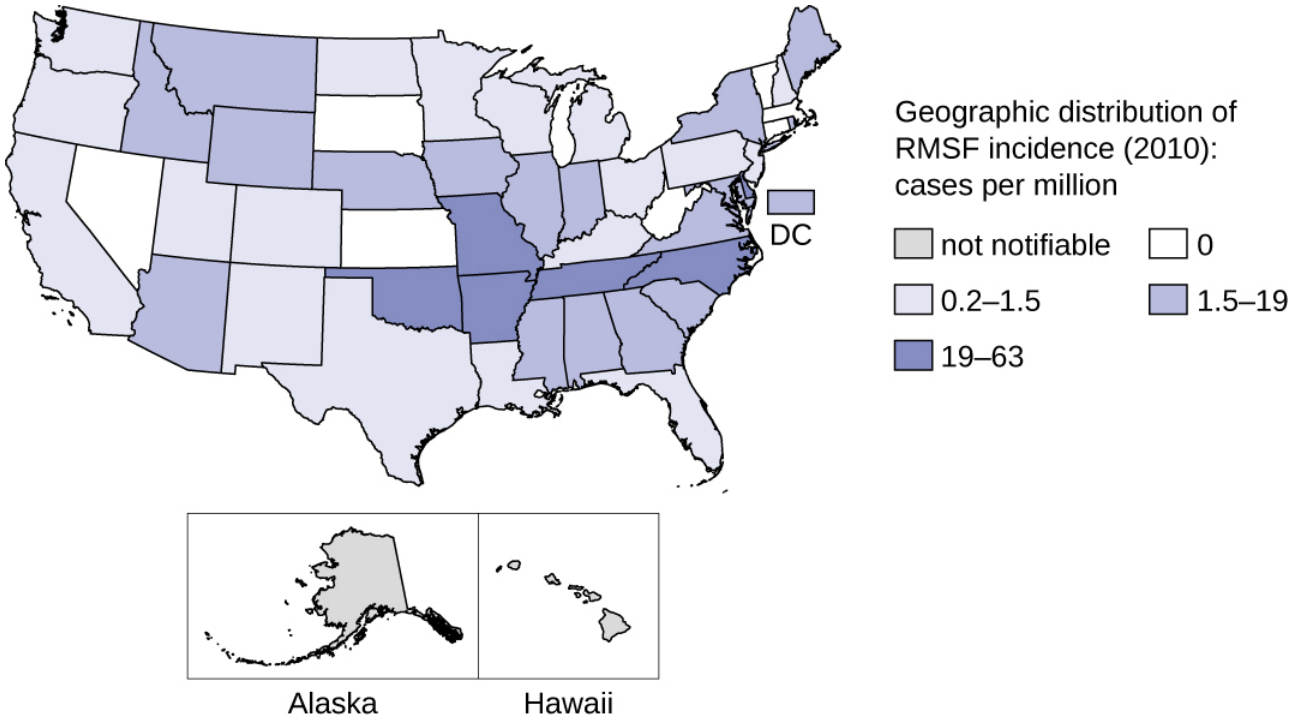


Figure 9.2.2.7: In the US, Rocky Mountain spotted fever is most prevalent in the southeastern states. (credit: modification of work by Centers for Disease Control and Prevention)

Signs and symptoms of RMSF include a high fever, headache, body aches, nausea, and vomiting. A petechial rash(similar in appearance to measles) begins on the hands and wrists, and spreads to the trunk, face, and extremities (Figure 9.2.2.8). If untreated, RMSF is a serious illness that can be fatal in the first 8 days even in otherwise healthy patients. Ideally, treatment should begin before petechiae develop, because this is a sign of progression to severe disease; however, the rash usually does not appear until day 6 or later after onset of symptoms and only occurs in 35%–60% of patients with the infection. Increased vascular permeability associated with petechiae formation can result in fatality rates of 3% or greater, even in the presence of clinical support. Most deaths are due to hypotension and cardiac arrest or from ischemia following blood coagulation.

Diagnosis can be challenging because the disease mimics several other diseases that are more prevalent. The diagnosis of RMSF is made based on symptoms, fluorescent antibody staining of a biopsy specimen from the rash, PCR for *Rickettsia rickettsii*, and acute and convalescent serologic testing. Primary treatment is doxycycline, with chloramphenicol as the second choice.



Figure 9.2.2.8: Rocky Mountain spotted fever causes a petechial rash. Unlike epidemic or murine typhus, the rash begins at the hands and wrists and then spreads to the trunk. (credit: modification of work by Centers for Disease Control and Prevention)

Lyme Disease

Lyme disease is caused by the spirochete *Borrelia burgdorferi* that is transmitted by the bite of a hard-bodied, black-legged *Ixodes* tick. *I. scapularis* is the biological vector transmitting *B. burgdorferi* in the eastern and north-central US and *I. pacificus* transmits *B. burgdorferi* in the western US (Figure 9.2.2.10). Different species of *Ixodes* ticks are responsible for *B. burgdorferi* transmission in Asia and Europe. In the US, Lyme disease is the most commonly reported vectorborne illness. In 2014, it was the fifth most common Nationally Notifiable disease.[22]

Ixodes ticks have complex life cycles and deer, mice, and even birds can act as reservoirs. Over 2 years, the ticks pass through four developmental stages and require a blood meal from a host at each stage. In the spring, tick eggs hatch into six-legged larvae. These larvae do not carry *B. burgdorferi* initially. They may acquire the spirochete when they take their first blood meal (typically from a mouse). The larvae then overwinter and molt into eight-legged nymphs in the following spring. Nymphs take blood meals primarily from small rodents, but may also feed on humans, burrowing into the skin. The feeding period can last several days to a week, and it typically takes 24 hours for an infected nymph to transmit enough *B. burgdorferi* to cause infection in a human host. Nymphs ultimately mature into male and female adult ticks, which tend to feed on larger animals like deer or, occasionally, humans. The adults then mate and produce eggs to continue the cycle (Figure 9.2.2.9).

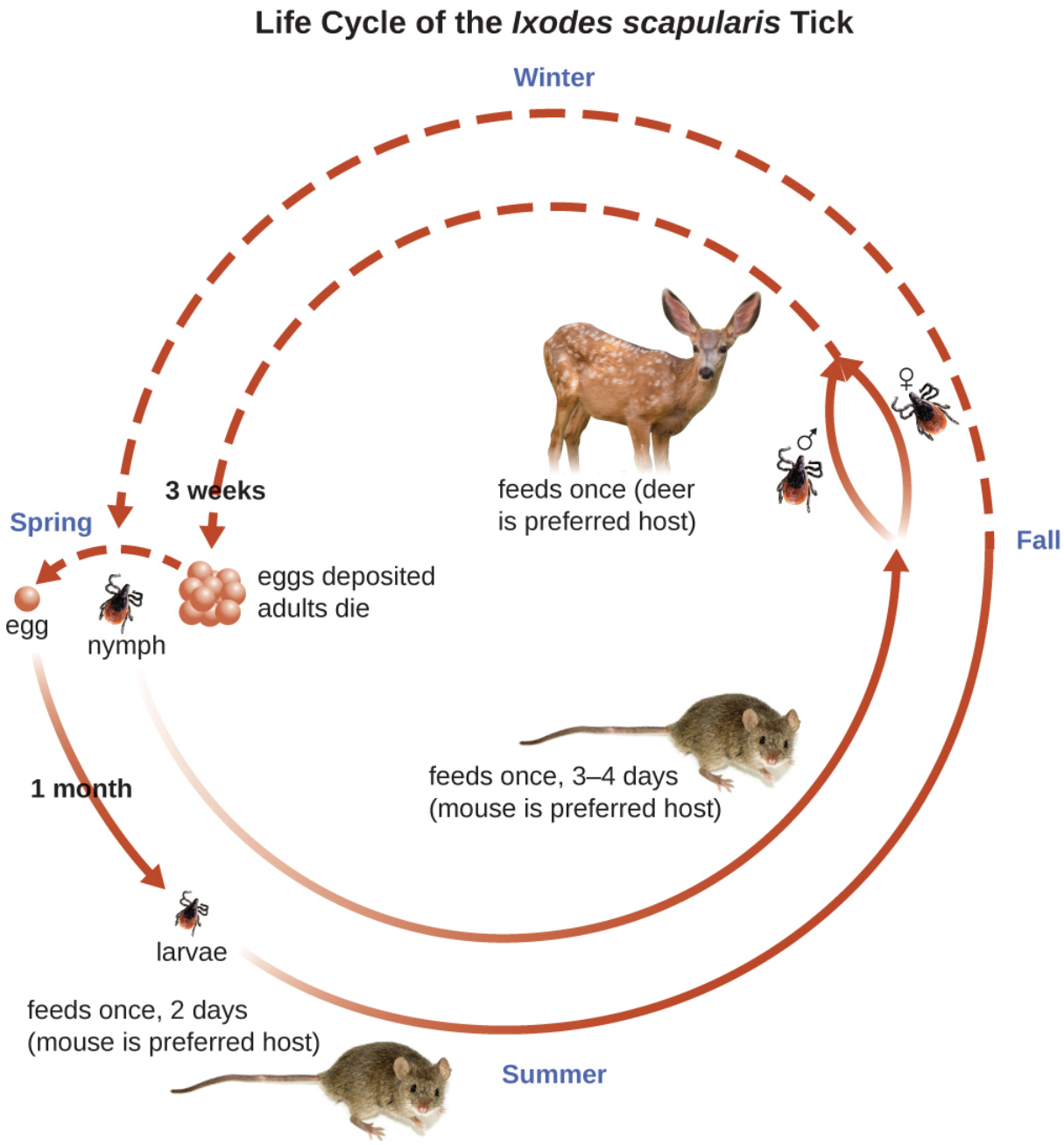


Figure 9.2.2.9: This image shows the 2-year life cycle of the black-legged tick, the biological vector of Lyme disease. (credit "mouse": modification of work by George Shuklin)

The symptoms of Lyme disease follow three stages: early localized, early disseminated, and late stage. During the early-localized stage, approximately 70%–80%[23] of cases may be characterized by a bull's-eye rash, called erythema migrans, at the site of the initial tick bite. The rash forms 3 to 30 days after the tick bite (7 days is the average) and may also be warm to the touch (Figure 9.2.2.10).[24] This diagnostic sign is often overlooked if the tick bite occurs on the scalp or another less visible location. Other early symptoms include flu-like symptoms such as malaise, headache, fever, and muscle stiffness. If the patient goes untreated, the second early-disseminated stage of the disease occurs days to weeks later. The symptoms at this stage may include severe headache, neck stiffness, facial paralysis, arthritis, and carditis. The late-stage manifestations of the disease may occur years after exposure. Chronic inflammation causes damage that can eventually cause severe arthritis, meningitis, encephalitis, and altered mental states. The disease may be fatal if untreated.

A presumptive diagnosis of Lyme disease can be made based solely on the presence of a bull's-eye rash at the site of infection, if it is present, in addition to other associated symptoms (Figure 9.2.2.10). In addition, indirect immunofluorescent antibody (IFA)

labeling can be used to visualize bacteria from blood or skin biopsy specimens. Serological tests like ELISA can also be used to detect serum antibodies produced in response to infection. During the early stage of infection (about 30 days), antibacterial drugs such as amoxicillin and doxycycline are effective. In the later stages, penicillin G, chloramphenicol, or ceftriaxone can be given intravenously.

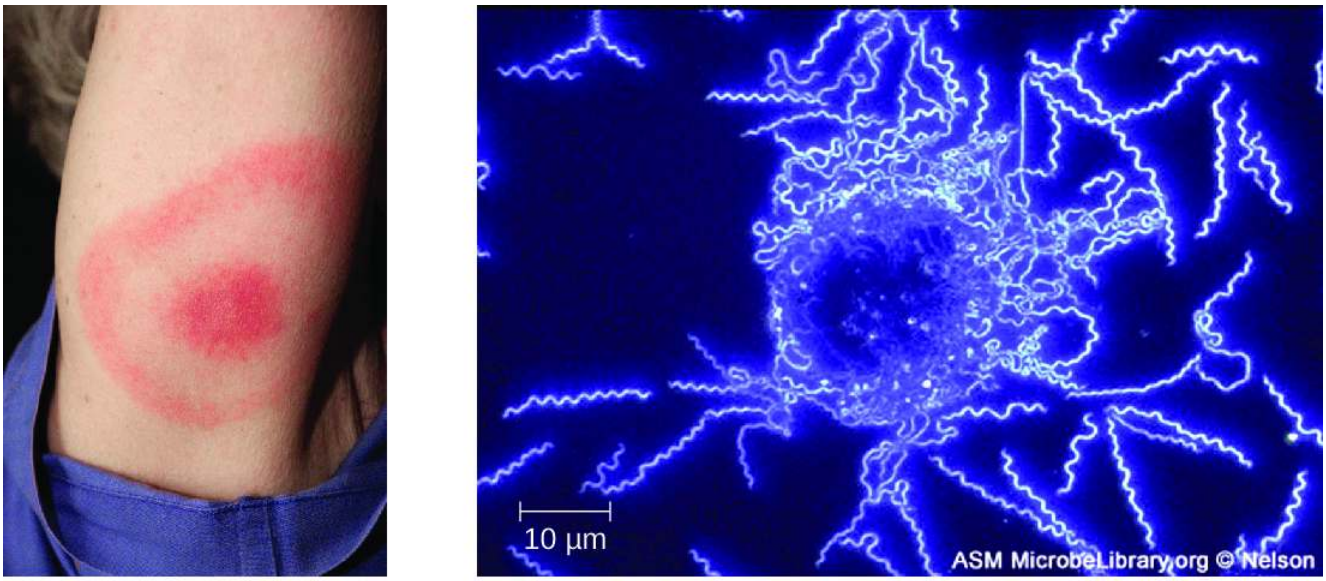


Figure 9.2.2.10: (a) A characteristic bull's eye rash of Lyme disease forms at the site of a tick bite. (b) A darkfield micrograph shows *Borrelia burgdorferi*, the causative agent of Lyme disease. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by American Society for Microbiology)

Relapsing Fever

Borrelia spp. also can cause relapsing fever. Two of the most common species are *B. recurrentis*, which causes epidemics of louseborne relapsing fever, and *B. hermsii*, which causes tickborne relapsing fevers. These *Borrelia* species are transmitted by the body louse *Pediculus humanus* and the soft-bodied tick *Ornithodoros hermsi*, respectively. Lice acquire the spirochetes from human reservoirs, whereas ticks acquire them from rodent reservoirs. Spirochetes infect humans when *Borrelia* in the vector's saliva or excreta enter the skin rapidly as the vector bites.

In both louse- and tickborne relapsing fevers, bacteremia usually occurs after the initial exposure, leading to a sudden high fever (39–43 °C [102.2–109.4 °F) typically accompanied by headache and muscle aches. After about 3 days, these symptoms typically subside, only to return again after about a week. After another 3 days, the symptoms subside again but return a week later, and this cycle may repeat several times unless it is disrupted by antibiotic treatment. Immune evasion through bacterial antigenic variation is responsible for the cyclical nature of the symptoms in these diseases.

The diagnosis of relapsing fever can be made by observation of spirochetes in blood, using darkfield microscopy (Figure 9.2.2.11). For louseborne relapsing fever, doxycycline or erythromycin are the first-line antibiotics. For tickborne relapsing fever, tetracycline or erythromycin are the first-line antibiotics.

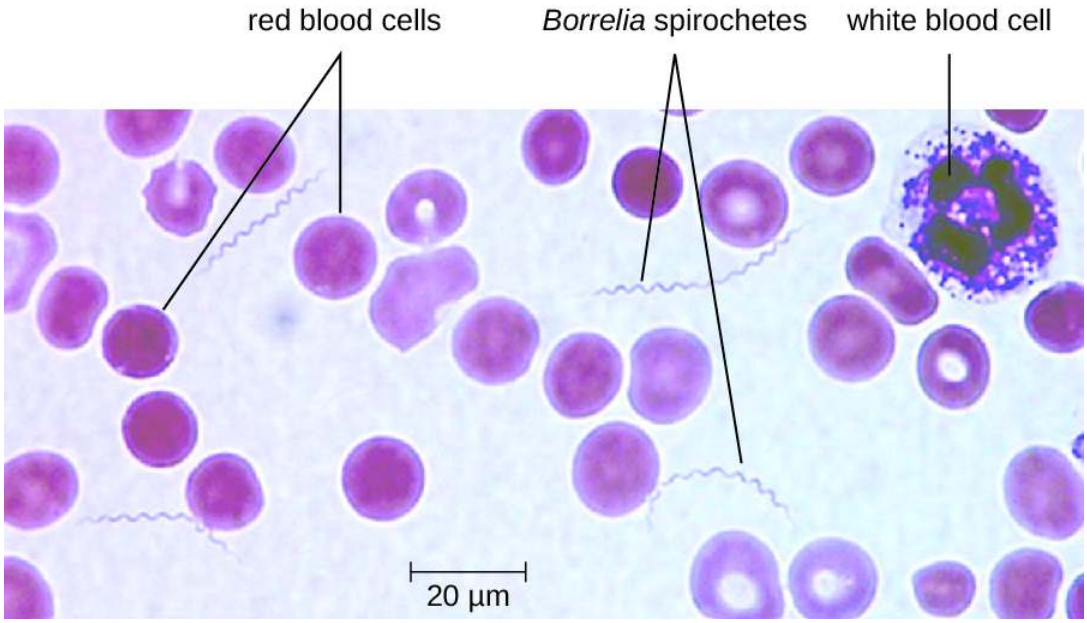


Figure 9.2.2.11: A peripheral blood smear from a patient with tickborne relapsing fever. *Borrelia* appears as thin spirochetes among the larger red blood cells. (credit: modification of work by Centers for Disease Control and Prevention)

Trench Fever

The louseborne disease trench fever was first characterized as a specific disease during World War I, when approximately 1 million soldiers were infected. Today, it is primarily limited to areas of the developing world where poor sanitation and hygiene lead to infestations of lice (e.g., overpopulated urban areas and refugee camps). Trench fever is caused by the gram-negative bacterium *Bartonella quintana*, which is transmitted when feces from infected body lice, *Pediculus humanus* var *corporis*, are rubbed into the louse bite, abraded skin, or the conjunctiva. The symptoms typically follow a 5-day course marked by a high fever, body aches, conjunctivitis, ocular pain, severe headaches, and severe bone pain in the shins, neck, and back. Diagnosis can be made using blood cultures; serological tests like ELISA can be used to detect antibody titers to the pathogen and PCR can also be used. The first-line antibiotics are doxycycline, macrolide antibiotics, and ceftriaxone.

? Exercise 9.2.2.7

1. What is the vector associated with epidemic typhus?
2. Describe the life cycle of the deer tick and how it spreads Lyme disease.

Tick Tips

Many of the diseases covered in this chapter involve arthropod vectors. Of these, ticks are probably the most commonly encountered in the US. Adult ticks have eight legs and two body segments, the cephalothorax and the head (Figure 9.2.2.12). They typically range from 2 mm to 4 mm in length, and feed on the blood of the host by attaching themselves to the skin.

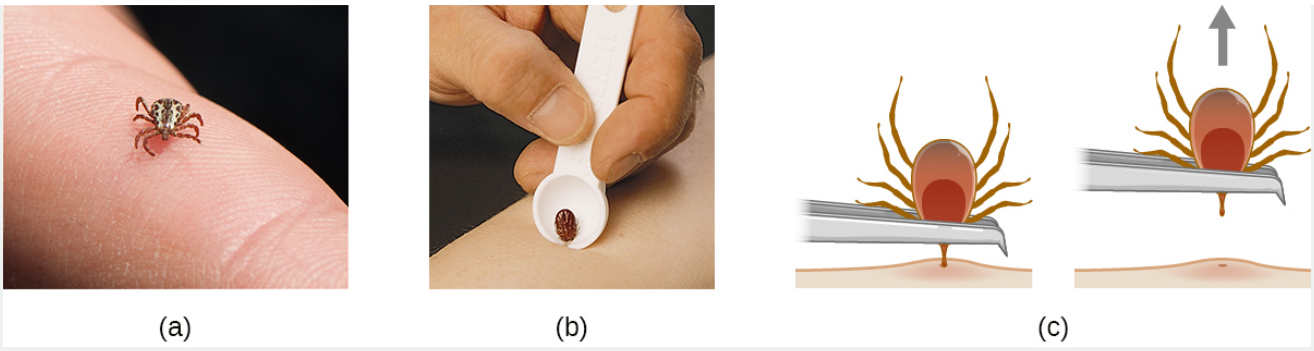


Figure 9.2.2.12: (a) This black-legged tick, also known as the deer tick, has not yet attached to the skin. (b) A notched tick extractor can be used for removal. (c) To remove an attached tick with fine-tipped tweezers, pull gently on the mouth parts until the tick releases its hold on the skin. Avoid squeezing the tick's body, because this could release pathogens and thus increase the risk of contracting Lyme disease. (credit a: modification of work by Jerry Kirkhart; credit c: modification of work by Centers for Disease Control and Prevention)

Unattached ticks should be removed and eliminated as soon as they are discovered. When removing a tick that has already attached itself, keep the following guidelines in mind to reduce the chances of exposure to pathogens:

- Use blunt tweezers to gently pull near the site of attachment until the tick releases its hold on the skin.
- Avoid crushing the tick's body and do not handle the tick with bare fingers. This could release bacterial pathogens and actually increase your exposure. The tick can be killed by drowning in water or alcohol, or frozen if it may be needed later for identification and analysis.
- Disinfect the area thoroughly by swabbing with an antiseptic such as isopropanol.
- Monitor the site of the bite for rashes or other signs of infection.

Many ill-advised home remedies for tick removal have become popular in recent years, propagated by social media and pseudojournalism. Health professionals should discourage patients from resorting to any of the following methods, which are NOT recommended:

- using chemicals (e.g., petroleum jelly or fingernail polish) to dislodge an attached tick, because it can cause the tick to release fluid, which can increase the chance of infection
- using hot objects (matches or cigarette butts) to dislodge an attached tick
- squeezing the tick's body with fingers or tweezers

Bacterial Infections of the Circulatory and Lymphatic Systems

Although the circulatory system is a closed system, bacteria can enter the bloodstream through several routes. Wounds, animal bites, or other breaks in the skin and mucous membranes can result in the rapid dissemination of bacterial pathogens throughout the body. Localized infections may also spread to the bloodstream, causing serious and often fatal systemic infections. Figure 9.2.2.13 and Figure 9.2.2.14 summarize the major characteristics of bacterial infections of the circulatory and lymphatic systems.

Bacterial Infections of the Circulatory and Lymphatic Systems					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Anaplasmosis (HGA)	*Anaplasma phagocytophilum*	Fever, flu-like symptoms	From small-mammal reservoirs via tick vector	Blood smear, PCR	Doxycycline
Brucellosis	*Brucella melitensis, B. abortus, B. canis, B. suis*	Granuloma, undulating fever, chronic flu-like symptoms	Direct contact with infected livestock or animals	Agglutination tests, ELISA	Doxycycline, rifampin
Cat-scratch disease	*Bartonella henselae*	Lymph-node swelling and pain, fever, chills, fatigue	Bite or scratch from domestic cats	Immunofluorescence, serological tests, PCR	None for immunocompetent patients
Ehrlichiosis (HME)	*Ehrlichia chaffeensis*	Flu-like symptoms, rash	Lone star tick vector	Serologic tests, PCR	Doxycycline
Endocarditis/ pericarditis	*SStaphylococcus* spp., *Streptococcus spp., Enterococcus spp., HACEK* bacilli	Chest pain, difficulty breathing, dry cough, fever; potentially fatal damage to heart valves	Pathogens introduced to bloodstream via contaminated catheters, dental procedures, piercings, or wounds	Echocardiogram, blood culture	Ampicillin, nafcillin, gentamicin, others; based on susceptibility testing
Epidemic typhus	*Rickettsia prowazekii*	High fever, body aches, rash; potentially fatal damage to heart and brain	From rodent reservoir via body louse vector	PCR, immunofluorescence	Doxycycline, chloramphenicol
Gas gangrene	*Clostridium perfringens,* other *Clostridium* spp.	Rapidly spreading myonecrosis, edema, yellowish and then purple discharge from wound, pockets of gas in tissues, septic shock and death	Germination of endospores in ischemic tissues, typically due to injury or chronic disease (e.g., diabetes)	Wound culture	Penicillin G, clindamycin, metronidazole
Infectious arthritis (septic arthritis)	*Staphylococcus aureus, Neisseria gonorrhoeae*	Joint pain and swelling, limited range of motion	Infection spreads to joint via circulatory system from wound or surgical site	Synovial fluid culture	Oxacillin, cefazolin, cephtriaxone
Lyme disease	*Borrelia burgdorferi*	Early localized: bull's eye rash, malaise, headache, fever, muscle stiffness; early disseminated: stiff neck, facial paralysis, arthritis, carditis; late-stage: arthritis, meningitis, possibly fatal	From deer, rodent, bird reservoirs via tick vector	IFA, serology, and ELISA	Amoxicillin, doxycycline, penicillin G, chloramphenicol, ceftriaxone
Murine (endemic) typhus	*Rickettsia typhi*	Low-grade fever, rash, headache, cough	From rodents or between humans via rat flea vector	Biopsy, IFA, PCR	Doxycycline, chloramphenicol
Osteomyelitis	*Staphylococcus aureus, Streptococcus pyogenes,* others	Inflammation of bone tissue, leading to fever, localized pain, edema, ulcers, bone loss	Pathogens introduced through trauma, prosthetic joint replacement, or from other infected body site via bloodstream	Radiograph of affected bone, culture of bone biopsy specimen	Cephalosporin, penicillins, others

Figure 9.2.2.13: Bacterial infections of Circulatory and Lymphatic systems.

Bacterial Infections of the Circulatory and Lymphatic Systems (continued)					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Plague	*Yersinia pestis*	Bubonic: buboes, fever, internal hemorrhaging; septicemic: fever, abdominal pain, shock, DIC, necrosis in extremities; pneumonic: acute pneumonia, respiratory failure, shock. All forms have high mortality rates.	Transmitted from mammal reservoirs via flea vectors or consumption of infected animal; transmission of pneumonic plague between humans via respiratory aerosols	Culture of bacteria from lymph, blood, or sputum samples; DFA, ELISA	Gentamycin, fluoroquinolones, others
Puerperal sepsis	*Streptococcus pyogenes,* many others	Rapid-onset fever, shock, and death	Pathogens introduced during or immediately following childbirth	Wound, urine,or blood culture	As determined by susceptibility testing
Rat-bite fever	*Streptobacillus moniliformis, Spirillum minor*	Fever, muscle and joint pain, rash, ulcer	Bite from infected rat or exposure to rat feces or body fluids in contaminated food or water	Observation of the organism from samples and antibody tests	Penicillin
Relapsing fever	*Borrelia recurrentis, B. hermsii,* other *Borrelia* spp.	Recurring fever, headache, muscle aches	From rodent or human reservoir via body louse or tick vector	Darkfield microscopy	Doxycycline, tetracycline, erythromycin
Rheumatic fever	*Streptococcus pyogenes*	Joint pain and swelling, inflammation and scarring of heart valves, heart murmur	Sequela of streptococcal pharyngitis	Serology, electrocardiogram, echocardiogram	Benzathine benzylpenicillin
Rocky Mountain spotted fever	*Rickettsia rickettsii*	High fever, headache, body aches, nausea and vomiting, petechial rash; potentially fatal hypotension and ischemia due to blood coagulation	From rodent reservoir via tick vectors	Biopsy, serology, PCR	Doxycycline, chloramphenicol
Toxic shock syndrome (TSS)	*Staphylococcus aureus*	Sudden high fever, vomiting, diarrhea, hypotension, death	Pathogens from localized infection spread to bloodstream; pathogens introduced on tampons or other intravaginal products	Serology, toxin identification from isolates	Clindamycin, vancomycin
Toxic shock-like syndrome (STSS)	*Streptococcus pyogenes*	Sudden high fever, vomiting, diarrhea, acute respiratory distress syndrome (ARDS), hypoxemia, necrotizing fasciitis, death	Sequela of streptococcal skin or soft-tissue infection	Serology, blood culture, urinalysis	Penicillin, cephalosporin
Trench fever	*Bartonella quintana*	High fever, conjunctivitis, ocular pain, headaches, severe pain in bones of shins, neck, and back	Between humans via body louse vector	Blood culture, ELISA, PCR	Doxycycline, macrolide antibiotics, ceftriaxone
Tularemia (rabbit fever)	*Francisella tularensis*	Skin lesions, fever, chills, headache, buboes	Eating or handling infected rabbit; transmission from infected animal via tick or fly vector; aerosol transmission (in laboratory or as bioweapon)	DFA	Streptomycin, gentamycin, others

Figure 9.2.2.14: Bacterial infections of Circulatory and Lymphatic systems (continued).

Key Concepts and Summary

- Bacterial infections of the circulatory system are almost universally serious. Left untreated, most have high mortality rates.
- Bacterial pathogens usually require a breach in the immune defenses to colonize the circulatory system. Most often, this involves a wound or the bite of an arthropod vector, but it can also occur in hospital settings and result in nosocomial infections.
- **Sepsis** from both gram-negative and gram-positive bacteria**, puerperal fever, rheumatic fever, endocarditis, gas gangrene, osteomyelitis,** and **toxic shock syndrome** are typically a result of injury or introduction of bacteria by medical or surgical intervention.
- **Tularemia, brucellosis, cat-scratch fever, rat-bite fever,** and **bubonic plague** are zoonotic diseases transmitted by biological vectors
- **Ehrlichiosis, anaplasmosis, endemic** and **murine typhus, Rocky Mountain spotted fever, Lyme disease, relapsing fever,** and **trench fever** are transmitted by arthropod vectors.
- Because their symptoms are so similar to those of other diseases, many bacterial infections of the circulatory system are difficult to diagnose.
- Standard antibiotic therapies are effective for the treatment of most bacterial infections of the circulatory system, unless the bacterium is resistant, in which case synergistic treatment may be required.
- The systemic immune response to a bacteremia, which involves the release of excessive amounts of cytokines, can sometimes be more damaging to the host than the infection itself.

Footnotes

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9.2.3: Viral Infections of the Circulatory and Lymphatic Systems

Learning Objectives

- Identify common viral pathogens that cause infections of the circulatory and lymphatic systems
- Compare the major characteristics of specific viral diseases affecting the circulatory and lymphatic systems

Viral pathogens of the circulatory system vary tremendously both in their virulence and distribution worldwide. Some of these pathogens are practically global in their distribution. Fortunately, the most ubiquitous viruses tend to produce the mildest forms of disease. In the majority of cases, those infected remain asymptomatic. On the other hand, other viruses are associated with life-threatening diseases that have impacted human history.

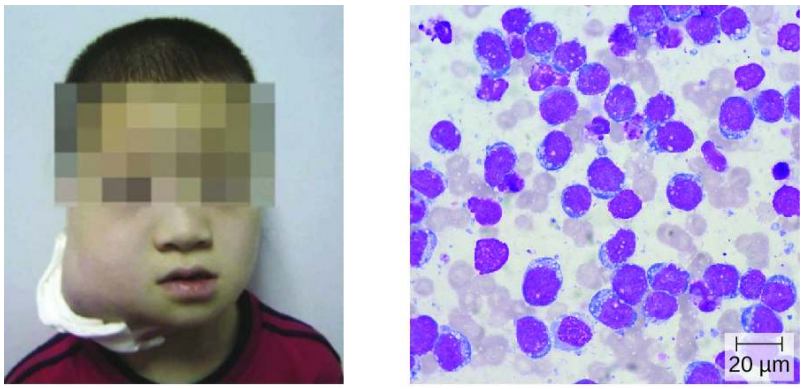
Infectious Mononucleosis and Burkitt Lymphoma

Human herpesvirus 4, also known as Epstein-Barr virus (EBV), has been associated with a variety of human diseases, such as mononucleosis and Burkitt lymphoma. Exposure to the human herpesvirus 4 (HHV-4) is widespread and nearly all people have been exposed at some time in their childhood, as evidenced by serological tests on populations. The virus primarily resides within B lymphocytes and, like all herpes viruses, can remain dormant in a latent state for a long time.

When uninfected young adults are exposed to EBV, they may experience infectious mononucleosis. The virus is mainly spread through contact with body fluids (e.g., saliva, blood, and semen). The main symptoms include pharyngitis, fever, fatigue, and lymph node swelling. Abdominal pain may also occur as a result of spleen and liver enlargement in the second or third week of infection. The disease typically is self-limiting after about a month. The main symptom, extreme fatigue, can continue for several months, however. Complications in immunocompetent patients are rare but can include jaundice, anemia, and possible rupture of the spleen caused by enlargement.

In patients with malaria or HIV, Epstein-Barr virus can lead to a fast-growing malignant cancer known as Burkitt lymphoma (Figure 9.2.3.1). This condition is a form of non-Hodgkin lymphoma that produces solid tumors chiefly consisting of aberrant B cells. Burkitt lymphoma is more common in Africa, where prevalence of HIV and malaria is high, and it more frequently afflicts children. Repeated episodes of viremia caused by reactivation of the virus are common in immunocompromised individuals. In some patients with AIDS, EBV may induce the formation of malignant B-cell lymphomas or oral hairy leukoplakia. Immunodeficiency-associated Burkitt lymphoma primarily occurs in patients with HIV. HIV infection, similar to malaria, leads to polyclonal B-cell activation and permits poorly controlled proliferation of EBV^+ B cells, leading to the formation of lymphomas.

Infectious mononucleosis is typically diagnosed based on the initial clinical symptoms and a test for antibodies to EBV-associated antigens. Because the disease is self-limiting, antiviral treatments are rare for mononucleosis. Cases of Burkitt lymphoma are diagnosed from a biopsy specimen from a lymph node or tissue from a suspected tumor. Staging of the cancer includes computed tomography (CT) scans of the chest, abdomen, pelvis, and cytologic and histologic evaluation of biopsy specimens. Because the tumors grow so rapidly, staging studies must be expedited and treatment must be initiated promptly. An intensive alternating regimen of cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, and cytarabine (CODOX-M/IVAC) plus rituximab results in a cure rate greater than 90% for children and adults.



(a) (b)

Figure 9.2.3.1: (a) Burkitt lymphoma can cause large tumors. (b) Characteristic irregularly shaped abnormal lymphocytes (large purple cells) with vacuoles (white spots) from a fine-needle aspirate of a tumor from a patient with Burkitt lymphoma. (credit a: modification of work by Bi CF, Tang Y, Zhang WY, Zhao S, Wang XQ, Yang QP, Li GD, and Liu WP; credit b: modification of work by Ed Uthman)

Cytomegalovirus Infections

Also known as cytomegalovirus (CMV), human herpesvirus 5 (HHV-5) is a virus with high infection rates in the human population. It is currently estimated that 50% of people in the US have been infected by the time they reach adulthood.[1]CMV is the major cause of non-Epstein-Barr infectious mononucleosis in the general human population. It is also an important pathogen in immunocompromised hosts, including patients with AIDS, neonates, and transplant recipients. However, the vast majority of CMV infections are asymptomatic. In adults, if symptoms do occur, they typically include fever, fatigue, swollen glands, and pharyngitis.

CMV can be transmitted between individuals through contact with body fluids such as saliva or urine. Common modes of transmission include sexual contact, nursing, blood transfusions, and organ transplants. In addition, pregnant women with active infections frequently pass this virus to their fetus, resulting in congenital CMV infections, which occur in approximately one in every 150 infants in US.[2] Infants can also be infected during passage through the birth canal or through breast milk and saliva from the mother.

Perinatal infections tend to be milder but can occasionally cause lung, spleen, or liver damage. Serious symptoms in newborns include growth retardation, jaundice, deafness, blindness, and mental retardation if the virus crosses the placenta during the embryonic state when the body systems are developing in utero. However, a majority (approximately 80%) of infected infants will never have symptoms or experience long-term problems.[3] Diagnosis of CMV infection during pregnancy is usually achieved by serology; CMV is the “C” in prenatal TORCH screening.

Many patients receiving blood transfusions and nearly all those receiving kidney transplants ultimately become infected with CMV. Approximately 60% of transplant recipients will have CMV infection and more than 20% will develop symptomatic disease.[4] These infections may result from CMV-contaminated tissues but also may be a consequence of immunosuppression required for transplantation causing reactivation of prior CMV infections. The resulting viremia can lead to fever and leukopenia, a decrease in the number of white blood cells in the bloodstream. Serious consequences may include liver damage, transplant rejection, and death. For similar reasons, many patients with AIDS develop active CMV infections that can manifest as encephalitis or progressive retinitis leading to blindness.[5]

Diagnosis of a localized CMV infection can be achieved through direct microscopic evaluation of tissue specimens stained with routine stains (e.g., Wright-Giemsa, hematoxylin and eosin, Papanicolaou) and immunohistochemical stains. Cells infected by CMV produce characteristic inclusions with an "owl's eye" appearance; this sign is less sensitive than molecular methods like PCR but more predictive of localized disease (Figure 9.2.3.2). For more severe CMV infection, tests such as enzyme immunoassay (EIA), indirect immunofluorescence antibody (IFA) tests, and PCR, which are based on detection of CMV antigen or DNA, have a higher sensitivity and can determine viral load. Cultivation of the virus from saliva or urine is still the method for detecting CMV in newborn babies up to 3 weeks old. Ganciclovir, valganciclovir, foscarnet, and cidofovir are the first-line antiviral drugs for serious CMV infections.

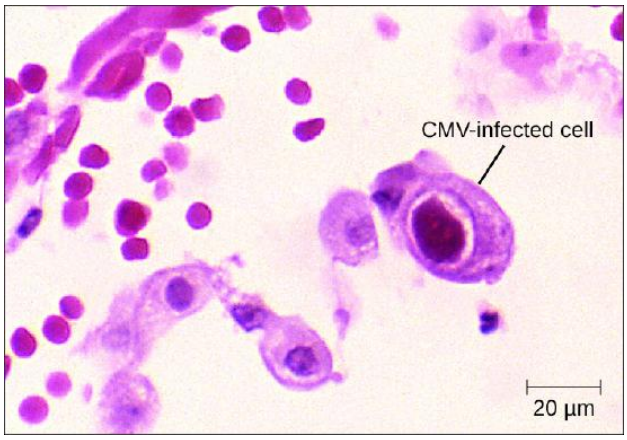


Figure 9.2.3.2: Cells infected with CMV become enlarged and have a characteristic “owl’s eye” nucleus. This micrograph shows kidney cells from a patient with CMV. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 9.2.3.1

Compare the diseases caused by HHV-4 and HHV-5.

Arthropod-Borne Viral Diseases

There are a number of arthropod-borne viruses, or arboviruses, that can cause human disease. Among these are several important hemorrhagic fevers transmitted by mosquitoes. We will discuss three that pose serious threats: yellow fever, chikungunya fever, and dengue fever.

Yellow Fever

Yellow fever was once common in the US and caused several serious outbreaks between 1700 and 1900.[6] Through vector control efforts, however, this disease has been eliminated in the US. Currently, yellow fever occurs primarily in tropical and subtropical areas in South America and Africa. It is caused by the yellow fever virus of the genus *Flavivirus* (named for the Latin word *flavus* meaning *yellow*), which is transmitted to humans by mosquito vectors. Sylvatic yellow fever occurs in tropical jungle regions of Africa and Central and South America, where the virus can be transmitted from infected monkeys to humans by the mosquitoes *Aedes africanus* or *Haemagogus* spp. In urban areas, the *Aedes aegypti* mosquito is mostly responsible for transmitting the virus between humans.

Most individuals infected with yellow fever virus have no illness or only mild disease. Onset of milder symptoms is sudden, with dizziness, fever of 39–40 °C (102–104 °F), chills, headache, and myalgias. As symptoms worsen, the face becomes flushed, and nausea, vomiting, constipation, severe fatigue, restlessness, and irritability are common. Mild disease may resolve after 1 to 3 days. However, approximately 15% of cases progress to develop moderate to severe yellow fever disease.[7]

In moderate or severe disease, the fever falls suddenly 2 to 5 days after onset, but recurs several hours or days later. Symptoms of jaundice, petechial rash, mucosal hemorrhages, oliguria (scant urine), epigastric tenderness with bloody vomit, confusion, and apathy also often occur for approximately 7 days of moderate to severe disease. After more than a week, patients may have a rapid recovery and no sequelae.

In its most severe form, called malignant yellow fever, symptoms include delirium, bleeding, seizures, shock, coma, and multiple organ failure; in some cases, death occurs. Patients with malignant yellow fever also become severely immunocompromised, and even those in recovery may become susceptible to bacterial superinfections and pneumonia. Of the 15% of patients who develop moderate or severe disease, up to half may die.

Diagnosis of yellow fever is often based on clinical signs and symptoms and, if applicable, the patient’s travel history, but infection can be confirmed by culture, serologic tests, and PCR. There are no effective treatments for patients with yellow fever. Whenever possible, patients with yellow fever should be hospitalized for close observation and given supportive care. Prevention is the best method of controlling yellow fever. Use of mosquito netting, window screens, insect repellents, and insecticides are all effective methods of reducing exposure to mosquito vectors. An effective vaccine is also available, but in the US, it is only administered to

those traveling to areas with endemic yellow fever. In West Africa, the World Health Organization (WHO) launched a Yellow Fever Initiative in 2006 and, since that time, significant progress has been made in combating yellow fever. More than 105 million people have been vaccinated, and no outbreaks of yellow fever were reported in West Africa in 2015.

Yellow Fever: Altering the Course of History

Yellow fever originated in Africa and is still most prevalent there today. This disease is thought to have been translocated to the Americas by the slave trade in the 16th century.[8] Since that time, yellow fever has been associated with many severe outbreaks, some of which had important impacts upon historic events.

Yellow fever virus was once an important cause of disease in the US. In the summer of 1793, there was a serious outbreak in Philadelphia (then the US capitol). It is estimated that 5,000 people (10% of the city's population) died. All of the government officials, including George Washington, fled the city in the face of this epidemic. The disease only abated when autumn frosts killed the mosquito vector population.

In 1802, Napoleon Bonaparte sent an army of 40,000 to Hispaniola to suppress a slave revolution. This was seen by many as a part of a plan to use the Louisiana Territory as a granary as he reestablished France as a global power. Yellow fever, however, decimated his army and they were forced to withdraw. Abandoning his aspirations in the New World, Napoleon sold the Louisiana Territory to the US for $15 million in 1803.

The most famous historic event associated with yellow fever is probably the construction of the Panama Canal. The French began work on the canal in the early 1880s. However, engineering problems, malaria, and yellow fever forced them to abandon the project. The US took over the task in 1904 and opened the canal a decade later. During those 10 years, yellow fever was a constant adversary. In the first few years of work, greater than 80% of the American workers in Panama were hospitalized with yellow fever. It was the work of Carlos Finlay and Walter Reed that turned the tide. Taken together, their work demonstrated that the disease was transmitted by mosquitoes. Vector control measures succeeded in reducing both yellow fever and malaria rates and contributed to the ultimate success of the project.

Dengue Fever

The disease dengue fever, also known as breakbone fever, is caused by four serotypes of dengue virus called dengue 1–4. These are *Flavivirus* species that are transmitted to humans by *A. aegypti* or *A. albopictus* mosquitoes. The disease is distributed worldwide but is predominantly located in tropical regions. The WHO estimates that 50 million to 100 million infections occur yearly, including 500,000 dengue hemorrhagic fever (DHF) cases and 22,000 deaths, most among children.[9] Dengue fever is primarily a self-limiting disease characterized by abrupt onset of high fever up to 40 °C (104 °F), intense headaches, rash, slight nose or gum bleeding, and extreme muscle, joint, and bone pain, causing patients to feel as if their bones are breaking, which is the reason this disease is also referred to as breakbone fever. As the body temperature returns to normal, in some patients, signs of dengue hemorrhagic fever may develop that include drowsiness, irritability, severe abdominal pain, severe nose or gum bleeding, persistent vomiting, vomiting blood, and black tarry stools, as the disease progresses to DHF or dengue shock syndrome (DSS). Patients who develop DHF experience circulatory system failure caused by increased blood vessel permeability. Patients with dengue fever can also develop DSS from vascular collapse because of the severe drop in blood pressure. Patients who develop DHF or DSS are at greater risk for death without prompt appropriate supportive treatment. About 30% of patients with severe hemorrhagic disease with poor supportive treatment die, but mortality can be less than 1% with experienced support.[10]

Diagnostic tests for dengue fever include serologic testing, ELISA, and reverse transcriptase-polymerase chain reaction (RT-PCR) of blood. There are no specific treatments for dengue fever, nor is there a vaccine. Instead, supportive clinical care is provided to treat the symptoms of the disease. The best way to limit the impact of this viral pathogen is vector control.

Chikungunya Fever

The arboviral disease chikungunya fever is caused by chikungunya virus (CHIKV), which is transmitted to humans by *A. aegypti* and *A. albopictus* mosquitoes. Until 2013, the disease had not been reported outside of Africa, Asia, and a few European countries; however, CHIKV has now spread to mosquito populations in North and South America. Chikungunya fever is characterized by high fever, joint pain, rash, and blisters, with joint pain persisting for several months. These infections are typically self-limiting and rarely fatal.

The diagnostic approach for chikungunya fever is similar to that for dengue fever. Viruses can be cultured directly from patient serum during early infections. IFA, EIA, ELISA, PCR, and RT-PCR are available to detect CHIKV antigens and patient antibody response to the infection. There are no specific treatments for this disease except to manage symptoms with fluids, analgesics, and bed rest. As with most arboviruses, the best strategy for combating the disease is vector control.

Link to Learning

Use this interactive map to explore the global distribution of dengue.

Exercise 9.2.3.2

1. Name three arboviral diseases and explain why they are so named.
2. What is the best method for controlling outbreaks of arboviral diseases?

Ebola Virus Disease

The Ebola virus disease (EVD) is a highly contagious disease caused by species of *Ebolavirus*, a BSL-4 filovirus (Figure 9.2.3.3). Transmission to humans occurs through direct contact with body fluids (e.g., blood, saliva, sweat, urine, feces, or vomit), and indirect contact by contaminated fomites. Infected patients can easily transmit Ebola virus to others if appropriate containment and use of personal protective equipment is not available or used. Handling and working with patients with EVD is extremely hazardous to the general population and health-care workers. In almost every EVD outbreak there have been Ebola infections among health-care workers. This ease of Ebola virus transmission was recently demonstrated in the Ebola epidemic in Guinea, Liberia, and Sierra Leone in 2014, in which more than 28,000 people in 10 countries were infected and more than 11,000 died.[11]

After infection, the initial symptoms of Ebola are unremarkable: fever, severe headache, myalgia, cough, chest pain, and pharyngitis. As the disease progresses, patients experience abdominal pain, diarrhea, and vomiting. Hemorrhaging begins after about 3 days, with bleeding occurring in the gastrointestinal tract, skin, and many other sites. This often leads to delirium, stupor, and coma, accompanied by shock, multiple organ failure, and death. The mortality rates of EVD often range from 50% to 90%.

The initial diagnosis of Ebola is difficult because the early symptoms are so similar to those of many other illnesses. It is possible to directly detect the virus from patient samples within a few days after symptoms begin, using antigen-capture ELISA, immunoglobulin M (IgM) ELISA, PCR, and virus isolation. There are currently no effective, approved treatments for Ebola other than supportive care and proper isolation techniques to contain its spread.

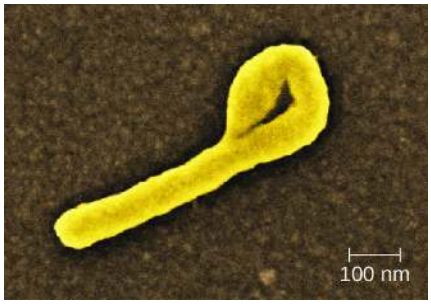


Figure 9.2.3.3: An Ebola virus particle viewed with electron microscopy. These filamentous viruses often exhibit looped or hooked ends. (credit: modification of work by Centers for Disease Control and Prevention)

Exercise 9.2.3.3

How is Ebola transmitted?

Hantavirus

The genus *Hantavirus* consists of at least four serogroups with nine viruses causing two major clinical (sometimes overlapping) syndromes: hantavirus pulmonary syndrome (HPS) in North America and hemorrhagic fever with renal syndrome (HFRS) in other continents. Hantaviruses are found throughout the world in wild rodents that shed the virus in their urine and feces. Transmission

occurs between rodents and to humans through inhalation of aerosols of the rodent urine and feces. Hantaviruses associated with outbreaks in the US and Canada are transmitted by the deer mouse, white-footed mouse, or cotton rat.

HPS begins as a nonspecific flu-like illness with headache, fever, myalgia, nausea, vomiting, diarrhea, and abdominal pain. Patients rapidly develop pulmonary edema and hypotension resulting in pneumonia, shock, and death, with a mortality rate of up to 50%.[12] This virus can also cause HFRS, which has not been reported in the US. The initial symptoms of this condition include high fever, headache, chills, nausea, inflammation or redness of the eyes, or a rash. Later symptoms are hemorrhaging, hypotension, kidney failure, shock, and death. The mortality rate of HFRS can be as high as 15%.[13]

ELISA, Western blot, rapid immunoblot strip assay (RIBA), and RT-PCR detect host antibodies or viral proteins produced during infection. Immunohistological staining may also be used to detect the presence of viral antigens. There are no clinical treatments other than general supportive care available for HPS infections. Patients with HFRS can be treated with ribavirin.[14]

? Exercise 9.2.3.4

Compare the two Hantavirus diseases discussed in this section.

Human Immunodeficiency Virus

Human T-lymphotropic viruses (HTLV), also called human immunodeficiency viruses (HIV) are retroviruses that are the causative agent of acquired immune deficiency syndrome (AIDS). There are two main variants of human immunodeficiency virus (HIV). HIV-1 (Figure 9.2.3.4) occurs in human populations worldwide, whereas HIV-2 is concentrated in West Africa. Currently, the most affected region in the world is sub-Saharan Africa, with an estimated 25.6 million people living with HIV in 2015.[15] Sub-Saharan Africa also accounts for two-thirds of the global total of new HIV infections (Figure 9.2.3.5).[16]

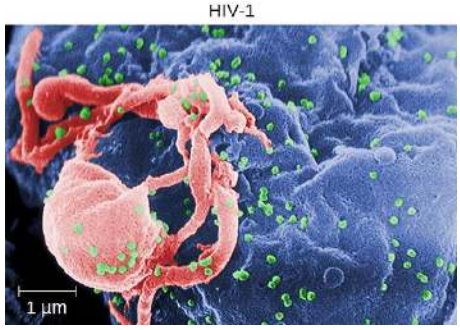


Figure 9.2.3.4: This micrograph shows HIV particles (green) budding from a lymphocyte (top right). (credit: modification of work by Centers for Disease Control and Prevention)

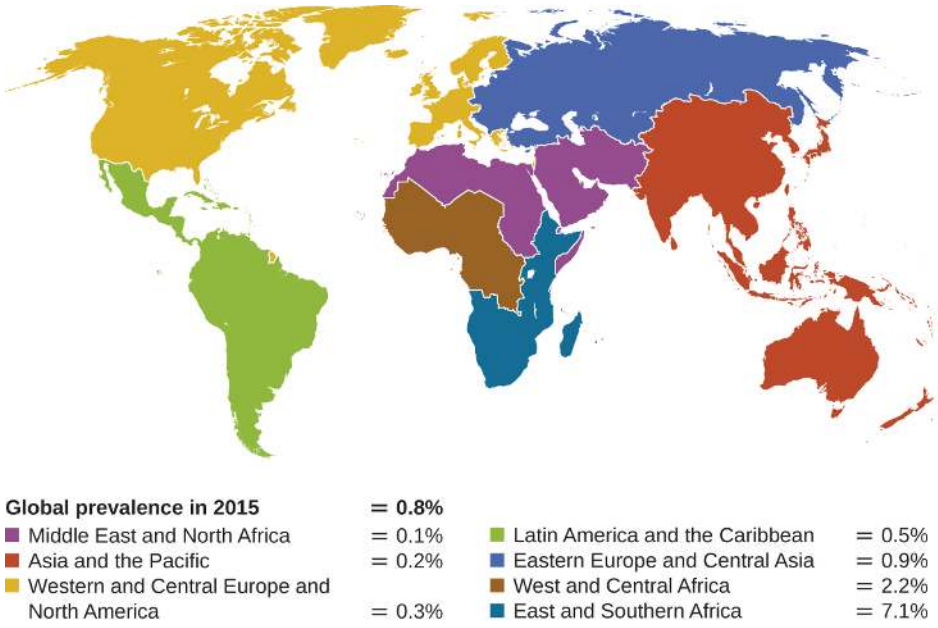


Figure 9.2.3.5: This map shows the prevalence of HIV worldwide in 2015 among adults ages 15–49 years.

HIV is spread through direct contact with body fluids. Casual contact and insect vectors are not sufficient for disease transmission; common modes of transmission include sexual contact and sharing of needles by intravenous (IV) drug users. It generally takes many years before the effects of an HIV infection are detected. HIV infections are not dormant during this period: virions are continually produced, and the immune system continually attempts to clear the viral infection, while the virus persistently infects additional CD4 T cells. Over time, the CD4 T-cell population is devastated, ultimately leading to AIDS.

When people are infected with HIV, their disease progresses through three stages based on CD4 T-cell counts and the presence of clinical symptoms (Figure 9.2.3.6).

- **Stage 1: Acute HIV infection.** Two to 4 weeks after infection with HIV, patients may experience a flu-like illness, which can last for a few weeks. Patients with acute HIV infection have more than 500 cells/μL CD4 T cells and a large amount of virus in their blood. Patients are very contagious during this stage. To confirm acute infection, either a fourth-generation antibody-antigen test or a nucleic acid test (NAT) must be performed.
- **Stage 2: Clinical latency.** During this period, HIV enters a period of dormancy. Patients have between 200 and 499 cells/μL CD4 T cells; HIV is still active but reproduces at low levels, and patients may not experience any symptoms of illness. For patients who are not taking medicine to treat HIV, this period can last a decade or longer. For patients receiving antiretroviral therapy, the stage may last for several decades, and those with low levels of the virus in their blood are much less likely to transmit HIV than those who are not virally suppressed. Near the end of the latent stage, the patient's viral load starts to increase and the CD4 T-cell count begins to decrease, leading to the development of symptoms and increased susceptibility to opportunistic infections.
- **Stage 3: Acquired immunodeficiency syndrome (AIDS).** Patients are diagnosed with AIDS when their CD4 T-cell count drops below 200 cells/μL or when they develop certain opportunistic illnesses. During this stage, the immune system becomes severely damaged by HIV. Common symptoms of AIDS include chills, fever, sweats, swollen lymph glands, weakness, and weight loss; in addition, patients often develop rare cancers such as Kaposi's sarcoma and opportunistic infections such as *Pneumocystis* pneumonia, tuberculosis, cryptosporidiosis, and toxoplasmosis. This is a fatal progression that, in the terminal stages, includes wasting syndrome and dementia complex. Patients with AIDS have a high viral load and are highly infectious; they typically survive about 3 years without treatment.

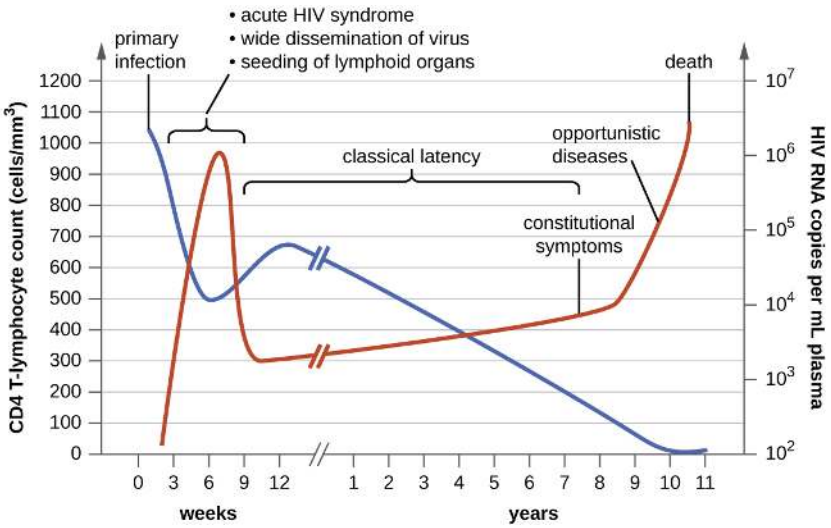


Figure 9.2.3.6: This graph shows the clinical progression of CD4 T cells (blue line), clinical symptoms, and viral RNA (red line) during an HIV infection. (credit: modification of work by Kogan M, and Rappaport J)

The initial diagnosis of HIV is performed using a serological test for antibody production against the pathogen. Positive test results are confirmed by Western blot or PCR tests. It can take weeks or months for the body to produce antibodies in response to an infection. There are fourth-generation tests that detect HIV antibodies and HIV antigens that are present even before the body begins producing antibodies. Nucleic acid tests (NATs) are a third type of test that is relatively expensive and uncommon; NAT can detect HIV in blood and determine the viral load.

As a consequence of provirus formation, it is currently not possible to eliminate HIV from an infected patient's body. Elimination by specific antibodies is ineffective because the virus mutates rapidly—a result of the error-prone reverse transcriptase and the inability to correct errors. Antiviral treatments, however, can greatly extend life expectancy. To combat the problem of drug resistance, combinations of antiretroviral drugs called antiretroviral therapy (ART), sometimes called highly active ART or combined ART, are used. There are several different targets for antiviral drug action (and a growing list of drugs for each of these targets). One class of drugs inhibits HIV entry; other classes inhibit reverse transcriptase by blocking viral RNA-dependent and DNA-dependent DNA polymerase activity; and still others inhibit one of the three HIV enzymes needed to replicate inside human cells.

? Exercise 9.2.3.5

Why is it not yet possible to cure HIV infections?

HIV, AIDS, and Education

When the first outbreaks of AIDS in the US occurred in the early 1980s, very little was known about the disease or its origins. Erroneously, the disease quickly became stigmatized as one associated with what became identified as at-risk behaviors such as sexual promiscuity, homosexuality, and IV drug use, even though mounting evidence indicated the disease was also contracted through transfusion of blood and blood products or by fetuses of infected mothers. In the mid-1980s, scientists elucidated the identity of the virus, its mode of transmission, and mechanisms of pathogenesis. Campaigns were undertaken to educate the public about how HIV spreads to stem infection rates and encourage behavioral changes that reduced the risk for infection. Approaches to this campaign, however, emphasized very different strategies. Some groups favored educational programs that emphasized sexual abstinence, monogamy, heterosexuality, and "just say no to drugs." Other groups placed an emphasis on "safe sex" in sex education programs and advocated social services programs that passed out free condoms to anyone, including sexually active minors, and provided needle exchange programs for IV drug users.

These are clear examples of the intersection between disease and cultural values. As a future health professional, what is your responsibility in terms of educating patients about behaviors that put them at risk for HIV or other diseases while possibly setting your own personal opinions aside? You will no doubt encounter patients whose cultural and moral values differ from

your own. Is it ethical for you to promote your own moral agenda to your patients? How can you advocate for practical disease prevention while still respecting the personal views of your patients?

Viral Diseases of the Circulatory and Lymphatic Systems

Many viruses are able to cause systemic, difficult-to-treat infections because of their ability to replicate within the host. Some of the more common viruses that affect the circulatory system are summarized in Figure 9.2.3.7.

Viral Diseases of the Circulatory and Lymphatic Systems

Disease	Pathogen	Signs and Symptoms	Transmission	Diagnostic Tests	Antimicrobial Drugs
AIDS/HIV infection	Human immunodeficiency virus (HIV)	Flu-like symptoms during acute stage, followed by long period of clinical latency; final stage (AIDS) includes fever, weight loss, wasting syndrome, dementia, and opportunistic secondary infections leading to death	Contact with body fluids (e.g., sexual contact, use of contaminated needles)	Serological tests for antibodies and/or HIV antigens; nucleic acid test (NAT) for presence of virus	Antiretroviral therapy (ART) using various combinations of drugs
Burkitt lymphoma	Epstein-Barr virus (human herpesvirus-4 [HHV-4])	Rapid formation of malignant B-cell tumors, oral hairy leukoplakia; fatal if not promptly treated	Contact with body fluids (e.g., saliva, blood, semen); primarily affects patients immunocompromised by HIV or malaria	CT scans, tumor biopsy	Intensive alternating chemotherapy regimen
Chikungunya fever	Chikungunya virus	Fever, rash, joint pain	Transmitted between humans by *Aedes aegypti* and *A. albopictus* vectors	Viral culture, IFA, EIA, ELISA, PCR, RT-PCR	None
Cytomegalovirus infection	Cytomegalovirus (HHV-5)	Usually asymptomatic but may cause non-Epstein-Barr mononucleosis in adults; may cause developmental issues in developing fetus; in transplant recipients, may cause fever, transplant rejection, death	Contact with body fluids, blood transfusions, organ transplants; infected mothers can transmit virus to fetus transplacentally or to newborn in breastmilk, saliva	Histology, culture, EIA, IFA, PCR	Ganciclovir, valganciclovir, foscarnet, cidofovir
Dengue fever (breakbone fever)	Dengue fever viruses 1–4	Fever, headache, extreme bone and joint pain, abdominal pain, vomiting, hemorrhaging; can be fatal	Transmitted between humans by *A. aegypti* and *A. albopictus* vectors	Serologic testing, ELISA, and PCR	None
Ebola virus disease (EVD)	Ebola virus	Fever, headache, joint pain, diarrhea, vomiting, hemorrhaging in gastrointestinal tract, organ failure; often fatal	Contact with body fluids (e.g., blood, saliva, sweat, urine, feces, vomit); highly contagious	ELISA, IgM ELISA, PCR, virus isolation	None
Hantavirus pulmonary syndrome (HPS)	Hantavirus	Initial flu-like symptoms followed by pulmonary edema and hypotension leading to pneumonia and shock; can be fatal	Inhalation of dried feces, urine from infected mouse or rat	ELISA, Western blot, RIBA, RT-PCR	None
Hemorrhagic fever with renal syndrome	Hantavirus	Fever, headache, nausea, rash, or eye inflammation, followed by hemorrhaging and kidney failure; can be fatal	Inhalation of dried feces, urine from infected mouse or rat	ELISA, Western blot, RIBA, RT-PCR	None
Infectious mononucleosis	Epstein-Barr virus (HHV-4), cytomegalovirus (HHV-5)	Pharyngitis, fever, extreme fatigue; swelling of lymph nodes, spleen, and liver	Contact with body fluids (e.g., saliva, blood, semen)	Tests for antibodies to various EBV-associated antigens	None
Yellow fever	Yellow fever virus	Dizziness, fever, chills, headache, myalgia, nausea, vomiting, constipation, fatigue; moderate to severe cases may include jaundice, rash, mucosal hemorrhaging, seizures, shock, and death	From monkeys to humans or between humans via *Aedes* or *Haemagogus* mosquito vectors	Culture, serology, PCR	None for treatment; preventive vaccine available

Figure 9.2.3.7: Viral diseases of the Circulatory and Lymphatic systems.

Key Concepts and Summary

- Human herpesviruses such **Epstein-Barr virus** (HHV-4) and **cytomegalovirus** (HHV-5) are widely distributed. The former is associated with infectious mononucleosis and Burkitt lymphoma, and the latter can cause serious congenital infections as well as serious disease in immunocompromised adults.

- Arboviral diseases such as y**ellow fever, dengue fever,** and **chikungunya fever** are characterized by high fevers and vascular damage that can often be fatal. **Ebola virus disease** is a highly contagious and often fatal infection spread through contact with bodily fluids.
- Although there is a vaccine available for yellow fever, treatments for patients with yellow fever, dengue, chikungunya fever, and Ebola virus disease are limited to supportive therapies.
- Patients infected with **human immunodeficiency virus (HIV)** progress through three stages of disease, culminating in **AIDS**. **Antiretroviral therapy (ART)** uses various combinations of drugs to suppress viral loads, extending the period of latency and reducing the likelihood of transmission.
- Vector control and animal reservoir control remain the best defenses against most viruses that cause diseases of the circulatory system.

Footnotes

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9.2.4: Parasitic Infections of the Circulatory and Lymphatic Systems

Learning Objectives

- Identify common parasites that cause infections of the circulatory and lymphatic systems
- Compare the major characteristics of specific parasitic diseases affecting the circulatory and lymphatic systems

Some protozoa and parasitic flukes are also capable of causing infections of the human circulatory system. Although these infections are rare in the US, they continue to cause widespread suffering in the developing world today. Fungal infections of the circulatory system are very rare. Therefore, they are not discussed in this chapter.

Malaria

Despite more than a century of intense research and clinical advancements, malaria remains one of the most important infectious diseases in the world today. Its widespread distribution places more than half of the world's population in jeopardy. In 2015, the WHO estimated there were about 214 million cases of malaria worldwide, resulting in about 438,000 deaths; about 88% of cases and 91% of deaths occurred in Africa.[1] Although malaria is not currently a major threat in the US, the possibility of its reintroduction is a concern. Malaria is caused by several protozoan parasites in the genus *Plasmodium*: *P. falciparum*, *P. knowlesi*, *P. malariae*, *P. ovale*, and *P. vivax*. *Plasmodium* primarily infect red blood cells and are transmitted through the bite of *Anopheles* mosquitoes.

Currently, *P. falciparum* is the most common and most lethal cause of malaria, often called falciparum malaria. Falciparum malaria is widespread in highly populated regions of Africa and Asia, putting many people at risk for the most severe form of the disease.

The classic signs and symptoms of malaria are cycles of extreme fever and chills. The sudden, violent symptoms of malaria start with malaise, abrupt chills, and fever (39–41° C [102.2–105.8 °F]), rapid and faint pulse, polyuria, headache, myalgia, nausea, and vomiting. After 2 to 6 hours of these symptoms, the fever falls, and profuse sweating occurs for 2 to 3 hours, followed by extreme fatigue. These symptoms are a result of *Plasmodium* emerging from red blood cells synchronously, leading to simultaneous rupture of a large number of red blood cells, resulting in damage to the spleen, liver, lymph nodes, and bone marrow. The organ damage resulting from hemolysis causes patients to develop sludge blood (i.e., blood in which the red blood cells agglutinate into clumps) that can lead to lack of oxygen, necrosis of blood vessels, organ failure, and death.

In established infections, malarial cycles of fever and chills typically occur every 2 days in the disease described as tertian malaria, which is caused by *P. vivax* and *P. ovale*. The cycles occur every 3 days in the disease described as quartan malaria, which is caused by *P. malariae*. These intervals may vary among cases.

Plasmodium has a complex life cycle that includes several developmental stages alternately produced in mosquitoes and humans (Figure 9.2.4.1). When an infected mosquito takes a blood meal, sporozoites in the mosquito salivary gland are injected into the host's blood. These parasites circulate to the liver, where they develop into schizonts. The schizonts then undergo schizogony, resulting in the release of many merozoites at once. The merozoites move to the bloodstream and infect red blood cells. Inside red blood cells, merozoites develop into trophozoites that produce more merozoites. The synchronous release of merozoites from red blood cells in the evening leads to the symptoms of malaria.

In addition, some trophozoites alternatively develop into male and female gametocytes. The gametocytes are taken up when the mosquito takes a blood meal from an infected individual. Sexual sporogony occurs in the gut of the mosquito. The gametocytes fuse to form zygotes in the insect gut. The zygotes become motile and elongate into an ookinete. This form penetrates the midgut wall and develops into an oocyst. Finally, the oocyst releases new sporozoites that migrate to the mosquito salivary glands to complete the life cycle.

Diagnosis of malaria is by microscopic observation of developmental forms of *Plasmodium* in blood smears and rapid EIA assays that detect *Plasmodium* antigens or enzymes (Figure 9.2.4.2). Drugs such as chloroquine, atovaquone , artemether, and lumefantrine may be prescribed for both acute and prophylactic therapy, although some *Plasmodium* spp. have shown resistance to antimalarial drugs. Use of insecticides and insecticide-treated bed nets can limit the spread of malaria. Despite efforts to develop a vaccine for malaria, none is currently available.

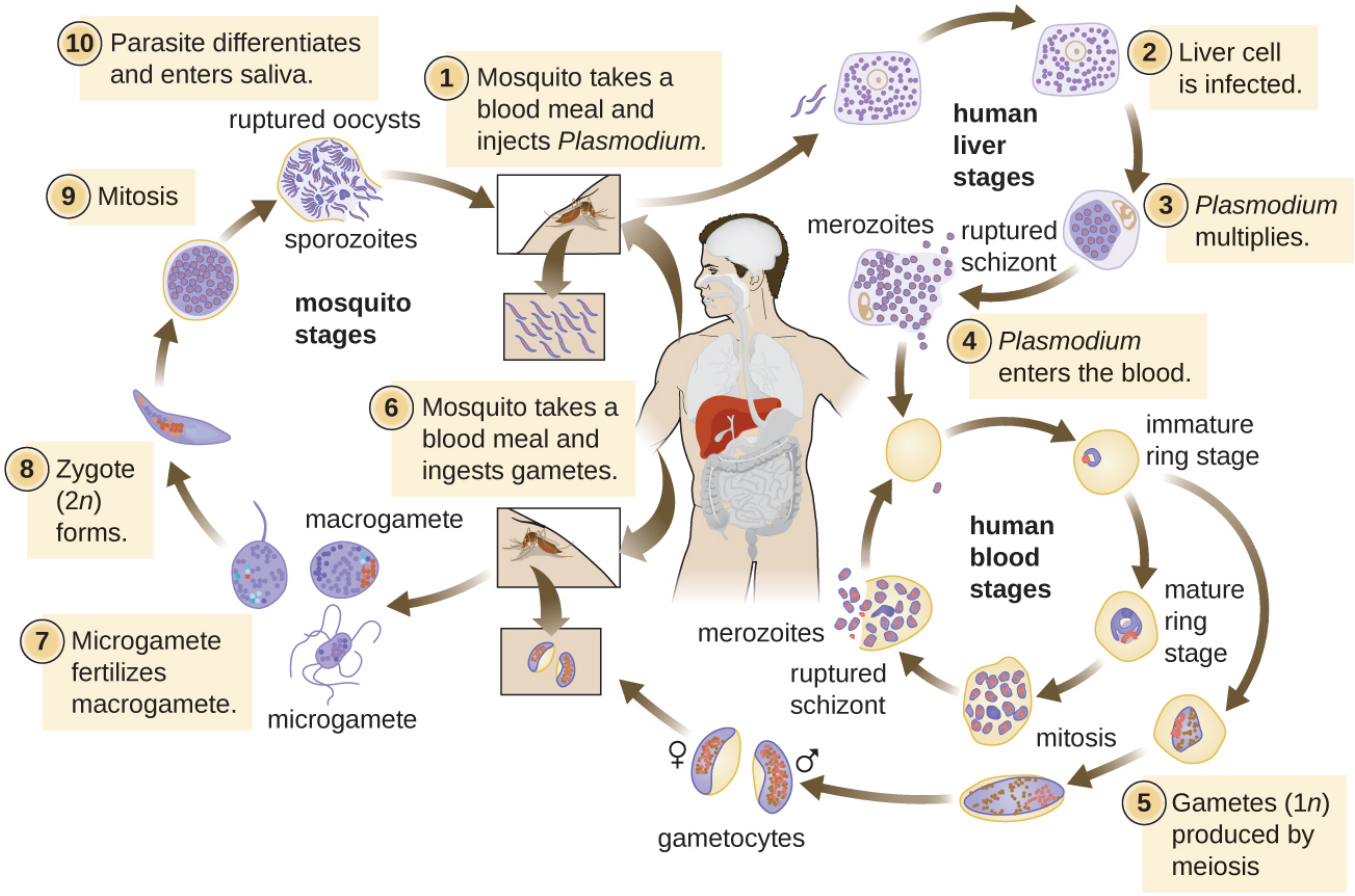


Figure 9.2.4.1: The life cycle of *Plasmodium*. (credit: modification of work by Centers for Disease Control and Prevention)

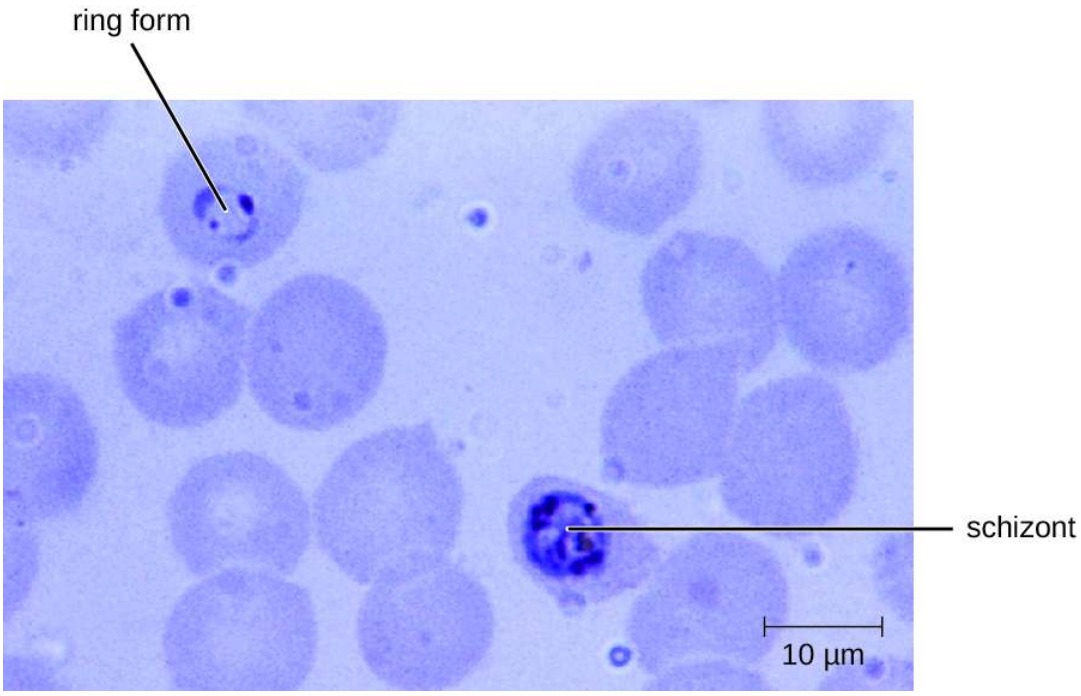


Figure 9.2.4.2: A blood smear (human blood stage) shows an early trophozoite in a delicate ring form (upper left) and an early stage schizont form (center) of *Plasmodium falciparum* from a patient with malaria. (credit: modification of work by Centers for Disease Control and Prevention)

Link to Learning

The Nothing But Nets campaign, an initiative of the United Nations Foundation, has partnered with the Bill and Melinda Gates Foundation to make mosquito bed nets available in developing countries in Africa. Visit their website to learn more about their efforts to prevent malaria.

Exercise 9.2.4.1

Why is malaria one of the most important infectious diseases?

Toxoplasmosis

The disease toxoplasmosis is caused by the protozoan *Toxoplasma gondii*. *T. gondii* is found in a wide variety of birds and mammals,[2] and human infections are common. The Centers for Disease Control and Prevention (CDC) estimates that 22.5% of the population 12 years and older has been infected with *T. gondii*; but immunocompetent individuals are typically asymptomatic, however.[3] Domestic cats are the only known definitive hosts for the sexual stages of *T. gondii* and, thus, are the main reservoirs of infection. Infected cats shed *T. gondii* oocysts in their feces, and these oocysts typically spread to humans through contact with fecal matter on cats' bodies, in litter boxes, or in garden beds where outdoor cats defecate.

T. gondii has a complex life cycle that involves multiple hosts. The *T. gondii* life cycle begins when unsporulated oocysts are shed in the cat's feces. These oocysts take 1–5 days to sporulate in the environment and become infective. Intermediate hosts in nature include birds and rodents, which become infected after ingesting soil, water, or plant material contaminated with the infective oocysts. Once ingested, the oocysts transform into tachyzoites that localize in the bird or rodent neural and muscle tissue, where they develop into tissue cysts. Cats may become infected after consuming birds and rodents harboring tissue cysts. Cats and other animals may also become infected directly by ingestion of sporulated oocysts in the environment. Interestingly, *Toxoplasma* infection appears to be able to modify the host's behavior. Mice infected by *Toxoplasma* lose their fear of cat pheromones. As a result, they become easier prey for cats, facilitating the transmission of the parasite to the cat definitive host[4] (Figure 9.2.4.3).

Toxoplasma infections in humans are extremely common, but most infected people are asymptomatic or have subclinical symptoms. Some studies suggest that the parasite may be able to influence the personality and psychomotor performance of infected humans, similar to the way it modifies behavior in other mammals.[5] When symptoms do occur, they tend to be mild and similar to those of mononucleosis. However, asymptomatic toxoplasmosis can become problematic in certain situations. Cysts can lodge in a variety of human tissues and lie dormant for years. Reactivation of these quiescent infections can occur in immunocompromised patients following transplantation, cancer therapy, or the development of an immune disorder such as AIDS. In patients with AIDS who have toxoplasmosis, the immune system cannot combat the growth of *T. gondii* in body tissues; as a result, these cysts can cause encephalitis, retinitis, pneumonitis, cognitive disorders, and seizures that can eventually be fatal.

Toxoplasmosis can also pose a risk during pregnancy because tachyzoites can cross the placenta and cause serious infections in the developing fetus. The extent of fetal damage resulting from toxoplasmosis depends on the severity of maternal disease, the damage to the placenta, the gestational age of the fetus when infected, and the virulence of the organism. Congenital toxoplasmosis often leads to fetal loss or premature birth and can result in damage to the central nervous system, manifesting as mental retardation, deafness, or blindness. Consequently, pregnant women are advised by the CDC to take particular care in preparing meat, gardening, and caring for pet cats.[6] Diagnosis of toxoplasmosis infection during pregnancy is usually achieved by serology including TORCH testing (the "T" in TORCH stands for toxoplasmosis). Diagnosis of congenital infections can also be achieved by detecting *T. gondii* DNA in amniotic fluid, using molecular methods such as PCR.

In adults, diagnosis of toxoplasmosis can include observation of tissue cysts in tissue specimens. Tissue cysts may be observed in Giemsa- or Wright-stained biopsy specimens, and CT, magnetic resonance imaging, and lumbar puncture can also be used to confirm infection (Figure 9.2.4.4).

Preventing infection is the best first-line defense against toxoplasmosis. Preventive measures include washing hands thoroughly after handling raw meat, soil, or cat litter, and avoiding consumption of vegetables possibly contaminated with cat feces. All meat should be cooked to an internal temperature of 73.9–76.7 °C (165–170 °F).

Most immunocompetent patients do not require clinical intervention for *Toxoplasma* infections. However, neonates, pregnant women, and immunocompromised patients can be treated with pyrimethamine and sulfadiazine—except during the first trimester of pregnancy, because these drugs can cause birth defects. Spiramycin has been used safely to reduce transmission in pregnant women with primary infection during the first trimester because it does not cross the placenta.

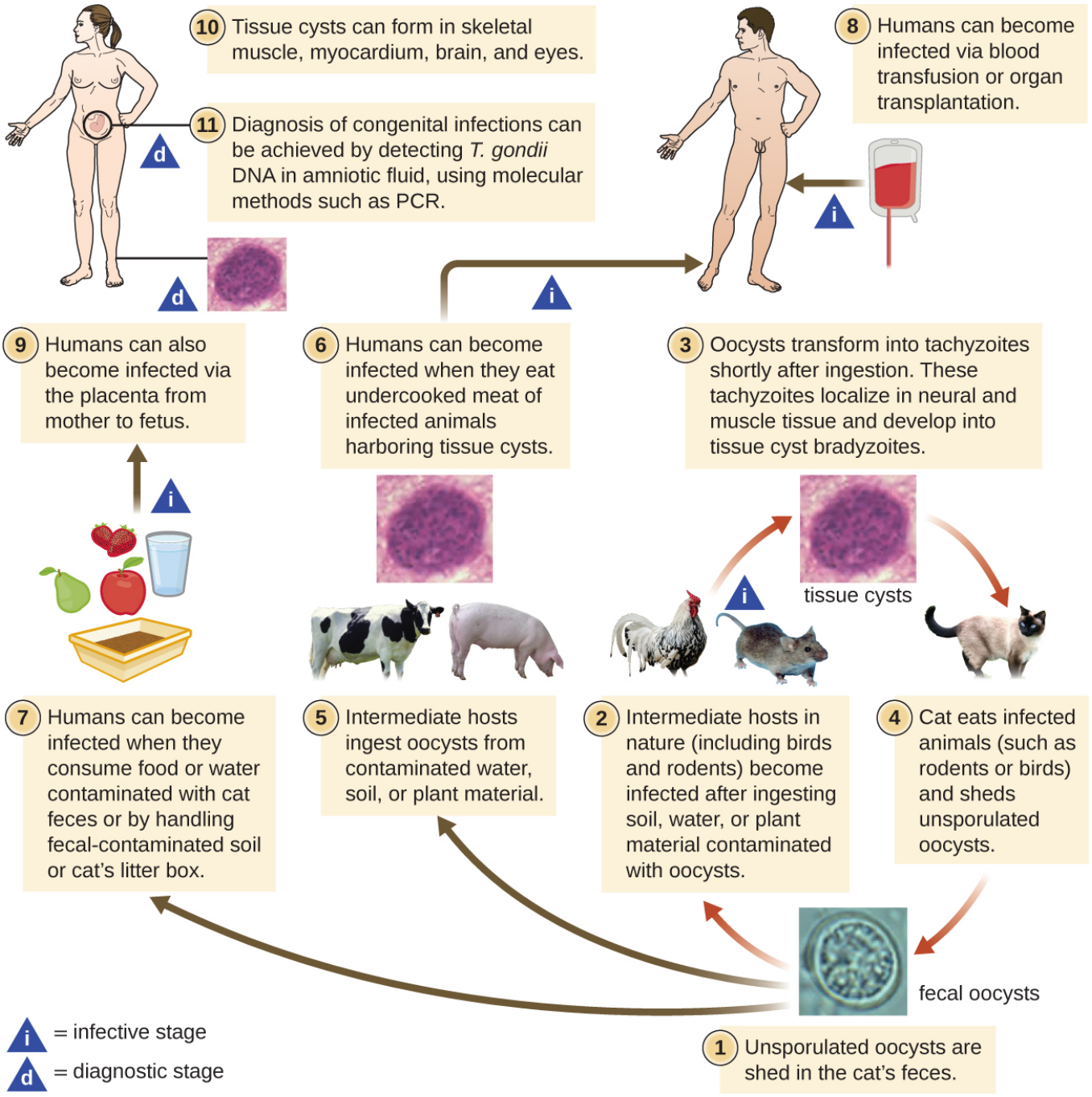


Figure 9.2.4.3: The infectious cycle of *Toxoplasma gondii*. (credit: "diagram": modification of work by Centers for Disease Control and Prevention; credit "cat": modification of work by "KaCey97078"/Flickr)

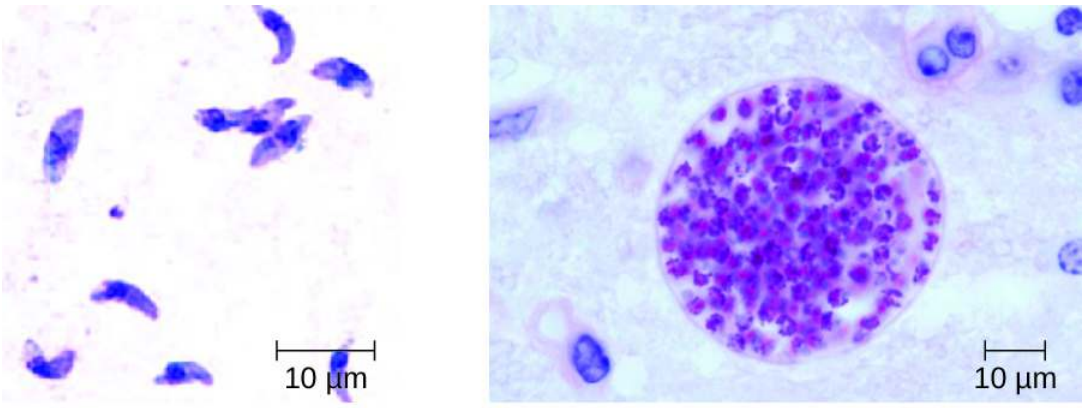


Figure 9.2.4.4: (a) Giemsa-stained *Toxoplasma gondii* tachyzoites from a smear of peritoneal fluid obtained from a mouse inoculated with *T. gondii*. Tachyzoites are typically crescent shaped with a prominent, centrally placed nucleus. (b) Microscopic cyst containing *T. gondii* from mouse brain tissue. Thousands of resting parasites (stained red) are contained in a thin parasite cyst wall. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by USDA)

? Exercise 9.2.4.2

How does *T. gondii* infect humans?

