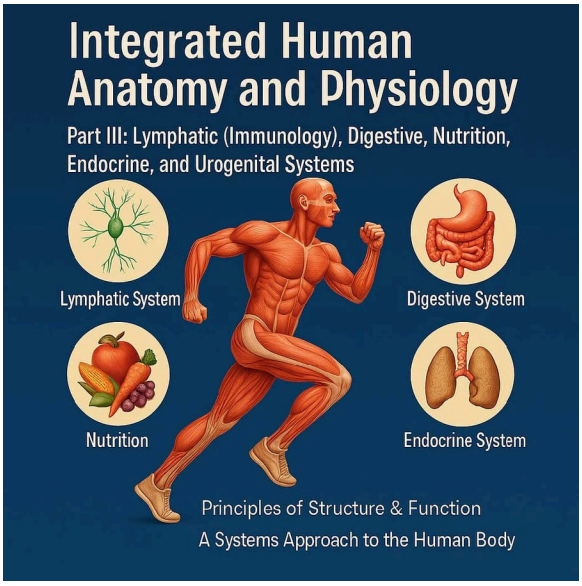
INTEGRATED HUMAN ANATOMY AND PHYSIOLOGY III



Lakshmikanta Sengupta and Susmita Sengupta

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Lakshmikanta Sengupta and Susmita Sengupta

De Anza College

Thumbnail: Detailed anatomical human figure with exposed muscles, alongside illustrations of cells and tissues. (AI-generated image created with Nano Banana)

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Program Page

De Anza College sits in the heart of Silicon Valley, where innovation and opportunity are part of daily life, and also has one of the highest costs of living in the country. For our students, that makes every dollar count, and the price of a textbook can be the difference between staying enrolled or dropping a class. Our Zero Textbook Cost (ZTC) program closes that gap by giving students full access to high-quality, faculty-created course materials at no cost from the first day of class.

De Anza is proud of its diverse student community, and we hold our ZTC materials to the same standard of excellence that defines the college. Faculty across departments write, adapt, and review these resources themselves, keeping them accurate, current, and grounded in the perspectives of the students who use them, with accessibility and inclusive design built in from the start.

This program reflects the time and care our faculty invest in their students. If you have questions, feedback, or come across any issues with a ZTC resource, contact De Anza College's ZTC Grants Coordinator, Shagun Kaur.

Learn more about De Anza ZTC Program [www.deanza.edu/academic-services/oer/]

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Accessibility Statement

Accessibility

De Anza College is dedicated to creating learning materials that are accessible and benefit all students. Our materials follow the Web Content Accessibility Guidelines (WCAG) 2.1 Level AA. Our authors and contracted accessibility specialists checked all resources using this ASCCC OERI checklist, the accessibility tool in LibreTexts, WAVE, JAWS, and other more detailed checks for complex materials such as interactive components.

We selected LibreTexts as our preferred platform because of its commitment to accessibility. In addition to the platform's inherent accessibility, we collaborated with the LibreTexts team to fix any accessibility issues we found.

Our Accessibility Review Process

Accessibility was built into the resource as it was written. This resource went through the following stages of review:

1. **Template check.** The project coordinator and instructional designers checked the first chapter for accessibility as a model to ensure later chapters meet accessibility standards.
2. **Progress checks.** The manuscript was checked at approximately 40%, 60%, and 80% completion to catch and correct accessibility issues in production.
3. **Specialist review.** Once the manuscript was complete, an accessibility expert conducted an accessibility check.
4. **Remediation.** The author and the project manager who conducted the earlier progress checks worked together to remediate the issues identified by the accessibility expert.
5. **Final check.** The resource underwent another full check by the accessibility expert before the book was deemed ready for publication.

This process combines ongoing checks during writing with a final specialist review, so issues are caught early and confirmed fixed before publication.

Report an Accessibility Problem

We are always looking for ways to make our resources more accessible. If you run into a barrier while using this resource, please let us know so we can look into it. When you contact us, it helps to include:

- The name of the resource
- The location of the problem (a web address or page/chapter description)
- A description of the problem you encountered
- The device, browser, and any assistive technology you were using (e.g., Windows 11, Google Chrome, JAWS screen reader)

Contact us: De Anza ZTC team

This statement was last updated August 2026

This resource was project-managed by **Shagun Kaur**, overseeing scope, budget, and schedule; stakeholder coordination via monthly meetings; training and platform support (LibreTexts, troubleshooting, technical support); QA/accessibility check scheduling; and licensing and copyright governance.

A Note on Known Limitations

No accessibility check is perfect. We've made a genuine, sustained effort to catch and fix issues throughout the writing and review process described above, but some barriers may remain, especially in complex or interactive content. We'd rather be upfront about that than claim a standard of perfection we can't guarantee.

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About the Book

About Integrated Human Anatomy and Physiology, Part III

Philosophy and Approach

Integrated Human Anatomy and Physiology, Part III is the third and final volume in a three-part textbook series designed for undergraduate, pre-nursing, and allied health students. It is written to support CSU- and UC-transferable coursework and aligns with program outcomes for the Medical Laboratory Technology Associate degree. The text adopts a student-centered, conversational style, uses intuitive figures, and emphasizes 21st-century critical thinking skills. Throughout, it aims to make complex concepts in anatomy and physiology understandable, relevant, and usable for students preparing for diverse health professions.

An equity-focused approach underlies the design. Many learners encountering this text are first-generation college students, returning adults, or students for whom English or scientific language is not their first language. The writing, examples, and learning supports are crafted to lower avoidable barriers, honor diverse experiences, and connect course content to real health and community contexts.

Chapter Organization and Scaffolding

Student-Centered Framework

Integrated Human Anatomy and Physiology, Part III is intentionally structured around the needs and realities of undergraduate students who may be encountering college-level science, medical vocabulary, and high-stakes transfer requirements for the first time. The book is organized into chapters (or modules) that build from orientation to deeper system-level understanding:

Masters of Homeostasis – The Endocrine System

- Endocrine glands and hormone pathways as long-distance regulators of homeostasis.
- Feedback loops (thyroid, adrenal, pancreatic) and how their disruption leads to common endocrine disorders.
- Clinical links to stress, diabetes, hormone therapy, and endocrine-related health inequities.

The Lymphatic and Immune Systems

- Structure of lymphatic vessels and organs with cells of innate and adaptive immunity.
- How immune defenses fight infection and how dysregulation leads to allergy, autoimmunity, and immunodeficiency.
- Connections to vaccination, infection prevention, and social/environmental influences on immune health.

The Digestive System

- Anatomy of the GI tract and accessory organs in digestion, absorption, and elimination.
- Links between microscopic structure (villi, glands) and motility, secretion, and nutrient uptake.
- Clinical and public health perspectives on malnutrition, liver disease, microbiome, and food access.

Metabolism and Nutrition

- Use and storage of carbohydrates, lipids, and proteins in whole-body energy balance.
- Hormonal control of absorptive and post-absorptive states and alterations in obesity and diabetes.
- Role of nutrition, culture, and social determinants in shaping metabolic health.

The Urinary System

- Kidney and nephron structure as the basis of filtration, reabsorption, secretion, and urine formation.
- Regulation of blood volume, blood pressure, osmolarity, and nitrogenous waste excretion.
- Clinical focus on hypertension, diabetic kidney disease, stones, dialysis, and access to renal care.

Fluid, Electrolytes, and Acid–Base Balance

- Movement of water and solutes between body compartments via hydrostatic and osmotic forces.
- Regulation of key ions and pH by kidneys, lungs, and buffer systems.
- Application to dehydration, heat stress, diuretic use, and chronic kidney or lung disease.

The Reproductive System

- Anatomy and physiology of gamete production and the hypothalamic–pituitary–gonadal axis.
- Ovarian, uterine, and testicular cycles, contraception, fertility, and STIs.
- Inclusive framing of reproductive health and its social, cultural, and legal contexts.

Development and Inheritance

- Human development from fertilization through embryonic and fetal stages, birth, and neonatal adaptation.
- Core genetic principles and patterns of inheritance linked to congenital conditions.
- Interactions among genes, prenatal care, environment, and social support in shaping lifelong health.

The central objective is to support student success by making it clear

- What students are expected to learn and do in each chapter
- Why these concepts and skills matter for future courses, clinical practice, and health professions
- How students can tell whether they are meeting the expectations and where they may need more practice

To achieve this, the textbook uses several student-centered design features

- Clearly defined objectives written in plain, actionable language, such as “Identify the major internal structures of the kidney,” “Trace the pathway of urine from the renal pelvis to the urethra,” “Differentiate between the functions of the proximal convoluted tubule and the collecting duct,” or “Predict how changes in blood pressure affect the glomerular filtration rate.” These specific statements provide a roadmap for reading, note-taking, and self-assessment.
- Purpose-driven explanations and examples that consistently connect content to real-world applications. A concept such as nephron filtration is connected to dialysis treatments and chronic kidney disease. The mechanics of the ureter and bladder are related to kidney stone pain, urinary incontinence, and infection risk. Instructors can adapt the emphasis—for example, a more clinical focus on how changes in urine composition signify systemic disease or a pathology focus on how urinary tract anatomy shapes infection patterns—while keeping the same core framework.
- Transparent criteria for success are built in through self-check questions and end-of-chapter review items that directly correspond to the learning objectives. Students can use these to identify what they understand, where they need further practice, and how to prepare for high-stakes exams and labs.
- Stepwise, scaffolded organization that moves from simpler to more complex ideas, and from microscopic (cells and tissues)

to macroscopic (organs and systems). Concepts are broken into manageable segments to reduce unnecessary cognitive load and to support students who are still building confidence with scientific reading.
- An end-of-chapter section of key terms - (integrated support for terminology). Terms are defined in clear, student-friendly language to help students gradually master the language of anatomy and physiology rather than feeling overwhelmed by unfamiliar Latin and Greek roots. Further, helps communicate clearly with peers and instructors and connect terminology to observable structures and physiological concepts.

Together, these design choices aim to

- Lower barriers for students with varied academic preparation
- Build confidence through clear expectations and frequent, low-stakes opportunities for feedback
- Promote durable, transferable skills in anatomical identification, physiological reasoning, scientific communication, and self-directed learning that will serve students throughout the full three-part series and into their professional training.

Integration Across Levels

Integration with the Laboratory Manual

This textbook is designed to function in tandem with a corresponding laboratory manual, especially for sections on the endocrine system, lymphatic system, urinary system, and reproductive system. The lecture text provides the conceptual and theoretical foundations for lab activities, preparing students to work confidently with models, microscopes, data, and specimens. It then reinforces lab learning with explanations, diagrams, and consistent terminology.

By aligning readings, figures, and vocabulary with the lab manual, the text supports a cohesive experience in which students repeatedly see, name, and explain structures and functions across settings. A student might encounter the nephron first in a figure, then on a model in lab, and then again in a case-based question about kidney function. This integration helps link abstract ideas to concrete observations and helps students practice moving between visual, verbal, and hands-on modes of learning.

Visuals, Images, and Accessibility

Visuals and Images

Visual resources are central to learning anatomy and physiology. Integrated Human Anatomy and Physiology, Part III is designed to make those resources as clear, accurate, and accessible as possible. The book includes high-resolution, clearly labeled diagrams and micrographs, such as anatomical drawings of endocrine glands, lymphatic vessels, and reproductive organs; histology of tissues relevant to immunity, digestion, and filtration; and schematics of feedback loops and physiological pathways.

These visuals are selected and created to emphasize conceptual clarity and structural accuracy, support transfer-level rigor, and help students connect structure to function and lab to lecture. Whenever possible, the book draws on openly licensed (Creative Commons) visuals and references. This allows instructors and institutions to adapt images, customize them for accessibility, and update content as science and pedagogy evolve.

Accessibility Features

The textbook reflects an accessibility-forward and equity-focused design philosophy. In both print and digital formats, it uses structured headings to support navigation and screen-reader use, readable typography and consistent page layout, and high color contrast for text and key visual elements. Figures and diagrams are accompanied by meaningful alternative text so that students using screen readers can access the same information as students viewing the images. Hyperlinks are written with descriptive text rather than bare URLs. Tables are simplified and tagged appropriately, and only used when they add clear value. Media are provided with captions and, where applicable, transcripts.

Language throughout the text is as plain as possible without sacrificing scientific accuracy. Explanations and instructions aim to reduce unnecessary complexity and cognitive load. These choices support students with disabilities, multilingual learners, students reading on mobile devices, and others who may be learning under constrained conditions. They also align with Universal Design for Learning principles and help institutions meet accessibility and accreditation expectations.

By providing zero-cost course materials in accessible formats from the outset, the textbook seeks to promote equitable access and support student persistence and success across diverse backgrounds, learning needs, and life circumstances.

Acknowledgements

Integrated Human Anatomy and Physiology, Part III was developed with support from the California Community Colleges Chancellor's Office through Zero Textbook Cost grants awarded to De Anza College. This funding made it possible to create accessible, no-cost materials for students across the three-part series.

The authors gratefully acknowledge the guidance and support of colleagues and staff whose work shaped this project. Shagun Kaur, Communication Studies faculty member and ZTC Grants Coordinator at De Anza College, provided weekly coaching, a structured process, and steady encouragement from initial outline through publication. Sam Bliss, Associate Vice President at De Anza College, offered leadership and advocacy for zero-cost, accessible learning and sustained institutional support during textbook development.

James Perla-Adams, Librarian and Open Educational Resources Coordinator at De Anza College, contributed expertise in designing and implementing accessible, zero-cost course materials. His input helped ensure robust alternative text for figures, high-contrast visual design, and accessible PDF and HTML formats aligned with Universal Design for Learning. Jyothsna Viswanadha, Mathematics faculty member at De Anza College, played a vital role in embedding equity and accessibility throughout the book, including adding and refining alternative text, improving color contrast, supporting tagged formats, and simplifying layout and navigation.

Their combined efforts, along with contributions from many unnamed colleagues and students, helped shape Integrated Human Anatomy and Physiology into an inclusive, accessible, and student-focused resource for the next generation of health professionals.

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About the Authors

Lakshmikanta Sengupta



Figure 1: Portrait of coauthor Lakshmikanta Sengupta.

Lakshmikanta Sengupta, Ph.D., is a biology educator with 40 years of experience teaching and mentoring in postsecondary settings. His teaching areas include genetics, biotechnology, human biology, and human anatomy and physiology.

Over four decades in the classroom, he has developed a strong understanding of how undergraduate students think and learn, the misconceptions they often bring to biology, and the explanations and learning activities that best support student success. He views educational institutions as vibrant communities where learning, mentorship, and collaboration can flourish.

Expertise in Biology Education

Dr. Sengupta combines deep disciplinary knowledge with strong teaching practice. He is well suited to author an undergraduate biology textbook because he brings both subject expertise and a student-centered approach to instruction.

His qualifications include:

- broad knowledge of the biological sciences
- familiarity with the history of biology, current debates, and emerging trends
- continued engagement with current scholarship to keep content accurate and relevant
- skill in explaining complex biological ideas in clear, accessible language

He uses engaging narratives, real-world examples, case studies, and carefully designed visuals such as diagrams, charts, and infographics to help students understand unfamiliar material.

Teaching and Learning Approach

Dr. Sengupta's teaching is grounded in evidence-based, student-centered methods. He designs learning activities and assessments that help students monitor their understanding and strengthen scientific reasoning.

Examples include:

- discussion questions

- quizzes
- hands-on activities
- application-focused exercises

He also promotes collaboration among educators and students to share effective practices, improve teaching, and increase the quality and inclusivity of educational materials.

Scholarship of Teaching and Learning

Beyond the classroom, Dr. Sengupta has contributed to the scholarship of teaching and learning in biology. He collaborated with the Community College Biology Faculty Enhancement through Scientific Teaching (CCB FEST), a National Science Foundation-funded program.

He has also coauthored research publications in the following venues:

- Proceedings of the National Academy of Sciences
- CBE—Life Sciences Education

This combination of research engagement and classroom experience informs his textbook authorship and helps ensure that the content is both scientifically rigorous and pedagogically effective.

Broader Interests

Dr. Sengupta's broader interests enrich his teaching with relatable and concrete examples. These interests include:

- macro and micro photography, which highlight the details of natural and anatomical structures
- cooking, which connects biology to nutrition and health
- gardening, which reflects a commitment to sustainability and the natural world

Together, his disciplinary depth, teaching expertise, assessment-driven approach, and long experience working with diverse undergraduate populations support his qualifications as a high-quality author of an undergraduate biology textbook.

Susmita Sengupta



Figure 2: Portrait of coauthor Susmita Sengupta.

Susmita Sengupta, Ph.D., is a scientist and educator who has taught at Bay Area community colleges for nearly two decades. She has more than 29 years of teaching experience at both the undergraduate and graduate levels.

She currently teaches Human Anatomy and Physiology and Human Biology. She has also taught:

- Genetics
- General Biology
- Mammalian Cell Culture
- Gene Expression in Cell Culture

Professional Development and Training

Dr. Sengupta has participated in a number of professional development programs that support effective biology instruction. These include:

- Summer Institute of Functional Genomics and Bioinformatics for Community College Faculty, University of California, Davis (2005)
- Instructional Skills Workshop, De Anza College (2018, 2020)
- RSI training (Winter 2025)

From 2010 to 2014, she was an active participant in CCB FEST (Community College Faculty Enhancement through Scientific Teaching), a National Science Foundation-funded project at San Francisco State University.

Leadership and Service

Dr. Sengupta is currently a member of the Academic Advisory Committee for Explorer's Guide to Biology.

She has also served on several college committees, including:

- Curriculum Committee
- Educational Policies Committee
- Evaluation Committee
- Professional Development Committee

Through this work, she has contributed to program development and instructional quality.

Scholarship and Publications

Dr. Sengupta is the author of more than 26 publications in peer-reviewed journals. She has also developed laboratory manuals to support the courses she teaches.

Her experience in both classroom and laboratory instruction, combined with her long-term engagement in evidence-based teaching and curriculum design, gives her a strong understanding of how students learn biology.

This combination of:

- disciplinary expertise
- pedagogical training
- curriculum experience
- practical teaching experience with diverse student populations

makes her especially well qualified to serve as the author of this undergraduate textbook.

Selected Publications

- 2004: Molecular mechanisms, proteinopathies and therapeutic strategies in neurodegenerative disorders. Current Genomics, 5(4), 327-346.
- 2002: Pharmacogenetic applications of the post genomic era. Current Pharmaceutical Biotechnology, 3(2), 141-150.
- 2001: Bioengineered crops: commercial and ethical considerations. Current Genomics, 2(2), 181-197.
- 1998: Calcium-dependent metabolic regulations in prokaryotes indicate conserved nature of calmodulin gene. Indian Journal

of Experimental Biology, 36(2), 136-147.
- 1997: Phytolectins: the natural molecules with immense biotechnological potential. Indian Journal of Experimental Biology, 35, 11-18.
- 1990: Cytogenetic studies in human populations exposed to gas leak in Bhopal, India. Environmental Health Perspectives, 86, 323-326.

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1: MASTERS OF HOMEOSTASIS - ENDOCRINE SYSTEM

Chapter Overview

In order to survive, animals must constantly adapt to changes in the environment. The nervous and endocrine systems both work together to bring about this adaptation. The endocrine system is a network of glands that secrete hormones directly into the bloodstream to regulate and coordinate many body functions. Unlike the rapid, short-term signals of the nervous system, endocrine signaling is typically slower in onset but longer lasting, influencing growth and development, metabolism, reproduction, fluid and electrolyte balance, stress responses, and circadian rhythms.

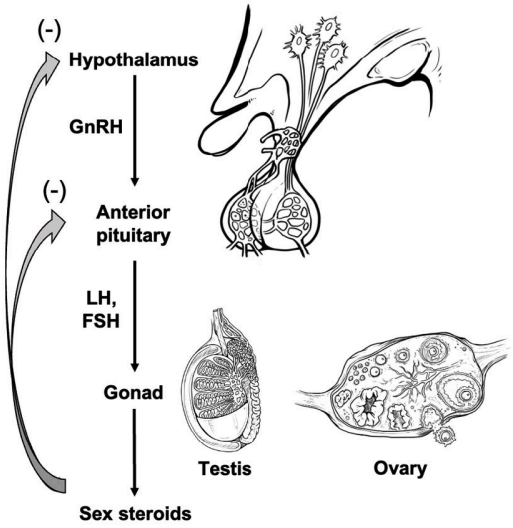


Figure 1.1: Hormonal regulation of the hypothalamic-pituitary-gonadal (HPG) axis through negative feedback. (CC BY 4.0; via Endocrine System). Detailed description of the Figure 1.1.

Neural vs Endocrine Communication

The endocrine system consists of cells, tissues, and organs that secrete hormones critical to homeostasis. The body coordinates its functions through two major types of communication: neural and endocrine. Neural communication includes both electrical and chemical signaling between neurons and target cells. Endocrine communication involves chemical signaling via the release of hormones into the extracellular fluid. From there, hormones diffuse into the bloodstream and may travel to distant body regions, where they elicit a response in target cells.

Endocrine Glands and Hormone-Secreting Organs

Endocrine glands are ductless glands that secrete hormones. Many organs of the body with other primary functions—such as the heart, stomach, and kidneys—also have hormone-secreting cells.

Chemical Nature and Classes of Hormones

Hormones are derived from amino acids or lipids. Amine hormones originate from the amino acids tryptophan or tyrosine. Larger amino acid hormones include peptides and protein hormones. Steroid hormones are derived from cholesterol.

Water-Soluble and Lipid-Soluble Hormones

Water-soluble hormones are mostly peptide/protein and non-thyroid amines. They dissolve in blood, travel without carrier

proteins, and bind to receptors on the cell membrane because they cannot cross the lipid bilayer. They act via second messengers (like cAMP), giving a fast but short-lived response.

Lipid-soluble hormones include steroid hormones and thyroid hormones (T3, T4). They are hydrophobic, so they travel in blood bound to carrier proteins and diffuse through cell membranes to bind intracellular (cytoplasmic or nuclear) receptors. They typically act by altering gene expression, leading to slower onset but longer-lasting effects.

Hormone Receptors and Second Messenger Systems

Hydrophobic hormones are able to diffuse through the membrane and interact with an intracellular receptor. In contrast, hydrophilic hormones must interact with cell membrane receptors. These are typically associated with a G protein, which becomes activated when the hormone binds the receptor. This initiates a signaling cascade that involves a second messenger, such as cyclic adenosine monophosphate (cAMP). Second messenger systems greatly amplify the hormone signal, creating a broader, more efficient, and faster response.

Control of Hormone Secretion and Feedback Mechanisms

Hormones are released upon stimulation that is of either chemical or neural origin. Regulation of hormone release is primarily achieved through negative feedback. Various stimuli may cause the release of hormones, but there are three major types. Humoral stimuli are changes in ion or nutrient levels in the blood. Hormonal stimuli are changes in hormone levels that initiate or inhibit the secretion of another hormone. Finally, a neural stimulus occurs when a nerve impulse prompts the secretion or inhibition of a hormone.

The Hypothalamus–Pituitary Complex

The hypothalamus–pituitary complex is located in the diencephalon of the brain. The hypothalamus and the pituitary gland are connected by a structure called the infundibulum, which contains vasculature and nerve axons. The pituitary gland is divided into two distinct structures with different embryonic origins.

Hormones of the Posterior Pituitary

The posterior lobe houses the axon terminals of hypothalamic neurons. It does not produce any hormones itself. Instead, it stores and releases into the bloodstream two hormones that are synthesized in the hypothalamus: oxytocin and antidiuretic hormone (ADH).

Hormones of the Anterior Pituitary

The anterior lobe is connected to the hypothalamus by vasculature in the infundibulum and produces and secretes six hormones. Their secretion is regulated, however, by releasing and inhibiting hormones from the hypothalamus. The six anterior pituitary hormones are: growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL).

Structure and Functions of the Thyroid Gland

The thyroid gland is a butterfly-shaped organ located in the neck anterior to the trachea. Its hormones regulate basal metabolism, oxygen use, nutrient metabolism, the production of ATP, and calcium homeostasis. They also contribute to protein synthesis and the normal growth and development of body tissues, including maturation of the nervous system, and they increase the body's sensitivity to catecholamines.

Thyroid Hormones (T3 and T4) and Iodine Requirement

The thyroid hormones triiodothyronine (T3) and thyroxine (T4) are produced and secreted by the thyroid gland in response to thyroid-stimulating hormone (TSH) from the anterior pituitary. Synthesis of the amino acid–derived T3 and T4 hormones requires iodine. Insufficient amounts of iodine in the diet can lead to goiter, cretinism, and many other disorders.

Calcium Homeostasis: Parathyroid Glands, PTH, and Calcitonin

Calcium is required for a variety of important physiologic processes, including neuromuscular functioning; thus, blood calcium levels are closely regulated. The parathyroid glands are small structures located on the posterior thyroid gland that produce parathyroid hormone (PTH), which regulates blood calcium levels. Low blood calcium levels cause the production and secretion of PTH. In contrast, elevated blood calcium levels inhibit secretion of PTH and trigger secretion of the thyroid hormone calcitonin. Underproduction of PTH can result in hypoparathyroidism. In contrast, overproduction of PTH can result in hyperparathyroidism.

Structure and Hormones of the Adrenal Glands

The adrenal glands, located superior to each kidney, consist of two regions: the adrenal cortex and adrenal medulla. The adrenal cortex—the outer layer of the gland—produces mineralocorticoids, glucocorticoids, and androgens. The adrenal medulla at the core of the gland produces epinephrine and norepinephrine.

Short-Term (Medullary) and Long-Term (Cortical) Stress Responses

The adrenal glands mediate a short-term stress response and a long-term stress response. A perceived threat results in the secretion of epinephrine and norepinephrine from the adrenal medulla, which mediate the fight-or-flight response. The long-term stress response is mediated by the secretion of CRH from the hypothalamus, which triggers ACTH, which in turn stimulates the secretion of corticosteroids from the adrenal cortex. The mineralocorticoids, chiefly aldosterone, cause sodium and fluid retention, which increases blood volume and blood pressure.