Babesiosis

Babesiosis is a rare zoonotic infectious disease caused by *Babesia* spp. These parasitic protozoans infect various wild and domestic animals and can be transmitted to humans by black-legged *Ixodes* ticks. In humans, *Babesia* infect red blood cells and replicate inside the cell until it ruptures. The *Babesia* released from the ruptured red blood cell continue the growth cycle by invading other red blood cells. Patients may be asymptomatic, but those who do have symptoms often initially experience malaise, fatigue, chills, fever, headache, myalgia, and arthralgia. In rare cases, particularly in asplenic (absence of the spleen) patients, the elderly, and patients with AIDS, babesiosis may resemble falciparum malaria, with high fever, hemolytic anemia, hemoglobinuria (hemoglobin or blood in urine), jaundice, and renal failure, and the infection can be fatal. Previously acquired asymptomatic Babesia infection may become symptomatic if a splenectomy is performed.

Diagnosis is based mainly on the microscopic observation of parasites in blood smears (Figure 9.2.4.5). Serologic and antibody detection by IFA can also be performed and PCR-based tests are available. Many people do not require clinical intervention for Babesia infections, however, serious infections can be cleared with a combination of atovaquone and azithromycin or a combination of clindamycin and quinine.

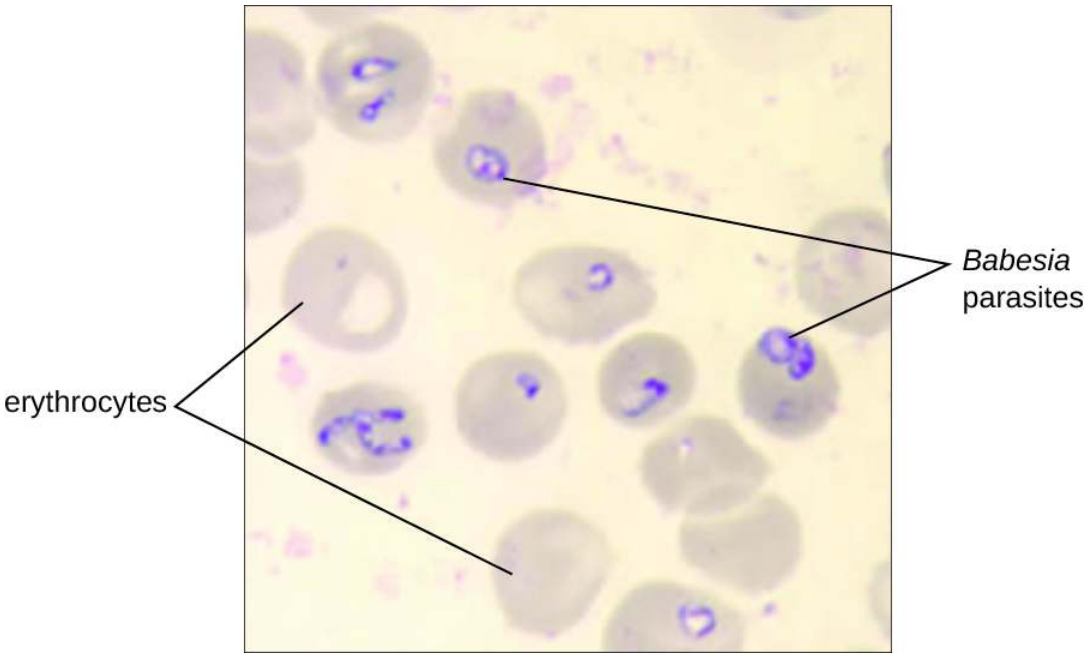


Figure 9.2.4.5: In this blood smear from a patient with babesiosis, *Babesia* parasites can be observed in the red blood cells. (credit: modification of work by Centers for Disease Control and Prevention)

Chagas Disease

Also called American trypanosomiasis, Chagas disease is a zoonosis classified as a neglected tropical disease(NTD). It is caused by the flagellated protozoan *Trypanosoma cruzi* and is most commonly transmitted to animals and people through the feces of triatomine bugs. The triatomine bug is nicknamed the kissing bug because it frequently bites humans on the face or around the eyes; the insect often defecates near the bite and the infected fecal matter may be rubbed into the bite wound by the bitten individual (Figure 9.2.4.6). The bite itself is painless and, initially, many people show no signs of the disease. Alternative modes of transmission include contaminated blood transfusions, organ transplants from infected donors, and congenital transmission from mother to fetus.

Chagas disease is endemic throughout much of Mexico, Central America, and South America, where, according to WHO, an estimated 6 million to 7 million people are infected.[7] Currently, Chagas disease is not endemic in the US, even though triatomine bugs are found in the southern half of the country.

Triatomine bugs typically are active at night, when they take blood meals by biting the faces and lips of people or animals as they sleep and often defecate near the site of the bite. Infection occurs when the host rubs the feces into their eyes, mouth, the bite wound, or another break in the skin. The protozoan then enters the blood and invades tissues of the heart and central nervous system, as well as macrophages and monocytes. Nonhuman reservoirs of *T. cruzi* parasites include wild animals and domesticated animals such as dogs and cats, which also act as reservoirs of the pathogen.[8]

There are three phases of Chagas disease: acute, intermediate, and chronic. These phases can be either asymptomatic or life-threatening depending on the immunocompetence status of the patient.

In acute phase disease, symptoms include fever, headache, myalgia, rash, vomiting, diarrhea, and enlarged spleen, liver, and lymph nodes. In addition, a localized nodule called a chagoma may form at the portal of entry, and swelling of the eyelids or the side of the face, called Romaña's sign, may occur near the bite wound. Symptoms of the acute phase may resolve spontaneously, but if untreated, the infection can persist in tissues, causing irreversible damage to the heart or brain. In rare cases, young children may die of myocarditis or meningoencephalitis during the acute phase of Chagas disease.

Following the acute phase is a prolonged intermediate phase during which few or no parasites are found in the blood and most people are asymptomatic. Many patients will remain asymptomatic for life; however, decades after exposure, an estimated 20%–30% of infected people will develop chronic disease that can be debilitating and sometimes life threatening. In the chronic phase, patients may develop painful swelling of the colon, leading to severe twisting, constipation, and bowel obstruction; painful

swelling of the esophagus, leading to dysphagia and malnutrition; and flaccid cardiomegaly (enlargement of the heart), which can lead to heart failure and sudden death.

Diagnosis can be confirmed through several different tests, including direct microscopic observation of trypanosomes in the blood, IFA, EIAs, PCR, and culturing in artificial media. In endemic regions, xenodiagnoses may be used; this method involves allowing uninfected kissing bugs to feed on the patient and then examining their feces for the presence of *T. cruzi*.

The medications nifurtimox and benznidazole are effective treatments during the acute phase of Chagas disease. The efficacy of these drugs is much lower when the disease is in the chronic phase. Avoiding exposure to the pathogen through vector control is the most effective method of limiting this disease.

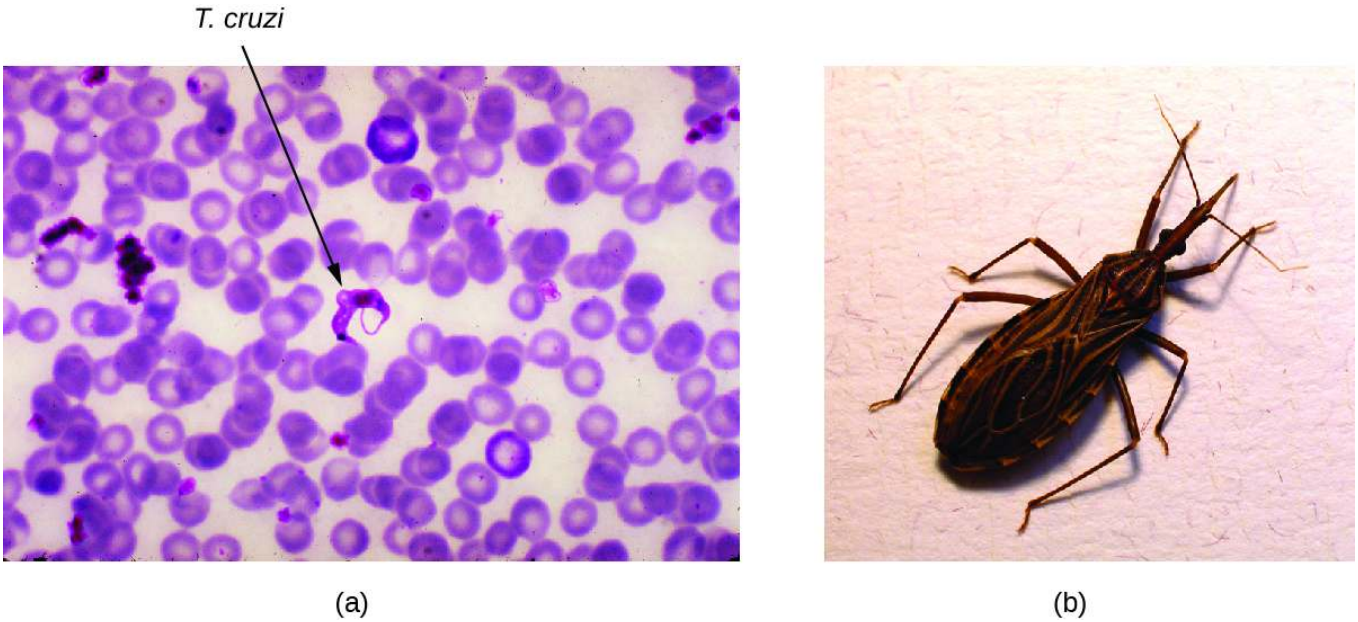


Figure 9.2.4.6: (a) *Trypanosoma cruzi* protozoan in a blood smear from a patient with Chagas disease. (b) The triatomine bug (also known as the kissing bug or assassin bug) is the vector of Chagas disease. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Erwin Huebner)

? Exercise 9.2.4.3

How do kissing bugs infect humans with *Trypanosoma cruzi*?

Leishmaniasis

Although it is classified as an NTD, leishmaniasis is relatively widespread in tropical and subtropical regions, affecting people in more than 90 countries. It is caused by approximately 20 different species of *Leishmania*, protozoan parasites that are transmitted by sand fly vectors such as *Phlebotomus* spp. and *Lutzomyia* spp. Dogs, cats, sheep, horses, cattle rodents, and humans can all serve as reservoirs.

The *Leishmania* protozoan is phagocytosed by macrophages but uses virulence factors to avoid destruction within the phagolysosome. The virulence factors inhibit the phagolysosome enzymes that would otherwise destroy the parasite. The parasite reproduces within the macrophage, lyses it, and the progeny infect new macrophages (see Micro Connections: When Phagocytosis Fails).

The three major clinical forms of leishmaniasis are cutaneous (oriental sore, Delhi boil, Aleppo boil), visceral (kala-azar, Dumdum fever), and mucosal (espundia). The most common form of disease is cutaneous leishmaniasis, which is characterized by the formation of sores at the site of the insect bite that may start out as papules or nodules before becoming large ulcers (Figure 9.2.4.7).

It may take visceral leishmaniasis months and sometimes years to develop, leading to enlargement of the lymph nodes, liver, spleen, and bone marrow. The damage to these body sites triggers fever, weight loss, and swelling of the spleen and liver. It also

causes a decrease in the number of red blood cells (anemia), white blood cells (leukopenia), and platelets (thrombocytopenia), causing the patient to become immunocompromised and more susceptible to fatal infections of the lungs and gastrointestinal tract.

The mucosal form of leishmaniasis is one of the less common forms of the disease. It causes a lesion similar to the cutaneous form but mucosal leishmaniasis is associated with mucous membranes of the mouth, nares, or pharynx, and can be destructive and disfiguring. Mucosal leishmaniasis occurs less frequently when the original cutaneous (skin) infection is promptly treated.

Definitive diagnosis of leishmaniasis is made by visualizing organisms in Giemsa-stained smears, by isolating *Leishmania* protozoans in cultures, or by PCR-based assays of aspirates from infected tissues. Specific DNA probes or analysis of cultured parasites can help to distinguish *Leishmania* species that are causing simple cutaneous leishmaniasis from those capable of causing mucosal leishmaniasis.

Cutaneous leishmaniasis is usually not treated. The lesions will resolve after weeks (or several months), but may result in scarring. Recurrence rates are low for this disease. More serious infections can be treated with stibogluconate(antimony gluconate), amphotericin B, and miltefosine.

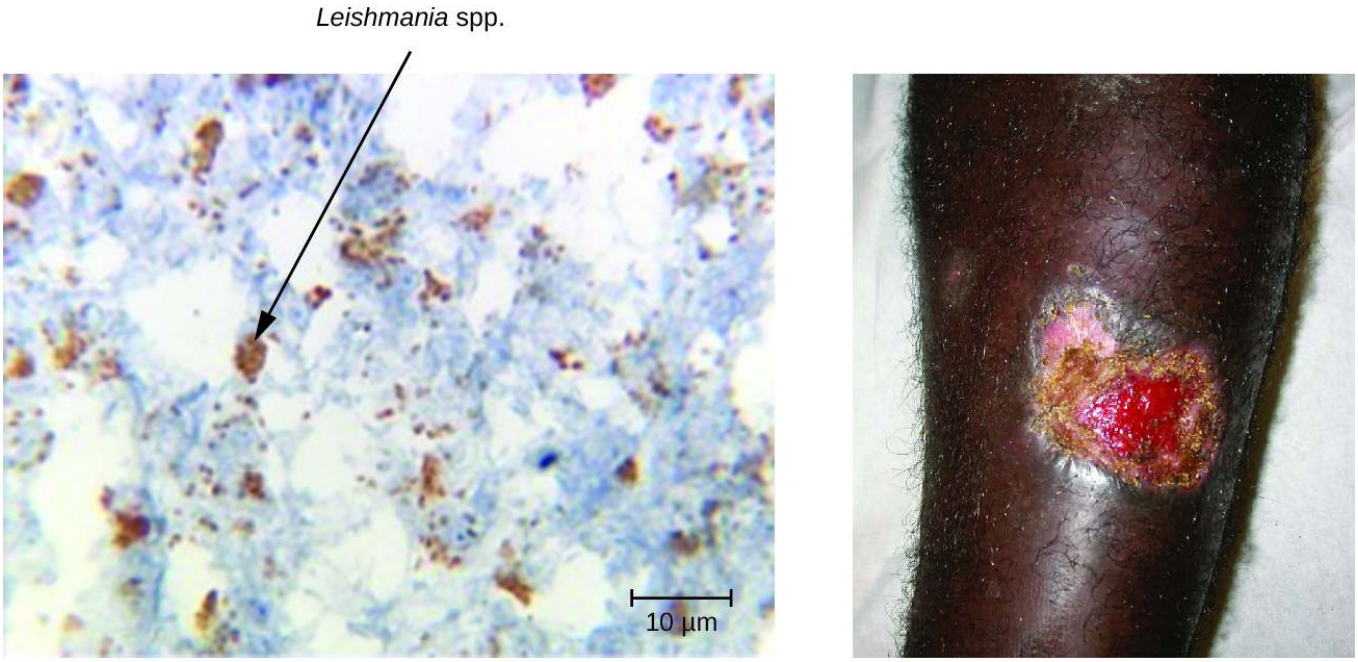


Figure 9.2.4.7: (a) A micrograph of a tissue sample from a patient with localized cutaneous leishmaniasis. Parasitic *Leishmania mexicana* (black arrow) are visible in and around the host cells. (b) Large skin ulcers are associated with cutaneous leishmaniasis. (credit a: modification of work by Fernández-Figueroa EA, Rangel-Escareño C, Espinosa-Mateos V, Carrillo-Sánchez K, Salaiza-Suazo N, Carrada-Figueroa G, March-Mifsut S, and Becker I; credit b: modification of work by Jean Fortunet)

? Exercise 9.2.4.4

Compare the mucosal and cutaneous forms of leishmaniasis.

Schistosomiasis

Schistosomiasis (bilharzia) is an NTD caused by blood flukes in the genus *Schistosoma* that are native to the Caribbean, South America, Middle East, Asia, and Africa. Most human schistosomiasis cases are caused by *Schistosoma mansoni*, *S. haematobium*, or *S. japonicum*. *Schistosoma* are the only trematodes that invade through the skin; all other trematodes infect by ingestion. WHO estimates that at least 258 million people required preventive treatment for schistosomiasis in 2014.[9]

Infected human hosts shed *Schistosoma* eggs in urine and feces, which can contaminate freshwater habitats of snails that serve as intermediate hosts. The eggs hatch in the water, releasing miracidia, an intermediate growth stage of the *Schistosoma* that infect the snails. The miracidia mature and multiply inside the snails, transforming into cercariae that leave the snail and enter the water,

where they can penetrate the skin of swimmers and bathers. The cercariae migrate through human tissue and enter the bloodstream, where they mature into adult male and female worms that mate and release fertilized eggs. The eggs travel through the bloodstream and penetrate various body sites, including the bladder or intestine, from which they are excreted in urine or stool to start the life cycle over again (Figure 5.2.4).

A few days after infection, patients may develop a rash or itchy skin associated with the site of cercariae penetration. Within 1–2 months of infection, symptoms may develop, including fever, chills, cough, and myalgia, as eggs that are not excreted circulate through the body. After years of infection, the eggs become lodged in tissues and trigger inflammation and scarring that can damage the liver, central nervous system, intestine, spleen, lungs, and bladder. This may cause abdominal pain, enlargement of the liver, blood in the urine or stool, and problems passing urine. Increased risk for bladder cancer is also associated with chronic *Schistosoma* infection. In addition, children who are repeatedly infected can develop malnutrition, anemia, and learning difficulties.

Diagnosis of schistosomiasis is made by the microscopic observation of eggs in feces or urine, intestine or bladder tissue specimens, or serologic tests. The drug praziquantel is effective for the treatment of all schistosome infections. Improving wastewater management and educating at-risk populations to limit exposure to contaminated water can help control the spread of the disease.

Cercarial Dermatitis

The cercaria of some species of *Schistosoma* can only transform into adult worms and complete their life cycle in animal hosts such as migratory birds and mammals. The cercaria of these worms are still capable of penetrating human skin, but they are unable to establish a productive infection in human tissue. Still, the presence of the cercaria in small blood vessels triggers an immune response, resulting in itchy raised bumps called cercarial dermatitis (also known as swimmer’s itch or clam digger's itch). Although it is uncomfortable, cercarial dermatitis is typically self-limiting and rarely serious. Antihistamines and antipruritics can be used to limit inflammation and itching, respectively.

? Exercise 9.2.4.5

How do schistosome infections in humans occur?

Common Eukaryotic Pathogens of the Human Circulatory System

Protozoan and helminthic infections are prevalent in the developing world. A few of the more important parasitic infections are summarized in Figure 9.2.4.8.

Parasitic Diseases of the Circulatory and Lymphatic Systems					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Protozoa					
Babesiosis	*Babesia* spp.	Malaise, chills, fever, headache, myalgia, arthralgia	From animals to humans via *Ixodes* tick vectors	Blood smear, serology, IFA, and PCR	Atovaquone and azithromycin or clindamycin and quinine
Chagas disease	*Trypanosoma cruzi*	Fever, headache, body aches, swollen lymph nodes; potentially fatal	Between humans or from animal reservoirs via triatomine (kissing bug) vector	Blood smear, IFA, EIA, PCR, xenodiagnosis	Nifurtimox, benznidazole
Leishmaniasis	*Leishmania* spp.	Ulcer; enlargement of the lymph nodes, liver, spleen, and other organs	Between humans or from animal reservoirs via sand fly (*Phlebotomus* spp., *Lutzomyia* spp.) vectors	Blood smear, culture, PCR, DNA probe, biopsy	Stibogluconate, amphotericin B.
Malaria	*Plasmodium vivax, P. malariae, P. falciparum, P. ovale, P. knowlesi*	Extreme fever, chills, myalgia, nausea, and vomiting, possibly leading to organ failure and death	Between humans via *Anopheles* mosquito vectors	Blood smear, EIA	Chloroquine, atovaquone, artemether, and lumefantrine
Toxoplasmosis	*Toxoplasma gondii*	Tissue cysts; in pregnant women, birth defects or miscarriage	Contact with feces of infected cat; eating contaminated vegetables or undercooked meat of infected animal	Serological tests, direct detection of pathogen in tissue sections	Sulfadiazine, pyrimethamine, spiramycin
Helminths					
Schistosomiasis	*Schistosoma* spp.	Rash, fever, chills, myalgia; chronic inflammation and scarring of liver, spleen, and other organs where cysts develop	Snail hosts release cercaria into freshwater; cercaria burrow into skin of swimmers and bathers	Eggs in stool or urine, tissue biopsy, serological testing	Praziquantel

Figure 9.2.4.8: Parasitic diseases of the Circulatory and Lymphatic systems.

Clinical Focus: Resolution

Despite continued antibiotic treatment and the removal of the venous catheter, Barbara's condition further declined. She began to show signs of shock and her blood pressure dropped to 77/50 mmHg. Anti-inflammatory drugs and drotrecogin-α were administered to combat sepsis. However, by the seventh day of hospitalization, Barbara experienced hepatic and renal failure and died.

Staphylococcus aureus most likely formed a biofilm on the surface of Barbara's catheter. From there, the bacteria were chronically shed into her circulation and produced the initial clinical symptoms. The chemotherapeutic therapies failed in large part because of the drug-resistant MRSA isolate. Virulence factors like leukocidin and hemolysins also interfered with her immune response. Barbara's ultimate decline may have been a consequence of the production of enterotoxins and toxic shock syndrome toxin (TSST), which can initiate toxic shock.

Venous catheters are common life-saving interventions for many patients requiring long-term administration of medication or fluids. However, they are also common sites of bloodstream infections. The World Health Organization estimates that there are up to 80,000 catheter-related bloodstream infections each year in the US, resulting in about 20,000 deaths.[10]

Key Concepts and Summary

- **Malaria** is a protozoan parasite that remains an important cause of death primarily in the tropics. Several species in the genus *Plasmodium* are responsible for malaria and all are transmitted by *Anopheles* mosquitoes. *Plasmodium* infects and destroys human red blood cells, leading to organ damage, anemia, blood vessel necrosis, and death. Malaria can be treated with various antimalarial drugs and prevented through vector control.
- **Toxoplasmosis** is a widespread protozoal infection that can cause serious infections in the immunocompromised and in developing fetuses. Domestic cats are the definitive host.
- Babesiosis is a generally asymptomatic infection of red blood cells that can causes malaria-like symptoms in elderly, immunocompromised, or asplenic patients.
- **Chagas disease** is a tropical disease transmitted by triatomine bugs. The trypanosome infects heart, neural tissues, monocytes, and phagocytes, often remaining latent for many years before causing serious and sometimes fatal damage to the digestive system and heart.
- **Leishmaniasis** is caused by the protozoan *Leishmania* and is transmitted by sand flies. Symptoms are generally mild, but serious cases may cause organ damage, anemia, and loss of immune competence.
- **Schistosomiasis** is caused by a fluke transmitted by snails. The fluke moves throughout the body in the blood stream and chronically infects various tissues, leading to organ damage.

Footnotes

1. 1 World Health Organization. "World Malaria Report 2015: Summary." 2015. http://www.who.int/malaria/publicati...015/report/en/. Accessed July 28, 2016.
2. 2 A.M. Tenter et al.. "*Toxoplasma gondii*: From Animals to Humans." *International Journal for Parasitology* 30 no. 12-13 (2000):1217–1258.
3. 3 Centers for Disease Control and Prevention. "Parasites - Toxoplasmosis (Toxoplasma Infection). Epidemiology & Risk Factors." 2015 http://www.cdc.gov/parasites/toxoplasmosis/epi.html. Accessed July 28, 2016.
4. 4 J. Flegr. "Effects of *Toxoplasma* on Human Behavior." *Schizophrenia Bulletin* 33, no. 3 (2007):757–760.
5. 5 Ibid
6. 6 Centers for Disease Control and Prevention. "Parasites - Toxoplasmosis (Toxoplasma infection). Toxoplasmosis Frequently Asked Questions (FAQs)." 2013. http://www.cdc.gov/parasites/toxopla...info/faqs.html. Accessed July 28, 2016.
7. 7 World Health Organization. "Chagas disease (American trypanosomiasis). Fact Sheet." 2016. http://www.who.int/mediacentre/factsheets/fs340/en/. Accessed July 29, 2016.
8. 8 C.E. Reisenman et al. "Infection of Kissing Bugs With *Trypanosoma cruzi*, Tucson, Arizona, USA." *Emerging Infectious Diseases* 16 no. 3 (2010):400–405.
9. 9 World Health Organization. "Schistosomiasis. Fact Sheet." 2016. http://www.who.int/mediacentre/factsheets/fs115/en/. Accessed July 29, 2016.

10. 10 World Health Organization. “Patient Safety, Preventing Bloodstream Infections From Central Line Venous Catheters.” 2016. www.who.int/patientsafety/imp...tation/bsi/en/. Accessed July 29, 2016.

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9.2.E: Circulatory and Lymphatic System Infections (Exercises)

25.1: Anatomy of the Circulatory and Lymphatic Systems

The circulatory and lymphatic systems are networks of vessels and a pump that transport blood and lymph, respectively, throughout the body. When these systems are infected with a microorganism, the network of vessels can facilitate the rapid dissemination of the microorganism to other regions of the body, sometimes with serious results. In this section, we examine some of the key anatomical features of the circulatory and lymphatic systems, as well as general signs and symptoms of infection.

Multiple Choice

Which term refers to an inflammation of the blood vessels?

A. lymphangitis
B. endocarditis
C. pericarditis
D. vasculitis

Answer

D

Which of the following is located in the interstitial spaces within tissues and releases nutrients, immune factors, and oxygen to those tissues?

A. lymphatics
B. arterioles
C. capillaries
D. veins

Answer

C

Which of these conditions results in the formation of a bubo?

A. lymphangitis
B. lymphadenitis
C. ischemia
D. vasculitis

Answer

B

Which of the following is where most microbes are filtered out of the fluids that accumulate in the body tissues?

A. spleen
B. lymph nodes
C. pericardium
D. blood capillaries

Answer

B

Fill in the Blank

Vasculitis can cause blood to leak from damaged vessels, forming purple spots called _____.

Answer

petechiae

The lymph reenters the vascular circulation at _____.

Answer

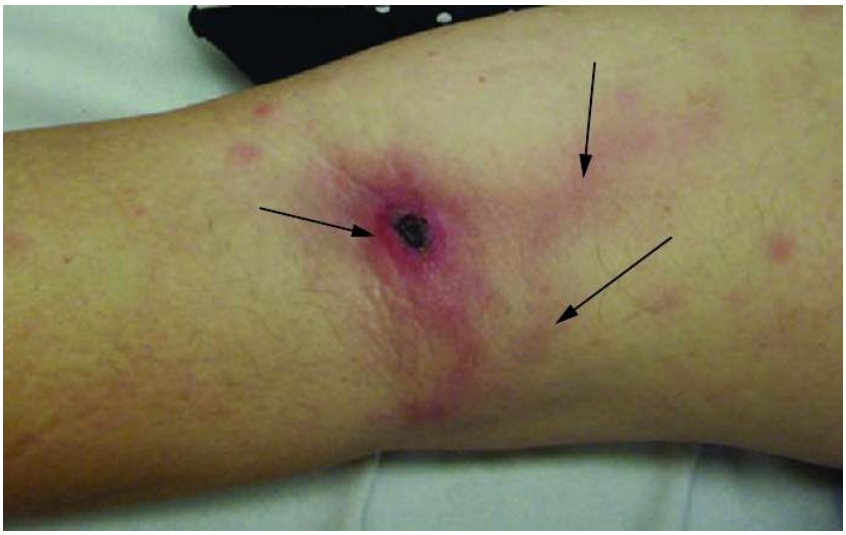
the subclavian veins

Short Answer

How do lymph nodes help to maintain a microbial-free circulatory and lymphatic system?

Critical Thinking

What term refers to the red streaks seen on this patient's skin? What is likely causing this condition?



(credit: modification of work by Centers for Disease Control and Prevention)

Why would septicemia be considered a more serious condition than bacteremia?

25.2: Bacterial Infections of the Circulatory and Lymphatic Systems

Bacterial infections of the circulatory system are almost universally serious. Left untreated, most have high mortality rates. Bacterial pathogens usually require a breach in the immune defenses to colonize the circulatory system. Most often, this involves a wound or the bite of an arthropod vector, but it can also occur in hospital settings and result in nosocomial infections.

Multiple Choice

Which of the following diseases is caused by a spirochete?

A. tularemia
B. relapsing fever
C. rheumatic fever
D. Rocky Mountain spotted fever

Answer

B

Which of the following diseases is transmitted by body lice?

A. tularemia
B. bubonic plague
C. murine typhus

D. epidemic typhus

Answer

D

What disease is most associated with *Clostridium perfringens*?

A. endocarditis
B. osteomyelitis
C. gas gangrene
D. rat bite fever

Answer

C

Which bacterial pathogen causes plague?

A. *Yersinia pestis*
B. *Bacillus moniliformis*
C. *Bartonella quintana*
D. *Rickettsia rickettsii*

Answer

A

Fill in the Blank

Lyme disease is characterized by a(n) _____ that forms at the site of infection.

Answer

bull's eye-rash

_____ refers to a loss of blood pressure resulting from a system-wide infection.

Answer

Septic shock

Short Answer

What are the three forms of plague and how are they contracted?

Compare epidemic and murine typhus.

Critical Thinking

Why are most vascular pathogens poorly communicable from person to person?

How have human behaviors contributed to the spread or control of arthropod-borne vascular diseases?

25.3: Viral Infections of the Circulatory and Lymphatic Systems

Viral pathogens of the circulatory system vary tremendously both in their virulence and distribution worldwide. Some of these pathogens are practically global in their distribution. Fortunately, the most ubiquitous viruses tend to produce the mildest forms of disease. In the majority of cases, those infected remain asymptomatic. On the other hand, other viruses are associated with life-threatening diseases that have impacted human history.

Multiple Choice

Which of the following viruses is most widespread in the human population?

A. human immunodeficiency virus
B. Ebola virus
C. Epstein-Barr virus
D. hantavirus

Answer

C

Which of these viruses is spread through mouse urine or feces?

A. Epstein-Barr
B. hantavirus
C. human immunodeficiency virus
D. cytomegalovirus

Answer

B

A patient at a clinic has tested positive for HIV. Her blood contained 700/µL CD4 T cells and she does not have any apparent illness. Her infection is in which stage?

A. 1
B. 2
C. 3

Answer

A

Fill in the Blank

_____ is a cancer that forms in patients with HHV-4 and malaria coinfections.

Answer

Burkitt lymphoma

_____ are transmitted by vectors such as ticks or mosquitoes.

Answer

Arboviruses

Infectious mononucleosis is caused by _____ infections.

Answer

Epstein-Barr virus

Short Answer

Describe the progression of an HIV infection over time with regard to the number of circulating viruses, host antibodies, and CD4 T cells.

Describe the general types of diagnostic tests used to diagnose patients infected with HIV.

Identify the general categories of drugs used in ART used to treat patients infected with HIV.

Critical Thinking

Which is a bigger threat to the US population, Ebola or yellow fever? Why?

25.4: Parasitic Infections of the Circulatory and Lymphatic Systems

Some protozoa and parasitic flukes are also capable of causing infections of the human circulatory system. Although these infections are rare in the US, they continue to cause widespread suffering in the developing world today. Malaria, toxoplasmosis, babesiosis, Chagas disease, leishmaniasis, and schistosomiasis are discussed in this section.

Multiple Choice

Which of the following diseases is caused by a helminth?

A. leishmaniasis
B. malaria
C. Chagas disease
D. schistosomiasis

Answer

D

Which of these is the most common form of leishmaniasis?

A. cutaneous
B. mucosal
C. visceral
D. intestinal

Answer

A

Which of the following is a causative agent of malaria?

A. *Trypanosoma cruzi*
B. *Toxoplasma gondii*
C. *Plasmodium falciparum*
D. *Schistosoma mansoni*

Answer

C

Which of the following diseases does not involve an arthropod vector?

A. schistosomiasis
B. malaria
C. Chagas disease
D. babesiosis

Answer

A

Fill in the Blank

The _____ mosquito is the biological vector for malaria.

Answer

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Anopheles

The kissing bug is the biological vector for _____.

Answer

Chagas disease

Cercarial dermatitis is also known as _____.

Answer

swimmer’s itch

Short Answer

Describe main cause of *Plasmodium falciparum* infection symptoms.

Why should pregnant women avoid cleaning their cat’s litter box or do so with protective gloves?

Critical Thinking

What measures can be taken to reduce the likelihood of malaria reemerging in the US?

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CHAPTER OVERVIEW

10: Infectious Diseases affecting the Gastrointestinal Tract and Respiratory System

Topic hierarchy

10.1: Animal Nutrition and the Digestive System
- 10.1.1: Prelude to Animal Nutrition and the Digestive System
- 10.1.2: Video - The Digestive System
- 10.1.3: Digestive Systems
- 10.1.4: Nutrition and Energy Production
- 10.1.5: Digestive System Processes
- 10.1.6: Digestive System Regulation
- 10.1.E: Animal Nutrition and the Digestive System (Exercises)

10.2: Digestive System Infections
- 10.2.1: Anatomy and Normal Microbiota of the Digestive System
- 10.2.2: Microbial Diseases of the Mouth and Oral Cavity
- 10.2.3: Bacterial Infections of the Gastrointestinal Tract
- 10.2.4: Viral Infections of the Gastrointestinal Tract
- 10.2.5: Protozoan Infections of the Gastrointestinal Tract
- 10.2.6: Helminthic Infections of the Gastrointestinal Tract
- 10.2.E: Digestive System Infections (Exercises)

10.3: The Respiratory System
- 10.3.1: Prelude to the Respiratory System
- 10.3.2: Systems of Gas Exchange
- 10.3.3: Gas Exchange across Respiratory Surfaces
- 10.3.4: Breathing
- 10.3.5: Transport of Gases in Human Bodily Fluids
- 10.3.E: The Respiratory System (Exercises)

10.4: Respiratory System Infections
- 10.4.1: Anatomy and Normal Microbiota of the Respiratory Tract
- 10.4.2: Bacterial Infections of the Respiratory Tract
- 10.4.3: Viral Infections of the Respiratory Tract
- 10.4.4: Respiratory Mycoses
- 10.4.E: Respiratory System Infections (Exercises)

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SECTION OVERVIEW

10.1: Animal Nutrition and the Digestive System

All living organisms need nutrients to survive. While plants can obtain the molecules required for cellular function through the process of photosynthesis, most animals obtain their nutrients by the consumption of other organisms. At the cellular level, the biological molecules necessary for animal function are amino acids, lipid molecules, nucleotides, and simple sugars. However, the food consumed consists of protein, fat, and complex carbohydrates. Animals must convert these macromolecules into the simple molecules required for maintaining cellular functions, such as assembling new molecules, cells, and tissues. The conversion of the food consumed to the nutrients required is a multi-step process involving digestion and absorption. During digestion, food particles are broken down to smaller components, and later, they are absorbed by the body.

10.1.1: Prelude to Animal Nutrition and the Digestive System

10.1.2: Video - The Digestive System

10.1.3: Digestive Systems

10.1.4: Nutrition and Energy Production

10.1.5: Digestive System Processes

10.1.6: Digestive System Regulation

10.1.E: Animal Nutrition and the Digestive System (Exercises)

Thumbnail: Intestine. (Image by JimCoote from Pixabay).

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10.1.1: Prelude to Animal Nutrition and the Digestive System

All living organisms need nutrients to survive. While plants can obtain the molecules required for cellular function through the process of photosynthesis, most animals obtain their nutrients by the consumption of other organisms. At the cellular level, the biological molecules necessary for animal function are amino acids, lipid molecules, nucleotides, and simple sugars. However, the food consumed consists of protein, fat, and complex carbohydrates. Animals must convert these macromolecules into the simple molecules required for maintaining cellular functions, such as assembling new molecules, cells, and tissues. The conversion of the food consumed to the nutrients required is a multi-step process involving digestion and absorption. During digestion, food particles are broken down to smaller components, and later, they are absorbed by the body.



Figure 10.1.1.1: For humans, fruits and vegetables are important in maintaining a balanced diet. (credit: modification of work by Julie Rybarczyk)

One of the challenges in human nutrition is maintaining a balance between food intake, storage, and energy expenditure. Imbalances can have serious health consequences. For example, eating too much food while not expending much energy leads to obesity, which in turn will increase the risk of developing illnesses such as type-2 diabetes and cardiovascular disease. The recent rise in obesity and related diseases makes understanding the role of diet and nutrition in maintaining good health all the more important.

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10.1.2: Video - The Digestive System

This video takes us through the bowels of the human digestive system and explains why it's all about surface area.



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10.1.3: Digestive Systems

Skills to Develop

- Explain the processes of digestion and absorption
- Compare and contrast different types of digestive systems
- Explain the specialized functions of the organs involved in processing food in the body
- Describe the ways in which organs work together to digest food and absorb nutrients

Animals obtain their nutrition from the consumption of other organisms. Depending on their diet, animals can be classified into the following categories: plant eaters (herbivores), meat eaters (carnivores), and those that eat both plants and animals (omnivores). The nutrients and macromolecules present in food are not immediately accessible to the cells. There are a number of processes that modify food within the animal body in order to make the nutrients and organic molecules accessible for cellular function. As animals evolved in complexity of form and function, their digestive systems have also evolved to accommodate their various dietary needs.

Herbivores, Omnivores, and Carnivores

Herbivores are animals whose primary food source is plant-based. Examples of herbivores, as shown in Figure 10.1.3.1 include vertebrates like deer, koalas, and some bird species, as well as invertebrates such as crickets and caterpillars. These animals have evolved digestive systems capable of handling large amounts of plant material. Herbivores can be further classified into frugivores (fruit-eaters), granivores (seed eaters), nectivores (nectar feeders), and folivores (leaf eaters).



(a) (b)

Figure 10.1.3.1: Herbivores, like this (a) mule deer and (b) monarch caterpillar, eat primarily plant material. (credit a: modification of work by Bill Ebbesen; credit b: modification of work by Doug Bowman)

Carnivores are animals that eat other animals. The word carnivore is derived from Latin and literally means “meat eater.” Wild cats such as lions, shown in Figure 10.1.3.2a and tigers are examples of vertebrate carnivores, as are snakes and sharks, while invertebrate carnivores include sea stars, spiders, and ladybugs, shown in Figure 10.1.3.2b. Obligate carnivores are those that rely entirely on animal flesh to obtain their nutrients; examples of obligate carnivores are members of the cat family, such as lions and cheetahs. Facultative carnivores are those that also eat non-animal food in addition to animal food. Note that there is no clear line that differentiates facultative carnivores from omnivores; dogs would be considered facultative carnivores.



(a)



(b)

Figure 10.1.3.2: Carnivores like the (a) lion eat primarily meat. The (b) ladybug is also a carnivore that consumes small insects called aphids. (credit a: modification of work by Kevin Pluck; credit b: modification of work by Jon Sullivan)

Omnivores are animals that eat both plant- and animal-derived food. In Latin, omnivore means to eat everything. Humans, bears (shown in Figure 10.1.3.3a), and chickens are example of vertebrate omnivores; invertebrate omnivores include cockroaches and crayfish (shown in Figure 10.1.3.3b).



(a)



(b)

Figure 10.1.3.3: Omnivores like the (a) bear and (b) crayfish eat both plant and animal based food. (credit a: modification of work by Dave Menke; credit b: modification of work by Jon Sullivan)

Invertebrate Digestive Systems

Animals have evolved different types of digestive systems to aid in the digestion of the different foods they consume. The simplest example is that of a gastrovascular cavity and is found in organisms with only one opening for digestion. Platyhelminthes (flatworms), Ctenophora (comb jellies), and Cnidaria (coral, jelly fish, and sea anemones) use this type of digestion. Gastrovascular cavities, as shown in Figure 10.1.3.4a, are typically a blind tube or cavity with only one opening, the “mouth”, which also serves as an “anus”. Ingested material enters the mouth and passes through a hollow, tubular cavity. Cells within the cavity secrete digestive enzymes that break down the food. The food particles are engulfed by the cells lining the gastrovascular cavity.

The alimentary canal, shown in Figure 10.1.3.4b, is a more advanced system: it consists of one tube with a mouth at one end and an anus at the other. Earthworms are an example of an animal with an alimentary canal. Once the food is ingested through the mouth, it passes through the esophagus and is stored in an organ called the crop; then it passes into the gizzard where it is churned and

digested. From the gizzard, the food passes through the intestine, the nutrients are absorbed, and the waste is eliminated as feces, called castings, through the anus.

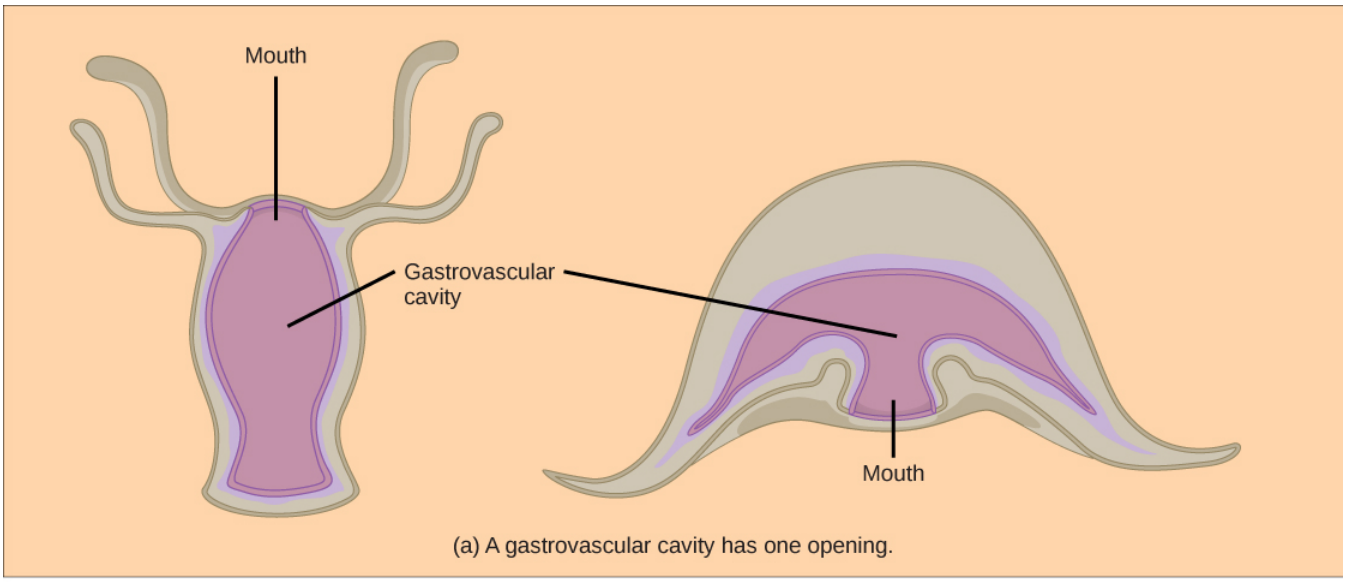


Figure 10.1.3.4: (a) A gastrovascular cavity has a single opening through which food is ingested and waste is excreted, as shown in this hydra and in this jellyfish medusa. (b) An alimentary canal has two openings: a mouth for ingesting food, and an anus for eliminating waste, as shown in this nematode.

Vertebrate Digestive Systems

Vertebrates have evolved more complex digestive systems to adapt to their dietary needs. Some animals have a single stomach, while others have multi-chambered stomachs. Birds have developed a digestive system adapted to eating unmasticated food.

Monogastric: Single-chambered Stomach

As the word monogastric suggests, this type of digestive system consists of one (“mono”) stomach chamber (“gastric”). Humans and many animals have a monogastric digestive system as illustrated in Figure 10.1.3.5. The process of digestion begins with the mouth and the intake of food. The teeth play an important role in masticating (chewing) or physically breaking down food into smaller particles. The enzymes present in saliva also begin to chemically break down food. The esophagus is a long tube that connects the mouth to the stomach. Using peristalsis, or wave-like smooth muscle contractions, the muscles of the esophagus push the food towards the stomach. In order to speed up the actions of enzymes in the stomach, the stomach is an extremely acidic environment, with a pH between 1.5 and 2.5. The gastric juices, which include enzymes in the stomach, act on the food particles and continue the process of digestion. Further breakdown of food takes place in the small intestine where enzymes produced by the liver, the small intestine, and the pancreas continue the process of digestion. The nutrients are absorbed into the blood stream across the epithelial cells lining the walls of the small intestines. The waste material travels on to the large intestine where water is absorbed and the drier waste material is compacted into feces; it is stored until it is excreted through the rectum.

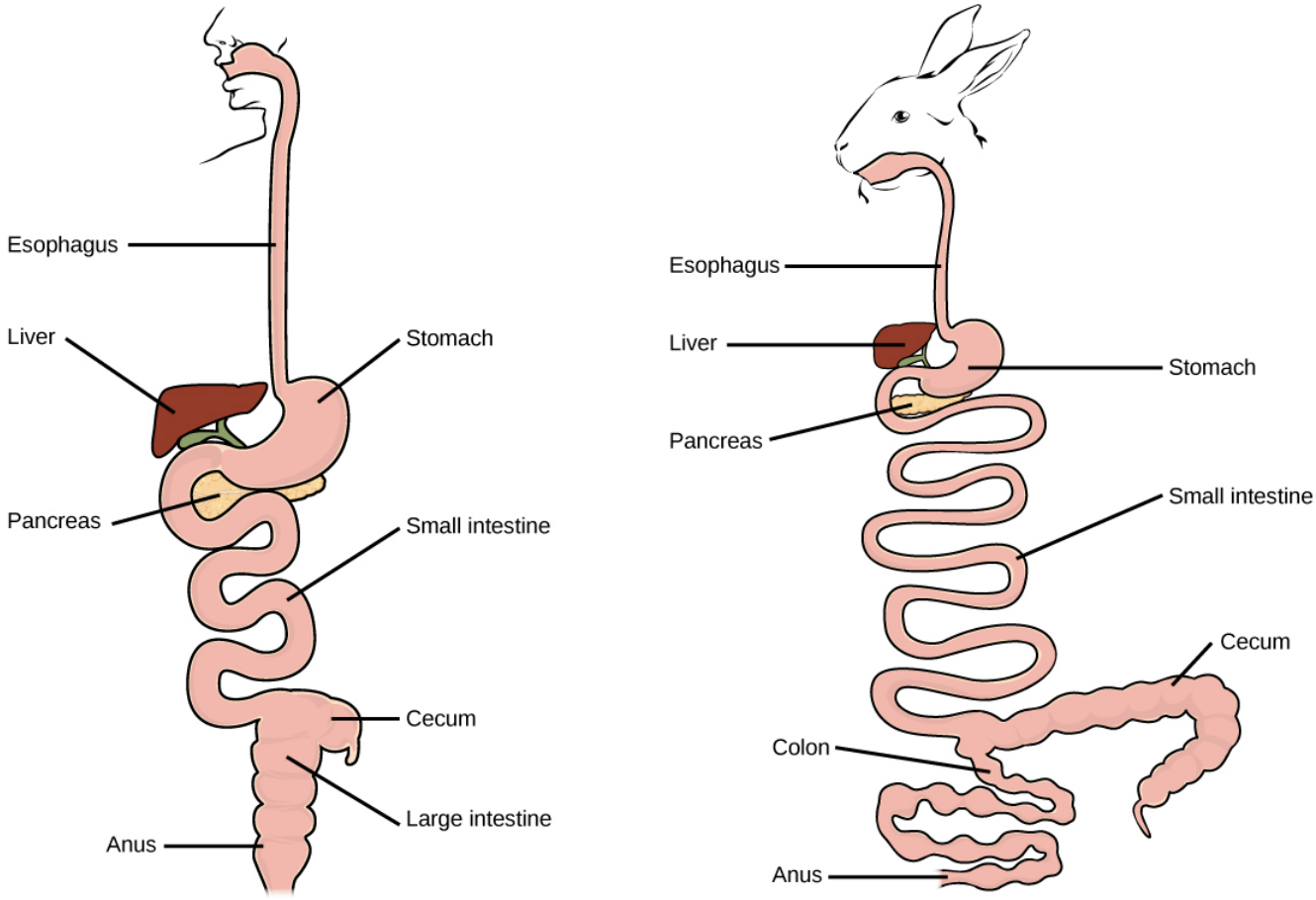


Figure 10.1.3.5: (a) Humans and herbivores, such as the (b) rabbit, have a monogastric digestive system. However, in the rabbit the small intestine and cecum are enlarged to allow more time to digest plant material. The enlarged organ provides more surface area for absorption of nutrients. Rabbits digest their food twice: the first time food passes through the digestive system, it collects in the cecum, and then it passes as soft feces called cecotrophes. The rabbit re-ingests these cecotrophes to further digest them.

Avian

Birds face special challenges when it comes to obtaining nutrition from food. They do not have teeth and so their digestive system, shown in Figure 10.1.3.6, must be able to process un-masticated food. Birds have evolved a variety of beak types that reflect the vast variety in their diet, ranging from seeds and insects to fruits and nuts. Because most birds fly, their metabolic rates are high in order to efficiently process food and keep their body weight low. The stomach of birds has two chambers: the proventriculus, where gastric juices are produced to digest the food before it enters the stomach, and the gizzard, where the food is stored, soaked, and mechanically ground. The undigested material forms food pellets that are sometimes regurgitated. Most of the chemical digestion and absorption happens in the intestine and the waste is excreted through the cloaca.

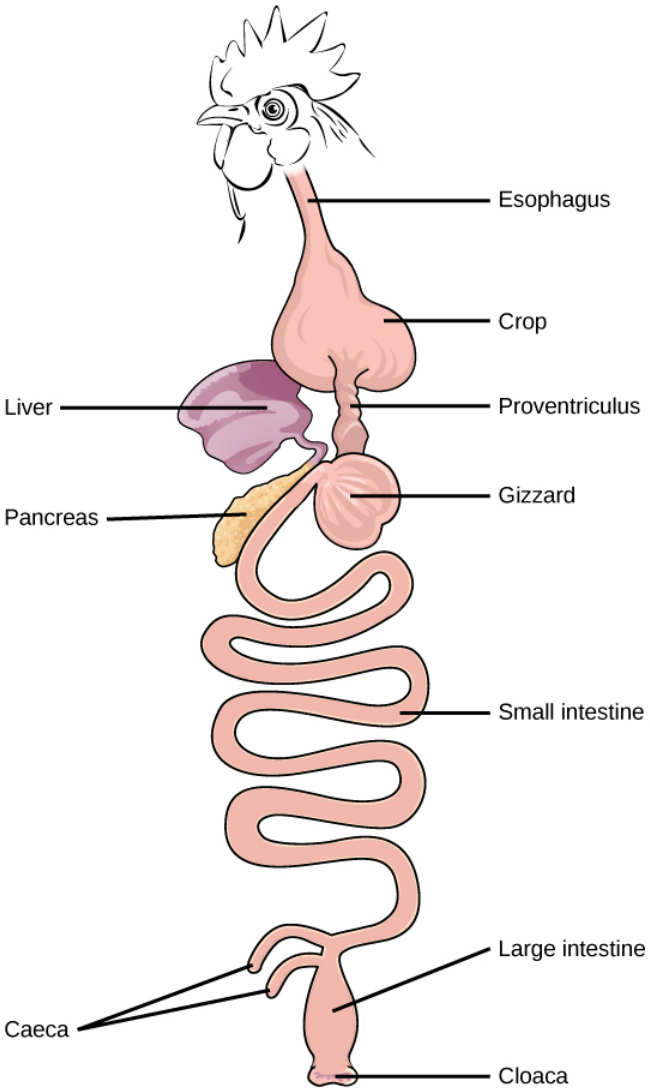


Figure 10.1.3.6: The avian esophagus has a pouch, called a crop, which stores food. Food passes from the crop to the first of two stomachs, called the proventriculus, which contains digestive juices that break down food. From the proventriculus, the food enters the second stomach, called the gizzard, which grinds food. Some birds swallow stones or grit, which are stored in the gizzard, to aid the grinding process. Birds do not have separate openings to excrete urine and feces. Instead, uric acid from the kidneys is secreted into the large intestine and combined with waste from the digestive process. This waste is excreted through an opening called the cloaca.

Evolution Connection: Avian Adaptations

Birds have a highly efficient, simplified digestive system. Recent fossil evidence has shown that the evolutionary divergence of birds from other land animals was characterized by streamlining and simplifying the digestive system. Unlike many other animals, birds do not have teeth to chew their food. In place of lips, they have sharp pointy beaks. The horny beak, lack of jaws, and the smaller tongue of the birds can be traced back to their dinosaur ancestors. The emergence of these changes seems to coincide with the inclusion of seeds in the bird diet. Seed-eating birds have beaks that are shaped for grabbing seeds and the two-compartment stomach allows for delegation of tasks. Since birds need to remain light in order to fly, their metabolic rates are very high, which means they digest their food very quickly and need to eat often. Contrast this with the ruminants, where the digestion of plant matter takes a very long time.

Ruminants

Ruminants are mainly herbivores like cows, sheep, and goats, whose entire diet consists of eating large amounts of roughage or fiber. They have evolved digestive systems that help them digest vast amounts of cellulose. An interesting feature of the ruminants' mouth is that they do not have upper incisor teeth. They use their lower teeth, tongue and lips to tear and chew their food. From the mouth, the food travels to the esophagus and on to the stomach.

To help digest the large amount of plant material, the stomach of the ruminants is a multi-chambered organ, as illustrated in Figure 10.1.3.7. The four compartments of the stomach are called the rumen, reticulum, omasum, and abomasum. These chambers contain many microbes that break down cellulose and ferment ingested food. The abomasum is the "true" stomach and is the equivalent of the monogastric stomach chamber where gastric juices are secreted. The four-compartment gastric chamber provides larger space and the microbial support necessary to digest plant material in ruminants. The fermentation process produces large amounts of gas in the stomach chamber, which must be eliminated. As in other animals, the small intestine plays an important role in nutrient absorption, and the large intestine helps in the elimination of waste.

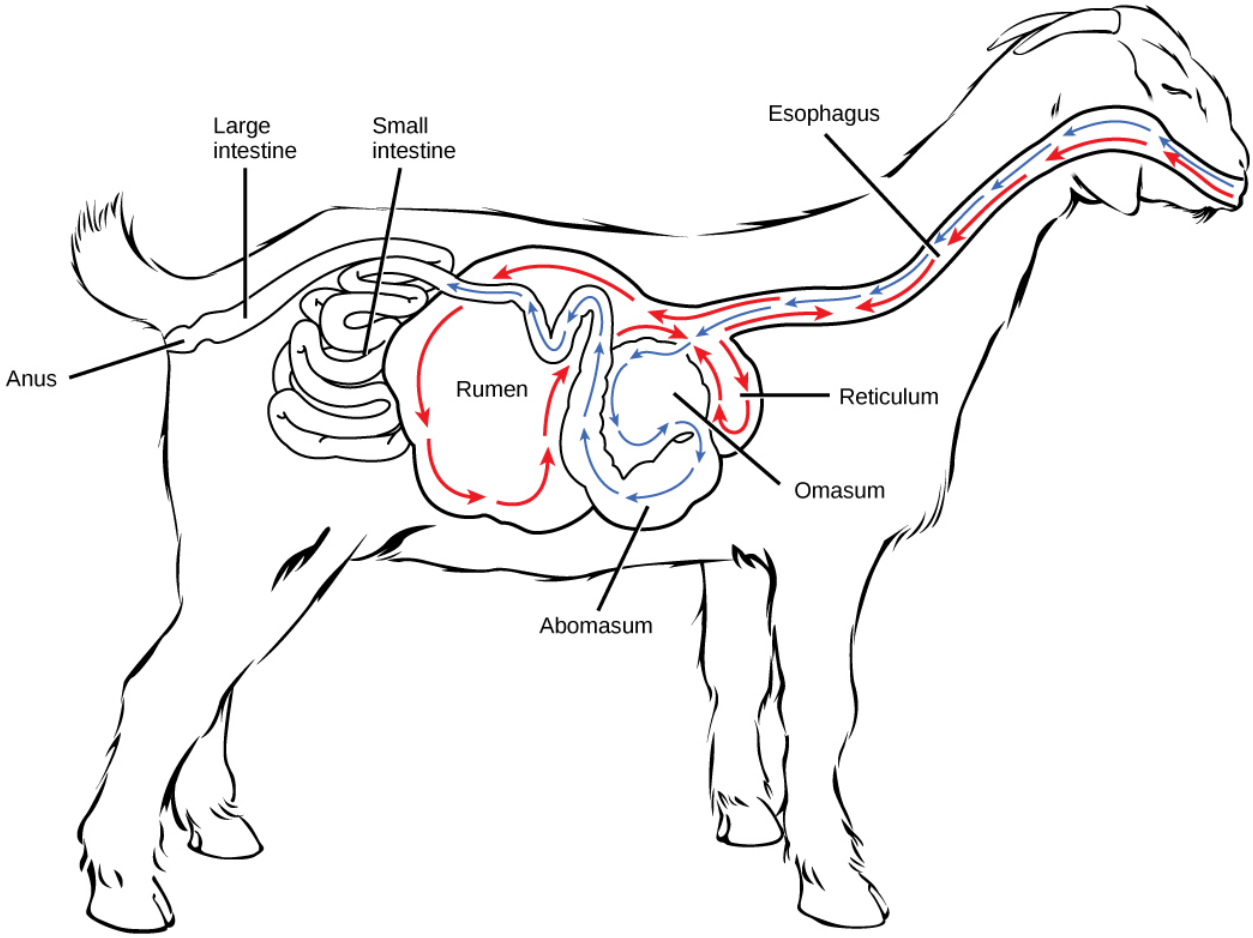


Figure 10.1.3.7: Ruminant animals, such as goats and cows, have four stomachs. The first two stomachs, the rumen and the reticulum, contain prokaryotes and protists that are able to digest cellulose fiber. The ruminant regurgitates cud from the reticulum, chews it, and swallows it into a third stomach, the omasum, which removes water. The cud then passes onto the fourth stomach, the abomasum, where it is digested by enzymes produced by the ruminant.

Pseudo-ruminants

Some animals, such as camels and alpacas, are pseudo-ruminants. They eat a lot of plant material and roughage. Digesting plant material is not easy because plant cell walls contain the polymeric sugar molecule cellulose. The digestive enzymes of these animals cannot break down cellulose, but microorganisms present in the digestive system can. Therefore, the digestive system must be able to handle large amounts of roughage and break down the cellulose. Pseudo-ruminants have a three-chamber stomach in the digestive system. However, their cecum—a pouched organ at the beginning of the large intestine containing many microorganisms that are necessary for the digestion of plant materials—is large and is the site where the roughage is fermented and digested. These animals do not have a rumen but have an omasum, abomasum, and reticulum.

Parts of the Digestive System

The vertebrate digestive system is designed to facilitate the transformation of food matter into the nutrient components that sustain organisms.

Oral Cavity

The oral cavity, or mouth, is the point of entry of food into the digestive system, illustrated in Figure 10.1.3.8. The food consumed is broken into smaller particles by mastication, the chewing action of the teeth. All mammals have teeth and can chew their food.

The extensive chemical process of digestion begins in the mouth. As food is being chewed, saliva, produced by the salivary glands, mixes with the food. Saliva is a watery substance produced in the mouths of many animals. There are three major glands that secrete saliva—the parotid, the submandibular, and the sublingual. Saliva contains mucus that moistens food and buffers the pH of the food. Saliva also contains immunoglobulins and lysozymes, which have antibacterial action to reduce tooth decay by inhibiting growth of some bacteria. Saliva also contains an enzyme called salivary amylase that begins the process of converting starches in the food into a disaccharide called maltose. Another enzyme called lipase is produced by the cells in the tongue. Lipases are a class of enzymes that can break down triglycerides. The lingual lipase begins the breakdown of fat components in the food. The chewing and wetting action provided by the teeth and saliva prepare the food into a mass called the bolus for swallowing. The tongue helps in swallowing—moving the bolus from the mouth into the pharynx. The pharynx opens to two passageways: the trachea, which leads to the lungs, and the esophagus, which leads to the stomach. The trachea has an opening called the glottis, which is covered by a cartilaginous flap called the epiglottis. When swallowing, the epiglottis closes the glottis and food passes into the esophagus and not the trachea. This arrangement allows food to be kept out of the trachea.

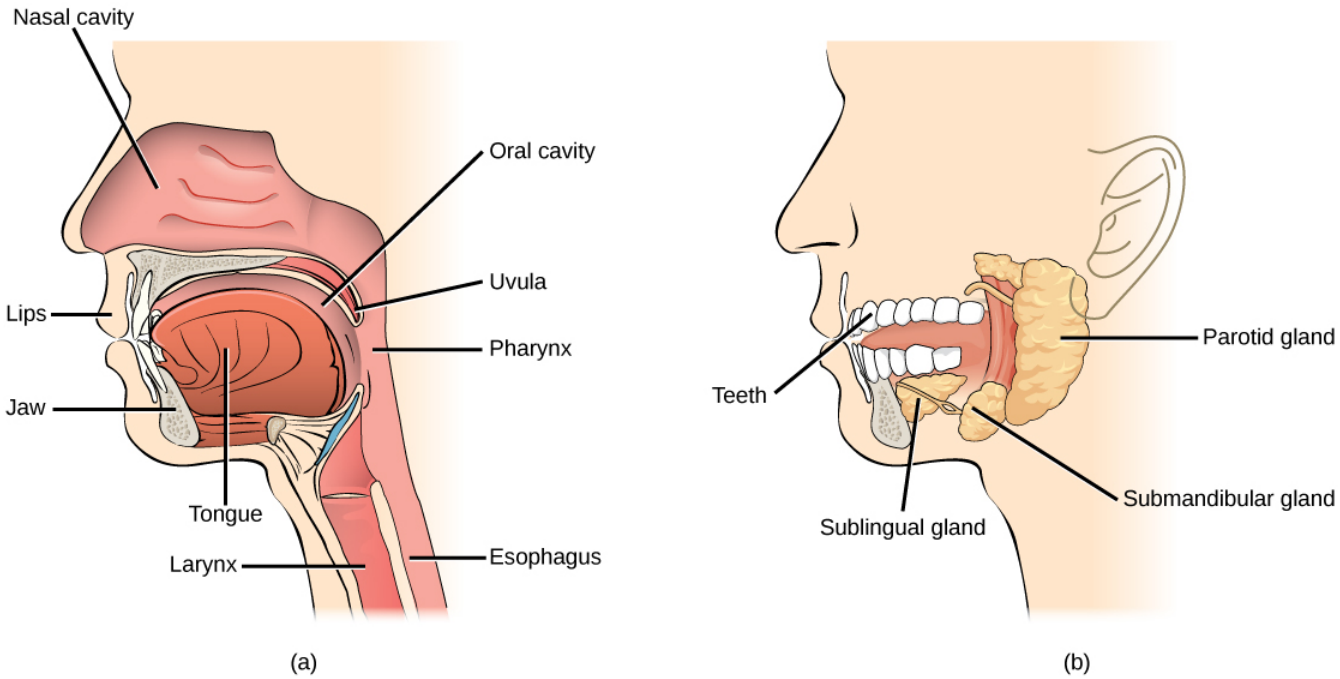


Figure 10.1.3.8: Digestion of food begins in the (a) oral cavity. Food is masticated by teeth and moistened by saliva secreted from the (b) salivary glands. Enzymes in the saliva begin to digest starches and fats. With the help of the tongue, the resulting bolus is moved into the esophagus by swallowing. (credit: modification of work by the National Cancer Institute)

Esophagus

The esophagus is a tubular organ that connects the mouth to the stomach. The chewed and softened food passes through the esophagus after being swallowed. The smooth muscles of the esophagus undergo a series of wave like movements called peristalsis that push the food toward the stomach, as illustrated in Figure 10.1.3.9. The peristalsis wave is unidirectional—it moves food from the mouth to the stomach, and reverse movement is not possible. The peristaltic movement of the esophagus is an involuntary reflex; it takes place in response to the act of swallowing.

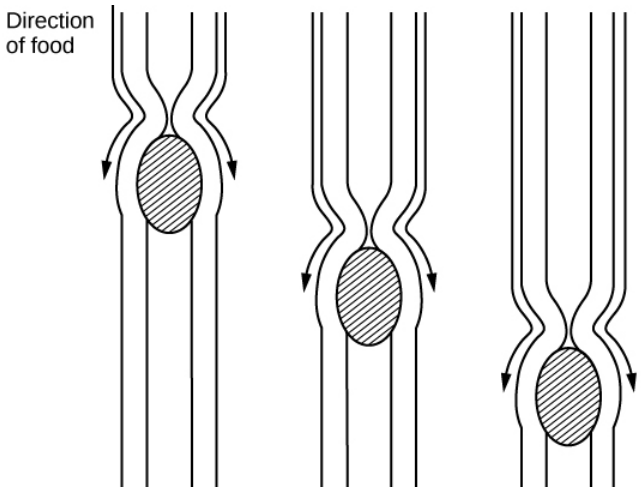


Figure 10.1.3.9: The esophagus transfers food from the mouth to the stomach through peristaltic movements.

A ring-like muscle called a sphincter forms valves in the digestive system. The gastro-esophageal sphincter is located at the stomach end of the esophagus. In response to swallowing and the pressure exerted by the bolus of food, this sphincter opens, and the bolus enters the stomach. When there is no swallowing action, this sphincter is shut and prevents the contents of the stomach from traveling up the esophagus. Many animals have a true sphincter; however, in humans, there is no true sphincter, but the esophagus remains closed when there is no swallowing action. Acid reflux or "heartburn" occurs when the acidic digestive juices escape into the esophagus.

Stomach

A large part of digestion occurs in the stomach, shown in Figure 10.1.3.10. The stomach is a saclike organ that secretes gastric digestive juices. The pH in the stomach is between 1.5 and 2.5. This highly acidic environment is required for the chemical breakdown of food and the extraction of nutrients. When empty, the stomach is a rather small organ; however, it can expand to up to 20 times its resting size when filled with food. This characteristic is particularly useful for animals that need to eat when food is available.

Art Connection

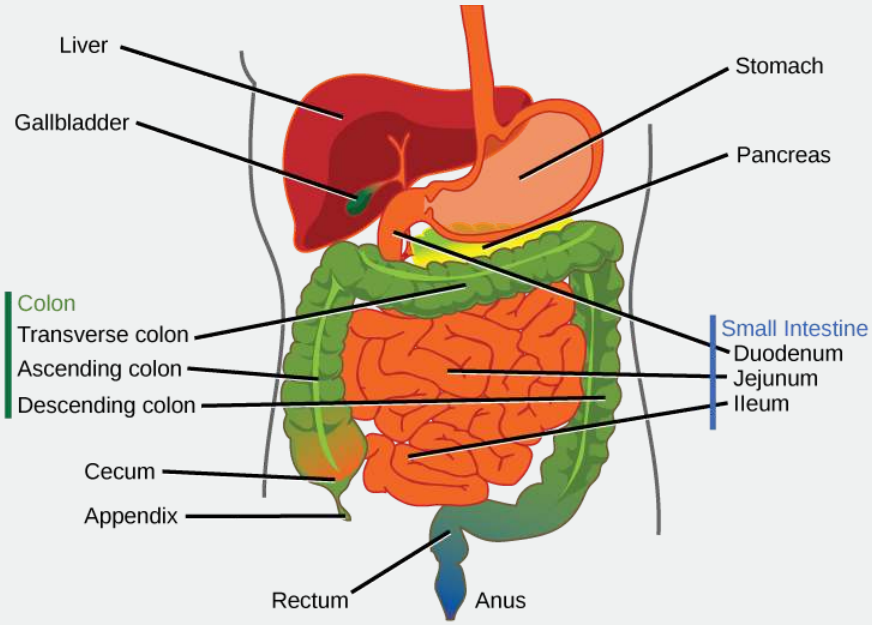


Figure 10.1.3.10: The human stomach has an extremely acidic environment where most of the protein gets digested. (credit: modification of work by Mariana Ruiz Villareal)

Which of the following statements about the digestive system is false?

A. Chyme is a mixture of food and digestive juices that is produced in the stomach.
B. Food enters the large intestine before the small intestine.
C. In the small intestine, chyme mixes with bile, which emulsifies fats.
D. The stomach is separated from the small intestine by the pyloric sphincter.

The stomach is also the major site for protein digestion in animals other than ruminants. Protein digestion is mediated by an enzyme called pepsin in the stomach chamber. Pepsin is secreted by the chief cells in the stomach in an inactive form called pepsinogen. Pepsin breaks peptide bonds and cleaves proteins into smaller polypeptides; it also helps activate more pepsinogen, starting a positive feedback mechanism that generates more pepsin. Another cell type—parietal cells—secrete hydrogen and chloride ions, which combine in the lumen to form hydrochloric acid, the primary acidic component of the stomach juices. Hydrochloric acid helps to convert the inactive pepsinogen to pepsin. The highly acidic environment also kills many microorganisms in the food and, combined with the action of the enzyme pepsin, results in the hydrolysis of protein in the food. Chemical digestion is facilitated by the churning action of the stomach. Contraction and relaxation of smooth muscles mixes the stomach contents about every 20 minutes. The partially digested food and gastric juice mixture is called chyme. Chyme passes from the stomach to the small intestine. Further protein digestion takes place in the small intestine. Gastric emptying occurs within two to six hours after a meal. Only a small amount of chyme is released into the small intestine at a time. The movement of chyme from the stomach into the small intestine is regulated by the pyloric sphincter.

When digesting protein and some fats, the stomach lining must be protected from getting digested by pepsin. There are two points to consider when describing how the stomach lining is protected. First, as previously mentioned, the enzyme pepsin is synthesized in the inactive form. This protects the chief cells, because pepsinogen does not have the same enzyme functionality of pepsin. Second, the stomach has a thick mucus lining that protects the underlying tissue from the action of the digestive juices. When this mucus lining is ruptured, ulcers can form in the stomach. Ulcers are open wounds in or on an organ caused by bacteria (*Helicobacter pylori*) when the mucus lining is ruptured and fails to reform.

Small Intestine

Chyme moves from the stomach to the small intestine. The small intestine is the organ where the digestion of protein, fats, and carbohydrates is completed. The small intestine is a long tube-like organ with a highly folded surface containing finger-like projections called the villi. The apical surface of each villus has many microscopic projections called microvilli. These structures, illustrated in Figure 10.1.3.11, are lined with epithelial cells on the luminal side and allow for the nutrients to be absorbed from the digested food and absorbed into the blood stream on the other side. The villi and microvilli, with their many folds, increase the surface area of the intestine and increase absorption efficiency of the nutrients. Absorbed nutrients in the blood are carried into the hepatic portal vein, which leads to the liver. There, the liver regulates the distribution of nutrients to the rest of the body and removes toxic substances, including drugs, alcohol, and some pathogens.

Art Connection

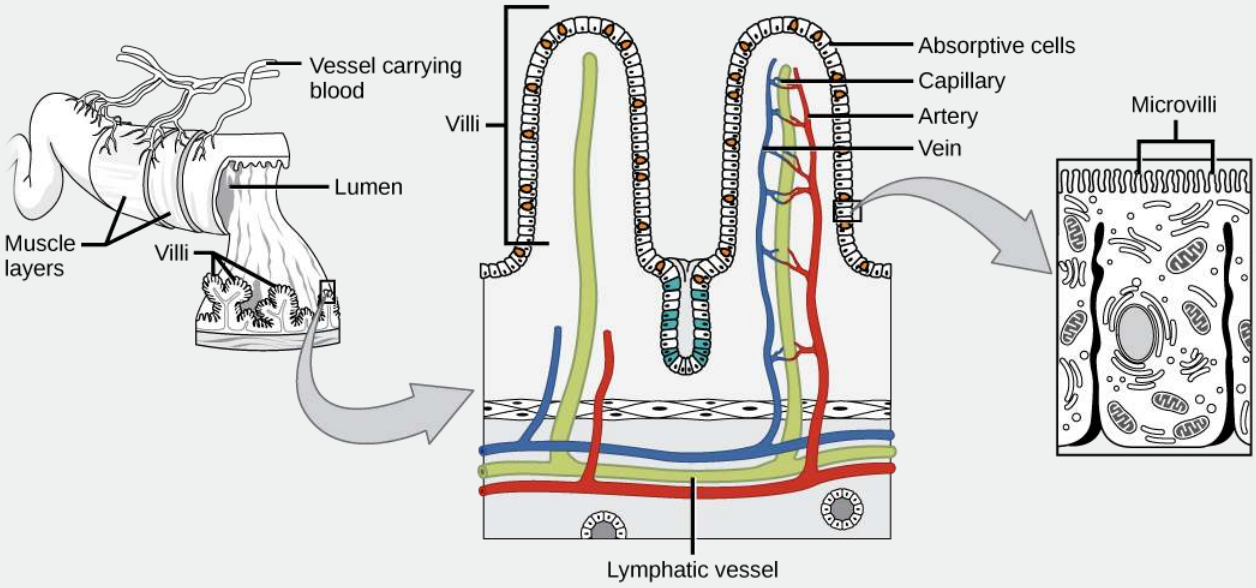


Figure 10.1.3.11: Villi are folds on the small intestine lining that increase the surface area to facilitate the absorption of nutrients.

Which of the following statements about the small intestine is false?

A. Absorptive cells that line the small intestine have microvilli, small projections that increase surface area and aid in the absorption of food.
B. The inside of the small intestine has many folds, called villi.
C. Microvilli are lined with blood vessels as well as lymphatic vessels.
D. The inside of the small intestine is called the lumen.

The human small intestine is over 6m long and is divided into three parts: the duodenum, the jejunum, and the ileum. The "C-shaped," fixed part of the small intestine is called the duodenum and is shown in Figure 10.1.3.11. The duodenum is separated from the stomach by the pyloric sphincter which opens to allow chyme to move from the stomach to the duodenum. In the duodenum, chyme is mixed with pancreatic juices in an alkaline solution rich in bicarbonate that neutralizes the acidity of chyme and acts as a buffer. Pancreatic juices also contain several digestive enzymes. Digestive juices from the pancreas, liver, and gallbladder, as well as from gland cells of the intestinal wall itself, enter the duodenum. Bile is produced in the liver and stored and concentrated in the gallbladder. Bile contains bile salts which emulsify lipids while the pancreas produces enzymes that catabolize starches, disaccharides, proteins, and fats. These digestive juices break down the food particles in the chyme into glucose, triglycerides, and amino acids. Some chemical digestion of food takes place in the duodenum. Absorption of fatty acids also takes place in the duodenum.

The second part of the small intestine is called the jejunum, shown in Figure 10.1.3.11. Here, hydrolysis of nutrients is continued while most of the carbohydrates and amino acids are absorbed through the intestinal lining. The bulk of chemical digestion and nutrient absorption occurs in the jejunum.

The ileum, also illustrated in Figure 10.1.3.11 is the last part of the small intestine and here the bile salts and vitamins are absorbed into blood stream. The undigested food is sent to the colon from the ileum via peristaltic movements of the muscle. The ileum ends and the large intestine begins at the ileocecal valve. The vermiform, "worm-like," appendix is located at the ileocecal valve. The appendix of humans secretes no enzymes and has an insignificant role in immunity.

Large Intestine

The large intestine, illustrated in Figure 10.1.3.12, reabsorbs the water from the undigested food material and processes the waste material. The human large intestine is much smaller in length compared to the small intestine but larger in diameter. It has three parts: the cecum, the colon, and the rectum. The cecum joins the ileum to the colon and is the receiving pouch for the waste matter. The colon is home to many bacteria or "intestinal flora" that aid in the digestive processes. The colon can be divided into four

regions, the ascending colon, the transverse colon, the descending colon and the sigmoid colon. The main functions of the colon are to extract the water and mineral salts from undigested food, and to store waste material. Carnivorous mammals have a shorter large intestine compared to herbivorous mammals due to their diet.

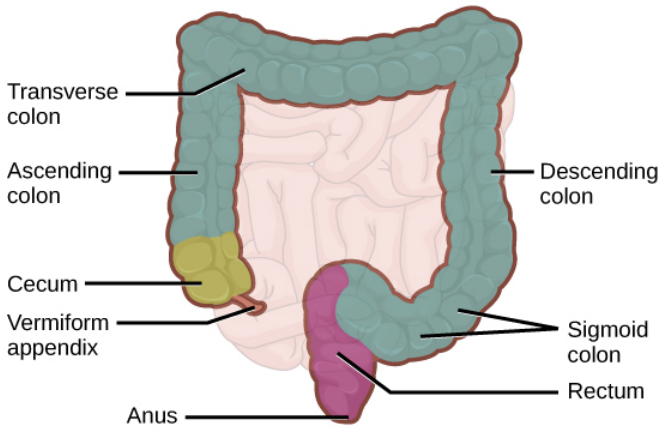


Figure 10.1.3.12: The large intestine reabsorbs water from undigested food and stores waste material until it is eliminated.

Rectum and Anus

The rectum is the terminal end of the large intestine, as shown in Figure 10.1.3.12. The primary role of the rectum is to store the feces until defecation. The feces are propelled using peristaltic movements during elimination. The anus is an opening at the far-end of the digestive tract and is the exit point for the waste material. Two sphincters between the rectum and anus control elimination: the inner sphincter is involuntary and the outer sphincter is voluntary.

Accessory Organs

The organs discussed above are the organs of the digestive tract through which food passes. Accessory organs are organs that add secretions (enzymes) that catabolize food into nutrients. Accessory organs include salivary glands, the liver, the pancreas, and the gallbladder. The liver, pancreas, and gallbladder are regulated by hormones in response to the food consumed.

The liver is the largest internal organ in humans and it plays a very important role in digestion of fats and detoxifying blood. The liver produces bile, a digestive juice that is required for the breakdown of fatty components of the food in the duodenum. The liver also processes the vitamins and fats and synthesizes many plasma proteins.

The pancreas is another important gland that secretes digestive juices. The chyme produced from the stomach is highly acidic in nature; the pancreatic juices contain high levels of bicarbonate, an alkali that neutralizes the acidic chyme. Additionally, the pancreatic juices contain a large variety of enzymes that are required for the digestion of protein and carbohydrates.

The gallbladder is a small organ that aids the liver by storing bile and concentrating bile salts. When chyme containing fatty acids enters the duodenum, the bile is secreted from the gallbladder into the duodenum.

Summary

Different animals have evolved different types of digestive systems specialized to meet their dietary needs. Humans and many other animals have monogastric digestive systems with a single-chambered stomach. Birds have evolved a digestive system that includes a gizzard where the food is crushed into smaller pieces. This compensates for their inability to masticate. Ruminants that consume large amounts of plant material have a multi-chambered stomach that digests roughage. Pseudo-ruminants have similar digestive processes as ruminants but do not have the four-compartment stomach. Processing food involves ingestion (eating), digestion (mechanical and enzymatic breakdown of large molecules), absorption (cellular uptake of nutrients), and elimination (removal of undigested waste as feces).

Many organs work together to digest food and absorb nutrients. The mouth is the point of ingestion and the location where both mechanical and chemical breakdown of food begins. Saliva contains an enzyme called amylase that breaks down carbohydrates. The food bolus travels through the esophagus by peristaltic movements to the stomach. The stomach has an extremely acidic

environment. An enzyme called pepsin digests protein in the stomach. Further digestion and absorption take place in the small intestine. The large intestine reabsorbs water from the undigested food and stores waste until elimination.

Art Connections

Figure 10.1.3.10: Which of the following statements about the digestive system is false?

A. Chyme is a mixture of food and digestive juices that is produced in the stomach.
B. Food enters the large intestine before the small intestine.
C. In the small intestine, chyme mixes with bile, which emulsifies fats.
D. The stomach is separated from the small intestine by the pyloric sphincter.

Answer

B

Figure 10.1.3.11: Which of the following statements about the small intestine is false?

A. Absorptive cells that line the small intestine have microvilli, small projections that increase surface area and aid in the absorption of food.
B. The inside of the small intestine has many folds, called villi.
C. Microvilli are lined with blood vessels as well as lymphatic vessels.
D. The inside of the small intestine is called the lumen.

Answer

C

Glossary

alimentary canal
tubular digestive system with a mouth and anus

anus
exit point for waste material

bile
digestive juice produced by the liver; important for digestion of lipids

bolus
mass of food resulting from chewing action and wetting by saliva

carnivore
animal that consumes animal flesh

chyme
mixture of partially digested food and stomach juices

duodenum
first part of the small intestine where a large part of digestion of carbohydrates and fats occurs

esophagus
tubular organ that connects the mouth to the stomach

gallbladder

organ that stores and concentrates bile

gastrovascular cavity
digestive system consisting of a single opening

gizzard
muscular organ that grinds food

herbivore
animal that consumes strictly plant diet

ileum
last part of the small intestine; connects the small intestine to the large intestine; important for absorption of B-12

jejunum
second part of the small intestine

large intestine
digestive system organ that reabsorbs water from undigested material and processes waste matter

lipase
enzyme that chemically breaks down lipids

liver
organ that produces bile for digestion and processes vitamins and lipids

monogastric
digestive system that consists of a single-chambered stomach

omnivore
animal that consumes both plants and animals

pancreas
gland that secretes digestive juices

pepsin
enzyme found in the stomach whose main role is protein digestion

pepsinogen
inactive form of pepsin

peristalsis
wave-like movements of muscle tissue

proventriculus
glandular part of a bird’s stomach

rectum
area of the body where feces is stored until elimination

roughage
component of food that is low in energy and high in fiber

ruminant

animal with a stomach divided into four compartments

salivary amylase
enzyme found in saliva, which converts carbohydrates to maltose

small intestine
organ where digestion of protein, fats, and carbohydrates is completed

sphincter
band of muscle that controls movement of materials throughout the digestive tract

stomach
saclike organ containing acidic digestive juices

villi
folds on the inner surface of the small intestine whose role is to increase absorption area

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10.1.4: Nutrition and Energy Production

Skills to Develop

- Explain why an animal's diet should be balanced and meet the needs of the body
- Define the primary components of food
- Describe the essential nutrients required for cellular function that cannot be synthesized by the animal body
- Explain how energy is produced through diet and digestion
- Describe how excess carbohydrates and energy are stored in the body

Given the diversity of animal life on our planet, it is not surprising that the animal diet would also vary substantially. The animal diet is the source of materials needed for building DNA and other complex molecules needed for growth, maintenance, and reproduction; collectively these processes are called biosynthesis. The diet is also the source of materials for ATP production in the cells. The diet must be balanced to provide the minerals and vitamins that are required for cellular function.

Food Requirements

What are the fundamental requirements of the animal diet? The animal diet should be well balanced and provide nutrients required for bodily function and the minerals and vitamins required for maintaining structure and regulation necessary for good health and reproductive capability. These requirements for a human are illustrated graphically in Figure 10.1.4.1.