The Pineal Gland and Melatonin

The pineal gland is an endocrine structure of the diencephalon of the brain, and is located inferior and posterior to the thalamus. It is made up of pinealocytes. These cells produce and secrete the hormone melatonin in response to low light levels. High blood levels of melatonin induce drowsiness. Jet lag, caused by traveling across several time zones, occurs because melatonin synthesis takes several days to readjust to the light-dark patterns in the new environment.

Endocrine Regulation of the Male Reproductive System

The reproductive system is regulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) produced by the anterior lobe of the pituitary gland in response to gonadotropin-releasing hormone (GnRH) from the hypothalamus. FSH stimulates sperm maturation, which is inhibited by the hormone inhibin. The steroid hormone testosterone, a type of androgen, is released in response to LH and is responsible for the maturation and maintenance of the testicular reproductive system, as well as the development of secondary sex characteristics.

Endocrine Regulation of the Female Reproductive System and Pregnancy

FSH also promotes egg maturation and LH signals the secretion of the sex hormones, the estrogens and progesterone. Both of these hormones are important in the development and maintenance of the ovarian reproductive system, as well as maintaining pregnancy. The placenta develops during early pregnancy, and secretes several hormones important for maintaining the pregnancy.

The Pancreas: Endocrine Cells and Hormones

The pancreas has both exocrine and endocrine functions. The pancreatic islet cell types include alpha cells, which produce glucagon; beta cells, which produce insulin; delta cells, which produce somatostatin; and PP cells, which produce pancreatic polypeptide.

Regulation of Blood Glucose: Insulin, Glucagon, and Diabetes Mellitus

Insulin and glucagon are involved in the regulation of glucose metabolism. Insulin is produced by the beta cells in response to high blood glucose levels. It enhances glucose uptake and utilization by target cells, as well as the storage of excess glucose for

later use. Dysfunction of the production of insulin or target cell resistance to the effects of insulin causes diabetes mellitus, a disorder characterized by high blood glucose levels. The hormone glucagon is produced and secreted by the alpha cells of the pancreas in response to low blood glucose levels. Glucagon stimulates mechanisms that increase blood glucose levels, such as the catabolism of glycogen into glucose.

Organs with Secondary Endocrine Functions

Some organs have a secondary endocrine function. For example, the walls of the atria of the heart produce the hormone atrial natriuretic peptide (ANP), the gastrointestinal tract produces the hormones gastrin, secretin, and cholecystokinin, which aid in digestion, and the kidneys produce erythropoietin (EPO), which stimulates the formation of red blood cells. Even bone, adipose tissue, and the skin have secondary endocrine functions.

Embryonic Origins of Endocrine Tissues

The endocrine system originates from all three germ layers of the embryo, including the endoderm, ectoderm, and mesoderm. In general, different hormone classes arise from distinct germ layers.

Effects of Aging on the Endocrine System

Aging affects the endocrine glands, potentially affecting hormone production and secretion, and can cause disease. The production of hormones, such as human growth hormone, cortisol, aldosterone, sex hormones, and the thyroid hormones, decreases with age.

Chapter Objectives

To achieve these chapter objectives, actively engage with the material. Learning tissues is not a passive process. Your understanding will grow as you interact with the content, peers, and your instructor. Regularly check your thinking against feedback. Revisit complex concepts until you can confidently explain and apply them on your own.

By the end of this chapter, you will be able to:

- Compare and contrast the structures, signaling mechanisms, and response times of the nervous and endocrine systems.
- Describe the location, gross anatomy, and primary functions of the major endocrine glands in maintaining homeostasis.
- Classify hormones according to major chemical classes and functional schemes.
- Explain the mechanisms of hormone action at target cells (including receptor binding and signal transduction).
- Discuss the regulation of hormone secretion, including feedback mechanisms and key regulatory factors.
- Describe hormone action, hormone classification, and regulation of hormone secretion.
- Describe the hypothalamic-pituitary axis and investigate the endocrine organs it regulates.
- Describe the neurosecretory cells of the hypothalamus and hypothalamic releasing hormones.
- Define the neurosecretory cells of the anterior and posterior pituitary glands and their effects.
- Describe the hormones that are stored and secreted by the posterior pituitary - target cells and actions.
- List the hormones of the anterior pituitary - and describe their target cells and their physiological effects.
- Relate the hormones of the adrenal gland to their target cells and the resulting cellular and systemic effects.
- Study the thyroid gland and thyroid hormones; identify the target cells for these hormones and the effects of the hormones on the target cells.
- Explain the role of the pancreatic endocrine cells in the regulation of blood glucose.
- Identify the hormones released by the heart, kidneys, and other organs with secondary endocrine functions.
- Discuss several common diseases associated with endocrine system dysfunction.

1.1: The Endocrine Pancreas

1.2: Organs with Secondary Endocrine Functions

1.3: Neural and Endocrine Signaling

1.4: Structures of the Endocrine System
1.5: Hormone Classes and Hormone Actions
1.6: The Pituitary Gland and Hypothalamus
1.7: The Thyroid Gland
1.8: The Parathyroid Glands
1.9: The Adrenal Glands
1.10: The Pineal Gland
1.11: Gonadal and Placental Hormones
1.12: Development and Aging of the Endocrine System
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1.14: Chapter Review Questions
1.15: Applied Thinking Self - Assessment
1.16: Alternate Text Descriptions

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1.1: The Endocrine Pancreas

The Pancreas and the Pancreatic Islets

The pancreas is a long, slender organ, most of which is located posterior to the bottom half of the stomach (Figure 1.1.1). Although it is primarily an exocrine gland, secreting a variety of digestive enzymes, the pancreas has an endocrine function. Its pancreatic islets —clusters of cells formerly known as the islets of Langerhans—secrete the hormones glucagon, insulin, somatostatin, and pancreatic polypeptide (PP).

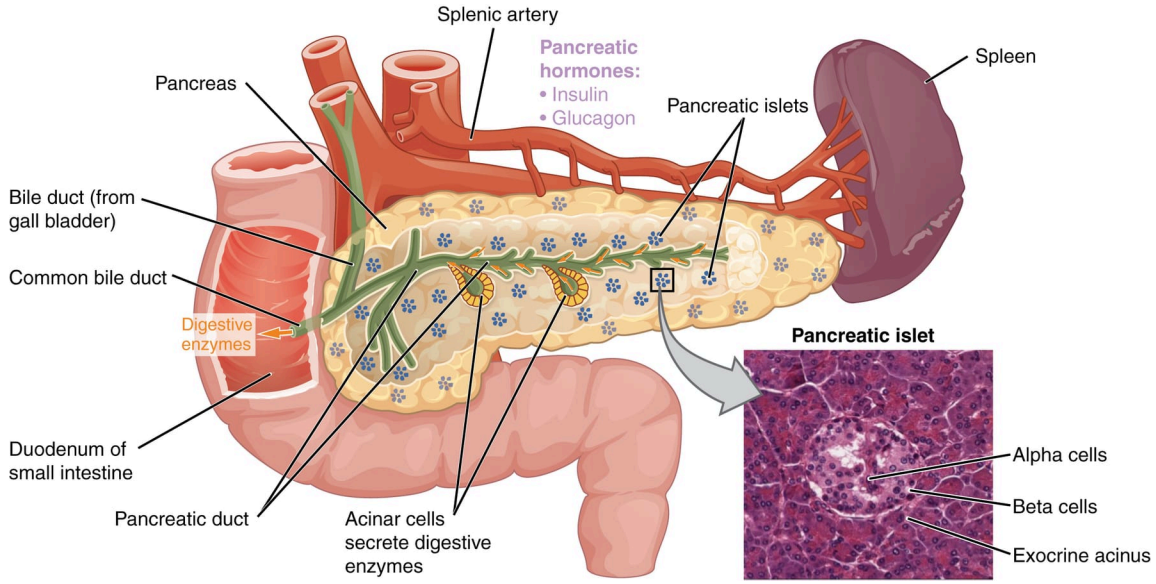


Figure 1.1.1: Anatomical illustration of the pancreas showing its ducts, blood supply, enzyme-secreting acinar cells, and hormone-producing islets, highlighting its dual role in digestion and hormone regulation. (CC BY 4.0; via The Endocrine Pancreas). Detailed description of the Figure 1.1.1.

Cells and Secretions of the Pancreatic Islets

The pancreatic islets each contain four varieties of cells:

- The alpha cell produces the hormone glucagon and makes up approximately 20 percent of each islet. Glucagon plays an important role in blood glucose regulation; low blood glucose levels stimulate its release.
- The beta cell produces the hormone insulin and makes up approximately 75 percent of each islet. Elevated blood glucose levels stimulate the release of insulin.
- The delta cell accounts for four percent of the islet cells and secretes the peptide hormone somatostatin. Recall that somatostatin is also released by the hypothalamus (as GHIH), and the stomach and intestines also secrete it. An inhibiting hormone, pancreatic somatostatin inhibits the release of both glucagon and insulin.
- The PP cell accounts for about one percent of islet cells and secretes the pancreatic polypeptide hormone. It is thought to play a role in appetite, as well as in the regulation of pancreatic exocrine and endocrine secretions. Pancreatic polypeptide released following a meal may reduce further food consumption; however, it is also released in response to fasting.

Regulation of Blood Glucose Levels by Insulin and Glucagon

Glucose is required for cellular respiration and is the preferred fuel for all body cells. The body derives glucose from the breakdown of the carbohydrate-containing foods and drinks we consume. Glucose not immediately taken up by cells for fuel can be stored by the liver and muscles as glycogen, or converted to triglycerides and stored in the adipose tissue. Hormones regulate both the storage and the utilization of glucose as required. Receptors located in the pancreas sense blood glucose levels, and

subsequently the pancreatic cells secrete glucagon or insulin to maintain normal levels.

Glucagon

Receptors in the pancreas can sense the decline in blood glucose levels, such as during periods of fasting or during prolonged labor or exercise (Figure 1.1.2). In response, the alpha cells of the pancreas secrete the hormone glucagon , which has several effects:

- It stimulates the liver to convert its stores of glycogen back into glucose. This response is known as glycogenolysis. The glucose is then released into the circulation for use by body cells.
- It stimulates the liver to take up amino acids from the blood and convert them into glucose. This response is known as gluconeogenesis.

Taken together, these actions increase blood glucose levels. The activity of glucagon is regulated through a negative feedback mechanism; rising blood glucose levels inhibit further glucagon production and secretion.

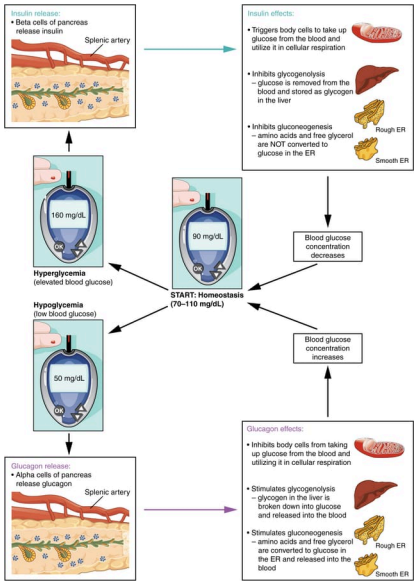


Figure 1.1.2: A flowchart illustrating the hormonal regulation of blood glucose. The diagram shows how insulin lowers elevated glucose levels and how glucagon raises low glucose levels, maintaining homeostasis between 70 and 110 mg/dL. (CC BY 4.0; via The Endocrine Pancreas). Detailed description of the Figure 1.1.2.

When blood glucose falls below the homeostatic range, or during hypoglycemia, alpha cells of the pancreas release glucagon. Glucagon prevents cells from taking up glucose for respiration, stimulates glycogenolysis by breaking down liver glycogen into glucose, and stimulates gluconeogenesis by converting amino acids and glycerol into glucose in the endoplasmic reticulum. These actions raise blood glucose concentration. Through insulin and glucagon, the body continually restores glucose levels to the normal range.

The primary function of insulin is to facilitate the uptake of glucose into body cells. Red blood cells, as well as cells of the brain, liver, kidneys, and the lining of the small intestine, do not have insulin receptors on their cell membranes and do not require insulin for glucose uptake. Although all other body cells do require insulin if they are to take glucose from the bloodstream, skeletal muscle cells and adipose cells are the primary targets of insulin.

The presence of food in the intestine triggers the release of gastrointestinal tract hormones such as glucose-dependent Insulinotropic peptide (previously known as gastric inhibitory peptide). This is in turn the initial trigger for insulin production and secretion by the beta cells of the pancreas. Once nutrient absorption occurs, the resulting surge in blood glucose levels further stimulates insulin secretion.

Precisely how insulin facilitates glucose uptake is not entirely clear. However, insulin appears to activate a tyrosine kinase receptor, triggering the phosphorylation of many substrates within the cell. These multiple biochemical reactions converge to support the movement of intracellular vesicles containing facilitative glucose transporters to the cell membrane. In the absence

of insulin, these transport proteins are normally recycled slowly between the cell membrane and cell interior. Insulin triggers the rapid movement of a pool of glucose transporter vesicles to the cell membrane, where they fuse and expose the glucose transporters to the extracellular fluid. The transporters then move glucose by facilitated diffusion into the cell interior.

Insulin also reduces blood glucose levels by stimulating glycolysis, the metabolism of glucose for generation of ATP. Moreover, it stimulates the liver to convert excess glucose into glycogen for storage, and it inhibits enzymes involved in glycogenolysis and gluconeogenesis. Finally, insulin promotes triglyceride and protein synthesis. The secretion of insulin is regulated through a negative feedback mechanism. As blood glucose levels decrease, further insulin release is inhibited. The pancreatic hormones are summarized in Table 1.1.1.

Table 1.1.1*: Hormones of the Pancreas*

Associated hormones	Chemical class	Effect
Insulin (beta cells)	Protein	Reduces blood glucose levels
Glucagon (alpha cells)	Protein	Increases blood glucose levels
Somatostatin (delta cells)	Protein	Inhibits insulin and glucagon release
Pancreatic polypeptide (PP cells)	Protein	Role in appetite

Disorders of the...

Endocrine System: Diabetes Mellitus

Dysfunction of insulin production and secretion, as well as the target cells' responsiveness to insulin, can lead to a condition called diabetes mellitus . An increasingly common disease, diabetes mellitus has been diagnosed in more than 18 million adults in the United States, and more than 200,000 children. It is estimated that up to 7 million more adults have the condition but have not been diagnosed. In addition, approximately 79 million people in the US are estimated to have pre-diabetes, a condition in which blood glucose levels are abnormally high, but not yet high enough to be classified as diabetes.

There are two main forms of diabetes mellitus. Type 1 diabetes is an autoimmune disease affecting the beta cells of the pancreas. Certain genes are recognized to increase susceptibility. The beta cells of people with type 1 diabetes do not produce insulin; thus, synthetic insulin must be administered by injection or infusion. This form of diabetes accounts for less than five percent of all diabetes cases.

Type 2 diabetes accounts for approximately 95 percent of all cases. It is acquired, and lifestyle factors such as poor diet, inactivity, and the presence of pre-diabetes greatly increase a person's risk. About 80 to 90 percent of people with type 2 diabetes are overweight or obese. In type 2 diabetes, cells become resistant to the effects of insulin. In response, the pancreas increases its insulin secretion, but over time, the beta cells become exhausted. In many cases, type 2 diabetes can be reversed by moderate weight loss, regular physical activity, and consumption of a healthy diet; however, if blood glucose levels cannot be controlled, the person with diabetes will eventually require insulin.

Two of the early manifestations of diabetes are excessive urination and excessive thirst. They demonstrate how the out-of-control levels of glucose in the blood affect kidney function. The kidneys are responsible for filtering glucose from the blood. Excessive blood glucose draws water into the urine, and as a result the person eliminates an abnormally large quantity of sweet urine. The use of body water to dilute the urine leaves the body dehydrated, and so the person is unusually and continually thirsty. The person may also experience persistent hunger because the body cells are unable to access the glucose in the bloodstream.

Over time, persistently high levels of glucose in the blood injure tissues throughout the body, especially those of the blood vessels and nerves. Inflammation and injury of the lining of arteries lead to atherosclerosis and an increased risk of heart attack and stroke. Damage to the microscopic blood vessels of the kidney impairs kidney function and can lead to kidney failure. Damage to blood vessels that serve the eyes can lead to blindness. Blood vessel damage also reduces circulation to the limbs, whereas nerve damage leads to a loss of sensation, called neuropathy, particularly in the hands and feet. Together, these changes increase the risk of injury, infection, and tissue death (necrosis), contributing to a high rate of toe, foot, and lower leg amputations in people with diabetes. Uncontrolled diabetes can also lead to a dangerous form of metabolic acidosis called ketoacidosis. Deprived of glucose, cells increasingly rely on fat stores for fuel. However, in a glucose-deficient

state, the liver is forced to use an alternative lipid metabolism pathway that results in the increased production of ketone bodies (or ketones), which are acidic. The build-up of ketones in the blood causes ketoacidosis, which—if left untreated—may lead to a life-threatening “diabetic coma.” Together, these complications make diabetes the seventh leading cause of death in the United States.

Diabetes is diagnosed when lab tests reveal that blood glucose levels are higher than normal, a condition called hyperglycemia . The treatment of diabetes depends on the type, the severity of the condition, and the ability of the patient to make lifestyle changes. As noted earlier, moderate weight loss, regular physical activity, and consumption of a healthful diet can reduce blood glucose levels. Some patients with type 2 diabetes may be unable to control their disease with these lifestyle changes, and will require medication. Historically, the first-line treatment of type 2 diabetes was insulin. Research advances have resulted in alternative options, including medications that enhance pancreatic function.

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1.2: Organs with Secondary Endocrine Functions

Overview

Several organs have primary functions outside the endocrine system but also secrete hormones that help regulate body processes. These organs include the heart, gastrointestinal tract, kidneys, skeleton, adipose tissue, skin, thymus, liver, and gonads.

Heart

When the body experiences an increase in blood volume or pressure, the cells of the heart's atrial wall stretch. In response, specialized cells in the wall of the atria produce and secrete the peptide hormone atrial natriuretic peptide (ANP). ANP signals the kidneys to reduce sodium reabsorption, thereby decreasing the amount of water reabsorbed from the urine filtrate and reducing blood volume. Other actions of ANP include the inhibition of renin secretion, thus inhibition of the renin-angiotensin-aldosterone system (RAAS) and vasodilation. Therefore, ANP aids in decreasing blood pressure, blood volume, and blood sodium levels.

Gastrointestinal Tract

The endocrine cells of the GI tract are located in the mucosa of the stomach and small intestine. Some of these hormones are secreted in response to eating a meal and aid in digestion. An example of a hormone secreted by the stomach cells is gastrin, a peptide hormone secreted in response to stomach distention that stimulates the release of hydrochloric acid. Secretin is a peptide hormone secreted by the small intestine as acidic chyme (partially digested food and fluid) moves from the stomach. It stimulates the release of bicarbonate from the pancreas, which buffers the acidic chyme, and inhibits the further secretion of hydrochloric acid by the stomach. Cholecystokinin (CCK) is another peptide hormone released from the small intestine. It promotes the secretion of pancreatic enzymes and the release of bile from the gallbladder, both of which facilitate digestion. Other hormones produced by the intestinal cells aid in glucose metabolism, such as by stimulating the pancreatic beta cells to secrete insulin, reducing glucagon secretion from the alpha cells, or enhancing cellular sensitivity to insulin.

Kidneys

The kidneys participate in several complex endocrine pathways and produce certain hormones. A decline in blood flow to the kidneys stimulates them to release the enzyme renin, triggering the renin-angiotensin-aldosterone (RAAS) system, and stimulating the reabsorption of sodium and water. The reabsorption increases blood flow and blood pressure. The kidneys also play a role in regulating blood calcium levels through the production of calcitriol from vitamin D_3, which is released in response to the secretion of parathyroid hormone (PTH). In addition, the kidneys produce the hormone erythropoietin (EPO) in response to low oxygen levels. EPO stimulates the production of red blood cells (erythrocytes) in the bone marrow, thereby increasing oxygen delivery to tissues. You may have heard of EPO as a performance-enhancing drug (in a synthetic form).

Skeleton

Although bone has long been recognized as a target for hormones, only recently have researchers recognized that the skeleton itself produces at least two hormones. Fibroblast growth factor 23 (FGF23) is produced by bone cells in response to increased blood levels of vitamin D_3 or phosphate. It triggers the kidneys to inhibit the formation of calcitriol from vitamin D_3 and to increase phosphorus excretion. Osteocalcin, produced by osteoblasts, stimulates the pancreatic beta cells to increase insulin production. It also acts on peripheral tissues to increase their sensitivity to insulin and their utilization of glucose.

Adipose Tissue

Adipose tissue produces and secretes several hormones involved in lipid metabolism and storage. One important example is leptin, a protein manufactured by adipose cells that circulates in amounts directly proportional to levels of body fat. Leptin is released in response to food consumption and acts by binding to brain neurons involved in energy intake and expenditure. Binding of leptin produces a feeling of satiety after a meal, thereby reducing appetite. It also appears that the binding of leptin to brain receptors triggers the sympathetic nervous system to regulate bone metabolism, increasing deposition of cortical bone.

Adiponectin—another hormone synthesized by adipose cells—appears to reduce cellular insulin resistance and to protect blood vessels from inflammation and atherosclerosis. Its levels are lower in people who are obese, and rise following weight loss.

Skin

The skin functions as an endocrine organ in the production of the inactive form of vitamin D_3, cholecalciferol. When cholesterol present in the epidermis is exposed to ultraviolet radiation, it is converted to cholecalciferol, which then enters the blood. In the liver, cholecalciferol is converted to an intermediate that travels to the kidneys and is further converted to calcitriol, the active form of vitamin D_3. Vitamin D is important in a variety of physiological processes, including intestinal calcium absorption and immune system function. In some studies, low levels of vitamin D have been associated with increased risks of cancer, severe asthma, and multiple sclerosis. Vitamin D deficiency in children causes rickets, and in adults, osteomalacia—both of which are characterized by bone deterioration.

Thymus

The thymus is an organ of the immune system that is larger and more active during infancy and early childhood, and begins to atrophy as we age. Its endocrine function is the production of a group of hormones called thymosins that contribute to the development and differentiation of T lymphocytes, which are immune cells. Although the role of thymosins is not yet well understood, it is clear that they contribute to the immune response. Thymosins have been found in tissues other than the thymus and have a wide variety of functions, so the thymosins cannot be strictly categorized as thymic hormones.

Liver

The liver is responsible for secreting at least four important hormones or hormone precursors: insulin-like growth factor (somatomedin), angiotensinogen, thrombopoietin, and hepcidin. Insulin-like growth factor-1 is the immediate stimulus for growth in the body, especially of the bones. Angiotensinogen is the precursor to angiotensin, mentioned earlier, which increases blood pressure. Thrombopoietin stimulates the production of the blood's platelets. Hepcidins block the release of iron from cells in the body, helping to regulate iron homeostasis in our body fluids. The major hormones of these other organs are summarized in Table 1.2.1.

Table 1.2.1: Organs with Secondary Endocrine Functions and Their Major Hormones

Organ	Major hormones	Effects
Heart	Atrial natriuretic peptide (ANP)	Reduces blood volume, blood pressure, and Na^+ concentration
Gastrointestinal tract	Gastrin, secretin, and cholecystokinin	Aid digestion of food and buffering of stomach acids
Gastrointestinal tract	Glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1)	Stimulate beta cells of the pancreas to release insulin
Kidneys	Renin	Stimulates release of aldosterone
Kidneys	Calcitriol	Aids in the absorption of Ca^{2+}
Kidneys	Erythropoietin	Triggers the formation of red blood cells in the bone marrow
Skeleton	FGF23	Inhibits production of calcitriol and increases phosphate excretion
Skeleton	Osteocalcin	Increases insulin production
Adipose tissue	Leptin	Promotes satiety signals in the brain
Adipose tissue	Adiponectin	Reduces insulin resistance
Skin	Cholecalciferol	Modified to form vitamin D

Organ	Major hormones	Effects
Thymus (and other organs)	Thymosins	Among other things, aids in the development of T lymphocytes of the immune system
Liver	Insulin-like growth factor-1	Stimulates bodily growth
Liver	Angiotensinogen	Raises blood pressure
Liver	Thrombopoietin	Causes increase in platelets
Liver	Hepcidin	Blocks release of iron into body fluids

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1.3: Neural and Endocrine Signaling

The Endocrine System and Intercellular Communication

Communication is a process in which a sender transmits signals to one or more receivers to control and coordinate actions. When you send a group text instructing your friends to meet at the dining hall at 18:00, you are transmitting digital signals intended to modify the behavior of individuals who are not in your immediate vicinity. Analogously, specific populations of cells release chemical messengers that travel through the internal environment to regulate the activity of distant target cells. This form of long-distance intercellular signaling provides systemic coordination and control, is essential for the maintenance of homeostasis, and represents the primary functional role of the endocrine system.

In the human body, two major organ systems participate in relatively "long distance" communication: the nervous system and the endocrine system. Together, these two systems are primarily responsible for maintaining homeostasis in the body. The nervous system uses two types of intercellular communication—electrical and chemical signaling—either by the direct action of an electrical potential, or in the latter case, through the action of chemical neurotransmitters such as serotonin or norepinephrine. Neurotransmitters act locally and rapidly. When an electrical signal in the form of an action potential arrives at the synaptic terminal, they diffuse across the synaptic cleft (the gap between a sending neuron and a receiving neuron or muscle cell). Once the neurotransmitters interact (bind) with receptors on the receiving (post-synaptic) cell, the receptor stimulation is transduced into a response such as continued electrical signaling or modification of cellular response. The target cell responds within milliseconds of receiving the chemical "message"; this response then ceases very quickly once the neural signaling ends. In this way, neural communication enables body functions that involve quick, brief actions, such as movement, sensation, and cognition.In contrast, the endocrine system uses just one method of communication: chemical signaling. These signals are sent by the endocrine organs, which secrete chemicals—the hormone—into the extracellular fluid. Hormones are transported primarily via the bloodstream throughout the body, where they bind to receptors on target cells, inducing a characteristic response. As a result, endocrine signaling requires more time than neural signaling to prompt a response in target cells, though the precise amount of time varies with different hormones. For example, the hormones released when you are confronted with a dangerous or frightening situation, called the fight-or-flight response, occur by the release of adrenal hormones—epinephrine and norepinephrine—within seconds. In contrast, it may take up to 48 hours for target cells to respond to certain reproductive hormones.