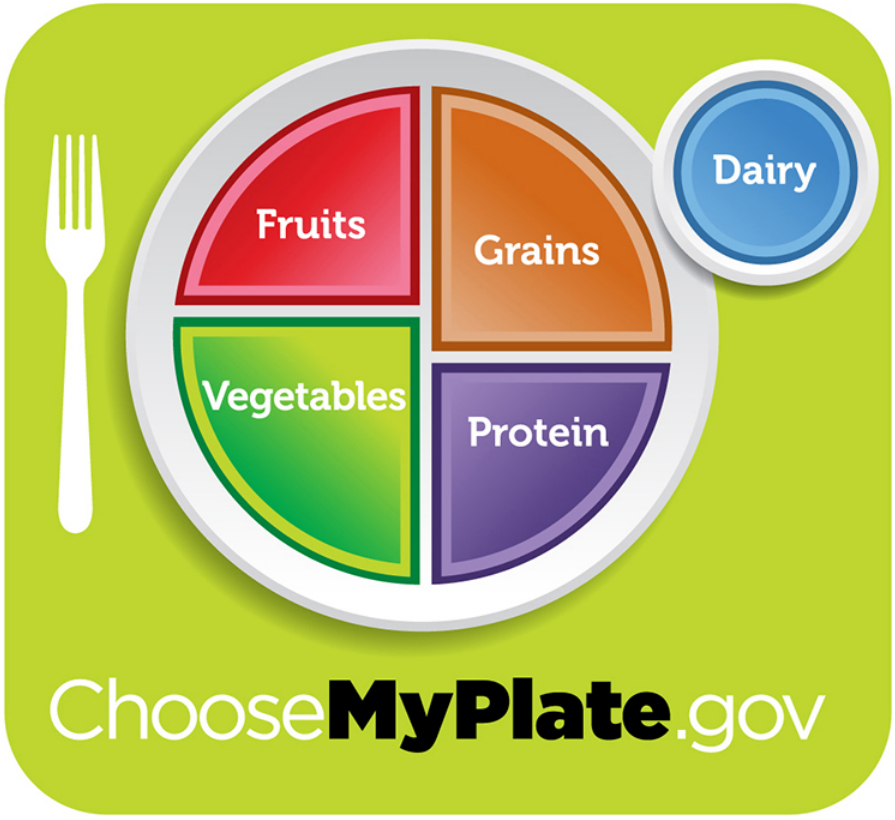


Figure 10.1.4.1: For humans, a balanced diet includes fruits, vegetables, grains, and protein. (credit: USDA)

Everyday Connection: Let's Move! Campaign

Obesity is a growing epidemic and the rate of obesity among children is rapidly rising in the United States. To combat childhood obesity and ensure that children get a healthy start in life, first lady Michelle Obama has launched the Let's Move! campaign. The goal of this campaign is to educate parents and caregivers on providing healthy nutrition and encouraging

active lifestyles to future generations. This program aims to involve the entire community, including parents, teachers, and healthcare providers to ensure that children have access to healthy foods—more fruits, vegetables, and whole grains—and consume fewer calories from processed foods. Another goal is to ensure that children get physical activity. With the increase in television viewing and stationary pursuits such as video games, sedentary lifestyles have become the norm. Learn more at www.letsmove.gov.

Organic Precursors

The organic molecules required for building cellular material and tissues must come from food. Carbohydrates or sugars are the primary source of organic carbons in the animal body. During digestion, digestible carbohydrates are ultimately broken down into glucose and used to provide energy through metabolic pathways. Complex carbohydrates, including polysaccharides, can be broken down into glucose through biochemical modification; however, humans do not produce the enzyme cellulase and lack the ability to derive glucose from the polysaccharide cellulose. In humans, these molecules provide the fiber required for moving waste through the large intestine and a healthy colon. The intestinal flora in the human gut are able to extract some nutrition from these plant fibers. The excess sugars in the body are converted into glycogen and stored in the liver and muscles for later use. Glycogen stores are used to fuel prolonged exertions, such as long-distance running, and to provide energy during food shortage. Excess glycogen can be converted to fats, which are stored in the lower layer of the skin of mammals for insulation and energy storage. Excess digestible carbohydrates are stored by mammals in order to survive famine and aid in mobility.

Another important requirement is that of nitrogen. Protein catabolism provides a source of organic nitrogen. Amino acids are the building blocks of proteins and protein breakdown provides amino acids that are used for cellular function. The carbon and nitrogen derived from these become the building block for nucleotides, nucleic acids, proteins, cells, and tissues. Excess nitrogen must be excreted as it is toxic. Fats add flavor to food and promote a sense of satiety or fullness. Fatty foods are also significant sources of energy because one gram of fat contains nine calories. Fats are required in the diet to aid the absorption of fat-soluble vitamins and the production of fat-soluble hormones.

Essential Nutrients

While the animal body can synthesize many of the molecules required for function from the organic precursors, there are some nutrients that need to be consumed from food. These nutrients are termed essential nutrients, meaning they must be eaten, and the body cannot produce them.

The omega-3 alpha-linolenic acid and the omega-6 linoleic acid are essential fatty acids needed to make some membrane phospholipids. Vitamins are another class of essential organic molecules that are required in small quantities for many enzymes to function and, for this reason, are considered to be co-enzymes. Absence or low levels of vitamins can have a dramatic effect on health, as outlined in the tables below. Both fat-soluble and water-soluble vitamins must be obtained from food. Minerals, listed in the table below, are inorganic essential nutrients that must be obtained from food. Among their many functions, minerals help in structure and regulation and are considered co-factors. Certain amino acids also must be procured from food and cannot be synthesized by the body. These amino acids are the “essential” amino acids. The human body can synthesize only 11 of the 20 required amino acids; the rest must be obtained from food. The essential amino acids are listed in the table below.

Table 10.1.4.1**:** Water-soluble Essential Vitamins

Vitamin	Function	Deficiencies Can Lead To	Sources
Vitamin B_1 (Thiamine)	Needed by the body to process lipids, proteins, and carbohydrates Coenzyme removes CO_2 from organic compounds	Muscle weakness, Beriberi: reduced heart function, CNS problems	Milk, meat, dried beans, whole grains
Vitamin B_2 (Riboflavin)	Takes an active role in metabolism, aiding in the conversion of food to energy (FAD and FMN)	Cracks or sores on the outer surface of the lips (cheliosis); inflammation and redness of the tongue; moist, scaly skin inflammation (seborrheic dermatitis)	Meat, eggs, enriched grains, vegetables
Vitamin B_3 (Niacin)	Used by the body to release energy from carbohydrates and to process alcohol; required for the synthesis of sex hormones; component of coenzyme NAD^+ and $NADP^+$	Pellagra, which can result in dermatitis, diarrhea, dementia, and death	Meat, eggs, grains, nuts, potatoes
Vitamin B_5 (Pantothenic acid)	Assists in producing energy from foods (lipids, in particular); component of coenzyme A	Fatigue, poor coordination, retarded growth, numbness, tingling of hands and feet	Meat, whole grains, milk, fruits, vegetables
Vitamin B_6 (Pyridoxine)	The principal vitamin for processing amino acids and lipids; also helps convert nutrients into energy	Irritability, depression, confusion, mouth sores or ulcers, anemia, muscular twitching	Meat, dairy products, whole grains, orange juice
Vitamin B_7 (Biotin)	Used in energy and amino acid metabolism, fat synthesis, and fat breakdown; helps the body use blood sugar	Hair loss, dermatitis, depression, numbness and tingling in the extremities; neuromuscular disorders	Meat, eggs, legumes and other vegetables
Vitamin B_9 (Folic acid)	Assists the normal development of cells, especially during fetal development; helps metabolize nucleic and amino acids	Deficiency during pregnancy is associated with birth defects, such as neural tube defects and anemia	Leafy green vegetables, whole wheat, fruits, nuts, legumes
Vitamin B_{12} (Cobalamin)	Maintains healthy nervous system and assists with blood cell formation; coenzyme in nucleic acid metabolism	Anemia, neurological disorders, numbness, loss of balance	Meat, eggs, animal products
Vitamin C (Ascorbic acid)	Helps maintain connective tissue: bone, cartilage, and dentin; boosts the immune system	Scurvy, which results in bleeding, hair and tooth loss; joint pain and swelling; delayed wound healing	Citrus fruits, broccoli, tomatoes, red sweet bell peppers

Table 10.1.4.2**:** Fat-soluble Essential Vitamins

Vitamin	Function	Deficiencies Can Lead To	Sources
Vitamin A (Retinol)	Critical to the development of bones, teeth, and skin; helps maintain eyesight, enhances the immune system, fetal development, gene expression	Night-blindness, skin disorders, impaired immunity	Dark green leafy vegetables, yellow-orange vegetables fruits, milk, butter
Vitamin D	Critical for calcium absorption for bone development and strength; maintains a stable nervous system; maintains a normal and strong heartbeat; helps in blood clotting	Rickets, osteomalacia, immunity	Cod liver oil, milk, egg yolk
Vitamin E (Tocopherol)	Lessens oxidative damage of cells,and prevents lung damage from pollutants; vital to the immune system	Deficiency is rare; anemia, nervous system degeneration	Wheat germ oil, unrefined vegetable oils, nuts, seeds, grains
Vitamin K (Phylloquinone)	Essential to blood clotting	Bleeding and easy bruising	Leafy green vegetables, tea



Figure 10.1.4.2: A healthy diet should include a variety of foods to ensure that needs for essential nutrients are met. (credit: Keith Weller, USDA ARS)

Table 10.1.4.3**:** Minerals and Their Function in the Human Body

Mineral	Function	Deficiencies Can Lead To	Sources
*Calcium	Needed for muscle and neuron function; heart health; builds bone and supports synthesis and function of blood cells; nerve function	Osteoporosis, rickets, muscle spasms, impaired growth	Milk, yogurt, fish, green leafy vegetables, legumes
*Chlorine	Needed for production of hydrochloric acid (HCl) in the stomach and nerve function; osmotic balance	Muscle cramps, mood disturbances, reduced appetite	Table salt
Copper (trace amounts)	Required component of many redox enzymes, including cytochrome c oxidase; cofactor for hemoglobin synthesis	Copper deficiency is rare	Liver, oysters, cocoa, chocolate, sesame, nuts
Iodine	Required for the synthesis of thyroid hormones	Goiter	Seafood, iodized salt, dairy products
Iron	Required for many proteins and enzymes, notably hemoglobin, to prevent anemia	Anemia, which causes poor concentration, fatigue, and poor immune function	Red meat, leafy green vegetables, fish (tuna, salmon), eggs, dried fruits, beans, whole grains
*Magnesium	Required co-factor for ATP formation; bone formation; normal membrane functions; muscle function	Mood disturbances, muscle spasms	Whole grains, leafy green vegetables
Manganese (trace amounts)	A cofactor in enzyme functions; trace amounts are required	Manganese deficiency is rare	Common in most foods
Molybdenum (trace amounts)	Acts as a cofactor for three essential enzymes in humans: sulfite oxidase, xanthine oxidase, and aldehyde oxidase	Molybdenum deficiency is rare	
*Phosphorus	A component of bones and teeth; helps regulate acid-base balance; nucleotide synthesis	Weakness, bone abnormalities, calcium loss	Milk, hard cheese, whole grains, meats
*Potassium	Vital for muscles, heart, and nerve function	Cardiac rhythm disturbance, muscle weakness	Legumes, potato skin, tomatoes, bananas
Selenium (trace amounts)	A cofactor essential to activity of antioxidant enzymes like glutathione peroxidase; trace amounts are required	Selenium deficiency is rare	Common in most foods
*Sodium	Systemic electrolyte required for many functions; acid-base balance; water balance; nerve function	Muscle cramps, fatigue, reduced appetite	Table salt
Zinc (trace amounts)	Required for several enzymes such as carboxypeptidase, liver	Anemia, poor wound healing, can lead to short stature	Common in most foods

Mineral	Function	Deficiencies Can Lead To	Sources
	alcohol dehydrogenase, and carbonic anhydrase		
*Greater than 200mg/day required			

Table 10.1.4.4**:** Essential Amino Acids

Amino acids that must be consumed	Amino acids anabolized by the body
isoleucine	alanine
leucine	selenocysteine
lysine	aspartate
methionine	cysteine
phenylalanine	glutamate
tryptophan	glycine
valine	proline
histidine*	serine
threonine	tyrosine
arginine*	asparagine
*The human body can synthesize histidine and arginine, but not in the quantities required, especially for growing children.	

Food Energy and ATP

Animals need food to obtain energy and maintain homeostasis. Homeostasis is the ability of a system to maintain a stable internal environment even in the face of external changes to the environment. For example, the normal body temperature of humans is 37°C (98.6°F). Humans maintain this temperature even when the external temperature is hot or cold. It takes energy to maintain this body temperature, and animals obtain this energy from food.

The primary source of energy for animals is carbohydrates, mainly glucose. Glucose is called the body's fuel. The digestible carbohydrates in an animal's diet are converted to glucose molecules through a series of catabolic chemical reactions.

Adenosine triphosphate, or ATP, is the primary energy currency in cells; ATP stores energy in phosphate ester bonds. ATP releases energy when the phosphodiester bonds are broken and ATP is converted to ADP and a phosphate group. ATP is produced by the oxidative reactions in the cytoplasm and mitochondrion of the cell, where carbohydrates, proteins, and fats undergo a series of metabolic reactions collectively called cellular respiration. For example, glycolysis is a series of reactions in which glucose is converted to pyruvic acid and some of its chemical potential energy is transferred to NADH and ATP.

ATP is required for all cellular functions. It is used to build the organic molecules that are required for cells and tissues; it provides energy for muscle contraction and for the transmission of electrical signals in the nervous system. When the amount of ATP is available in excess of the body's requirements, the liver uses the excess ATP and excess glucose to produce molecules called glycogen. Glycogen is a polymeric form of glucose and is stored in the liver and skeletal muscle cells. When blood sugar drops, the liver releases glucose from stores of glycogen. Skeletal muscle converts glycogen to glucose during intense exercise. The process of converting glucose and excess ATP to glycogen and the storage of excess energy is an evolutionarily important step in helping animals deal with mobility, food shortages, and famine.

Everyday Connection: Obesity

Obesity is a major health concern in the United States, and there is a growing focus on reducing obesity and the diseases it may lead to, such as type-2 diabetes, cancers of the colon and breast, and cardiovascular disease. How does the food consumed contribute to obesity?

Fatty foods are calorie-dense, meaning that they have more calories per unit mass than carbohydrates or proteins. One gram of carbohydrates has four calories, one gram of protein has four calories, and one gram of fat has nine calories. Animals tend to seek lipid-rich food for their higher energy content.

The signals of hunger (“time to eat”) and satiety (“time to stop eating”) are controlled in the hypothalamus region of the brain. Foods that are rich in fatty acids tend to promote satiety more than foods that are rich only in carbohydrates.

Excess carbohydrate and ATP are used by the liver to synthesize glycogen. The pyruvate produced during glycolysis is used to synthesize fatty acids. When there is more glucose in the body than required, the resulting excess pyruvate is converted into molecules that eventually result in the synthesis of fatty acids within the body. These fatty acids are stored in adipose cells—the fat cells in the mammalian body whose primary role is to store fat for later use.

It is important to note that some animals benefit from obesity. Polar bears and seals need body fat for insulation and to keep them from losing body heat during Arctic winters. When food is scarce, stored body fat provides energy for maintaining homeostasis. Fats prevent famine in mammals, allowing them to access energy when food is not available on a daily basis; fats are stored when a large kill is made or lots of food is available.

Summary

Animal diet should be balanced and meet the needs of the body. Carbohydrates, proteins, and fats are the primary components of food. Some essential nutrients are required for cellular function but cannot be produced by the animal body. These include vitamins, minerals, some fatty acids, and some amino acids. Food intake in more than necessary amounts is stored as glycogen in the liver and muscle cells, and in fat cells. Excess adipose storage can lead to obesity and serious health problems. ATP is the energy currency of the cell and is obtained from the metabolic pathways. Excess carbohydrates and energy are stored as glycogen in the body.

Glossary

essential nutrient
: nutrient that cannot be synthesized by the body; it must be obtained from food

mineral
: inorganic, elemental molecule that carries out important roles in the body

vitamin
: organic substance necessary in small amounts to sustain life

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10.1.5: Digestive System Processes

Skills to Develop

- Describe the process of digestion
- Detail the steps involved in digestion and absorption
- Define elimination
- Explain the role of both the small and large intestines in absorption

Obtaining nutrition and energy from food is a multi-step process. For true animals, the first step is ingestion, the act of taking in food. This is followed by digestion, absorption, and elimination. In the following sections, each of these steps will be discussed in detail.

Ingestion

The large molecules found in intact food cannot pass through the cell membranes. Food needs to be broken into smaller particles so that animals can harness the nutrients and organic molecules. The first step in this process is ingestion. Ingestion is the process of taking in food through the mouth. In vertebrates, the teeth, saliva, and tongue play important roles in mastication (preparing the food into bolus). While the food is being mechanically broken down, the enzymes in saliva begin to chemically process the food as well. The combined action of these processes modifies the food from large particles to a soft mass that can be swallowed and can travel the length of the esophagus.

Digestion and Absorption

Digestion is the mechanical and chemical break down of food into small organic fragments. It is important to break down macromolecules into smaller fragments that are of suitable size for absorption across the digestive epithelium. Large, complex molecules of proteins, polysaccharides, and lipids must be reduced to simpler particles such as simple sugar before they can be absorbed by the digestive epithelial cells. Different organs play specific roles in the digestive process. The animal diet needs carbohydrates, protein, and fat, as well as vitamins and inorganic components for nutritional balance. How each of these components is digested is discussed in the following sections.

Carbohydrates

The digestion of carbohydrates begins in the mouth. The salivary enzyme amylase begins the breakdown of food starches into maltose, a disaccharide. As the bolus of food travels through the esophagus to the stomach, no significant digestion of carbohydrates takes place. The esophagus produces no digestive enzymes but does produce mucous for lubrication. The acidic environment in the stomach stops the action of the amylase enzyme.

The next step of carbohydrate digestion takes place in the duodenum. Recall that the chyme from the stomach enters the duodenum and mixes with the digestive secretion from the pancreas, liver, and gallbladder. Pancreatic juices also contain amylase, which continues the breakdown of starch and glycogen into maltose, a disaccharide. The disaccharides are broken down into monosaccharides by enzymes called maltases, sucrases, and lactases, which are also present in the brush border of the small intestinal wall. Maltase breaks down maltose into glucose. Other disaccharides, such as sucrose and lactose are broken down by sucrase and lactase, respectively. Sucrase breaks down sucrose (or “table sugar”) into glucose and fructose, and lactase breaks down lactose (or “milk sugar”) into glucose and galactose. The monosaccharides (glucose) thus produced are absorbed and then can be used in metabolic pathways to harness energy. The monosaccharides are transported across the intestinal epithelium into the bloodstream to be transported to the different cells in the body. The steps in carbohydrate digestion are summarized in Figure 10.1.5.1.

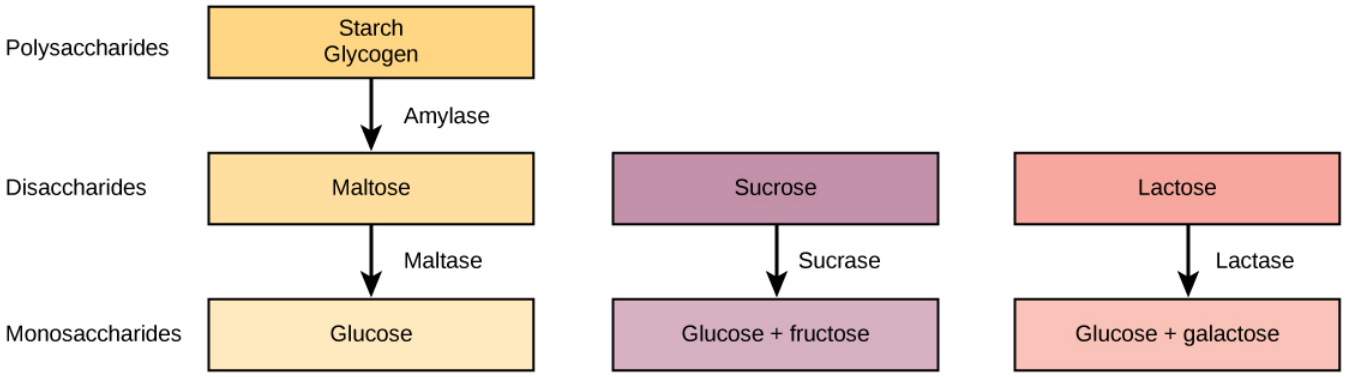


Figure 10.1.5.1: Digestion of carbohydrates is performed by several enzymes. Starch and glycogen are broken down into glucose by amylase and maltase. Sucrose (table sugar) and lactose (milk sugar) are broken down by sucrase and lactase, respectively.

Table 10.1.5.1**:** Digestion of Carbohydrates

Enzyme	Produced By	Site of Action	Substrate Acting On	End Products
Salivary amylase	Salivary glands	Mouth	Polysaccharides (Starch)	Disaccharides (maltose), oligosaccharides
Pancreatic amylase	Pancreas	Small intestine	Polysaccharides (starch)	Disaccharides (maltose), monosaccharides
Oligosaccharidases	Lining of the intestine; brush border membrane	Small intestine	Disaccharides	Monosaccharides (e.g., glucose, fructose, galactose)

Protein

A large part of protein digestion takes place in the stomach. The enzyme pepsin plays an important role in the digestion of proteins by breaking down the intact protein to peptides, which are short chains of four to nine amino acids. In the duodenum, other enzymes—trypsin, elastase, and chymotrypsin—act on the peptides reducing them to smaller peptides. Trypsin elastase, carboxypeptidase, and chymotrypsin are produced by the pancreas and released into the duodenum where they act on the chyme. Further breakdown of peptides to single amino acids is aided by enzymes called peptidases (those that break down peptides). Specifically, carboxypeptidase, dipeptidase, and aminopeptidase play important roles in reducing the peptides to free amino acids. The amino acids are absorbed into the bloodstream through the small intestines. The steps in protein digestion are summarized in Figure 10.1.5.2.

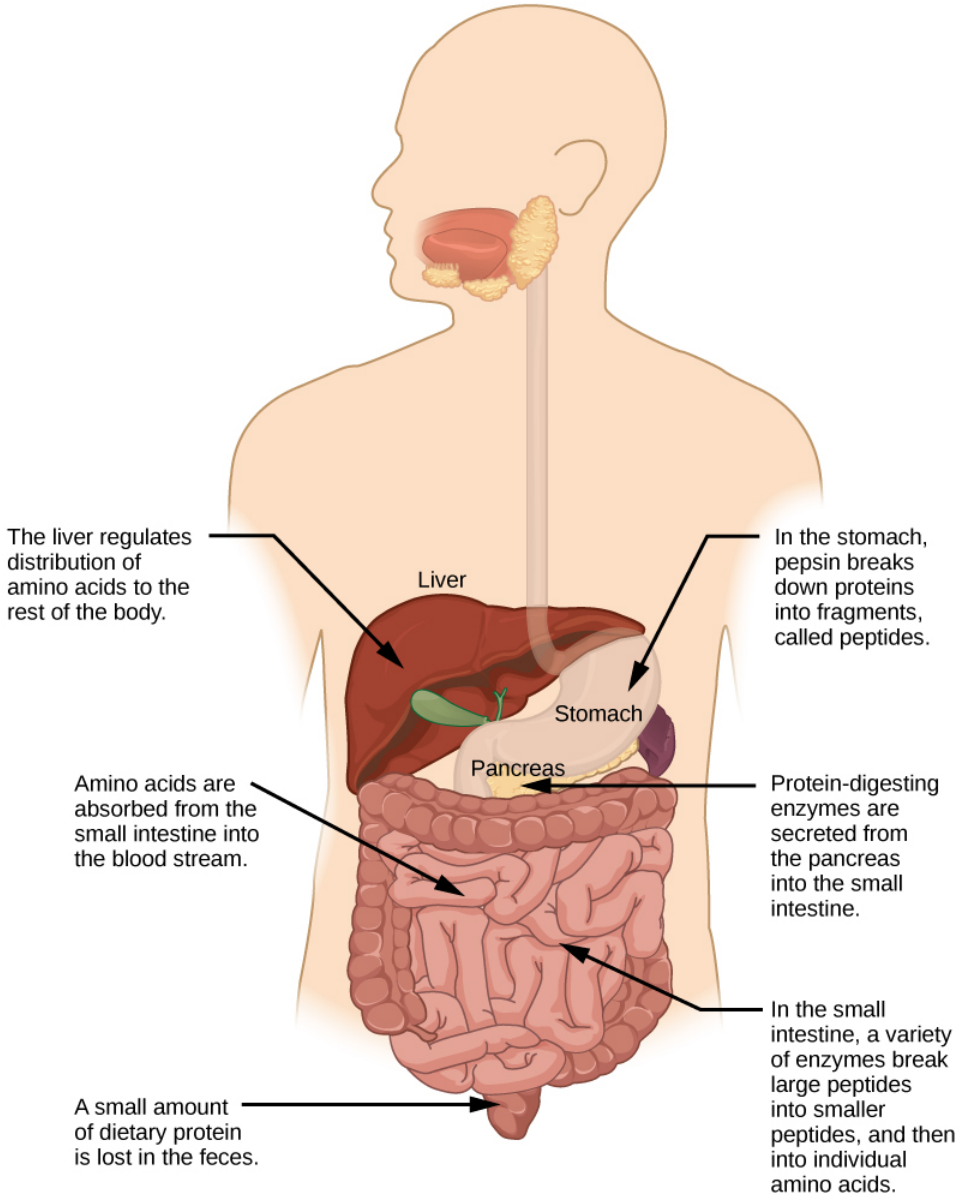


Figure 10.1.5.2: Protein digestion is a multistep process that begins in the stomach and continues through the intestines.

Table 10.1.5.2**:** Digestion of Protein

Enzyme	Produced By	Site of Action	Substrate Acting On	End Products
Pepsin	Stomach chief cells	Stomach	Proteins	Peptides
Trypsin Elastase Chymotrypsin	Pancreas	Small intestine	Proteins	Peptides
Carboxypeptidase	Pancreas	Small intestine	Peptides	Amino acids and peptides
Aminopeptidase Dipeptidase	Lining of intestine	Small intestine	Peptides	Amino acids

Lipids

Lipid digestion begins in the stomach with the aid of lingual lipase and gastric lipase. However, the bulk of lipid digestion occurs in the small intestine due to pancreatic lipase. When chyme enters the duodenum, the hormonal responses trigger the release of bile,

which is produced in the liver and stored in the gallbladder. Bile aids in the digestion of lipids, primarily triglycerides by emulsification. Emulsification is a process in which large lipid globules are broken down into several small lipid globules. These small globules are more widely distributed in the chyme rather than forming large aggregates. Lipids are hydrophobic substances: in the presence of water, they will aggregate to form globules to minimize exposure to water. Bile contains bile salts, which are amphipathic, meaning they contain hydrophobic and hydrophilic parts. Thus, the bile salts hydrophilic side can interface with water on one side and the hydrophobic side interfaces with lipids on the other. By doing so, bile salts emulsify large lipid globules into small lipid globules.

Why is emulsification important for digestion of lipids? Pancreatic juices contain enzymes called lipases (enzymes that break down lipids). If the lipid in the chyme aggregates into large globules, very little surface area of the lipids is available for the lipases to act on, leaving lipid digestion incomplete. By forming an emulsion, bile salts increase the available surface area of the lipids many fold. The pancreatic lipases can then act on the lipids more efficiently and digest them, as detailed in Figure 10.1.5.3. Lipases break down the lipids into fatty acids and glycerides. These molecules can pass through the plasma membrane of the cell and enter the epithelial cells of the intestinal lining. The bile salts surround long-chain fatty acids and monoglycerides forming tiny spheres called micelles. The micelles move into the brush border of the small intestine absorptive cells where the long-chain fatty acids and monoglycerides diffuse out of the micelles into the absorptive cells leaving the micelles behind in the chyme. The long-chain fatty acids and monoglycerides recombine in the absorptive cells to form triglycerides, which aggregate into globules and become coated with proteins. These large spheres are called chylomicrons. Chylomicrons contain triglycerides, cholesterol, and other lipids and have proteins on their surface. The surface is also composed of the hydrophilic phosphate "heads" of phospholipids. Together, they enable the chylomicron to move in an aqueous environment without exposing the lipids to water. Chylomicrons leave the absorptive cells via exocytosis. Chylomicrons enter the lymphatic vessels, and then enter the blood in the subclavian vein.

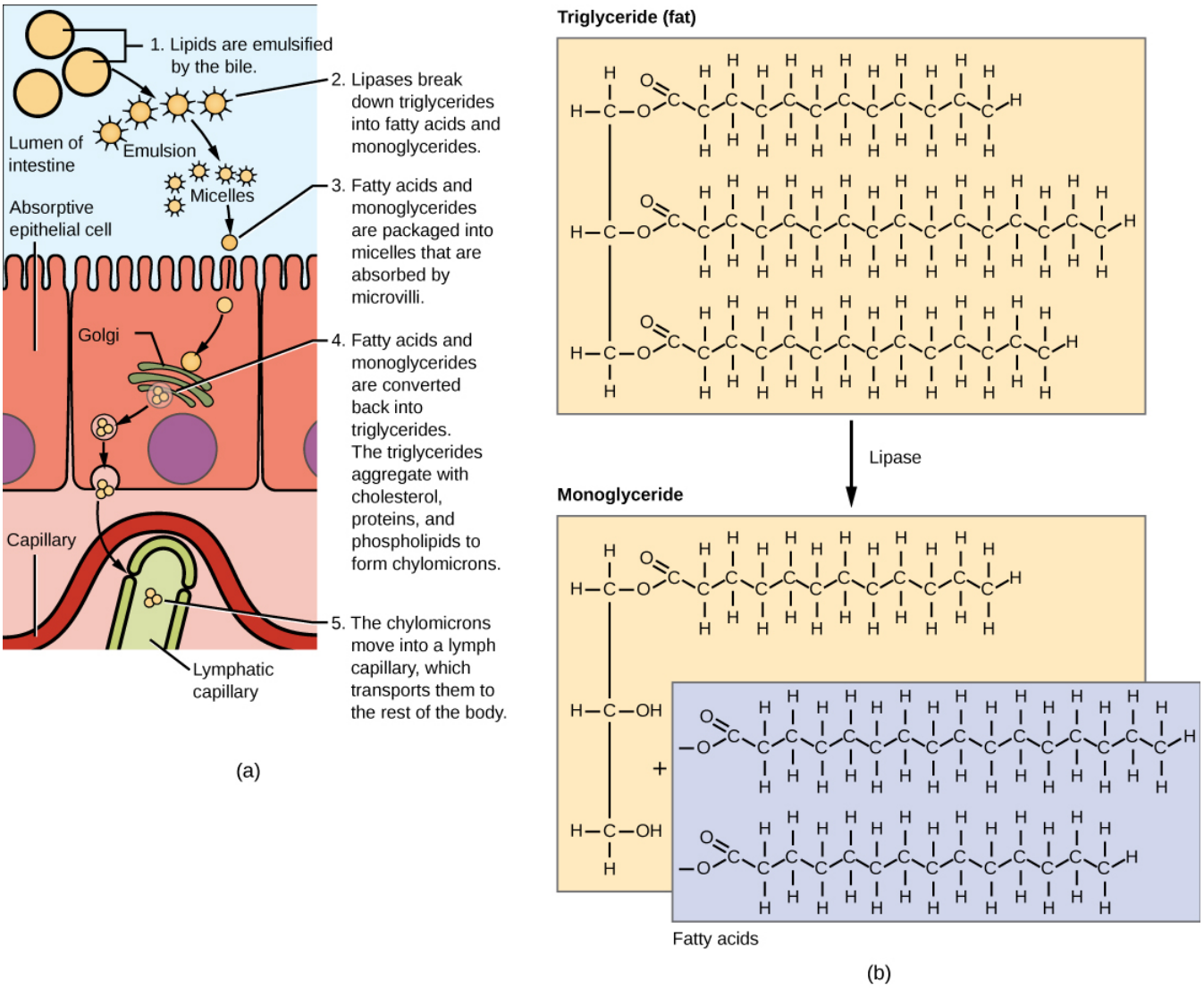


Figure 10.1.5.3: Lipids are digested and absorbed in the small intestine.

Vitamins

Vitamins can be either water-soluble or lipid-soluble. Fat soluble vitamins are absorbed in the same manner as lipids. It is important to consume some amount of dietary lipid to aid the absorption of lipid-soluble vitamins. Water-soluble vitamins can be directly absorbed into the bloodstream from the intestine.

Art Connection

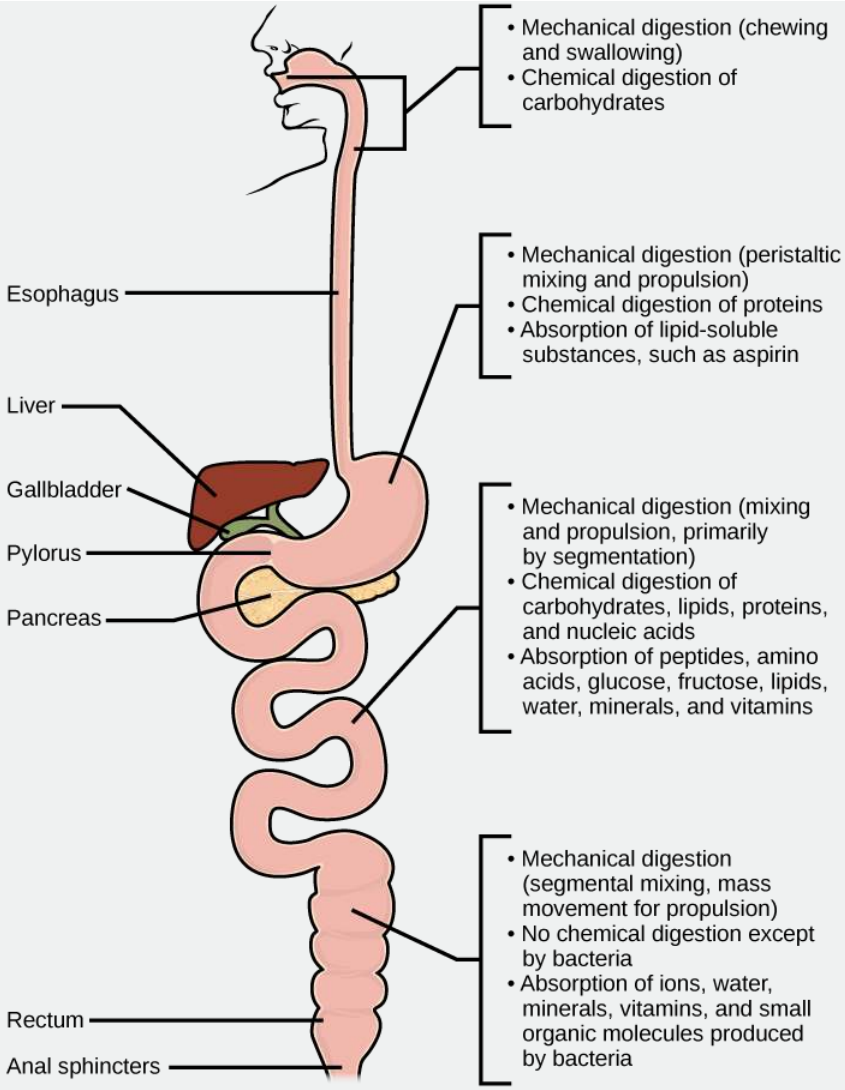


Figure 10.1.5.4: Mechanical and chemical digestion of food takes place in many steps, beginning in the mouth and ending in the rectum.

Which of the following statements about digestive processes is true?

A. Amylase, maltase, and lactase in the mouth digest carbohydrates.
B. Trypsin and lipase in the stomach digest protein.
C. Bile emulsifies lipids in the small intestine.
D. No food is absorbed until the small intestine.

Elimination

The final step in digestion is the elimination of undigested food content and waste products. The undigested food material enters the colon, where most of the water is reabsorbed. Recall that the colon is also home to the microflora called “intestinal flora” that aid in the digestion process. The semi-solid waste is moved through the colon by peristaltic movements of the muscle and is stored in the rectum. As the rectum expands in response to storage of fecal matter, it triggers the neural signals required to set up the urge to eliminate. The solid waste is eliminated through the anus using peristaltic movements of the rectum.

Common Problems with Elimination

Diarrhea and constipation are some of the most common health concerns that affect digestion. Constipation is a condition where the feces are hardened because of excess water removal in the colon. In contrast, if enough water is not removed from the feces, it

results in diarrhea. Many bacteria, including the ones that cause cholera, affect the proteins involved in water reabsorption in the colon and result in excessive diarrhea.

Emesis

Emesis, or vomiting, is elimination of food by forceful expulsion through the mouth. It is often in response to an irritant that affects the digestive tract, including but not limited to viruses, bacteria, emotions, sights, and food poisoning. This forceful expulsion of the food is due to the strong contractions produced by the stomach muscles. The process of emesis is regulated by the medulla.

Summary

Digestion begins with ingestion, where the food is taken in the mouth. Digestion and absorption take place in a series of steps with special enzymes playing important roles in digesting carbohydrates, proteins, and lipids. Elimination describes removal of undigested food contents and waste products from the body. While most absorption occurs in the small intestines, the large intestine is responsible for the final removal of water that remains after the absorptive process of the small intestines. The cells that line the large intestine absorb some vitamins as well as any leftover salts and water. The large intestine (colon) is also where feces is formed.

Art Connections

Figure 10.1.5.4: Which of the following statements about digestive processes is true?

A. Amylase, maltase and lactase in the mouth digest carbohydrates.
B. Trypsin and lipase in the stomach digest protein.
C. Bile emulsifies lipids in the small intestine.
D. No food is absorbed until the small intestine.

Answer

C

Glossary

aminopeptidase
protease that breaks down peptides to single amino acids; secreted by the brush border of small intestine

carboxypeptidase
protease that breaks down peptides to single amino acids; secreted by the brush border of the small intestine

chylomicron
small lipid globule

chymotrypsin
pancreatic protease

digestion
mechanical and chemical break down of food into small organic fragments

dipeptidase
protease that breaks down peptides to single amino acids; secreted by the brush border of small intestine

elastase
pancreatic protease

ingestion

act of taking in food

lactase
enzyme that breaks down lactose into glucose and galactose

maltase
enzyme that breaks down maltose into glucose

sucrase
enzyme that breaks down sucrose into glucose and fructose

trypsin
pancreatic protease that breaks down protein

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10.1.6: Digestive System Regulation

Skills to Develop

- Discuss the role of neural regulation in digestive processes
- Explain how hormones regulate digestion

The brain is the control center for the sensation of hunger and satiety. The functions of the digestive system are regulated through neural and hormonal responses.

Neural Responses to Food

In reaction to the smell, sight, or thought of food, like that shown in Figure 10.1.6.1, the first hormonal response is that of salivation. The salivary glands secrete more saliva in response to the stimulus presented by food in preparation for digestion. Simultaneously, the stomach begins to produce hydrochloric acid to digest the food. Recall that the peristaltic movements of the esophagus and other organs of the digestive tract are under the control of the brain. The brain prepares these muscles for movement as well. When the stomach is full, the part of the brain that detects satiety signals fullness. There are three overlapping phases of gastric control—the cephalic phase, the gastric phase, and the intestinal phase—each requires many enzymes and is under neural control as well.



Figure 10.1.6.1: Seeing a plate of food triggers the secretion of saliva in the mouth and the production of HCL in the stomach. (credit: Kelly Bailey)

Digestive Phases

The response to food begins even before food enters the mouth. The first phase of ingestion, called the cephalic phase, is controlled by the neural response to the stimulus provided by food. All aspects—such as sight, sense, and smell—trigger the neural responses resulting in salivation and secretion of gastric juices. The gastric and salivary secretion in the cephalic phase can also take place due to the thought of food. Right now, if you think about a piece of chocolate or a crispy potato chip, the increase in salivation is a cephalic phase response to the thought. The central nervous system prepares the stomach to receive food.

The gastric phase begins once the food arrives in the stomach. It builds on the stimulation provided during the cephalic phase. Gastric acids and enzymes process the ingested materials. The gastric phase is stimulated by (1) distension of the stomach, (2) a decrease in the pH of the gastric contents, and (3) the presence of undigested material. This phase consists of local, hormonal, and neural responses. These responses stimulate secretions and powerful contractions.

The intestinal phase begins when chyme enters the small intestine triggering digestive secretions. This phase controls the rate of gastric emptying. In addition to gastrin emptying, when chyme enters the small intestine, it triggers other hormonal and neural events that coordinate the activities of the intestinal tract, pancreas, liver, and gallbladder.

Hormonal Responses to Food

The endocrine system controls the response of the various glands in the body and the release of hormones at the appropriate times.

One of the important factors under hormonal control is the stomach acid environment. During the gastric phase, the hormone gastrin is secreted by G cells in the stomach in response to the presence of proteins. Gastrin stimulates the release of stomach acid, or hydrochloric acid (HCl) which aids in the digestion of the proteins. However, when the stomach is emptied, the acidic environment need not be maintained and a hormone called somatostatin stops the release of hydrochloric acid. This is controlled by a negative feedback mechanism.

In the duodenum, digestive secretions from the liver, pancreas, and gallbladder play an important role in digesting chyme during the intestinal phase. In order to neutralize the acidic chyme, a hormone called secretin stimulates the pancreas to produce alkaline bicarbonate solution and deliver it to the duodenum. Secretin acts in tandem with another hormone called cholecystokinin (CCK). Not only does CCK stimulate the pancreas to produce the requisite pancreatic juices, it also stimulates the gallbladder to release bile into the duodenum.

Another level of hormonal control occurs in response to the composition of food. Foods high in lipids take a long time to digest. A hormone called gastric inhibitory peptide is secreted by the small intestine to slow down the peristaltic movements of the intestine to allow fatty foods more time to be digested and absorbed.

Understanding the hormonal control of the digestive system is an important area of ongoing research. Scientists are exploring the role of each hormone in the digestive process and developing ways to target these hormones. Advances could lead to knowledge that may help to battle the obesity epidemic.

Summary

The brain and the endocrine system control digestive processes. The brain controls the responses of hunger and satiety. The endocrine system controls the release of hormones and enzymes required for digestion of food in the digestive tract.

Glossary

cephalic phase
first phase of digestion, controlled by the neural response to the stimulus provided by food

cholecystokinin
hormone that stimulates the contraction of the gallbladder to release bile

endocrine system
system that controls the response of the various glands in the body and the release of hormones at the appropriate times

gastric inhibitory peptide

hormone secreted by the small intestine in the presence of fatty acids and sugars; it also inhibits acid production and peristalsis in order to slow down the rate at which food enters the small intestine

gastric phase

digestive phase beginning once food enters the stomach; gastric acids and enzymes process the ingested materials

gastrin

hormone which stimulates hydrochloric acid secretion in the stomach

intestinal phase

third digestive phase; begins when chyme enters the small intestine triggering digestive secretions and controlling the rate of gastric emptying

secretin

hormone which stimulates sodium bicarbonate secretion in the small intestine

somatostatin

hormone released to stop acid secretion when the stomach is empty

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10.1.E: Animal Nutrition and the Digestive System (Exercises)

34.1: Digestive Systems

Animals obtain their nutrition from the consumption of other organisms. Depending on their diet, animals can be classified into the following categories: plant eaters (herbivores), meat eaters (carnivores), and those that eat both plants and animals (omnivores). The nutrients and macromolecules present in food are not immediately accessible to the cells. There are processes that modify food within the animal body to make the nutrients and organic molecules needed for cellular function.

Review Questions

Which of the following is a pseudo-ruminant?

A. cow
B. pig
C. crow
D. horse

Answer

D

Which of the following statements is untrue?

A. Roughage takes a long time to digest.
B. Birds eat large quantities at one time so that they can fly long distances.
C. Cows do not have upper teeth.
D. In pseudo-ruminants, roughage is digested in the cecum.

Answer

B

The acidic nature of chyme is neutralized by _____.

A. potassium hydroxide
B. sodium hydroxide
C. bicarbonates
D. vinegar

Answer

C

The digestive juices from the liver are delivered to the _____.

A. stomach
B. liver
C. duodenum
D. colon

Answer

C

Free Response

How does the polygastric digestive system aid in digesting roughage?

Answer

Animals with a polygastric digestive system have a multi-chambered stomach. The four compartments of the stomach are called the rumen, reticulum, omasum, and abomasum. These chambers contain many microbes that break down the cellulose and ferment the ingested food. The abomasum is the “true” stomach and is the equivalent of a monogastric stomach chamber where gastric juices are secreted. The four-compartment gastric chamber provides larger space and the microbial support necessary for ruminants to digest plant material.

How do birds digest their food in the absence of teeth?

Answer

Birds have a stomach chamber called a gizzard. Here, the food is stored, soaked, and ground into finer particles, often using pebbles. Once this process is complete, the digestive juices take over in the proventriculus and continue the digestive process.

What is the role of the accessory organs in digestion?

Answer

Accessory organs play an important role in producing and delivering digestive juices to the intestine during digestion and absorption. Specifically, the salivary glands, liver, pancreas, and gallbladder play important roles. Malfunction of any of these organs can lead to disease states.

Explain how the villi and microvilli aid in absorption.

Answer

The villi and microvilli are folds on the surface of the small intestine. These folds increase the surface area of the intestine and provide more area for the absorption of nutrients.

34.2: Nutrition and Energy Production

Given the diversity of animal life on our planet, it is not surprising that the animal diet would also vary substantially. The animal diet is the source of materials needed for building DNA and other complex molecules needed for growth, maintenance, and reproduction; collectively these processes are called biosynthesis. The diet is also the source of materials for ATP production in the cells. The diet must be balanced to provide the minerals and vitamins that are required for cellular function.

Review Questions

Which of the following statements is not true?

A. Essential nutrients can be synthesized by the body.
B. Vitamins are required in small quantities for bodily function.
C. Some amino acids can be synthesized by the body, while others need to be obtained from diet.
D. Vitamins come in two categories: fat-soluble and water-soluble.

Answer

A

Which of the following is a water-soluble vitamin?

A. vitamin A
B. vitamin E
C. vitamin K
D. vitamin C

Answer

D

What is the primary fuel for the body?

A. carbohydrates
B. lipids
C. protein
D. glycogen

Answer

A

Excess glucose is stored as _____.

A. fat
B. glucagon
C. glycogen
D. it is not stored in the body

Answer

C

Free Response

What are essential nutrients?

Answer

Essential nutrients are those nutrients that must be obtained from the diet because they cannot be produced by the body. Vitamins and minerals are examples of essential nutrients.

What is the role of minerals in maintaining good health?

Answer

Minerals—such as potassium, sodium, and calcium—are required for the functioning of many cellular processes, including muscle contraction and nerve conduction. While minerals are required in trace amounts, not having minerals in the diet can be potentially harmful.

Discuss why obesity is a growing epidemic.

Answer

In the United States, obesity, particularly childhood obesity, is a growing concern. Some of the contributors to this situation include sedentary lifestyles and consuming more processed foods and less fruits and vegetables. As a result, even young children who are obese can face health concerns.

There are several nations where malnourishment is a common occurrence. What may be some of the health challenges posed by malnutrition?

Answer

Malnutrition, often in the form of not getting enough calories or not enough of the essential nutrients, can have severe consequences. Many malnourished children have vision and dental problems, and over the years may develop many serious health problems.

34.3: Digestive System Processes

Obtaining nutrition and energy from food is a multi-step process. For true animals, the first step is ingestion, the act of taking in food. This is followed by digestion, absorption, and elimination. In the following sections, each of these steps will be discussed in detail.

Review Questions

Where does the majority of protein digestion take place?

A. stomach
B. duodenum
C. mouth
D. jejunum

Answer

A

Lipases are enzymes that break down _____.

A. disaccharides
B. lipids
C. proteins
D. cellulose

Answer

B

Free Response

Explain why some dietary lipid is a necessary part of a balanced diet.

Answer

Lipids add flavor to food and promote a sense of satiety or fullness. Fatty foods are sources of high energy; one gram of lipid contains nine calories. Lipids are also required in the diet to aid the absorption of lipid-soluble vitamins and for the production of lipid-soluble hormones.

34.4: Digestive System Regulation

The brain is the control center for the sensation of hunger and satiety. The functions of the digestive system are regulated through neural and hormonal responses.

Review Questions

Which hormone controls the release of bile from the gallbladder

A. pepsin
B. amylase
C. CCK
D. gastrin

Answer

C

Which hormone stops acid secretion in the stomach?

A. gastrin
B. somatostatin
C. gastric inhibitory peptide
D. CCK

Answer

B

Free Response

Describe how hormones regulate digestion.

Answer

Hormones control the different digestive enzymes that are secreted in the stomach and the intestine during the process of digestion and absorption. For example, the hormone gastrin stimulates stomach acid secretion in response to food intake. The hormone somatostatin stops the release of stomach acid.

Describe one or more scenarios where loss of hormonal regulation of digestion can lead to diseases.

Answer

There are many cases where loss of hormonal regulation can lead to illnesses. For example, the bilirubin produced by the breakdown of red blood cells is converted to bile by the liver. When there is malfunction of this process, there is excess bilirubin in the blood and bile levels are low. As a result, the body struggles with dealing with fatty food. This is why a patient suffering from jaundice is asked to eat a diet with almost zero fat.

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SECTION OVERVIEW

10.2: Digestive System Infections

Gastrointestinal (GI) diseases are so common that, unfortunately, most people have had first-hand experience with the unpleasant symptoms, such as diarrhea, vomiting, and abdominal discomfort. The causes of gastrointestinal illness can vary widely, but such diseases can be grouped into two categories: those caused by infection (the growth of a pathogen in the GI tract) or intoxication (the presence of a microbial toxin in the GI tract).

Foodborne pathogens like *Escherichia coli* O157:H7 are among the most common sources of gastrointestinal disease. Contaminated food and water have always posed a health risk for humans, but in today's global economy, outbreaks can occur on a much larger scale. *E. coli* O157:H7 is a potentially deadly strain of *E. coli* with a history of contaminating meat and produce that are not properly processed. The source of an *E. coli* O157:H7 outbreak can be difficult to trace, especially if the contaminated food is processed in a foreign country. Once the source is identified, authorities may issue recalls of the contaminated food products, but by then there are typically numerous cases of food poisoning, some of them fatal.

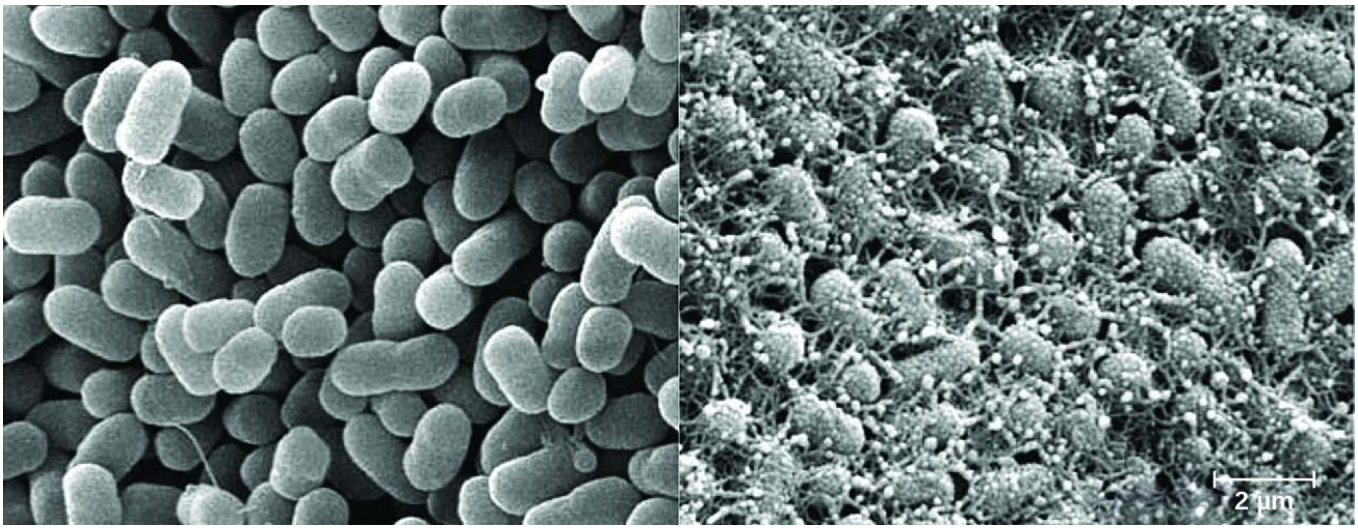


Figure 10.2.1: *E. coli* O157:H7 causes serious foodborne illness. Curli fibers (adhesive surface fibers that are part of the extracellular matrix) help these bacteria adhere to surfaces and form biofilms. Pictured are two groups of cells, curli non-producing cells (left) and curli producing cells (right). (credit left, right: modification of work by USDA)

10.2.1: Anatomy and Normal Microbiota of the Digestive System

10.2.2: Microbial Diseases of the Mouth and Oral Cavity

10.2.3: Bacterial Infections of the Gastrointestinal Tract

10.2.4: Viral Infections of the Gastrointestinal Tract

10.2.5: Protozoan Infections of the Gastrointestinal Tract

10.2.6: Helminthic Infections of the Gastrointestinal Tract

10.2.E: Digestive System Infections (Exercises)

Thumbnail: This is an adult Taenia saginata tapeworm. Humans become infected by ingesting raw or undercooked infected meat. In the human intestine, the cysticercus develops over 2 mo. into an adult tapeworm, which can survive for years, attaching to, and residing in the small intestine. (Public Domain; UC CDC)

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10.2.1: Anatomy and Normal Microbiota of the Digestive System

Learning Objectives

- Describe the major anatomical features of the human digestive system
- Describe the normal microbiota of various regions in the human digestive system
- Explain how microorganisms overcome the defenses of the digestive tract to cause infection or intoxication
- Describe general signs and symptoms associated with infections of the digestive system

Clinical Focus: Part 1

After a morning of playing outside, four-year-old Carli ran inside for lunch. After taking a bite of her fried egg, she pushed it away and whined, “It’s too slimy, Mommy. I don’t want any more.” But her mother, in no mood for games, curtly replied that if she wanted to go back outside she had better finish her lunch. Reluctantly, Carli complied, trying hard not to gag as she choked down the runny egg.

That night, Carli woke up feeling nauseated. She cried for her parents and then began to vomit. Her parents tried to comfort her, but she continued to vomit all night and began to have diarrhea and run a fever. By the morning, her parents were very worried. They rushed her to the emergency room.

Exercise 10.2.1.1

What could have caused Carli’s signs and symptoms?

The human digestive system, or the gastrointestinal (GI) tract, begins with the mouth and ends with the anus. The parts of the mouth include the teeth, the gums, the tongue, the oral vestibule (the space between the gums, lips, and teeth), and the oral cavity proper (the space behind the teeth and gums). Other parts of the GI tract are the pharynx, esophagus, stomach, small intestine, large intestine, rectum, and anus (Figure 10.2.1.1). Accessory digestive organs include the salivary glands, liver, gallbladder, spleen, and pancreas.

The digestive system contains normal microbiota, including archaea, bacteria, fungi, protists, and even viruses. Because this microbiota is important for normal functioning of the digestive system, alterations to the microbiota by antibiotics or diet can be harmful. Additionally, the introduction of pathogens to the GI tract can cause infections and diseases. In this section, we will review the microbiota found in a healthy digestive tract and the general signs and symptoms associated with oral and GI infections.

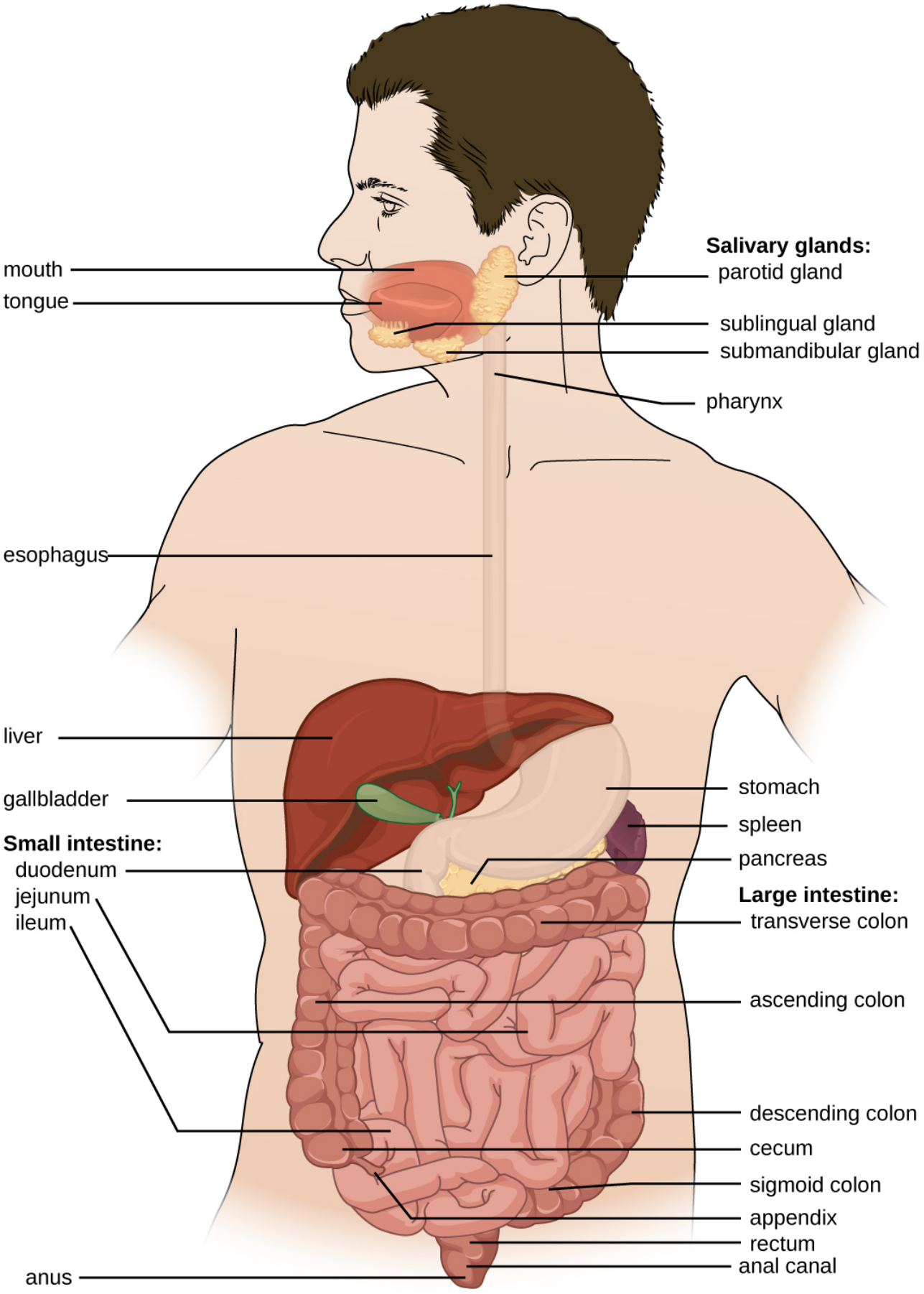

mouth
tongue
Salivary glands:
parotid gland
sublingual gland
submandibular gland
pharynx
esophagus
liver
gallbladder
Small intestine:
duodenum
jejunum
ileum
stomach
spleen
pancreas
Large intestine:
transverse colon
ascending colon
descending colon
cecum
sigmoid colon
appendix
rectum
anal canal
anus

Figure 10.2.1.1: The digestive system, or the gastrointestinal tract, includes all of the organs associated with the digestion of food.

Anatomy and Normal Microbiota of the Oral Cavity

Food enters the digestive tract through the mouth, where mechanical digestion (by chewing) and chemical digestion (by enzymes in saliva) begin. Within the mouth are the tongue, teeth, and salivary glands, including the parotid, sublingual, and submandibular glands (Figure 10.2.1.2). The salivary glands produce saliva, which lubricates food and contains digestive enzymes.

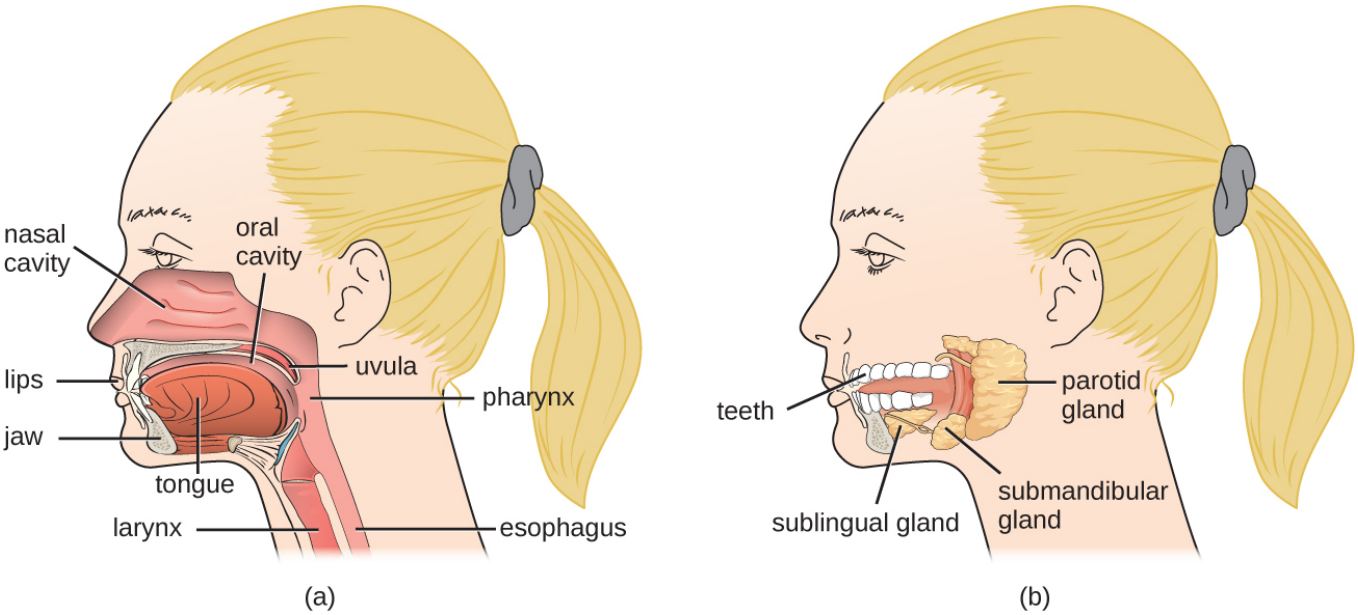


Figure 10.2.1.2: (a) When food enters the mouth, digestion begins. (b) Salivary glands are accessory digestive organs. (credit: modification of work by National Cancer Institute)

The structure of a tooth (Figure 10.2.1.3) begins with the visible outer surface, called the crown, which has to be extremely hard to withstand the force of biting and chewing. The crown is covered with enamel, which is the hardest material in the body. Underneath the crown, a layer of relatively hard dentin extends into the root of the tooth around the innermost pulp cavity, which includes the pulp chamber at the top of the tooth and pulp canal, or root canal, located in the root. The pulp that fills the pulp cavity is rich in blood vessels, lymphatic vessels, connective tissue, and nerves. The root of the tooth and some of the crown are covered with cementum, which works with the periodontal ligament to anchor the tooth in place in the jaw bone. The soft tissues surrounding the teeth and bones are called gums, or gingiva. The gingival space or gingival crevice is located between the gums and teeth.

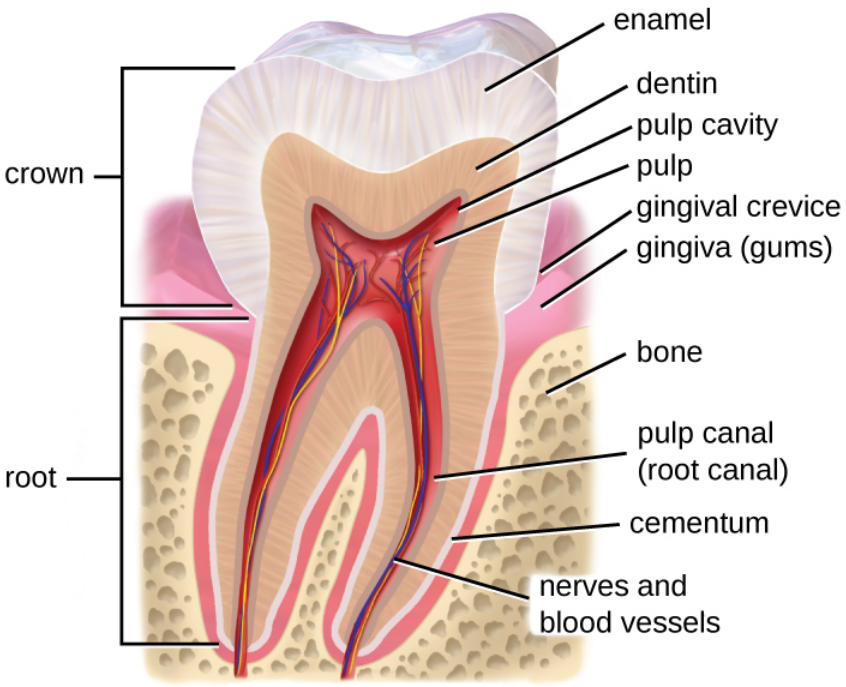


Figure 10.2.1.3: The tooth has a visible crown with an outer layer of enamel, a layer of dentin, and an inner pulp. The root, hidden by the gums, contains the pulp canal (root canal). (credit: modification of work by Bruce Blaus)

Microbes such as bacteria and archaea are abundant in the mouth and coat all of the surfaces of the oral cavity. However, different structures, such as the teeth or cheeks, host unique communities of both aerobic and anaerobic microbes. Some factors appear to work against making the mouth hospitable to certain microbes. For example, chewing allows microbes to mix better with saliva so they can be swallowed or spit out more easily. Saliva also contains enzymes, including lysozyme, which can damage microbial cells. Recall that lysozyme is part of the first line of defense in the innate immune system and cleaves the β-(1,4) glycosidic linkages between N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) in bacterial peptidoglycan (see Chemical Defenses). Additionally, fluids containing immunoglobulins and phagocytic cells are produced in the gingival spaces. Despite all of these chemical and mechanical activities, the mouth supports a large microbial community.

? Exercise 10.2.1.2

What factors make the mouth inhospitable for certain microbes?

Anatomy and Normal Microbiota of the GI Tract

As food leaves the oral cavity, it travels through the pharynx, or the back of the throat, and moves into the esophagus, which carries the food from the pharynx to the stomach without adding any additional digestive enzymes. The stomach produces mucus to protect its lining, as well as digestive enzymes and acid to break down food. Partially digested food then leaves the stomach through the pyloric sphincter, reaching the first part of the small intestine called the duodenum. Pancreatic juice, which includes enzymes and bicarbonate ions, is released into the small intestine to neutralize the acidic material from the stomach and to assist in digestion. Bile, produced by the liver but stored in the gallbladder, is also released into the small intestine to emulsify fats so that they can travel in the watery environment of the small intestine. Digestion continues in the small intestine, where the majority of nutrients contained in the food are absorbed. Simple columnar epithelial cells called enterocytes line the lumen surface of the small intestinal folds called villi. Each enterocyte has smaller microvilli (cytoplasmic membrane extensions) on the cellular apical surface that increase the surface area to allow more absorption of nutrients to occur (Figure 10.2.1.4).

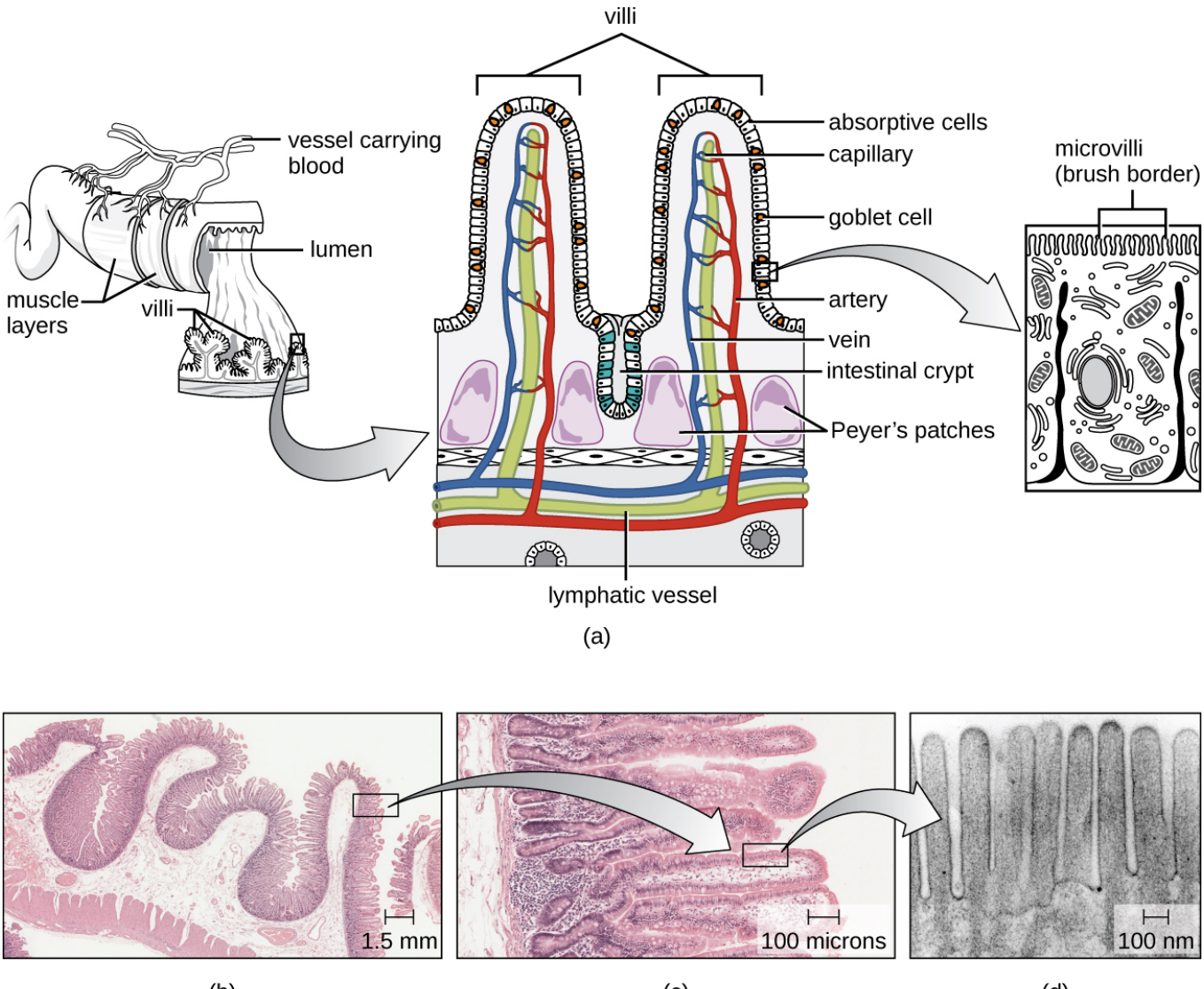


Figure 10.2.1.4: (a) The structure of the wall of the small intestine allows for the majority of nutrient absorption in the body. (b) Villi are folds in the surface of the small intestine. Microvilli are cytoplasmic extensions on individual cells that increase the surface area for absorption. (c) A light micrograph shows the shape of the villi. (d) An electron micrograph shows the shape of the microvilli. (credit b, c, d: Modification of micrographs provided by the Regents of University of Michigan Medical School © 2012)

Digested food leaves the small intestine and moves into the large intestine, or colon, where there is a more diverse microbiota. Near this junction, there is a small pouch in the large intestine called the cecum, which attaches to the appendix. Further digestion occurs throughout the colon and water is reabsorbed, then waste is excreted through the rectum, the last section of the colon, and out of the body through the anus (Figure 10.2.1.1).

The environment of most of the GI tract is harsh, which serves two purposes: digestion and immunity. The stomach is an extremely acidic environment (pH 1.5–3.5) due to the gastric juices that break down food and kill many ingested microbes; this helps prevent infection from pathogens. The environment in the small intestine is less harsh and is able to support microbial communities. Microorganisms present in the small intestine can include lactobacilli, diptherioids and the fungus *Candida*. On the other hand, the large intestine (colon) contains a diverse and abundant microbiota that is important for normal function. These microbes include *Bacteriodetes* (especially the genera *Bacteroides* and *Prevotella*) and *Firmicutes* (especially members of the genus *Clostridium*). Methanogenic archaea and some fungi are also present, among many other species of bacteria. These microbes all aid in digestion and contribute to the production of feces, the waste excreted from the digestive tract, and flatus, the gas produced from microbial fermentation of undigested food. They can also produce valuable nutrients. For example, lactic acid bacteria such as bifidobacteria

can synthesize vitamins, such as vitamin B12, folate, and riboflavin, that humans cannot synthesize themselves. *E. coli* found in the intestine can also break down food and help the body produce vitamin K, which is important for blood coagulation.

The GI tract has several other methods of reducing the risk of infection by pathogens. Small aggregates of underlying lymphoid tissue in the ileum, called Peyer's patches (Figure 10.2.1.4), detect pathogens in the intestines via microfold (M) cells, which transfer antigens from the lumen of the intestine to the lymphocytes on Peyer's patches to induce an immune response. The Peyer's patches then secrete IgA and other pathogen-specific antibodies into the intestinal lumen to help keep intestinal microbes at safe levels. Goblet cells, which are modified simple columnar epithelial cells, also line the GI tract (Figure 10.2.1.5). Goblet cells secrete a gel-forming mucin, which is the major component of mucus. The production of a protective layer of mucus helps reduce the risk of pathogens reaching deeper tissues.

The constant movement of materials through the gastrointestinal tract also helps to move transient pathogens out of the body. In fact, feces are composed of approximately 25% microbes, 25% sloughed epithelial cells, 25% mucus, and 25% digested or undigested food. Finally, the normal microbiota provides an additional barrier to infection via a variety of mechanisms. For example, these organisms outcompete potential pathogens for space and nutrients within the intestine. This is known as competitive exclusion. Members of the microbiota may also secrete protein toxins known as bacteriocins that are able to bind to specific receptors on the surface of susceptible bacteria.

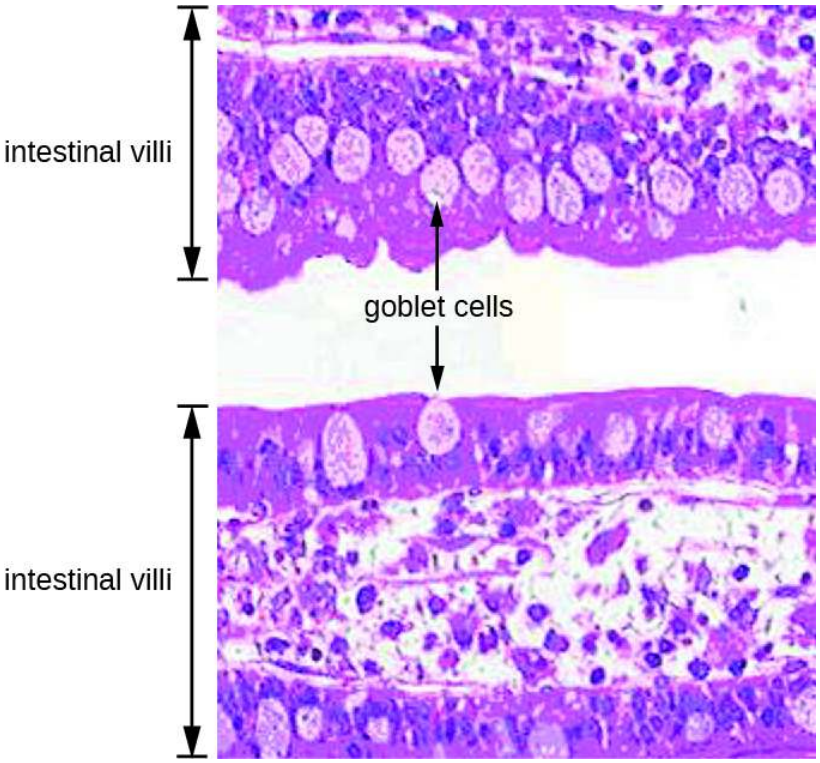


Figure 10.2.1.5: A magnified image of intestinal villi in the GI tract shows goblet cells. These cells are important in producing a protective layer of mucus.

? Exercise 10.2.1.3

Compare and contrast the microbiota of the small and large intestines.

General Signs and Symptoms of Oral and GI Disease

Despite numerous defense mechanisms that protect against infection, all parts of the digestive tract can become sites of infection or intoxication. The term food poisoning is sometimes used as a catch-all for GI infections and intoxications, but not all forms of GI disease originate with foodborne pathogens or toxins.

In the mouth, fermentation by anaerobic microbes produces acids that damage the teeth and gums. This can lead to tooth decay, cavities, and periodontal disease, a condition characterized by chronic inflammation and erosion of the gums. Additionally, some

pathogens can cause infections of the mucosa, glands, and other structures in the mouth, resulting in inflammation, sores, cankers, and other lesions. An open sore in the mouth or GI tract is typically called an ulcer.

Infections and intoxications of the lower GI tract often produce symptoms such as nausea, vomiting, diarrhea, aches, and fever. In some cases, vomiting and diarrhea may cause severe dehydration and other complications that can become serious or fatal. Various clinical terms are used to describe gastrointestinal symptoms. For example, gastritis is an inflammation of the stomach lining that results in swelling and enteritis refers to inflammation of the intestinal mucosa. When the inflammation involves both the stomach lining and the intestinal lining, the condition is called gastroenteritis. Inflammation of the liver is called hepatitis. Inflammation of the colon, called colitis, commonly occurs in cases of food intoxication. Because an inflamed colon does not reabsorb water as effectively as it normally does, stools become watery, causing diarrhea. Damage to the epithelial cells of the colon can also cause bleeding and excess mucus to appear in watery stools, a condition called dysentery.

? Exercise 10.2.1.4

List possible causes and signs and symptoms of food poisoning.

Key Concepts and Summary

- The digestive tract, consisting of the oral cavity, pharynx, esophagus, stomach, small intestine, and large intestine, has a normal microbiota that is important for health.
- The constant movement of materials through the gastrointestinal canal, the protective layer of mucus, the normal microbiota, and the harsh chemical environment in the stomach and small intestine help to prevent colonization by pathogens.
- Infections or microbial toxins in the oral cavity can cause **tooth decay**, **periodontal disease**, and various types of **ulcers**.
- Infections and intoxications of the gastrointestinal tract can cause general symptoms such as nausea, vomiting, diarrhea, and fever. Localized inflammation of the GI tract can result in **gastritis**, **enteritis**, **gastroenteritis**, **hepatitis**, or **colitis**, and damage to epithelial cells of the colon can lead to **dysentery**.
- **Foodborne illness** refers to infections or intoxications that originate with pathogens or toxins ingested in contaminated food or water.

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10.2.2: Microbial Diseases of the Mouth and Oral Cavity

Learning Objectives

- Explain the role of microbial activity in diseases of the mouth and oral cavity
- Compare the major characteristics of specific oral diseases and infections

Despite the presence of saliva and the mechanical forces of chewing and eating, some microbes thrive in the mouth. These microbes can cause damage to the teeth and can cause infections that have the potential to spread beyond the mouth and sometimes throughout the body.

Dental Caries

Cavities of the teeth, known clinically as dental caries, are microbial lesions that cause damage to the teeth. Over time, the lesion can grow through the outer enamel layer to infect the underlying dentin or even the innermost pulp. If dental caries are not treated, the infection can become an abscess that spreads to the deeper tissues of the teeth, near the roots, or to the bloodstream.

Tooth decay results from the metabolic activity of microbes that live on the teeth. A layer of proteins and carbohydrates forms when clean teeth come into contact with saliva. Microbes are attracted to this food source and form a biofilmcalled plaque. The most important cariogenic species in these biofilms is *Streptococcus mutans*. When sucrose, a disaccharide sugar from food, is broken down by bacteria in the mouth, glucose and fructose are produced. The glucose is used to make dextran, which is part of the extracellular matrix of the biofilm. Fructose is fermented, producing organic acids such as lactic acid. These acids dissolve the minerals of the tooth, including enamel, even though it is the hardest material in the body. The acids work even more quickly on exposed dentin (Figure 10.2.2.1). Over time, the plaque biofilm can become thick and eventually calcify. When a heavy plaque deposit becomes hardened in this way, it is called tartar or dental calculus (Figure 10.2.2.2). These substantial plaque biofilms can include a variety of bacterial species, including *Streptococcus* and *Actinomyces* species.

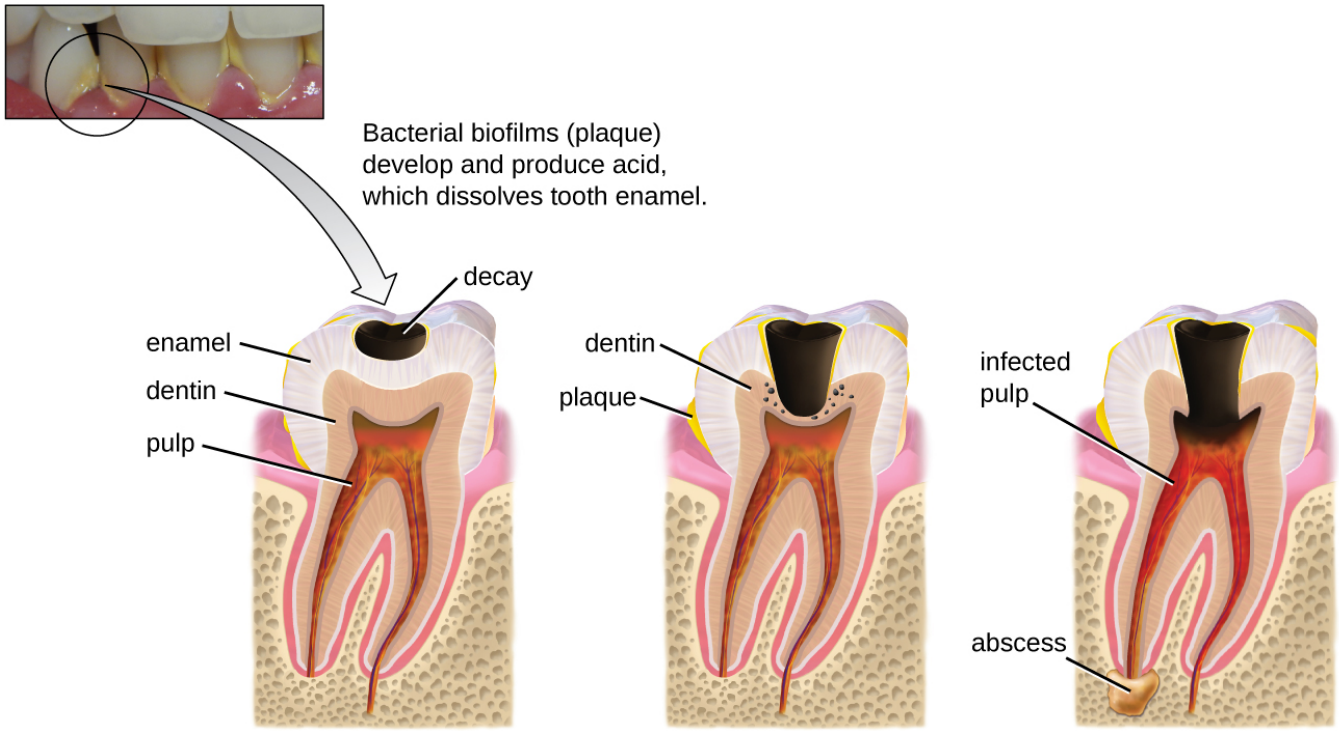


Figure 10.2.2.1: Tooth decay occurs in stages. When bacterial biofilms (plaque) develop on teeth, the acids produced gradually dissolve the enamel, followed by the dentin. Eventually, if left untreated, the lesion may reach the pulp and cause an abscess. (credit: modification of work by “BruceBlaus”/Wikimedia Commons)

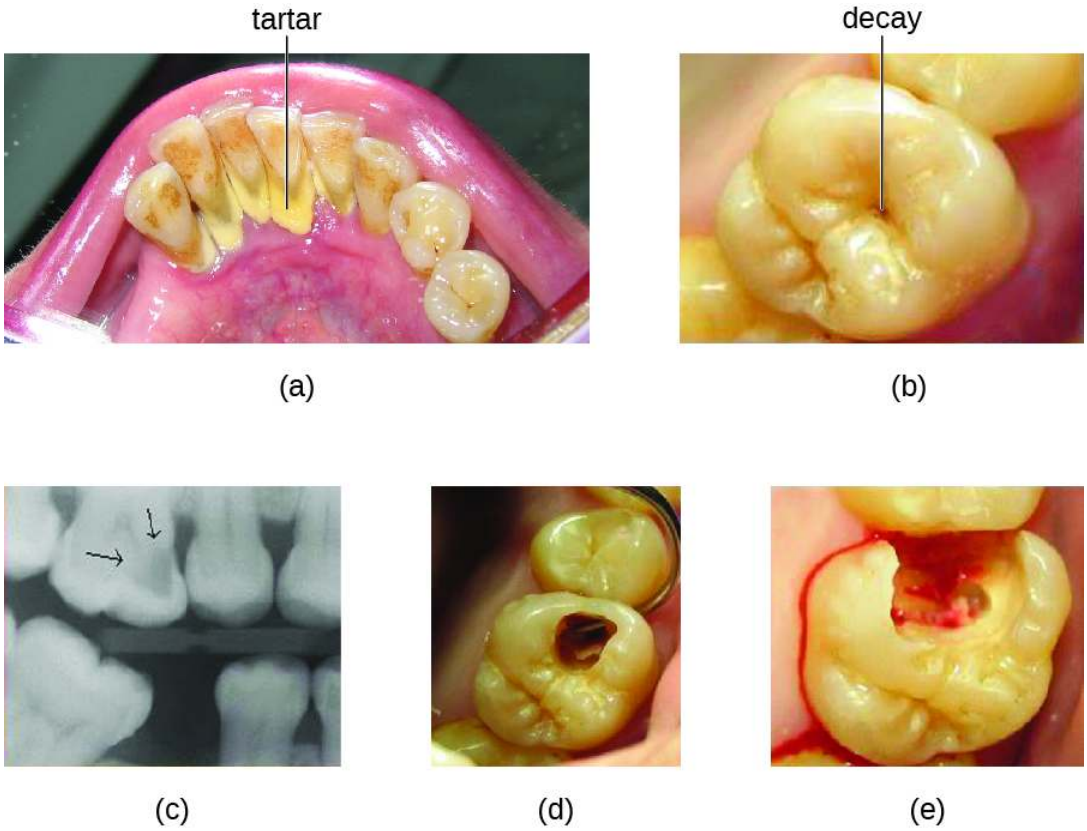


Figure 10.2.2.2: (a) Tartar (dental calculus) is visible at the bases of these teeth. The darker deposits higher on the crowns are staining. (b) This tooth shows only a small amount of visible decay. (c) An X-ray of the same tooth shows that there is a dark area representing more decay inside the tooth. (d) Removal of a portion of the crown reveals the area of damage. (e) All of the cavity must be removed before filling. (credit: modification of work by "DRosenbach"/Wikimedia Commons)

Some tooth decay is visible from the outside, but it is not always possible to see all decay or the extent of the decay. X-ray imaging is used to produce radiographs that can be studied to look for deeper decay and damage to the root or bone (Figure 10.2.2.2). If not detected, the decay can reach the pulp or even spread to the bloodstream. Painful abscesses can develop.