In addition, endocrine signaling is typically less specific than neural signaling. The same hormone may play a role in a variety of different physiological processes depending on the target cells involved. For example, the hormone oxytocin promotes uterine contractions in people in labor. It is also important in breastfeeding, and may be involved in the sexual response and in feelings of emotional attachment in humans.

In general, the nervous system involves quick responses to rapid changes in the external environment, and the endocrine system is usually slower acting—taking care of the internal environment of the body, maintaining homeostasis, and controlling reproduction (Table 1.3.1). So how does the fight-or-flight response that was mentioned earlier happen so quickly if hormones are usually slower acting? It is because the two systems are connected. It is the fast action of the nervous system in response to the danger in the environment that stimulates the adrenal glands to secrete their hormones. As a result, the nervous system can cause rapid endocrine responses to keep up with sudden changes in both the external and internal environments when necessary.

Table 1.3.1: Endocrine and Nervous Systems

Characteristic	Endocrine system	Nervous system
Signaling mechanism(s)	Chemical	Chemical/electrical
Primary chemical signal	Hormones	Neurotransmitters
Distance traveled	Long or short	Always short
Response time	Fast or slow	Always fast
Environment targeted	Internal	Internal and external

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1.4: Structures of the Endocrine System

Endocrine Glands and Cells

The endocrine system consists of cells, tissues, and organs that secrete hormones as a primary or secondary function. The endocrine gland is the major player in this system. The primary function of these ductless glands is to secrete their hormones directly into the surrounding fluid. The interstitial fluid and the blood vessels then transport the hormones throughout the body. The endocrine system includes the pituitary, thyroid, parathyroid, adrenal, and pineal glands (Figure 1.4.1). Some of these glands have both endocrine and non-endocrine functions. For example, the pancreas contains cells that function in digestion as well as cells that secrete the hormones insulin and glucagon, which regulate blood glucose levels. The hypothalamus, thymus, heart, kidneys, stomach, small intestine, liver, skin, ovaries, and testes are other organs that contain cells with endocrine function. Moreover, adipose tissue has long been known to produce hormones, and recent research has revealed that even bone tissue has endocrine functions.

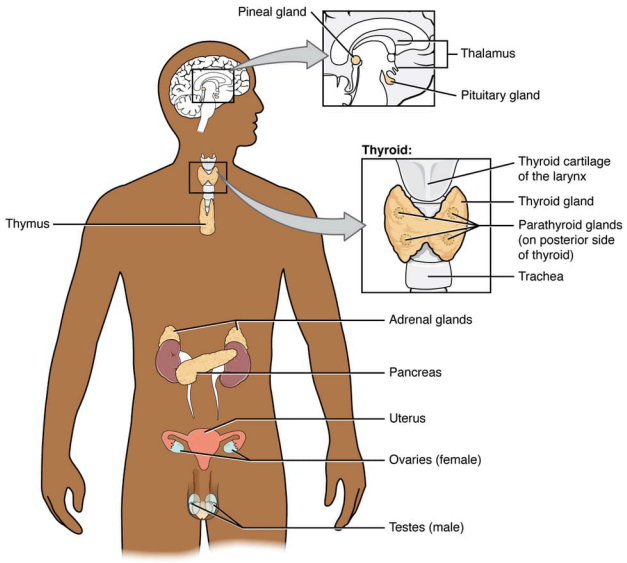


Figure 1.4.1: Endocrine glands and cells are located throughout the body and play an essential role in homeostasis. Organs that have primary endocrine functions are displayed in this figure. (CC BY 4.0; via OpenStax). Detailed text description of the Figure 1.4.1.

Endocrine glands are ductless and are different from the body's exocrine glands, which release their secretions through small tubes called ducts. Examples of exocrine glands include the sebaceous, mucous, and sudoriferous (sweat) glands of the skin. The pancreas secretes hormones as part of its endocrine function, but it also has an exocrine function where pancreatic acinar cells secrete digestive enzymes through ducts to help digest food that passes through the lumen of the small intestine.As just noted, the pancreas also has an exocrine function: most of its cells secrete pancreatic juice through the pancreatic and accessory ducts to the lumen of the small intestine.

Career Connection

Endocrinologist

Endocrinology is a specialty in the field of medicine that focuses on the treatment of endocrine system disorders. Endocrinologists—medical doctors who specialize in this field—are experts in treating diseases associated with hormonal systems, ranging from thyroid disease to diabetes mellitus. Endocrine surgeons treat endocrine disease through the removal, or resection, of the affected endocrine gland.

Patients who are referred to endocrinologists may have signs and symptoms or blood test results that suggest excessive or impaired functioning of an endocrine gland or endocrine cells. The endocrinologist may order additional blood tests to determine whether the patient's hormonal levels are abnormal, or they may stimulate or suppress the function of the suspect endocrine gland and then have blood taken for analysis. Treatment varies according to the diagnosis. Some endocrine disorders, such as type 2 diabetes, may respond to lifestyle changes such as modest weight loss, adoption of a healthy diet, and regular physical activity. Other disorders may require medication, such as hormone replacement, and routine monitoring by the endocrinologist. These include disorders of the pituitary gland that can affect growth and disorders of the thyroid gland that can result in a variety of metabolic problems.

Some patients experience health problems as a result of the normal decline in hormones that can accompany aging. These patients can consult with an endocrinologist to weigh the risks and benefits of hormone replacement therapy intended to boost their natural levels of reproductive hormones.

In addition to treating patients, endocrinologists may be involved in research to improve the understanding of endocrine system disorders and develop new treatments for these diseases.

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1.5: Hormone Classes and Hormone Actions

Local Hormones

In endocrine signaling, circulating hormones are those which are secreted into the extracellular fluid and diffuse into the blood or lymph, and they can then travel great distances throughout the body. In contrast, local hormones act on self or neighboring cells. Autocrine (auto- = self) signaling occurs when the cell secretes a hormone or molecule that causes a response in itself. For example, interleukin-1, or IL-1, is a signaling molecule that plays a primary role in the inflammatory response. Cells that secrete IL-1 have receptors on their cell surface that bind to IL-1, resulting in autocrine signaling that causes a response in the same cell that secreted IL-1. On the other hand, paracrine (para- = near) signaling occurs when the local hormones induce a response in neighboring cells. Although paracrine hormones may enter the bloodstream, their concentration is generally too low to elicit a response from distant tissues. For people with asthma, a familiar example is histamine, a paracrine hormone released by immune cells in the bronchial tree of the lungs. Histamine causes smooth muscle cells of the bronchi to constrict, thus narrowing the airways and making it harder to breathe.

Circulating Hormones

Although a given hormone may travel throughout the body in the bloodstream, it will affect the activity only of its target cells; that is, cells with receptors for that particular hormone. Once the hormone binds to the receptor, a chain of events is initiated that leads to the target cell's response. Hormones play a critical role in the regulation of physiological processes because of the target cell responses they regulate. These responses contribute to human reproduction, growth and development of body tissues, metabolism, fluid, and electrolyte balance, sleep, and many other body functions. The major hormones of the human body and their effects are identified in Table 1.5.1.

Table 1.5.1: Endocrine Glands and Their Major Hormones

Endocrine gland	Associated hormones	Chemical class	Effect
Pituitary (anterior)	Growth hormone (GH)	Protein	Promotes growth of body tissues
Pituitary (anterior)	Prolactin (PRL)	Peptide	Promotes milk production
Pituitary (anterior)	Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates thyroid hormone release
Pituitary (anterior)	Adrenocorticotropic hormone (ACTH)	Peptide	Stimulates hormone release by adrenal cortex
Pituitary (anterior)	Follicle-stimulating hormone (FSH)	Glycoprotein	Stimulates gamete production
Pituitary (anterior)	Luteinizing hormone (LH)	Glycoprotein	Stimulates androgen production by gonads
Pituitary (posterior)	Antidiuretic hormone (ADH)	Peptide	Stimulates water reabsorption by kidneys
Pituitary (posterior)	Oxytocin	Peptide	Stimulates uterine contractions during childbirth
Thyroid	Thyroxine (T_4), triiodothyronine (T_3)	Amine	Stimulate basal metabolic rate
Thyroid	Calcitonin	Peptide	Reduces blood Ca^{2+} levels

Endocrine gland	Associated hormones	Chemical class	Effect
Parathyroid	Parathyroid hormone (PTH)	Peptide	Increases blood Ca^{2+} levels
Adrenal (cortex)	Aldosterone	Steroid	Increases blood Na^{+} levels
Adrenal (cortex)	Cortisol, corticosterone, cortisone	Steroid	Increase blood glucose levels
Adrenal (medulla)	Epinephrine, norepinephrine	Amine	Stimulate fight-or-flight response
Pineal	Melatonin	Amine	Regulates sleep cycles
Pancreas	Insulin	Protein	Reduces blood glucose levels
Pancreas	Glucagon	Protein	Increases blood glucose levels
Testes	Testosterone	Steroid	Stimulates development of sex characteristics including a deeper voice, increased muscle mass, development of body hair, and sperm production
Ovaries	Estrogens and progesterone	Steroid	Stimulate development of sex characteristics including the development of adipose and breast tissue, and prepare the body for childbirth

Chemical Classification of Hormones

The hormones of the human body can also be divided into two major groups based on how they interact with water. Hormones derived from amino acids include amines, peptides, and proteins are water-soluble hormones. Others derived from lipids or have lipid-like characteristics are lipid-soluble hormones. These chemical classifications further relate to the hormone's distribution in blood, the type of receptors it binds to, and how signals are relayed inside the target cells.

Water-Soluble Hormones

There are three types of water-soluble hormones: amine, peptide, and protein hormones. Whereas amine hormones are derived from a single amino acid, peptide, and protein hormones consist of multiple amino acids that link to form an amino acid chain. These water-soluble hormones are "hydrophilic" as they love interacting with water and are easily soluble in water.

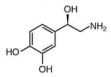
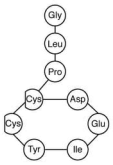
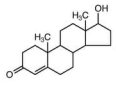
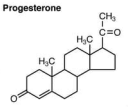
Hormone Class	Components	Example(s)
Amine Hormone	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	Norepinephrine 
Peptide Hormone	Short chains of linked amino acids	Oxytocin 
Protein Hormone	Long chains of linked amino acids	Human Growth Hormone 
Steroid Hormones	Derived from the lipid cholesterol	Testosterone  Progesterone 

Figure 1.5.1: Amine, Peptide, Protein, and Steroid Hormone Structure. (CC BY 4.0; via Hormones). Detailed text description of the Figure 1.5.1.

Amine Hormones

Hormones derived from the modification of amino acids are referred to as amine hormones. Typically, the original structure of the amino acid is modified such that a –COOH, or carboxyl, group is removed, whereas the $-\mathrm{NH}_3^+$, or amine, group remains.

Amine hormones are synthesized from the amino acids tryptophan or tyrosine. An example of a hormone derived from tryptophan is melatonin, which is secreted by the pineal gland and helps regulate circadian rhythm. Tyrosine derivatives include the metabolism-regulating thyroid hormones, as well as the catecholamines, such as epinephrine, norepinephrine, and dopamine. Epinephrine and norepinephrine are secreted by the adrenal medulla and play a role in the fight-or-flight response, whereas dopamine is secreted by the hypothalamus and inhibits the release of certain anterior pituitary hormones.

Peptide and Protein Hormones

Whereas the amine hormones are derived from a single amino acid, peptide and protein hormones consist of multiple amino acids that link to form an amino acid chain. Peptide hormones consist of short chains of amino acids, whereas protein hormones are longer polypeptides. Both types are synthesized like other body proteins: DNA is transcribed into mRNA, which is translated into an amino acid chain.

Examples of peptide hormones include antidiuretic hormone (ADH), a pituitary hormone important in fluid balance, and atrial-natriuretic peptide, which is produced by the heart and helps to decrease blood pressure. Some examples of protein hormones include growth hormone, which is produced by the pituitary gland, and follicle-stimulating hormone (FSH), which has an attached carbohydrate group and is thus classified as a glycoprotein. FSH helps stimulate the maturation of eggs in the ovaries and sperm in the testes.

Lipid-Soluble Hormones

The lipid-soluble hormones include steroids, thyroid hormones, nitric oxide, and eicosanoids. Although thyroid hormones are synthesized by attaching iodine to the amino acid tyrosine, they are classified as lipid-soluble hormones. Thyroid hormones have two hexagonal benzene rings, and these structures make them very lipid-soluble. Nitric oxide (NO) is a gas, and it acts as a hormone and a neurotransmitter and plays a critical role as a vasodilator that relaxes the smooth muscle in blood vessels, causing them to widen. Eicosanoids are derived from arachidonic acid, a 20-carbon fatty acid, so they are lipid-soluble as well. Eicosanoids act more as paracrine factors and local hormones as they tend to travel limited distances in the body. Prostaglandins and leukotrienes are examples of eicosanoids that act in a variety of mechanisms, such as inflammation.

Steroid Hormones

The primary hormones derived from lipids are steroids. Steroid hormones are derived from the lipid cholesterol. For example, the reproductive hormones testosterone and the estrogens—which are produced by the gonads (testes and ovaries)—are steroid hormones. The adrenal glands produce the steroid hormone aldosterone, which is involved in osmoregulation, and cortisol, which plays a role in metabolism.

Like cholesterol, steroid hormones are not soluble in water (they are hydrophobic). Because blood is water-based, lipid-derived hormones must travel to their target cell bound to a transport protein. This more complex structure extends the half-life of steroid hormones much longer than that of hormones derived from amino acids. A hormone's half-life is the time required for half the concentration of the hormone to be degraded. For example, the lipid-derived hormone cortisol has a half-life of approximately 60 to 90 minutes. In contrast, the amino acid–derived hormone epinephrine has a half-life of approximately one minute.

Mechanisms of Hormone Action

Have you ever wondered how hormones produce their actions on their target cells? Imagine that you are going home after school, and you have a specific key to your door that does not work on any other door. Hormones are similar to the key in this example. It will fit into a specific door called a hormone receptor. In cells, a hormone will bind to a specific hormone receptor, a protein located either inside the cell or embedded in the cell membrane, depending on whether the hormone is water-soluble or lipid-soluble. Hormone receptors recognize molecules with specific shapes and chemical functional groups and respond only to hormones that correctly "fit" into the receptor. Moreover, the same hormone receptor may be located on cells in different body tissues and trigger different responses in different tissues. For example, insulin stimulates glycogen synthesis when it binds to insulin receptors in liver cells but it activates fat synthesis when it binds to insulin receptors in adipose cells. Thus, the response triggered by a hormone depends not only on the hormone and receptor, but also on the target cell.

Mechanism of Lipid-Soluble Hormones and Intracellular Hormone Receptors

Intracellular hormone receptors are located inside the cell. Hormones that bind to this type of receptor must be able to cross the cell membrane. Steroid hormones are derived from cholesterol and therefore can readily diffuse through the lipid bilayer of the cell membrane to reach the intracellular receptor (Figure 1.5.2). Thyroid hormones, cross the cell membrane by a specific carrier-mediated mechanism that is energy and Na^+ dependent.

The location of steroid and thyroid hormone binding differs slightly: a steroid hormone may bind to its receptor within the cytosol or within the nucleus. In either case, this binding generates a hormone-receptor complex that moves toward the chromatin in the cell nucleus and binds to a particular segment of the cell's DNA. In contrast, thyroid hormones bind to receptors already bound to DNA. For both steroid and thyroid hormones, binding of the hormone-receptor complex with DNA triggers transcription of a target gene to mRNA, which moves to the cytosol and directs protein synthesis by ribosomes.

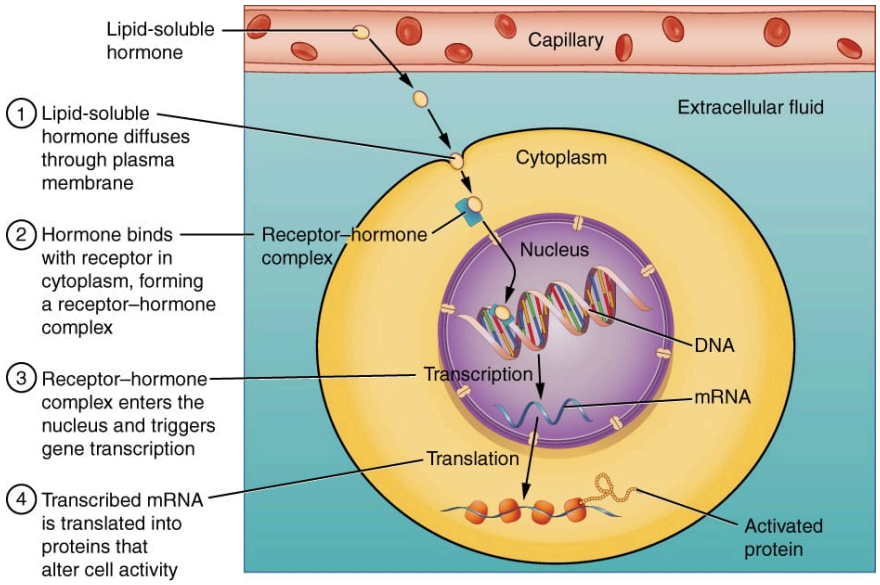


Figure 1.5.2: Diagram illustrating how a lipid-soluble hormone diffuses into a cell, binds an intracellular receptor, enters the nucleus to activate gene transcription, and produces proteins that change cell activity. (CC BY 4.0; via Hormones). Detailed text description of the Figure 1.5.2.

Mechanism of Water-Soluble Hormone and Cell Membrane Hormone Receptors

Hydrophilic, or water-soluble, hormones are unable to diffuse through the lipid bilayer of the cell membrane and must therefore pass on their message to a receptor located at the surface of the cell. Except for thyroid hormones, which are lipid-soluble, all amino acid–derived hormones bind to cell membrane receptors that are located, at least in part, on the extracellular surface of the cell membrane. Therefore, they do not directly affect the transcription of target genes, but instead initiate a signaling cascade that is carried out by a molecule called a second messenger. In this case, the hormone is called a first messenger.

The second messenger used by most hormones is cyclic adenosine monophosphate (cAMP). In the cAMP second messenger system, a water-soluble hormone binds to its receptor in the cell membrane (Step 1 in Figure 1.5.3). This receptor is associated with an intracellular component called a G protein, and binding of the hormone activates the G-protein component (Step 2). The activated G protein in turn activates an enzyme called adenylyl cyclase, also known as adenylate cyclase (Step 3), which converts adenosine triphosphate (ATP) to cAMP (Step 4). As the second messenger, cAMP activates a type of enzyme called a protein kinase that is present in the cytosol (Step 5). Activated protein kinases initiate a phosphorylation cascade, in which multiple protein kinases phosphorylate (add a phosphate group to) numerous and various cellular proteins, including other enzymes (Step 6).

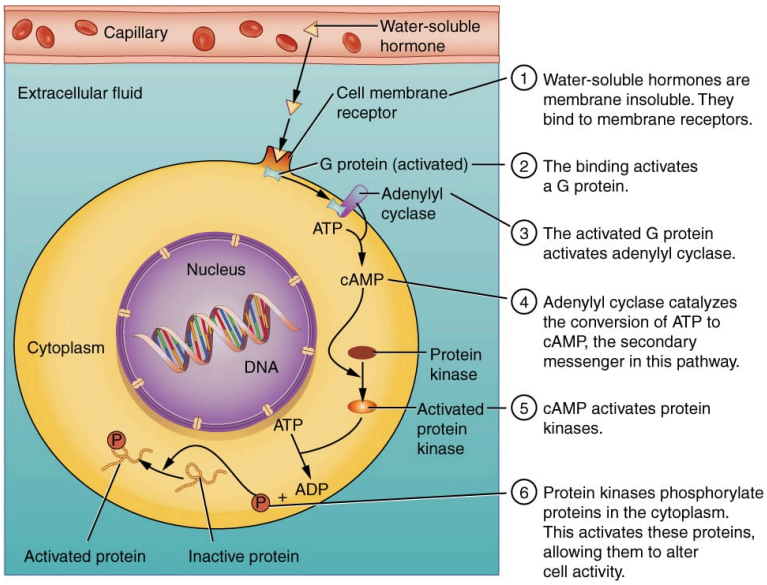


Figure 1.5.3: Water-soluble hormones bind to membrane receptors, activate a G protein, generate cAMP, and trigger protein phosphorylation inside the cell. (CC BY 4.0; via Hormones). Detailed text description of the Figure 1.5.3.

The phosphorylation of cellular proteins can trigger a wide variety of effects, from nutrient metabolism to the synthesis of different hormones and other products. The effects vary according to the type of target cell, the G proteins and kinases involved, and the phosphorylation of proteins. Examples of hormones that use cAMP as a second messenger include calcitonin, which is important for bone construction and regulating blood calcium levels; glucagon, which plays a role in blood glucose levels; and thyroid-stimulating hormone, which causes the release of T_3 and T_4 from the thyroid gland.

Overall, the phosphorylation cascade significantly increases the efficiency, speed, and specificity of the hormonal response, as thousands of signaling events can be initiated simultaneously in response to a very low concentration of hormone in the bloodstream. However, the duration of the hormone signal is short, as cAMP is quickly deactivated by the enzyme phosphodiesterase (PDE), which is located in the cytosol. The action of PDE helps to ensure that a target cell's response ceases quickly unless new hormones arrive at the cell membrane.

Importantly, there are also G proteins that decrease the levels of cAMP in the cell in response to hormone binding. For example, when growth hormone–inhibiting hormone (GHIH), also known as somatostatin, binds to its receptors in the pituitary gland, the level of cAMP decreases, thereby inhibiting the secretion of human growth hormone.

Not all water-soluble hormones initiate the cAMP second messenger system. One common alternative system uses calcium ions as a second messenger. In this system, G proteins activate the enzyme phospholipase C (PLC), which functions similarly to adenylyl cyclase. Once activated, PLC cleaves a membrane-bound phospholipid into two molecules: diacylglycerol (DAG) and inositol triphosphate (IP_3). Like cAMP, DAG activates protein kinases that initiate a phosphorylation cascade. At the same time, IP_3 causes calcium ions to be released from storage sites within the cytosol, such as from within the smooth endoplasmic reticulum. The calcium ions then act as second messengers in two ways: they can influence enzymatic and other cellular activities directly, or they can bind to calcium-binding proteins, the most common of which is calmodulin. Upon binding calcium, calmodulin is able to modulate protein kinase within the cell. Examples of hormones that use calcium ions as a second messenger system include angiotensin II, which helps regulate blood pressure through vasoconstriction, and growth hormone–releasing hormone (GHRH), which causes the pituitary gland to release growth hormones.

Factors Affecting Target Cell Response

You will recall that target cells must have receptors specific to a given hormone if that hormone is to trigger a response. But several other factors influence the target cell response. For example, the presence of a significant level of a hormone circulating in the bloodstream can cause its target cells to decrease their number of receptors for that hormone. This process is called down regulation, and it allows cells to become less reactive to the excessive hormone levels. When the level of a hormone is chronically reduced, target cells engage in up regulation to increase their number of receptors. This process allows cells to be

more sensitive to the hormone that is present. Cells can also alter the sensitivity of the receptors themselves to various hormones.

Two or more hormones can interact to affect the response of cells in a variety of ways. The three most common types of interaction are as follows:

- The permissive effect, in which the presence of one hormone enables another hormone to act. For example, thyroid hormones have complex permissive relationships with certain reproductive hormones. A dietary deficiency of iodine, a component of thyroid hormones, can therefore affect reproductive system development and functioning.
- The synergistic effect, in which two hormones with similar effects produce an amplified response. In some cases, two hormones are required for an adequate response. For example, two different reproductive hormones—FSH from the pituitary gland and estrogens from the ovaries—are required for the maturation of female ova (egg cells).
- The antagonistic effect, in which two hormones have opposing effects. A familiar example is the effect of two pancreatic hormones, insulin and glucagon. Insulin increases the liver's storage of glucose as glycogen, decreasing blood glucose, whereas glucagon stimulates the breakdown of glycogen stores, increasing blood glucose.

Regulation of Hormone Secretion

To prevent abnormal hormone levels and a potential disease state, hormone levels must be tightly controlled. The body maintains this control by balancing hormone production and degradation. Feedback loops govern the initiation and maintenance of most hormone secretion in response to various stimuli.

Role of Feedback Loops

The contribution of feedback loops to homeostasis will only be briefly reviewed here. Positive feedback loops are characterized by the release of additional hormone in response to an original hormone release. The release of oxytocin during childbirth is a positive feedback loop. The initial release of oxytocin begins to signal the uterine muscles to contract, which pushes the fetus toward the cervix, causing it to stretch. This, in turn, signals the pituitary gland to release more oxytocin, causing labor contractions to intensify. The release of oxytocin decreases after the birth of the child.

The more common method of hormone regulation is the negative feedback loop. Negative feedback is characterized by the inhibition of further secretion of a hormone in response to adequate levels of that hormone. This allows blood levels of the hormone to be regulated within a narrow range. An example of a negative feedback loop is the release of glucocorticoid hormones from the adrenal glands, as directed by the hypothalamus and pituitary gland. As glucocorticoid concentrations in the blood rise, the hypothalamus and pituitary gland reduce their signaling to the adrenal glands to prevent additional glucocorticoid secretion (Figure 1.5.4).

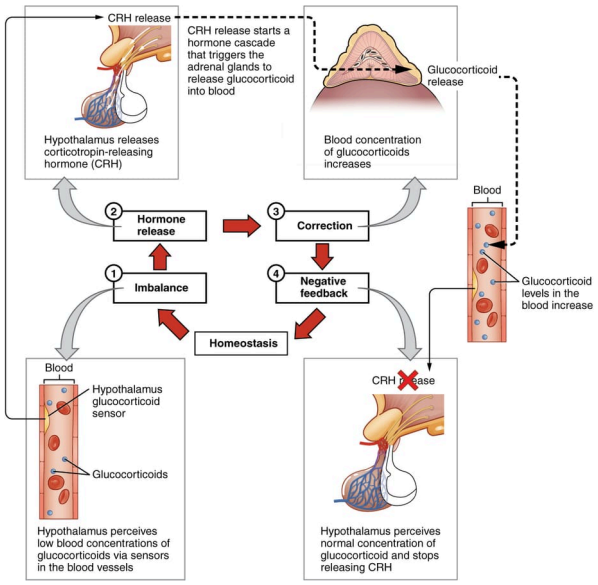


Figure 1.5.4: Negative-feedback regulation of glucocorticoids: low hormone levels trigger CRH release, adrenal activation, and correction until homeostasis is restored. (CC BY 4.0; via Hormones). Detailed text description of the Figure 1.5.4.