To prevent tooth decay, prophylactic treatment and good hygiene are important. Regular tooth brushing and flossing physically removes microbes and combats microbial growth and biofilm formation. Toothpaste contains fluoride, which becomes incorporated into the hydroxyapatite of tooth enamel, protecting it against acidity caused by fermentation of mouth microbiota. Fluoride is also bacteriostatic, thus slowing enamel degradation. Antiseptic mouthwashes commonly contain plant-derived phenolics like thymol and eucalyptol and/or heavy metals like zinc chloride (see Using Chemicals to Control Microorganisms). Phenolics tend to be stable and persistent on surfaces, and they act through denaturing proteins and disrupting membranes.

Regular dental cleanings allow for the detection of decay at early stages and the removal of tartar. They may also help to draw attention to other concerns, such as damage to the enamel from acidic drinks. Reducing sugar consumption may help prevent damage that results from the microbial fermentation of sugars. Additionally, sugarless candies or gum with sugar alcohols (such as xylitol) can reduce the production of acids because these are fermented to nonacidic compounds (although excess consumption may lead to gastrointestinal distress). Fluoride treatment or ingesting fluoridated water strengthens the minerals in teeth and reduces the incidence of dental caries.

If caries develop, prompt treatment prevents worsening. Smaller areas of decay can be drilled to remove affected tissue and then filled. If the pulp is affected, then a root canal may be needed to completely remove the infected tissues to avoid continued spread of the infection, which could lead to painful abscesses.

? Exercise 10.2.2.1

1. Name some ways that microbes contribute to tooth decay.
2. What is the most important cariogenic species of bacteria?

Periodontal Disease

In addition to damage to the teeth themselves, the surrounding structures can be affected by microbes. Periodontal disease is the result of infections that lead to inflammation and tissue damage in the structures surrounding the teeth. The progression from mild to severe periodontal disease is generally reversible and preventable with good oral hygiene.

Inflammation of the gums that can lead to irritation and bleeding is called gingivitis. When plaque accumulates on the teeth, bacteria colonize the gingival space. As this space becomes increasingly blocked, the environment becomes anaerobic. This allows a wide variety of microbes to colonize, including *Porphyromonas*, *Streptococcus*, and *Actinomyces*. The bacterial products, which include lipopolysaccharide (LPS), proteases, lipoteichoic acids, and others, cause inflammation and gum damage (Figure 10.2.2.3). It is possible that methanogenic archaeans (including *Methanobrevibacter oralis* and other *Methanobrevibacter* species) also contribute to disease progression as some species have been identified in patients with periodontal disease, but this has proven difficult to study.[123] Gingivitis is diagnosed by visual inspection, including measuring pockets in the gums, and X-rays, and is usually treated using good dental hygiene and professional dental cleaning, with antibiotics reserved for severe cases.



Figure 10.2.2.3: Redness and irritation of the gums are evidence of gingivitis.

Over time, chronic gingivitis can develop into the more serious condition of periodontitis (Figure 10.2.2.4). When this happens, the gums recede and expose parts of the tooth below the crown. This newly exposed area is relatively unprotected, so bacteria can grow on it and spread underneath the enamel of the crown and cause cavities. Bacteria in the gingival space can also erode the cementum, which helps to hold the teeth in place. If not treated, erosion of cementum can lead to the movement or loss of teeth. The bones of the jaw can even erode if the infection spreads. This condition can be associated with bleeding and halitosis (bad breath). Cleaning and appropriate dental hygiene may be sufficient to treat periodontitis. However, in cases of severe periodontitis, an antibiotic may be given. Antibiotics may be given in pill form or applied directly to the gum (local treatment). Antibiotics given can include tetracycline, doxycycline, macrolides or β-lactams. Because periodontitis can be caused by a mix of microbes, a combination of antibiotics may be given.

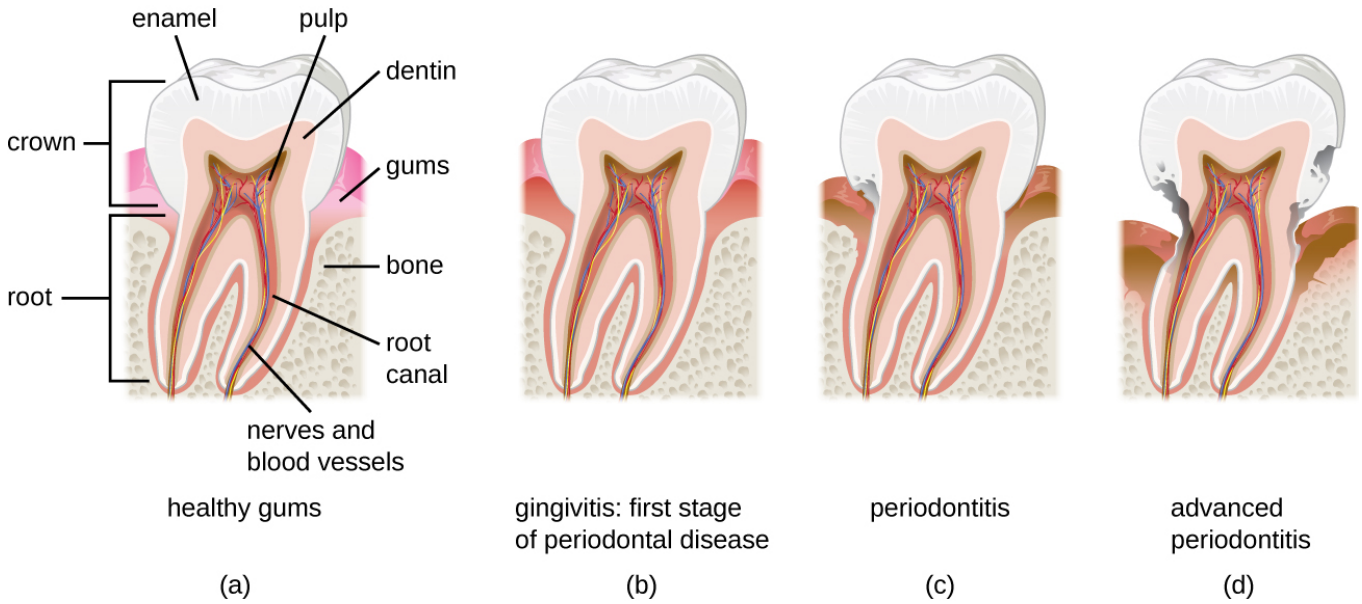


Figure 10.2.2.4: (a) Healthy gums hold the teeth firmly and do not bleed. (b) Gingivitis is the first stage of periodontal disease. Microbial infection causes gums to become inflamed and irritated, with occasional bleeding. (c) In periodontitis, gums recede and expose parts of the tooth normally covered. (d) In advanced periodontitis, the infection spreads to ligaments and bone tissue supporting the teeth. Tooth loss may occur, or teeth may need to be surgically removed. (credit: modification of work by "BruceBlaus"/Wikimedia Commons)

Trench Mouth

When certain bacteria, such as *Prevotella intermedia*, *Fusobacterium* species, and *Treponema vicentii*, are involved and periodontal disease progresses, acute necrotizing ulcerative gingivitis or trench mouth, also called Vincent's disease, can develop. This is severe periodontitis characterized by erosion of the gums, ulcers, substantial pain with chewing, and halitosis (Figure 10.2.2.5) that can be diagnosed by visual examination and X-rays. In countries with good medical and dental care, it is most common in individuals with weakened immune systems, such as patients with AIDS. In addition to cleaning and pain medication, patients may be prescribed antibiotics such as amoxicillin, amoxicillin clavulanate, clindamycin, or doxycycline.



Figure 10.2.2.5: These inflamed, eroded gums are an example of a mild case of acute necrotizing ulcerative gingivitis, also known as trench mouth. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 10.2.2.2

How does gingivitis progress to periodontitis?

Healthy Mouth, Healthy Body

Good oral health promotes good overall health, and the reverse is also true. Poor oral health can lead to difficulty eating, which can cause malnutrition. Painful or loose teeth can also cause a person to avoid certain foods or eat less. Malnutrition due to dental problems is of greatest concern for the elderly, for whom it can worsen other health conditions and contribute to mortality. Individuals who have serious illnesses, especially AIDS, are also at increased risk of malnutrition from dental problems.

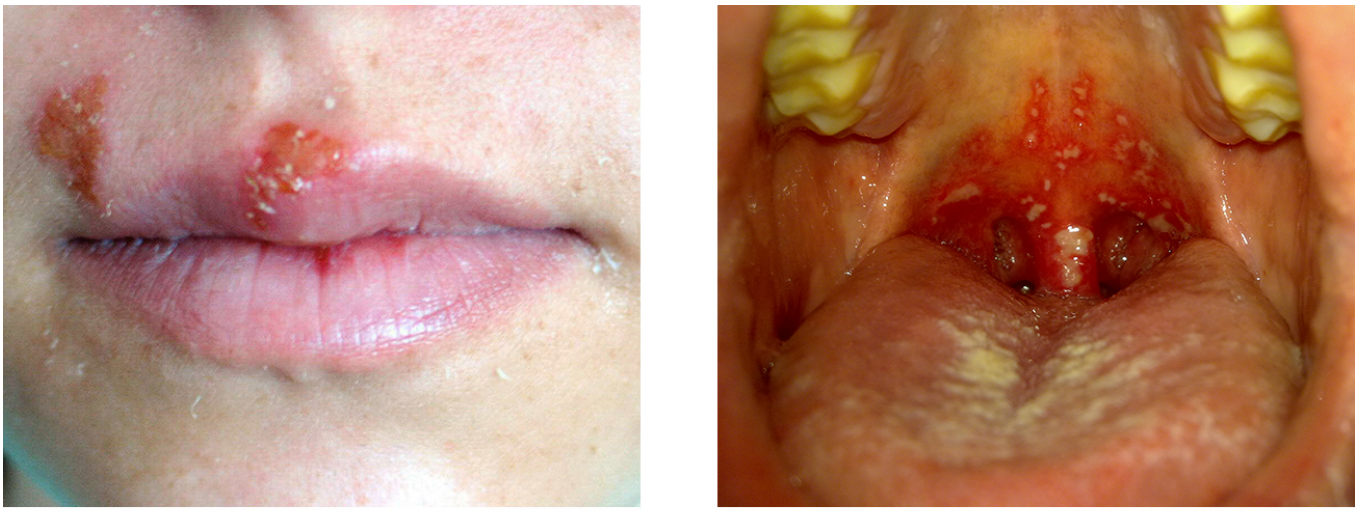
Additionally, poor oral health can contribute to the development of disease. Increased bacterial growth in the mouth can cause inflammation and infection in other parts of the body. For example, *Streptococcus* in the mouth, the main contributor to biofilms on teeth, tartar, and dental caries, can spread throughout the body when there is damage to the tissues inside the mouth, as can happen during dental work. *S. mutans* produces a surface adhesin known as P1, which binds to salivary agglutinin on the surface of the tooth. P1 can also bind to extracellular matrix proteins including fibronectin and collagen. When *Streptococcus* enters the bloodstream as a result of tooth brushing or dental cleaning, it causes inflammation that can lead to the accumulation of plaque in the arteries and contribute to the development of atherosclerosis, a condition associated with cardiovascular disease, heart attack, and stroke. In some cases, bacteria that spread through the blood vessels can lodge in the heart and cause endocarditis (an example of a focal infection).

Oral Infections

As noted earlier, normal oral microbiota can cause dental and periodontal infections. However, there are number of other infections that can manifest in the oral cavity when other microbes are present.

Herpetic Gingivostomatitis

As described in Viral Infections of the Skin and Eyes, infections by herpes simplex virus type 1 (HSV-1) frequently manifest as oral herpes, also called acute herpes labialis and characterized by cold sores on the lips, mouth, or gums. HSV-1 can also cause acute herpetic gingivostomatitis, a condition that results in ulcers of the mucous membranes inside the mouth (Figure 10.2.2.6). Herpetic gingivostomatitis is normally self-limiting except in immunocompromised patients. Like oral herpes, the infection is generally diagnosed through clinical examination, but cultures or biopsies may be obtained if other signs or symptoms suggest the possibility of a different causative agent. If treatment is needed, mouthwashes or antiviral medications such as acyclovir, famciclovir, or valacyclovir may be used.



(a) (b)

Figure 10.2.2.6: (a) This cold sore is caused by infection with herpes simplex virus type 1 (HSV-1). (b) HSV-1 can also cause acute herpetic gingivostomatitis. (credit b: modification of work by Klaus D. Peter)

Oral Thrush

The yeast *Candida* is part of the normal human microbiota, but overgrowths, especially of *Candida albicans*, can lead to infections in several parts of the body. When *Candida* infection develops in the oral cavity, it is called oral thrush. Oral thrush is most common in infants because they do not yet have well developed immune systems and have not acquired the robust normal microbiota that keeps *Candida* in check in adults. Oral thrush is also common in immunodeficient patients and is a common infection in patients with AIDS.

Oral thrush is characterized by the appearance of white patches and pseudomembranes in the mouth (Figure 10.2.2.7) and can be associated with bleeding. The infection may be treated topically with nystatin or clotrimazole oral suspensions, although systemic treatment is sometimes needed. In serious cases, systemic azoles such as fluconazole or itraconazole (for strains resistant to fluconazole), may be used. Amphotericin B can also be used if the infection is severe or if the *Candida* species is azole-resistant.



Figure 10.2.2.7: Overgrowth of *Candida* in the mouth is called thrush. It often appears as white patches. (credit: modification of work by Centers for Disease Control and Prevention)

Mumps

The viral disease mumps is an infection of the parotid glands, the largest of the three pairs of salivary glands (Figure 24.1.2). The causative agent is mumps virus (MuV), a paramyxovirus with an envelope that has hemagglutinin and neuraminidase spikes. A fusion protein located on the surface of the envelope helps to fuse the viral envelope to the host cell plasma membrane.

Mumps virus is transmitted through respiratory droplets or through contact with contaminated saliva, making it quite contagious so that it can lead easily to epidemics. It causes fever, muscle pain, headache, pain with chewing, loss of appetite, fatigue, and weakness. There is swelling of the salivary glands and associated pain (Figure 10.2.2.8). The virus can enter the bloodstream (viremia), allowing it to spread to the organs and the central nervous system. The infection ranges from subclinical cases to cases with serious complications, such as encephalitis, meningitis, and deafness. Inflammation of the pancreas, testes, ovaries, and breasts may also occur and cause permanent damage to those organs; despite these complications, a mumps infection rarely cause sterility.

Mumps can be recognized based on clinical signs and symptoms, and a diagnosis can be confirmed with laboratory testing. The virus can be identified using culture or molecular techniques such as RT-PCR. Serologic tests are also available, especially enzyme immunoassays that detect antibodies. There is no specific treatment for mumps, so supportive therapies are used. The most effective way to avoid infection is through vaccination. Although mumps used to be a common childhood disease, it is now rare in the United States due to vaccination with the measles, mumps, and rubella (MMR) vaccine.



Figure 10.2.2.8: This child shows the characteristic parotid swelling associated with mumps. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 10.2.2.3

Compare and contrast the signs and symptoms of herpetic gingivostomatitis, oral thrush, and mumps.

Oral Infections

Infections of the mouth and oral cavity can be caused by a variety of pathogens, including bacteria, viruses, and fungi. Many of these infections only affect the mouth, but some can spread and become systemic infections. Figure 10.2.2.9 summarizes the main characteristics of common oral infections.

Oral Infections					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Dental caries	*Streptococcus mutans*	Discoloration, softening, cavities in teeth	Non-transmissible; caused by bacteria of the normal oral microbiota	Visual examinations, X-rays	Oral antiseptics (e.g., Listerine)
Gingivitis and periodontitis	*Porphyromonas, Streptococcus, Actinomyces*	Inflammation and erosion of gums, bleeding, halitosis; erosion of cementum, leading to tooth loss in advanced infections	Non-transmissible; caused by bacteria of the normal oral microbiota	Visual examination, X-rays, measuring pockets in gums	Tetracycline, doxycycline, macrolides or beta-lactams. Mixture of antibiotics may be given.
Herpetic gingivostomatitis	Herpes simplex virus type 1 (HSV-1)	Lesions in mucous membranes of mouth	Contact with saliva or lesions of an infected person	Culture or biopsy	Acyclovir, famcyclovir, valacyclovir
Mumps	Mumps virus (a paramyxovirus)	Swelling of parotid glands, fever, headache, muscle pain, weakness, fatigue, loss of appetite, pain while chewing; in serious cases, encephalitis, meningitis, and inflammation of testes, ovaries, and breasts	Contact with saliva or respiratory droplets of an infected person	Virus culture or serologic tests for antibodies, enzyme immunoassay, RT-PCR	None for treatment; MMR vaccine for prevention
Oral thrush	*Candida albicans*, other *Candida* spp.	White patches and pseudomembranes in mouth, may cause bleeding	Non-transmissible; caused by overgrowth of *Candida* spp. in the normal oral microbiota; primarily affects infants and the immuno-compromised	Microscopic analysis of oral samples	Clotrimazole, nystatin, fluconazole, or itraconazole; amphotericin B in severe cases
Trench mouth (acute necrotizing ulcerative gingivitis)	*Prevotella intermedia Fusobacterium* species, *Treponema vincentii,* others	Erosion of gums, ulcers, substantial pain with chewing, halitosis	Non-transmissible; caused by members of the normal oral microbiota	Visual examinations, X-rays	Amoxicillin, amoxicillin clavulanate, clindamycin, or doxycylcine

Figure 10.2.2.9: Oral infections.

Key Concepts and Summary

- **Dental caries**, **tartar**, and **gingivitis** are caused by overgrowth of oral bacteria, usually *Streptococcus* and *Actinomyces* species, as a result of insufficient dental hygiene.
- Gingivitis can worsen, allowing *Porphyromonas*, *Streptococcus*, and *Actinomyces* species to spread and cause **periodontitis**. When *Prevotella intermedia*, *Fusobacterium* species, and *Treponema vicentii* are involved, it can lead to **acute necrotizing**

ulcerative gingivitis.

- The herpes simplex virus type 1 can cause lesions of the mouth and throat called **herpetic gingivostomatitis.**
- Other infections of the mouth include **oral thrush**, a fungal infection caused by overgrowth of *Candida* yeast, and **mumps**, a viral infection of the salivary glands caused by the mumps virus, a paramyxovirus.

Footnotes

1. 1 Hans-Peter Horz and Georg Conrads. "Methanogenic *Archaea* and Oral Infections—Ways to Unravel the Black Box." *Journal of Oral Microbiology* 3(2011). doi: 10.3402/jom.v3i0.5940.
2. 2 Hiroshi Maeda, Kimito Hirai, Junji Mineshiba, Tadashi Yamamoto, Susumu Kokeguchi, and Shogo Takashiba. "Medical Microbiological Approach to Archaea in Oral Infectious Diseases." *Japanese Dental Science Review* 49: 2, p. 72–78.
3. 3 Paul W. Lepp, Mary M. Brinig, Cleber C. Ouverney, Katherine Palm, Gary C. Armitage, and David A. Relman. "Methanogenic *Archaea* and Human Periodontal Disease." *Proceedings of the National Academy of Sciences of the United States of America* 101 (2003): 16, pp. 6176–6181. doi: 10.1073/pnas.0308766101.

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10.2.3: Bacterial Infections of the Gastrointestinal Tract

Learning Objectives

- Identify the most common bacteria that can cause infections of the GI tract
- Compare the major characteristics of specific bacterial diseases affecting the GI tract

A wide range of gastrointestinal diseases are caused by bacterial contamination of food. Recall that foodborne diseasecan arise from either infection or intoxication. In both cases, bacterial toxins are typically responsible for producing disease signs and symptoms. The distinction lies in where the toxins are produced. In an infection, the microbial agent is ingested, colonizes the gut, and then produces toxins that damage host cells. In an intoxication, bacteria produce toxins in the food before it is ingested. In either case, the toxins cause damage to the cells lining the gastrointestinal tract, typically the colon. This leads to the common signs and symptoms of diarrhea or watery stool and abdominal cramps, or the more severe dysentery. Symptoms of foodborne diseases also often include nausea and vomiting, which are mechanisms the body uses to expel the toxic materials.

Most bacterial gastrointestinal illness is short-lived and self-limiting; however, loss of fluids due to severe diarrheal illness can lead to dehydration that can, in some cases, be fatal without proper treatment. Oral rehydration therapy with electrolyte solutions is an essential aspect of treatment for most patients with GI disease, especially in children and infants.

Staphylococcal Food Poisoning

Staphylococcal food poisoning is one form of food intoxication. When *Staphylococcus aureus* grows in food, it may produce enterotoxins that, when ingested, can cause symptoms such as nausea, diarrhea, cramping, and vomiting within one to six hours. In some severe cases, it may cause headache, dehydration, and changes in blood pressure and heart rate. Signs and symptoms resolve within 24 to 48 hours. *S. aureus* is often associated with a variety of raw or undercooked and cooked foods including meat (e.g., canned meat, ham, and sausages) and dairy products (e.g., cheeses, milk, and butter). It is also commonly found on hands and can be transmitted to prepared foods through poor hygiene, including poor handwashing and the use of contaminated food preparation surfaces, such as cutting boards. The greatest risk is for food left at a temperature below 60 °C (140 °F), which allows the bacteria to grow. Cooked foods should generally be reheated to at least 60 °C (140 °F) for safety and most raw meats should be cooked to even higher internal temperatures (Figure 10.2.3.1).

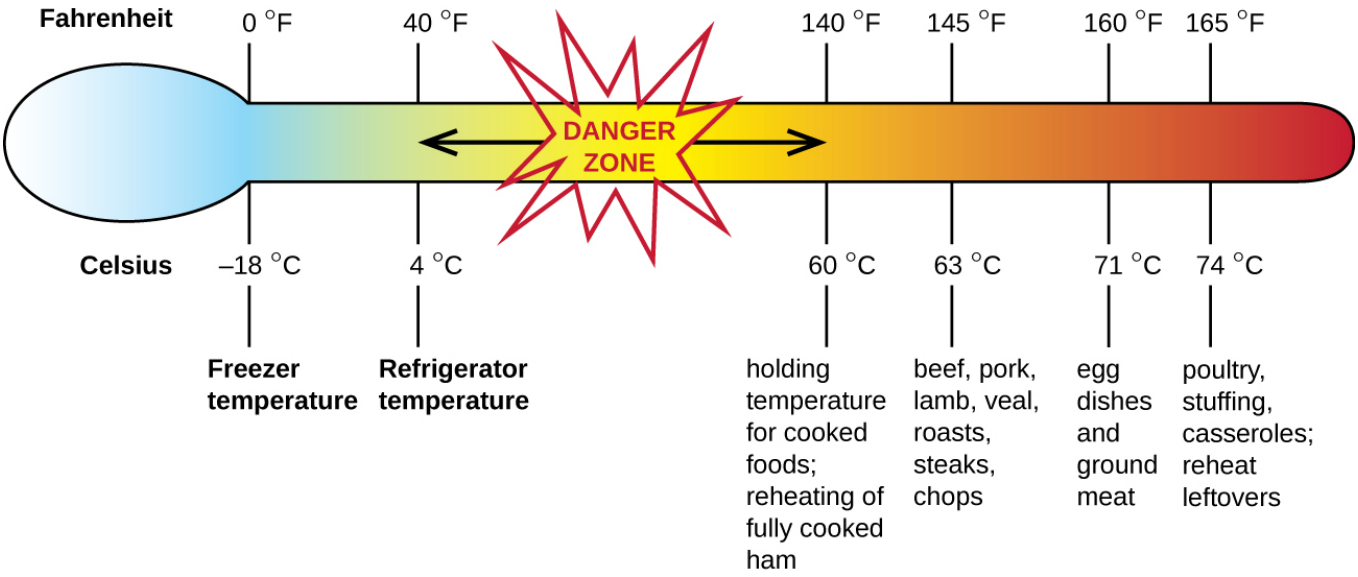


Figure 10.2.3.1: This figure indicates safe internal temperatures associated with the refrigeration, cooking, and reheating of different foods. Temperatures above refrigeration and below the minimum cooking temperature may allow for microbial growth, increasing the likelihood of foodborne disease. (credit: modification of work by USDA)

There are at least 21 *Staphylococcal* enterotoxins and *Staphylococcal* enterotoxin-like toxins that can cause food intoxication. The enterotoxins are proteins that are resistant to low pH, allowing them to pass through the stomach. They are heat stable and are not

destroyed by boiling at 100 °C. Even though the bacterium itself may be killed, the enterotoxins alone can cause vomiting and diarrhea, although the mechanisms are not fully understood. At least some of the symptoms may be caused by the enterotoxin functioning as a superantigen and provoking a strong immune response by activating T cell proliferation.

The rapid onset of signs and symptoms helps to diagnose this foodborne illness. Because the bacterium does not need to be present for the toxin to cause symptoms, diagnosis is confirmed by identifying the toxin in a food sample or in biological specimens (feces or vomitus) from the patient. Serological techniques, including ELISA, can also be used to identify the toxin in food samples.

The condition generally resolves relatively quickly, within 24 hours, without treatment. In some cases, supportive treatment in a hospital may be needed.

? Exercise 10.2.3.1

How can *S. aureus* cause food intoxication?

Shigellosis (Bacillary Dysentery)

When gastrointestinal illness is associated with the rod-shaped, gram-negative bacterium *Shigella*, it is called bacillary dysentery, or shigellosis. Infections can be caused by *S. dysenteriae*, *S. flexneri*, *S. boydii*, and/or *S. sonnei* that colonize the GI tract. Shigellosis can be spread from hand to mouth or through contaminated food and water. Most commonly, it is transmitted through the fecal-oral route.

Shigella bacteria invade intestinal epithelial cells. When taken into a phagosome, they can escape and then live within the cytoplasm of the cell or move to adjacent cells. As the organisms multiply, the epithelium and structures with M cells of the Peyer's patches in the intestine may become ulcerated and cause loss of fluid. Stomach cramps, fever, and watery diarrhea that may also contain pus, mucus, and/or blood often develop. More severe cases may result in ulceration of the mucosa, dehydration, and rectal bleeding. Additionally, patients may later develop hemolytic uremic syndrome (HUS), a serious condition in which damaged blood cells build up in the kidneys and may cause kidney failure, or reactive arthritis, a condition in which arthritis develops in multiple joints following infection. Patients may also develop chronic post-infection irritable bowel syndrome (IBS).

S. dysenteriae type 1 is able to produce Shiga toxin, which targets the endothelial cells of small blood vessels in the small and large intestine by binding to a glycosphingolipid. Once inside the endothelial cells, the toxin targets the large ribosomal subunit, thus affecting protein synthesis of these cells. Hemorrhaging and lesions in the colon can result. The toxin can target the kidney's glomerulus, the blood vessels where filtration of blood in the kidney begins, thus resulting in HUS.

Stool samples, which should be processed promptly, are analyzed using serological or molecular techniques. One common method is to perform immunoassays for *S. dysenteriae*. (Other methods that can be used to identify *Shigella* include API test strips, Enterotube systems, or PCR testing. The presence of white blood cells and blood in fecal samples occurs in about 70% of patients[1] (Figure 10.2.3.2). Severe cases may require antibiotics such as ciprofloxacin and azithromycin, but these must be carefully prescribed because resistance is increasingly common.

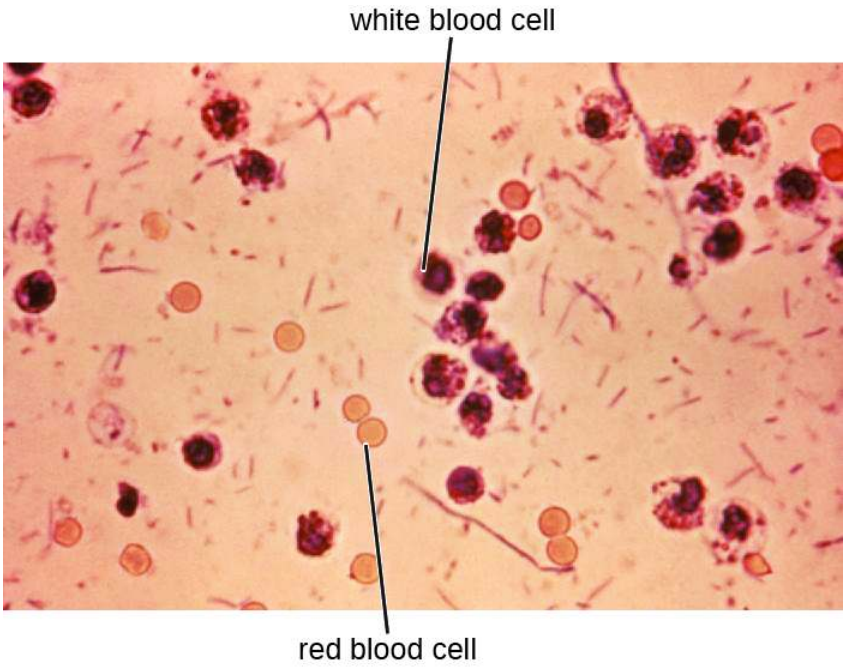


Figure 10.2.3.2: Red and white blood cells can be seen in this micrograph of a stool sample from a patient with shigellosis.

? Exercise 10.2.3.2

Compare and contrast *Shigella* infections and intoxications.

Salmonellosis

Salmonella gastroenteritis, also called salmonellosis, is caused by the rod-shaped, gram-negative bacterium *Salmonella*. Two species, *S. enterica* and *S. bongori*, cause disease in humans, but *S. enterica* is the most common. The most common serotypes of *S. enterica* are Enteritidis and Typhi. We will discuss typhoid fever caused by serotypes Typhi and Paratyphi A separately. Here, we will focus on salmonellosis caused by other serotypes.

Salmonella is a part of the normal intestinal microbiota of many individuals. However, salmonellosis is caused by exogenous agents, and infection can occur depending on the serotype, size of the inoculum, and overall health of the host. Infection is caused by ingestion of contaminated food, handling of eggshells, or exposure to certain animals. *Salmonella* is part of poultry's microbiota, so exposure to raw eggs and raw poultry can increase the risk of infection. Handwashing and cooking foods thoroughly greatly reduce the risk of transmission. *Salmonella* bacteria can survive freezing for extended periods but cannot survive high temperatures.

Once the bacteria are ingested, they multiply within the intestines and penetrate the epithelial mucosal cells via M cells where they continue to grow (Figure 10.2.3.3). They trigger inflammatory processes and the hypersecretion of fluids. Once inside the body, they can persist inside the phagosomes of macrophages. *Salmonella* can cross the epithelial cell membrane and enter the bloodstream and lymphatic system. Some strains of *Salmonella* also produce an enterotoxin that can cause an intoxication.

Infected individuals develop fever, nausea, abdominal cramps, vomiting, headache, and diarrhea. These signs and symptoms generally last a few days to a week. According to the Centers for Disease Control and Prevention (CDC), there are 1,000,000 cases annually, with 380 deaths each year.[2] However, because the disease is usually self-limiting, many cases are not reported to doctors and the overall incidence may be underreported. Diagnosis involves culture followed by serotyping and DNA fingerprinting if needed. Positive results are reported to the CDC. When an unusual serotype is detected, samples are sent to the CDC for further analysis. Serotyping is important for determining treatment. Oral rehydration therapy is commonly used. Antibiotics are only recommended for serious cases. When antibiotics are needed, as in immunocompromised patients, fluoroquinolones, third-generation cephalosporins, and ampicillin are recommended. Antibiotic resistance is a serious concern.



Figure 10.2.3.3: Salmonella entering an intestinal epithelial cell by reorganizing the host cell's cytoskeleton via the trigger mechanism. (credit: modification of work by National Institutes for Health)

Typhoid Fever

Certain serotypes of *S. enterica*, primarily serotype Typhi (*S. typhi*) but also Paratyphi, cause a more severe type of salmonellosis called typhoid fever. This serious illness, which has an untreated mortality rate of 10%, causes high fever, body aches, headache, nausea, lethargy, and a possible rash.

Some individuals carry *S. typhi* without presenting signs or symptoms (known as asymptomatic carriers) and continually shed them through their feces. These carriers often have the bacteria in the gallbladder or intestinal epithelium. Individuals consuming food or water contaminated with these feces can become infected.

S. typhi penetrate the intestinal mucosa, grow within the macrophages, and are transported through the body, most notably to the liver and gallbladder. Eventually, the macrophages lyse, releasing *S. typhi* into the bloodstream and lymphatic system. Mortality can result from ulceration and perforation of the intestine. A wide range of complications, such as pneumonia and jaundice, can occur with disseminated disease.

S. typhi have *Salmonella* pathogenicity islands (SPIs) that contain the genes for many of their virulence factors. Two examples of important typhoid toxins are the Vi antigen, which encodes for capsule production, and chimeric A2B5 toxin, which causes many of the signs and symptoms of the acute phase of typhoid fever.

Clinical examination and culture are used to make the diagnosis. The bacteria can be cultured from feces, urine, blood, or bone marrow. Serology, including ELISA, is used to identify the most pathogenic strains, but confirmation with DNA testing or culture is needed. A PCR test can also be used, but is not widely available.

The recommended antibiotic treatment involves fluoroquinolones, ceftriaxone, and azithromycin. Individuals must be extremely careful to avoid infecting others during treatment. Typhoid fever can be prevented through vaccination for individuals traveling to parts of the world where it is common.

? Exercise 10.2.3.3

Why is serotyping particularly important in *Salmonella* infections and typhoid fever?

Typhoid Mary

Mary Mallon was an Irish immigrant who worked as a cook in New York in the early 20th century. Over seven years, from 1900 to 1907, Mallon worked for a number of different households, unknowingly spreading illness to the people who lived in each one. In 1906, one family hired George Soper, an expert in typhoid fever epidemics, to determine the cause of the illnesses in their household. Eventually, Soper tracked Mallon down and directly linked 22 cases of typhoid fever to her. He discovered that Mallon was a carrier for typhoid but was immune to it herself. Although active carriers had been recognized before, this was the first time that an asymptomatic carrier of infection had been identified.

Because she herself had never been ill, Mallon found it difficult to believe she could be the source of the illness. She fled from Soper and the authorities because she did not want to be quarantined or forced to give up her profession, which was relatively well paid for someone with her background. However, Mallon was eventually caught and kept in an isolation facility in the Bronx, where she remained until 1910, when the New York health department released her under the condition that she never again work with food. Unfortunately, Mallon did not comply, and she soon began working as a cook again. After new cases began to appear that resulted in the death of two individuals, the authorities tracked her down again and returned her to isolation, where she remained for 23 more years until her death in 1938. Epidemiologists were able to trace 51 cases of typhoid fever and three deaths directly to Mallon, who is unflatteringly remembered as "Typhoid Mary."

The Typhoid Mary case has direct correlations in the health-care industry. Consider Kaci Hickox, an American nurse who treated Ebola patients in West Africa during the 2014 epidemic. After returning to the United States, Hickox was quarantined against her will for three days and later found not to have Ebola. Hickox vehemently opposed the quarantine. In an editorial published in the British newspaper *The Guardian*,[3] Hickox argued that quarantining asymptomatic health-care workers who had not tested positive for a disease would not only prevent such individuals from practicing their profession, but discourage others from volunteering to work in disease-ridden areas where health-care workers are desperately needed.

What is the responsibility of an individual like Mary Mallon to change her behavior to protect others? What happens when an individual believes that she is not a risk, but others believe that she is? How would you react if you were in Mallon's shoes and were placed in a quarantine you did not believe was necessary, at the expense of your own freedom and possibly your career? Would it matter if you were definitely infected or not?

E. coli Infections

The gram-negative rod *Escherichia coli* is a common member of the normal microbiota of the colon. Although the vast majority of *E. coli* strains are helpful commensal bacteria, some can be pathogenic and may cause dangerous diarrheal disease. The pathogenic strains have additional virulence factors such as type 1 fimbriae that promote colonization of the colon or may produce toxins (see Virulence Factors of Bacterial and Viral Pathogens). These virulence factors are acquired through horizontal gene transfer.

Extraintestinal disease can result if the bacteria spread from the gastrointestinal tract. Although these bacteria can be spread from person to person, they are often acquired through contaminated food or water. There are six recognized pathogenic groups of *E. coli*, but we will focus here on the four that are most commonly transmitted through food and water.

Enterotoxigenic *E. coli* (ETEC), also known as traveler's diarrhea, causes diarrheal illness and is common in less developed countries. In Mexico, ETEC infection is called Montezuma's Revenge. Following ingestion of contaminated food or water, infected individuals develop a watery diarrhea, abdominal cramps, malaise (a feeling of being unwell), and a low fever. ETEC produces a heat-stable enterotoxin similar to cholera toxin, and adhesins called colonization factors that help the bacteria to attach to the intestinal wall. Some strains of ETEC also produce heat-labile toxins. The disease is usually relatively mild and self-limiting. Diagnosis involves culturing and PCR. If needed, antibiotic treatment with fluoroquinolones, doxycycline, rifaximin, and trimethoprim-sulfamethoxazole (TMP/SMZ) may shorten infection duration. However, antibiotic resistance is a problem.

Enteroinvasive *E. coli* (EIEC) is very similar to shigellosis, including its pathogenesis of intracellular invasion into intestinal epithelial tissue. This bacterium carries a large plasmid that is involved in epithelial cell penetration. The illness is usually self-limiting, with symptoms including watery diarrhea, chills, cramps, malaise, fever, and dysentery. Culturing and PCR testing can be used for diagnosis. Antibiotic treatment is not recommended, so supportive therapy is used if needed.

Enteropathogenic *E. coli* (EPEC) can cause a potentially fatal diarrhea, especially in infants and those in less developed countries. Fever, vomiting, and diarrhea can lead to severe dehydration. These *E. coli* inject a protein (Tir) that attaches to the surface of the

intestinal epithelial cells and triggers rearrangement of host cell actin from microvilli to pedestals. Tir also happens to be the receptor for Intimin, a surface protein produced by EPEC, thereby allowing *E. coli* to “sit” on the pedestal. The genes necessary for this pedestal formation are encoded on the locus for enterocyte effacement (LEE) pathogenicity island. As with ETEC, diagnosis involves culturing and PCR. Treatment is similar to that for ETEC.

The most dangerous strains are enterohemorrhagic *E. coli* (EHEC), which are the strains capable of causing epidemics. In particular, the strain O157:H7 has been responsible for several recent outbreaks. Recall that the O and H refer to surface antigens that contribute to pathogenicity and trigger a host immune response (“O” refers to the O-side chain of the lipopolysaccharide and the “H” refers to the flagella). Similar to EPEC, EHEC also forms pedestals. EHEC also produces a Shiga-like toxin. Because the genome of this bacterium has been sequenced, it is known that the Shiga toxin genes were most likely acquired through transduction (horizontal gene transfer). The Shiga toxin genes originated from *Shigella dysenteriae*. Prophage from a bacteriophage that previously infected *Shigella* integrated into the chromosome of *E. coli*. The Shiga-like toxin is often called verotoxin.

EHEC can cause disease ranging from relatively mild to life-threatening. Symptoms include bloody diarrhea with severe cramping, but no fever. Although it is often self-limiting, it can lead to hemorrhagic colitis and profuse bleeding. One possible complication is HUS. Diagnosis involves culture, often using MacConkey with sorbitol agar to differentiate between *E. coli* O157:H7, which does not ferment sorbitol, and other less virulent strains of *E. coli* that can ferment sorbitol.

Serological typing or PCR testing also can be used, as well as genetic testing for Shiga toxin. To distinguish EPEC from EHEC, because they both form pedestals on intestinal epithelial cells, it is necessary to test for genes encoding for both the Shiga-like toxin and for the LEE. Both EPEC and EHEC have LEE, but EPEC lacks the gene for Shiga toxin. Antibiotic therapy is not recommended and may worsen HUS because of the toxins released when the bacteria are killed, so supportive therapies must be used. Table 10.2.3.1 summarizes the characteristics of the four most common pathogenic groups.

Table 10.2.3.1: Some Pathogenic Groups of E. coli

Group	Virulence Factors and Genes	Signs and Symptoms	Diagnostic Tests	Treatment
Enterotoxigenic *E. coli* (ETEC)	Heat stable enterotoxin similar to cholera toxin	Relatively mild, watery diarrhea	Culturing, PCR	Self-limiting; if needed, fluoroquinolones, doxycycline, rifaximin, TMP/SMZ; antibiotic resistance is a problem
Enteroinvasive *E. coli* (EIEC)	*Inv* (invasive plasmid) genes	Relatively mild, watery diarrhea; dysentery or inflammatory colitis may occur	Culturing, PCR; testing for *inv* gene; additional assays to distinguish from *Shigella*	Supportive therapy only; antibiotics not recommended
Enteropathogenic *E. coli* (EPEC)	Locus of enterocyte effacement (LEE) pathogenicity island	Severe fever, vomiting, nonbloody diarrhea, dehydration; potentially fatal	Culturing, PCR; detection of LEE lacking Shiga-like toxin genes	Self-limiting; if needed, fluoroquinolones, doxycycline, rifaximin (TMP/SMZ); antibiotic resistance is a problem
Enterohemorrhagic *E. coli* (EHEC)	Verotoxin	May be mild or very severe; bloody diarrhea; may result in HUS	Culturing; plate on MacConkey agar with sorbitol agar as it does not ferment sorbitol; PCR detection of LEE containing Shiga-like toxin genes	Antibiotics are not recommended due to the risk of HUS

? Exercise 10.2.3.4

Compare and contrast the virulence factors and signs and symptoms of infections with the four main *E. coli* groups.

Cholera and Other Vibrios

The gastrointestinal disease cholera is a serious infection often associated with poor sanitation, especially following natural disasters, because it is spread through contaminated water and food that has not been heated to temperatures high enough to kill the bacteria. It is caused by *Vibrio cholerae* serotype O1, a gram-negative, flagellated bacterium in the shape of a curved rod (vibrio). According to the CDC, cholera causes an estimated 3 to 5 million cases and 100,000 deaths each year.[4]

Because *V. cholerae* is killed by stomach acid, relatively large doses are needed for a few microbial cells to survive to reach the intestines and cause infection. The motile cells travel through the mucous layer of the intestines, where they attach to epithelial cells and release cholera enterotoxin. The toxin is an A-B toxin with activity through adenylate cyclase (see Virulence Factors of Bacterial and Viral Pathogens). Within the intestinal cell, cyclic AMP (cAMP) levels increase, which activates a chloride channel and results in the release of ions into the intestinal lumen. This increase in osmotic pressure in the lumen leads to water also entering the lumen. As the water and electrolytes leave the body, it causes rapid dehydration and electrolyte imbalance. Diarrhea is so profuse that it is often called “rice water stool,” and patients are placed on cots with a hole in them to monitor the fluid loss (Figure 10.2.3.4).

Cholera is diagnosed by taking a stool sample and culturing for *Vibrio*. The bacteria are oxidase positive and show non-lactose fermentation on MacConkey agar. Gram-negative lactose fermenters will produce red colonies while non-fermenters will produce white/colorless colonies. Gram-positive bacteria will not grow on MacConkey. Lactose fermentation is commonly used for pathogen identification because the normal microbiota generally ferments lactose while pathogens do not. *V. cholerae* may also be cultured on thiosulfate citrate bile salts sucrose (TCBS) agar, a selective and differential media for *Vibrio* spp., which produce a distinct yellow colony.

Cholera may be self-limiting and treatment involves rehydration and electrolyte replenishment. Although antibiotics are not typically needed, they can be used for severe or disseminated disease. Tetracyclines are recommended, but doxycycline, erythromycin, orfloxacin, ciprofloxacin, and TMP/SMZ may be used. Recent evidence suggests that azithromycin is also a good first-line antibiotic. Good sanitation—including appropriate sewage treatment, clean supplies for cooking, and purified drinking water—is important to prevent infection (Figure 10.2.3.4)



(a) (b) (c)

Figure 10.2.3.4: (a) Outbreaks of cholera often occur in areas with poor sanitation or after natural disasters that compromise sanitation infrastructure. (b) At a cholera treatment center in Haiti, patients are receiving intravenous fluids to combat the dehydrating effects of this disease. They often lie on a cot with a hole in it and a bucket underneath to allow for monitoring of fluid loss. (c) This scanning electron micrograph shows *Vibrio cholera*. (credit a, b: modification of work by Centers for Disease Control and Prevention; credit c: modification of work by Janice Carr, Centers for Disease Control and Prevention)

V. cholera is not the only *Vibrio* species that can cause disease. *V. parahemolyticus* is associated with consumption of contaminated seafood and causes gastrointestinal illness with signs and symptoms such as watery diarrhea, nausea, fever, chills, and abdominal cramps. The bacteria produce a heat-stable hemolysin, leading to dysentery and possible disseminated disease. It also sometimes causes wound infections. *V. parahemolyticus* is diagnosed using cultures from blood, stool, or a wound. As with *V. cholera*,

selective medium (especially TCBS agar) works well. Tetracycline and ciprofloxacin can be used to treat severe cases, but antibiotics generally are not needed.

Vibrio vulnificus is found in warm seawater and, unlike *V. cholerae*, is not associated with poor sanitary conditions. The bacteria can be found in raw seafood, and ingestion causes gastrointestinal illness. It can also be acquired by individuals with open skin wounds who are exposed to water with high concentrations of the pathogen. In some cases, the infection spreads to the bloodstream and causes septicemia. Skin infection can lead to edema, ecchymosis (discoloration of skin due to bleeding), and abscesses. Patients with underlying disease have a high fatality rate of about 50%. It is of particular concern for individuals with chronic liver disease or who are otherwise immunodeficient because a healthy immune system can often prevent infection from developing. *V. vulnificus* is diagnosed by culturing for the pathogen from stool samples, blood samples, or skin abscesses. Adult patients are treated with doxycycline combined with a third generation cephalosporin or with fluoroquinolones, and children are treated with TMP/SMZ.

Two other vibrios, *Aeromonas hydrophila* and *Plesiomonas shigelloides*, are also associated with marine environments and raw seafood; they can also cause gastroenteritis. Like *V. vulnificus*, *A. hydrophila* is more often associated with infections in wounds, generally those acquired in water. In some cases, it can also cause septicemia. Other species of *Aeromonas* can cause illness. *P. shigelloides* is sometimes associated with more serious systemic infections if ingested in contaminated food or water. Culture can be used to diagnose *A. hydrophila* and *P. shigelloides* infections, for which antibiotic therapy is generally not needed. When necessary, tetracycline and ciprofloxacin, among other antibiotics, may be used for treatment of *A. hydrophila*, and fluoroquinolones and trimethoprim are the effective treatments for *P. shigelloides*.

? Exercise 10.2.3.5

How does *V. cholera* infection cause rapid dehydration?

Campylobacter jejuni Gastroenteritis

Campylobacter is a genus of gram-negative, spiral or curved bacteria. They may have one or two flagella. *Campylobacter jejuni* gastroenteritis, a form of campylobacteriosis, is a widespread illness that is caused by *Campylobacter jejuni*. The primary route of transmission is through poultry that becomes contaminated during slaughter. Handling of the raw chicken in turn contaminates cooking surfaces, utensils, and other foods. Unpasteurized milk or contaminated water are also potential vehicles of transmission. In most cases, the illness is self-limiting and includes fever, diarrhea, cramps, vomiting, and sometimes dysentery. More serious signs and symptoms, such as bacteremia, meningitis, pancreatitis, cholecystitis, and hepatitis, sometimes occur. It has also been associated with autoimmune conditions such as Guillain-Barré syndrome, a neurological disease that occurs after some infections and results in temporary paralysis. HUS following infection can also occur. The virulence in many strains is the result of hemolysin production and the presence of *Campylobacter* cytolethal distending toxin (CDT), a powerful deoxyribonuclease (DNase) that irreversibly damages host cell DNA.

Diagnosis involves culture under special conditions, such as elevated temperature, low oxygen tension, and often medium supplemented with antimicrobial agents. These bacteria should be cultured on selective medium (such as Campy CV, charcoal selective medium, or cefaperazone charcoal deoxycholate agar) and incubated under microaerophilic conditions for at least 72 hours at 42 °C. Antibiotic treatment is not usually needed, but erythromycin or ciprofloxacin may be used.

Peptic Ulcers

The gram-negative bacterium *Helicobacter pylori* is able to tolerate the acidic environment of the human stomach and has been shown to be a major cause of peptic ulcers, which are ulcers of the stomach or duodenum. The bacterium is also associated with increased risk of stomach cancer (Figure 10.2.3.5). According to the CDC, approximately two-thirds of the population is infected with *H. pylori*, but less than 20% have a risk of developing ulcers or stomach cancer. *H. pylori* is found in approximately 80% of stomach ulcers and in over 90% of duodenal ulcers.[5]

H. pylori colonizes epithelial cells in the stomach using pili for adhesion. These bacteria produce urease, which stimulates an immune response and creates ammonia that neutralizes stomach acids to provide a more hospitable microenvironment. The infection damages the cells of the stomach lining, including those that normally produce the protective mucus that serves as a barrier between the tissue and stomach acid. As a result, inflammation (gastritis) occurs and ulcers may slowly develop. Ulcer

formation can also be caused by toxin activity. It has been reported that 50% of clinical isolates of *H. pylori* have detectable levels of exotoxin activity *in vitro*.[6] This toxin, VacA, induces vacuole formation in host cells. VacA has no primary sequence homology with other bacterial toxins, and in a mouse model, there is a correlation between the presence of the toxin gene, the activity of the toxin, and gastric epithelial tissue damage.

Signs and symptoms include nausea, lack of appetite, bloating, burping, and weight loss. Bleeding ulcers may produce dark stools. If no treatment is provided, the ulcers can become deeper, more tissues can be involved, and stomach perforation can occur. Because perforation allows digestive enzymes and acid to leak into the body, it is a very serious condition.

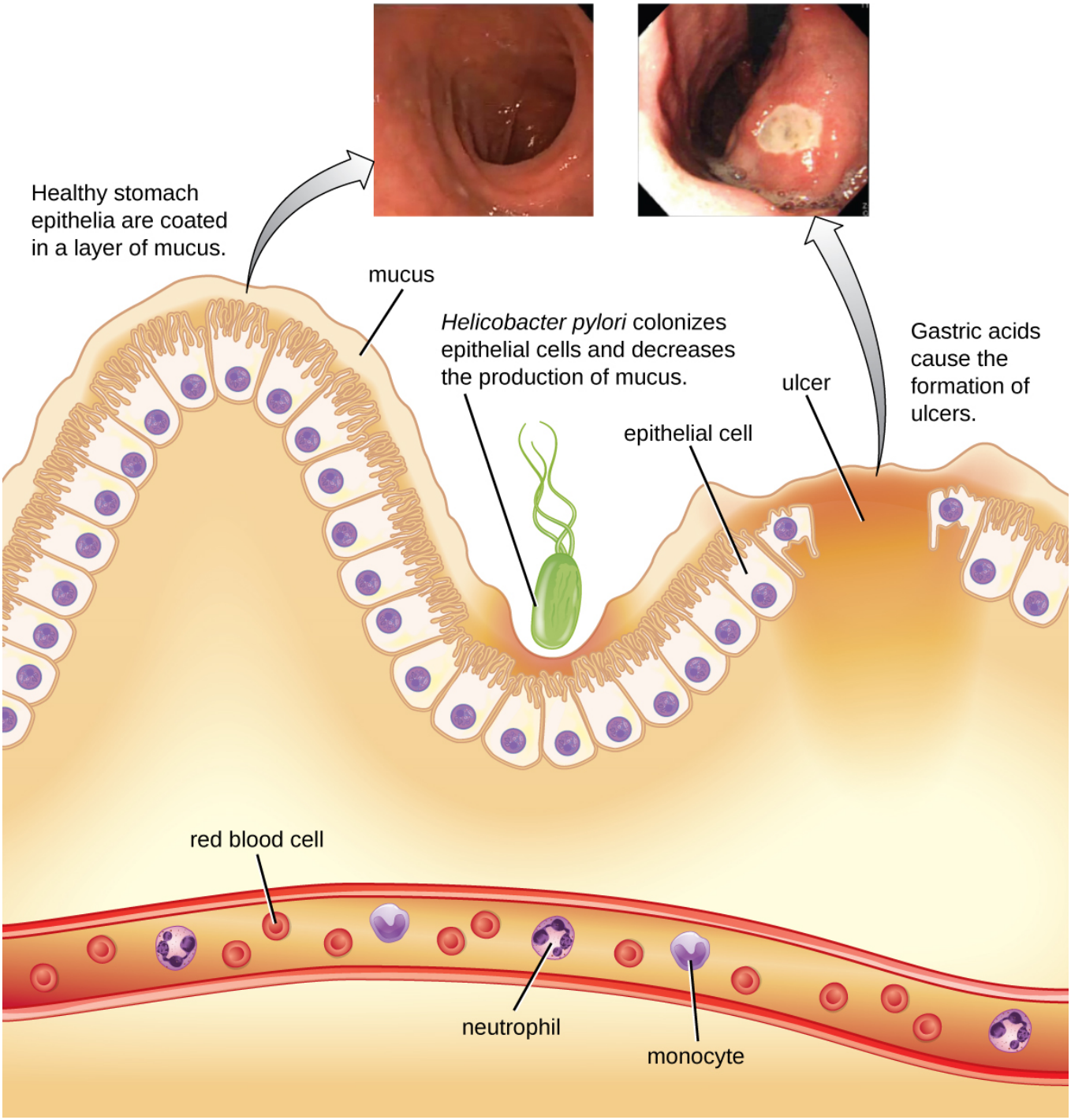


Figure 10.2.3.5: Helicobacter infection decreases mucus production and causes peptic ulcers. (credit top left photo: modification of work by "Santhosh Thomas"/YouTube; credit top right photo: modification of work by Moriya M, Uehara A, Okumura T, Miyamoto M, and Kohgo Y)

To diagnose *H. pylori* infection, multiple methods are available. In a breath test, the patient swallows radiolabeled urea. If *H. pylori* is present, the bacteria will produce urease to break down the urea. This reaction produces radiolabeled carbon dioxide that can be detected in the patient's breath. Blood testing can also be used to detect antibodies to *H. pylori*. The bacteria themselves can be detected using either a stool test or a stomach wall biopsy.

Antibiotics can be used to treat the infection. However, unique to *H. pylori*, the recommendation from the US Food and Drug Administration is to use a triple therapy. The current protocols are 10 days of treatment with omeprazole, amoxicillin, and clarithromycin (OAC); 14 days of treatment with bismuth subsalicylate, metronidazole, and tetracycline (BMT); or 10 or 14 days of treatment with lansoprazole, amoxicillin, and clarithromycin (LAC). Omeprazole, bismuth subsalicylate, and lansoprazole are not antibiotics but are instead used to decrease acid levels because *H. pylori* prefers acidic environments.

Although treatment is often valuable, there are also risks to *H. pylori* eradication. Infection with *H. pylori* may actually protect against some cancers, such as esophageal adenocarcinoma and gastroesophageal reflux disease.[78]

? Exercise 10.2.3.6

How does *H. pylori* cause peptic ulcers?

Clostridium perfringens Gastroenteritis

Clostridium perfringens gastroenteritis is a generally mild foodborne disease that is associated with undercooked meats and other foods. *C. perfringens* is a gram-positive, rod-shaped, endospore-forming anaerobic bacterium that is tolerant of high and low temperatures. At high temperatures, the bacteria can form endospores that will germinate rapidly in foods or within the intestine. Food poisoning by type A strains is common. This strain always produces an enterotoxin, sometimes also present in other strains, that causes the clinical symptoms of cramps and diarrhea. A more severe form of the illness, called pig-bel or enteritis necroticans, causes hemorrhaging, pain, vomiting, and bloating. Gangrene of the intestines may result. This form has a high mortality rate but is rare in the United States.

Diagnosis involves detecting the *C. perfringens* toxin in stool samples using either molecular biology techniques (PCR detection of the toxin gene) or immunology techniques (ELISA). The bacteria itself may also be detected in foods or in fecal samples. Treatment includes rehydration therapy, electrolyte replacement, and intravenous fluids. Antibiotics are not recommended because they can damage the balance of the microbiota in the gut, and there are concerns about antibiotic resistance. The illness can be prevented through proper handling and cooking of foods, including prompt refrigeration at sufficiently low temperatures and cooking food to a sufficiently high temperature.

Clostridium difficile

Clostridium difficile is a gram-positive rod that can be a commensal bacterium as part of the normal microbiota of healthy individuals. When the normal microbiota is disrupted by long-term antibiotic use, it can allow the overgrowth of this bacterium, resulting in antibiotic-associated diarrhea caused by *C. difficile*. Antibiotic-associated diarrhea can also be considered a nosocomial disease. Patients at the greatest risk of *C. difficile* infection are those who are immunocompromised, have been in health-care settings for extended periods, are older, have recently taken antibiotics, have had gastrointestinal procedures done, or use proton pump inhibitors, which reduce stomach acidity and allow proliferation of *C. difficile*. Because this species can form endospores, it can survive for extended periods of time in the environment under harsh conditions and is a considerable concern in health-care settings.

This bacterium produces two toxins, *Clostridium difficile* toxin A (TcdA) and *Clostridium difficile* toxin B (TcdB). These toxins inactivate small GTP-binding proteins, resulting in actin condensation and cell rounding, followed by cell death. Infections begin with focal necrosis, then ulceration with exudate, and can progress to pseudomembranous colitis, which involves inflammation of the colon and the development of a pseudomembrane of fibrin containing dead epithelial cells and leukocytes (Figure 10.2.3.6). Watery diarrhea, dehydration, fever, loss of appetite, and abdominal pain can result. Perforation of the colon can occur, leading to septicemia, shock, and death. *C. difficile* is also associated with necrotizing enterocolitis in premature babies and neutropenic enterocolitis associated with cancer therapies.

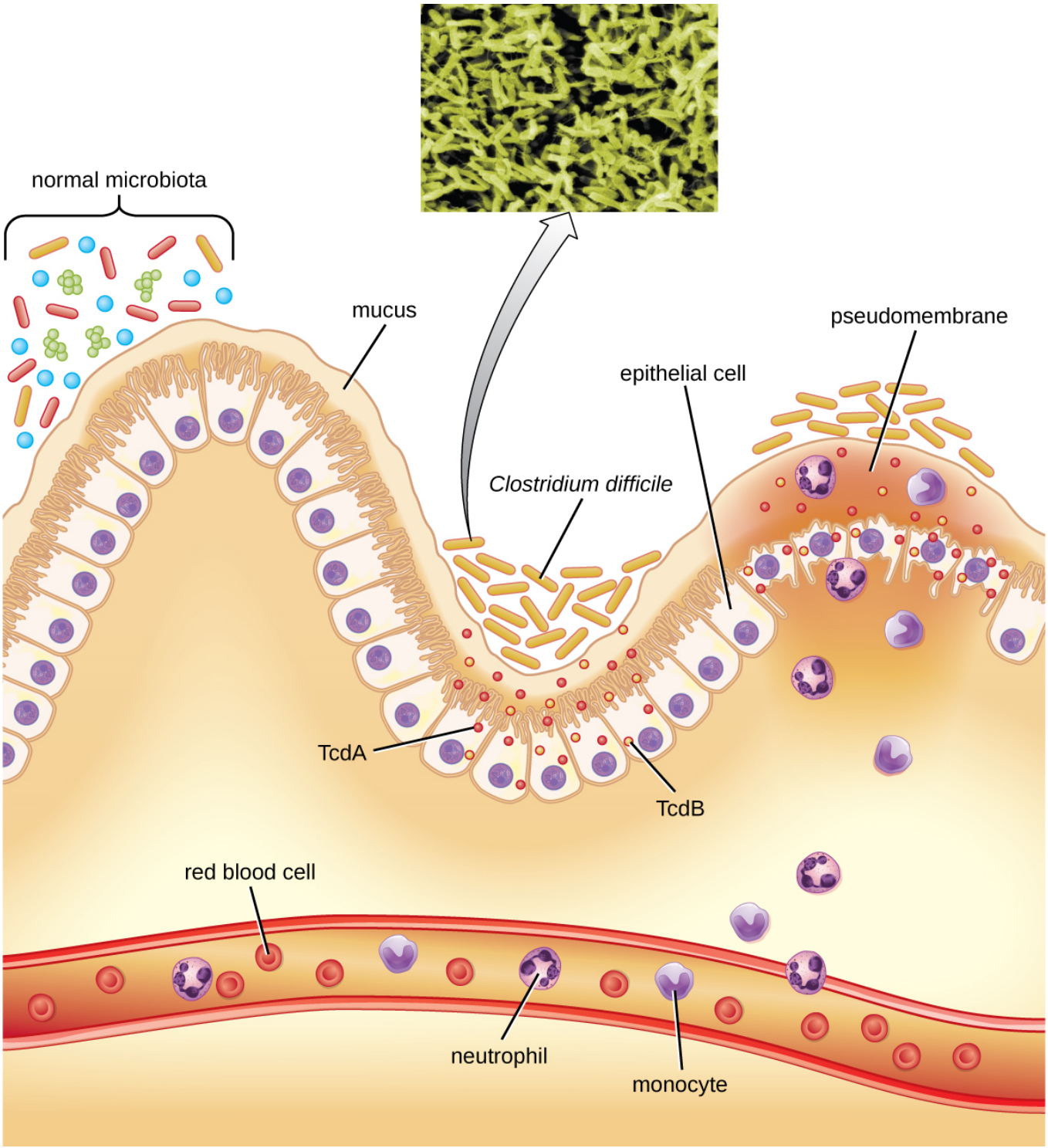


Figure 10.2.3.6: Clostridium difficile is able to colonize the mucous membrane of the colon when the normal microbiota is disrupted. The toxins TcdA and TcdB trigger an immune response, with neutrophils and monocytes migrating from the bloodstream to the site of infection. Over time, inflammation and dead cells contribute to the development of a pseudomembrane. (credit micrograph: modification of work by Janice Carr, Centers for Disease Control and Prevention)

Diagnosis is made by considering the patient history (such as exposure to antibiotics), clinical presentation, imaging, endoscopy, lab tests, and other available data. Detecting the toxin in stool samples is used to confirm diagnosis. Although culture is preferred, it is rarely practical in clinical practice because the bacterium is an obligate anaerobe. Nucleic acid amplification tests, including PCR, are considered preferable to ELISA testing for molecular analysis.

The first step of conventional treatment is to stop antibiotic use, and then to provide supportive therapy with electrolyte replacement and fluids. Metronidazole is the preferred treatment if the *C. difficile* diagnosis has been confirmed. Vancomycin can also be used, but it should be reserved for patients for whom metronidazole was ineffective or who meet other criteria (e.g., under 10 years of age, pregnant, or allergic to metronidazole).

A newer approach to treatment, known as a fecal transplant, focuses on restoring the microbiota of the gut in order to combat the infection. In this procedure, a healthy individual donates a stool sample, which is mixed with saline and transplanted to the recipient via colonoscopy, endoscopy, sigmoidoscopy, or enema. It has been reported that this procedure has greater than 90% success in resolving *C. difficile* infections.[9]

? Exercise 10.2.3.7

How does antibiotic use lead to *C. difficile* infections?

Foodborne Illness Due to *Bacillus cereus*

Bacillus cereus, commonly found in soil, is a gram-positive endospore-forming bacterium that can sometimes cause foodborne illness. *B. cereus* endospores can survive cooking and produce enterotoxins in food after it has been heated; illnesses often occur after eating rice and other prepared foods left at room temperature for too long. The signs and symptoms appear within a few hours of ingestion and include nausea, pain, and abdominal cramps. *B. cereus* produces two toxins: one causing diarrhea, and the other causing vomiting. More severe signs and symptoms can sometimes develop.

Diagnosis can be accomplished by isolating bacteria from stool samples or vomitus and uneaten infected food. Treatment involves rehydration and supportive therapy. Antibiotics are not typically needed, as the illness is usually relatively mild and is due to toxin activity.

Foodborne Illness Due to *Yersinia*

The genus *Yersinia* is best known for *Yersinia pestis*, a gram-negative rod that causes the plague. However, *Y. enterocolitica* and *Y. pseudotuberculosis* can cause gastroenteritis. The infection is generally transmitted through the fecal-oral route, with ingestion of food or water that has been contaminated by feces. Intoxication can also result because of the activity of its endotoxin and exotoxins (enterotoxin and cytotoxin necrotizing factor). The illness is normally relatively mild and self-limiting. However, severe diarrhea and dysentery can develop in infants. In adults, the infection can spread and cause complications such as reactive arthritis, thyroid disorders, endocarditis, glomerulonephritis, eye inflammation, and/or erythema nodosum. Bacteremia may develop in rare cases.

Diagnosis is generally made by detecting the bacteria in stool samples. Samples may also be obtained from other tissues or body fluids. Treatment is usually supportive, including rehydration, without antibiotics. If bacteremia or other systemic disease is present, then antibiotics such as fluoroquinolones, aminoglycosides, doxycycline, and trimethoprim-sulfamethoxazole may be used. Recovery can take up to two weeks.

? Exercise 10.2.3.8

Compare and contrast foodborne illnesses due to *B. cereus* and *Yersinia*.

Bacterial Infections of the Gastrointestinal Tract

Bacterial infections of the gastrointestinal tract generally occur when bacteria or bacterial toxins are ingested in contaminated food or water. Toxins and other virulence factors can produce gastrointestinal inflammation and general symptoms such as diarrhea and vomiting. Bacterial GI infections can vary widely in terms of severity and treatment. Some can be treated with antibiotics, but in other cases antibiotics may be ineffective in combating toxins or even counterproductive if they compromise the GI microbiota. Figure 10.2.3.7 and Figure 10.2.3.8 the key features of common bacterial GI infections.

Bacterial Infections of the GI Tract					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Bacillus cereus infection	*Bacillus cereus*	Nausea, pain, abdominal cramps, diarrhea, or vomiting	Ingestion of contaminated rice or meat, even after cooking	Testing stool sample, vomitus, or uneaten food for presence of bacteria	None
Campylobacter jejuni gastroenteritis	*Campylobacter jejuni*	Fever, diarrhea, cramps, vomiting, and sometimes dysentery; sometimes more severe organ or autoimmune effects	Ingestion of unpasteurized milk, under-cooked chicken, or contaminated water	Culture on selective medium with elevated temperature and low oxygen concentration	Generally none; erythromycin or ciprofloxacin if necessary
Cholera	*Vibrio cholerae*	Severe diarrhea and fluid loss, potentially leading to shock, renal failure, and death	Ingestion of contaminated water or food	Culture on selective medium (TCBS agar); distinguished as oxidase positive with fermentative metabolisms	Generally none; tetracyclines, azithromycin, others if necessary
Clostridium difficile infection	*Clostridium difficile*	Pseudomem-branous colitis, watery diarrhea, fever, abdominal pain, loss of appe-tite, dehydration; in severe cases, perforation of the colon, septicemia, shock, and death	Overgrowth of *C. difficile* in the normal microbiota due to antibiotic use; hospital-acquired infections in immunocompro-mised patients	Detection of toxin in stool, nucleic acid amplification tests (e.g., PCR)	Discontinuation of previous antibiotic treatment; metronidazole or vancomycin
Clostridium perfringens gastroenteritis	*Clostridium perfringens* (especially type A)	Mild cramps and diarrhea in most cases; in rare cases, hemor-rhaging, vomiting, intestinal gangrene, and death	Ingestion of undercooked meats containing *C. perfringens* endospores	Detection of toxin or bacteria in stool or uneaten food	None
E. coli infection	ETEC, EPEC, EIEC, EHEC	Watery diarrhea, dysentery, cramps, malaise, fever, chills, dehydration; in EHEC, possible severe compli-cations such as hematolytic uremic syndrome	Ingestion of contaminated food or water	Tissue culture, immunochemi-cal assays, PCR, gene probes	Not recommended for EIEC and EHEC; fluoroquinolones, doxycycline, rifaximin, and TMP/SMZ possible for ETEC and EPEC

Figure 10.2.3.7: Bacterial infections of the GI tract.

Bacterial Infections of the GI Tract (continued)					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Peptic ulcers	*Helicobacter pylori*	Nausea, bloating, burping, lack of appetite, weight loss, perforation of stomach, blood in stools	Normal flora, can also be acquired via saliva; fecal-oral route via contaminated food and water	Breath test, detection of antibodies in blood, detection of bacteria in stool sample or stomach biopsy	Amoxicillin, clarithromycin metronidazole, tetracycline, lansoprazole; antacids may also be given in combination with antibiotics
Salmonellosis	*Salmonella enterica,* serotype Enteritides	Fever, nausea, vomiting, abdominal cramps, headache, diarrhea; can be fatal in infants	Ingestion of contaminated food, handling of eggshells or contaminated animals	Culturing, serotyping and DNA fingerprinting	Not generally recommended; fluoroquinolones, ampicillin, others for immunocompromised patients
Shigella dysentery	*Shigella dysenteriae, S. flexneri, S. boydii,* and *S. sonnei*	Abdominal cramps, fever, diarrhea, dysentery; possible complications: reactive arthritis and hemolytic uremic syndrome	Fecal-oral route via contaminated food and water	Testing of stool samples for presence of blood and leukocytes; culturing, PCR, immunoassay for *S. dysenteriae*	Ciprofloxacin, azithromycin
Staphylococcal food poisoning	*Staphylococcus aureus*	Rapid-onset nausea, diarrhea, vomiting lasting 24–48 hours; possible dehydration and change in blood pressure and heart rate	Ingestion of raw or undercooked meat or dairy products conta-minated with staphylococcal enterotoxins	ELISA to detect enterotoxins in uneaten food, stool, or vomitus	None
Typhoid fever	*S. entrica*, subtypes Typhi or Paratyphi	Aches, headaches, nausea, lethargy, diarrhea or constipation, possible rash; lethal perforation of intestine can occur	Fecal-oral route; may be spread by asymptomatic carriers	Culture of blood, stool, or bone marrow, serologic tests; PCR tests when available	Fluoroquinolones, ceftriaxone, azithromycin; preventive vaccine available
Yersinia infection	*Yersinia enterocolitica, Y. pseudo-tuberculosis*	Generally mild diarrhea and abdominal cramps; in some cases, bacteremia can occur, leading to severe complications	Fecal-oral route, typically via contaminated food or water	Testing stool samples, tissues, body fluids	Generally none; fluoroquinolones, aminoglycosides, others for systemic infections

Figure 10.2.3.8: Bacterial infections of the GI tract (continued).

Clinical Focus: Part 2

At the hospital, Carli's doctor began to think about possible causes of her severe gastrointestinal distress. One possibility was food poisoning, but no one else in her family was sick. The doctor asked about what Carli had eaten the previous day; her mother mentioned that she'd had eggs for lunch, and that they may have been a little undercooked. The doctor took a sample of Carli's stool and sent it for laboratory testing as part of her workup. She suspected that Carli could have a case of bacterial or viral gastroenteritis, but she needed to know the cause in order to prescribe an appropriate treatment.

In the laboratory, technicians microscopically identified gram-negative bacilli in Carli's stool sample. They also established a pure culture of the bacteria and analyzed it for antigens. This testing showed that the causative agent was *Salmonella*.

Exercise 10.2.3.9

What should the doctor do now to treat Carli?

Key Concepts and Summary

- Major causes of gastrointestinal illness include *Salmonella* spp., *Staphylococcus* spp., *Helicobacter pylori*, *Clostridium perfringens*, *Clostridium difficile*, *Bacillus cereus*, and *Yersinia* bacteria.
- *C. difficile* is an important cause of hospital acquired infection.
- *Vibrio cholerae* causes **cholera**, which can be a severe diarrheal illness.
- Different strains of *E. coli*, including **ETEC**, **EPEC**, **EIEC**, and **EHEC**, cause different illnesses with varying degrees of severity.
- *H. pylori* is associated with **peptic ulcers**.
- *Salmonella enterica* serotypes can cause **typhoid fever**, a more severe illness than **salmonellosis**.
- Rehydration and other supportive therapies are often used as general treatments.
- Careful antibiotic use is required to reduce the risk of causing *C. difficile* infections and when treating antibiotic-resistant infections.

Footnotes

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10.2.4: Viral Infections of the Gastrointestinal Tract

Learning Objectives

- Identify the most common viruses that can cause infections of the GI tract
- Compare the major characteristics of specific viral diseases affecting the GI tract and liver

In the developing world, acute viral gastroenteritis is devastating and a leading cause of death for children.[1] Worldwide, diarrhea is the second leading cause of mortality for children under age five, and 70% of childhood gastroenteritis is viral.[2] As discussed, there are a number of bacteria responsible for diarrhea, but viruses can also cause diarrhea. *E. coli* and rotavirus are the most common causative agents in the developing world. In this section, we will discuss rotaviruses and other, less common viruses that can also cause gastrointestinal illnesses.

Gastroenteritis Caused by Rotaviruses

Rotaviruses are double-stranded RNA viruses in the family Reoviridae. They are responsible for common diarrheal illness, although prevention through vaccination is becoming more common. The virus is primarily spread by the fecal-oral route (Figure 10.2.4.1).

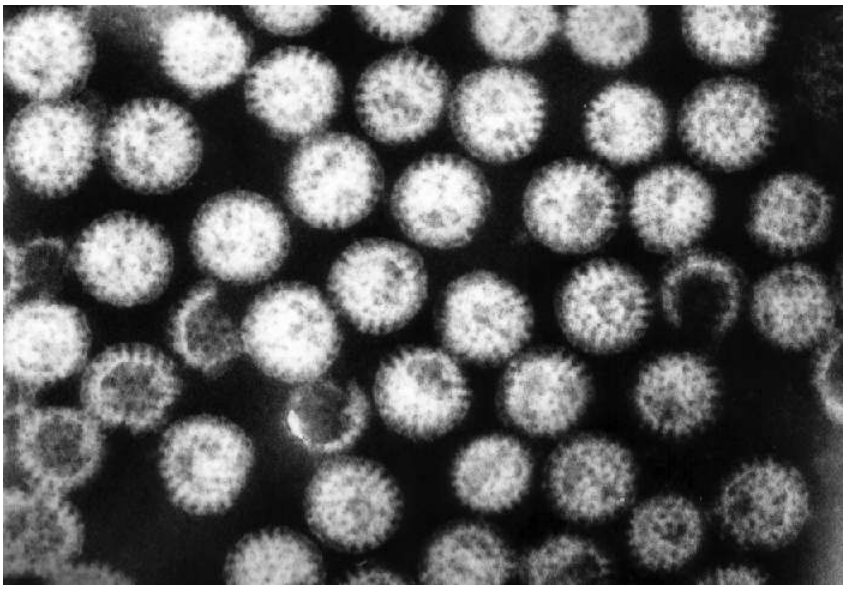


Figure 10.2.4.1: Rotaviruses in a fecal sample are visualized using electron microscopy. (credit: Dr. Graham Beards)

These viruses are widespread in children, especially in day-care centers. The CDC estimates that 95% of children in the United States have had at least one rotavirus infection by the time they reach age five.[3] Due to the memory of the body's immune system, adults who come into contact with rotavirus will not contract the infection or, if they do, are asymptomatic. The elderly, however, are vulnerable to rotavirus infection due to weakening of the immune system with age, so infections can spread through nursing homes and similar facilities. In these cases, the infection may be transmitted from a family member who may have subclinical or clinical disease. The virus can also be transmitted from contaminated surfaces, on which it can survive for some time.

Infected individuals exhibit fever, vomiting, and diarrhea. The virus can survive in the stomach following a meal, but is normally found in the small intestines, particularly the epithelial cells on the villi. Infection can cause food intolerance, especially with respect to lactose. The illness generally appears after an incubation period of about two days and lasts for approximately one week (three to eight days). Without supportive treatment, the illness can cause severe fluid loss, dehydration, and even death. Even with milder illness, repeated infections can potentially lead to malnutrition, especially in developing countries, where rotavirus infection is common due to poor sanitation and lack of access to clean drinking water. Patients (especially children) who are malnourished after an episode of diarrhea are more susceptible to future diarrheal illness, increasing their risk of death from rotavirus infection.

The most common clinical tool for diagnosis is enzyme immunoassay, which detects the virus from fecal samples. Latex agglutination assays are also used. Additionally, the virus can be detected using electron microscopy and RT-PCR.

Treatment is supportive with oral rehydration therapy. Preventive vaccination is also available. In the United States, rotavirus vaccines are part of the standard vaccine schedule and administration follows the guidelines of the World Health Organization (WHO). The WHO recommends that all infants worldwide receive the rotavirus vaccine, the first dose between six and 15 weeks of age and the second before 32 weeks.[4]

Gastroenteritis Caused by Noroviruses

Noroviruses, commonly identified as Norwalk viruses, are caliciviruses. Several strains can cause gastroenteritis. There are millions of cases a year, predominately in infants, young children, and the elderly. These viruses are easily transmitted and highly contagious. They are known for causing widespread infections in groups of people in confined spaces, such as on cruise ships. The viruses can be transmitted through direct contact, through touching contaminated surfaces, and through contaminated food. Because the virus is not killed by disinfectants used at standard concentrations for killing bacteria, the risk of transmission remains high, even after cleaning.

The signs and symptoms of norovirus infection are similar to those for rotavirus, with watery diarrhea, mild cramps, and fever. Additionally, these viruses sometimes cause projectile vomiting. The illness is usually relatively mild, develops 12 to 48 hours after exposure, and clears within a couple of days without treatment. However, dehydration may occur.

Norovirus can be detected using PCR or enzyme immunoassay (EIA) testing. RT-qPCR is the preferred approach as EIA is insufficiently sensitive. If EIA is used for rapid testing, diagnosis should be confirmed using PCR. No medications are available, but the illness is usually self-limiting. Rehydration therapy and electrolyte replacement may be used. Good hygiene, hand washing, and careful food preparation reduce the risk of infection.

Gastroenteritis Caused by Astroviruses

Astroviruses are single-stranded RNA viruses (family Astroviridae) that can cause severe gastroenteritis, especially in infants and children. Signs and symptoms include diarrhea, nausea, vomiting, fever, abdominal pain, headache, and malaise. The viruses are transmitted through the fecal-oral route (contaminated food or water). For diagnosis, stool samples are analyzed. Testing may involve enzyme immunoassays and immune electron microscopy. Treatment involves supportive rehydration and electrolyte replacement if needed.

? Exercise 10.2.4.1

Why are rotaviruses, noroviruses, and astroviruses more common in children?

Viral Infections of the Gastrointestinal Tract

A number of viruses can cause gastroenteritis, characterized by inflammation of the GI tract and other signs and symptoms with a range of severities. As with bacterial GI infections, some cases can be relatively mild and self-limiting, while others can become serious and require intensive treatment. Antimicrobial drugs are generally not used to treat viral gastroenteritis; generally, these illnesses can be treated effectively with rehydration therapy to replace fluids lost in bouts of diarrhea and vomiting. Because most viral causes of gastroenteritis are quite contagious, the best preventive measures involve avoiding and/or isolating infected individuals and limiting transmission through good hygiene and sanitation.

Viral Causes of Gastroenteritis					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Vaccine**
Astrovirus gastroenteritis	Astroviruses	Fever, headache, abdominal pain, malaise, diarrhea, vomiting	Fecal-oral route, contaminated food or water	Enzyme immunoassays, immune electron microscopy	None
Norovirus gastroenteritis	Noroviruses	Fever, diarrhea, projectile vomiting, dehydration; generally self-limiting within two days	Highly contagious via direct contact or contact with contaminated food or fomites	Rapid enzyme immunoassay confirmed with RT-qPCR	None
Rotavirus gastroenteritis	Rotaviruses	Fever, diarrhea, vomiting, severe dehydration; recurring infections can lead to malnutrition and death	Fecal-oral route; children and elderly most susceptible	Enzyme immunoassay of stool sample, latex agglutination assays, RT-PCR	Preventive vaccine recommended for infants

Figure 10.2.4.2: Viral causes of Gastroenteritis.

Hepatitis

Hepatitis is a general term meaning inflammation of the liver, which can have a variety of causes. In some cases, the cause is viral infection. There are five main hepatitis viruses that are clinically significant: hepatitisviruses A (HAV), B (HBV), C (HCV), D, (HDV) and E (HEV) (Figure 10.2.4.3). Note that other viruses, such as Epstein-Barr virus (EBV), yellow fever, and cytomegalovirus (CMV) can also cause hepatitis and are discussed in Viral Infections of the Circulatory and Lymphatic Systems.

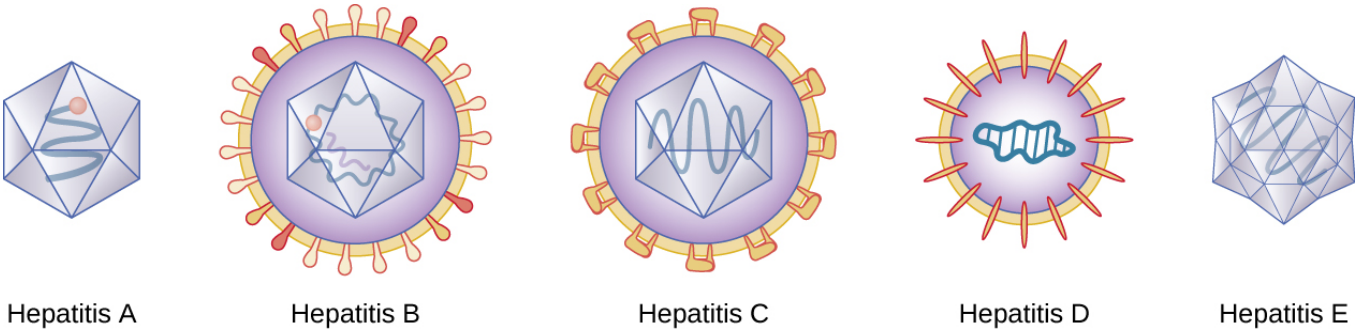


Figure 10.2.4.3: Five main types of viruses cause hepatitis. HAV is a non-enveloped ssRNA(+) virus and is a member of the picornavirus family (Baltimore Group IV). HBV is a dsDNA enveloped virus, replicates using reverse transcriptase, and is a member of the hepadnavirus family (Baltimore Group VII). HCV is an enveloped ssRNA(+) virus and is a member of the flavivirus family (Baltimore Group IV). HDV is an enveloped ssRNA(–) that is circular (Baltimore Group V). This virus can only propagate in the presence of HBV. HEV is a non-enveloped ssRNA(+) virus and a member of the hepeviridae family (Baltimore Group IV).