Chemical and Neural Regulations on Endocrine Function

Besides the feedback loops, endocrine activity can also be controlled through chemical and neural regulations. Humoral (related to body fluids) stimuli are changes in blood levels of non-hormone chemicals, such as nutrients or ions. The change in the chemical composition of the blood causes the release or inhibition of a particular hormone. For example, high blood glucose levels cause the release of insulin from the pancreas. The release of insulin increases glucose uptake by cells and liver storage of glucose as glycogen. This action of insulin will cause glucose levels to decrease in the bloodstream and return it to normal homeostatic levels.

In addition to these chemical signals, hormones can also be released in response to neural stimuli. A common example of neural stimuli is the activation of the fight-or-flight response by the sympathetic nervous system. When an individual perceives danger, sympathetic neurons signal the adrenal glands to secrete epinephrine and norepinephrine to prepare the body for sudden danger. The two hormones dilate blood vessels, increase the heart and respiratory rate, and suppress the digestive, urinary, reproductive, and immune systems. These hormonal responses boost the body's transport of oxygen to the brain and muscles, thereby improving the body's ability to fight or flee.

Everyday Connection

Bisphenol A and Endocrine Disruption

You may have heard news reports about the effects of a chemical called bisphenol A (BPA) in various types of food packaging. BPA is used in the manufacturing of hard plastics and epoxy resins. Common food-related items that may contain BPA include the lining of aluminum cans, plastic food-storage containers, drinking cups, as well as baby bottles and "sippy" cups. Other uses of BPA include medical equipment, dental fillings, and the lining of water pipes.

Research suggests that BPA is an endocrine disruptor, meaning that it negatively interferes with the endocrine system, particularly during the prenatal and postnatal development period. In particular, BPA mimics the hormonal effects of estrogens and has the opposite effect—that of androgens. The U.S. Food and Drug Administration (FDA) notes in their statement about BPA safety that although traditional toxicology studies have supported the safety of low levels of exposure to BPA, recent studies using novel approaches to test for subtle effects have led to some concern about the potential effects of BPA on the brain, behavior, and prostate gland in fetuses, infants, and young children. The FDA is currently facilitating

decreased use of BPA in food-related materials. Many US companies have voluntarily removed BPA from baby bottles, “sippy” cups, and the linings of infant formula cans, and most plastic reusable water bottles sold today boast that they are “BPA free.” In contrast, both Canada and the European Union have completely banned the use of BPA in baby products.

The potential harmful effects of BPA have been studied in both animal models and humans and include a large variety of health effects, such as developmental delay and disease. For example, prenatal exposure to BPA during the first trimester of human pregnancy may be associated with wheezing and aggressive behavior during childhood. Adults exposed to high levels of BPA may experience altered thyroid signaling and male sexual dysfunction. BPA exposure during the prenatal or postnatal period of development in animal models has been observed to cause neurological delays, changes in brain structure and function, sexual dysfunction, asthma, and increased risk for multiple cancers. In vitro studies have also shown that BPA exposure causes molecular changes that initiate the development of cancers of the breast, prostate, and brain. Although these studies have implicated BPA in numerous ill health effects, some experts caution that some of these studies may be flawed and that more research needs to be done. In the meantime, the FDA recommends that consumers take precautions to limit their exposure to BPA. In addition to purchasing foods in packaging free of BPA, consumers should avoid carrying or storing foods or liquids in bottles with the recycling code 3 or 7. Foods and liquids should not be microwave-heated in any form of plastic: use paper, glass, or ceramics instead.

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1.6: The Pituitary Gland and Hypothalamus

The HPA (hypothalamic-pituitary-adrenal) axis

The hypothalamus–pituitary complex can be thought of as the “command center” of the endocrine system. This complex secretes several hormones that directly produce responses in target tissues, as well as hormones that regulate the synthesis and secretion of hormones of other glands. In addition, the hypothalamus–pituitary complex coordinates the messages of the endocrine and nervous systems. In many cases, a stimulus received by the nervous system must pass through the hypothalamus–pituitary complex to be translated into hormones that can initiate a response.

The hypothalamus is a structure of the diencephalon of the brain located anterior and inferior to the thalamus (Figure 1.6.1). It has both neural and endocrine functions, producing and secreting many hormones. In addition, the hypothalamus is anatomically and functionally related to the pituitary gland (or hypophysis), a bean-sized organ suspended from it by a stem called the infundibulum (or pituitary stalk). The pituitary gland is cradled within the sella turcica of the sphenoid bone of the skull. It consists of two lobes that arise from distinct parts of embryonic tissue: the posterior pituitary (neurohypophysis) is neural tissue, whereas the anterior pituitary (also known as the adenohypophysis) is glandular tissue that develops from the primitive digestive tract. The hormones secreted by the posterior and anterior pituitary, and the intermediate zone between the lobes are summarized in Table 1.6.1.

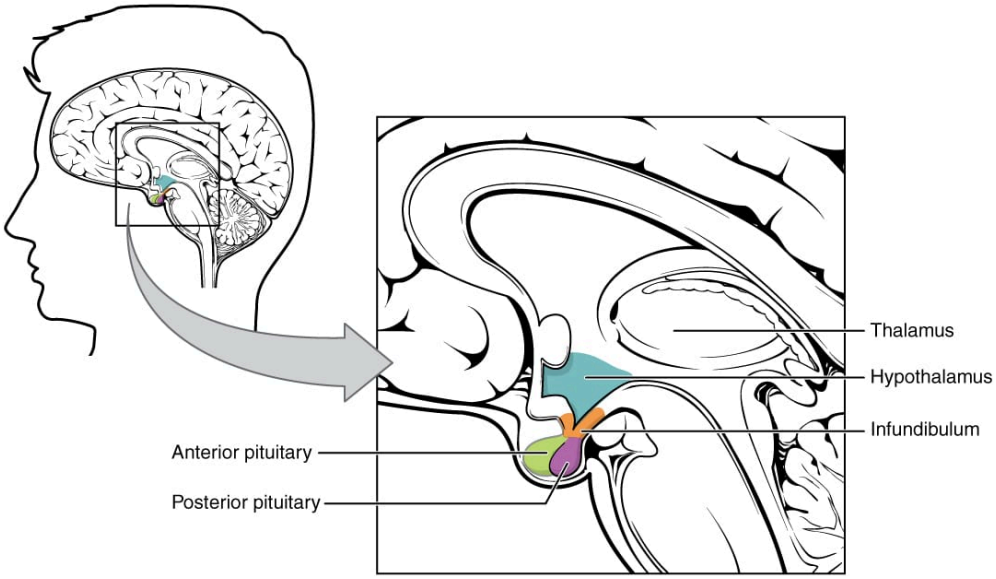


Figure 1.6.1: The hypothalamus region lies inferior and anterior to the thalamus. It connects to the pituitary gland by the stalk-like infundibulum. The pituitary gland. (CC BY 4.0; via The Pituitary Glands and Hypothalamus). Detailed text description of the Figure 1.6.1.

Table 1.6.1: The hormones secreted by the posterior and anterior pituitary, and the intermediate zone between the lobes

Pituitary lobe	Associated hormones	Chemical class	Effect
Anterior	Growth hormone (GH)	Protein	Promotes growth of body tissues
Anterior	Prolactin (PRL)	Peptide	Promotes milk production from mammary glands
Anterior	Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates thyroid hormone release from thyroid
Anterior	Adrenocorticotropic hormone (ACTH)	Peptide	Stimulates hormone release by adrenal cortex
Anterior	Follicle-stimulating hormone (FSH)	Glycoprotein	Stimulates gamete production in gonads
Anterior	Luteinizing hormone (LH)	Glycoprotein	Stimulates androgen production by gonads
Posterior	Antidiuretic hormone (ADH)	Peptide	Stimulates water reabsorption by kidneys

Pituitary lobe	Associated hormones	Chemical class	Effect
Posterior	Oxytocin	Peptide	Stimulates uterine contractions during childbirth
Intermediate zone	Melanocyte-stimulating hormone	Peptide	Stimulates melanin formation in melanocytes

Posterior Pituitary

The posterior pituitary is actually an extension of the neurons of the paraventricular and supraoptic nuclei of the hypothalamus. The cell bodies of these regions rest in the hypothalamus, but their axons descend as the hypothalamic–hypophyseal tract within the infundibulum, and end in axon terminals that comprise the posterior pituitary (Figure 1.6.2).

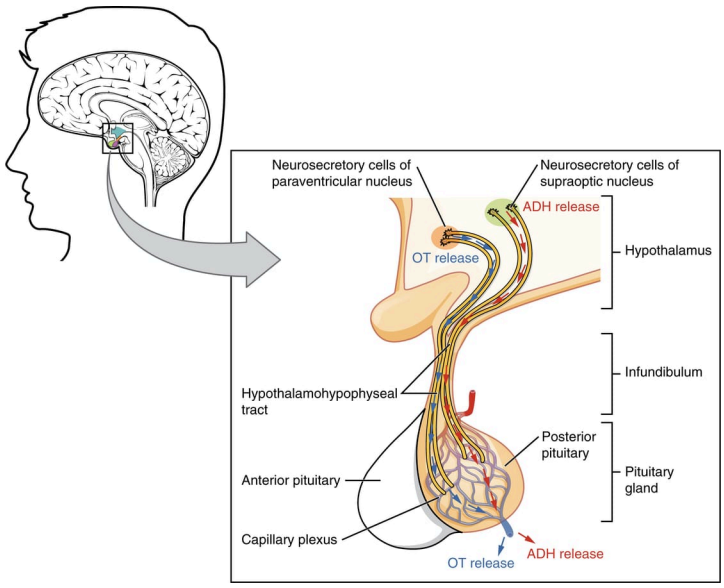


Figure 1.6.2: Neurosecretory cells in the hypothalamus produce oxytocin (OT) and antidiuretic hormone (ADH), which are transported to the posterior lobe of the pituitary gland. There, these hormones are stored and released into the blood through the capillary plexus. (CC BY 4.0; via The Pituitary Glands and Hypothalamus). Detailed text description of the Figure 1.6.2.

The posterior pituitary gland does not produce hormones, but rather stores and secretes hormones produced by the hypothalamus. The paraventricular nuclei produce the hormone oxytocin, whereas the supraoptic nuclei produce ADH. These hormones travel along the axons into storage sites in the axon terminals of the posterior pituitary. In response to signals from the same hypothalamic neurons, the hormones are released from the axon terminals into the bloodstream.

Oxytocin

When fetal development is complete, the peptide-derived hormone oxytocin (tocia- = “childbirth”) stimulates uterine contractions and dilation of the cervix. Throughout most of pregnancy, oxytocin hormone receptors are not expressed at high levels in the uterus. Toward the end of pregnancy, the synthesis of oxytocin receptors in the uterus increases, and the smooth muscle cells of the uterus become more sensitive to its effects. Oxytocin is continually released throughout childbirth through a positive feedback mechanism. As noted earlier, oxytocin prompts uterine contractions that push the fetal head toward the cervix. In response, cervical stretching stimulates additional oxytocin to be synthesized by the hypothalamus and released from the pituitary. This increases the intensity and effectiveness of uterine contractions and prompts additional dilation of the cervix. The feedback loop continues until birth.

Although the high blood levels of oxytocin begin to decrease immediately following birth, oxytocin continues to play a role in female and newborn health. First, oxytocin is necessary for the milk ejection reflex (commonly referred to as “let-down”) in breastfeeding people. As the newborn begins suckling, sensory receptors in the nipples transmit signals to the hypothalamus. In response, oxytocin is secreted and released into the bloodstream. Within seconds, cells in the milk ducts contract, ejecting milk into the infant’s mouth. Secondly, in ball people, oxytocin is thought to contribute to parent–newborn bonding, known as attachment. Oxytocin is also thought to be involved in feelings of love and closeness, as well as in the sexual response.

Antidiuretic Hormone (ADH)

The solute concentration of the blood, or blood osmolarity, may change in response to the consumption of certain foods and fluids, as well as in response to disease, injury, medications, or other factors. Blood osmolarity is constantly monitored by osmoreceptors—specialized cells within the hypothalamus that are particularly sensitive to the concentration of sodium ions and other solutes.

In response to high blood osmolarity, which can occur during dehydration or following a very salty meal, the osmoreceptors signal the posterior pituitary to release antidiuretic hormone (ADH). The target cells of ADH are located in the tubular cells of the kidneys. Its effect is to increase epithelial permeability to water, allowing increased water reabsorption. The more water reabsorbed from the filtrate, the greater the amount of water that is returned to the blood and the less that is excreted in the urine. A greater concentration of water results in a reduced concentration of solutes. ADH is also known as vasopressin because, in very high concentrations, it causes constriction of blood vessels, which increases blood pressure by increasing peripheral resistance. The release of ADH is controlled by a negative feedback loop. As blood osmolarity decreases, the hypothalamic osmoreceptors sense the change and prompt a corresponding decrease in the secretion of ADH. As a result, less water is reabsorbed from the urine filtrate.