Although the five hepatitis viruses differ, they can cause some similar signs and symptoms because they all have an affinity for hepatocytes (liver cells). HAV and HEV can be contracted through ingestion while HBV, HCV, and HDV are transmitted by parenteral contact. It is possible for individuals to become long term or chronic carriers of hepatitis viruses.

The virus enters the blood (viremia), spreading to the spleen, the kidneys, and the liver. During viral replication, the virus infects hepatocytes. The inflammation is caused by the hepatocytes replicating and releasing more hepatitis virus. Signs and symptoms include malaise, anorexia, loss of appetite, dark urine, pain in the upper right quadrant of the abdomen, vomiting, nausea, diarrhea, joint pain, and gray stool. Additionally, when the liver is diseased or injured, it is unable to break down hemoglobin effectively, and bilirubin can build up in the body, giving the skin and mucous membranes a yellowish color, a condition called jaundice (Figure 10.2.4.4). In severe cases, death from liver necrosis may occur.

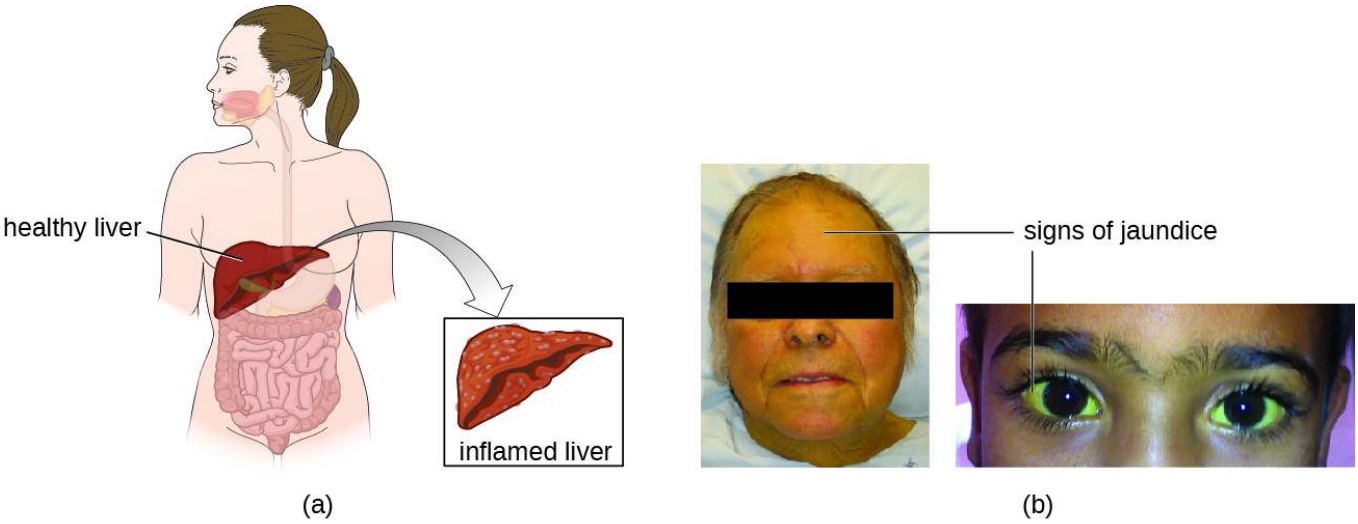


Figure 10.2.4.4: (a) Hepatitis is inflammation of the liver resulting from a variety of root causes. It can cause jaundice. (b) Jaundice is characterized by yellowing of the skin, mucous membranes, and sclera of the eyes. (credit b left: modification of work by James Heilman, MD; credit b right: modification of work by "Sab3el3eish"/Wikimedia Commons)

Despite having many similarities, each of the hepatitis viruses has its own unique characteristics. HAV is generally transmitted through the fecal-oral route, close personal contact, or exposure to contaminated water or food. Hepatitis A can develop after an incubation period of 15 to 50 days (the mean is 30). It is normally mild or even asymptomatic and is usually self-limiting within weeks to months. A more severe form, fulminant hepatitis, rarely occurs but has a high fatality rate of 70–80%. Vaccination is available and is recommended especially for children (between ages one and two), those traveling to countries with higher risk, those with liver disease and certain other conditions, and drug users.

Although HBV is associated with similar signs and symptoms, transmission and outcomes differ. This virus has a mean incubation period of 120 days and is generally associated with exposure to infectious blood or body fluids such as semen or saliva. Exposure can occur through skin puncture, across the placenta, or through mucosal contact, but it is not spread through casual contact such as hugging, hand holding, sneezing, or coughing, or even through breastfeeding or kissing. Risk of infection is greatest for those who use intravenous drugs or who have sexual contact with an infected individual. Health-care workers are also at risk from needle sticks and other injuries when treating infected patients. The infection can become chronic and may progress to cirrhosis or liver failure. It is also associated with liver cancer. Chronic infections are associated with the highest mortality rates and are more common in infants. Approximately 90% of infected infants become chronic carriers, compared with only 6–10% of infected adults.[5] Vaccination is available and is recommended for children as part of the standard vaccination schedule (one dose at birth and the second by 18 months of age) and for adults at greater risk (e.g., those with certain diseases, intravenous drug users, and those who have sex with multiple partners). Health-care agencies are required to offer the HBV vaccine to all workers who have occupational exposure to blood and/or other infectious materials.

HCV is often undiagnosed and therefore may be more widespread than is documented. It has a mean incubation period of 45 days and is transmitted through contact with infected blood. Although some cases are asymptomatic and/or resolve spontaneously, 75%–85% of infected individuals become chronic carriers. Nearly all cases result from parenteral transmission often associated with IV drug use or transfusions. The risk is greatest for individuals with past or current history of intravenous drug use or who have had sexual contact with infected individuals. It has also been spread through contaminated blood products and can even be transmitted through contaminated personal products such as toothbrushes and razors. New medications have recently been developed that show great effectiveness in treating HCV and that are tailored to the specific genotype causing the infection.

HDV is uncommon in the United States and only occurs in individuals who are already infected with HBV, which it requires for replication. Therefore, vaccination against HBV is also protective against HDV infection. HDV is transmitted through contact with infected blood.

HEV infections are also rare in the United States but many individuals have a positive antibody titer for HEV. The virus is most commonly spread by the fecal-oral route through food and/or water contamination, or person-to-person contact, depending on the genotype of the virus, which varies by location. There are four genotypes that differ somewhat in their mode of transmission,

distribution, and other factors (for example, two are zoonotic and two are not, and only one causes chronic infection). Genotypes three and four are only transmitted through food, while genotypes one and two are also transmitted through water and fecal-oral routes. Genotype one is the only type transmitted person-to-person and is the most common cause of HEV outbreaks. Consumption of undercooked meat, especially deer or pork, and shellfish can lead to infection. Genotypes three and four are zoonoses, so they can be transmitted from infected animals that are consumed. Pregnant women are at particular risk. This disease is usually self-limiting within two weeks and does not appear to cause chronic infection.

General laboratory testing for hepatitis begins with blood testing to examine liver function (Figure 10.2.4.5). When the liver is not functioning normally, the blood will contain elevated levels of alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct bilirubin, total bilirubin, serum albumin, serum total protein, and calculated globulin, albumin/globulin (A/G) ratio. Some of these are included in a complete metabolic panel (CMP), which may first suggest a possible liver problem and indicate the need for more comprehensive testing. A hepatitis virus serological test panel can be used to detect antibodies for hepatitis viruses A, B, C, and sometimes D. Additionally, other immunological and genomic tests are available.

Specific treatments other than supportive therapy, rest, and fluids are often not available for hepatitis virus infection, except for HCV, which is often self-limited. Immunoglobulins can be used prophylactically following possible exposure. Medications are also used, including interferon alpha 2b and antivirals (e.g., lamivudine, entecavir, adefovir, and telbivudine) for chronic infections. Hepatitis C can be treated with interferon (as monotherapy or combined with other treatments), protease inhibitors, and other antivirals (e.g., the polymerase inhibitor sofosbuvir). Combination treatments are commonly used. Antiviral and immunosuppressive medications may be used for chronic cases of HEV. In severe cases, liver transplants may be necessary. Additionally, vaccines are available to prevent infection with HAV and HBV. The HAV vaccine is also protective against HEV. The HBV vaccine is also protective against HDV. There is no vaccine against HCV.

Link to Learning

Learn more information about hepatitis virus infections.

Exercise 10.2.4.2

Why do the five different hepatitis viruses all cause similar signs and symptoms?

Preventing HBV Transmission in Health-Care Settings

Hepatitis B was once a leading on-the-job hazard for health-care workers. Many health-care workers over the years have become infected, some developing cirrhosis and liver cancer. In 1982, the CDC recommended that health-care workers be vaccinated against HBV, and rates of infection have declined since then. Even though vaccination is now common, it is not always effective and not all individuals are vaccinated. Therefore, there is still a small risk for infection, especially for health-care workers working with individuals who have chronic infections, such as drug addicts, and for those with higher risk of needle sticks, such as phlebotomists. Dentists are also at risk.

Health-care workers need to take appropriate precautions to prevent infection by HBV and other illnesses. Blood is the greatest risk, but other body fluids can also transmit infection. Damaged skin, as occurs with eczema or psoriasis, can also allow transmission. Avoiding contact with body fluids, especially blood, by wearing gloves and face protection and using disposable syringes and needles reduce the risk of infection. Washing exposed skin with soap and water is recommended. Antiseptics may also be used, but may not help. Post-exposure treatment, including treatment with hepatitis B immunoglobulin (HBIG) and vaccination, may be used in the event of exposure to the virus from an infected patient. Detailed protocols are available for managing these situations. The virus can remain infective for up to seven days when on surfaces, even if no blood or other fluids are visible, so it is important to consider the best choices for disinfecting and sterilizing equipment that could potentially transmit the virus. The CDC recommends a solution of 10% bleach to disinfect surfaces.[6] Finally, testing blood products is important to reduce the risk of transmission during transfusions and similar procedures.

Viral Hepatitis

Hepatitis involves inflammation of the liver that typically manifests with signs and symptoms such as jaundice, nausea, vomiting, joint pain, gray stool, and loss of appetite. However, the severity and duration of the disease can vary greatly depending on the causative agent. Some infections may be completely asymptomatic, whereas others may be life threatening. The five different viruses capable of causing hepatitis are compared in Figure 10.2.4.5. For the sake of comparison, this table presents only the unique aspects of each form of viral hepatitis, not the commonalities.

Viral Forms of Hepatitis					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Antimicrobial Drugs**	**Vaccine**
Hepatitis A	Hepatitisvirus A (HAV)	Usually asymptomatic or mild and self-limiting within one to two weeks to a few months, sometimes longer but not, chronic; in rare cases leads to serious or fatal fulminant hepatitis	Contaminated food, water, objects, and person to person	None	Vaccine recommended for one year olds and high-risk adults
Hepatitis B	Hepatitisvirus B (HBV)	Similar to Hepatitis A, but may progress to cirrhosis and liver failure; associated with liver cancer	Contact with infected body fluids (blood, semen, saliva), e.g., via IV drug use, sexual transmission, health-care workers treating infected patients	Interferon, entecavir, tenofovir, lamivudine, adefovir	Vaccine recommended for infants and high-risk adults
Hepatitis C	Hepatitisvirus C (HCV)	Often asymptomatic, with 75%–85% chronic carriers; may progress to cirrhosis and liver failure; associated with liver cancer	Contact with infected body fluids, e.g., via IV drug use, transfusions, sexual transmission	Depends on geno-type and on whether cirrhosis is present; interferons, new treatment such as simeprevir plus sofosbuvir, ombitasvir/ paritaprevir/ritonavir and dasabuvir	None available
Hepatitis D	Hepatitisvirus D (HDV)	Similar to hepatitis B; usually self-limiting within one to two weeks but can become chronic or fulminant in rare cases	Contact with infected blood; infections can only occur in patients already infected with hepatitis B	None	Hepatitis B vaccine protects against HDV
Hepatitis E	Hepatitisvirus E (HEV)	Generally asymptomatic or mild and self-limiting; typically does not cause chronic disease	Fecal-oral route, often in contaminated water or undercooked meat; most common in developing countries	Supportive treatment; usually self-limiting, but some strains can become chronic; antiviral and immunosuppressive possible for chronic cases	Vaccine available in China only

Figure 10.2.4.5: Viral forms of Hepatitis.

Key Concepts and Summary

- Common viral causes of gastroenteritis include rotaviruses, noroviruses, and astroviruses.
- Hepatitis may be caused by several unrelated viruses: hepatitis viruses A, B, C, D, and E.
- The hepatitis viruses differ in their modes of transmission, treatment, and potential for chronic infection.

Footnotes

1. 1 Caleb K. King, Roger Glass, Joseph S. Bresee, Christopher Duggan. “Managing Acute Gastroenteritis Among Children: Oral Rehydration, Maintenance, and Nutritional Therapy.” *MMWR* 52 (2003) RR16: pp. 1–16. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5216a1.htm.
2. 2 Elizabeth Jane Elliott. “Acute Gastroenteritis in Children.” *British Medical Journal* 334 (2007) 7583: 35–40, doi: 10.1136/bmj.39036.406169.80; S. Ramani and G. Kang. “Viruses Causing Diarrhoea in the Developing World.” *Current Opinions in Infectious Diseases* 22 (2009) 5: pp. 477–482. doi: 10.1097/QCO.0b013e328330662f; Michael Vincent F Tablang. “Viral Gastroenteritis.” *Medscape*. http://emedicine.medscape.com/article/176515-overview.
3. 3 Centers for Disease Control and Prevention. “Rotavirus,” *The Pink Book.* Updated September 8, 2015. http://www.cdc.gov/vaccines/pubs/pinkbook/rota.html.
4. 4 World Health Organization. “Rotavirus.” *Immunization, Vaccines, and Biologicals.* Updated April 21, 2010. www.who.int/immunization/topics/rotavirus/en/.
5. 5 Centers for Disease Control and Prevention. “The ABCs of Hepatitis.” Updated 2016. http://www.cdc.gov/hepatitis/resourc...s/abctable.pdf.
6. 6 Centers for Disease Control and Prevention. “Hepatitis B FAQs for Health Professionals.” Updated August 4, 2016. http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm.

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10.2.5: Protozoan Infections of the Gastrointestinal Tract

Learning Objectives

- Identify the most common protozoans that can cause infections of the GI tract
- Compare the major characteristics of specific protozoan diseases affecting the GI tract

Like other microbes, protozoa are abundant in natural microbiota but can also be associated with significant illness. Gastrointestinal diseases caused by protozoa are generally associated with exposure to contaminated food and water, meaning that those without access to good sanitation are at greatest risk. Even in developed countries, infections can occur and these microbes have sometimes caused significant outbreaks from contamination of public water supplies.

Giardiasis

Also called backpacker's diarrhea or beaver fever, giardiasis is a common disease in the United States caused by the flagellated protist *Giardia lamblia*, also known as *Giardia intestinalis* or *Giardia duodenalis* (Figure 1.3.5). To establish infection, *G. lamblia* uses a large adhesive disk to attach to the intestinal mucosa. The disk is comprised of microtubules. During adhesion, the flagella of *G. lamblia* move in a manner that draws fluid out from under the disk, resulting in an area of lower pressure that promotes its adhesion to the intestinal epithelial cells. Due to its attachment, *Giardia* also blocks absorption of nutrients, including fats.

Transmission occurs through contaminated food or water or directly from person to person. Children in day-care centers are at risk due to their tendency to put items into their mouths that may be contaminated. Large outbreaks may occur if a public water supply becomes contaminated. *Giardia* have a resistant cyst stage in their life cycle that is able to survive cold temperatures and the chlorination treatment typically used for drinking water in municipal reservoirs. As a result, municipal water must be filtered to trap and remove these cysts. Once consumed by the host, *Giardia* develops into the active tropozoite.

Infected individuals may be asymptomatic or have gastrointestinal signs and symptoms, sometimes accompanied by weight loss. Common symptoms, which appear one to three weeks after exposure, include diarrhea, nausea, stomach cramps, gas, greasy stool (because fat absorption is being blocked), and possible dehydration. The parasite remains in the colon and does not cause systemic infection. Signs and symptoms generally clear within two to six weeks. Chronic infections may develop and are often resistant to treatment. These are associated with weight loss, episodic diarrhea, and malabsorption syndrome due to the blocked nutrient absorption.

Diagnosis may be made using observation under the microscope. A stool ova and parasite (O&P) exam involves direct examination of a stool sample for the presence of cysts and trophozoites; it can be used to distinguish common parasitic intestinal infections. ELISA and other immunoassay tests, including commercial direct fluorescence antibody kits, are also used. The most common treatments use metronidazole as the first-line choice, followed by tinidazole. If the infection becomes chronic, the parasites may become resistant to medications.

Cryptosporidiosis

Another protozoan intestinal illness is cryptosporidiosis, which is usually caused by *Cryptosporidium parvum* or *C. hominis*. (Figure 10.2.5.1) These pathogens are commonly found in animals and can be spread in feces from mice, birds, and farm animals. Contaminated water and food are most commonly responsible for transmission. The protozoan can also be transmitted through human contact with infected animals or their feces.

In the United States, outbreaks of cryptosporidiosis generally occur through contamination of the public water supply or contaminated water at water parks, swimming pools, and day-care centers. The risk is greatest in areas with poor sanitation, making the disease more common in developing countries.

Signs and symptoms include watery diarrhea, nausea, vomiting, cramps, fever, dehydration, and weight loss. The illness is generally self-limiting within a month. However, immunocompromised patients, such as those with HIV/AIDS, are at particular risk of severe illness or death.

Diagnosis involves direct examination of stool samples, often over multiple days. As with giardiasis, a stool O&P exam may be helpful. Acid fast staining is often used. Enzyme immunoassays and molecular analysis (PCR) are available.

The first line of treatment is typically oral rehydration therapy. Medications are sometimes used to treat the diarrhea. The broad-range anti-parasitic drug nitazoxanide can be used to treat cryptosporidiosis. Other anti-parasitic drugs that can be used include azithromycin and paromomycin.

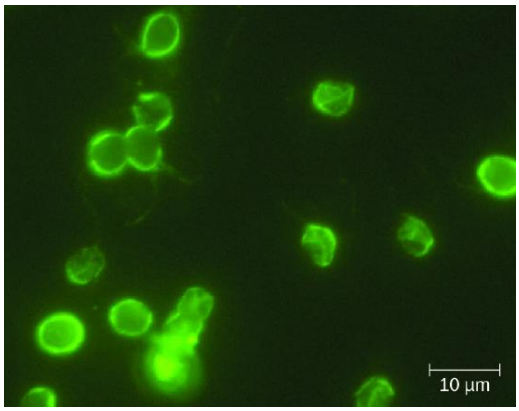


Figure 10.2.5.1: Immunofluorescent staining allows for visualization of *Cryptosporidium* spp. (credit: modification of work by EPA/H.D.A. Lindquist)

Amoebiasis (Amebiasis)

The protozoan parasite *Entamoeba histolytica* causes amoebiasis, which is known as amoebic dysentery in severe cases. *E. histolytica* is generally transmitted through water or food that has fecal contamination. The disease is most widespread in the developing world and is one of the leading causes of mortality from parasitic disease worldwide. Disease can be caused by as few as 10 cysts being transmitted.

Signs and symptoms range from nonexistent to mild diarrhea to severe amoebic dysentery. Severe infection causes the abdomen to become distended and may be associated with fever. The parasite may live in the colon without causing signs or symptoms or may invade the mucosa to cause colitis. In some cases, the disease spreads to the spleen, brain, genitourinary tract, or lungs. In particular, it may spread to the liver and cause an abscess. When a liver abscess develops, fever, nausea, liver tenderness, weight loss, and pain in the right abdominal quadrant may occur. Chronic infection may occur and is associated with intermittent diarrhea, mucus, pain, flatulence, and weight loss.

Direct examination of fecal specimens may be used for diagnosis. As with cryptosporidiosis, samples are often examined on multiple days. A stool O&P exam of fecal or biopsy specimens may be helpful. Immunoassay, serology, biopsy, molecular, and antibody detection tests are available. Enzyme immunoassay may not distinguish current from past illness. Magnetic resonance imaging (MRI) can be used to detect any liver abscesses. The first line of treatment is metronidazole or tinidazole, followed by diloxanide furoate, iodoquinol, or paromomycin to eliminate the cysts that remain.

Cyclosporiasis

The intestinal disease cyclosporiasis is caused by the protozoan *Cyclospora cayetanensis*. It is endemic to tropical and subtropical regions and therefore uncommon in the United States, although there have been outbreaks associated with contaminated produce imported from regions where the protozoan is more common. This protist is transmitted through contaminated food and water and reaches the lining of the small intestine, where it causes infection. Signs and symptoms begin within seven to ten days after ingestion. Based on limited data, it appears to be seasonal in ways that differ regionally and that are poorly understood.

Some individuals do not develop signs or symptoms. Those who do may exhibit explosive and watery diarrhea, fever, nausea, vomiting, cramps, loss of appetite, fatigue, and bloating. These symptoms may last for months without treatment. Trimethoprim-sulfamethoxazole is the recommended treatment. Microscopic examination is used for diagnosis. A stool O&P examination may be helpful. The oocysts have a distinctive blue halo when viewed using ultraviolet fluorescence microscopy (Figure 10.2.5.2).

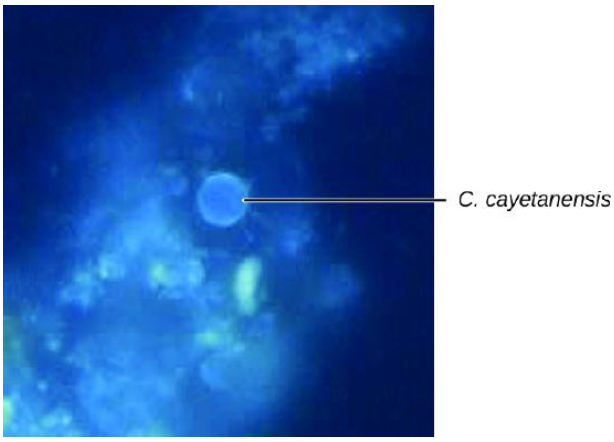


Figure 10.2.5.2: Cyclospora cayetanensis are autofluorescent under ultraviolet light. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 10.2.5.1

Which protozoan GI infections are common in the United States?

Protozoan Gastrointestinal Infections

Protozoan GI infections are generally transmitted through contaminated food or water, triggering diarrhea and vomiting that can lead to dehydration. Rehydration therapy is an important aspect of treatment, but most protozoan GI infections can also be treated with drugs that target protozoans.

Protozoan Infections of the GI Tract

Disease	Pathogen	Signs and Symptoms	Transmission	Diagnostic Tests	Antimicrobial Drugs
Amoebiasis (amoebic dysentery)	*Entamoeba histolytica*	From mild diarrhea to severe dysentery and colitis; may cause abscess on the liver	Fecal-oral route; ingestion of cysts from fecally contaminated water, food, or hands	Stool O&P exam, enzyme immunoassay	Metronidazole, tinidazole, diloxanide furoate, iodoquinol, paromomycin
Cryptosporidiosis	*Cryptosporidium parvum, Cryptosporidium hominis*	Watery diarrhea, nausea, vomiting, cramps, fever, dehydration, and weight loss	Contact with feces of infected mice, birds, farm animals; ingestion of contaminated food or water; exposure to contaminated water while swimming or bathing	Stool O&P exam, enzyme immunoassay, PCR	Nitazoxanide, azithromycin, and paromomycin
Cyclosporiasis	*Cyclospora cayetanensis*	Explosive diarrhea, fever, nausea, vomiting, cramps, loss of appetite, fatigue, bloating	Ingestion of contaminated food or water	Stool O&P exam using ultraviolet fluorescence microscopy	Trimethoprim-sulfmethoxazole
Giardiasis	*Giardia lamblia*	Diarrhea, nausea, stomach cramps, gas, greasy stool, dehydration if severe; sometimes malabsorption syndrome	Contact with infected individual or contaminated fomites; ingestion of contaminated food or water	Stool O&P exam; ELISA, direct fluorescence antibody assays	Metronidazole, tinidazole

Figure 10.2.5.3: Protozoan infections of the GI tract.

Key Concepts and Summary

- **Giardiasis**, **cryptosporidiosis**, **amoebiasis**, and **cyclosporiasis** are intestinal infections caused by protozoans.
- Protozoan intestinal infections are commonly transmitted through contaminated food and water.
- Treatment varies depending on the causative agent, so proper diagnosis is important.
- Microscopic examination of stool or biopsy specimens is often used in diagnosis, in combination with other approaches.

Footnotes

1. 1 Centers for Disease Control and Prevention. “Cyclosporiasis FAQs for Health Professionals.” Updated June 13, 2014. http://www.cdc.gov/parasites/cyclosp...s/hp-faqs.html.

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10.2.6: Helminthic Infections of the Gastrointestinal Tract

Learning Objectives

- Identify the most common helminths that cause infections of the GI tract
- Compare the major characteristics of specific helminthic diseases affecting GI tract

Helminths are widespread intestinal parasites. These parasites can be divided into three common groups: round-bodied worms also described as nematodes, flat-bodied worms that are segmented (also described as cestodes), and flat-bodied worms that are non-segmented (also described as trematodes). The nematodes include roundworms, pinworms, hookworms, and whipworms. Cestodes include beef, pork, and fish tapeworms. Trematodes are collectively called flukes and more uniquely identified with the body site where the adult flukes are located. Although infection can have serious consequences, many of these parasites are so well adapted to the human host that there is little obvious disease.

Ascariasis

Infections caused by the large nematode roundworm *Ascaris lumbricoides*, a soil-transmitted helminth, are called ascariasis. Over 800 million to 1 billion people are estimated to be infected worldwide.[1] Infections are most common in warmer climates and at warmer times of year. At present, infections are uncommon in the United States. The eggs of the worms are transmitted through contaminated food and water. This may happen if food is grown in contaminated soil, including when manure is used as fertilizer.

When an individual consumes embryonated eggs (those with a developing embryo), the eggs travel to the intestine and the larvae are able to hatch. *Ascaris* is able to produce proteases that allow for penetration and degradation of host tissue. The juvenile worms can then enter the circulatory system and migrate to the lungs where they enter the alveoli (air sacs). From here they crawl to the pharynx and then follow the gut lumen to return to the small intestine, where they mature into adult roundworms. Females in the host will produce and release eggs that leave the host via feces. In some cases, the worms can block ducts such as those of the pancreas or gallbladder.

The infection is commonly asymptomatic. When signs and symptoms are present, they include shortness of breath, cough, nausea, diarrhea, blood in the stool, abdominal pain, weight loss, and fatigue. The roundworms may be visible in the stool. In severe cases, children with substantial infections may experience intestinal blockage.

The eggs can be identified by microscopic examination of the stool (Figure 10.2.6.1). In some cases, the worms themselves may be identified if coughed up or excreted in stool. They can also sometimes be identified by X-rays, ultrasounds, or MRIs.

Ascariasis is self-limiting, but can last one to two years because the worms can inhibit the body's inflammatory response through glycan gimmickry (see Virulence Factors of Eukaryotic Pathogens). The first line of treatment is mebendazole or albendazole. In some severe cases, surgery may be required.



(a) (b) (c)

Figure 10.2.6.1: (a) Adult *Ascaris lumbricoides* roundworms can cause intestinal blockage. (b) This mass of *A. lumbricoides* worms was excreted by a child. (c) A micrograph of a fertilized egg of *A. lumbricoides*. Fertilized eggs can be distinguished from unfertilized eggs because they are round rather than elongated and have a thicker cell wall. (credit a: modification of work by South African Medical Research Council; credit b: modification of work by James Gathany, Centers for Disease Control and Prevention; credit c: modification of work by Centers for Disease Control and Prevention)

? Exercise 10.2.6.1

Describe the route by which *A. lumbricoides* reaches the host's intestines as an adult worm.

Hookworm

Two species of nematode worms are associated with hookworm infection. Both species are found in the Americas, Africa, and Asia. *Necator americanus* is found predominantly in the United States and Australia. Another species, *Ancylostoma doudenale*, is found in southern Europe, North Africa, the Middle East, and Asia. The eggs of these species develop into larvae in soil contaminated by dog or cat feces. These larvae can penetrate the skin. After traveling through the venous circulation, they reach the lungs. When they are coughed up, they are then swallowed and can enter the intestine and develop into mature adults. At this stage, they attach to the wall of the intestine, where they feed on blood and can potentially cause anemia. Signs and symptoms include cough, an itchy rash, loss of appetite, abdominal pain, and diarrhea. In children, hookworms can affect physical and cognitive growth.

Some hookworm species, such as *Ancylostoma braziliense* that is commonly found in animals such as cats and dogs, can penetrate human skin and migrate, causing cutaneous larva migrans, a skin disease caused by the larvae of hookworms. As they move across the skin, in the subcutaneous tissue, pruritic tracks appear (Figure 10.2.6.2).



Figure 10.2.6.2: (a) This animal hookworm, *Ancylostoma caninum*, is attached to the intestinal wall. (b) The tracks of hookworms are visible in this individual with cutaneous larva migrans. (c) This micrograph shows the microscopic egg of a hookworm. (credit a, c: modification of work by Centers for Disease Control and Prevention).

The infection is diagnosed using microscopic examination of the stool, allowing for observation of eggs in the feces. Medications such as albendazole, mebendazole, and pyrantel pamoate are used as needed to treat systemic infection. In addition to systemic medication for symptoms associated with cutaneous larva migrans, topical thiabendazole is applied to the affected areas.

Strongyloidiasis

Strongyloidiasis is generally caused by *Strongyloides stercoralis*, a soil-transmitted helminth with both free-living and parasitic forms. In the parasitic form, the larvae of these nematodes generally penetrate the body through the skin, especially through bare feet, although transmission through organ transplantation or at facilities like day-care centers can also occur. When excreted in the stool, larvae can become free-living adults rather than developing into the parasitic form. These free-living worms reproduce, laying eggs that hatch into larvae that can develop into the parasitic form. In the parasitic life cycle, infective larvae enter the skin, generally through the feet. The larvae reach the circulatory system, which allows them to travel to the alveolar spaces of the lungs. They are transported to the pharynx where, like many other helminths, the infected patient coughs them up and swallows them again so that they return to the intestine. Once they reach the intestine, females live in the epithelium and produce eggs that develop asexually, unlike the free-living forms, which use sexual reproduction. The larvae may be excreted in the stool or can reinfect the host by entering the tissue of the intestines and skin around the anus, which can lead to chronic infections.

The condition is generally asymptomatic, although severe symptoms can develop after treatment with corticosteroids for asthma or chronic obstructive pulmonary disease, or following other forms of immunosuppression. When the immune system is suppressed, the rate of autoinfection increases, and huge amounts of larvae migrate to organs throughout the body.

Signs and symptoms are generally nonspecific. The condition can cause a rash at the site of skin entry, cough (dry or with blood), fever, nausea, difficulty breathing, bloating, pain, heartburn, and, rarely, arthritis, or cardiac or kidney complications. Disseminated strongyloidiasis or hyperinfection is a life-threatening form of the disease that can occur, usually following immunosuppression such as that caused by glucocorticoid treatment (most commonly), with other immunosuppressive medications, with HIV infection, or with malnutrition.

As with other helminths, direct examination of the stool is important in diagnosis. Ideally, this should be continued over seven days. Serological testing, including antigen testing, is also available. These can be limited by cross-reactions with other similar parasites and by the inability to distinguish current from resolved infection. Ivermectin is the preferred treatment, with albendazole as a secondary option.

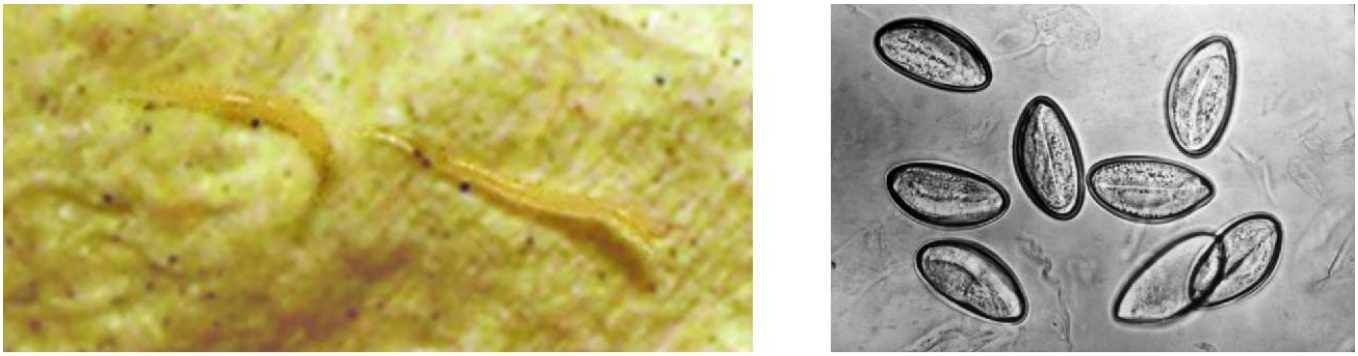
? Exercise 10.2.6.2

How does an acute infection of *S. stercoralis* become chronic?

Pinworms (Enterobiasis)

Enterobius vermicularis, commonly called pinworms, are tiny (2–13 mm) nematodes that cause enterobiasis. Of all helminthic infections, enterobiasis is the most common in the United States, affecting as many as one-third of American children.[2] Although the signs and symptoms are generally mild, patients may experience abdominal pain and insomnia from itching of the perianal region, which frequently occurs at night when worms leave the anus to lay eggs. The itching contributes to transmission, as the disease is transmitted through the fecal-oral route. When an infected individual scratches the anal area, eggs may get under the fingernails and later be deposited near the individual's mouth, causing reinfection, or on fomites, where they can be transferred to new hosts. After being ingested, the larvae hatch within the small intestine and then take up residence in the colon and develop into adults. From the colon, the female adult exits the body at night to lay eggs (Figure 10.2.6.3).

Infection is diagnosed in any of three ways. First, because the worms emerge at night to lay eggs, it is possible to inspect the perianal region for worms while an individual is asleep. An alternative is to use transparent tape to remove eggs from the area around the anus first thing in the morning for three days to yield eggs for microscopic examination. Finally, it may be possible to detect eggs through examination of samples from under the fingernails, where eggs may lodge due to scratching. Once diagnosis has been made, mebendazole, albendazole, and pyrantel pamoate are effective for treatment.



(a) (b)

Figure 10.2.6.3: (a) *E. vermicularis* are tiny nematodes commonly called pinworms. (b) This micrograph shows pinworm eggs.

Trichuriasis

The nematode whipworm *Trichuris trichiura* is a parasite that is transmitted by ingestion from soil-contaminated hands or food and causes trichuriasis. Infection is most common in warm environments, especially when there is poor sanitation and greater risk of fecal contamination of soil, or when food is grown in soil using manure as a fertilizer. The signs and symptoms may be minimal or nonexistent. When a substantial infection develops, signs and symptoms include painful, frequent diarrhea that may contain mucus and blood. It is possible for the infection to cause rectal prolapse, a condition in which a portion of the rectum becomes detached from the inside of the body and protrudes from the anus (Figure 10.2.6.4). Severely infected children may experience reduced growth and their cognitive development may be affected.

When fertilized eggs are ingested, they travel to the intestine and the larvae emerge, taking up residence in the walls of the colon and cecum. They attach themselves with part of their bodies embedded in the mucosa. The larvae mature and live in the cecum and ascending colon. After 60 to 70 days, females begin to lay 3000 to 20,000 eggs per day.

Diagnosis involves examination of the feces for the presence of eggs. It may be necessary to use concentration techniques and to collect specimens on multiple days. Following diagnosis, the infection may be treated with mebendazole, albendazole, or ivermectin.

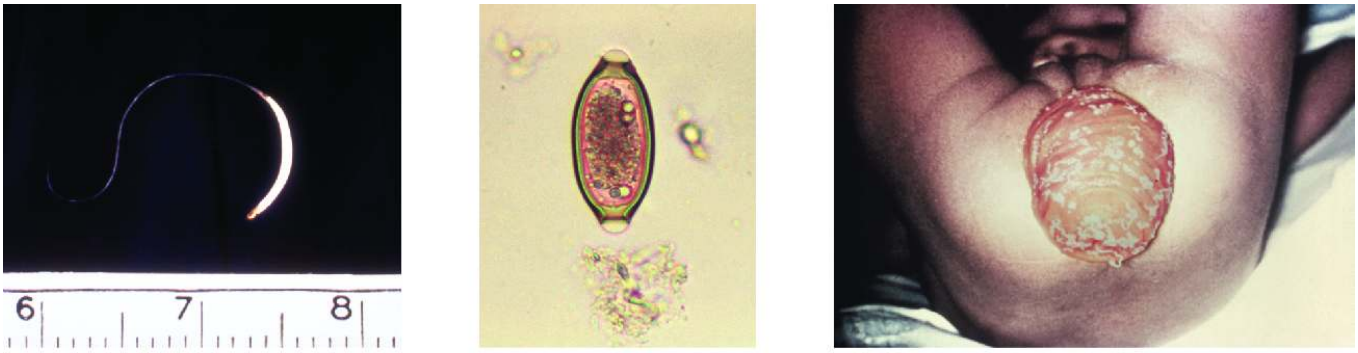


Figure 10.2.6.4: (a) This adult female *Trichuris* whipworm is a soil-transmitted parasite. (b) *Trichuris trichiura* eggs are ingested and travel to the intestines where the larvae emerge and take up residence. (c) Rectal prolapse is a condition that can result from whipworm infections. It occurs when the rectum loses its attachment to the internal body structure and protrudes from the anus. (credit a, b, c: modification of work by Centers for Disease Control and Prevention)

Trichinosis

Trichinosis (trichenellosis) develops following consumption of food that contains *Trichinella spiralis* (most commonly) or other *Trichinella* species. These microscopic nematode worms are most commonly transmitted in meat, especially pork, that has not been cooked thoroughly. *T. spiralis* larvae in meat emerge from cysts when exposed to acid and pepsin in the stomach. They develop into mature adults within the large intestine. The larvae produced in the large intestine are able to migrate into the muscles mechanically via the stylet of the parasite, forming cysts. Muscle proteins are reduced in abundance or undetectable in cells that contain *Trichinella* (nurse cells). Animals that ingest the cysts from other animals can later develop infection (Figure 10.2.6.5).

Although infection may be asymptomatic, symptomatic infections begin within a day or two of consuming the nematodes. Abdominal symptoms arise first and can include diarrhea, constipation, and abdominal pain. Other possible symptoms include headache, light sensitivity, muscle pain, fever, cough, chills, and conjunctivitis. More severe symptoms affecting motor coordination, breathing, and the heart sometimes occur. It may take months for the symptoms to resolve, and the condition is occasionally fatal. Mild cases may be mistaken for influenza or similar conditions.

Infection is diagnosed using clinical history, muscle biopsy to look for larvae, and serological testing, including immunoassays. Enzyme immunoassay is the most common test. It is difficult to effectively treat larvae that have formed cysts in the muscle, although medications may help. It is best to begin treatment as soon as possible because medications such as mebendazole and albendazole are effective in killing only the adult worms in the intestine. Steroids may be used to reduce inflammation if larvae are in the muscles.

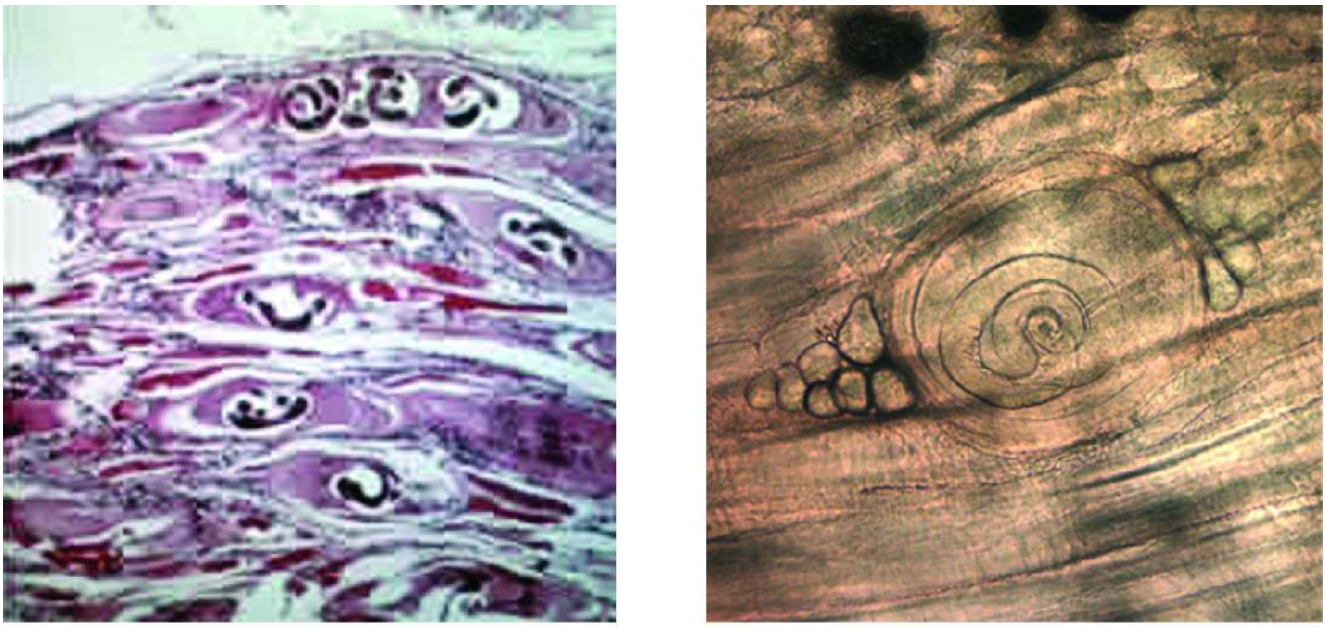


Figure 10.2.6.5: (a) This image shows larvae of *T. spiralis* within muscle. (b) In meat, the larvae have a characteristic coiled appearance, as seen in this partially digested larva in bear meat. (credit a, b: modification of work by Centers for Disease Control and Prevention)

? Exercise 10.2.6.3

Compare and contrast the transmissions of pinworms and whipworms.

Tapeworms (Taeniasis)

Taeniasis is a tapeworm infection, generally caused by pork (*Taenia solium*), beef (*Taenia saginata*), and Asian (*Taenia asiatica*) tapeworms found in undercooked meat. Consumption of raw or undercooked fish, including contaminated sushi, can also result in infection from the fish tapeworm (*Diphyllobothrium latum*). Tapeworms are flatworms (cestodes) with multiple body segments and a head called a scolex that attaches to the intestinal wall. Tapeworms can become quite large, reaching 4 to 8 meters long (Figure 10.2.6.6). Figure 5.2.5 illustrates the life cycle of a tapeworm.

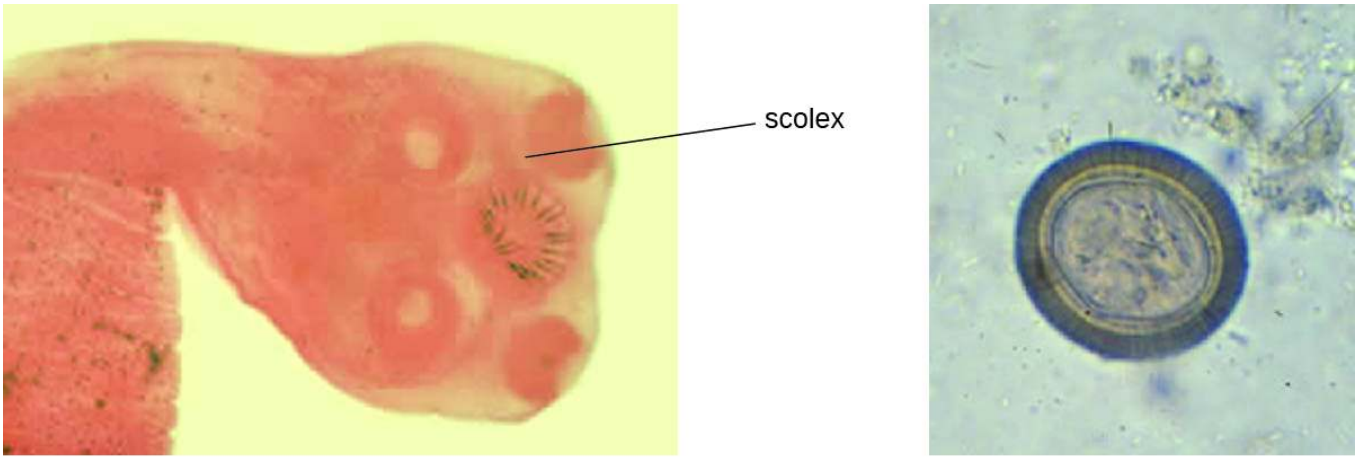


Figure 10.2.6.6: (a) An adult tapeworm uses the scolex to attach to the intestinal wall. (b) The egg of a pork tapeworm (*Taenia solium*) is visible in this micrograph. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Tapeworms attached to the intestinal wall produce eggs that are excreted in feces. After ingestion by animals, the eggs hatch and the larvae emerge. They may take up residence in the intestine, but can sometimes move to other tissues, especially muscle or brain tissue. When *T. solium* larvae form cysts in tissue, the condition is called cysticercosis. This occurs through ingestion of eggs via the fecal-oral route, not through consumption of undercooked meat. It can develop in the muscles, eye (ophthalmic cysticercosis), or brain (neurocysticercosis).

Infections may be asymptomatic or they may cause mild gastrointestinal symptoms such as epigastric discomfort, nausea, diarrhea, flatulence, or hunger pains. It is also common to find visible tapeworm segments passed in the stool. In cases of cysticercosis, symptoms differ depending upon where the cysts become established. Neurocysticercosis can have severe, life-threatening consequences and is associated with headaches and seizures because of the presence of the tapeworm larvae encysted in the brain. Cysts in muscles may be asymptomatic, or they may be painful.

To diagnose these conditions, microscopic analysis of stool samples from three separate days is generally recommended. Eggs or body segments, called proglottids, may be visible in these samples. Molecular methods have been developed but are not yet widely available. Imaging, such as CT and MRI, may be used to detect cysts. Praziquantel or niclosamide are used for treatment.

What's in Your Sushi Roll?

As foods that contain raw fish, such as sushi and sashimi, continue to increase in popularity throughout the world, so does the risk of parasitic infections carried by raw or undercooked fish. *Diphyllobothrium* species, known as fish tapeworms, is one of the main culprits. Evidence suggests that undercooked salmon caused an increase in *Diphyllobothrium* infections in British Columbia in the 1970s and early 1980s. In the years since, the number of reported cases in the United States and Canada has been low, but it is likely that cases are underreported because the causative agent is not easily recognized.[3]

Another illness transmitted in undercooked fish is herring worm disease, or anisakiasis, in which nematodes attach to the epithelium of the esophagus, stomach, or small intestine. Cases have increased around the world as raw fish consumption has increased.[4]

Although the message may be unpopular with sushi lovers, fish should be frozen or cooked before eating. The extremely low and high temperatures associated with freezing and cooking kill worms and larvae contained in the meat, thereby preventing infection. Ingesting fresh, raw sushi may make for a delightful meal, but it also entails some risk.

Hydatid Disease

Another cestode, *Echinococcus granulosus*, causes a serious infection known as hydatid disease (cystic echinococcosis). *E. granulosus* is found in dogs (the definitive host), as well as several intermediate hosts (sheep, pigs, goats, cattle). The cestodes are transmitted through eggs in the feces from infected animals, which can be an occupational hazard for individuals who work in agriculture.

Once ingested, *E. granulosus* eggs hatch in the small intestine and release the larvae. The larvae invade the intestinal wall to gain access to the circulatory system. They form hydatid cysts in internal organs, especially in the lungs and liver, that grow slowly and are often undetected until they become large. If the cysts burst, a severe allergic reaction (anaphylaxis) may occur.

Cysts present in the liver can cause enlargement of the liver, nausea, vomiting, right epigastric pain, pain in the right upper quadrant, and possible allergic signs and symptoms. Cysts in the lungs can lead to alveolar disease. Abdominal pain, weight loss, pain, and malaise may occur, and inflammatory processes develop.

E. granulosus can be detected through imaging (ultrasonography, CT, MRI) that shows the cysts. Serologic tests, including ELISA and indirect hemagglutinin tests, are used. Cystic disease is most effectively treated with surgery to remove cysts, but other treatments are also available, including chemotherapy with anti-helminthic drugs (albendazoleor mebendazole).

Exercise 10.2.6.4

Describe the risks of the cysts associated with taeniasis and hydatid disease.

Flukes

Flukes are flatworms that have a leaflike appearance. They are a type of trematode worm, and multiple species are associated with disease in humans. The most common are liver flukes and intestinal flukes (Figure 10.2.6.7).

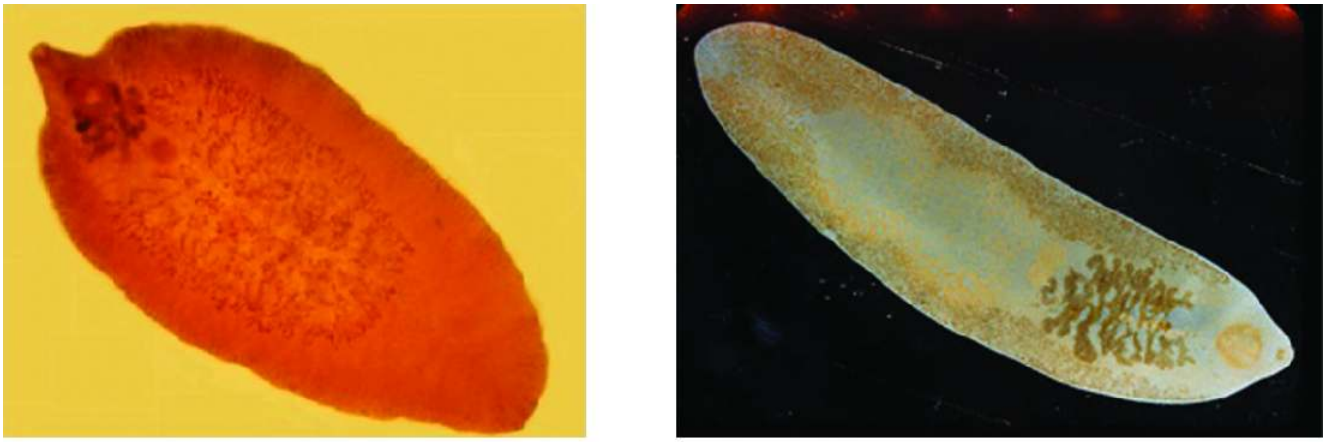


Figure 10.2.6.7: (a) A liver fluke infects the bile ducts. (b) An intestinal fluke infects the intestines. (credit a: modification of work by Shafiei R, Sarkari B, Sadjjadi SM, Mowlavi GR, and Moshfe A; credit b: modification of work by Georgia Division of Public Health)

Liver Flukes

The liver flukes are several species of trematodes that cause disease by interfering with the bile duct. Fascioliasis is caused by *Fasciola hepatica* and *Fasciola gigantica* in contaminated raw or undercooked aquatic plants (e.g., watercress). In *Fasciola* infection, adult flukes develop in the bile duct and release eggs into the feces. Clonochiasis is caused by *Clonorchis sinensis* in contaminated freshwater fish. Other flukes, such as *Opisthorchis viverrini* (found in fish) and *Opisthorchis felineus* (found in freshwater snails), also cause infections. Liver flukes spend part of their life cycle in freshwater snails, which serve as an intermediate host. Humans are typically infected after eating aquatic plants contaminated by the infective larvae after they have left the snail. Once they reach the human intestine, they migrate back to the bile duct, where they mature. The life cycle is similar for the other infectious liver flukes (see Figure 5.2.4).

When *Fasciola* flukes cause acute infection, signs and symptoms include nausea, vomiting, abdominal pain, rash, fever, malaise, and breathing difficulties. If the infection becomes chronic, with adult flukes living in the bile duct, then cholangitis, cirrhosis, pancreatitis, cholecystitis, and gallstones may develop. Symptoms are similar for infections by other liver flukes. Cholangiocarcinoma can occur from *C. sinensis* infection. The *Opisthorchis* species can also be associated with cancer development.

Diagnosis is accomplished using patient history and examination of samples from feces or other samples (such as vomitus). Because the eggs may appear similar, immunoassay techniques are available that can help distinguish species. The preferred treatment for fascioliasis is triclabendazole. *C. sinensis* and *Opisthorchis* spp. infections are treated with praziquantel or albendazole.

Intestinal Flukes

The intestinal flukes are trematodes that develop in the intestines. Many, such as *Fasciolopsis buski*, which causes fasciolopsiasis, are closely related to liver flukes. Intestinal flukes are ingested from contaminated aquatic plants that have not been properly cooked. When the cysts are consumed, the larvae emerge in the duodenum and develop into adults while attached to the intestinal epithelium. The eggs are released in stool.

Intestinal fluke infection is often asymptomatic, but some cases may involve mild diarrhea and abdominal pain. More severe symptoms such as vomiting, nausea, allergic reactions, and anemia can sometimes occur, and high parasite loads may sometimes lead to intestinal obstructions.

Diagnosis is the same as with liver flukes: examination of feces or other samples and immunoassay. Praziquantel is used to treat infections caused by intestinal flukes.

Exercise 10.2.6.5

How are flukes transmitted?

Helminthic Gastrointestinal Infections

Numerous helminths are capable of colonizing the GI tract. Many such infections are asymptomatic, but others may cause signs and symptoms ranging from mild GI stress to severe systemic infection. Helminths have complex and unique life cycles that dictate their specific modes of transmission. Most helminthic infections can be treated with medications.

Common Helminthic Infections of the GI Tract					
Disease	**Causative Agent(s)**	**Mode of Transmission**	**Laboratory Tests**	**Symptoms**	**Treatments**
Ascariasis	*Ascaris lumbricoides*	Eggs in fecally contaminated food or water	Microscopic examination of the stool, imaging	Shortness of breath, cough, nausea, diarrhea, blood in stool, abdominal pain, weight loss, fatigue	Self-limiting within 1 to 2 years; albendazole and mebendazole if needed
Hookworm	*Necator americanus, Ancyclostoma doudenale*	Larvae in soil contaminated by dog or cat feces penetrate skin	Microscopic examination of stool (may require a concentration procedure)	Cough, itchy rash, loss of appetite, abdominal pain, diarrhea; in children, may affect physical and cognitive growth	Albendazole and mebendazole; pyrantel pamoatemay if needed
Strongyloidiasis	*Strongyloides stercoralis*	Soil-dwelling larvae penetrate the skin, usually bare feet	Microscopic examination of stool over several days (ideally at least 7); some serologic testing available	Often asymptomatic; cough (sometimes bloody), skin rash, abdominal pain, and diarrhea; in immunosuppressed patients, may become disseminated, causing serious and potentially fatal complications	Ivermectin (preferred), albendazole
Enterobiasis (pinworm)	*Enterobius vermicularis*	Fecal–oral route	Observation of eggs or worms from anal area; examination of samples under fingernails	Itching around the anus, abdominal pain, insomnia, irritation of female genital tract	Mebendazole, albendazole, pyrantel pamoate
Trichiuriasis (whipworm)	*Trichuris trichiura*	Fecal contamination or fertilization in soil	Microscopic examination of stool	Abdominal pain, anemia, diarrhea that may be bloody	Albendazole, mebendazole, ivermectin if needed
Trichinosis	*Trichinella spiralis*	Eating raw or undercooked pork or other meat of infected animal	Clinical history, muscle biopsy, serological testing, enzyme immunoassay	Diarrhea, constipation, abdominal pain, headache, cough, chills, light sensitivity, muscle pain, fever, conjunctivitis; in severe cases may affect motor coordination, breathing, heart function	Albendazole, mebendazole if needed
Taeniasis and cysticercosis	*Taenia solium, T. saginata, T. asiatica, Diphyllobo-thrium latum*	Eating raw or undercooked beef or pork from infected animal	Observation of worm segments or microscopic eggs in stool samples	Asymptomatic or mild GI distress; cysts in muscle, eye, or brain (cysticercosis); brain cysts can cause headaches, seizures, or death	Praziquantel or niclosamide
Cystic echinococcosis (hydatid disease)	*Echinococcus granulosus* (cystic)	Exposure to eggs in feces of infected dogs or livestock	Imaging; serological testing including ELISA and indirect hemagglutinin test	Cysts in lungs, liver, and other organs causing nausea, GI distress, and weight loss; severe anaphylaxis or death if cysts burst	Surgical removal or aspiration of cysts or chemotherapy with albendazole or mebenazole
Liver fluke infections	*Fasciola hepatica, F. gigantica, Clonorchis sinensis, Opisthorchis viverrini, O. felineus*	Eating raw or undercooked aquatic plants (*Fasciola* spp.) or freshwater fish (*Clonorchis* spp.) contaminated with eggs or cysts	Microscopic examination of eggs in stool or other samples; immunoassays	Fever, malaise, anemia, abdominal symptoms, transaminitis; cholangitis, cirrhosis, pancreatitis, cholecystitis, gall stones in chronic phase	Triclabendazole (preferred) for *Fasciola* spp.; praziquantel and albendazole for *C. sinensis* and *Opisthorchis* spp.
Fasciolopiasis (intestinal fluke)	*Fasciola buski*	Eating raw or undercooked aquatic plants containing cysts	Microscopic examination of eggs in stool or other samples; immunoassays	Diarrhea, abdominal pain; in severe cases, vomiting, nausea, intestinal obstruction, anemia, allergic reactions	Praziquantel

Figure 10.2.6.8: Helminthic infections of the GI tract.

Helminthic Infections of the GI Tract (continued)					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Strongyloidiasis	*Strongyloides stercoralis*	Often asymptomatic; cough (sometimes bloody), skin rash, abdominal pain, diarrhea; in immunosuppressed patients, may become disseminated, causing serious and potentially fatal complications	Soil-dwelling larvae penetrate the skin, usually bare feet	Microscopic observation of larvae in stool; serological testing for antigens	Ivermectin, albendazole
Tapeworms (taeniasis)	*Taenia solium, T. saginata, T. asiatica, Diphyllobothrium latum*	Asymptomatic or mild GI distress; cysts in muscle, eye, or brain (cysticercosis); brain cysts can cause headaches, seizures, or death	Ingestion of raw or undercooked pork or beef from infected animal	Observation of worm segments or microscopic eggs in stool; CT or MRI to detect cysts	Praziquantel, niclosamide
Trichinosis	*Trichinella spiralis,* other *Trichinella* spp.	Diarrhea, constipation, abdominal pain, headache, cough, chills, light sensitivity, muscle pain, fever, conjunctivitis; in severe cases may affect motor coordination, breathing, heart function	Ingestion of raw or undercooked pork or other meat of infected animal	Observation of cysts in muscle biopsy, enzyme immunoassay	Albendazole, mebendazole
Whipworm (trichuriasis)	*Trichuris trichiura*	Abdominal pain, anemia, diarrhea (possibly bloody), rectal prolapse	Ingestion of eggs in fecally contaminated food	Microscopic observation of eggs in stool	Albendazole, mebendazole, ivermectin

Figure 10.2.6.9: Helminthic infections of the GI tract (continued).

Clinical Focus: Resolution

Carli's doctor explained that she had bacterial gastroenteritis caused by *Salmonella* bacteria. The source of these bacteria was likely the undercooked egg. Had the egg been fully cooked, the high temperature would have been sufficient to kill any *Salmonella* in or on the egg. In this case, enough bacteria survived to cause an infection once the egg was eaten.

Carli's signs and symptoms continued to worsen. Her fever became higher, her vomiting and diarrhea continued, and she began to become dehydrated. She felt thirsty all the time and had continual abdominal cramps. Carli's doctor treated her with intravenous fluids to help with her dehydration, but did not prescribe antibiotics. Carli's parents were confused because they thought a bacterial infection should always be treated with antibiotics.

The doctor explained that the worst medical problem for Carli was dehydration. Except in the most vulnerable and sick patients, such as those with HIV/AIDS, antibiotics do not reduce recovery time or improve outcomes in *Salmonella* infections. In fact, antibiotics can actually delay the natural excretion of bacteria from the body. Rehydration therapy replenishes lost fluids, diminishing the effects of dehydration and improving the patient's condition while the infection resolves.

After two days of rehydration therapy, Carli's signs and symptoms began to fade. She was still somewhat thirsty, but the amount of urine she passed became larger and the color lighter. She stopped vomiting. Her fever was gone, and so was the

diarrhea. At that point, stool analysis found very few *Salmonella* bacteria. In one week, Carli was discharged as fully recovered.

Key Concepts and Summary

- Helminths often cause intestinal infections after transmission to humans through exposure to contaminated soil, water, or food. Signs and symptoms are often mild, but severe complications may develop in some cases.
- *Ascaris lumbricoides* eggs are transmitted through contaminated food or water and hatch in the intestine. Juvenile larvae travel to the lungs and then to the pharynx, where they are swallowed and returned to the intestines to mature. These nematode roundworms cause **ascariasis**.
- *Necator americanus* and *Ancylostoma doudenale* cause **hookworm infection** when larvae penetrate the skin from soil contaminated by dog or cat feces. They travel to the lungs and are then swallowed to mature in the intestines.
- *Strongyloides stercoralis* are transmitted from soil through the skin to the lungs and then to the intestine where they cause **strongyloidiasis**.
- *Enterobius vermicularis* are nematode pinworms transmitted by the fecal-oral route. After ingestion, they travel to the colon where they cause **enterobiasis**.
- *Trichuris trichiura* can be transmitted through soil or fecal contamination and cause **trichuriasis**. After ingestion, the eggs travel to the intestine where the larvae emerge and mature, attaching to the walls of the colon and cecum.
- *Trichinella* spp. is transmitted through undercooked meat. Larvae in the meat emerge from cysts and mature in the large intestine. They can migrate to the muscles and form new cysts, causing **trichinosis**.
- *Taenia* spp. and *Diphyllobothrium latum* are tapeworms transmitted through undercooked food or the fecal-oral route. *Taenia* infections cause **taeniasis**. Tapeworms use their scolex to attach to the intestinal wall. Larvae may also move to muscle or brain tissue.
- *Echinococcus granulosus* is a cestode transmitted through eggs in the feces of infected animals, especially dogs. After ingestion, eggs hatch in the small intestine, and the larvae invade the intestinal wall and travel through the circulatory system to form dangerous cysts in internal organs, causing **hydatid disease**.
- Flukes are transmitted through aquatic plants or fish. **Liver flukes** cause disease by interfering with the bile duct. **Intestinal flukes** develop in the intestines, where they attach to the intestinal epithelium.

Footnotes

1. 1 Centers for Disease Control and Prevention. “Parasites–Ascariasis.” Updated May 24, 2016. http://www.cdc.gov/parasites/ascariasis/index.html.
2. 2 “Roundworms.” *University of Maryland Medical Center Medical Reference Guide*. Last reviewed December 9, 2014. https://umm.edu/health/medical/altme...ion/roundworms.
3. 3 Nancy Craig. “Fish Tapeworm and Sushi.” *Canadian Family Physician* 58 (2012) 6: pp. 654–658. www.ncbi.nlm.nih.gov/pmc/articles/PMC3374688/.
4. 4 Centers for Disease Control and Prevention. “Anisakiasis FAQs.” Updated November 12, 2012. http://www.cdc.gov/parasites/anisakiasis/faqs.html.

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10.2.E: Digestive System Infections (Exercises)

24.1: Anatomy and Normal Microbiota of the Digestive System

The human digestive system, or the gastrointestinal (GI) tract, begins with the mouth and ends with the anus. The parts of the mouth include the teeth, the gums, the tongue, the oral vestibule (the space between the gums, lips, and teeth), and the oral cavity proper (the space behind the teeth and gums). Other parts of the GI tract are the pharynx, esophagus, stomach, small intestine, large intestine, rectum, and anus.

Multiple Choice

Which of the following is NOT a way the normal microbiota of the intestine helps to prevent infection?

A. It produces acids that lower the pH of the stomach.
B. It speeds up the process by which microbes are flushed from the digestive tract.
C. It consumes food and occupies space, outcompeting potential pathogens.
D. It generates large quantities of oxygen that kill anaerobic pathogens.

Answer

D

What types of microbes live in the intestines?

A. Diverse species of bacteria, archaea, and fungi, especially *Bacteroides* and *Firmicutes* bacteria
B. A narrow range of bacteria, especially *Firmicutes*
C. A narrow range of bacteria and fungi, especially *Bacteroides*
D. Archaea and fungi only

Answer

A

Fill in the Blank

The part of the gastrointestinal tract with the largest natural microbiota is the _____.

Answer

Large intestine or colon

Short Answer

How does the diarrhea caused by dysentery differ from other types of diarrhea?

24.2: Microbial Diseases of the Mouth and Oral Cavity

Despite the presence of saliva and the mechanical forces of chewing and eating, some microbes thrive in the mouth. These microbes can cause damage to the teeth and can cause infections that have the potential to spread beyond the mouth and sometimes throughout the body.

Multiple Choice

What pathogen is the most important contributor to biofilms in plaque?

A. *Staphylococcus aureus*
B. *Streptococcus mutans*
C. *Escherichia coli*
D. *Clostridium difficile*

Answer

B

What type of organism causes thrush?

A. a bacterium
B. a virus
C. a fungus
D. a protozoan

Answer

C

In mumps, what glands swell to produce the disease's characteristic appearance?

A. the sublingual glands
B. the gastric glands
C. the parotid glands
D. the submandibular glands

Answer

C

Which of the following is true of HSV-1?

A. It causes oral thrush in immunocompromised patients.
B. Infection is generally self-limiting.
C. It is a bacterium.
D. It is usually treated with amoxicillin.

Answer

B

Fill in the Blank

When plaque becomes heavy and hardened, it is called dental calculus or _____.

Answer

tartar

Short Answer

Why do sugary foods promote dental caries?

24.3: Bacterial Infections of the Gastrointestinal Tract

Major causes of gastrointestinal illness include *Salmonella* spp., *Staphylococcus* spp., *Helicobacter pylori*, *Clostridium perfringens*, *Clostridium difficile*, *Bacillus cereus*, and *Yersinia* bacteria. *C. difficile* is an important cause of hospital acquired infection. *Vibrio cholerae* causes cholera, which can be a severe diarrheal illness. Different strains of *E. coli*, including ETEC, EPEC, EIEC, and EHEC, cause different illnesses with varying degrees of severity.

Multiple Choice

Which type of *E. coli* infection can be severe with life-threatening consequences such as hemolytic uremic syndrome?

A. ETEC
B. EPEC
C. EHEC
D. EIEC

Answer

C

Which species of *Shigella* has a type that produces Shiga toxin?

A. *S. boydii*
B. *S. flexneri*
C. *S. dysenteriae*
D. *S. sonnei*

Answer

C

Which type of bacterium produces an A-B toxin?

A. *Salmonella*
B. *Vibrio cholera*
C. ETEC
D. *Shigella dysenteriae*

Answer

B

Fill in the Blank

Antibiotic associated pseudomembranous colitis is caused by _____.

Answer

Clostridium difficile

Critical Thinking

Why does use of antibiotics and/or proton pump inhibitors contribute to the development of *C. difficile* infections?

Why did scientists initially think it was unlikely that a bacterium caused peptic ulcers?

Does it makes a difference in treatment to know if a particular illness is caused by a bacterium (an infection) or a toxin (an intoxication)?

24.4: Viral Infections of the Gastrointestinal Tract

Common viral causes of gastroenteritis include rotaviruses, noroviruses, and astroviruses. Hepatitis may be caused by several unrelated viruses: hepatitis viruses A, B, C, D, and E. The hepatitis viruses differ in their modes of transmission, treatment, and potential for chronic infection.

Multiple Choice

Which form of hepatitisvirus can only infect an individual who is already infected with another hepatitisvirus?

A. HDV
B. HAV
C. HBV
D. HEV

Answer

A

Which cause of viral gastroenteritis commonly causes projectile vomiting?

A. hepatitisvirus
B. Astroviruses
C. Rotavirus
D. Noroviruses

Answer

D

Fill in the Blank

Jaundice results from a buildup of _____.

Answer

bilirubin

Short Answer

Which forms of viral hepatitis are transmitted through the fecal-oral route?

Critical Thinking

Based on what you know about HBV, what are some ways that its transmission could be reduced in a health-care setting?

24.5: Protozoan Infections of the Gastrointestinal Tract

Like other microbes, protozoa are abundant in natural microbiota but can also be associated with significant illness. Gastrointestinal diseases caused by protozoa are generally associated with exposure to contaminated food and water, meaning that those without access to good sanitation are at greatest risk. Even in developed countries, infections can occur and these microbes have sometimes caused significant outbreaks from contamination of public water supplies.

Multiple Choice

Which protozoan is associated with the ability to cause severe dysentery?

A. *Giardia lamblia*
B. *Cryptosporidium hominis*
C. *Cyclospora cayetanesis*
D. *Entamoeba histolytica*

Answer

D

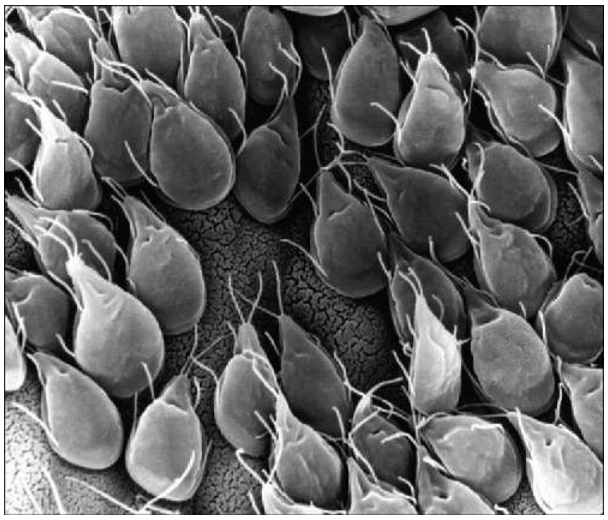
Which protozoan has a unique appearance, with a blue halo, when viewed using ultraviolet fluorescence microscopy?

A. *Giardia lamblia*
B. *Cryptosporidium hominis*
C. *Cyclospora cayetanesis*
D. *Entamoeba histolytica*

Answer

C

The micrograph shows protozoans attached to the intestinal wall of a gerbil. Based on what you know about protozoan intestinal parasites, what is it?



(credit: Dr. Stan Erlandsen, Centers for Disease Control and Prevention)

A. *Giardia lamblia*
B. *Cryptosporidium hominis*
C. *Cyclospora cayetanesis*
D. *Entamoeba histolytica*

Fill in the Blank

Chronic _____ infections cause the unique sign of disease of greasy stool and are often resistant to treatment.

Answer

giardia

Short Answer

What is an O&P exam?

24.6: Helminthic Infections of the Gastrointestinal Tract

Helminths are widespread intestinal parasites. These parasites can be divided into three common groups: round-bodied worms also described as nematodes, flat-bodied worms that are segmented (also described as cestodes), and flat-bodied worms that are non-segmented (also described as trematodes). The nematodes include roundworms, pinworms, hookworms, and whipworms. Many of these parasites are so well adapted to the human host that there is little obvious disease.

Multiple Choice

What is another name for *Trichuris trichiura*?

A. pinworm
B. whipworm
C. hookworm
D. ascariasis

Answer

B

Which type of helminth infection can be diagnosed using tape?

A. pinworm
B. whipworm

C. hookworm
D. tapeworm

Answer

A

Fill in the Blank

Liver flukes are often found in the _____ duct.

Answer

bile

Short Answer

Why does the coughing up of worms play an important part in the life cycle of some helminths, such as the roundworm *Ascaris lumbricoides*?

Critical Thinking

Cases of strongyloidiasis are often more severe in patients who are using corticosteroids to treat another disorder. Explain why this might occur.

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SECTION OVERVIEW

10.3: The Respiratory System

Breathing is an involuntary event. How often a breath is taken and how much air is inhaled or exhaled are tightly regulated by the respiratory center in the brain. Humans, when they aren't exerting themselves, breathe approximately 15 times per minute on average. Canines have a respiratory rate of about 15–30 breaths per minute. With every inhalation, air fills the lungs, and with every exhalation, air rushes back out. That air is doing more than just inflating and deflating the lungs in the chest cavity. The air contains oxygen that crosses the lung tissue, enters the bloodstream, and travels to organs and tissues.

10.3.1: Prelude to the Respiratory System

10.3.2: Systems of Gas Exchange

10.3.3: Gas Exchange across Respiratory Surfaces

10.3.4: Breathing

10.3.5: Transport of Gases in Human Bodily Fluids

10.3.E: The Respiratory System (Exercises)

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10.3.1: Prelude to the Respiratory System

Breathing is an involuntary event. How often a breath is taken and how much air is inhaled or exhaled are tightly regulated by the respiratory center in the brain. Humans, when they aren't exerting themselves, breathe approximately 15 times per minute on average. Canines have a respiratory rate of about 15–30 breaths per minute. With every inhalation, air fills the lungs, and with every exhalation, air rushes back out. That air is doing more than just inflating and deflating the lungs in the chest cavity. The air contains oxygen that crosses the lung tissue, enters the bloodstream, and travels to organs and tissues. Oxygen (O_2) enters the cells where it is used for metabolic reactions that produce ATP, a high-energy compound. At the same time, these reactions release carbon dioxide (CO_2) as a by-product. CO_2 is toxic and must be eliminated. Carbon dioxide exits the cells, enters the bloodstream, travels back to the lungs, and is expired out of the body during exhalation.



Figure 10.3.1.1: Lungs, which appear as nearly transparent tissue surrounding the heart in this X-ray of a dog (left), are the central organs of the respiratory system. The left lung is smaller than the right lung to accommodate space for the heart. A dog's nose (right) has a slit on the side of each nostril. When tracking a scent, the slits open, blocking the front of the nostrils. This allows the dog to exhale though the now-open area on the side of the nostrils without losing the scent that is being followed. (credit a: modification of work by Geoff Stearns; credit b: modification of work by Cory Zanker)

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10.3.2: Systems of Gas Exchange

Skills to Develop

- Describe the passage of air from the outside environment to the lungs
- Explain how the lungs are protected from particulate matter

The primary function of the respiratory system is to deliver oxygen to the cells of the body's tissues and remove carbon dioxide, a cell waste product. The main structures of the human respiratory system are the nasal cavity, the trachea, and lungs.

All aerobic organisms require oxygen to carry out their metabolic functions. Along the evolutionary tree, different organisms have devised different means of obtaining oxygen from the surrounding atmosphere. The environment in which the animal lives greatly determines how an animal respires. The complexity of the respiratory system is correlated with the size of the organism. As animal size increases, diffusion distances increase and the ratio of surface area to volume drops. In unicellular organisms, diffusion across the cell membrane is sufficient for supplying oxygen to the cell (Figure 10.3.2.1). Diffusion is a slow, passive transport process. In order for diffusion to be a feasible means of providing oxygen to the cell, the rate of oxygen uptake must match the rate of diffusion across the membrane. In other words, if the cell were very large or thick, diffusion would not be able to provide oxygen quickly enough to the inside of the cell. Therefore, dependence on diffusion as a means of obtaining oxygen and removing carbon dioxide remains feasible only for small organisms or those with highly-flattened bodies, such as many flatworms (Platyhelminthes). Larger organisms had to evolve specialized respiratory tissues, such as gills, lungs, and respiratory passages accompanied by complex circulatory systems, to transport oxygen throughout their entire body.



Figure 10.3.2.1: The cell of the unicellular algae *Ventricaria ventricosa* is one of the largest known, reaching one to five centimeters in diameter. Like all single-celled organisms, *V. ventricosa* exchanges gases across the cell membrane.

Direct Diffusion

For small multicellular organisms, diffusion across the outer membrane is sufficient to meet their oxygen needs. Gas exchange by direct diffusion across surface membranes is efficient for organisms less than 1 mm in diameter. In simple organisms, such as cnidarians and flatworms, every cell in the body is close to the external environment. Their cells are kept moist and gases diffuse quickly via direct diffusion. Flatworms are small, literally flat worms, which 'breathe' through diffusion across the outer membrane (Figure 10.3.2.2). The flat shape of these organisms increases the surface area for diffusion, ensuring that each cell within the body is close to the outer membrane surface and has access to oxygen. If the flatworm had a cylindrical body, then the cells in the center would not be able to get oxygen.



Figure 10.3.2.2: This flatworm's process of respiration works by diffusion across the outer membrane. (credit: Stephen Childs)

Skin and Gills

Earthworms and amphibians use their skin (integument) as a respiratory organ. A dense network of capillaries lies just below the skin and facilitates gas exchange between the external environment and the circulatory system. The respiratory surface must be kept moist in order for the gases to dissolve and diffuse across cell membranes.

Organisms that live in water need to obtain oxygen from the water. Oxygen dissolves in water but at a lower concentration than in the atmosphere. The atmosphere has roughly 21 percent oxygen. In water, the oxygen concentration is much smaller than that. Fish and many other aquatic organisms have evolved gills to take up the dissolved oxygen from water (Figure 10.3.2.3). Gills are thin tissue filaments that are highly branched and folded. When water passes over the gills, the dissolved oxygen in water rapidly diffuses across the gills into the bloodstream. The circulatory system can then carry the oxygenated blood to the other parts of the body. In animals that contain coelomic fluid instead of blood, oxygen diffuses across the gill surfaces into the coelomic fluid. Gills are found in mollusks, annelids, and crustaceans.



Figure 10.3.2.3: This common carp, like many other aquatic organisms, has gills that allow it to obtain oxygen from water. (credit: "Guitardude012"/Wikimedia Commons)

The folded surfaces of the gills provide a large surface area to ensure that the fish gets sufficient oxygen. Diffusion is a process in which material travels from regions of high concentration to low concentration until equilibrium is reached. In this case, blood with a low concentration of oxygen molecules circulates through the gills. The concentration of oxygen molecules in water is higher than the concentration of oxygen molecules in gills. As a result, oxygen molecules diffuse from water (high concentration) to blood (low concentration), as shown in Figure 10.3.2.4. Similarly, carbon dioxide molecules in the blood diffuse from the blood (high concentration) to water (low concentration).

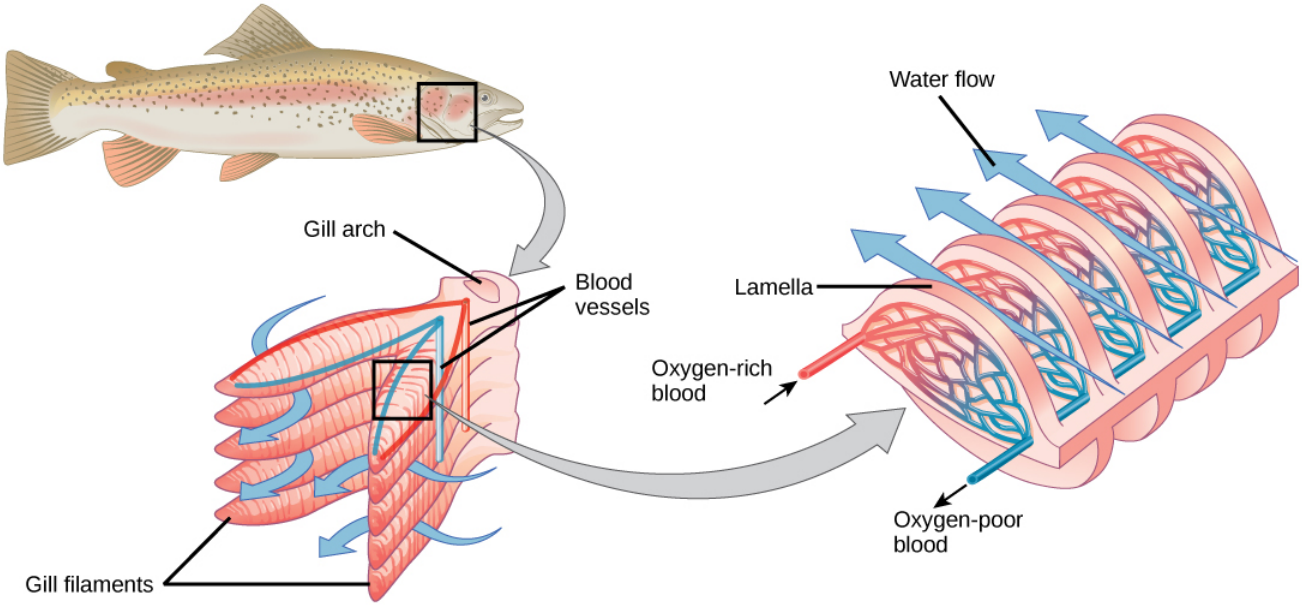


Figure 10.3.2.4: As water flows over the gills, oxygen is transferred to blood via the veins. (credit "fish": modification of work by Duane Raver, NOAA)

Tracheal Systems

Insect respiration is independent of its circulatory system; therefore, the blood does not play a direct role in oxygen transport. Insects have a highly specialized type of respiratory system called the tracheal system, which consists of a network of small tubes that carries oxygen to the entire body. The tracheal system is the most direct and efficient respiratory system in active animals. The tubes in the tracheal system are made of a polymeric material called chitin.

Insect bodies have openings, called spiracles, along the thorax and abdomen. These openings connect to the tubular network, allowing oxygen to pass into the body (Figure 10.3.2.5) and regulating the diffusion of CO_2 and water vapor. Air enters and leaves the tracheal system through the spiracles. Some insects can ventilate the tracheal system with body movements.

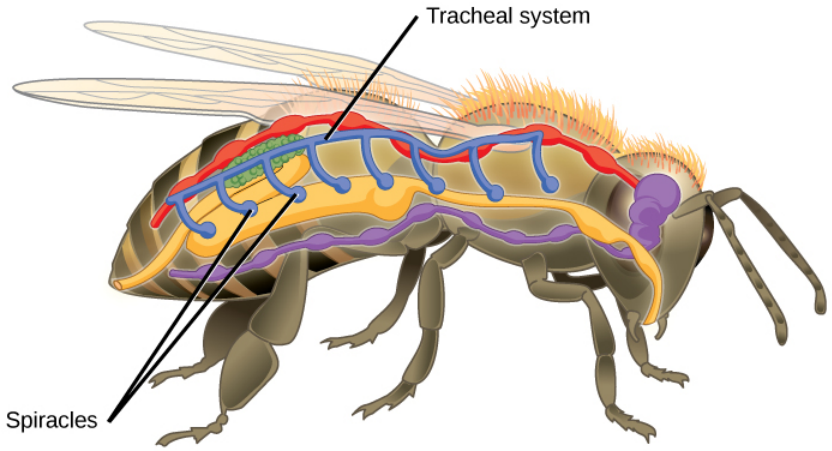


Figure 10.3.2.5: Insects perform respiration via a tracheal system.

Mammalian Systems

In mammals, pulmonary ventilation occurs via inhalation (breathing). During inhalation, air enters the body through the nasal cavity located just inside the nose (Figure 10.3.2.6). As air passes through the nasal cavity, the air is warmed to body temperature and humidified. The respiratory tract is coated with mucus to seal the tissues from direct contact with air. Mucus is high in water. As air crosses these surfaces of the mucous membranes, it picks up water. These processes help equilibrate the air to the body conditions, reducing any damage that cold, dry air can cause. Particulate matter that is floating in the air is removed in the nasal passages via mucus and cilia. The processes of warming, humidifying, and removing particles are important protective mechanisms

that prevent damage to the trachea and lungs. Thus, inhalation serves several purposes in addition to bringing oxygen into the respiratory system.

Art Connection

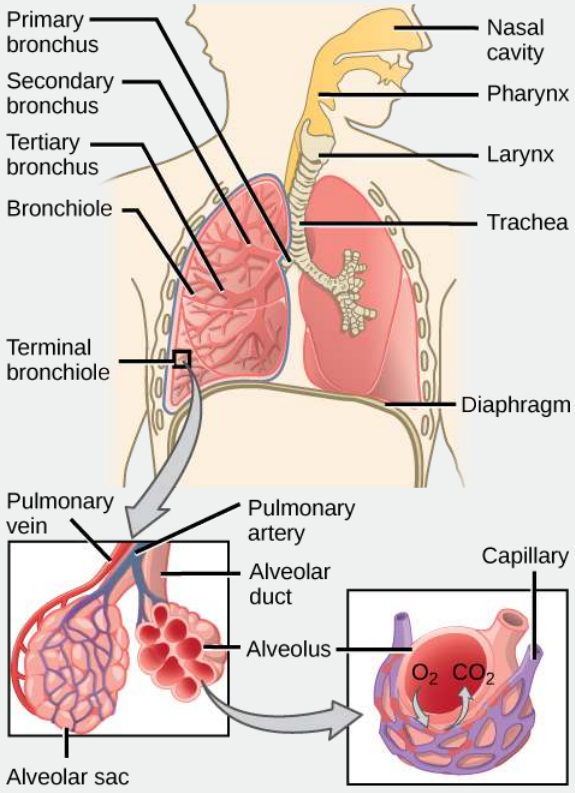


Figure 10.3.2.6: Air enters the respiratory system through the nasal cavity and pharynx, and then passes through the trachea and into the bronchi, which bring air into the lungs. (credit: modification of work by NCI)

Which of the following statements about the mammalian respiratory system is false?

A. When we breathe in, air travels from the pharynx to the trachea.
B. The bronchioles branch into bronchi.
C. Alveolar ducts connect to alveolar sacs.
D. Gas exchange between the lung and blood takes place in the alveolus.

From the nasal cavity, air passes through the pharynx (throat) and the larynx (voice box), as it makes its way to the trachea (Figure 10.3.2.6). The main function of the trachea is to funnel the inhaled air to the lungs and the exhaled air back out of the body. The human trachea is a cylinder about 10 to 12 cm long and 2 cm in diameter that sits in front of the esophagus and extends from the larynx into the chest cavity where it divides into the two primary bronchi at the midthorax. It is made of incomplete rings of hyaline cartilage and smooth muscle (Figure 10.3.2.7). The trachea is lined with mucus-producing goblet cells and ciliated epithelia. The cilia propel foreign particles trapped in the mucus toward the pharynx. The cartilage provides strength and support to the trachea to keep the passage open. The smooth muscle can contract, decreasing the trachea's diameter, which causes expired air to rush upwards from the lungs at a great force. The forced exhalation helps expel mucus when we cough. Smooth muscle can contract or relax, depending on stimuli from the external environment or the body's nervous system.

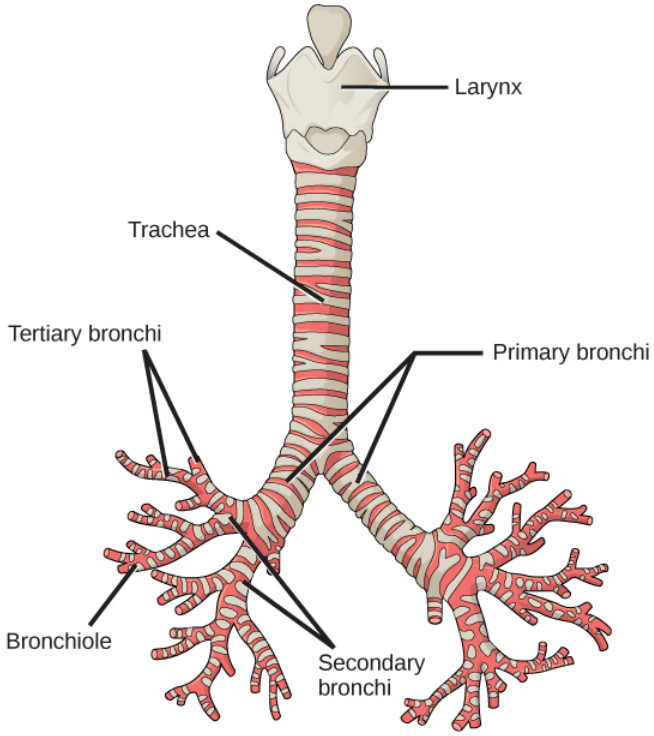


Figure 10.3.2.7: The trachea and bronchi are made of incomplete rings of cartilage. (credit: modification of work by Gray's Anatomy)

Lungs: Bronchi and Alveoli

The end of the trachea bifurcates (divides) to the right and left lungs. The lungs are not identical. The right lung is larger and contains three lobes, whereas the smaller left lung contains two lobes (Figure 10.3.2.8). The muscular diaphragm, which facilitates breathing, is inferior to (below) the lungs and marks the end of the thoracic cavity.

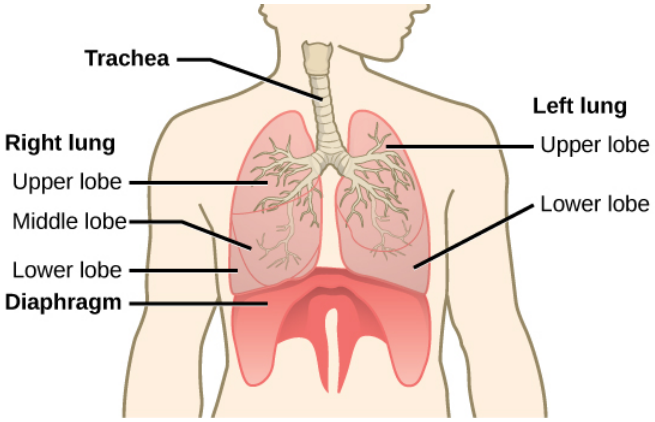


Figure 10.3.2.8: The trachea bifurcates into the right and left bronchi in the lungs. The right lung is made of three lobes and is larger. To accommodate the heart, the left lung is smaller and has only two lobes.

In the lungs, air is diverted into smaller and smaller passages, or bronchi. Air enters the lungs through the two primary (main) bronchi (singular: bronchus). Each bronchus divides into secondary bronchi, then into tertiary bronchi, which in turn divide, creating smaller and smaller diameter bronchioles as they split and spread through the lung. Like the trachea, the bronchi are made of cartilage and smooth muscle. At the bronchioles, the cartilage is replaced with elastic fibers. Bronchi are innervated by nerves of both the parasympathetic and sympathetic nervous systems that control muscle contraction (parasympathetic) or relaxation (sympathetic) in the bronchi and bronchioles, depending on the nervous system's cues. In humans, bronchioles with a diameter smaller than 0.5 mm are the respiratory bronchioles. They lack cartilage and therefore rely on inhaled air to support their shape. As the passageways decrease in diameter, the relative amount of smooth muscle increases.

The terminal bronchioles subdivide into microscopic branches called respiratory bronchioles. The respiratory bronchioles subdivide into several alveolar ducts. Numerous alveoli and alveolar sacs surround the alveolar ducts. The alveolar sacs resemble bunches of grapes tethered to the end of the bronchioles (Figure 10.3.2.9). In the acinar region, the alveolar ducts are attached to the end of each bronchiole. At the end of each duct are approximately 100 alveolar sacs, each containing 20 to 30 alveoli that are 200 to 300 microns in diameter. Gas exchange occurs only in alveoli. Alveoli are made of thin-walled parenchymal cells, typically one-cell thick, that look like tiny bubbles within the sacs. Alveoli are in direct contact with capillaries (one-cell thick) of the circulatory system. Such intimate contact ensures that oxygen will diffuse from alveoli into the blood and be distributed to the cells of the body. In addition, the carbon dioxide that was produced by cells as a waste product will diffuse from the blood into alveoli to be exhaled. The anatomical arrangement of capillaries and alveoli emphasizes the structural and functional relationship of the respiratory and circulatory systems. Because there are so many alveoli (~300 million per lung) within each alveolar sac and so many sacs at the end of each alveolar duct, the lungs have a sponge-like consistency. This organization produces a very large surface area that is available for gas exchange. The surface area of alveoli in the lungs is approximately 75 m^2. This large surface area, combined with the thin-walled nature of the alveolar parenchymal cells, allows gases to easily diffuse across the cells.

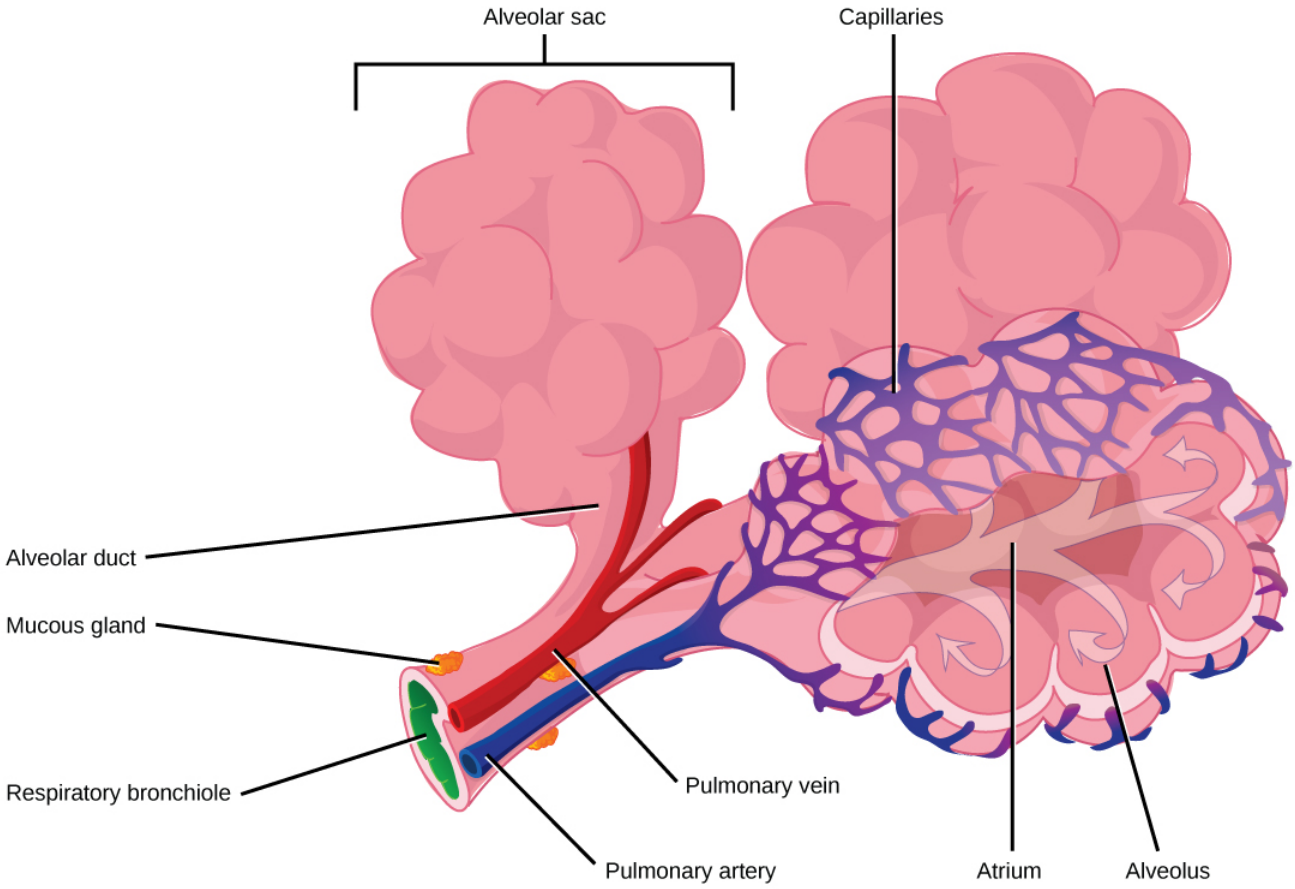
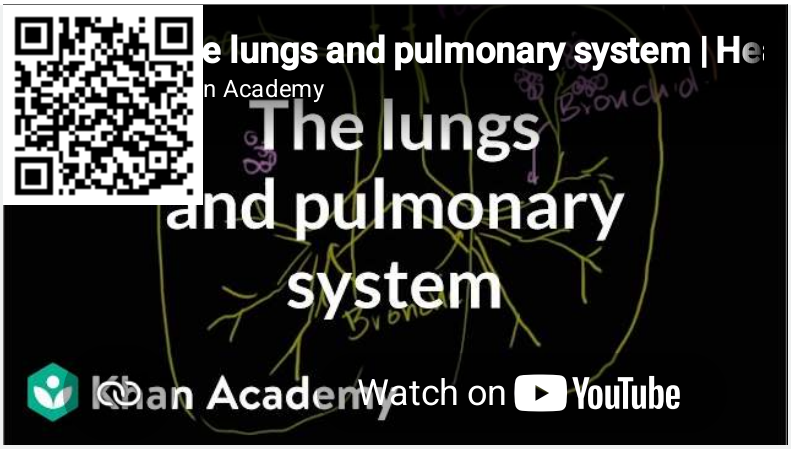


Figure 10.3.2.9: Terminal bronchioles are connected by respiratory bronchioles to alveolar ducts and alveolar sacs. Each alveolar sac contains 20 to 30 spherical alveoli and has the appearance of a bunch of grapes. Air flows into the atrium of the alveolar sac, then circulates into alveoli where gas exchange occurs with the capillaries. Mucous glands secrete mucous into the airways, keeping them moist and flexible. (credit: modification of work by Mariana Ruiz Villareal)

Link to Learning



Watch the following video to review the respiratory system.

Protective Mechanisms

The air that organisms breathe contains particulate matter such as dust, dirt, viral particles, and bacteria that can damage the lungs or trigger allergic immune responses. The respiratory system contains several protective mechanisms to avoid problems or tissue damage. In the nasal cavity, hairs and mucus trap small particles, viruses, bacteria, dust, and dirt to prevent their entry.

If particulates do make it beyond the nose, or enter through the mouth, the bronchi and bronchioles of the lungs also contain several protective devices. The lungs produce mucus—a sticky substance made of mucin, a complex glycoprotein, as well as salts and water—that traps particulates. The bronchi and bronchioles contain cilia, small hair-like projections that line the walls of the bronchi and bronchioles (Figure 10.3.2.10). These cilia beat in unison and move mucus and particles out of the bronchi and bronchioles back up to the throat where it is swallowed and eliminated via the esophagus.

In humans, for example, tar and other substances in cigarette smoke destroy or paralyze the cilia, making the removal of particles more difficult. In addition, smoking causes the lungs to produce more mucus, which the damaged cilia are not able to move. This causes a persistent cough, as the lungs try to rid themselves of particulate matter, and makes smokers more susceptible to respiratory ailments.

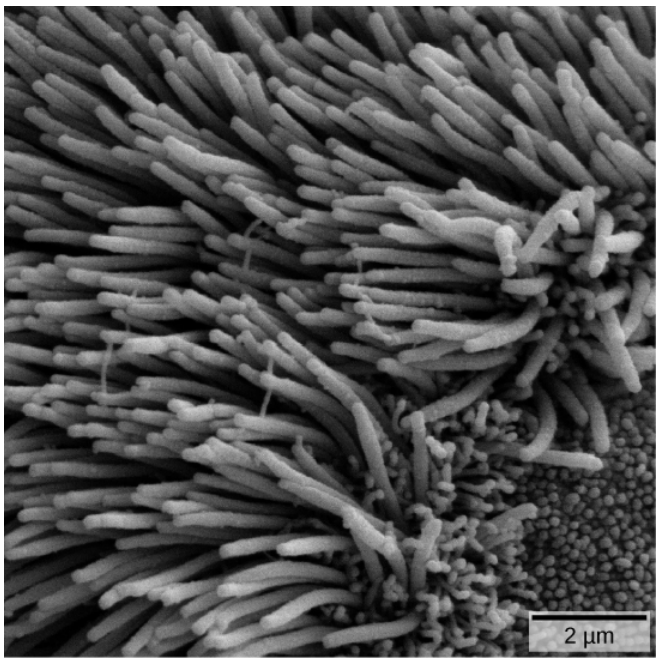


Figure 10.3.2.10: The bronchi and bronchioles contain cilia that help move mucus and other particles out of the lungs. (credit: Louisa Howard, modification of work by Dartmouth Electron Microscope Facility)

Summary

Animal respiratory systems are designed to facilitate gas exchange. In mammals, air is warmed and humidified in the nasal cavity. Air then travels down the pharynx, through the trachea, and into the lungs. In the lungs, air passes through the branching bronchi, reaching the respiratory bronchioles, which house the first site of gas exchange. The respiratory bronchioles open into the alveolar ducts, alveolar sacs, and alveoli. Because there are so many alveoli and alveolar sacs in the lung, the surface area for gas exchange is very large. Several protective mechanisms are in place to prevent damage or infection. These include the hair and mucus in the nasal cavity that trap dust, dirt, and other particulate matter before they can enter the system. In the lungs, particles are trapped in a mucus layer and transported via cilia up to the esophageal opening at the top of the trachea to be swallowed.

Art Connections

Figure 10.3.2.6: Which of the following statements about the mammalian respiratory system is false?

A. When we breathe in, air travels from the pharynx to the trachea.
B. The bronchioles branch into bronchi.
C. Alveolar ducts connect to alveolar sacs.
D. Gas exchange between the lung and blood takes place in the alveolus.

Answer

B

Glossary

alveolar duct
duct that extends from the terminal bronchiole to the alveolar sac

alveolar sac
structure consisting of two or more alveoli that share a common opening

alveolus
(plural: alveoli) (also, air sac) terminal region of the lung where gas exchange occurs

bronchus
(plural: bronchi) smaller branch of cartilaginous tissue that stems off of the trachea; air is funneled through the bronchi to the region where gas exchange occurs in alveoli

bronchiole
airway that extends from the main tertiary bronchi to the alveolar sac

diaphragm
domed-shaped skeletal muscle located under lungs that separates the thoracic cavity from the abdominal cavity

larynx
voice box, a short passageway connecting the pharynx and the trachea

mucin
complex glycoprotein found in mucus

mucus
sticky protein-containing fluid secretion in the lung that traps particulate matter to be expelled from the body

nasal cavity
opening of the respiratory system to the outside environment

particulate matter

small particle such as dust, dirt, viral particles, and bacteria that are in the air

pharynx

throat; a tube that starts in the internal nares and runs partway down the neck, where it opens into the esophagus and the larynx

primary bronchus

(also, main bronchus) region of the airway within the lung that attaches to the trachea and bifurcates to each lung where it branches into secondary bronchi

respiratory bronchiole

terminal portion of the bronchiole tree that is attached to the terminal bronchioles and alveoli ducts, alveolar sacs, and alveoli

terminal bronchiole

region of bronchiole that attaches to the respiratory bronchioles

trachea

cartilaginous tube that transports air from the larynx to the primary bronchi

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10.3.3: Gas Exchange across Respiratory Surfaces

Skills to Develop

- Name and describe lung volumes and capacities
- Understand how gas pressure influences how gases move into and out of the body

The structure of the lung maximizes its surface area to increase gas diffusion. Because of the enormous number of alveoli (approximately 300 million in each human lung), the surface area of the lung is very large (75 m^2). Having such a large surface area increases the amount of gas that can diffuse into and out of the lungs.

Basic Principles of Gas Exchange

Gas exchange during respiration occurs primarily through diffusion. Diffusion is a process in which transport is driven by a concentration gradient. Gas molecules move from a region of high concentration to a region of low concentration. Blood that is low in oxygen concentration and high in carbon dioxide concentration undergoes gas exchange with air in the lungs. The air in the lungs has a higher concentration of oxygen than that of oxygen-depleted blood and a lower concentration of carbon dioxide. This concentration gradient allows for gas exchange during respiration.

Partial pressure is a measure of the concentration of the individual components in a mixture of gases. The total pressure exerted by the mixture is the sum of the partial pressures of the components in the mixture. The rate of diffusion of a gas is proportional to its partial pressure within the total gas mixture. This concept is discussed further in detail below.

Lung Volumes and Capacities

Different animals have different lung capacities based on their activities. Cheetahs have evolved a much higher lung capacity than humans; it helps provide oxygen to all the muscles in the body and allows them to run very fast. Elephants also have a high lung capacity. In this case, it is not because they run fast but because they have a large body and must be able to take up oxygen in accordance with their body size.

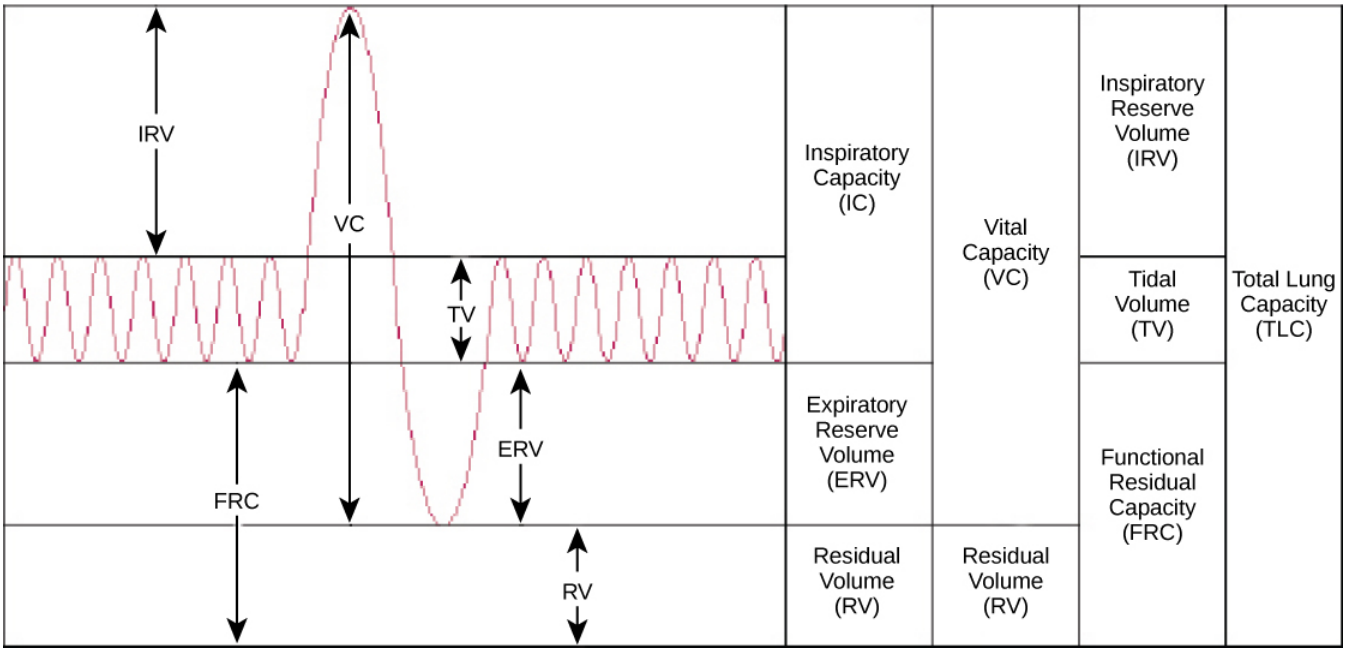


Figure 10.3.3.1: Human lung volumes and capacities are shown. The total lung capacity of the adult male is six liters. Tidal volume is the volume of air inhaled in a single, normal breath. Inspiratory capacity is the amount of air taken in during a deep breath, and residual volume is the amount of air left in the lungs after forceful respiration.

Human lung size is determined by genetics, gender, and height. At maximal capacity, an average lung can hold almost six liters of air, but lungs do not usually operate at maximal capacity. Air in the lungs is measured in terms of lung volumes and lung capacities

(Figure 10.3.3.1 and Table 10.3.3.1). Volume measures the amount of air for one function (such as inhalation or exhalation). Capacity is any two or more volumes (for example, how much can be inhaled from the end of a maximal exhalation).

Table 10.3.3.1**:** Lung Volumes and Capacities (Avg Adult Male)

Volume/Capacity	Definition	Volume (liters)	Equations
Tidal volume (TV)	Amount of air inhaled during a normal breath	0.5	-
Expiratory reserve volume (ERV)	Amount of air that can be exhaled after a normal exhalation	1.2	-
Inspiratory reserve volume (IRV)	Amount of air that can be further inhaled after a normal inhalation	3.1	-
Residual volume (RV)	Air left in the lungs after a forced exhalation	1.2	-
Vital capacity (VC)	Maximum amount of air that can be moved in or out of the lungs in a single respiratory cycle	4.8	ERV+TV+IRV
Inspiratory capacity (IC)	Volume of air that can be inhaled in addition to a normal exhalation	3.6	TV+IRV
Functional residual capacity (FRC)	Volume of air remaining after a normal exhalation	2.4	ERV+RV
Total lung capacity (TLC)	Total volume of air in the lungs after a maximal inspiration	6.0	RV+ERV+TV+IRV
Forced expiratory volume (FEV1)	How much air can be forced out of the lungs over a specific time period, usually one second	~4.1 to 5.5	-

The volume in the lung can be divided into four units: tidal volume, expiratory reserve volume, inspiratory reserve volume, and residual volume. Tidal volume (TV) measures the amount of air that is inspired and expired during a normal breath. On average, this volume is around one-half liter, which is a little less than the capacity of a 20-ounce drink bottle. The expiratory reserve volume (ERV) is the additional amount of air that can be exhaled after a normal exhalation. It is the reserve amount that can be exhaled beyond what is normal. Conversely, the inspiratory reserve volume (IRV) is the additional amount of air that can be inhaled after a normal inhalation. The residual volume (RV) is the amount of air that is left after expiratory reserve volume is exhaled. The lungs are never completely empty: There is always some air left in the lungs after a maximal exhalation. If this residual volume did not exist and the lungs emptied completely, the lung tissues would stick together and the energy necessary to re-inflate the lung could be too great to overcome. Therefore, there is always some air remaining in the lungs. Residual volume is also important for preventing large fluctuations in respiratory gases (O_2 and CO_2). The residual volume is the only lung volume that cannot be measured directly because it is impossible to completely empty the lung of air. This volume can only be calculated rather than measured.

Capacities are measurements of two or more volumes. The vital capacity (VC) measures the maximum amount of air that can be inhaled or exhaled during a respiratory cycle. It is the sum of the expiratory reserve volume, tidal volume, and inspiratory reserve volume. The inspiratory capacity (IC) is the amount of air that can be inhaled after the end of a normal expiration. It is, therefore, the sum of the tidal volume and inspiratory reserve volume. The functional residual capacity (FRC) includes the expiratory reserve

volume and the residual volume. The FRC measures the amount of additional air that can be exhaled after a normal exhalation. Lastly, the total lung capacity (TLC) is a measurement of the total amount of air that the lung can hold. It is the sum of the residual volume, expiratory reserve volume, tidal volume, and inspiratory reserve volume.

Lung volumes are measured by a technique called spirometry. An important measurement taken during spirometry is the forced expiratory volume (FEV), which measures how much air can be forced out of the lung over a specific period, usually one second (FEV1). In addition, the forced vital capacity (FVC), which is the total amount of air that can be forcibly exhaled, is measured. The ratio of these values (FEV1/FVC ratio) is used to diagnose lung diseases including asthma, emphysema, and fibrosis. If the FEV1/FVC ratio is high, the lungs are not compliant (meaning they are stiff and unable to bend properly), and the patient most likely has lung fibrosis. Patients exhale most of the lung volume very quickly. Conversely, when the FEV1/FVC ratio is low, there is resistance in the lung that is characteristic of asthma. In this instance, it is hard for the patient to get the air out of his or her lungs, and it takes a long time to reach the maximal exhalation volume. In either case, breathing is difficult and complications arise.

Career Connection: Respiratory Therapist

Respiratory therapists or respiratory practitioners evaluate and treat patients with lung and cardiovascular diseases. They work as part of a medical team to develop treatment plans for patients. Respiratory therapists may treat premature babies with underdeveloped lungs, patients with chronic conditions such as asthma, or older patients suffering from lung disease such as emphysema and chronic obstructive pulmonary disease (COPD). They may operate advanced equipment such as compressed gas delivery systems, ventilators, blood gas analyzers, and resuscitators. Specialized programs to become a respiratory therapist generally lead to a bachelor's degree with a respiratory therapist specialty. Because of a growing aging population, career opportunities as a respiratory therapist are expected to remain strong.

Gas Pressure and Respiration

The respiratory process can be better understood by examining the properties of gases. Gases move freely, but gas particles are constantly hitting the walls of their vessel, thereby producing gas pressure.

Air is a mixture of gases, primarily nitrogen (N_2; 78.6 percent), oxygen (O_2; 20.9 percent), water vapor (H_2O; 0.5 percent), and carbon dioxide (CO_2; 0.04 percent). Each gas component of that mixture exerts a pressure. The pressure for an individual gas in the mixture is the partial pressure of that gas. Approximately 21 percent of atmospheric gas is oxygen. Carbon dioxide, however, is found in relatively small amounts, 0.04 percent. The partial pressure for oxygen is much greater than that of carbon dioxide. The partial pressure of any gas can be calculated by:

$$\mathrm{P} = (\mathrm{P}_{\mathrm{atm}}) * (\text{percent content in mixture})$$

P_{atm}, the atmospheric pressure, is the sum of all of the partial pressures of the atmospheric gases added together,

$$\mathrm{P}_{\mathrm{atm}} = \mathrm{P}_{\mathrm{N}_2} + \mathrm{P}_{\mathrm{O}_2} + \mathrm{P}_{\mathrm{H}_2\mathrm{O}} + \mathrm{P}_{\mathrm{CO}_2} = 760 \text{ mm Hg}$$

× (percent content in mixture).

The pressure of the atmosphere at sea level is 760 mm Hg. Therefore, the partial pressure of oxygen is:

$$\mathrm{P}_{\mathrm{O}_2} = (760 \text{ mm Hg})(0.21) = 160 \text{ mm Hg}$$

and for carbon dioxide:

$$\mathrm{P}_{\mathrm{CO}_2} = (760 \text{ mm Hg})(0.0004) = 0.3 \text{ mm Hg}$$

At high altitudes, P_{atm} decreases but concentration does not change; the partial pressure decrease is due to the reduction in P_{atm}.

When the air mixture reaches the lung, it has been humidified. The pressure of the water vapor in the lung does not change the pressure of the air, but it must be included in the partial pressure equation. For this calculation, the water pressure (47 mm Hg) is subtracted from the atmospheric pressure:

$$760 \text{ mm Hg} - 47 \text{ mm Hg} = 713 \text{ mm Hg}$$

and the partial pressure of oxygen is:

$$(760 \text{ mm Hg} - 47 \text{ mm Hg})(0.21) = 150 \text{ mm Hg}$$

These pressures determine the gas exchange, or the flow of gas, in the system. Oxygen and carbon dioxide will flow according to their pressure gradient from high to low. Therefore, understanding the partial pressure of each gas will aid in understanding how gases move in the respiratory system.

Gas Exchange across the Alveoli

In the body, oxygen is used by cells of the body's tissues and carbon dioxide is produced as a waste product. The ratio of carbon dioxide production to oxygen consumption is the respiratory quotient (RQ). RQ varies between 0.7 and 1.0. If just glucose were used to fuel the body, the RQ would equal one. One mole of carbon dioxide would be produced for every mole of oxygen consumed. Glucose, however, is not the only fuel for the body. Protein and fat are also used as fuels for the body. Because of this, less carbon dioxide is produced than oxygen is consumed and the RQ is, on average, about 0.7 for fat and about 0.8 for protein.

The RQ is used to calculate the partial pressure of oxygen in the alveolar spaces within the lung, the alveolar P_{O_2}. Above, the partial pressure of oxygen in the lungs was calculated to be 150 mm Hg. However, lungs never fully deflate with an exhalation; therefore, the inspired air mixes with this residual air and lowers the partial pressure of oxygen within the alveoli. This means that there is a lower concentration of oxygen in the lungs than is found in the air outside the body. Knowing the RQ, the partial pressure of oxygen in the alveoli can be calculated:

$$\text{alveolar } P_{O_2} = \text{inspired } P_{O_2} - \frac{\text{alveolar } P_{O_2}}{\text{RQ}}$$

With an RQ of 0.8 and a P_{CO_2} in the alveoli of 40 mm Hg, the alveolar P_{O_2} is equal to:

$$\text{alveolar } P_{O_2} = 150 \text{ mm Hg} - \frac{40 \text{ mm Hg}}{0.8} = \text{mm Hg}$$

Notice that this pressure is less than the external air. Therefore, the oxygen will flow from the inspired air in the lung (P_{O_2} = 150 mm Hg) into the bloodstream (P_{O_2} = 100 mm Hg) (Figure 10.3.3.2).

In the lungs, oxygen diffuses out of the alveoli and into the capillaries surrounding the alveoli. Oxygen (about 98 percent) binds reversibly to the respiratory pigment hemoglobin found in red blood cells (RBCs). RBCs carry oxygen to the tissues where oxygen dissociates from the hemoglobin and diffuses into the cells of the tissues. More specifically, alveolar P_{O_2} is higher in the alveoli P_{ALVO_2} = 100 mm Hg) than blood P_{O_2} (40 mm Hg) in the capillaries. Because this pressure gradient exists, oxygen diffuses down its pressure gradient, moving out of the alveoli and entering the blood of the capillaries where O_2 binds to hemoglobin. At the same time, alveolar P_{CO_2} is lower P_{ALVO_2} = 40 mm Hg than blood P_{CO_2} = (45 mm Hg). CO_2 diffuses down its pressure gradient, moving out of the capillaries and entering the alveoli.

Oxygen and carbon dioxide move independently of each other; they diffuse down their own pressure gradients. As blood leaves the lungs through the pulmonary veins, the venous P_{O_2}= 100 mm Hg, whereas the venous P_{CO_2}= 40 mm Hg. As blood enters the systemic capillaries, the blood will lose oxygen and gain carbon dioxide because of the pressure difference of the tissues and blood. In systemic capillaries, P_{O_2}= 100 mm Hg, but in the tissue cells, P_{O_2}= 40 mm Hg. This pressure gradient drives the diffusion of oxygen out of the capillaries and into the tissue cells. At the same time, blood P_{CO_2}= 40 mm Hg and systemic tissue P_{CO_2}= 45 mm Hg. The pressure gradient drives CO_2 out of tissue cells and into the capillaries. The blood returning to the lungs through the pulmonary arteries has a venous P_{O_2}= 40 mm Hg and a P_{CO_2}= 45 mm Hg. The blood enters the lung capillaries where the process of exchanging gases between the capillaries and alveoli begins again (Figure 10.3.3.2).

Art Connection

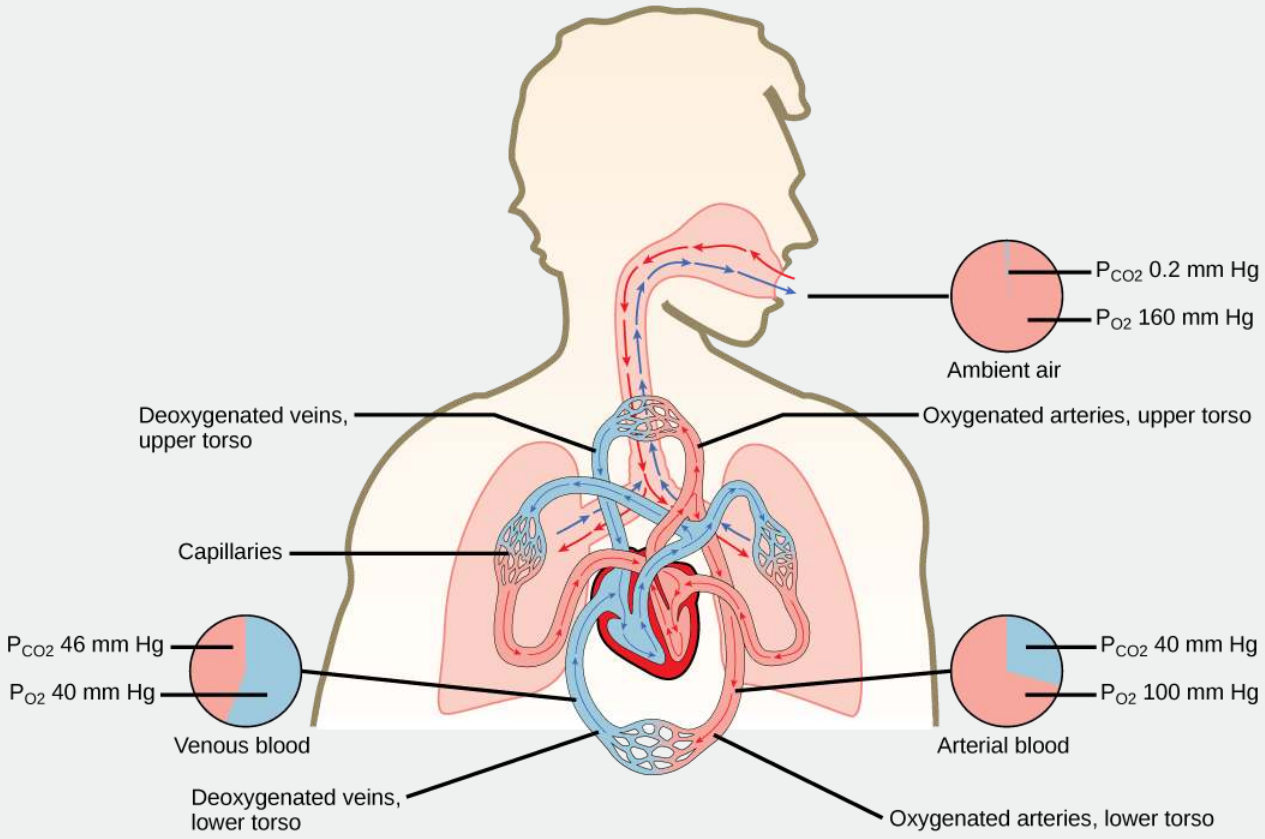


Figure 10.3.3.2: The partial pressures of oxygen and carbon dioxide change as blood moves through the body.

Which of the following statements is false?

A. In the tissues, P_{O_2} drops as blood passes from the arteries to the veins, while P_{CO_2} increases.
B. Blood travels from the lungs to the heart to body tissues, then back to the heart, then the lungs.
C. Blood travels from the lungs to the heart to body tissues, then back to the lungs, then the heart.
D. P_{O_2} is higher in air than in the lungs.

In short, the change in partial pressure from the alveoli to the capillaries drives the oxygen into the tissues and the carbon dioxide into the blood from the tissues. The blood is then transported to the lungs where differences in pressure in the alveoli result in the movement of carbon dioxide out of the blood into the lungs, and oxygen into the blood.

Link to Learning



Watch this video to learn how to carry out spirometry.

Summary

The lungs can hold a large volume of air, but they are not usually filled to maximal capacity. Lung volume measurements include tidal volume, expiratory reserve volume, inspiratory reserve volume, and residual volume. The sum of these equals the total lung capacity. Gas movement into or out of the lungs is dependent on the pressure of the gas. Air is a mixture of gases; therefore, the partial pressure of each gas can be calculated to determine how the gas will flow in the lung. The difference between the partial pressure of the gas in the air drives oxygen into the tissues and carbon dioxide out of the body.

Art Connections

Figure 10.3.3.2: Which of the following statements is false?

A. In the tissues, P_{O_2} drops as blood passes from the arteries to the veins, while P_{CO_2} increases.
B. Blood travels from the lungs to the heart to body tissues, then back to the heart, then the lungs.
C. Blood travels from the lungs to the heart to body tissues, then back to the lungs, then the heart.
D. P_{O_2} is higher in air than in the lungs.

Answer

C

Glossary

alveolar P_{O_2}
partial pressure of oxygen in the alveoli (usually around 100 mmHg)

expiratory reserve volume (ERV)
amount of additional air that can be exhaled after a normal exhalation

FEV1/FVC ratio
ratio of how much air can be forced out of the lung in one second to the total amount that is forced out of the lung; a measurement of lung function that can be used to detect disease states

forced expiratory volume (FEV)

(also, forced vital capacity) measure of how much air can be forced out of the lung from maximal inspiration over a specific amount of time

functional residual capacity (FRC)
expiratory reserve volume plus residual volume

inspiratory capacity (IC)
tidal volume plus inspiratory reserve volume

inspiratory reserve volume (IRV)
amount of additional air that can be inspired after a normal inhalation

lung capacity
measurement of two or more lung volumes (how much air can be inhaled from the end of an expiration to maximal capacity)

lung volume
measurement of air for one lung function (normal inhalation or exhalation)

partial pressure
amount of pressure exerted by one gas within a mixture of gases

residual volume (RV)
amount of air remaining in the lung after a maximal expiration

respiratory quotient (RQ)
ratio of carbon dioxide production to each oxygen molecule consumed

spirometry
method to measure lung volumes and to diagnose lung diseases

tidal volume (TV)
amount of air that is inspired and expired during normal breathing

total lung capacity (TLC)
sum of the residual volume, expiratory reserve volume, tidal volume, and inspiratory reserve volume

venous P_{CO_2}
partial pressure of carbon dioxide in the veins (40 mm Hg in the pulmonary veins)

venous P_{O_2}
partial pressure of oxygen in the veins (100 mm Hg in the pulmonary veins)

vital capacity (VC)
sum of the expiratory reserve volume, tidal volume, and inspiratory reserve volume

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10.3.4: Breathing

Skills to Develop

- Describe how the structures of the lungs and thoracic cavity control the mechanics of breathing
- Explain the importance of compliance and resistance in the lungs
- Discuss problems that may arise due to a V/Q mismatch

Mammalian lungs are located in the thoracic cavity where they are surrounded and protected by the rib cage, intercostal muscles, and bound by the chest wall. The bottom of the lungs is contained by the diaphragm, a skeletal muscle that facilitates breathing. Breathing requires the coordination of the lungs, the chest wall, and most importantly, the diaphragm.

Types of Breathing

Amphibians have evolved multiple ways of breathing. Young amphibians, like tadpoles, use gills to breathe, and they don't leave the water. Some amphibians retain gills for life. As the tadpole grows, the gills disappear and lungs grow. These lungs are primitive and not as evolved as mammalian lungs. Adult amphibians are lacking or have a reduced diaphragm, so breathing via lungs is forced. The other means of breathing for amphibians is diffusion across the skin. To aid this diffusion, amphibian skin must remain moist.

Birds face a unique challenge with respect to breathing: They fly. Flying consumes a great amount of energy; therefore, birds require a lot of oxygen to aid their metabolic processes. Birds have evolved a respiratory system that supplies them with the oxygen needed to enable flying. Similar to mammals, birds have lungs, which are organs specialized for gas exchange. Oxygenated air, taken in during inhalation, diffuses across the surface of the lungs into the bloodstream, and carbon dioxide diffuses from the blood into the lungs and expelled during exhalation. The details of breathing between birds and mammals differ substantially.

In addition to lungs, birds have air sacs inside their body. Air flows in one direction from the posterior air sacs to the lungs and out of the anterior air sacs. The flow of air is in the opposite direction from blood flow, and gas exchange takes place much more efficiently. This type of breathing enables birds to obtain the requisite oxygen, even at higher altitudes where the oxygen concentration is low. This directionality of airflow requires two cycles of air intake and exhalation to completely get the air out of the lungs.

Evolution Connection: Avian Respiration

Birds have evolved a respiratory system that enables them to fly. Flying is a high-energy process and requires a lot of oxygen. Furthermore, many birds fly in high altitudes where the concentration of oxygen in low. How did birds evolve a respiratory system that is so unique?

Decades of research by paleontologists have shown that birds evolved from therapods, meat-eating dinosaurs (Figure 10.3.4.1). In fact, fossil evidence shows that meat-eating dinosaurs that lived more than 100 million years ago had a similar flow-through respiratory system with lungs and air sacs. *Archaeopteryx* and *Xiaotingia*, for example, were flying dinosaurs and are believed to be early precursors of birds.

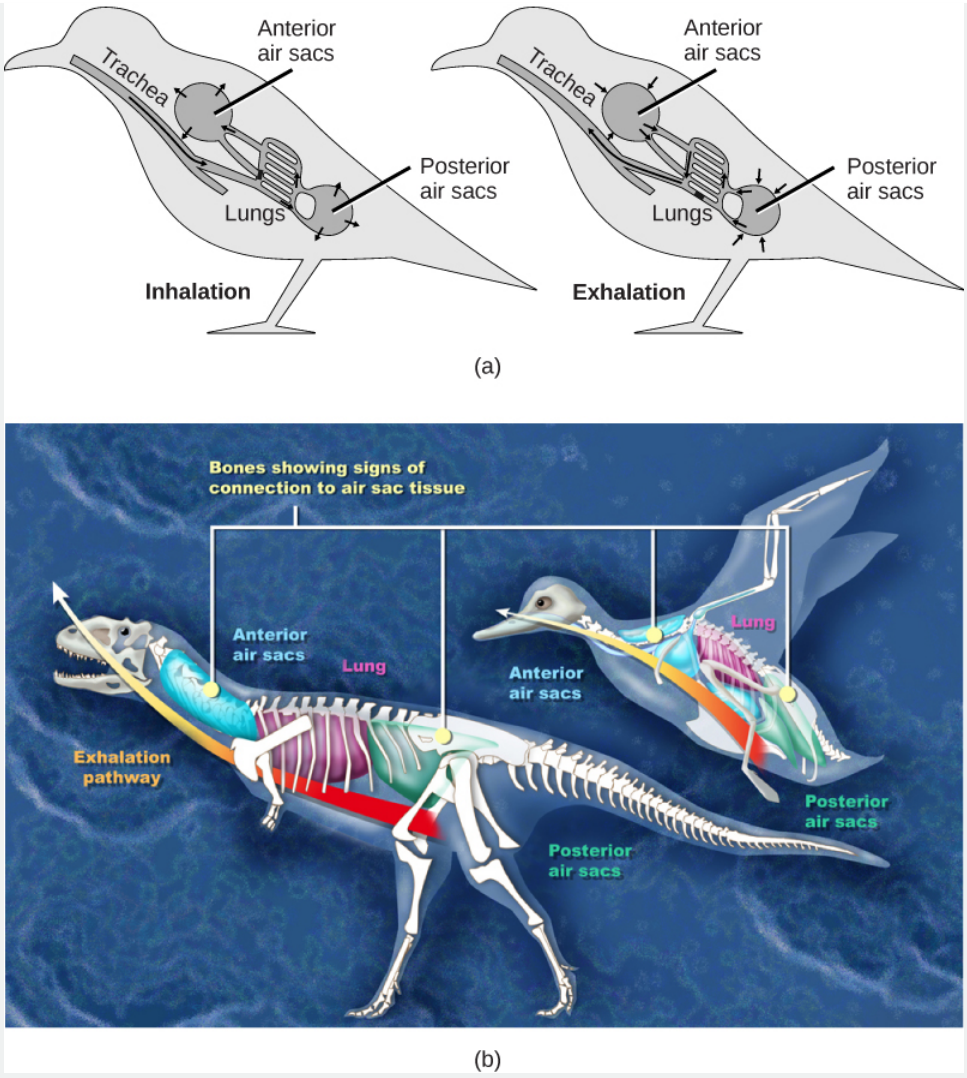


Figure 10.3.4.1: (a) Birds have a flow-through respiratory system in which air flows unidirectionally from the posterior sacs into the lungs, then into the anterior air sacs. The air sacs connect to openings in hollow bones. (b) Dinosaurs, from which birds descended, have similar hollow bones and are believed to have had a similar respiratory system. (credit b: modification of work by Zina Deretsky, National Science Foundation)

Most of us consider that dinosaurs are extinct. However, modern birds are descendants of avian dinosaurs. The respiratory system of modern birds has been evolving for hundreds of millions of years.

All mammals have lungs that are the main organs for breathing. Lung capacity has evolved to support the animal's activities. During inhalation, the lungs expand with air, and oxygen diffuses across the lung's surface and enters the bloodstream. During exhalation, the lungs expel air and lung volume decreases. In the next few sections, the process of human breathing will be explained.

The Mechanics of Human Breathing

Boyle's Law is the gas law that states that in a closed space, pressure and volume are inversely related. As volume decreases, pressure increases and vice versa (Figure 10.3.4.2). The relationship between gas pressure and volume helps to explain the mechanics of breathing.

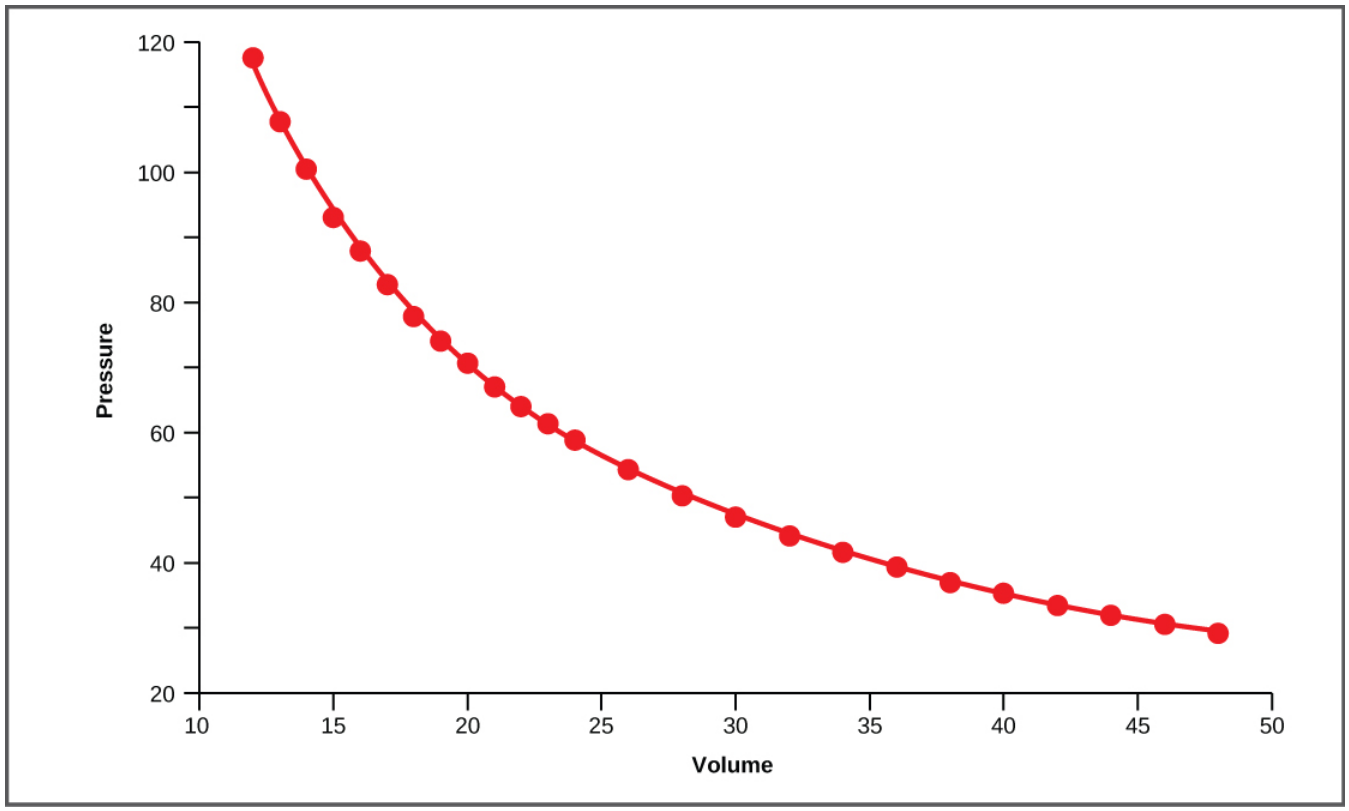


Figure 10.3.4.2: This graph shows data from Boyle's original 1662 experiment, which shows that pressure and volume are inversely related. No units are given as Boyle used arbitrary units in his experiments.

There is always a slightly negative pressure within the thoracic cavity, which aids in keeping the airways of the lungs open. During inhalation, volume increases as a result of contraction of the diaphragm, and pressure decreases (according to Boyle's Law). This decrease of pressure in the thoracic cavity relative to the environment makes the cavity less than the atmosphere (Figure 10.3.4.3a). Because of this drop in pressure, air rushes into the respiratory passages. To increase the volume of the lungs, the chest wall expands. This results from the contraction of the intercostal muscles, the muscles that are connected to the rib cage. Lung volume expands because the diaphragm contracts and the intercostals muscles contract, thus expanding the thoracic cavity. This increase in the volume of the thoracic cavity lowers pressure compared to the atmosphere, so air rushes into the lungs, thus increasing its volume. The resulting increase in volume is largely attributed to an increase in alveolar space, because the bronchioles and bronchi are stiff structures that do not change in size.

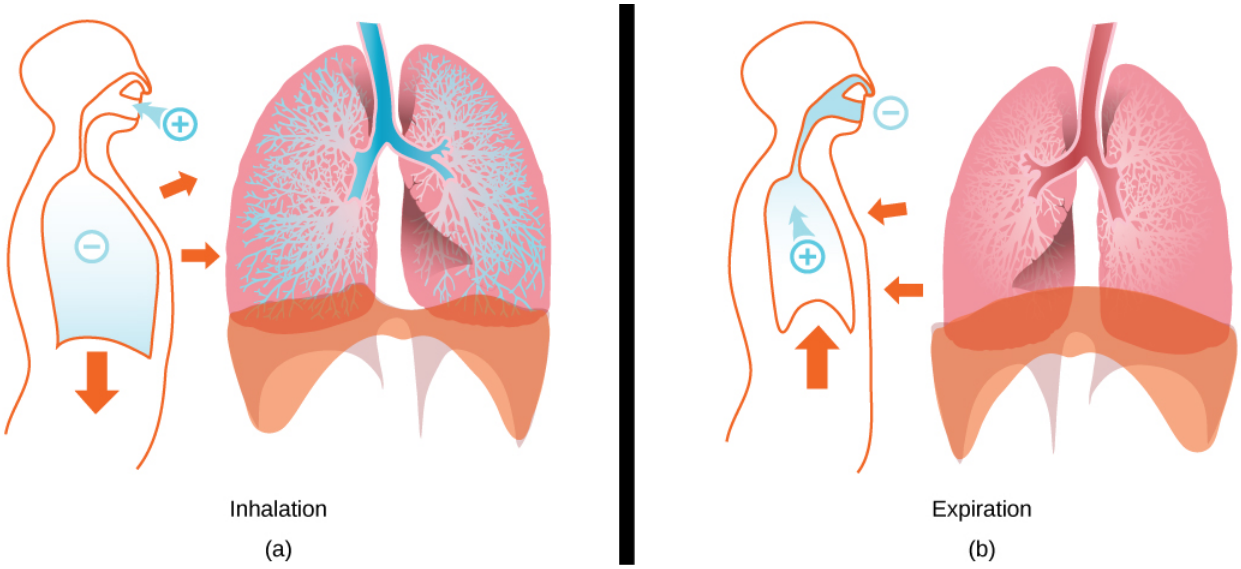


Figure 10.3.4.3: The lungs, chest wall, and diaphragm are all involved in respiration, both (a) inhalation and (b) expiration. (credit: modification of work by Mariana Ruiz Villareal)

The chest wall expands out and away from the lungs. The lungs are elastic; therefore, when air fills the lungs, the elastic recoil within the tissues of the lung exerts pressure back toward the interior of the lungs. These outward and inward forces compete to inflate and deflate the lung with every breath. Upon exhalation, the lungs recoil to force the air out of the lungs, and the intercostal muscles relax, returning the chest wall back to its original position (Figure 10.3.4.3b). The diaphragm also relaxes and moves higher into the thoracic cavity. This increases the pressure within the thoracic cavity relative to the environment, and air rushes out of the lungs. The movement of air out of the lungs is a passive event. No muscles are contracting to expel the air.

Each lung is surrounded by an invaginated sac. The layer of tissue that covers the lung and dips into spaces is called the visceral pleura. A second layer of parietal pleura lines the interior of the thorax (Figure 10.3.4.4). The space between these layers, the intrapleural space, contains a small amount of fluid that protects the tissue and reduces the friction generated from rubbing the tissue layers together as the lungs contract and relax. Pleurisy results when these layers of tissue become inflamed; it is painful because the inflammation increases the pressure within the thoracic cavity and reduces the volume of the lung.

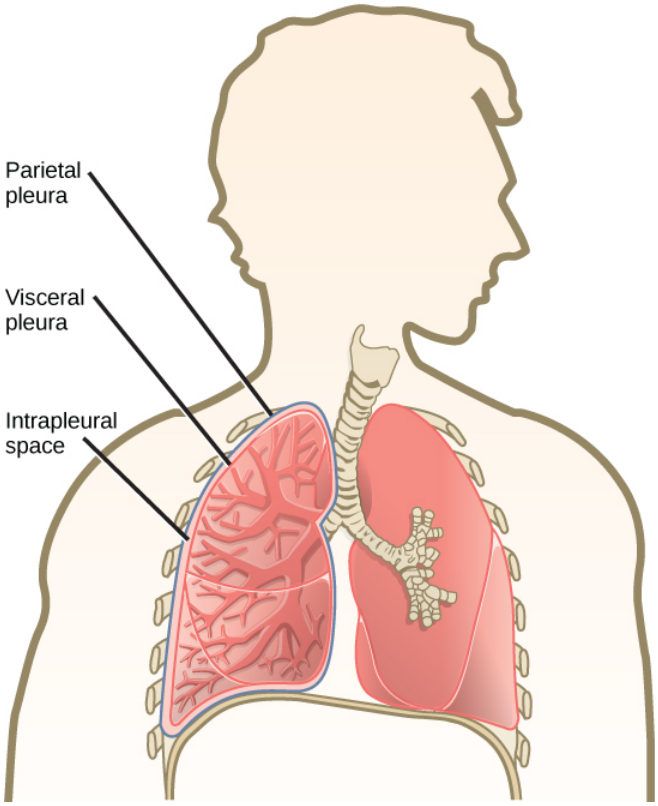


Figure 10.3.4.4: A tissue layer called pleura surrounds the lung and interior of the thoracic cavity. (credit: modification of work by NCI)

Link to Learning



View how Boyle's Law is related to breathing and watch this video on Boyle's Law.

The Work of Breathing

The number of breaths per minute is the respiratory rate. On average, under non-exertion conditions, the human respiratory rate is 12–15 breaths/minute. The respiratory rate contributes to the alveolar ventilation, or how much air moves into and out of the alveoli. Alveolar ventilation prevents carbon dioxide buildup in the alveoli. There are two ways to keep the alveolar ventilation

constant: increase the respiratory rate while decreasing the tidal volume of air per breath (shallow breathing), or decrease the respiratory rate while increasing the tidal volume per breath. In either case, the ventilation remains the same, but the work done and type of work needed are quite different. Both tidal volume and respiratory rate are closely regulated when oxygen demand increases.

There are two types of work conducted during respiration, flow-resistive and elastic work. Flow-resistive refers to the work of the alveoli and tissues in the lung, whereas elastic work refers to the work of the intercostal muscles, chest wall, and diaphragm. Increasing the respiration rate increases the flow-resistive work of the airways and decreases the elastic work of the muscles. Decreasing the respiratory rate reverses the type of work required.

Surfactant

The air-tissue/water interface of the alveoli has a high surface tension. This surface tension is similar to the surface tension of water at the liquid-air interface of a water droplet that results in the bonding of the water molecules together. Surfactant is a complex mixture of phospholipids and lipoproteins that works to reduce the surface tension that exists between the alveoli tissue and the air found within the alveoli. By lowering the surface tension of the alveolar fluid, it reduces the tendency of alveoli to collapse.

Surfactant works like a detergent to reduce the surface tension and allows for easier inflation of the airways. When a balloon is first inflated, it takes a large amount of effort to stretch the plastic and start to inflate the balloon. If a little bit of detergent was applied to the interior of the balloon, then the amount of effort or work needed to begin to inflate the balloon would decrease, and it would become much easier to start blowing up the balloon. This same principle applies to the airways. A small amount of surfactant to the airway tissues reduces the effort or work needed to inflate those airways. Babies born prematurely sometimes do not produce enough surfactant. As a result, they suffer from respiratory distress syndrome, because it requires more effort to inflate their lungs. Surfactant is also important for preventing collapse of small alveoli relative to large alveoli.

Lung Resistance and Compliance

Pulmonary diseases reduce the rate of gas exchange into and out of the lungs. Two main causes of decreased gas exchange are compliance (how elastic the lung is) and resistance (how much obstruction exists in the airways). A change in either can dramatically alter breathing and the ability to take in oxygen and release carbon dioxide.

Examples of restrictive diseases are respiratory distress syndrome and pulmonary fibrosis. In both diseases, the airways are less compliant and they are stiff or fibrotic. There is a decrease in compliance because the lung tissue cannot bend and move. In these types of restrictive diseases, the intrapleural pressure is more positive and the airways collapse upon exhalation, which traps air in the lungs. Forced or functional vital capacity (FVC), which is the amount of air that can be forcibly exhaled after taking the deepest breath possible, is much lower than in normal patients, and the time it takes to exhale most of the air is greatly prolonged (Figure 10.3.4.5). A patient suffering from these diseases cannot exhale the normal amount of air.

Obstructive diseases and conditions include emphysema, asthma, and pulmonary edema. In emphysema, which mostly arises from smoking tobacco, the walls of the alveoli are destroyed, decreasing the surface area for gas exchange. The overall compliance of the lungs is increased, because as the alveolar walls are damaged, lung elastic recoil decreases due to a loss of elastic fibers, and more air is trapped in the lungs at the end of exhalation. Asthma is a disease in which inflammation is triggered by environmental factors. Inflammation obstructs the airways. The obstruction may be due to edema (fluid accumulation), smooth muscle spasms in the walls of the bronchioles, increased mucus secretion, damage to the epithelia of the airways, or a combination of these events. Those with asthma or edema experience increased occlusion from increased inflammation of the airways. This tends to block the airways, preventing the proper movement of gases (Figure 10.3.4.5). Those with obstructive diseases have large volumes of air trapped after exhalation and breathe at a very high lung volume to compensate for the lack of airway recruitment.

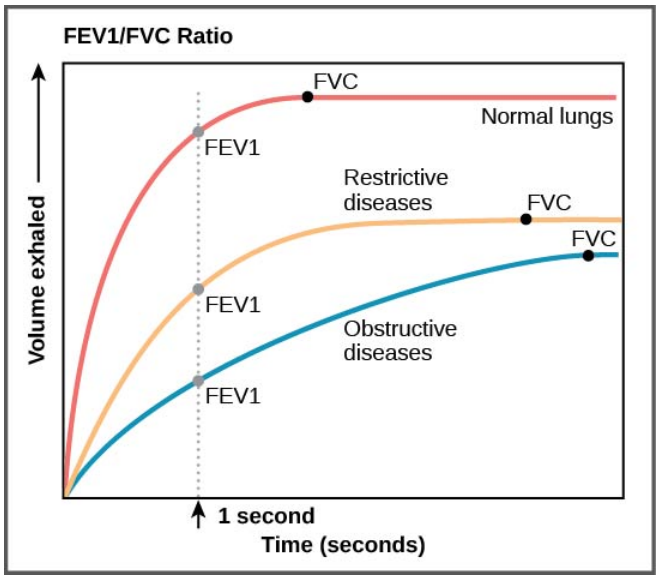


Figure 10.3.4.5: The ratio of FEV1 (the amount of air that can be forcibly exhaled in one second after taking a deep breath) to FVC (the total amount of air that can be forcibly exhaled) can be used to diagnose whether a person has restrictive or obstructive lung disease. In restrictive lung disease, FVC is reduced but airways are not obstructed, so the person is able to expel air reasonably fast. In obstructive lung disease, airway obstruction results in slow exhalation as well as reduced FVC. Thus, the FEV1/FVC ratio is lower in persons with obstructive lung disease (less than 69 percent) than in persons with restrictive disease (88 to 90 percent).

Dead Space: V/Q Mismatch

Pulmonary circulation pressure is very low compared to that of the systemic circulation. It is also independent of cardiac output. This is because of a phenomenon called recruitment, which is the process of opening airways that normally remain closed when cardiac output increases. As cardiac output increases, the number of capillaries and arteries that are perfused (filled with blood) increases. These capillaries and arteries are not always in use but are ready if needed. At times, however, there is a mismatch between the amount of air (ventilation, V) and the amount of blood (perfusion, Q) in the lungs. This is referred to as ventilation/perfusion (V/Q) mismatch.

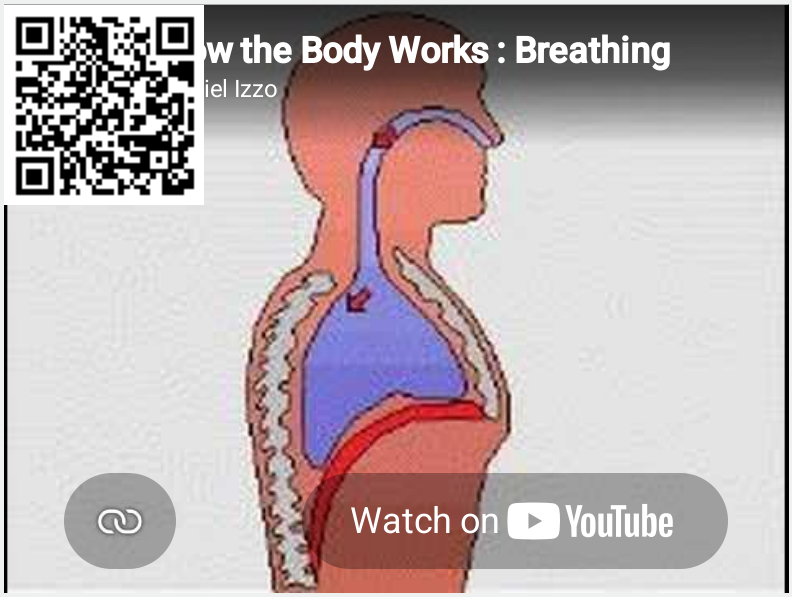
There are two types of V/Q mismatch. Both produce dead space, regions of broken down or blocked lung tissue. Dead spaces can severely impact breathing, because they reduce the surface area available for gas diffusion. As a result, the amount of oxygen in the blood decreases, whereas the carbon dioxide level increases. Dead space is created when no ventilation and/or perfusion takes place. Anatomical dead space or anatomical shunt, arises from an anatomical failure, while physiological dead space or physiological shunt, arises from a functional impairment of the lung or arteries.

An example of an anatomical shunt is the effect of gravity on the lungs. The lung is particularly susceptible to changes in the magnitude and direction of gravitational forces. When someone is standing or sitting upright, the pleural pressure gradient leads to increased ventilation further down in the lung. As a result, the intrapleural pressure is more negative at the base of the lung than at the top, and more air fills the bottom of the lung than the top. Likewise, it takes less energy to pump blood to the bottom of the lung than to the top when in a prone position. Perfusion of the lung is not uniform while standing or sitting. This is a result of hydrostatic forces combined with the effect of airway pressure. An anatomical shunt develops because the ventilation of the airways does not match the perfusion of the arteries surrounding those airways. As a result, the rate of gas exchange is reduced. Note that this does not occur when lying down, because in this position, gravity does not preferentially pull the bottom of the lung down.

A physiological shunt can develop if there is infection or edema in the lung that obstructs an area. This will decrease ventilation but not affect perfusion; therefore, the V/Q ratio changes and gas exchange is affected.

The lung can compensate for these mismatches in ventilation and perfusion. If ventilation is greater than perfusion, the arterioles dilate and the bronchioles constrict. This increases perfusion and reduces ventilation. Likewise, if ventilation is less than perfusion, the arterioles constrict and the bronchioles dilate to correct the imbalance.

Link to Learning



Visit this site to view the mechanics of breathing.

Summary

The structure of the lungs and thoracic cavity control the mechanics of breathing. Upon inspiration, the diaphragm contracts and lowers. The intercostal muscles contract and expand the chest wall outward. The intrapleural pressure drops, the lungs expand, and air is drawn into the airways. When exhaling, the intercostal muscles and diaphragm relax, returning the intrapleural pressure back to the resting state. The lungs recoil and airways close. The air passively exits the lung. There is high surface tension at the air-airway interface in the lung. Surfactant, a mixture of phospholipids and lipoproteins, acts like a detergent in the airways to reduce surface tension and allow for opening of the alveoli.

Breathing and gas exchange are both altered by changes in the compliance and resistance of the lung. If the compliance of the lung decreases, as occurs in restrictive diseases like fibrosis, the airways stiffen and collapse upon exhalation. Air becomes trapped in the lungs, making breathing more difficult. If resistance increases, as happens with asthma or emphysema, the airways become obstructed, trapping air in the lungs and causing breathing to become difficult. Alterations in the ventilation of the airways or perfusion of the arteries can affect gas exchange. These changes in ventilation and perfusion, called V/Q mismatch, can arise from anatomical or physiological changes.

Glossary

alveolar ventilation
how much air is in the alveoli

anatomical dead space
(also, anatomical shunt) region of the lung that lacks proper ventilation/perfusion due to an anatomical block

compliance
measurement of the elasticity of the lung

dead space
area in the lung that lacks proper ventilation or perfusion

elastic recoil
property of the lung that drives the lung tissue inward

elastic work
work conducted by the intercostal muscles, chest wall, and diaphragm

flow-resistive
work of breathing performed by the alveoli and tissues in the lung

functional vital capacity (FVC)
amount of air that can be forcibly exhaled after taking the deepest breath possible

intercostal muscle
muscle connected to the rib cage that contracts upon inspiration

intrapleural space
space between the layers of pleura

obstructive disease
disease (such as emphysema and asthma) that arises from obstruction of the airways; compliance increases in these diseases

physiological dead space
(also, physiological shunt) region of the lung that lacks proper ventilation/perfusion due to a physiological change in the lung (like inflammation or edema)

pleura
tissue layer that surrounds the lungs and lines the interior of the thoracic cavity

pleurisy
painful inflammation of the pleural tissue layers

recruitment
process of opening airways that normally remain closed when the cardiac output increases

resistance
measurement of lung obstruction

respiratory distress syndrome
disease that arises from a deficient amount of surfactant

respiratory rate
number of breaths per minute

restrictive disease
disease that results from a restriction and decreased compliance of the alveoli; respiratory distress syndrome and pulmonary fibrosis are examples

surfactant
detergent-like liquid in the airways that lowers the surface tension of the alveoli to allow for expansion

ventilation/perfusion (V/Q) mismatch
region of the lung that lacks proper alveolar ventilation (V) and/or arterial perfusion (Q)

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10.3.5: Transport of Gases in Human Bodily Fluids

Skills to Develop

- Describe how oxygen is bound to hemoglobin and transported to body tissues
- Explain how carbon dioxide is transported from body tissues to the lungs

Once the oxygen diffuses across the alveoli, it enters the bloodstream and is transported to the tissues where it is unloaded, and carbon dioxide diffuses out of the blood and into the alveoli to be expelled from the body. Although gas exchange is a continuous process, the oxygen and carbon dioxide are transported by different mechanisms.

Transport of Oxygen in the Blood

Although oxygen dissolves in blood, only a small amount of oxygen is transported this way. Only 1.5 percent of oxygen in the blood is dissolved directly into the blood itself. Most oxygen—98.5 percent—is bound to a protein called hemoglobin and carried to the tissues.

Hemoglobin

Hemoglobin, or Hb, is a protein molecule found in red blood cells (erythrocytes) made of four subunits: two alpha subunits and two beta subunits (Figure 10.3.5.1). Each subunit surrounds a central heme group that contains iron and binds one oxygen molecule, allowing each hemoglobin molecule to bind four oxygen molecules. Molecules with more oxygen bound to the heme groups are brighter red. As a result, oxygenated arterial blood where the Hb is carrying four oxygen molecules is bright red, while venous blood that is deoxygenated is darker red.

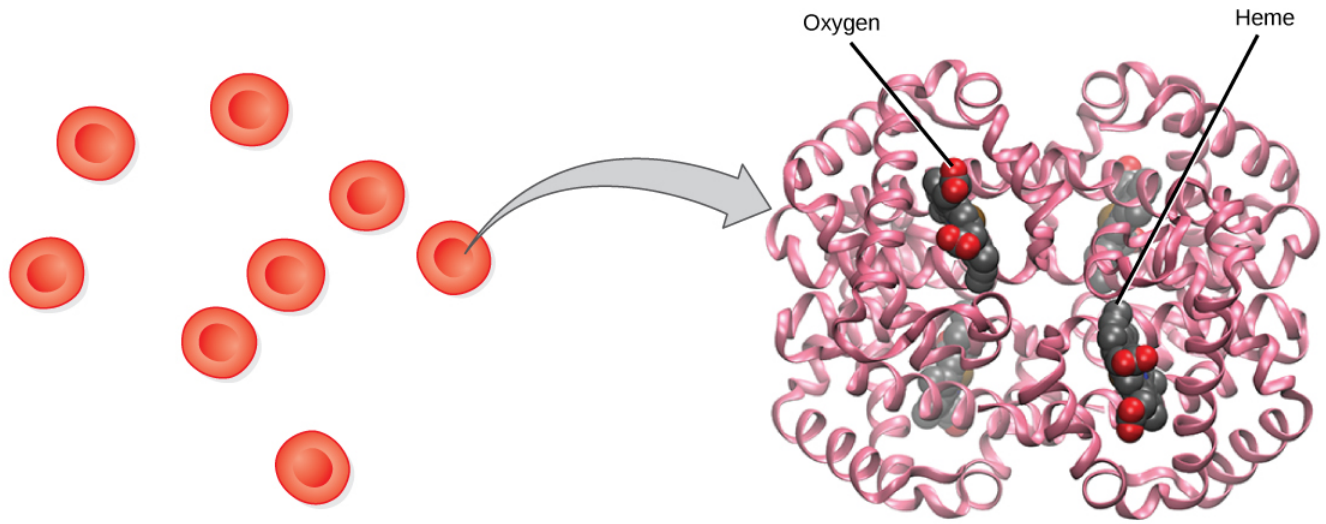


Figure 10.3.5.1: The protein inside (a) red blood cells that carries oxygen to cells and carbon dioxide to the lungs is (b) hemoglobin. Hemoglobin is made up of four symmetrical subunits and four heme groups. Iron associated with the heme binds oxygen. It is the iron in hemoglobin that gives blood its red color.

It is easier to bind a second and third oxygen molecule to Hb than the first molecule. This is because the hemoglobin molecule changes its shape, or conformation, as oxygen binds. The fourth oxygen is then more difficult to bind. The binding of oxygen to hemoglobin can be plotted as a function of the partial pressure of oxygen in the blood (x-axis) versus the relative Hb-oxygen saturation (y-axis). The resulting graph—an oxygen dissociation curve—is sigmoidal, or S-shaped (Figure 10.3.5.2). As the partial pressure of oxygen increases, the hemoglobin becomes increasingly saturated with oxygen.

Art Connection

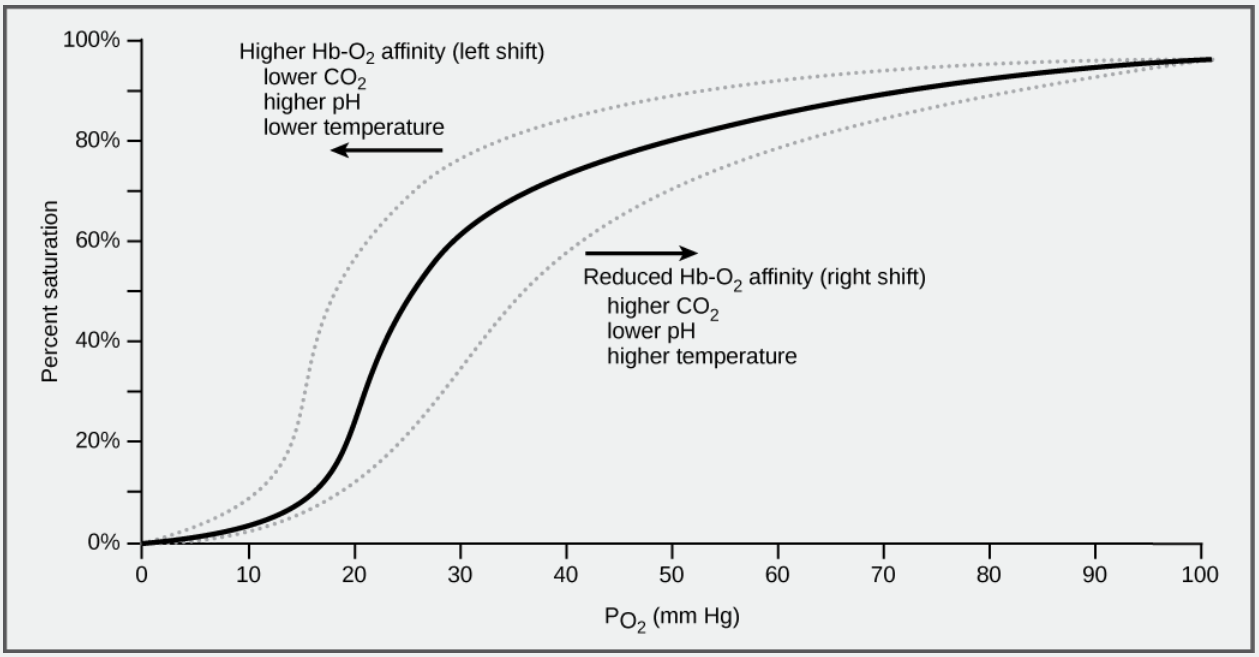


Figure 10.3.5.2: The oxygen dissociation curve demonstrates that, as the partial pressure of oxygen increases, more oxygen binds hemoglobin. However, the affinity of hemoglobin for oxygen may shift to the left or the right depending on environmental conditions.

The kidneys are responsible for removing excess H^+ ions from the blood. If the kidneys fail, what would happen to blood pH and to hemoglobin affinity for oxygen?

Factors That Affect Oxygen Binding

The oxygen-carrying capacity of hemoglobin determines how much oxygen is carried in the blood. In addition to P_{O_2}, other environmental factors and diseases can affect oxygen carrying capacity and delivery.

Carbon dioxide levels, blood pH, and body temperature affect oxygen-carrying capacity (Figure 10.3.5.2). When carbon dioxide is in the blood, it reacts with water to form bicarbonate (HCO_3^-) and hydrogen ions (H^+). As the level of carbon dioxide in the blood increases, more H^+ is produced and the pH decreases. This increase in carbon dioxide and subsequent decrease in pH reduce the affinity of hemoglobin for oxygen. The oxygen dissociates from the Hb molecule, shifting the oxygen dissociation curve to the right. Therefore, more oxygen is needed to reach the same hemoglobin saturation level as when the pH was higher. A similar shift in the curve also results from an increase in body temperature. Increased temperature, such as from increased activity of skeletal muscle, causes the affinity of hemoglobin for oxygen to be reduced.

Diseases like sickle cell anemia and thalassemia decrease the blood's ability to deliver oxygen to tissues and its oxygen-carrying capacity. In sickle cell anemia, the shape of the red blood cell is crescent-shaped, elongated, and stiffened, reducing its ability to deliver oxygen (Figure 10.3.5.3). In this form, red blood cells cannot pass through the capillaries. This is painful when it occurs. Thalassemia is a rare genetic disease caused by a defect in either the alpha or the beta subunit of Hb. Patients with thalassemia produce a high number of red blood cells, but these cells have lower-than-normal levels of hemoglobin. Therefore, the oxygen-carrying capacity is diminished.

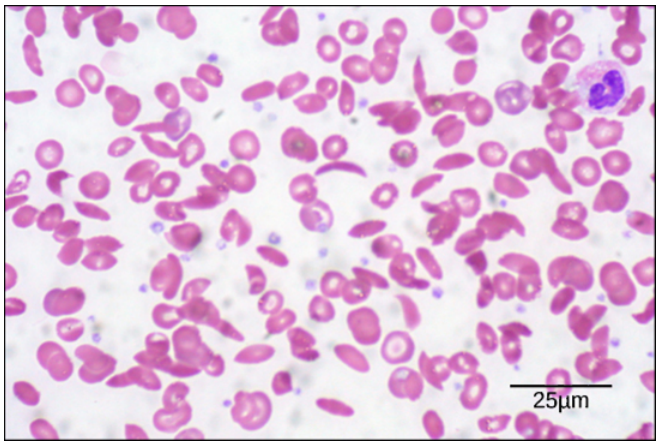


Figure 10.3.5.3: Individuals with sickle cell anemia have crescent-shaped red blood cells. (credit: modification of work by Ed Uthman; scale-bar data from Matt Russell)

Transport of Carbon Dioxide in the Blood

Carbon dioxide molecules are transported in the blood from body tissues to the lungs by one of three methods: dissolution directly into the blood, binding to hemoglobin, or carried as a bicarbonate ion. Several properties of carbon dioxide in the blood affect its transport. First, carbon dioxide is more soluble in blood than oxygen. About 5 to 7 percent of all carbon dioxide is dissolved in the plasma. Second, carbon dioxide can bind to plasma proteins or can enter red blood cells and bind to hemoglobin. This form transports about 10 percent of the carbon dioxide. When carbon dioxide binds to hemoglobin, a molecule called carbaminohemoglobin is formed. Binding of carbon dioxide to hemoglobin is reversible. Therefore, when it reaches the lungs, the carbon dioxide can freely dissociate from the hemoglobin and be expelled from the body.

Third, the majority of carbon dioxide molecules (85 percent) are carried as part of the bicarbonate buffer system. In this system, carbon dioxide diffuses into the red blood cells. Carbonic anhydrase (CA) within the red blood cells quickly converts the carbon dioxide into carbonic acid (H_2CO_3). Carbonic acid is an unstable intermediate molecule that immediately dissociates into bicarbonate ions (HCO_3^-) and hydrogen (H^+) ions. Since carbon dioxide is quickly converted into bicarbonate ions, this reaction allows for the continued uptake of carbon dioxide into the blood down its concentration gradient. It also results in the production of H^+ ions. If too much H^+ is produced, it can alter blood pH. However, hemoglobin binds to the free H^+ ions and thus limits shifts in pH. The newly synthesized bicarbonate ion is transported out of the red blood cell into the liquid component of the blood in exchange for a chloride ion (Cl^-); this is called the chloride shift. When the blood reaches the lungs, the bicarbonate ion is transported back into the red blood cell in exchange for the chloride ion. The H^+ ion dissociates from the hemoglobin and binds to the bicarbonate ion. This produces the carbonic acid intermediate, which is converted back into carbon dioxide through the enzymatic action of CA. The carbon dioxide produced is expelled through the lungs during exhalation.

$$CO_2 + H_2O \leftrightharpoons \underset{\text{(carbonic acid)}}{H_2CO_3} \leftrightarrow \underset{\text{(bicarbonate)}}{HCO_3} + H^+$$

The benefit of the bicarbonate buffer system is that carbon dioxide is “soaked up” into the blood with little change to the pH of the system. This is important because it takes only a small change in the overall pH of the body for severe injury or death to result. The presence of this bicarbonate buffer system also allows for people to travel and live at high altitudes: When the partial pressure of oxygen and carbon dioxide change at high altitudes, the bicarbonate buffer system adjusts to regulate carbon dioxide while maintaining the correct pH in the body.

Carbon Monoxide Poisoning

While carbon dioxide can readily associate and dissociate from hemoglobin, other molecules such as carbon monoxide (CO) cannot. Carbon monoxide has a greater affinity for hemoglobin than oxygen. Therefore, when carbon monoxide is present, it binds to hemoglobin preferentially over oxygen. As a result, oxygen cannot bind to hemoglobin, so very little oxygen is transported through the body (Figure 10.3.5.4). Carbon monoxide is a colorless, odorless gas and is therefore difficult to detect. It is produced by gas-powered vehicles and tools. Carbon monoxide can cause headaches, confusion, and nausea; long-term exposure can cause

brain damage or death. Administering 100 percent (pure) oxygen is the usual treatment for carbon monoxide poisoning. Administration of pure oxygen speeds up the separation of carbon monoxide from hemoglobin.

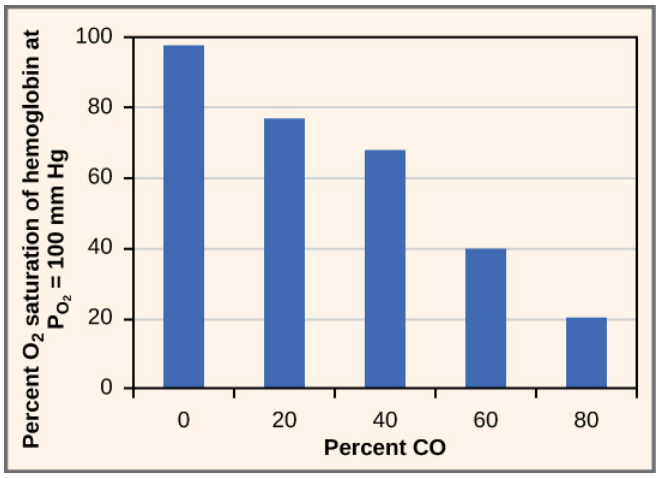


Figure 10.3.5.4: As percent CO increases, the oxygen saturation of hemoglobin decreases.

Summary

Hemoglobin is a protein found in red blood cells that is comprised of two alpha and two beta subunits that surround an iron-containing heme group. Oxygen readily binds this heme group. The ability of oxygen to bind increases as more oxygen molecules are bound to heme. Disease states and altered conditions in the body can affect the binding ability of oxygen, and increase or decrease its ability to dissociate from hemoglobin.

Carbon dioxide can be transported through the blood via three methods. It is dissolved directly in the blood, bound to plasma proteins or hemoglobin, or converted into bicarbonate. The majority of carbon dioxide is transported as part of the bicarbonate system. Carbon dioxide diffuses into red blood cells. Inside, carbonic anhydrase converts carbon dioxide into carbonic acid (H_2CO_3), which is subsequently hydrolyzed into bicarbonate (HCO_3^-) and H^+. The H^+ ion binds to hemoglobin in red blood cells, and bicarbonate is transported out of the red blood cells in exchange for a chloride ion. This is called the chloride shift. Bicarbonate leaves the red blood cells and enters the blood plasma. In the lungs, bicarbonate is transported back into the red blood cells in exchange for chloride. The H^+ dissociates from hemoglobin and combines with bicarbonate to form carbonic acid with the help of carbonic anhydrase, which further catalyzes the reaction to convert carbonic acid back into carbon dioxide and water. The carbon dioxide is then expelled from the lungs.

Art Connections

Figure 10.3.5.2: The kidneys are responsible for removing excess H^+ ions from the blood. If the kidneys fail, what would happen to blood pH and to hemoglobin affinity for oxygen?

Answer

The blood pH will drop and hemoglobin affinity for oxygen will decrease.

Glossary

bicarbonate buffer system

system in the blood that absorbs carbon dioxide and regulates pH levels

bicarbonate (HCO_3^-) ion

ion created when carbonic acid dissociates into H^+ and (HCO_3^-)

carbaminohemoglobin

molecule that forms when carbon dioxide binds to hemoglobin

carbonic anhydrase (CA)
enzyme that catalyzes carbon dioxide and water into carbonic acid

chloride shift
chloride shift exchange of chloride for bicarbonate into or out of the red blood cell

heme group
centralized iron-containing group that is surrounded by the alpha and beta subunits of hemoglobin

hemoglobin
molecule in red blood cells that can bind oxygen, carbon dioxide, and carbon monoxide

oxygen-carrying capacity
amount of oxygen that can be transported in the blood

oxygen dissociation curve
curve depicting the affinity of oxygen for hemoglobin

sickle cell anemia
genetic disorder that affects the shape of red blood cells, and their ability to transport oxygen and move through capillaries

thalassemia
rare genetic disorder that results in mutation of the alpha or beta subunits of hemoglobin, creating smaller red blood cells with less hemoglobin

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10.3.E: The Respiratory System (Exercises)

39.1: Systems of Gas Exchange

Review Questions

The respiratory system _____.

A. provides body tissues with oxygen
B. provides body tissues with oxygen and carbon dioxide
C. establishes how many breaths are taken per minute
D. provides the body with carbon dioxide

Answer

A

Air is warmed and humidified in the nasal passages. This helps to _____.

A. ward off infection
B. decrease sensitivity during breathing
C. prevent damage to the lungs
D. all of the above

Answer

C

Which is the order of airflow during inhalation?

A. nasal cavity, trachea, larynx, bronchi, bronchioles, alveoli
B. nasal cavity, larynx, trachea, bronchi, bronchioles, alveoli
C. nasal cavity, larynx, trachea, bronchioles, bronchi, alveoli
D. nasal cavity, trachea, larynx, bronchi, bronchioles, alveoli

Answer

B

Free Response

Describe the function of these terms and describe where they are located: main bronchus, trachea, alveoli, and acinus.

Answer

The main bronchus is the conduit in the lung that funnels air to the airways where gas exchange occurs. The main bronchus attaches the lungs to the very end of the trachea where it bifurcates. The trachea is the cartilaginous structure that extends from the pharynx to the primary bronchi. It serves to funnel air to the lungs. The alveoli are the sites of gas exchange; they are located at the terminal regions of the lung and are attached to the respiratory bronchioles. The acinus is the structure in the lung where gas exchange occurs.

How does the structure of alveoli maximize gas exchange?

Answer

The sac-like structure of the alveoli increases their surface area. In addition, the alveoli are made of thin-walled parenchymal cells. These features allow gases to easily diffuse across the cells.

39.2: Gas Exchange across Respiratory Surfaces

Review Questions

The inspiratory reserve volume measures the _____.

A. amount of air remaining in the lung after a maximal exhalation
B. amount of air that the lung holds
C. amount of air the can be further exhaled after a normal breath
D. amount of air that can be further inhaled after a normal breath

Answer

D

Of the following, which does not explain why the partial pressure of oxygen is lower in the lung than in the external air?

A. Air in the lung is humidified; therefore, water vapor pressure alters the pressure.
B. Carbon dioxide mixes with oxygen.
C. Oxygen is moved into the blood and is headed to the tissues.
D. Lungs exert a pressure on the air to reduce the oxygen pressure.

Answer

D

The total lung capacity is calculated using which of the following formulas?

A. residual volume + tidal volume + inspiratory reserve volume
B. residual volume + expiratory reserve volume + inspiratory reserve volume
C. expiratory reserve volume + tidal volume + inspiratory reserve volume
D. residual volume + expiratory reserve volume + tidal volume + inspiratory reserve volume

Answer

D

Free Response

What does FEV1/FVC measure? What factors may affect FEV1/FVC?

Answer

FEV1/FVC measures the forced expiratory volume in one second in relation to the total forced vital capacity (the total amount of air that is exhaled from the lung from a maximal inhalation). This ratio changes with alterations in lung function that arise from diseases such as fibrosis, asthma, and COPD.

What is the reason for having residual volume in the lung?

Answer

If all the air in the lung were exhaled, then opening the alveoli for the next inspiration would be very difficult. This is because the tissues would stick together.

How can a decrease in the percent of oxygen in the air affect the movement of oxygen in the body?

Answer

Oxygen moves from the lung to the bloodstream to the tissues according to the pressure gradient. This is measured as the partial pressure of oxygen. If the amount of oxygen drops in the inspired air, there would be reduced partial pressure. This would decrease the driving force that moves the oxygen into the blood and into the tissues. P_{O_2} is also reduced at high elevations: P_{O_2} at high elevations is lower than at sea level because the total atmospheric pressure is less than atmospheric pressure at sea level.

If a patient has increased resistance in his or her lungs, how can this detected by a doctor? What does this mean?

Answer

A doctor can detect a restrictive disease using spirometry. By detecting the rate at which air can be expelled from the lung, a diagnosis of fibrosis or another restrictive disease can be made.

39.3: Breathing

Review Questions

How would paralysis of the diaphragm alter inspiration?

A. It would prevent contraction of the intercostal muscles.
B. It would prevent inhalation because the intrapleural pressure would not change.
C. It would decrease the intrapleural pressure and allow more air to enter the lungs.
D. It would slow expiration because the lung would not relax.

Answer

B

Restrictive airway diseases _____.

A. increase the compliance of the lung
B. decrease the compliance of the lung
C. increase the lung volume
D. decrease the work of breathing

Answer

B

Alveolar ventilation remains constant when _____.

A. the respiratory rate is increased while the volume of air per breath is decreased
B. the respiratory rate and the volume of air per breath are increased
C. the respiratory rate is decreased while increasing the volume per breath
D. both a and c

Answer

D

Free Response

How would increased airway resistance affect intrapleural pressure during inhalation?

Answer

Increased airway resistance increases the volume and pressure in the lung; therefore, the intrapleural pressure would be less negative and breathing would be more difficult.

Explain how a puncture to the thoracic cavity (from a knife wound, for instance) could alter the ability to inhale.

Answer

A puncture to the thoracic cavity would equalize the pressure inside the thoracic cavity to the outside environment. For the lung to function properly, the intrapleural pressure must be negative. This is caused by the contraction of the diaphragm pulling the lungs down and drawing air into the lungs.

When someone is standing, gravity stretches the bottom of the lung down toward the floor to a greater extent than the top of the lung. What implication could this have on the flow of air in the lungs? Where does gas exchange occur in the lungs?

Answer

The lung is particularly susceptible to changes in the magnitude and direction of gravitational forces. When someone is standing or sitting upright, the pleural pressure gradient leads to increased ventilation further down in the lung.

39.4: Transport of Gases in Human Bodily Fluids

Review Questions

Which of the following will NOT facilitate the transfer of oxygen to tissues?

A. decreased body temperature
B. decreased pH of the blood
C. increased carbon dioxide
D. increased exercise

Answer

A

The majority of carbon dioxide in the blood is transported by _____.

A. binding to hemoglobin
B. dissolution in the blood
C. conversion to bicarbonate
D. binding to plasma proteins

Answer

C

The majority of oxygen in the blood is transported by _____.

A. dissolution in the blood
B. being carried as bicarbonate ions
C. binding to blood plasma
D. binding to hemoglobin

Answer

D

Free Response

What would happen if no carbonic anhydrase were present in red blood cells?

Answer

Without carbonic anhydrase, carbon dioxide would not be hydrolyzed into carbonic acid or bicarbonate. Therefore, very little carbon dioxide (only 15 percent) would be transported in the blood away from the tissues.

How does the administration of 100 percent oxygen save a patient from carbon monoxide poisoning? Why wouldn't giving carbon dioxide work?

Answer

Carbon monoxide has a higher affinity for hemoglobin than oxygen. This means that carbon monoxide will preferentially bind to hemoglobin over oxygen. Administration of 100 percent oxygen is an effective therapy because at that concentration, oxygen will displace the carbon monoxide from the hemoglobin.

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SECTION OVERVIEW

10.4: Respiratory System Infections

The respiratory tract is one of the main portals of entry into the human body for microbial pathogens. On average, a human takes about 20,000 breaths each day. This roughly corresponds to 10,000 liters, or 10 cubic meters, of air. Suspended within this volume of air are millions of microbes of terrestrial, animal, and human origin—including many potential pathogens. A few of these pathogens will cause relatively mild infections like sore throats and colds. Others, however, are less benign. According to the World Health Organization, respiratory tract infections such as tuberculosis, influenza, and pneumonia were responsible for more than 4 million deaths worldwide in 2012.[1]

At one time, it was thought that antimicrobial drugs and preventive vaccines might hold respiratory infections in check in the developed world, but recent developments suggest otherwise. The rise of multiple-antibiotic resistance in organisms like *Mycobacterium tuberculosis* has rendered many of our modern drugs ineffective. In addition, there has been a recent resurgence in diseases like whooping cough and measles, once-common childhood illnesses made rare by effective vaccines. Despite advances in medicine and public health programs, it is likely that respiratory pathogens will remain formidable adversaries for the foreseeable future.



Figure 10.4.1: Aerosols produced by sneezing, coughing, or even just speaking are an important mechanism for respiratory pathogen transmission. Simple actions, like covering your mouth when coughing or sneezing, can reduce the spread of these microbes. (credit: modification of work by Centers for Disease Control and Prevention)

10.4.1: Anatomy and Normal Microbiota of the Respiratory Tract

10.4.2: Bacterial Infections of the Respiratory Tract

10.4.3: Viral Infections of the Respiratory Tract

10.4.4: Respiratory Mycoses

10.4.E: Respiratory System Infections (Exercises)

Footnotes

1. 1 World Health Organization. “The Top Ten Causes of Death.” May 2014. http://www.who.int/mediacentre/factsheets/fs310/en/

Thumbnail: Coronaviruses are a group of viruses known for causing the common cold. They have a halo or crown-like (corona) appearance when viewed under an electron microscope. (Public Domain; CDC/Dr. Fred Murphy).

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10.4.1: Anatomy and Normal Microbiota of the Respiratory Tract

Learning Objectives

- Describe the major anatomical features of the upper and lower respiratory tract
- Describe the normal microbiota of the upper and lower respiratory tracts
- Explain how microorganisms overcome defenses of upper and lower respiratory-tract membranes to cause infection
- Explain how microbes and the respiratory system interact and modify each other in healthy individuals and during an infection

Clinical Focus: Part 1

John, a 65-year-old man with asthma and type 2 diabetes, works as a sales associate at a local home improvement store. Recently, he began to feel quite ill and made an appointment with his family physician. At the clinic, John reported experiencing headache, chest pain, coughing, and shortness of breath. Over the past day, he had also experienced some nausea and diarrhea. A nurse took his temperature and found that he was running a fever of 40 °C (104 °F).

John suggested that he must have a case of influenza (flu), and regretted that he had put off getting his flu vaccine this year. After listening to John's breathing through a stethoscope, the physician ordered a chest radiography and collected blood, urine, and sputum samples.

Exercise 10.4.1.1

Based on this information, what factors may have contributed to John's illness?

The primary function of the respiratory tract is to exchange gases (oxygen and carbon dioxide) for metabolism. However, inhalation and exhalation (particularly when forceful) can also serve as a vehicle of transmission for pathogens between individuals.

Anatomy of the Upper Respiratory System

The respiratory system can be conceptually divided into upper and lower regions at the point of the epiglottis, the structure that seals off the lower respiratory system from the pharynx during swallowing (Figure 10.4.1.1). The upper respiratory system is in direct contact with the external environment. The nares (or nostrils) are the external openings of the nose that lead back into the nasal cavity, a large air-filled space behind the nares. These anatomical sites constitute the primary opening and first section of the respiratory tract, respectively. The nasal cavity is lined with hairs that trap large particles, like dust and pollen, and prevent their access to deeper tissues. The nasal cavity is also lined with a mucous membrane and Bowman's glands that produce mucus to help trap particles and microorganisms for removal. The nasal cavity is connected to several other air-filled spaces. The sinuses, a set of four, paired small cavities in the skull, communicate with the nasal cavity through a series of small openings. The nasopharynx is part of the upper throat extending from the posterior nasal cavity. The nasopharynx carries air inhaled through the nose. The middle ear is connected to the nasopharynx through the eustachian tube. The middle ear is separated from the outer ear by the tympanic membrane, or ear drum. And finally, the lacrimal glands drain to the nasal cavity through the nasolacrimal ducts (tear ducts). The open connections between these sites allow microorganisms to move from the nasal cavity to the sinuses, middle ears (and back), and down into the lower respiratory tract from the nasopharynx.

The oral cavity is a secondary opening for the respiratory tract. The oral and nasal cavities connect through the fauces to the pharynx, or throat. The pharynx can be divided into three regions: the nasopharynx, the oropharynx, and the laryngopharynx. Air inhaled through the mouth does not pass through the nasopharynx; it proceeds first through the oropharynx and then through the laryngopharynx. The palatine tonsils, which consist of lymphoid tissue, are located within the oropharynx. The laryngopharynx, the last portion of the pharynx, connects to the larynx, which contains the vocal fold (Figure 10.4.1.1).

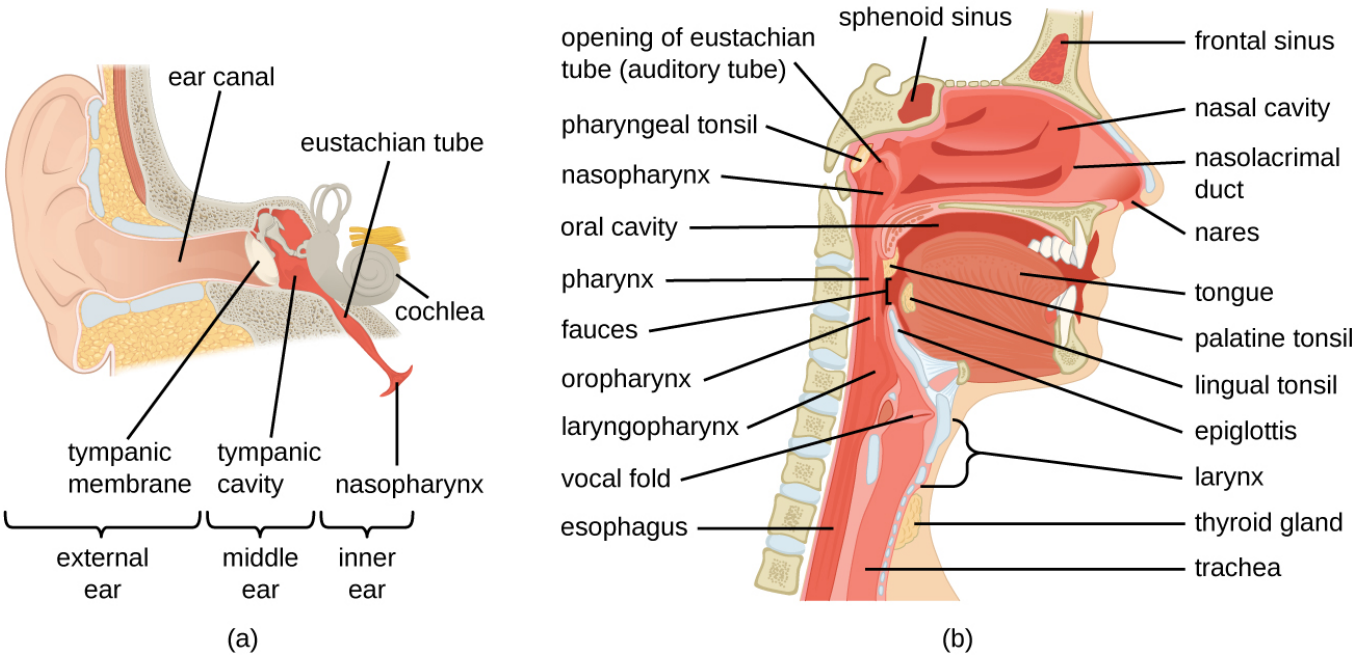


Figure 10.4.1.1: (a) The ear is connected to the upper respiratory tract by the eustachian tube, which opens to the nasopharynx. (b) The structures of the upper respiratory tract.

? Exercise 10.4.1.2

1. Identify the sequence of anatomical structures through which microbes would pass on their way from the nares to the larynx.
2. What two anatomical points do the eustachian tubes connect?

Anatomy of the Lower Respiratory System

The lower respiratory system begins below the epiglottis in the larynx or voice box (Figure 10.4.1.2). The trachea, or windpipe, is a cartilaginous tube extending from the larynx that provides an unobstructed path for air to reach the lungs. The trachea bifurcates into the left and right bronchi as it reaches the lungs. These paths branch repeatedly to form smaller and more extensive networks of tubes, the bronchioles. The terminal bronchioles formed in this tree-like network end in cul-de-sacs called the alveoli. These structures are surrounded by capillary networks and are the site of gas exchange in the respiratory system. Human lungs contain on the order of 400,000,000 alveoli. The outer surface of the lungs is protected with a double-layered pleural membrane. This structure protects the lungs and provides lubrication to permit the lungs to move easily during respiration.

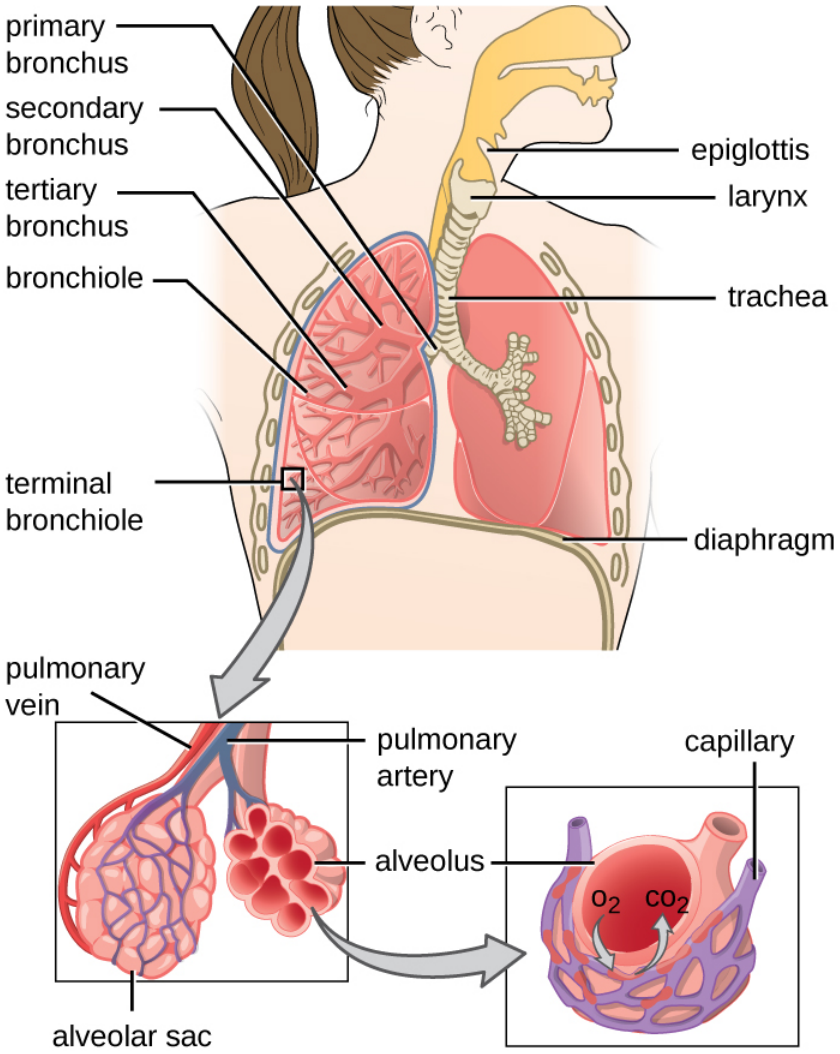


Figure 10.4.1.2: The structures of the lower respiratory tract are identified in this illustration. (credit: modification of work by National Cancer Institute)

Defenses of the Respiratory System

The inner lining of the respiratory system consists of mucous membranes (Figure 10.4.1.3) and is protected by multiple immune defenses. The goblet cells within the respiratory epithelium secrete a layer of sticky mucus. The viscosity and acidity of this secretion inhibits microbial attachment to the underlying cells. In addition, the respiratory tract contains ciliated epithelial cells. The beating cilia dislodge and propel the mucus, and any trapped microbes, upward to the epiglottis, where they will be swallowed. Elimination of microbes in this manner is referred to as the mucociliary escalator effect and is an important mechanism that prevents inhaled microorganisms from migrating further into the lower respiratory tract.

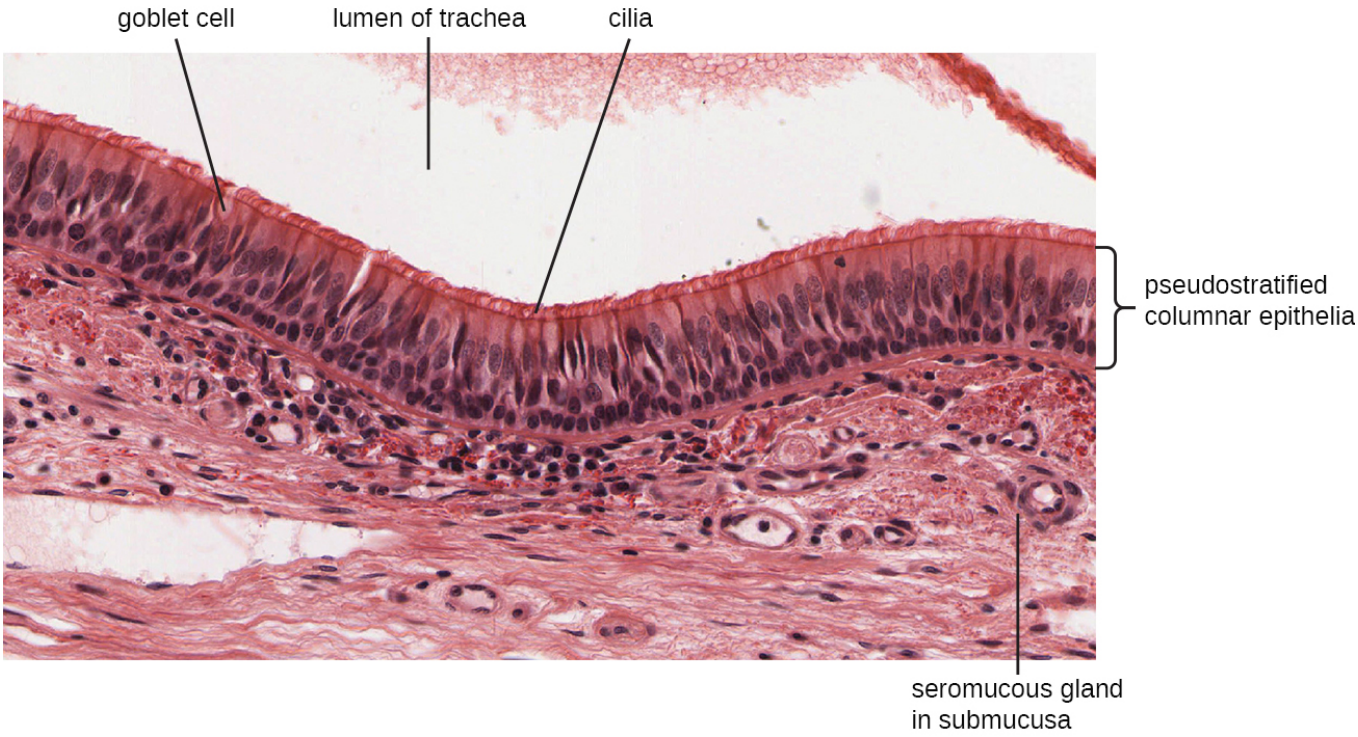


Figure 10.4.1.3: This micrograph shows the structure of the mucous membrane of the respiratory tract. (credit: modification of micrograph provided by the Regents of University of Michigan Medical School © 2012)

The upper respiratory system is under constant surveillance by mucosa-associated lymphoid tissue (MALT), including the adenoids and tonsils. Other mucosal defenses include secreted antibodies (IgA), lysozyme, surfactant, and antimicrobial peptides called defensins. Meanwhile, the lower respiratory tract is protected by alveolar macrophages. These phagocytes efficiently kill any microbes that manage to evade the other defenses. The combined action of these factors renders the lower respiratory tract nearly devoid of colonized microbes.

? Exercise 10.4.1.3

1. Identify the sequence of anatomical structures through which microbes would pass on their way from the larynx to the alveoli.
2. Name some defenses of the respiratory system that protect against microbial infection.

Normal Microbiota of the Respiratory System

The upper respiratory tract contains an abundant and diverse microbiota. The nasal passages and sinuses are primarily colonized by members of the Firmicutes, Actinobacteria, and Proteobacteria. The most common bacteria identified include *Staphylococcus epidermidis*, viridans group streptococci (VGS), *Corynebacterium* spp. (diphtheroids), *Propionibacterium* spp., and *Haemophilus* spp. The oropharynx includes many of the same isolates as the nose and sinuses, with the addition of variable numbers of bacteria like species of *Prevotella*, *Fusobacterium*, *Moraxella*, and *Eikenella*, as well as some *Candida* fungal isolates. In addition, many healthy humans asymptomatically carry potential pathogens in the upper respiratory tract. As much as 20% of the population carry *Staphylococcus aureus* in their nostrils.[1] The pharynx, too, can be colonized with pathogenic strains of *Streptococcus*, *Haemophilus*, and *Neisseria*.

The lower respiratory tract, by contrast, is scantily populated with microbes. Of the organisms identified in the lower respiratory tract, species of *Pseudomonas*, *Streptococcus*, *Prevotella*, *Fusobacterium*, and *Veillonella* are the most common. It is not clear at this time if these small populations of bacteria constitute a normal microbiota or if they are transients.

Many members of the respiratory system's normal microbiota are opportunistic pathogens. To proliferate and cause host damage, they first must overcome the immune defenses of respiratory tissues. Many mucosal pathogens produce virulence factors such as adhesins that mediate attachment to host epithelial cells, or polysaccharide capsules that allow microbes to evade phagocytosis. The

endotoxins of gram-negative bacteria can stimulate a strong inflammatory response that damages respiratory cells. Other pathogens produce exotoxins, and still others have the ability to survive within the host cells. Once an infection of the respiratory tract is established, it tends to impair the mucociliary escalator, limiting the body's ability to expel the invading microbes, thus making it easier for pathogens to multiply and spread.

Vaccines have been developed for many of the most serious bacterial and viral pathogens. Several of the most important respiratory pathogens and their vaccines, if available, are summarized in Table 10.4.1.1. Components of these vaccines will be explained later in the chapter.

Table 10.4.1.1: Some Important Respiratory Diseases and Vaccines

Disease	Pathogen	Available Vaccine(s)[2]
Chickenpox/shingles	Varicella-zoster virus	Varicella (chickenpox) vaccine, herpes zoster (shingles) vaccine
Common cold	Rhinovirus	None
Diphtheria	*Corynebacterium diphtheriae*	DtaP, Tdap, DT,Td, DTP
Epiglottitis, otitis media	*Haemophilus influenzae*	Hib
Influenza	Influenza viruses	Inactivated, FluMist
Measles	Measles virus	MMR
Pertussis	*Bordetella pertussis*	DTaP, Tdap
Pneumonia	*Streptococcus pneumoniae*	Pneumococcal conjugate vaccine (PCV13), pneumococcal polysaccharide vaccine (PPSV23)
Rubella (German measles)	Rubella virus	MMR
Severe acute respiratory syndrome (SARS)	SARS-associated coronavirus (SARS-CoV)	None
Tuberculosis	*Mycobacterium tuberculosis*	BCG

? Exercise 10.4.1.4

1. What are some pathogenic bacteria that are part of the normal microbiota of the respiratory tract?
2. What virulence factors are used by pathogens to overcome the immune protection of the respiratory tract?

Signs and Symptoms of Respiratory Infection

Microbial diseases of the respiratory system typically result in an acute inflammatory response. These infections can be grouped by the location affected and have names ending in "itis", which literally means *inflammation of*. For instance, rhinitis is an inflammation of the nasal cavities, often characteristic of the common cold. Rhinitis may also be associated with hay fever allergies or other irritants. Inflammation of the sinuses is called sinusitis inflammation of the ear is called otitis. Otitis media is an inflammation of the middle ear. A variety of microbes can cause pharyngitis, commonly known as a sore throat. An inflammation of the larynx is called laryngitis. The resulting inflammation may interfere with vocal cord function, causing voice loss. When tonsils are inflamed, it is called tonsillitis. Chronic cases of tonsillitis may be treated surgically with tonsillectomy. More rarely, the epiglottis can be infected, a condition called epiglottitis. In the lower respiratory system, the inflammation of the bronchial tubes results in bronchitis. Most serious of all is pneumonia, in which the alveoli in the lungs are infected and become inflamed. Pus and edema accumulate and fill the alveoli with fluids (called consolidations). This reduces the lungs' ability to exchange gases and often results in a productive cough expelling phlegm and mucus. Cases of pneumonia can range from mild to life-threatening, and remain an important cause of mortality in the very young and very old.

Exercise 10.4.1.5

Describe the typical symptoms of rhinitis, sinusitis, pharyngitis, and laryngitis.

Smoking-Associated Pneumonia

Camila is a 22-year-old student who has been a chronic smoker for 5 years. Recently, she developed a persistent cough that has not responded to over-the-counter treatments. Her doctor ordered a chest radiograph to investigate. The radiological results were consistent with pneumonia. In addition, *Streptococcus pneumoniae* was isolated from Camila's sputum.

Smokers are at a greater risk of developing pneumonia than the general population. Several components of tobacco smoke have been demonstrated to impair the lungs' immune defenses. These effects include disrupting the function of the ciliated epithelial cells, inhibiting phagocytosis, and blocking the action of antimicrobial peptides. Together, these lead to a dysfunction of the mucociliary escalator effect. The organisms trapped in the mucus are therefore able to colonize the lungs and cause infections rather than being expelled or swallowed.

Key Concepts and Summary

- The respiratory tract is divided into upper and lower regions at the **epiglottis**.
- Air enters the upper respiratory tract through the **nasal cavity** and mouth, which both lead to the **pharynx**. The lower respiratory tract extends from the **larynx** into the **trachea** before branching into the **bronchi**, which divide further to form the **bronchioles**, which terminate in **alveoli**, where gas exchange occurs.
- The upper respiratory tract is colonized by an extensive and diverse normal microbiota, many of which are potential pathogens. Few microbial inhabitants have been found in the lower respiratory tract, and these may be transients.
- Members of the normal microbiota may cause opportunistic infections, using a variety of strategies to overcome the innate nonspecific defenses (including the mucociliary escalator) and adaptive specific defenses of the respiratory system.
- Effective vaccines are available for many common respiratory pathogens, both bacterial and viral.
- Most respiratory infections result in inflammation of the infected tissues; these conditions are given names ending in *-itis*, such as **rhinitis**, **sinusitis**, **otitis**, **pharyngitis**, and **bronchitis**.

Footnotes

1. 1 J. Kluytmans et al. "Nasal Carriage of *Staphylococcus aureus*: Epidemiology, Underlying Mechanisms, and Associated Risks." *Clinical Microbiology Reviews* 10 no. 3 (1997):505–520.
2. 2 Full names of vaccines listed in table: *Haemophilus influenzae* type B (Hib); Diphtheria, tetanus, and acellular pertussis (DtaP); tetanus, diphtheria, and acellular pertussis (Tdap); diphtheria and tetanus (DT); tetanus and diphtheria (Td); diphtheria, pertussis, and tetanus (DTP); Bacillus Calmette-Guérin; Measles, mumps, rubella (MMR)

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10.4.2: Bacterial Infections of the Respiratory Tract

Learning Objectives

- Identify the most common bacteria that can cause infections of the upper and lower respiratory tract
- Compare the major characteristics of specific bacterial diseases of the respiratory tract

The respiratory tract can be infected by a variety of bacteria, both gram positive and gram negative. Although the diseases that they cause may range from mild to severe, in most cases, the microbes remain localized within the respiratory system. Fortunately, most of these infections also respond well to antibiotic therapy.

Streptococcal Infections

A common upper respiratory infection, streptococcal pharyngitis (strep throat) is caused by *Streptococcus pyogenes*. This gram-positive bacterium appears as chains of cocci, as seen in Figure 10.4.2.1. Rebecca Lancefieldserologically classified streptococci in the 1930s using carbohydrate antigens from the bacterial cell walls. *S. pyogenes* is the sole member of the Lancefield group A streptococci and is often referred to as GAS, or group A strep.

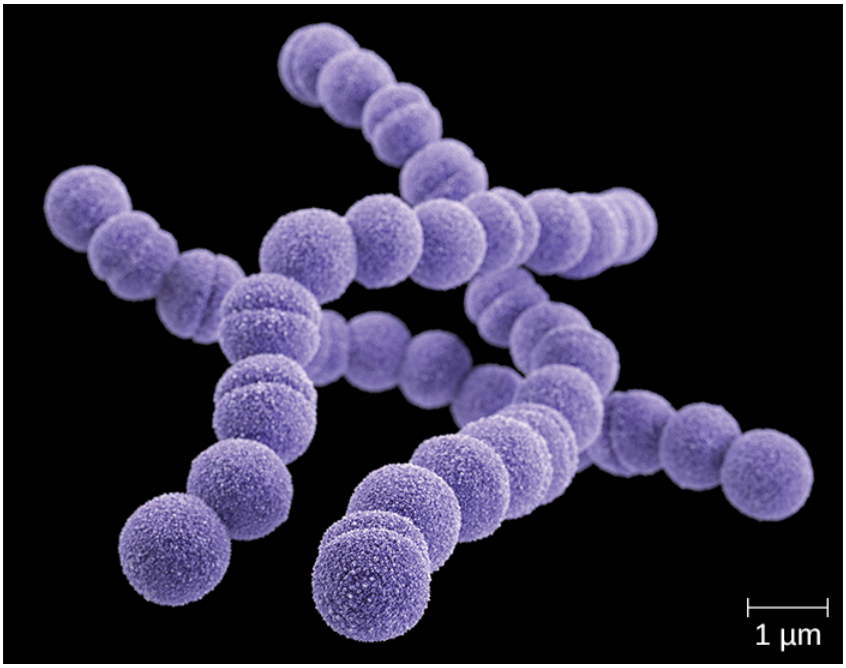


Figure 10.4.2.1: This scanning electron micrograph of *Streptococcus pyogenes* shows the characteristic cellular phenotype resembling chains of cocci. (credit: modification of work by U.S. Centers for Disease Control and Prevention - Medical Illustrator)

Similar to streptococcal infections of the skin, the mucosal membranes of the pharynx are damaged by the release of a variety of exoenzymes and exotoxins by this extracellular pathogen. Many strains of *S. pyogenes* can degrade connective tissues by using hyaluronidase, collagenase and streptokinase. Streptokinase activates plasmin, which leads to degradation of fibrin and, in turn, dissolution of blood clots, which assists in the spread of the pathogen. Released toxins include streptolysins that can destroy red and white blood cells. The classic signs of streptococcal pharyngitis are a fever higher than 38 °C (100.4 °F); intense pharyngeal pain; erythema associated with pharyngeal inflammation; and swollen, dark-red palatine tonsils, often dotted with patches of pus; and petechiae (microcapillary hemorrhages) on the soft or hard palate (roof of the mouth) (Figure 10.4.2.2). The submandibular lymph nodes beneath the angle of the jaw are also often swollen during strep throat.

Some strains of group A streptococci produce erythrogenic toxin. This exotoxin is encoded by a temperate bacteriophage (bacterial virus) and is an example of phage conversion (see The Viral Life Cycle). The toxin attacks the plasma membranes of capillary endothelial cells and leads to scarlet fever (or scarlatina), a disseminated fine red rash on the skin, and strawberry tongue, a red rash on the tongue (Figure 10.4.2.2). Severe cases may even lead to streptococcal toxic shock syndrome (STSS), which results from massive superantigen production that leads to septic shock and death.

S. pyogenes can be easily spread by direct contact or droplet transmission through coughing and sneezing. The disease can be diagnosed quickly using a rapid enzyme immunoassay for the group A antigen. However, due to a significant rate of false-negative results (up to 30%[1]), culture identification is still the gold standard to confirm pharyngitis due to *S. pyogenes*. *S. pyogenes* can be identified as a catalase-negative, beta hemolytic bacterium that is susceptible to 0.04 units of bacitracin. Antibiotic resistance is limited for this bacterium, so most β-lactams remain effective; oral amoxicillin and intramuscular penicillin G are those most commonly prescribed.

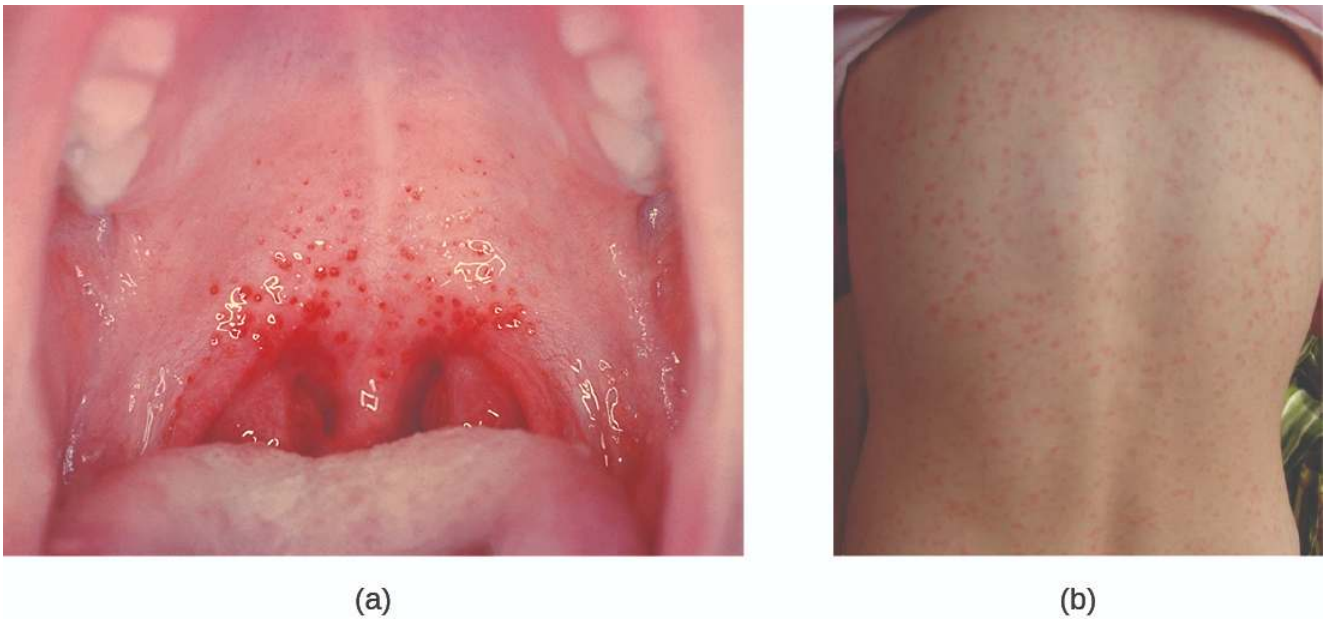


Figure 10.4.2.2: Streptococcal infections of the respiratory tract may cause localized pharyngitis or systemic signs and symptoms. (a) The characteristic appearance of strep throat: bright red arches of inflammation with the presence of dark-red spots (petechiae). (b) Scarlet fever presents as a rash on the skin. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Alicia Williams)

Sequelae of *S. pyogenes* Infections

One reason strep throat infections are aggressively treated with antibiotics is because they can lead to serious sequelae, later clinical consequences of a primary infection. It is estimated that 1%–3% of untreated *S. pyogenes* infections can be followed by nonsuppurative (without the production of pus) sequelae that develop 1–3 weeks after the acute infection has resolved. Two such sequelae are acute rheumatic fever and acute glomerulonephritis.

Acute rheumatic fever can follow pharyngitis caused by specific rheumatogenic strains of *S. pyogenes* (strains 1, 3, 5, 6, and 18). Although the exact mechanism responsible for this sequela remains unclear, molecular mimicry between the M protein of rheumatogenic strains of *S. pyogenes* and heart tissue is thought to initiate the autoimmune attack. The most serious and lethal clinical manifestation of rheumatic fever is damage to and inflammation of the heart (carditis). Acute glomerulonephritis also results from an immune response to streptococcal antigens following pharyngitis and cutaneous infections. Acute glomerulonephritis develops within 6–10 days after pharyngitis, but can take up to 21 days after a cutaneous infection. Similar to acute rheumatic fever, there are strong associations between specific nephritogenic strains of *S. pyogenes* and acute glomerulonephritis, and evidence suggests a role for antigen mimicry and autoimmunity. However, the primary mechanism of acute glomerulonephritis appears to be the formation of immune complexes between *S. pyogenes* antigens and antibodies, and their deposition between endothelial cells of the glomeruli of kidney. Inflammatory response against the immune complexes leads to damage and inflammation of the glomeruli (glomerulonephritis).

? Exercise 10.4.2.1

1. What are the symptoms of strep throat?
2. What is erythrogenic toxin and what effect does it have?
3. What are the causes of rheumatic fever and acute glomerulonephritis?

Acute Otitis Media

An infection of the middle ear is called acute otitis media (AOM), but often it is simply referred to as an earache. The condition is most common between ages 3 months and 3 years. In the United States, AOM is the second-leading cause of visits to pediatricians by children younger than age 5 years, and it is the leading indication for antibiotic prescription.[2]

AOM is characterized by the formation and accumulation of pus in the middle ear. Unable to drain, the pus builds up, resulting in moderate to severe bulging of the tympanic membrane and otalgia (ear pain). Inflammation resulting from the infection leads to swelling of the eustachian tubes, and may also lead to fever, nausea, vomiting, and diarrhea, particularly in infants. Infants and toddlers who cannot yet speak may exhibit nonverbal signs suggesting AOM, such as holding, tugging, or rubbing of the ear, as well as uncharacteristic crying or distress in response to the pain.

AOM can be caused by a variety of bacteria. Among neonates, *S. pneumoniae* is the most common cause of AOM, but *Escherichia coli*, *Enterococcus* spp., and group B *Streptococcus* species can also be involved. In older infants and children younger than 14 years old, the most common bacterial causes are *S. pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*. Among *S. pneumoniae* infections, encapsulated strains are frequent causes of AOM. By contrast, the strains of *H. influenzae* and *M. cattarhalis* that are responsible for AOM do not possess a capsule. Rather than direct tissue damage by these pathogens, bacterial components such as lipopolysaccharide (LPS) in gram-negative pathogens induce an inflammatory response that causes swelling, pus, and tissue damage within the middle ear (Figure 10.4.2.3).

Any blockage of the eustachian tubes, with or without infection, can cause fluid to become trapped and accumulate in the middle ear. This is referred to as otitis media with effusion (OME). The accumulated fluid offers an excellent reservoir for microbial growth and, consequently, secondary bacterial infections often ensue. This can lead to recurring and chronic earaches, which are especially common in young children. The higher incidence in children can be attributed to many factors. Children have more upper respiratory infections, in general, and their eustachian tubes are also shorter and drain at a shallower angle. Young children also tend to spend more time lying down than adults, which facilitates drainage from the nasopharynx through the eustachian tube and into the middle ear. Bottle feeding while lying down enhances this risk because the sucking action on the bottle causes negative pressure to build up within the eustachian tube, promoting the movement of fluid and bacteria from the nasopharynx.

Diagnosis is typically made based on clinical signs and symptoms, without laboratory testing to determine the specific causative agent. Antibiotics are frequently prescribed for the treatment of AOM. High-dose amoxicillin is the first-line drug, but with increasing resistance concerns, macrolides and cephalosporins may also be used. The pneumococcal conjugate vaccine (PCV13) contains serotypes that are important causes of AOM, and vaccination has been shown to decrease the incidence of AOM. Vaccination against influenza has also been shown to decrease the risk for AOM, likely because viral infections like influenza predispose patients to secondary infections with *S. pneumoniae*. Although there is a conjugate vaccine available for the invasive serotype B of *H. influenzae*, this vaccine does not impact the incidence of *H. influenzae* AOM. Because unencapsulated strains of *H. influenzae* and *M. catarrhalis* are involved in AOM, vaccines against bacterial cellular factors other than capsules will need to be developed.

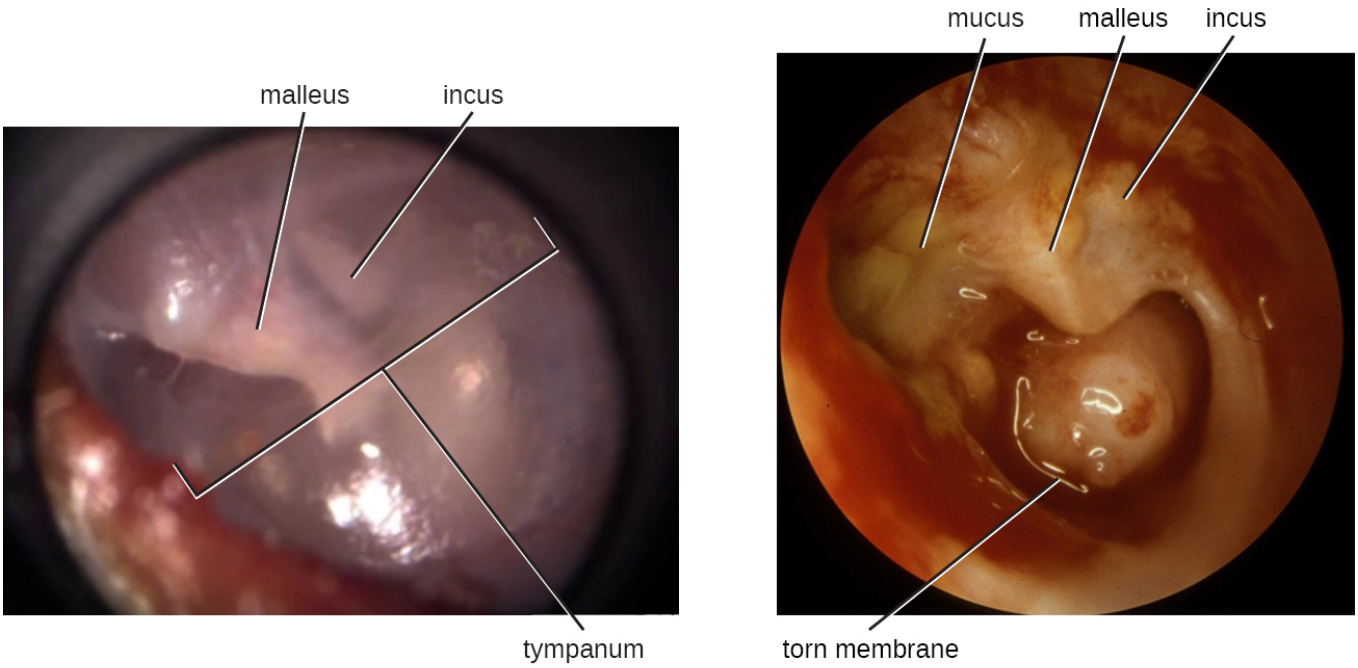


Figure 10.4.2.3: (a) A healthy tympanic membrane; the middle ear bones can be seen behind the membrane. (b) An ear with chronic inflammation that has resulted in a torn membrane, erosion of the inner ear bones, and mucus buildup. (credit a: modification of work by "DrER.tv"/YouTube; credit b: modification of work by Li Mg, Hotez PJ, Vrabec JT, Donovan DT)

Bacterial Rhinosinusitis

The microbial community of the nasopharynx is extremely diverse and harbors many opportunistic pathogens, so it is perhaps not surprising that infections leading to rhinitis and sinusitis have many possible causes. These conditions often occur as secondary infections after a viral infection, which effectively compromises the immune defenses and allows the opportunistic bacteria to establish themselves. Bacterial sinusitis involves infection and inflammation within the paranasal sinuses. Because bacterial sinusitis rarely occurs without rhinitis, the preferred term is rhinosinusitis. The most common causes of bacterial rhinosinusitis are similar to those for AOM, including *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

? Exercise 10.4.2.2

1. What are the usual causative agents of acute otitis media?
2. What factors facilitate acute otitis media with effusion in young children?
3. What factor often triggers bacterial rhinosinusitis?

Diphtheria

The causative agent of diphtheria, *Corynebacterium diphtheriae*, is a club-shaped, gram-positive rod that belongs to the phylum Actinobacteria. Diphtheroids are common members of the normal nasopharyngeal microbiota. However, some strains of *C. diphtheriae* become pathogenic because of the presence of a temperate bacteriophage-encoded protein—the diphtheria toxin. Diphtheria is typically a respiratory infection of the oropharynx but can also cause impetigo-like lesions on the skin. Although the disease can affect people of all ages, it tends to be most severe in those younger than 5 years or older than 40 years. Like strep throat, diphtheria is commonly transmitted in the droplets and aerosols produced by coughing. After colonizing the throat, the bacterium remains in the oral cavity and begins producing the diphtheria toxin. This protein is an A-B toxin that blocks host-cell protein synthesis by inactivating elongation factor (EF)-2 (see Virulence Factors of Bacterial and Viral Pathogens). The toxin's action leads to the death of the host cells and an inflammatory response. An accumulation of grayish exudate consisting of dead host cells, pus, red blood cells, fibrin, and infectious bacteria results in the formation of a pseudomembrane. The pseudomembrane can cover mucous membranes of the nasal cavity, tonsils, pharynx, and larynx (Figure 10.4.2.4). This is a classic sign of diphtheria. As the disease progresses, the pseudomembrane can enlarge to obstruct the fauces of the pharynx or trachea and can lead to

suffocation and death. Sometimes, intubation, the placement of a breathing tube in the trachea, is required in advanced infections. If the diphtheria toxin spreads throughout the body, it can damage other tissues as well. This can include myocarditis (heart damage) and nerve damage that may impair breathing.

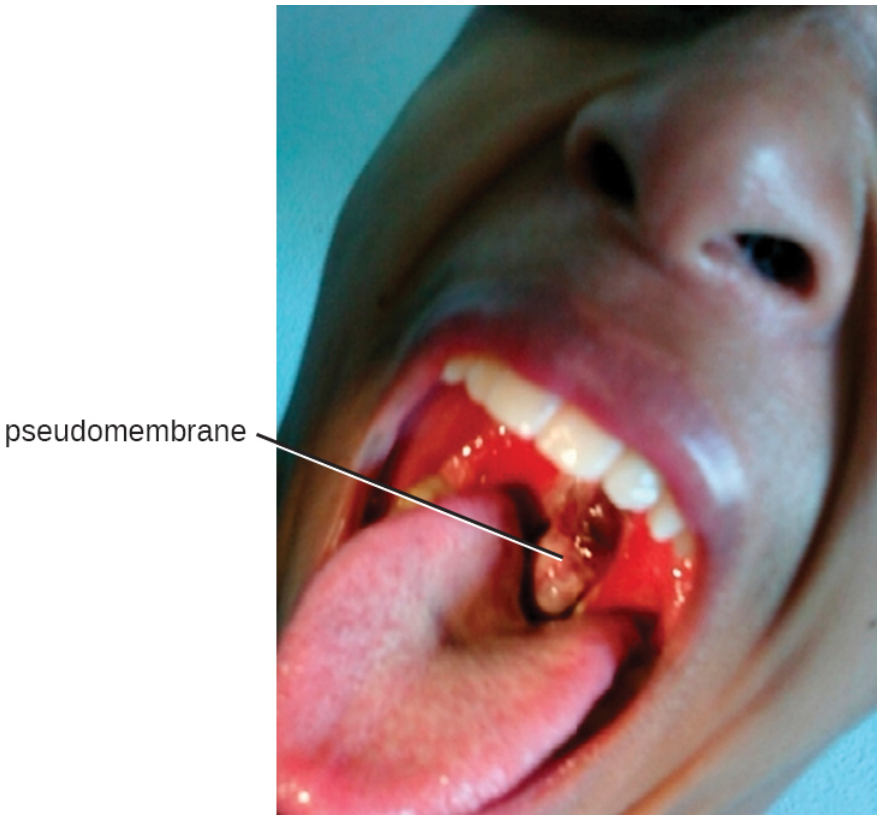


Figure 10.4.2.4: The pseudomembrane in a patient with diphtheria presents as a leathery gray patch consisting of dead cells, pus, fibrin, red blood cells, and infectious microbes. (credit: modification of work by Putnong N, Agustin G, Pasubillo M, Miyagi K, Dimaano EM)

The presumptive diagnosis of diphtheria is primarily based on the clinical symptoms (i.e., the pseudomembrane) and vaccination history, and is typically confirmed by identifying bacterial cultures obtained from throat swabs. The diphtheria toxin itself can be directly detected in vitro using polymerase chain reaction (PCR)-based, direct detection systems for the diphtheria *tox* gene, and immunological techniques like radial immunodiffusion or Elek's immunodiffusion test.

Broad-spectrum antibiotics like penicillin and erythromycin tend to effectively control *C. diphtheriae* infections. Regrettably, they have no effect against preformed toxins. If toxin production has already occurred in the patient, antitoxins (preformed antibodies against the toxin) are administered. Although this is effective in neutralizing the toxin, the antitoxins may lead to serum sickness because they are produced in horses (see Hypersensitivities).

Widespread vaccination efforts have reduced the occurrence of diphtheria worldwide. There are currently four combination toxoid vaccines available that provide protection against diphtheria and other diseases: DTaP, Tdap, DT, and Td. In all cases, the letters "d," "t," and "p" stand for diphtheria, tetanus, and pertussis, respectively; the "a" stands for acellular. If capitalized, the letters indicate a full-strength dose; lowercase letters indicate reduced dosages. According to current recommendations, children should receive five doses of the DTaP vaccine in their youth and a Td booster every 10 years. Children with adverse reactions to the pertussis vaccine may be given the DT vaccine in place of the DTaP.

? Exercise 10.4.2.3

1. What effect does diphtheria toxin have?
2. What is the pseudomembrane composed of?

Bacterial Pneumonia

Pneumonia is a general term for infections of the lungs that lead to inflammation and accumulation of fluids and white blood cells in the alveoli. Pneumonia can be caused by bacteria, viruses, fungi, and other organisms, although the vast majority of pneumonias are bacterial in origin. Bacterial pneumonia is a prevalent, potentially serious infection; it caused more 50,000 deaths in the United States in 2014.[3] As the alveoli fill with fluids and white blood cells (consolidation), air exchange becomes impaired and patients experience respiratory distress (Figure 10.4.2.5). In addition, pneumonia can lead to pleurisy, an infection of the pleural membrane surrounding the lungs, which can make breathing very painful. Although many different bacteria can cause pneumonia under the right circumstances, three bacterial species cause most clinical cases: *Streptococcus pneumoniae*, *H. influenzae*, and *Mycoplasma pneumoniae*. In addition to these, we will also examine some of the less common causes of pneumonia.

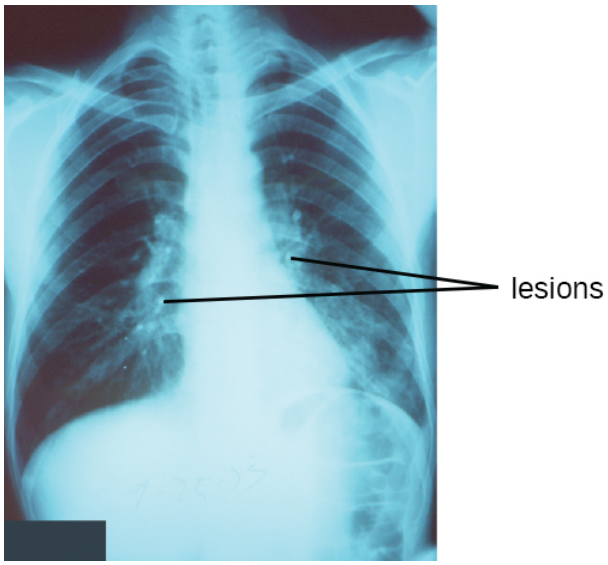
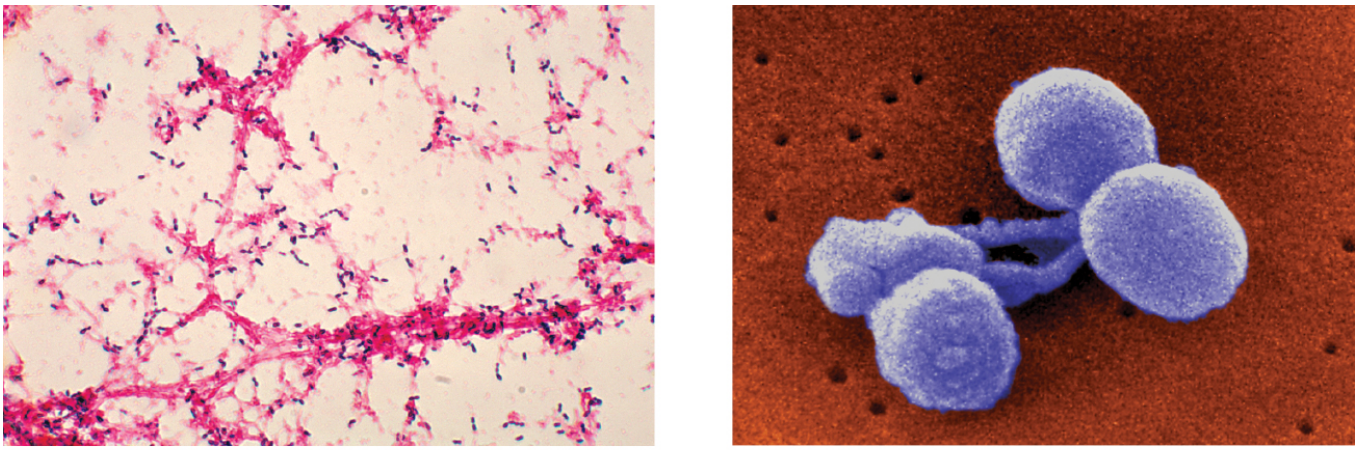


Figure 10.4.2.5: A chest radiograph of a patient with pneumonia shows the consolidations (lesions) present as opaque patches. (credit: modification of work by Centers for Disease Control and Prevention)

Pneumococcal Pneumonia

The most common cause of community-acquired bacterial pneumonia is *Streptococcus pneumoniae*. This gram-positive, alpha hemolytic streptococcus is commonly found as part of the normal microbiota of the human respiratory tract. The cells tend to be somewhat lancet-shaped and typically appear as pairs (Figure 10.4.2.6). The pneumococci initially colonize the bronchioles of the lungs. Eventually, the infection spreads to the alveoli, where the microbe's polysaccharide capsule interferes with phagocytic clearance. Other virulence factors include autolysins like Lyt A, which degrade the microbial cell wall, resulting in cell lysis and the release of cytoplasmic virulence factors. One of these factors, pneumolysin O, is important in disease progression; this pore-forming protein damages host cells, promotes bacterial adherence, and enhances pro-inflammatory cytokine production. The resulting inflammatory response causes the alveoli to fill with exudate rich in neutrophils and red blood cells. As a consequence, infected individuals develop a productive cough with bloody sputum.



(a) (b)

Figure 10.4.2.6: (a) This micrograph of *Streptococcus pneumoniae* grown from a blood culture shows the characteristic lancet-shaped diplococcal morphology. (b) A colorized scanning electron micrograph of *S. pneumoniae*. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Janice Carr, Centers for Disease Control and Prevention)

Pneumococci can be presumptively identified by their distinctive gram-positive, lancet-shaped cell morphology and diplococcal arrangement. In blood agar cultures, the organism demonstrates alpha hemolytic colonies that are autolytic after 24 to 48 hours. In addition, *S. pneumoniae* is extremely sensitive to optochin and colonies are rapidly destroyed by the addition of 10% solution of sodium deoxycholate. All clinical pneumococcal isolates are serotyped using the quellung reaction with typing antisera produced by the CDC. Positive quellung reactions are considered definitive identification of pneumococci.

Antibiotics remain the mainstay treatment for pneumococci. β-Lactams like penicillin are the first-line drugs, but resistance to β-lactams is a growing problem. When β-lactam resistance is a concern, macrolides and fluoroquinolones may be prescribed. However, *S. pneumoniae* resistance to macrolides and fluoroquinolones is increasing as well, limiting the therapeutic options for some infections. There are currently two pneumococcal vaccines available: pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23). These are generally given to the most vulnerable populations of individuals: children younger than 2 years and adults older than 65 years.

Haemophilus Pneumonia

Encapsulated strains of *Haemophilus influenzae* are known for causing meningitis, but nonencapsulated strains are important causes of pneumonia. This small, gram-negative coccobacillus is found in the pharynx of the majority of healthy children; however, *Haemophilus* pneumonia is primarily seen in the elderly. Like other pathogens that cause pneumonia, *H. influenzae* is spread by droplets and aerosols produced by coughing. A fastidious organism, *H. influenzae* will only grow on media with available factor X (hemin) and factor V (NAD), like chocolate agar (Figure 10.4.2.7). Serotyping must be performed to confirm identity of *H. influenzae* isolates.

Infections of the alveoli by *H. influenzae* result in inflammation and accumulation of fluids. Increasing resistance to β-lactams, macrolides, and tetracyclines presents challenges for the treatment of *Haemophilus* pneumonia. Resistance to the fluoroquinolones is rare among isolates of *H. influenzae* but has been observed. As discussed for AOM, a vaccine directed against nonencapsulated *H. influenzae*, if developed, would provide protection against pneumonia caused by this pathogen.

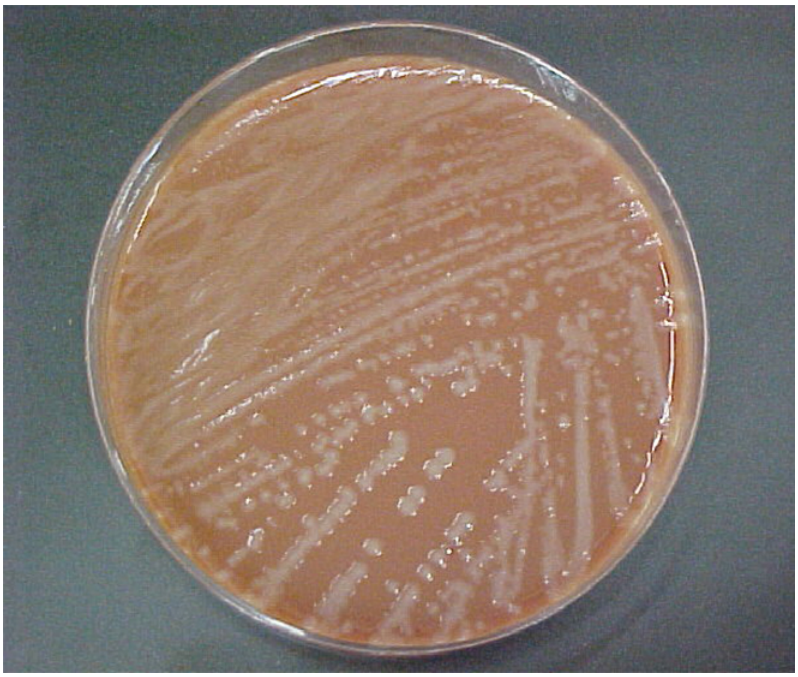


Figure 10.4.2.7: Culture of *Haemophilus influenzae* on a chocolate agar plate. (credit: modification of work by Centers for Disease Control and Prevention)

Why Me?

Tracy is a 6-year old who developed a serious cough that would not seem to go away. After 2 weeks, her parents became concerned and took her to the pediatrician, who suspected a case of bacterial pneumonia. Tests confirmed that the cause was *Haemophilus influenzae*. Fortunately, Tracy responded well to antibiotic treatment and eventually made a full recovery.

Because there had been several other cases of bacterial pneumonia at Tracy's elementary school, local health officials urged parents to have their children screened. Of the children who were screened, it was discovered that greater than 50% carried *H. influenzae* in their nasal cavities, yet all but two of them were asymptomatic.

Why is it that some individuals become seriously ill from bacterial infections that seem to have little or no effect on others? The pathogenicity of an organism—its ability to cause host damage—is not solely a property of the microorganism. Rather, it is the product of a complex relationship between the microbe's virulence factors and the immune defenses of the individual. Preexisting conditions and environmental factors such as exposure to secondhand smoke can make some individuals more susceptible to infection by producing conditions favorable to microbial growth or compromising the immune system. In addition, individuals may have genetically determined immune factors that protect them—or not—from particular strains of pathogens. The interactions between these host factors and the pathogenicity factors produced by the microorganism ultimately determine the outcome of the infection. A clearer understanding of these interactions may allow for better identification of at-risk individuals and prophylactic interventions in the future.

Mycoplasma Pneumonia (Walking Pneumonia)

Primary atypical pneumonia is caused by *Mycoplasma pneumoniae*. This bacterium is not part of the respiratory tract's normal microbiota and can cause epidemic disease outbreaks. Also known as walking pneumonia, *mycoplasma*pneumonia infections are common in crowded environments like college campuses and military bases. It is spread by aerosols formed when coughing or sneezing. The disease is often mild, with a low fever and persistent cough. These bacteria, which do not have cell walls, use a specialized attachment organelle to bind to ciliated cells. In the process, epithelial cells are damaged and the proper function of the cilia is hindered (Figure 10.4.2.8).

Mycoplasma grow very slowly when cultured. Therefore, penicillin and thallium acetate are added to agar to prevent the overgrowth by faster-growing potential contaminants. Since *M. pneumoniae* does not have a cell wall, it is resistant to these substances. Without a cell wall, the microbial cells appear pleomorphic. *M. pneumoniae* infections tend to be self-limiting but may

also respond well to macrolide antibiotic therapy. β-lactams, which target cell wall synthesis, are not indicated for treatment of infections with this pathogen.

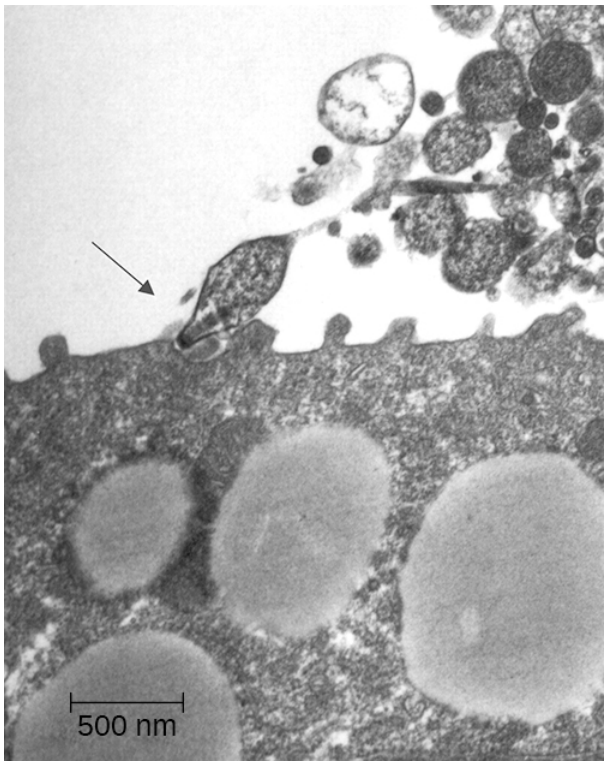


Figure 10.4.2.8: The micrograph shows *Mycoplasma pneumoniae* using their specialized receptors to attach to epithelial cells in the trachea of an infected hamster. (credit: modification of work by American Society for Microbiology)

Chlamydial Pneumonias and Psittacosis

Chlamydial pneumonia can be caused by three different species of bacteria: *Chlamydophila pneumoniae* (formerly known as *Chlamydia pneumoniae*), *Chlamydophila psittaci* (formerly known as *Chlamydia psittaci*), and *Chlamydia trachomatis*. All three are obligate intracellular pathogens and cause mild to severe pneumonia and bronchitis. Of the three, *Chlamydophila pneumoniae* is the most common and is transmitted via respiratory droplets or aerosols. *C. psittaci* causes psittacosis, a zoonotic disease that primarily affects domesticated birds such as parakeets, turkeys, and ducks, but can be transmitted from birds to humans. Psittacosis is a relatively rare infection and is typically found in people who work with birds. *Chlamydia trachomatis*, the causative agent of the sexually transmitted disease chlamydia, can cause pneumonia in infants when the infection is passed from mother to baby during birth.

Diagnosis of chlamydia by culturing tends to be difficult and slow. Because they are intracellular pathogens, they require multiple passages through tissue culture. Recently, a variety of PCR- and serologically based tests have been developed to enable easier identification of these pathogens. Tetracycline and macrolide antibiotics are typically prescribed for treatment.

Health Care-Associated Pneumonia

A variety of opportunistic bacteria that do not typically cause respiratory disease in healthy individuals are common causes of health care-associated pneumonia. These include *Klebsiella pneumoniae*, *Staphylococcus aureus*, and proteobacteria such as species of *Escherichia*, *Proteus*, and *Serratia*. Patients at risk include the elderly, those who have other preexisting lung conditions, and those who are immunocompromised. In addition, patients receiving supportive therapies such as intubation, antibiotics, and immunomodulatory drugs may also be at risk because these interventions disrupt the mucociliary escalator and other pulmonary defenses. Invasive medical devices such as catheters, medical implants, and ventilators can also introduce opportunistic pneumonia-causing pathogens into the body.[4]

Pneumonia caused by *K. pneumoniae* is characterized by lung necrosis and “currant jelly sputum,” so named because it consists of clumps of blood, mucus, and debris from the thick polysaccharide capsule produced by the bacterium. *K. pneumoniae* is often

multidrug resistant. Aminoglycoside and cephalosporin are often prescribed but are not always effective. *Klebsiella* pneumonia is frequently fatal even when treated.

Pseudomonas Pneumonia

Pseudomonas aeruginosa is another opportunistic pathogen that can cause serious cases of bacterial pneumonia in patients with cystic fibrosis (CF) and hospitalized patients assisted with artificial ventilators. This bacterium is extremely antibiotic resistant and can produce a variety of exotoxins. Ventilator-associated pneumonia with *P. aeruginosa* is caused by contaminated equipment that causes the pathogen to be aspirated into the lungs. In patients with CF, a genetic defect in the cystic fibrosis transmembrane receptor (CFTR) leads to the accumulation of excess dried mucus in the lungs. This decreases the effectiveness of the defensins and inhibits the mucociliary escalator. *P. aeruginosa* is known to infect more than half of all patients with CF. It adapts to the conditions in the patient's lungs and begins to produce alginate, a viscous exopolysaccharide that inhibits the mucociliary escalator. Lung damage from the chronic inflammatory response that ensues is the leading cause of mortality in patients with CF.[5]

? Exercise 10.4.2.4

1. What three pathogens are responsible for the most prevalent types of bacterial pneumonia?
2. Which cause of pneumonia is most likely to affect young people?
3. In what contexts does *Pseudomonas aeruginosa* cause pneumonia?

Clinical Focus: Part 2

John's chest radiograph revealed an extensive consolidation in the right lung, and his sputum cultures revealed the presence of a gram-negative rod. His physician prescribed a course of the antibiotic clarithromycin. He also ordered the rapid influenza diagnostic tests (RIDTs) for type A and B influenza to rule out a possible underlying viral infection. Despite antibiotic therapy, John's condition continued to deteriorate, so he was admitted to the hospital.

Exercise 10.4.2.5

What are some possible causes of pneumonia that would not have responded to the prescribed antibiotic?

Tuberculosis

Tuberculosis (TB) is one of the deadliest infectious diseases in human history. Although tuberculosis infection rates in the United States are extremely low, the CDC estimates that about one-third of the world's population is infected with *Mycobacterium tuberculosis*, the causal organism of TB, with 9.6 million new TB cases and 1.5 million deaths worldwide in 2014.[6]

M. tuberculosis is an acid-fast, high G + C, gram-positive, nonspore-forming rod. Its cell wall is rich in waxy mycolic acids, which make the cells impervious to polar molecules. It also causes these organisms to grow slowly. *M. tuberculosis* causes a chronic granulomatous disease that can infect any area of the body, although it is typically associated with the lungs. *M. tuberculosis* is spread by inhalation of respiratory droplets or aerosols from an infected person. The infectious dose of *M. tuberculosis* is only 10 cells.[7]

After inhalation, the bacteria enter the alveoli (Figure 10.4.2.9). The cells are phagocytized by macrophages but can survive and multiply within these phagocytes because of the protection by the waxy mycolic acid in their cell walls. If not eliminated by macrophages, the infection can progress, causing an inflammatory response and an accumulation of neutrophils and macrophages in the area. Several weeks or months may pass before an immunological response is mounted by T cells and B cells. Eventually, the lesions in the alveoli become walled off, forming small round lesions called tubercles. Bacteria continue to be released into the center of the tubercles and the chronic immune response results in tissue damage and induction of apoptosis (programmed host-cell death) in a process called liquefaction. This creates a caseous center, or air pocket, where the aerobic *M. tuberculosis* can grow and multiply. Tubercles may eventually rupture and bacterial cells can invade pulmonary capillaries; from there, bacteria can spread through the bloodstream to other organs, a condition known as miliary tuberculosis. The rupture of tubercles also facilitates transmission of the bacteria to other individuals via droplet aerosols that exit the body in coughs. Because these droplets can be

very small and stay aloft for a long time, special precautions are necessary when caring for patients with TB, such as the use of face masks and negative-pressure ventilation and filtering systems.

Eventually, most lesions heal to form calcified Ghon complexes. These structures are visible on chest radiographs and are a useful diagnostic feature. But even after the disease has apparently ended, viable bacteria remain sequestered in these locations. Release of these organisms at a later time can produce reactivation tuberculosis (or secondary TB). This is mainly observed in people with alcoholism, the elderly, or in otherwise immunocompromised individuals (Figure 10.4.2.9).

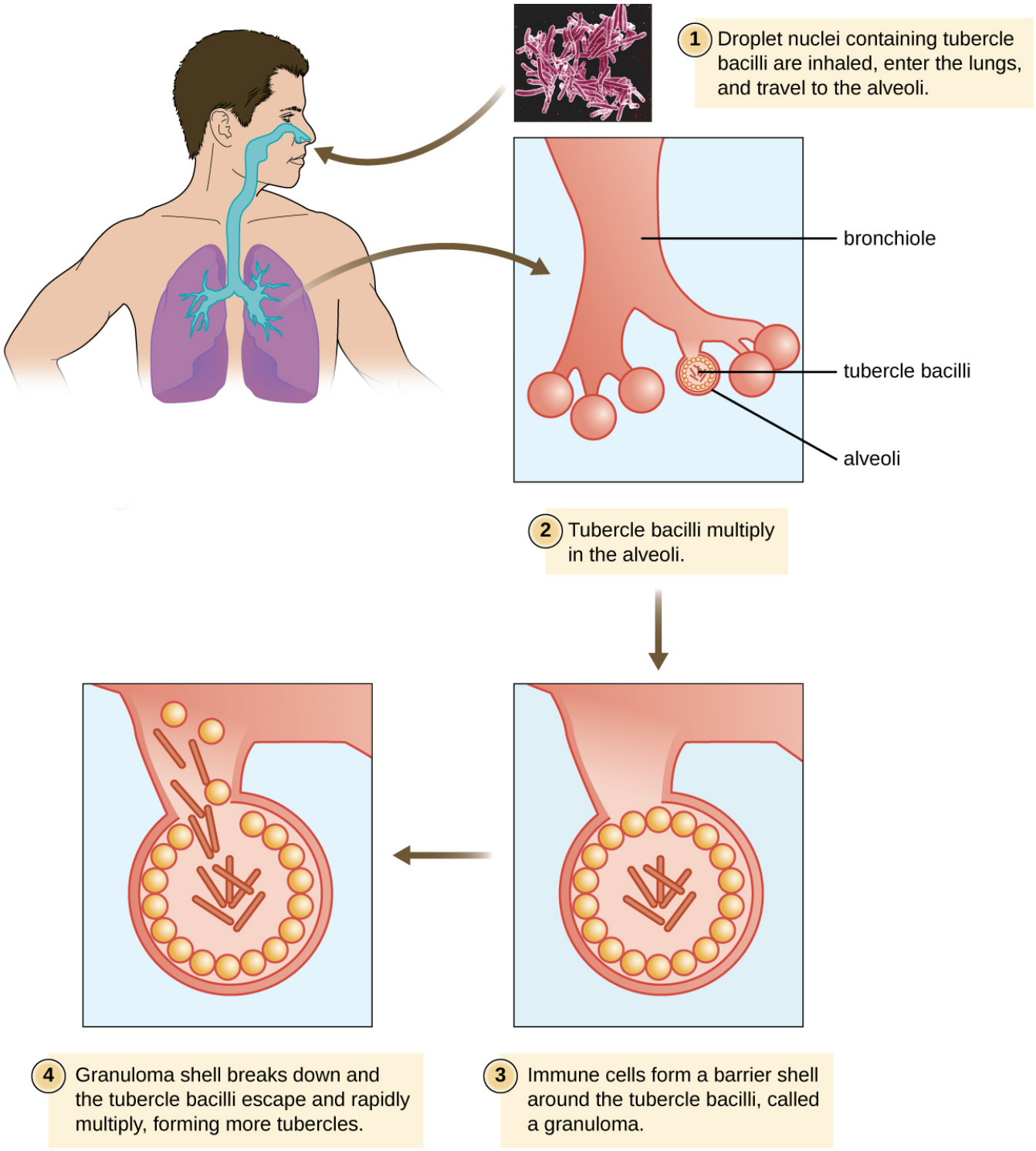


Figure 10.4.2.9: In the infectious cycle of tuberculosis, the immune response of most infected individuals (approximately 90%) results in the formation of tubercles in which the infection is walled off.[8] The remainder will suffer progressive primary tuberculosis. The sequestered bacteria may be reactivated to form secondary tuberculosis in immunocompromised patients at a later time. (credit: modification of work by Centers for Disease Control and Prevention)

Because TB is a chronic disease, chemotherapeutic treatments often continue for months or years. Multidrug resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains of *M. tuberculosis* are a growing clinical concern. These strains can arise due to misuse or mismanagement of antibiotic therapies. Therefore, it is imperative that proper multidrug protocols are used to treat these infections. Common antibiotics included in these mixtures are isoniazid, rifampin, ethambutol, and pyrazinamide.

A TB vaccine is available that is based on the so-called bacillus Calmette-Guérin (BCG) strain of *M. bovis* commonly found in cattle. In the United States, the BCG vaccine is only given to health-care workers and members of the military who are at risk of exposure to active cases of TB. It is used more broadly worldwide. Many individuals born in other countries have been vaccinated with BCG strain. BCG is used in many countries with a high prevalence of TB, to prevent childhood tuberculous meningitis and miliary disease.

The Mantoux tuberculin skin test (Figure 10.4.2.10) is regularly used in the United States to screen for potential TB exposure (see Hypersensitivities). However, prior vaccinations with the BCG vaccine can cause false-positive results. Chest radiographs to detect Ghon complex formation are required, therefore, to confirm exposure.



Figure 10.4.2.10: (a) The Mantoux skin test for tuberculosis involves injecting the subject with tuberculin protein derivative. The injection should initially produce a raised wheal. (b) The test should be read in 48–72 hours. A positive result is indicated by redness, swelling, or hardness; the size of the responding region is measured to determine the final result. (credit a, b: modification of work by Centers for Disease Control and Prevention)

? Exercise 10.4.2.6

1. What characteristic of *Mycobacterium tuberculosis* allows it to evade the immune response?
2. What happens to cause miliary tuberculosis?
3. Explain the limitations of the Mantoux tuberculin skin test.

Pertussis (Whooping Cough)

The causative agent of pertussis, commonly called whooping cough, is *Bordetella pertussis*, a gram-negative coccobacillus. The disease is characterized by mucus accumulation in the lungs that leads to a long period of severe coughing. Sometimes, following a bout of coughing, a sound resembling a “whoop” is produced as air is inhaled through the inflamed and restricted airway—hence the name whooping cough. Although adults can be infected, the symptoms of this disease are most pronounced in infants and children. Pertussis is highly communicable through droplet transmission, so the uncontrollable coughing produced is an efficient means of transmitting the disease in a susceptible population.

Following inhalation, *B. pertussis* specifically attaches to epithelial cells using an adhesin, filamentous hemagglutinin. The bacteria then grow at the site of infection and cause disease symptoms through the production of exotoxins. One of the main virulence factors of this organism is an A-B exotoxin called the pertussis toxin (PT). When PT enters the host cells, it increases the cyclic adenosine monophosphate (cAMP) levels and disrupts cellular signaling. PT is known to enhance inflammatory responses involving histamine and serotonin. In addition to PT, *B. pertussis* produces a tracheal cytotoxin that damages ciliated epithelial cells and results in accumulation of mucus in the lungs. The mucus can support the colonization and growth of other microbes and, as a consequence, secondary infections are common. Together, the effects of these factors produce the cough that characterizes this infection.

A pertussis infection can be divided into three distinct stages. The initial infection, termed the catarrhal stage, is relatively mild and unremarkable. The signs and symptoms may include nasal congestion, a runny nose, sneezing, and a low-grade fever. This, however, is the stage in which *B. pertussis* is most infectious. In the paroxysmal stage, mucus accumulation leads to uncontrollable

coughing spasms that can last for several minutes and frequently induce vomiting. The paroxysmal stage can last for several weeks. A long convalescence stage follows the paroxysmal stage, during which time patients experience a chronic cough that can last for up to several months. In fact, the disease is sometimes called the 100-day cough.

In infants, coughing can be forceful enough to cause fractures to the ribs, and prolonged infections can lead to death. The CDC reported 20 pertussis-related deaths in 2012,[9] but that number had declined to five by 2015.[10]

During the first 2 weeks of infection, laboratory diagnosis is best performed by culturing the organism directly from a nasopharyngeal (NP) specimen collected from the posterior nasopharynx. The NP specimen is streaked onto Bordet-Gengou medium. The specimens must be transported to the laboratory as quickly as possible, even if transport media are used. Transport times of longer than 24 hours reduce the viability of *B. pertussis* significantly.

Within the first month of infection, *B. pertussis* can be diagnosed using PCR techniques. During the later stages of infection, pertussis-specific antibodies can be immunologically detected using an enzyme-linked immunosorbent assay (ELISA).

Pertussis is generally a self-limiting disease. Antibiotic therapy with erythromycin or tetracycline is only effective at the very earliest stages of disease. Antibiotics given later in the infection, and prophylactically to uninfected individuals, reduce the rate of transmission. Active vaccination is a better approach to control this disease. The DPT vaccine was once in common use in the United States. In that vaccine, the P component consisted of killed whole-cell *B. pertussis* preparations. Because of some adverse effects, that preparation has now been superseded by the DTaP and Tdap vaccines. In both of these new vaccines, the “aP” component is a pertussis toxoid.

Widespread vaccination has greatly reduced the number of reported cases and prevented large epidemics of pertussis. Recently, however, pertussis has begun to reemerge as a childhood disease in some states because of declining vaccination rates and an increasing population of susceptible children.

? Exercise 10.4.2.7

1. What accounts for the mucus production in a pertussis infection?
2. What are the signs and symptoms associated with the three stages of pertussis?
3. Why is pertussis becoming more common in the United States?

Legionnaires Disease

An atypical pneumonia called Legionnaires disease (also known as legionellosis) is caused by an aerobic gram-negative bacillus, *Legionella pneumophila*. This bacterium infects free-living amoebae that inhabit moist environments, and infections typically occur from human-made reservoirs such as air-conditioning cooling towers, humidifiers, misting systems, and fountains. Aerosols from these reservoirs can lead to infections of susceptible individuals, especially those suffering from chronic heart or lung disease or other conditions that weaken the immune system.

When *L. pneumophila* bacteria enter the alveoli, they are phagocytized by resident macrophages. However, *L. pneumophila* uses a secretion system to insert proteins in the endosomal membrane of the macrophage; these proteins prevent lysosomal fusion, allowing *L. pneumophila* to continue to proliferate within the phagosome. The resulting respiratory disease can range from mild to severe pneumonia, depending on the status of the host’s immune defenses. Although this disease primarily affects the lungs, it can also cause fever, nausea, vomiting, confusion, and other neurological effects.

Diagnosis of Legionnaires disease is somewhat complicated. *L. pneumophila* is a fastidious bacterium and is difficult to culture. In addition, since the bacterial cells are not efficiently stained with the Gram stain, other staining techniques, such as the Warthin-Starry silver-precipitate procedure, must be used to visualize this pathogen. A rapid diagnostic test has been developed that detects the presence of *Legionella* antigen in a patient’s urine; results take less than 1 hour, and the test has high selectivity and specificity (greater than 90%). Unfortunately, the test only works for one serotype of *L. pneumophila* (type 1, the serotype responsible for most infections). Consequently, isolation and identification of *L. pneumophila* from sputum remains the defining test for diagnosis.

Once diagnosed, Legionnaire disease can be effectively treated with fluoroquinolone and macrolide antibiotics. However, the disease is sometimes fatal; about 10% of patients die of complications.[11] There is currently no vaccine available.

Exercise 10.4.2.8

- Why is Legionnaires disease associated with air-conditioning systems?
- How does *Legionella pneumophila* circumvent the immune system?

Q Fever

The zoonotic disease Q fever is caused by a rickettsia, *Coxiella burnetii*. The primary reservoirs for this bacterium are domesticated livestock such as cattle, sheep, and goats. The bacterium may be transmitted by ticks or through exposure to the urine, feces, milk, or amniotic fluid of an infected animal. In humans, the primary route of infection is through inhalation of contaminated farmyard aerosols. It is, therefore, largely an occupational disease of farmers. Humans are acutely sensitive to *C. burnetii*—the infective dose is estimated to be just a few cells.[12] In addition, the organism is hardy and can survive in a dry environment for an extended time. Symptoms associated with acute Q fever include high fever, headache, coughing, pneumonia, and general malaise. In a small number of patients (less than 5%[13]), the condition may become chronic, often leading to endocarditis, which may be fatal.

Diagnosing rickettsial infection by cultivation in the laboratory is both difficult and hazardous because of the easy aerosolization of the bacteria, so PCR and ELISA are commonly used. Doxycycline is the first-line drug to treat acute Q fever. In chronic Q fever, doxycycline is often paired with hydroxychloroquine.

Bacterial Diseases of the Respiratory Tract

Numerous pathogens can cause infections of the respiratory tract. Many of these infections produce similar signs and symptoms, but appropriate treatment depends on accurate diagnosis through laboratory testing. The tables in Figure 10.4.2.11 and Figure 10.4.2.12 summarize the most important bacterial respiratory infections, with the latter focusing specifically on forms of bacterial pneumonia.

Bacterial Infections of the Respiratory Tract						
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**	**Vaccine**
Acute otitis media (AOM)	*Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, others*	Earache, possible effusion; may cause fever, nausea, vomiting, diarrhea	Often a secondary infection; bacteria from respiratory tract become trapped in eustachian tube, cause infection	None	Cephalosporins, fluoroquinolones	None
Diphtheria	*Corynebacterium diphtheriae*	Pseudomembrane on throat, possibly leading to suffocation and death	Inhalation of respiratory droplets or aerosols from infected person	Identification of bacteria in throat swabs; PCR to detect diphtheria toxin in vitro	Erythromycin, penicillin, antitoxin produced in horses	DtaP, Tdap, DT, Td, DTP
Legionnaires disease	*Legionella pneumophila*	Cough, fever, muscle aches, headaches, nausea, vomiting, confusion; sometimes fatal	Inhalation of aerosols from contaminated water reservoirs	Isolation, using Warthin-Starry procedure, of bacteria in sputum	Fluoroquinolones, macrolides	None
Pertussis (whooping cough)	*Bordetella pertussis*	Severe coughing with “whoop” sound; chronic cough lasting several months; can be fatal in infants	Inhalation of respiratory droplets from infected person	Direct culture of throat swab, PCR, ELISA	Macrolides	DTaP, Tdap
Q fever	*Coxiella burnetii*	High fever, coughing, pneumonia, malaise; in chronic cases, potentially fatal endocarditis	Inhalation of aerosols of urine, feces, milk, or amniotic fluid of infected cattle, sheep, goats	PCR, ELISA	Doxycycline, hydroxychloroquine	None
Streptococcal pharyngitis, scarlet fever	*Streptococcus pyogenes*	Fever, sore throat, inflammation of pharynx and tonsils, petechiae, swollen lymph nodes; skin rash (scarlet fever), strawberry tongue	Direct contact, inhalation of respiratory droplets or aerosols from infected person	Direct culture of throat swab, rapid enzyme immunoassay	β-lactams	None
Tuberculosis	*Mycobacterium tuberculosis*	Formation of tubercles in lungs; rupture of tubercles, leading to chronic, bloody cough; healed tubercles (Ghon complexes) visible in radiographs; can be fatal	Inhalation of respiratory droplets or aerosols from infected person	Mantoux tuberculin skin test with chest radiograph to identify Ghon complexes	Isoniazid, rifampin, ethambutol, pyrazinamide	BCG

Figure 10.4.2.11: Bacterial infections of the respiratory tract

Bacterial Causes of Pneumonia						
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**	**Vaccine**
Chlamydial pneumonia	*Chlamydophila pneumoniae, C. psittaci, Chlamydia trachomatis*	Bronchitis; mild to severe respiratory distress	Inhalation of respiratory droplets or aerosols from infected person (*C. pneumoniae*); exposure to infected bird (*C. psittaci*); exposure in the birth canal (*Chlamydia trachomatis*)	Tissue culture, PCR	Tetracycline, macrolides	None
Haemophilus pneumonia	*Haemophilus influenzae*	Cough, fever or low body temperature, chills, chest pain, headache, fatigue	Inhalation of respiratory droplets or aerosols from infected person or asymptomatic carrier	Culture on chocolate agar, serotyping of blood or cerebrospinal fluid samples	Cephalosporins, fluoroquinolones	Hib
Klebsiella pneumonia	*Klebsiella pneumoniae,* others	Lung necrosis, "currant jelly" sputum; often fatal	Health care associated; bacteria introduced via contaminated ventilators, intubation, or other medical equipment	Culture, PCR	Multidrug resistant; antibiotic susceptibility testing necessary	None
Mycoplasma pneumonia (walking pneumonia)	*Mycoplasma pneumoniae*	Low fever, persistent cough	Inhalation of respiratory droplets or aerosols from infected person	Culture with penicillin, thallium acetate	Macrolides	None
Pneumococcal pneumonia	*Streptococcus pneumoniae*	Productive cough, bloody sputum, fever, chills, chest pain, respiratory distress	Direct contact with respiratory secretions	Gram stain, blood agar culture with optichin and sodium deoxycholate, quellung reaction	β-lactams, macrolides, fluoroquinolones	Pneumococcal conjugate vaccine (PCV13), pneumococcal polysaccharide vaccine (PPSV23)
Pseudomonas pneumonia	*Pseudomonas aeruginosa*	Viscous fluid and chronic inflammation of lungs; often fatal	Health care associated; bacteria introduced via contaminated ventilators; also frequently affects patients with cystic fibrosis	Culture from sputum or other body fluid	Multidrug resistant; antibiotic susceptibility testing necessary	None

Figure 10.4.2.12: Bacterial causes of pneumonia

Key Concepts and Summary

- A wide variety of bacteria can cause respiratory diseases; most are treatable with antibiotics or preventable with vaccines.
- *Streptococcus pyogenes* causes **strep throat**, an infection of the pharynx that also causes high fever and can lead to **scarlet fever**, **acute rheumatic fever**, and **acute glomerulonephritis**.
- **Acute otitis media** is an infection of the middle ear that may be caused by several bacteria, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. The infection can block the eustachian tubes, leading to **otitis media with effusion**.
- **Diphtheria**, caused by *Corynebacterium diphtheriae*, is now a rare disease because of widespread vaccination. The bacteria produce exotoxins that kill cells in the pharynx, leading to the formation of a **pseudomembrane**; and damage other parts of the body.
- **Bacterial pneumonia** results from infections that cause inflammation and fluid accumulation in the alveoli. It is most commonly caused by *S. pneumoniae* or *H. influenzae*. The former is commonly multidrug resistant.
- ***Mycoplasma* pneumonia** results from infection by *Mycoplasma pneumoniae*; it can spread quickly, but the disease is mild and self-limiting.
- **Chlamydial pneumonia** can be caused by three pathogens that are obligate intracellular parasites. *Chlamydophila pneumoniae* is typically transmitted from an infected person, whereas *C. psittaci* is typically transmitted from an infected bird. *Chlamydia trachomatis*, may cause pneumonia in infants.
- Several other bacteria can cause pneumonia in immunocompromised individuals and those with cystic fibrosis.
- **Tuberculosis** is caused by *Mycobacterium tuberculosis*. Infection leads to the production of protective **tubercles** in the alveoli and calcified **Ghon complexes** that can harbor the bacteria for a long time. Antibiotic-resistant forms are common and treatment is typically long term.
- **Pertussis** is caused by *Bordetella pertussis*. Mucus accumulation in the lungs leads to prolonged severe coughing episodes (whooping cough) that facilitate transmission. Despite an available vaccine, outbreaks are still common.
- **Legionnaires disease** is caused by infection from environmental reservoirs of the *Legionella pneumophila* bacterium. The bacterium is endocytic within macrophages and infection can lead to pneumonia, particularly among immunocompromised individuals.
- **Q fever** is caused by *Coxiella burnetii*, whose primary hosts are domesticated mammals (zoonotic disease). It causes pneumonia primarily in farm workers and can lead to serious complications, such as endocarditis.

Footnotes

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10.4.3: Viral Infections of the Respiratory Tract

Learning Objectives

- Identify the most common viruses that can cause infections of the upper and lower respiratory tract
- Compare the major characteristics of specific viral diseases of the respiratory tract

Viruses are the most frequent cause of respiratory tract infections. Unlike the bacterial pathogens, we have few effective therapies to combat viral respiratory infections. Fortunately, many of these diseases are mild and self-limiting. A few respiratory infections manifest their primary symptoms at other locations in the body.

The Common Cold

The common cold is a generic term for a variety of mild viral infections of the nasal cavity. More than 200 different viruses are known to cause the common cold. The most common groups of cold viruses include rhinoviruses, coronaviruses, and adenoviruses. These infections are widely disseminated in the human population and are transmitted through direct contact and droplet transmission. Coughing and sneezing efficiently produce infectious aerosols, and rhinoviruses are known to persist on environmental surfaces for up to a week.[1]

Viral contact with the nasal mucosa or eyes can lead to infection. Rhinoviruses tend to replicate best between 33 °C (91.4 °F) and 35 °C (95 °F), somewhat below normal body temperature (37 °C [98.6 °F]). As a consequence, they tend to infect the cooler tissues of the nasal cavities. Colds are marked by an irritation of the mucosa that leads to an inflammatory response. This produces common signs and symptoms such as nasal excess nasal secretions (runny nose), congestion, sore throat, coughing, and sneezing. The absence of high fever is typically used to differentiate common colds from other viral infections, like influenza. Some colds may progress to cause otitis media, pharyngitis, or laryngitis, and patients may also experience headaches and body aches. The disease, however, is self-limiting and typically resolves within 1–2 weeks.

There are no effective antiviral treatments for the common cold and antibacterial drugs should not be prescribed unless secondary bacterial infections have been established. Many of the viruses that cause colds are related, so immunity develops throughout life. Given the number of viruses that cause colds, however, individuals are never likely to develop immunity to all causes of the common cold.

Exercise 10.4.3.1

1. How are colds transmitted?
2. What is responsible for the symptoms of a cold?

Clinical Focus: Part 3

Since antibiotic treatment had proven ineffective, John's doctor suspects that a viral or fungal pathogen may be the culprit behind John's case of pneumonia. Another possibility is that John could have an antibiotic-resistant bacterial infection that will require a different antibiotic or combination of antibiotics to clear.

The RIDT tests both came back negative for type A and type B influenza. However, the diagnostic laboratory identified the sputum isolate as *Legionella pneumophila*. The doctor ordered tests of John's urine and, on the second day after his admission, results of an enzyme immunoassay (EIA) were positive for the *Legionella* antigen. John's doctor added levofloxacin to his antibiotic therapy and continued to monitor him. The doctor also began to ask John where he had been over the past 10 to 14 days.

Exercise 10.4.3.2

1. Do negative RIDT results absolutely rule out influenza virus as the etiologic agent? Why or why not?
2. What is John's prognosis?

Influenza

Commonly known as the flu, influenza is a common viral disease of the lower respiratory system caused by an orthomyxovirus. Influenza is pervasive worldwide and causes 3,000–50,000 deaths each year in the United States. The annual mortality rate can vary greatly depending on the virulence of the strain(s) responsible for seasonal epidemics. [2]

Influenza infections are most typically characterized by fever, chills, and body aches. This is followed by symptoms similar to the common cold that may last a week or more. Table 10.4.3.1 compares the signs and symptoms of influenza and the common cold.

Table 10.4.3.1: Comparing the Common Cold and Influenza

Sign/Symptom	Common Cold	Influenza
Fever	Low (37.2 °C [99 °F])	High (39 °C [102.2 °F])
Headache	Common	Common
Aches and pains	Mild	Severe
Fatigue	Slight	Severe
Nasal congestion	Common	Rare
Sneezing	Common	Rare

In general, influenza is self-limiting. However, serious cases can lead to pneumonia and other complications that can be fatal. Such cases are more common in the very young and the elderly; however, certain strains of influenza virus (like the 1918–1919 variant discussed later in this chapter) are more lethal to young adults than to the very young or old. Strains that affect young adults are believed to involve a cytokine storm—a positive feedback loop that forms between cytokine production and leukocytes. This cytokine storm produces an acute inflammatory response that leads to rapid fluid accumulation in the lungs, culminating in pulmonary failure. In such cases, the ability to mount a vigorous immune response is actually detrimental to the patient. The very young and very old are less susceptible to this effect because their immune systems are less robust.

A complication of influenza that occurs primarily in children and teenagers is Reye syndrome. This sequela causes swelling in the liver and brain, and may progress to neurological damage, coma, or death. Reye syndrome may follow other viral infections, like chickenpox, and has been associated with the use of aspirin. For this reason, the CDC and other agencies recommend that aspirin and products containing aspirin never be used to treat viral illnesses in children younger than age 19 years.[3]

The influenza virus is primarily transmitted by direct contact and inhalation of aerosols. The RNA genome of this virus exists as seven or eight segments, each coated with ribonucleoprotein and encoding one or two specific viral proteins. The influenza virus is surrounded by a lipid membrane envelope, and two of the main antigens of the influenza virus are the spike proteins hemagglutinin (H) and neuraminidase (N), as shown in Figure 10.4.3.1. These spike proteins play important roles in the viral infectious cycle.

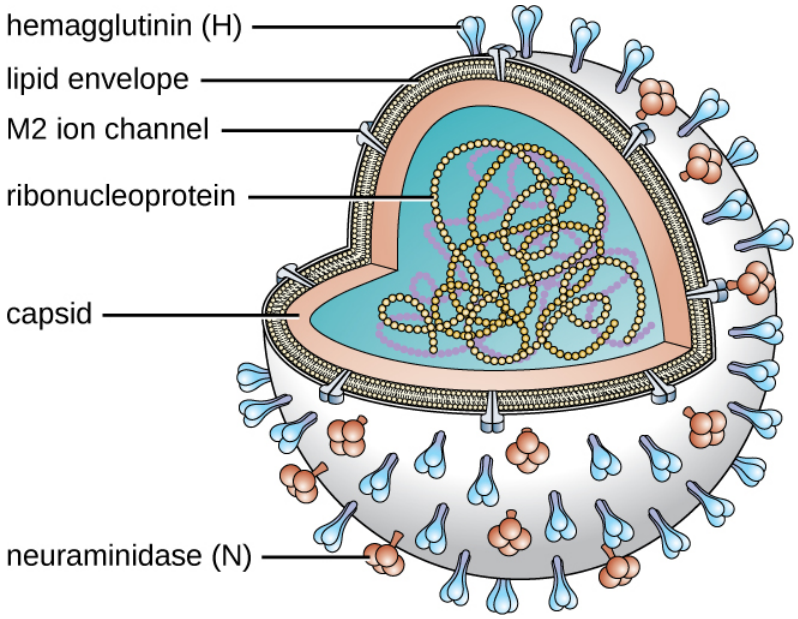


Figure 10.4.3.1: The illustration shows the structure of an influenza virus. The viral envelope is studded with copies of the proteins neuraminidase and hemagglutinin, and surrounds the individual seven or eight RNA genome segments. (credit: modification of work by Dan Higgins, Centers for Disease Control and Prevention)

Following inhalation, the influenza virus uses the hemagglutinin protein to bind to sialic acid receptors on host respiratory epithelial cells. This facilitates endocytosis of the viral particle. Once inside the host cell, the negative strand viral RNA is replicated by the viral RNA polymerase to form mRNA, which is translated by the host to produce viral proteins. Additional viral RNA molecules are transcribed to produce viral genomic RNA, which assemble with viral proteins to form mature virions. Release of the virions from the host cell is facilitated by viral neuraminidase, which cleaves sialic-acid receptors to allow progeny viruses to make a clean exit when budding from an infected cell.

There are three genetically related influenza viruses, called A, B, and C. The influenza A viruses have different subtypes based on the structure of their hemagglutinin and neuraminidase proteins. There are currently 18 known subtypes of hemagglutinin and 11 known subtypes of neuraminidase. Influenza viruses are serologically characterized by the type of H and N proteins that they possess. Of the nearly 200 different combinations of H and N, only a few, such as the H1N1 strain, are associated with human disease. The influenza viruses A, B, and C make up three of the five major groups of orthomyxoviruses. The differences between the three types of influenza are summarized in Table 10.4.3.2. The most virulent group is the influenza A viruses, which cause seasonal pandemics of influenza each year. Influenza A virus can infect a variety of animals, including pigs, horses, pigs, and even whales and dolphins. Influenza B virus is less virulent and is sometimes associated with epidemic outbreaks. Influenza C virus generally produces the mildest disease symptoms and is rarely connected with epidemics. Neither influenza B virus nor influenza C virus has significant animal reservoirs.

Table 10.4.3.2: The Three Major Groups of Influenza Viruses

	Influenza A virus	Influenza B virus	Influenza C virus
Severity	Severe	Moderate	Mild
Animal reservoir	Yes	No	No
Genome segments	8	8	7
Population spread	Epidemic and pandemic	Epidemic	Sporadic
Antigenic variation	Shift/drift	Drift	Drift

Influenza virus infections elicit a strong immune response, particularly to the hemagglutinin protein, which would protect the individual if they encountered the same virus. Unfortunately, the antigenic properties of the virus change relatively rapidly, so new

strains are evolving that immune systems previously challenged by influenza virus cannot recognize. When an influenza virus gains a new hemagglutinin or neuraminidase type, it is able to evade the host's immune response and be successfully transmitted, often leading to an epidemic.

There are two mechanisms by which these evolutionary changes may occur. The mechanisms of antigen drift and antigenic shift for influenza virus have been described in Virulence Factors of Bacterial and Viral Pathogens. Of these two genetic processes, it is viruses produced by antigenic shift that have the potential to be extremely virulent because individuals previously infected by other strains are unlikely to produce any protective immune response against these novel variants.

The most lethal influenza pandemic in recorded history occurred from 1918 through 1919. Near the end of World War I, an antigenic shift involving the recombination of avian and human viruses is thought to have produced a new H1N1 virus. This strain rapidly spread worldwide and is commonly claimed to have killed as many as 40 million to 50 million people—more than double the number killed in the war. Although referred to as the Spanish flu, this disease is thought to have originated in the United States. Regardless of its source, the conditions of World War I greatly contributed to the spread of this disease. Crowding, poor sanitation, and rapid mobilization of large numbers of personnel and animals facilitated the dissemination of the new virus once it appeared.

Several of the most important influenza pandemics of modern times have been associated with antigenic shifts. A few of these are summarized in Table 10.4.3.3.

Table 10.4.3.3: Historical Influenza Outbreaks[4 5 6]

Years	Common Name	Serotype	Estimated Number of Deaths
1918–1919	Spanish flu	H1N1	20,000,000–40,000,000
1957–1958	Asian flu	N2N2	1,000,000–2,000,000
1968–1969	Hong Kong flu	H3N2	1,000,000–3,000,000
2009–2010	Swine flu	H1N1/09	152,000–575,000

Laboratory diagnosis of influenza is typically performed using a variety of RIDTs. These tests are inoculated by point-of-care personnel and give results within 15–20 minutes. Unfortunately, these tests have variable sensitivity and commonly yield false-negative results. Other tests include hemagglutination of erythrocytes (due to hemagglutinin action) or complement fixation. Patient serum antibodies against influenza viruses can also be detected in blood samples. Because influenza is self-limiting disease, diagnosis through these more time-consuming and expensive methods is not typically used.

Three drugs that inhibit influenza neuraminidase activity are available: inhaled zanamivir, oral oseltamivir, and intravenous peramivir. If taken at the onset of symptoms, these drugs can shorten the course of the disease. These drugs are thought to impair the ability of the virus to efficiently exit infected host cells. A more effective means of controlling influenza outbreaks, though, is vaccination. Every year, new influenza vaccines are developed to be effective against the strains expected to be predominant. This is determined in February by a review of the dominant strains around the world from a network of reporting sites; their reports are used to generate a recommendation for the vaccine combination for the following winter in the northern hemisphere. In September, a similar recommendation is made for the winter in the southern hemisphere.[7] These recommendations are used by vaccine manufacturers to formulate each year's vaccine. In most cases, three or four viruses are selected—the two most prevalent influenza A strains and one or two influenza B strains. The chosen strains are typically cultivated in eggs and used to produce either an inactivated or a live attenuated vaccine (e.g., FluMist). For individuals 18 years or older with an allergy to egg products, a recombinant egg-free trivalent vaccine is available. Most of the influenza vaccines over the past decade have had an effectiveness of about 50%.[8]

Flu Pandemic

During the spring of 2013, a new strain of H7N9 influenza was reported in China. A total of 132 people were infected. Of those infected, 44 (33%) died. A genetic analysis of the virus suggested that this strain arose from the reassortment of three different influenza viruses: a domestic duck H7N3 virus, a wild bird H7N9 virus, and a domestic poultry H9N2 virus. The virus was detected in the Chinese domestic bird flocks and contact with this reservoir is thought to have been the primary source of

infection. This strain of influenza was not able to spread from person to person. Therefore, the disease did not become a global problem. This case does, though, illustrate the potential threat that influenza still represents. If a strain like the H7N9 virus were to undergo another antigenic shift, it could become more communicable in the human population. With a mortality rate of 33%, such a pandemic would be disastrous. For this reason, organizations like the World Health Organization and the Centers for Disease Control and Prevention keep all known influenza outbreaks under constant surveillance.

Exercise 10.4.3.3

1. Compare the severity of the three types of influenza viruses.
2. Why must new influenza vaccines be developed each year?

Viral Pneumonia

Viruses cause fewer cases of pneumonia than bacteria; however, several viruses can lead to pneumonia in children and the elderly. The most common sources of viral pneumonia are adenoviruses, influenza viruses, parainfluenza viruses, and respiratory syncytial viruses. The signs and symptoms produced by these viruses can range from mild cold-like symptoms to severe cases of pneumonia, depending on the virulence of the virus strain and the strength of the host defenses of the infected individual. Occasionally, infections can result in otitis media.

Respiratory syncytial virus (RSV) infections are fairly common in infants; most people have been infected by the age of 2 years. During infection, a viral surface protein causes host cells to fuse and form multinucleated giant cells called syncytia. There are no specific antiviral therapies or vaccines available for viral pneumonia. In adults, these infections are self-limiting, resemble the common cold, and tend to resolve uneventfully within 1 or 2 weeks. Infections in infants, however, can be life-threatening. RSV is highly contagious and can be spread through respiratory droplets from coughing and sneezing. RSV can also survive for a long time on environmental surfaces and, thus, be transmitted indirectly via fomites.

Exercise 10.4.3.4

1. Who is most likely to contract viral pneumonia?
2. What is the recommended treatment for viral pneumonia?

SARS and MERS

Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are two acute respiratory infections caused by coronaviruses. In both cases, these are thought to be zoonotic infections. Bats and civet cats are thought to have been the reservoirs for SARS; camels seem to be the reservoir for MERS.

SARS originated in southern China in the winter of 2002 and rapidly spread to 37 countries. Within about 1 year, more than 8,000 people experienced influenza-like symptoms and nearly 800 people died. The rapid spread and severity of these infections caused grave concern at the time. However, the outbreak was controlled in 2003 and no further cases of SARS have been recorded since 2004.[9] Signs and symptoms of SARS include high fever, headache, body aches, and cough, and most patients will develop pneumonia.

MERS was first reported in Saudi Arabia in 2013. Although some infected individuals will be asymptomatic or have mild cold-like symptoms, most will develop a high fever, aches, cough and a severe respiratory infection that can progress to pneumonia. As of 2015, over 1,300 people in 27 countries have been infected. About 500 people have died. There are no specific treatments for either MERS or SARS. In addition, no vaccines are currently available. Several recombinant vaccines, however, are being developed.

Exercise 10.4.3.5

1. What is the cause of SARS?
2. What are the signs and symptoms of MERS?

Viral Respiratory Diseases Causing Skin Rashes

Measles, rubella (German measles), and chickenpox are three important viral diseases often associated with skin rashes. However, their symptoms are systemic, and because their portal of entry is the respiratory tract, they can be considered respiratory infections.

Measles (Rubeola)

The measles virus (MeV) causes the highly contagious disease measles, also known as rubeola, which is a major cause of childhood mortality worldwide. Although vaccination efforts have greatly reduced the incidence of measles in much of the world, epidemics are still common in unvaccinated populations in certain countries.[10]

The measles virus is a single-stranded, negative-strand RNA virus and, like the influenza virus, it possesses an envelope with spikes of embedded hemagglutinin. The infection is spread by direct contact with infectious secretions or inhalation of airborne droplets spread by breathing, coughing, or sneezing. Measles is initially characterized by a high fever, conjunctivitis, and a sore throat. The virus then moves systemically through the bloodstream and causes a characteristic rash. The measles rash initially forms on the face and later spreads to the extremities. The red, raised macular rash will eventually become confluent and can last for several days. At the same time, extremely high fevers (higher than 40.6 °C [105 °F]) can occur. Another diagnostic sign of measles infections is Koplik's spots, white spots that form on the inner lining of inflamed cheek tissues (Figure 10.4.3.2).

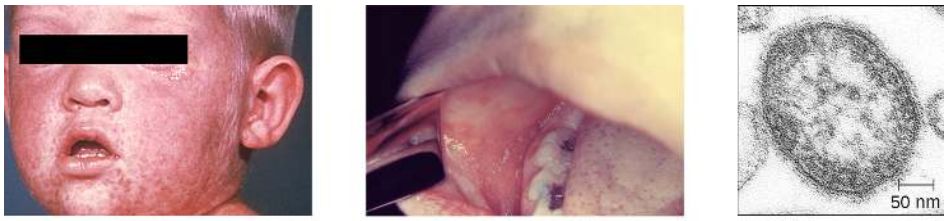


Figure 10.4.3.2: (a) Measles typically presents as a raised macular rash that begins on the face and spreads to the extremities. (b) Koplik's spots on the oral mucosa are also characteristic of measles. (c) A thin-section transmission electron micrograph of a measles virion. (credit a, b, c: modification of work by Centers for Disease Control and Prevention)

Although measles is usually self-limiting, it can lead to pneumonia, encephalitis, and death. In addition, the inhibition of immune system cells by the measles virus predisposes patients to secondary infections. In severe infections with highly virulent strains, measles fatality rates can be as high as 10% to 15%. There were more than 145,000 measles deaths (mostly young children) worldwide in 2013.[11]

The preliminary diagnosis of measles is typically based on the appearance of the rash and Koplik's spots. Hemagglutination inhibition tests and serological tests may be used to confirm measles infections in low-prevalence settings.

There are no effective treatments for measles. Vaccination is widespread in developed countries as part of the measles, mumps, and rubella (MMR) vaccine. As a result, there are typically fewer than 200 cases of measles in the United States annually.[12] When it is seen, it is often associated with children who have not been vaccinated.

Preventable Measles Outbreaks

In December 2014, a measles epidemic began at Disneyland in southern California. Within just 4 months, this outbreak affected 134 people in 24 states.[13] Characterization of the virus suggests that an unidentified infected individual brought the disease to the United States from the Philippines, where a similar virus had sickened more than 58,000 people and killed 110.[14] Measles is highly communicable, and its spread at Disneyland may have been facilitated by the low vaccination rate in some communities in California.[15]

Several factors could conceivably lead to a strong comeback of measles in the U.S. Measles is still an epidemic disease in many locations worldwide. Air travel enables infected individuals to rapidly translocate these infections globally. Compounding this problem, low vaccination rates in some local areas in the United States (such as in Amish communities) provide populations of susceptible hosts for the virus to establish itself. Finally, measles has been a low-prevalence infection in the U.S. for some time. As a consequence, physicians are not as likely to recognize the initial symptoms and make accurate diagnoses. Until vaccination rates become high enough to ensure herd immunity, measles is likely to be an ongoing problem in the United States.

Rubella (German Measles)

Rubella, or the German measles, is a relatively mild viral disease that produces a rash somewhat like that caused by the measles, even though the two diseases are unrelated. The rubella virus is an enveloped RNA virus that can be found in the respiratory tract. It is transmitted from person to person in aerosols produced by coughing or sneezing. Nearly half of all infected people remain asymptomatic. However, the virus is shed and spread by asymptomatic carriers. Like rubeola, rubella begins with a facial rash that spreads to the extremities (Figure 10.4.3.3). However, the rash is less intense, shorter lived (2–3 days), not associated with Koplik's spots, and the resulting fever is lower (101 °F [38.3 °C]).

Congenital rubella syndrome is the most severe clinical complication of the German measles. This occurs if a woman is infected with rubella during pregnancy. The rubella virus is teratogenic, meaning it can cause developmental defects if it crosses the placenta during pregnancy. There is a very high incidence of stillbirth, spontaneous abortion, or congenital birth defects if the mother is infected before 11 weeks of pregnancy and 35% if she is infected between weeks 13–16; after this time the incidence is low.[16] For this reason, prenatal screening for rubella is commonly practiced in the United States. Postnatal infections are usually self-limiting and rarely cause severe complications.

Like measles, the preliminary diagnosis of rubella is based on the patient's history, vaccination records, and the appearance of the rash. The diagnosis can be confirmed by hemagglutinin inhibition assays and a variety of other immunological techniques. There are no antiviral therapies for rubella, but an effective vaccine (MMR) is widely available. Vaccination efforts have essentially eliminated rubella in the United States; fewer than a dozen cases are reported in a typical year.

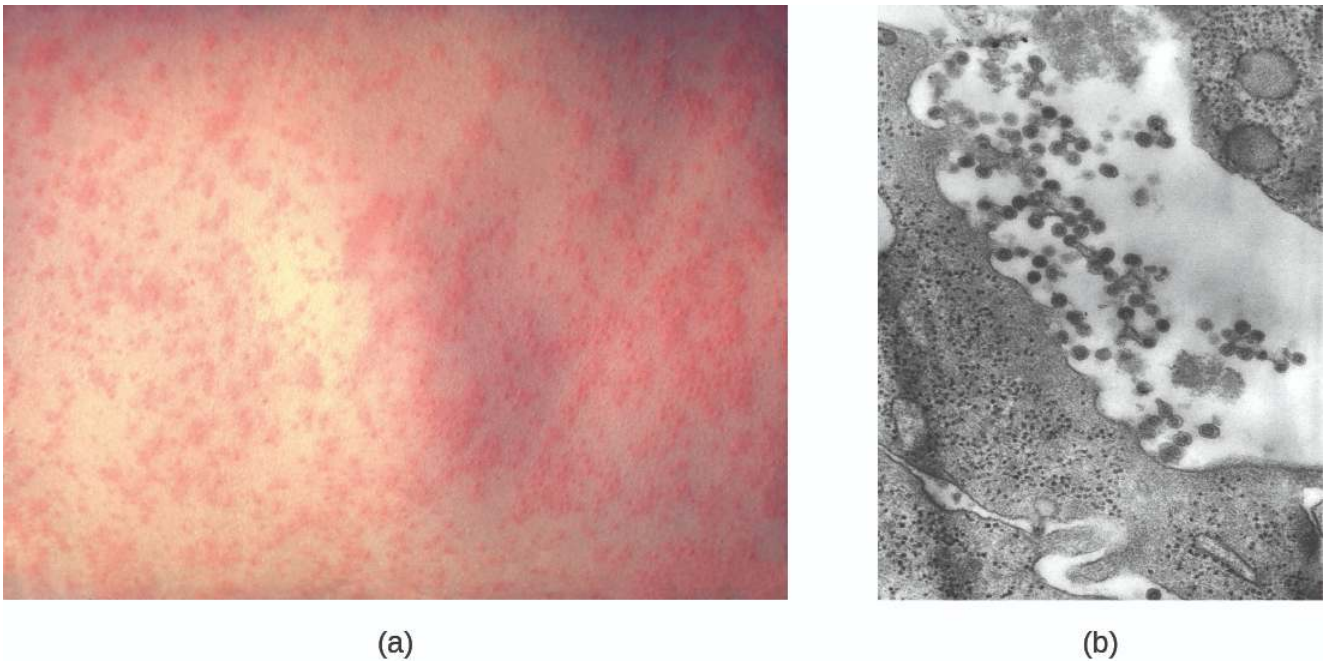


Figure 10.4.3.3: (a) This photograph shows the appearance of the German measles (rubella) rash. Note that this is less intense than the rash of measles and the lesions are not confluent. (b) This transmission electron micrograph shows rubella virus virions just budding from a host cell. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Chickenpox and Shingles

Chickenpox, also known as varicella, was once a common viral childhood disease. The causative agent of chickenpox, the varicella-zoster virus, is a member of the herpesvirus family. In children, the disease is mild and self-limiting, and is easily transmitted by direct contact or inhalation of material from the skin lesions. In adults, however, chickenpox infections can be much more severe and can lead to pneumonia and birth defects in the case of infected pregnant women. Reye syndrome, mentioned earlier in this chapter, is also a serious complication associated with chickenpox, generally in children.

Once infected, most individuals acquire a lifetime immunity to future chickenpox outbreaks. For this reason, parents once held "chickenpox parties" for their children. At these events, uninfected children were intentionally exposed to an infected individual so

they would contract the disease earlier in life, when the incidence of complications is very low, rather than risk a more severe infection later.

After the initial viral exposure, chickenpox has an incubation period of about 2 weeks. The initial infection of the respiratory tract leads to viremia and eventually produces fever and chills. A pustular rash then develops on the face, progresses to the trunk, and then the extremities, although most form on the trunk (Figure 10.4.3.4). Eventually, the lesions burst and form a crusty scab. Individuals with chickenpox are infectious from about 2 days before the outbreak of the rash until all the lesions have scabbed over.

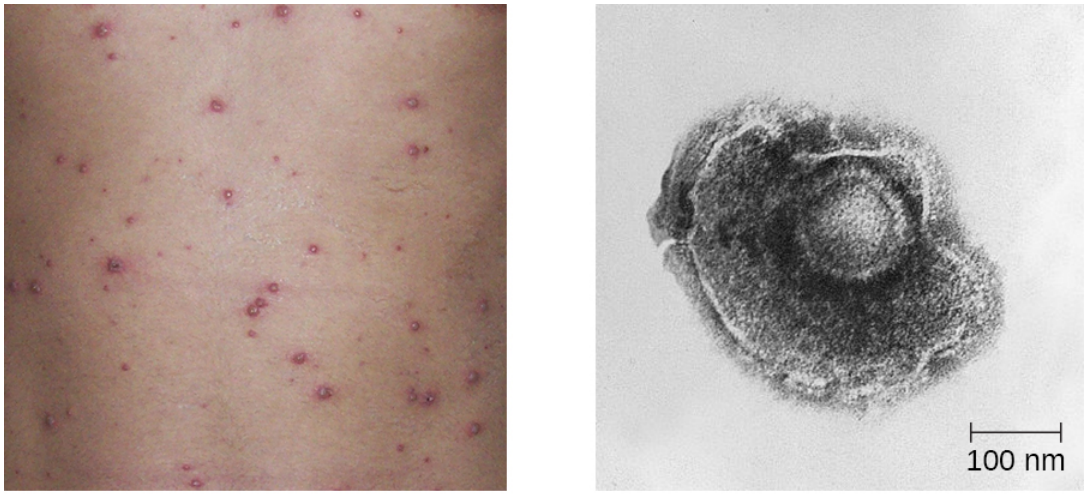


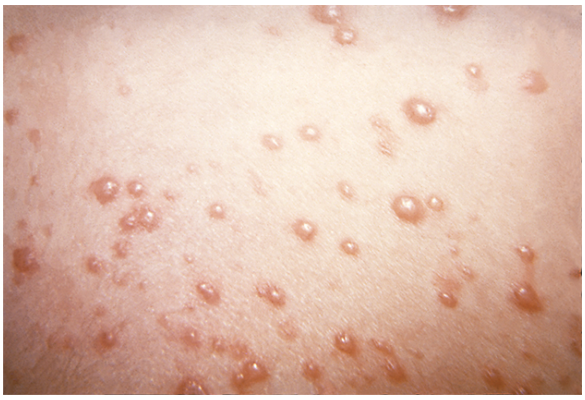
Figure 10.4.3.4: (a) The characteristic appearance of the pustular chickenpox rash is concentrated on the trunk region. (b) This transmission electron micrograph shows a viroid of human herpesvirus 3, the virus that causes chickenpox in children and shingles when it is reactivated in adults. (credit b: modification of work by Centers for Disease Control and Prevention)

Like other herpesviruses, the varicella-zoster virus can become dormant in nerve cells. While the pustular vesicles are developing, the virus moves along sensory nerves to the dorsal ganglia in the spinal cord. Once there, the varicella-zoster virus can remain latent for decades. These dormant viruses may be reactivated later in life by a variety of stimuli, including stress, aging, and immunosuppression. Once reactivated, the virus moves along sensory nerves to the skin of the face or trunk. This results in the production of the painful lesions in a condition known as shingles (Figure 10.4.3.5). These symptoms generally last for 2–6 weeks, and may recur more than once. Postherpetic neuralgia, pain signals sent from damaged nerves long after the other symptoms have subsided, is also possible. In addition, the virus can spread to other organs in immunocompromised individuals. A person with shingles lesions can transmit the virus to a nonimmune contact, and the newly infected individual would develop chickenpox as the primary infection. Shingles cannot be transmitted from one person to another.

The primary diagnosis of chickenpox in children is mainly based on the presentation of a pustular rash of the trunk. Serological and PCR-based tests are available to confirm the initial diagnosis. Treatment for chickenpox infections in children is usually not required. In patients with shingles, acyclovir treatment can often reduce the severity and length of symptoms, and diminish the risk of postherpetic neuralgia. An effective vaccine is now available for chickenpox. A vaccine is also available for adults older than 60 years who were infected with chickenpox in their youth. This vaccine reduces the likelihood of a shingles outbreak by boosting the immune defenses that are keeping the latent infection in check and preventing reactivation.



(a)



(b)

Figure 10.4.3.5: (a) An individual suffering from shingles. (b) The rash is formed because of the reactivation of a varicella-zoster infection that was initially contracted in childhood. (credit a: modification of work by National Institute of Allergy and Infectious Diseases (NIAID); credit b: modification of work by Centers for Disease Control and Prevention)

? Exercise 10.4.3.6

1. Why does measles often lead to secondary infections?
2. What signs or symptoms would distinguish rubella and measles?
3. Why can chickenpox lead to shingles later in life?

Smallpox Stockpiles

Smallpox has probably killed more humans than any other infectious disease, with the possible exception of tuberculosis. This disease, caused by the variola major virus, is transmitted by inhalation of viral particles shed from lesions in the throat. The smallpox virus spreads systemically in the bloodstream and produces a pustular skin rash. Historical epidemics of smallpox had fatality rates of 50% or greater in susceptible populations. Concerted worldwide vaccination efforts eradicated smallpox from the general population in 1977. This was the first microbial disease in history to be eradicated, a feat made possible by the fact that the only reservoir for the smallpox virus is infected humans.

Although the virus is no longer present in the wild, laboratory samples of the virus still exist in the United States and Russia.[17] The question is, why do these samples still exist? Some claim that these stocks should be maintained for research purposes. Should the smallpox virus ever reappear, they say, we would need access to such stocks for development of vaccines and treatments. Concerns about a re-emergence of the virus are not totally unfounded. Although there are no living reservoirs of the virus, there is always the possibility that smallpox could re-emerge from mummified human bodies or human remains preserved in permafrost. It is also possible that there are as-yet undiscovered samples of the virus in other locations around the world. An example of such "lost" samples was discovered in a drawer in a Food and Drug Administration lab in Maryland.[18] If an outbreak from such a source were to occur, it could lead to uncontrolled epidemics, since the population is largely unvaccinated now.

Critics of this argument, including many research scientists and the World Health Organization, claim that there is no longer any rational argument for keeping the samples. They view the “re-emergence scenarios” as a thinly veiled pretense for harboring biological weapons. These scenarios, they say, are less probable than an intentional reintroduction of the virus from militarized stocks by humans. Furthermore, they point out that if we needed to research smallpox in the future, we could rebuild the virus from its DNA sequence.

What do you think? Are there legitimate arguments for maintaining stockpiles of smallpox, or should all forms of this deadly disease be eradicated?

Viral Infections of the Respiratory Tract

Many viruses are capable of entering and causing disease in the respiratory system, and a number are able to spread beyond the respiratory system to cause systemic infections. Most of these infections are highly contagious and, with a few exceptions, antimicrobial drugs are not effective for treatment. Although some of these infections are self-limiting, others can have serious or fatal complications. Effective vaccines have been developed for several of these diseases, as summarized in Figure 10.4.3.6.

Viral Infections of the Respiratory Tract

Disease	Pathogen	Signs and Symptoms	Transmission	Vaccine
Chickenpox (varicella)	Varicella-zoster virus	In children, fever, chills, pustular rash of lesions that burst and form crusty scabs; in adults, more severe symptoms and complications (e.g., pneumonia)	Highly contagious via contact with aerosols, particles, or droplets from infected individual's blisters or respiratory secretions	Varicella (chickenpox) vaccine
Common cold	Rhinoviruses, adenoviruses, coronaviruses, others	Runny nose, congestion, sore throat, sneezing, headaches and muscle aches; may lead to otitis media, pharyngitis, laryngitis	Highly contagious via contact with respiratory secretions or inhalation of droplets or aerosols	None
Influenza	Influenza viruses A, B, C	Fever, chills, headaches, body aches, fatigue; may lead to pneumonia or complications such as Reye syndrome. Highly virulent strains may cause lethal complications	Highly contagious between humans via contact with respiratory secretions or inhalation of droplets or aerosols. Influenza A virus can be transmitted from animal reservoirs.	Vaccines developed yearly against most prevalent strains
Measles	Measles virus (MeV)	High fever, conjunctivitis, sore throat, macular rash becoming confluent, Koplik's spots on oral mucosa; in severe cases, can lead to fatal pneumonia or encephalitis, especially in children	Highly contagious via contact with respiratory secretions, skin rash, or eye secretions of infected individual	MMR
MERS	Middle East respiratory syndrome coronavirus (MERS-CoV)	Fever, cough, shortness of breath; in some cases, complications such as pneumonia and kidney failure; can be fatal	Contact with respiratory secretions or inhalation of droplets or aerosols	None
Rubella (German measles)	Rubella virus	Facial rash spreading to extremities, followed by low-grade fever, headache, conjunctivitis, cough, runny nose, swollen lymph nodes; congenital rubella may cause birth defects, miscarriage, or stillbirth	Contagious via inhalation of droplets or aerosols from infected person or asymptomatic carrier; transplacental infection from mother to fetus	MMR
SARS	SARS-associated coronavirus (SARS-CoV)	High fever, headache, body aches, dry cough, pneumonia; can be fatal	Contact with respiratory secretions or inhalation of droplets or aerosols	None
Shingles	Varicella-zoster virus	Painful lesions on face or trunk lasting several weeks; may cause postherpetic neuralgia (chronic pain) or spread to organs in severe cases	Nontransmissible; occurs when dormant virus is reactivated, generally many years after initial chicken-pox infection	Herpes zoster (shingles) vaccine
Viral pneumonia	Adenoviruses, influenza viruses, parainfluenza viruses, respiratory syncytial viruses,others	From mild cold-like symptoms to severe pneumonia; in infants, RSV infections may be life-threatening	Highly contagious via contact with respiratory secretions or inhalation of droplets or aerosols	None

Figure 10.4.3.6: Viral infections of respiratory tract

Key Concepts and Summary

- Viruses cause respiratory tract infections more frequently than bacteria, and most viral infections lead to mild symptoms.

- The **common cold** can be caused by more than 200 viruses, typically rhinoviruses, coronaviruses, and adenoviruses, transmitted by direct contact, aerosols, or environmental surfaces.
- Due to its ability to rapidly mutate through **antigenic drift** and **antigenic shift**, **influenza** remains an important threat to human health. Two new influenza vaccines are developed annually.
- Several viral infections, including **respiratory syncytial virus** infections, which frequently occur in the very young, can begin with mild symptoms before progressing to viral pneumonia.
- **SARS** and **MERS** are acute respiratory infections caused by coronaviruses, and both appear to originate in animals. SARS has not been seen in the human population since 2004 but had a high mortality rate during its outbreak. MERS also has a high mortality rate and continues to appear in human populations.
- **Measles**, **rubella**, and **chickenpox** are highly contagious, systemic infections that gain entry through the respiratory system and cause rashes and fevers. Vaccines are available for all three. Measles is the most severe of the three and is responsible for significant mortality around the world. Chickenpox typically causes mild infections in children but the virus can reactivate to cause painful cases of **shingles** later in life.

Footnotes

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16. 16 E. Miller et al. "Consequences of Confirmed Maternal Rubella at Successive Stages of Pregnancy." *The Lancet* 320, no. 8302 (1982):781–784.
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18. 18 Ibid.

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10.4.4: Respiratory Mycoses

Learning Objectives

- Identify the most common fungi that can cause infections of the respiratory tract
- Compare the major characteristics of specific fungal diseases of the respiratory tract

Fungal pathogens are ubiquitous in the environment. Serological studies have demonstrated that most people have been exposed to fungal respiratory pathogens during their lives. Yet symptomatic infections by these microbes are rare in healthy individuals. This demonstrates the efficacy of the defenses of our respiratory system. In this section, we will examine some of the fungi that can cause respiratory infections.

Histoplasmosis

Histoplasmosis is a fungal disease of the respiratory system and most commonly occurs in the Mississippi Valley of the United States and in parts of Central and South America, Africa, Asia, and Australia. The causative agent, *Histoplasma capsulatum*, is a dimorphic fungus. This microbe grows as a filamentous mold in the environment but occurs as a budding yeast during human infections. The primary reservoir for this pathogen is soil, particularly in locations rich in bat or bird feces.

Histoplasmosis is acquired by inhaling microconidial spores in the air; this disease is not transmitted from human to human. The incidence of histoplasmosis exposure is high in endemic areas, with 60%–90% of the population having anti-*Histoplasma* antibodies, depending on location;[1] however, relatively few individuals exposed to the fungus actually experience symptoms. Those most likely to be affected are the very young, the elderly, and immunocompromised people.

In many ways, the course of this disease is similar to that of tuberculosis. Following inhalation, the spores enter the lungs and are phagocytized by alveolar macrophages. The fungal cells then survive and multiply within these phagocytes (see Figure 5.3.2). Focal infections cause the formation of granulomatous lesions, which can lead to calcifications that resemble the Ghon complexes of tuberculosis, even in asymptomatic cases. Also like tuberculosis, histoplasmosis can become chronic and reactivation can occur, along with dissemination to other areas of the body (e.g., the liver or spleen).

Signs and symptoms of pulmonary histoplasmosis include fever, headache, and weakness with some chest discomfort. The initial diagnosis is often based on chest radiographs and cultures grown on fungal selective media like Sabouraud's dextrose agar. Direct fluorescence antibody staining and Giemsa staining can also be used to detect this pathogen. In addition, serological tests including a complement fixation assay and histoplasmin sensitivity can be used to confirm the diagnosis. In most cases, these infections are self-limiting and antifungal therapy is not required. However, in disseminated disease, the antifungal agents amphotericin B and ketoconazole are effective; itraconazole may be effective in immunocompromised patients, in whom the disease can be more serious.

Exercise 10.4.4.1

1. In what environments is one more likely to be infected with histoplasmosis?
2. Identify at least two similarities between histoplasmosis and tuberculosis.

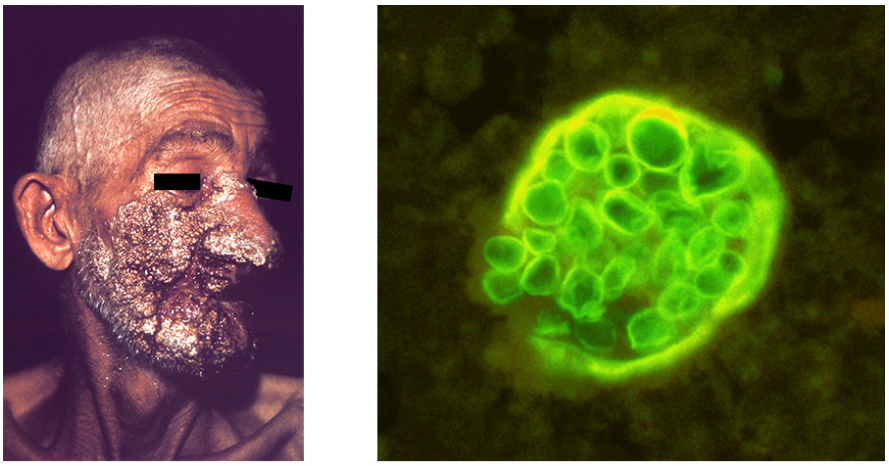
Coccidioidomycosis

Infection by the dimorphic fungus *Coccidioides immitis* causes coccidioidomycosis. Because the microbe is endemic to the San Joaquin Valley of California, the disease is sometimes referred to as Valley fever. A related species that causes similar infections is found in semi-arid and arid regions of the southwestern United States, Mexico, and Central and South America.[2]

Like histoplasmosis, coccidioidomycosis is acquired by inhaling fungal spores—in this case, arthrospores formed by hyphal fragmentation. Once in the body, the fungus differentiates into spherules that are filled with endospores. Most *C. immitis* infections are asymptomatic and self-limiting. However, the infection can be very serious for immunocompromised patients. The endospores may be transported in the blood, disseminating the infection and leading to the formation of granulomatous lesions on the face and

nose (Figure 10.4.4.1). In severe cases, other major organs can become infected, leading to serious complications such as fatal meningitis.

Coccidioidomycosis can be diagnosed by culturing clinical samples. *C. immitis* readily grows on laboratory fungal media, such as Sabouraud's dextrose agar, at 35 °C (95 °F). Culturing the fungus, however, is rather dangerous. *C. immitis* is one of the most infectious fungal pathogens known and is capable of causing laboratory-acquired infections. Indeed, until 2012, this organism was considered a “select agent” of bioterrorism and classified as a BSL-3 microbe. Serological tests for antibody production are more often used for diagnosis. Although mild cases generally do not require intervention, disseminated infections can be treated with intravenous antifungal drugs like amphotericin B.



(a) (b)

Figure 10.4.4.1: (a) This patient has extensive facial lesions due to a disseminated *Coccidioides* infection. (b) This fluorescent micrograph depicts a spherule of *C. immitis* containing endospores. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Clinical Focus: Resolution

John’s negative RIDT tests do not rule out influenza, since false-negative results are common, but the *Legionella* infection still must be treated with antibiotic therapy and is the more serious condition. John's prognosis is good, provided the physician can find an antibiotic therapy to which the infection responds.

While John was undergoing treatment, three of the employees from the home improvement store also reported to the clinic with very similar symptoms. All three were older than 55 years and had *Legionella* antigen in their urine; *L. pneumophila* was also isolated from their sputum. A team from the health department was sent to the home improvement store to identify a probable source for these infections. Their investigation revealed that about 3 weeks earlier, the store's air conditioning system, which was located where the employees ate lunch, had been undergoing maintenance. *L. pneumophila* was isolated from the cooling coils of the air conditioning system and intracellular *L. pneumophila* was observed in amoebae in samples of condensed water from the cooling coils as well (Figure 10.4.4.2). The amoebae provide protection for the *Legionella* bacteria and are known to enhance their pathogenicity.

In the wake of the infections, the store ordered a comprehensive cleaning of the air conditioning system and implemented a regular maintenance program to prevent the growth of biofilms within the cooling tower. They also reviewed practices at their other facilities.

After a month of rest at home, John recovered from his infection enough to return to work, as did the other three employees of the store. However, John experienced lethargy and joint pain for more than a year after his treatment.

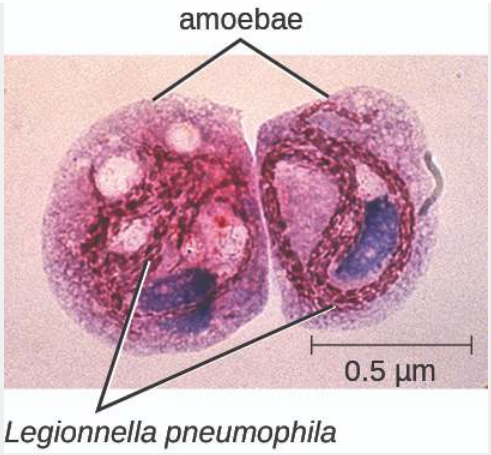
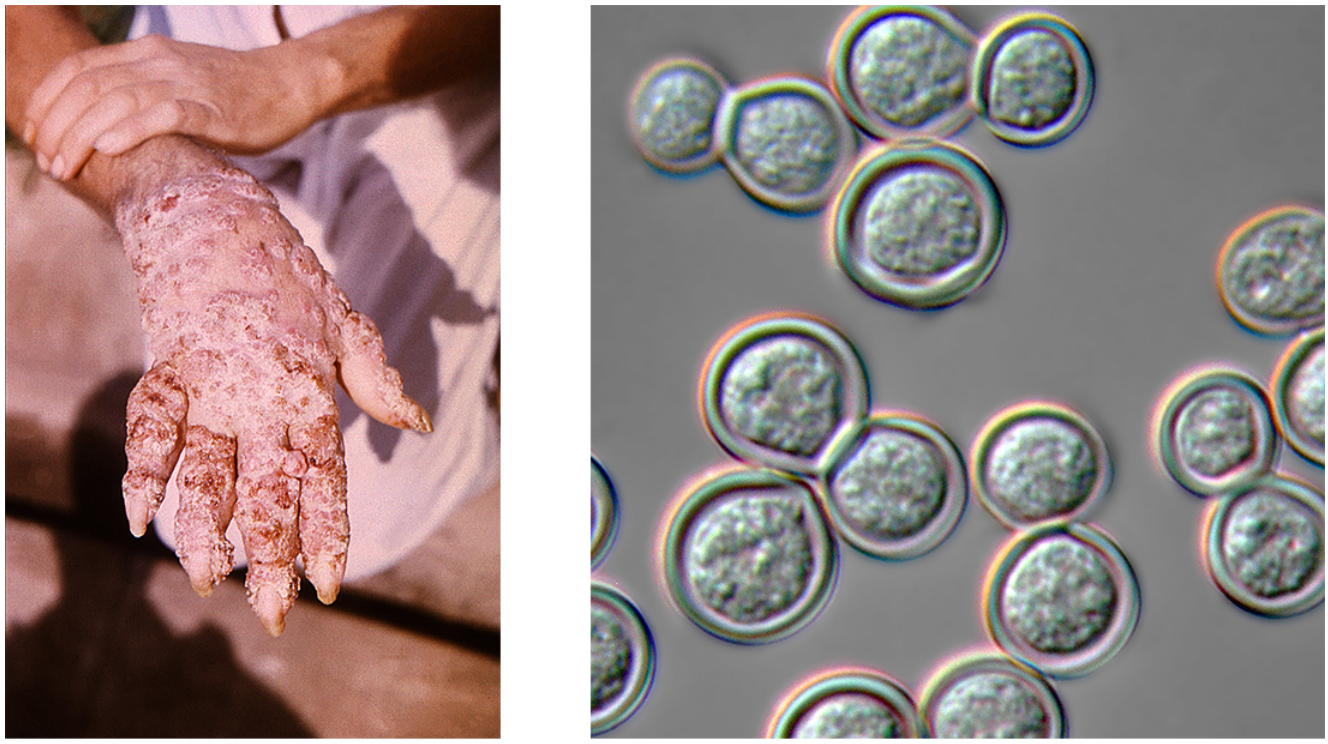


Figure 10.4.4.2: Legionella pneumophila (red intracellular rods) infecting amoebae from a contaminated water sample. (credit: modification of work by Centers for Disease Control and Prevention)

Blastomycosis

Blastomycosis is a rare disease caused by another dimorphic fungus, *Blastomyces dermatitidis*. Like *Histoplasma* and *Coccidioides*, *Blastomyces* uses the soil as a reservoir, and fungal spores can be inhaled from disturbed soil. The pulmonary form of blastomycosis generally causes mild flu-like symptoms and is self-limiting. It can, however, become disseminated in immunocompromised people, leading to chronic cutaneous disease with subcutaneous lesions on the face and hands (Figure 10.4.4.3). These skin lesions eventually become crusty and discolored and can result in deforming scars. Systemic blastomycosis is rare, but if left untreated, it is always fatal.

Preliminary diagnosis of pulmonary blastomycosis can be made by observing the characteristic budding yeast forms in sputum samples. Commercially available urine antigen tests are now also available. Additional confirmatory tests include serological assays such as immunodiffusion tests or EIA. Most cases of blastomycosis respond well to amphotericin Bor ketoconazole treatments.



(a) (b)

Figure 10.4.4.3: (a) These skin lesions are the result of disseminated cutaneous blastomycosis. (b) A differential interference contrast micrograph of *B. dermatitidis* yeast cultured on blood agar. (credit a: modification of work by Centers for Disease Control and Prevention)

Mucormycosis

A variety of fungi in the order Mucorales cause mucormycosis, a rare fungal disease. These include bread molds, like *Rhizopus* and *Mucor*; the most commonly associated species is *Rhizopus arrhizus (oryzae)* (see Figure 5.3.4). These fungi can colonize many different tissues in immunocompromised patients, but often infect the skin, sinuses, or the lungs.

Although most people are regularly exposed to the causative agents of mucormycosis, infections in healthy individuals are rare. Exposure to spores from the environment typically occurs through inhalation, but the spores can also infect the skin through a wound or the gastrointestinal tract if ingested. Respiratory mucormycosis primarily affects immunocompromised individuals, such as patients with cancer or those who have had a transplant.[4]

After the spores are inhaled, the fungi grow by extending hyphae into the host's tissues. Infections can occur in both the upper and lower respiratory tracts. Rhinocerebral mucormycosis is an infection of the sinuses and brain; symptoms include headache, fever, facial swelling, congestion, and tissue necrosis causing black lesions in the oral cavity. Pulmonary mucormycosis is an infection of the lungs; symptoms include fever, cough, chest pain, and shortness of breath. In severe cases, infections may become disseminated and involve the central nervous system, leading to coma and death.[5]

Diagnosing mucormycosis can be challenging. Currently, there are no serological or PCR-based tests available to identify these infections. Tissue biopsy specimens must be examined for the presence of the fungal pathogens. The causative agents, however, are often difficult to distinguish from other filamentous fungi. Infections are typically treated by the intravenous administration of amphotericin B, and superficial infections are removed by surgical debridement. Since the patients are often immunocompromised, viral and bacterial secondary infections commonly develop. Mortality rates vary depending on the site of the infection, the causative fungus, and other factors, but a recent study found an overall mortality rate of 54%.[6]

Exercise 10.4.4.2

1. Compare the modes of transmission for coccidioidomycosis, blastomycosis, and mucormycosis.
2. In general, which are more serious: the pulmonary or disseminated forms of these infections?

Aspergillosis

Aspergillus is a common filamentous fungus found in soils and organic debris. Nearly everyone has been exposed to this mold, yet very few people become sick. In immunocompromised patients, however, *Aspergillus* may become established and cause aspergillosis. Inhalation of spores can lead to asthma-like allergic reactions. The symptoms commonly include shortness of breath, wheezing, coughing, runny nose, and headaches. Fungal balls, or aspergilloma, can form when hyphal colonies collect in the lungs (Figure 10.4.4.4). The fungal hyphae can invade the host tissues, leading to pulmonary hemorrhage and a bloody cough. In severe cases, the disease may progress to a disseminated form that is often fatal. Death most often results from pneumonia or brain hemorrhages.

Laboratory diagnosis typically requires chest radiographs and a microscopic examination of tissue and respiratory fluid samples. Serological tests are available to identify *Aspergillus* antigens. In addition, a skin test can be performed to determine if the patient has been exposed to the fungus. This test is similar to the Mantoux tuberculin skin test used for tuberculosis. Aspergillosis is treated with intravenous antifungal agents, including itraconazole and voriconazole. Allergic symptoms can be managed with corticosteroids because these drugs suppress the immune system and reduce inflammation. However, in disseminated infections, corticosteroids must be discontinued to allow a protective immune response to occur.

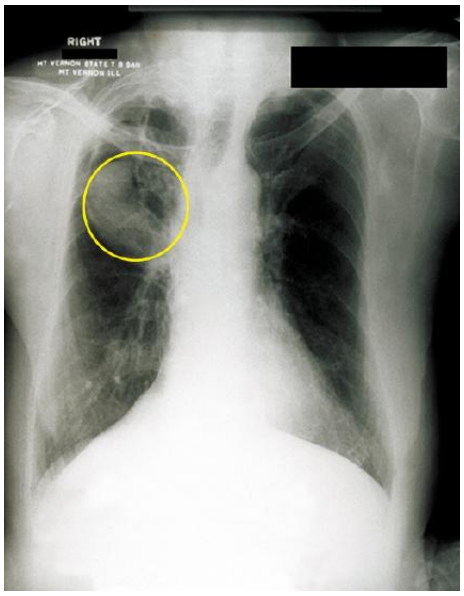


Figure 10.4.4.4: A fungal ball can be observed in the upper lobe of the right lung in this chest radiograph of a patient with aspergilloma. (credit: modification of work by Centers for Disease Control and Prevention)

Pneumocystis Pneumonia

A type of pneumonia called *Pneumocystis* pneumonia (PCP) is caused by *Pneumocystis jirovecii*. Once thought to be a protozoan, this organism was formerly named *P. carinii* but it has been reclassified as a fungus and renamed based on biochemical and genetic analyses. *Pneumocystis* is a leading cause of pneumonia in patients with acquired immunodeficiency syndrome (AIDS) and can be seen in other compromised patients and premature infants. Respiratory infection leads to fever, cough, and shortness of breath. Diagnosis of these infections can be difficult. The organism is typically identified by microscopic examination of tissue and fluid samples from the lungs (Figure 10.4.4.5). A PCR-based test is available to detect *P. jirovecii* in asymptomatic patients with AIDS. The best treatment for these infections is the combination drug trimethoprim-sulfamethoxazole (TMP/SMZ). These sulfa drugs often have adverse effects, but the benefits outweigh these risks. Left untreated, PCP infections are often fatal.

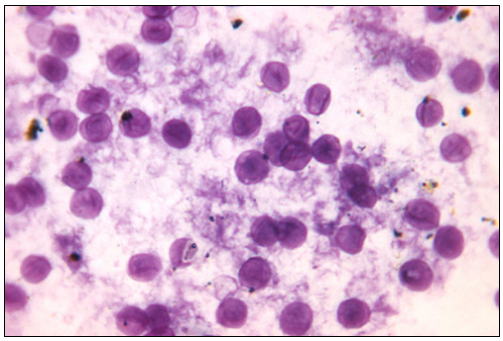


Figure 10.4.4.5: A light micrograph of a smear containing *Pneumocystis jirovecii* (dark purple cells) obtained from human lung tissue and stained with toluidine blue. (credit: Centers for Disease Control and Prevention)

Cryptococcosis

Infection by the encapsulated yeast *Cryptococcus neoformans* causes cryptococcosis. This fungus is ubiquitous in the soil and can be isolated from bird feces. Immunocompromised people are infected by inhaling basidiospores found in aerosols. The thick polysaccharide capsule surrounding these microbes enables them to avoid clearance by the alveolar macrophage. Initial symptoms of infection include fever, fatigue, and a dry cough. In immunocompromised patients, pulmonary infections often disseminate to the brain. The resulting meningitis produces headaches, sensitivity to light, and confusion. Left untreated, such infections are often fatal.

Cryptococcus infections are often diagnosed based on microscopic examination of lung tissues or cerebrospinal fluids. India ink preparations (Figure 10.4.4.6) can be used to visualize the extensive capsules that surround the yeast cells. Serological tests are also available to confirm the diagnosis. Amphotericin B, in combination with flucytosine, is typically used for the initial treatment of pulmonary infections. Amphotericin B is a broad-spectrum antifungal drug that targets fungal cell membranes. It can also adversely impact host cells and produce side effects. For this reason, clinicians must carefully balance the risks and benefits of treatments in these patients. Because it is difficult to eradicate cryptococcal infections, patients usually need to take fluconazole for up to 6 months after treatment with amphotericin B and flucytosine to clear the fungus. Cryptococcal infections are more common in immunocompromised people, such as those with AIDS. These patients typically require life-long suppressive therapy to control this fungal infection.

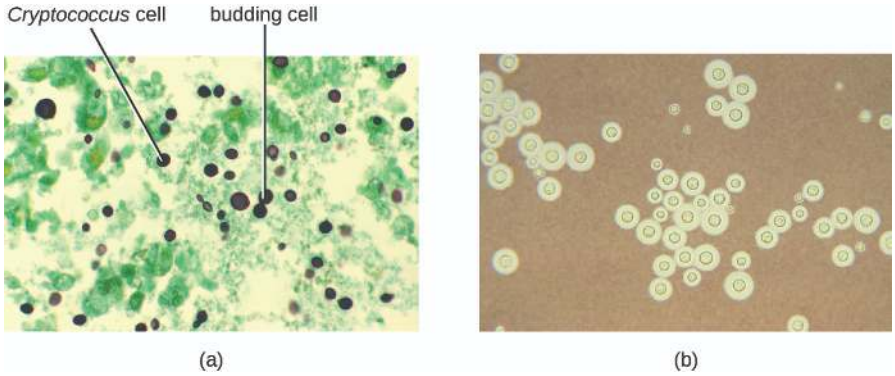


Figure 10.4.4.6: (a) The micrograph shows stained budding *Cryptococcus* yeast cells from the lungs of a patient with AIDS. (b) The large capsule of *Cryptococcus neoformans* is visible in this negative stain micrograph. (credit a, b: modification of work by Centers for Disease Control and Prevention)

? Exercise 10.4.4.3

1. What populations are most at risk for developing *Pneumocystis* pneumonia or cryptococcosis?
2. Why are these infections fatal if left untreated?

Fungal Diseases of the Respiratory Tract

Most respiratory mycoses are caused by fungi that inhabit the environment. Such infections are generally transmitted via inhalation of fungal spores and cannot be transmitted between humans. In addition, healthy people are generally not susceptible to infection even when exposed; the fungi are only virulent enough to establish infection in patients with HIV, AIDS, or another condition that compromises the immune defenses. Figure 10.4.4.7 summarizes the features of important respiratory mycoses.

Fungal Infections of the Respiratory Tract

Disease	Pathogen	Signs and Symptoms	Diagnostic Tests	Antimicrobial Drugs
Aspergillosis	*Aspergillus fumigatus*	Shortness of breath, wheezing, coughing, runny nose, headaches; formation of aspergil-lomas causing severe pneumonia and pulmo-nary or brain hemor-rhages; can be fatal	Chest radiograph, skin test, microscopic observation of sputum samples	Itraconazole, voriconazole
Blastomycosis	*Blastomyces dermatitidis*	Fever, chills, cough, headache, fatigue, chest pain, body aches; in disseminated infections, chronic, crusted lesions on face and hands with permanent scarring; can be fatal	Microscopic observa-tion of sputum samples; urine antigen test; EIA	Amphotericin B, ketoconazole
Coccidioidomy-cosis (Valley fever)	*Coccidioides immitis*	Granulomatous lesions on face and nose; may spread to organs or brain, causing fatal meningitis	Culture (in BSL-3 lab only), serological anti-body tests	Amphotericin B
Cryptococcosis	*Cryptococcus neoformans*	Fever, cough, shortness of breath; can cause fatal meningitis if disseminated to brain	Microscopic examination of lung tissue or cerebrospinal fluid	Amphotericin B, fluconazole, flucytosine
Histoplasmosis	*Histoplasma capsulatum*	Fever, headache, weakness, chest pain, lesions on lungs	Chest radiograph, culture, direct fluores-cence antibody staining, complement fixation assay, histoplasmin sensitivity test	Amphotericin B, ketoconazole, itraconazole
Mucormycosis	*Rhizopus arrhizus*, other *Rhizopus* spp., *Mucor* spp.	Headache, fever, facial swelling, congestion, black lesions in oral cavity, cough, chest pain, shortness of breath; often fatal	Microscopic examination of tissue biopsy specimens	Amphotericin B
Pneumocystis pneumonia (PCP)	*Pneumocystis jirovecii*	Fever, cough, shortness of breath; can be fatal if untreated	Microscopic examination of lung tissue and fluid, PCR	Trimethoprim-sulfamethoxa-zole

Figure 10.4.4.7: Fungal infections of the respiratory tract.

Key Concepts and Summary

- Fungal pathogens rarely cause respiratory disease in healthy individuals, but inhalation of fungal spores can cause severe pneumonia and systemic infections in immunocompromised patients.
- Antifungal drugs like amphotericin B can control most fungal respiratory infections.
- **Histoplasmosis** is caused by a mold that grows in soil rich in bird or bat droppings. Few exposed individuals become sick, but vulnerable individuals are susceptible. The yeast-like infectious cells grow inside phagocytes.
- **Coccidioidomycosis** is also acquired from soil and, in some individuals, will cause lesions on the face. Extreme cases may infect other organs, causing death.
- **Blastomycosis**, a rare disease caused by a soil fungus, typically produces a mild lung infection but can become disseminated in the immunocompromised. Systemic cases are fatal if untreated.
- **Mucormycosis** is a rare disease, caused by fungi of the order Mucorales. It primarily affects immunocompromised people. Infection involves growth of the hyphae into infected tissues and can lead to death in some cases.

- **Aspergillosis**, caused by the common soil fungus *Aspergillus*, infects immunocompromised people. Hyphal balls may impede lung function and hyphal growth into tissues can cause damage. Disseminated forms can lead to death.
- ***Pneumocystis* pneumonia** is caused by the fungus *P. jirovecii*. The disease is found in patients with AIDS and other immunocompromised individuals. Sulfa drug treatments have side effects, but untreated cases may be fatal.
- **Cryptococcosis** is caused by *Cryptococcus neoformans*. Lung infections may move to the brain, causing meningitis, which can be fatal.

Footnotes

1. 1 NE Manos et al. “Geographic Variation in the Prevalence of Histoplasmin Sensitivity.” *Dis Chest* 29, no. 6 (1956):649–668.
2. 2 DR Hospenthal. “Coccioidomycosis.” Medscape. 2015. http://emedicine.medscape.com/article/215978-overview. Accessed July 7, 2016.
3. 3 HY Lau and NJ Ashbolt. “The Role of Biofilms and Protozoa in *Legionella* Pathogenesis: Implications for Drinking Water.” *Journal of Applied Microbiology* 107 no. 2 (2009):368–378.
4. 4 Centers for Disease Control and Prevention. “Fungal Diseases. Definition of Mucormycosis.” 2015 http://www.cdc.gov/fungal/diseases/m...efinition.html. Accessed July 7, 2016.
5. 5 Centers for Disease Control and Prevention. “Fungal Diseases. Symptoms of Mucormycosis.” 2015 http://www.cdc.gov/fungal/diseases/m.../symptoms.html. Accessed July 7, 2016.
6. 6 MM Roden et al. “Epidemiology and Outcome of Zygomycosis: A Review of 929 Reported Cases.” *Clinical Infectious Diseases* 41 no. 5 (2005):634–653.

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10.4.E: Respiratory System Infections (Exercises)

22.1: Anatomy and Normal Microbiota of the Respiratory Tract

The upper respiratory tract is colonized by an extensive and diverse normal microbiota, many of which are potential pathogens. Few microbial inhabitants have been found in the lower respiratory tract, and these may be transients. Members of the normal microbiota may cause opportunistic infections, using a variety of strategies to overcome the innate nonspecific defenses (including the mucociliary escalator) and adaptive specific defenses of the respiratory system.

Multiple Choice

Which of the following is not directly connected to the nasopharynx?

A. middle ear
B. oropharynx
C. lacrimal glands
D. nasal cavity

Answer

C

What type of cells produce the mucus for the mucous membranes?

A. goblet cells
B. macrophages
C. phagocytes
D. ciliated epithelial cells

Answer

A

Which of these correctly orders the structures through which air passes during inhalation?

A. pharynx → trachea → larynx → bronchi
B. pharynx → larynx → trachea → bronchi
C. larynx → pharynx → bronchi → trachea
D. larynx → pharynx → trachea → bronchi

Answer

B

The _____ separates the upper and lower respiratory tract.

A. bronchi
B. larynx
C. epiglottis
D. palatine tonsil

Answer

C

Which microbial virulence factor is most important for attachment to host respiratory tissues?

A. adhesins
B. lipopolysaccharide
C. hyaluronidase

D. capsules

Answer

A

Fill in the Blank

Unattached microbes are moved from the lungs to the epiglottis by the _____ effect.

Answer

mucociliary escalator

Many bacterial pathogens produce _____ to evade phagocytosis.

Answer

capsules

The main type of antibody in the mucous membrane defenses is _____.

Answer

IgA

_____ results from an inflammation of the “voice box.”

Answer

Laryngitis

_____ phagocytize potential pathogens in the lower lung.

Answer

Alveolar macrophages

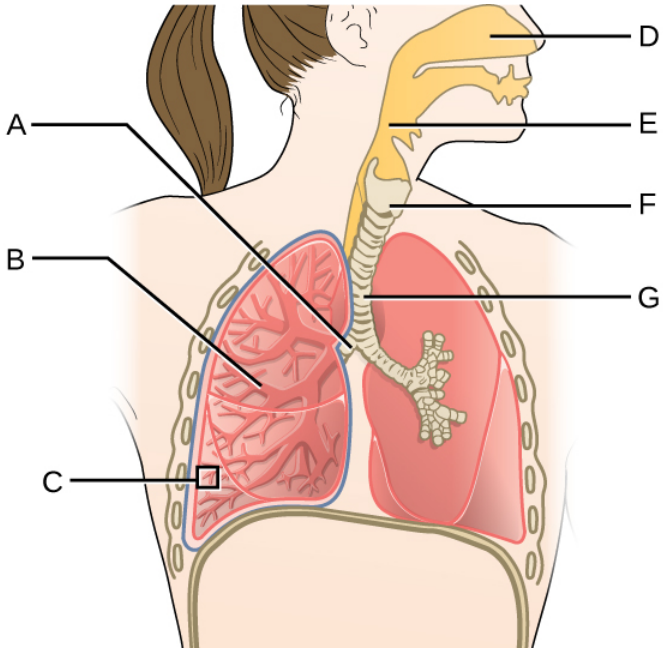
Short Answer

Explain why the lower respiratory tract is essentially sterile.

Explain why pneumonia is often a life-threatening disease.

Critical Thinking

Name each of the structures of the respiratory tract shown, and state whether each has a relatively large or small normal microbiota.



(credit: modification of work by National Cancer Institute)

Cystic fibrosis causes, among other things, excess mucus to be formed in the lungs. The mucus is very dry and caked, unlike the moist, more-fluid mucus of normal lungs. What effect do you think that has on the lung's defenses?

Why do you think smokers are more likely to suffer from respiratory tract infections?

22.2: Bacterial Infections of the Respiratory Tract

The respiratory tract can be infected by a variety of bacteria, both gram positive and gram negative. Although the diseases that they cause may range from mild to severe, in most cases, the microbes remain localized within the respiratory system. Fortunately, most of these infections also respond well to antibiotic therapy.

Multiple Choice

Which of the following does not involve a bacterial exotoxin?

A. diphtheria
B. whooping cough
C. scarlet fever
D. Q fever

Answer

D

What disease is caused by *Coxiella burnetii*?

A. Q fever
B. tuberculosis
C. diphtheria
D. walking pneumonia

Answer

A

In which stage of pertussis is the characteristic whooping sound made?

A. convalescence
B. catarrhal
C. paroxysmal
D. prodromal

Answer

C

What is the causative agent of Q fever?

A. *Coxiella burnetii*
B. *Chlamydophila psittaci*
C. *Mycoplasma pneumoniae*
D. *Streptococcus pyogenes*

Answer

A

Which of these microbes causes “walking pneumonia”?

A. *Klebsiella pneumoniae*
B. *Streptococcus pneumoniae*
C. *Mycoplasma pneumoniae*
D. *Chlamydophila pneumoniae*

Answer

C

Fill in the Blank

Calcified lesions called _____ form in the lungs of patients with TB.

Answer

Ghon complexes

An inflammation of the middle ear is called _____.

Answer

otitis media

The _____ is used to serologically identify *Streptococcus pneumoniae* isolates.

Answer

quellung reaction

_____ is a zoonotic infection that can be contracted by people who handle birds.

Answer

Psittacosis

The main virulence factor involved in scarlet fever is the _____.

Answer

erythrogenic toxin

Short Answer

Name three bacteria that commonly cause pneumonia. Which is the most common cause?

How does smoking make an individual more susceptible to infections?

How does the diphtheria pathogen form a pseudomembrane?

Critical Thinking

Why might β-lactam antibiotics be ineffective against *Mycoplasma pneumoniae* infections?

Why is proper antibiotic therapy especially important for patients with tuberculosis?

22.3: Viral Infections of the Respiratory Tract

Viruses cause respiratory tract infections more frequently than bacteria, and most viral infections lead to mild symptoms. The common cold can be caused by more than 200 viruses, typically rhinoviruses, coronaviruses, and adenoviruses, transmitted by direct contact, aerosols, or environmental surfaces. Due to its ability to rapidly mutate through antigenic drift and antigenic shift, influenza remains an important threat to human health. Two new influenza vaccines are developed annually.

Multiple Choice

Which of the following viruses is not commonly associated with the common cold?

A. coronavirus
B. adenovirus
C. rhinovirus
D. varicella-zoster virus

Answer

D

Which of the following viral diseases has been eliminated from the general population worldwide?

A. smallpox
B. measles
C. German measles
D. influenza

Answer

A

What term refers to multinucleated cells that form when many host cells fuse together during infections?

A. Ghon elements
B. Reye syndrome
C. Koplik’s spots
D. syncytia

Answer

D

Which of the following diseases is not associated with coronavirus infections?

A. Middle East respiratory syndrome
B. German measles
C. the common cold
D. severe acute respiratory syndrome

Answer

B

Which of these viruses is responsible for causing shingles?

A. rubella virus
B. measles virus
C. varicella-zoster virus
D. variola major virus

Answer

C

Fill in the Blank

The _____ virus is responsible for causing German measles.

Answer

rubella

A(n) _____ is an uncontrolled positive feedback loop between cytokines and leucocytes.

Answer

cytokine storm

In cases of shingles, the antiviral drug _____ may be prescribed.

Answer

acyclovir

The slow accumulation of genetic changes to an influenza virus over time is referred to as _____.

Answer

antigenic drift

The _____ vaccine is effective in controlling both measles and rubella.

Answer

MMR

Short Answer

Since we all have experienced many colds in our lifetime, why are we not resistant to future infections?

Critical Thinking

What role does the common cold have in the rise of antibiotic-resistant strains of bacteria in the United States?

Why is it highly unlikely that influenza A virus will ever be eradicated, like the smallpox virus?

22.4: Respiratory Mycoses

Fungal pathogens are ubiquitous in the environment. Serological studies have demonstrated that most people have been exposed to fungal respiratory pathogens during their lives. Yet symptomatic infections by these microbes are rare in healthy individuals. This demonstrates the efficacy of the defenses of our respiratory system. In this section, we examine some of the fungi that can cause respiratory infections.

Multiple Choice

Which of these infections is also referred to as Valley fever?

A. histoplasmosis
B. coccidioidomycosis
C. blastomycosis
D. aspergillosis

Answer

B

Which of the following is not caused by a dimorphic fungus?

A. histoplasmosis
B. coccidioidomycosis
C. blastomycosis
D. aspergillosis

Answer

D

Which of the following is caused by infections by bread molds?

A. mucormycosis
B. coccidioidomycosis
C. cryptococcosis
D. *Pneumocystis* pneumonia

Answer

A

In the United States, most histoplasmosis cases occur

A. in the Pacific northwest.
B. in the desert southwest.
C. in the Mississippi river valley.
D. in Colorado river valley.

Answer

C

Which of the following infections can be diagnosed using a skin test similar to the tuberculin test?

A. histoplasmosis
B. cryptococcosis
C. blastomycosis
D. aspergillosis

Answer

D

Fill in the Blank

In coccidioidomycosis, _____ containing many endospores form in the lungs.

Answer

spherules

In cryptococcosis, the main fungal virulence factor is the _____, which helps the pathogen avoid phagocytosis.

Answer

capsule

In some mycoses, fungal balls called _____ form in the lungs

Answer

aspergillomas

Most US cases of coccidioidomycosis occur in _____.

Answer

the desert southwest

Coccidioidomycosis may develop when *Coccidioides immitis* _____ are inhaled.

Answer

arthrospores

Short Answer

Which pulmonary fungal infection is most likely to be confused with tuberculosis? How can we discriminate between these two types of infection?

Compare and contrast aspergillosis and mucormycosis.

Critical Thinking

Why are fungal pulmonary infections rarely transmissible from person to person?

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