Interestingly, drugs can affect the secretion of ADH. For example, alcohol consumption inhibits the release of ADH, resulting in increased urine production that can eventually lead to dehydration and a hangover. A disease called diabetes insipidus is characterized by chronic underproduction of ADH that causes chronic dehydration. Because little ADH is produced and secreted, not enough water is reabsorbed by the kidneys. Although patients feel thirsty, and increase their fluid consumption, this doesn't effectively decrease the solute concentration in their blood because ADH levels are not high enough to trigger water reabsorption in the kidneys. Electrolyte imbalances can occur in severe cases of diabetes insipidus.

Anterior Pituitary

The anterior pituitary originates from the digestive tract in the embryo and migrates toward the brain during fetal development. There are three regions: the pars distalis is the most anterior, the pars intermedia is adjacent to the posterior pituitary, and the pars tuberalis is a slender "tube" that wraps the infundibulum.

Recall that the posterior pituitary does not synthesize hormones, but merely stores them. In contrast, the anterior pituitary does manufacture hormones. However, the secretion of hormones from the anterior pituitary is regulated by two classes of hormones. These hormones—secreted by the hypothalamus—are the releasing hormones that stimulate the secretion of hormones from the anterior pituitary and the inhibiting hormones that inhibit secretion.

Hypothalamic hormones are secreted by neurons, but enter the anterior pituitary through blood vessels (Figure $1.6.3$). Within the infundibulum is a bridge of capillaries that connects the hypothalamus to the anterior pituitary. This network, called the hypophyseal portal system, allows hypothalamic hormones to be transported to the anterior pituitary without first entering the systemic circulation. The system originates from the superior hypophyseal artery, which branches off the carotid arteries and transports blood to the hypothalamus. The branches of the superior hypophyseal artery form the hypophyseal portal system (see Figure $1.6.3$ produced by the anterior pituitary (in response to releasing hormones) enter a secondary capillary plexus, and from there drain into the circulation.

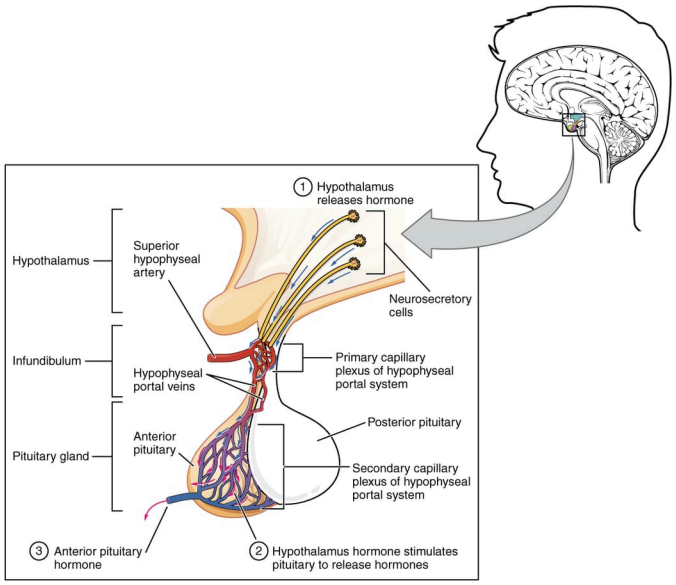


Figure 1.6.3: The anterior pituitary manufactures seven hormones. The hypothalamus produces separate hormones that stimulate or inhibit hormone production in the anterior pituitary. Hormones from the hypothalamus reach the anterior pituitary via the hypophyseal portal system. (CC BY 4.0; via The Pituitary Glands and Hypothalamus). Detailed text description of the Figure 1.6.3.

The anterior pituitary produces seven hormones. These are the growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), beta endorphin, and prolactin. Of the hormones of the anterior pituitary, TSH, ACTH, FSH, and LH are collectively referred to as tropic hormones (trope- = “turning”) because they turn on or off the function of other endocrine glands.

Growth Hormone

The endocrine system regulates the growth of the human body, protein synthesis, and cellular replication. A major hormone involved in this process is growth hormone (GH), also called somatotropin—a protein hormone produced and secreted by the anterior pituitary gland. Its primary function is anabolic; it promotes protein synthesis and tissue building through direct and indirect mechanisms (Figure 1.6.4). GH levels are controlled by the release of GHRH and GHIH (also known as somatostatin) from the hypothalamus.

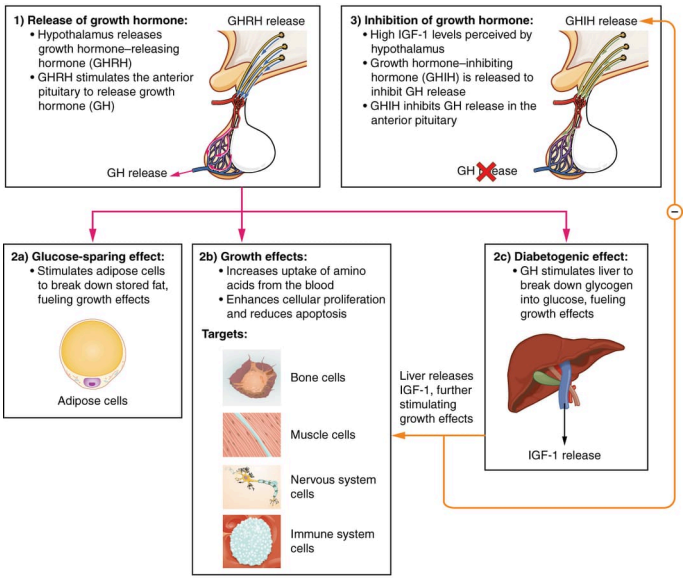


Figure 1.6.4: Growth hormone (GH) directly accelerates the rate of protein synthesis in skeletal muscle and bones. Insulin-like growth factor 1 (IGF-1) is activated by growth hormone and indirectly supports the formation of new proteins in muscle cells and bone. (CC BY 4.0; via The Pituitary Glands and Hypothalamus). Detailed text description of the Figure 1.6.4.

Figure 1.6.4 is a flow chart that illustrates the hormone cascade that stimulates human growth. The diagram explains how growth hormone, abbreviated as GH, is released, how it affects the body, and how its release is reduced through negative feedback.

A glucose-sparing effect occurs when GH stimulates lipolysis, or the breakdown of adipose tissue, releasing fatty acids into the blood. As a result, many tissues switch from glucose to fatty acids as their main energy source, which means that less glucose is taken up from the bloodstream.

GH also initiates the diabetogenic effect in which GH stimulates the liver to break down glycogen to glucose, which is then deposited into the blood. The name “diabetogenic” is derived from the similarity in elevated blood glucose levels observed between individuals with untreated diabetes mellitus and individuals experiencing GH excess. Blood glucose levels rise as the result of a combination of glucose-sparing and diabetogenic effects.

GH indirectly mediates growth and protein synthesis by triggering the liver and other tissues to produce a group of proteins called insulin-like growth factors (IGFs). These proteins enhance cellular proliferation and inhibit apoptosis, or programmed cell death. IGFs stimulate cells to increase their uptake of amino acids from the blood for protein synthesis. Skeletal muscle and cartilage cells are particularly sensitive to stimulation from IGFs.

Dysfunction of the endocrine system’s control of growth can result in several disorders. For example, gigantism is a disorder in children that is caused by the secretion of abnormally large amounts of GH, resulting in excessive growth. A similar condition in adults is acromegaly, a disorder that results in the growth of bones in the face, hands, and feet in response to excessive levels of GH in individuals who have stopped growing. Abnormally low levels of GH in children can cause growth impairment—a disorder called pituitary dwarfism (also known as growth hormone deficiency).

Thyroid-Stimulating Hormone

The activity of the thyroid gland is regulated by thyroid-stimulating hormone (TSH), also called thyrotropin. TSH is released from the anterior pituitary in response to thyrotropin-releasing hormone (TRH) from the hypothalamus. As discussed shortly, it triggers the secretion of thyroid hormones by the thyroid gland. In a classic negative feedback loop, elevated levels of thyroid hormones in the bloodstream then trigger a drop in production of TRH and subsequently TSH.

Adrenocorticotropic Hormone

The adrenocorticotropic hormone (ACTH), also called corticotropin, stimulates the adrenal cortex (the more superficial “bark” of the adrenal glands) to secrete corticosteroid hormones such as cortisol. ACTH come from a precursor molecule known as

pro-opiomelanocortin (POMC) which produces several biologically active molecules when cleaved, including ACTH, melanocyte-stimulating hormone, and the brain opioid peptides known as endorphins.

The release of ACTH is regulated by the corticotropin-releasing hormone (CRH) from the hypothalamus in response to normal physiologic rhythms. A variety of stressors can also influence its release, and the role of ACTH in the stress response is discussed later in this chapter.

Follicle-Stimulating Hormone and Luteinizing Hormone

The endocrine glands secrete a variety of hormones that control the development and regulation of the reproductive system (these glands include the anterior pituitary, the adrenal cortex, and the gonads—the testes and the ovaries). Much of the development of the reproductive system occurs during puberty and is marked by the development of sex-specific characteristics in adolescents. Puberty is initiated by gonadotropin-releasing hormone (GnRH), a hormone produced and secreted by the hypothalamus. GnRH stimulates the anterior pituitary to secrete gonadotropins—hormones that regulate the function of the gonads. The levels of GnRH are regulated through a negative feedback loop; high levels of reproductive hormones inhibit the release of GnRH. Throughout life, gonadotropins regulate reproductive function and, in the case of females, the onset and cessation of reproductive capacity.

The gonadotropins include two glycoprotein hormones: follicle-stimulating hormone (FSH) stimulates the production and maturation of sex cells, or gametes, including ova and sperm. FSH also promotes follicular growth; these follicles then release estrogens in ovaries. Luteinizing hormone (LH) triggers ovulation, as well as the production of estrogens and progesterone by the ovaries. LH stimulates production of testosterone by the testes.

Prolactin

As its name implies, prolactin (PRL) promotes lactation (milk production). During pregnancy, it contributes to development of the mammary glands, and after birth, it stimulates the mammary glands to produce breast milk. However, the effects of prolactin depend heavily upon the permissive effects of estrogens, progesterone, and other hormones. And as noted earlier, the let-down of milk occurs in response to stimulation from oxytocin.

In non-pregnant females, prolactin secretion is inhibited by prolactin-inhibiting hormone (PIH), which is actually the neurotransmitter dopamine, and is released from neurons in the hypothalamus. Only during pregnancy do prolactin levels rise in response to prolactin-releasing hormone (PRH) from the hypothalamus.

Intermediate Pituitary: Melanocyte-Stimulating Hormone

The cells in the zone between the pituitary lobes secrete a hormone known as melanocyte-stimulating hormone (MSH) that is formed by cleavage of the pro-opiomelanocortin (POMC) precursor protein. Local production of MSH in the skin is responsible for melanin production in response to UV light exposure. The role of MSH made by the pituitary is more complicated. For instance, people with lighter skin generally have the same amount of MSH as people with darker skin. Nevertheless, this hormone is capable of darkening of the skin by inducing melanin production in the skin's melanocytes. People also show increased MSH production during pregnancy; in combination with estrogens, it can lead to darker skin pigmentation, especially the skin of the areolas and labia minora. Figure 1.6.5 is a summary of the pituitary hormones and their principal effects.

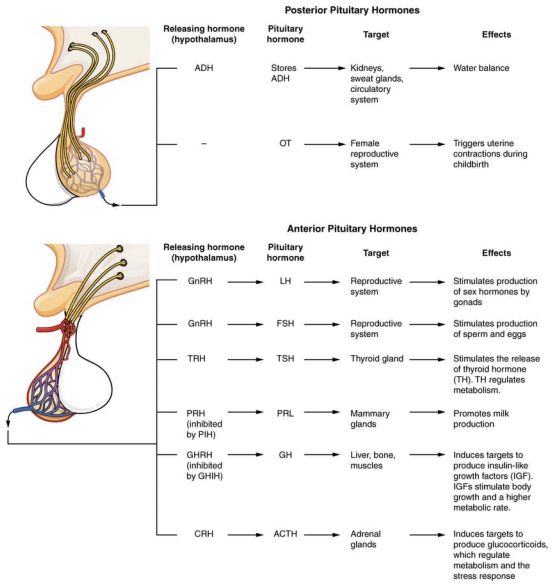


Figure 1.6.5 Major pituitary hormones and their target organs. (CC BY 4.0; via The Pituitary Glands and Hypothalamus). Detailed text description of the Figure 1.6.5.

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1.7: The Thyroid Gland

Thyroid Hormone Synthesis, Regulation, and Function

A butterfly-shaped organ, the thyroid gland is located anterior to the trachea, just inferior to the larynx (Figure 1.7.1). The medial region, called the isthmus, is flanked by wing-shaped left and right lobes. Each of the thyroid lobes are embedded with parathyroid glands, primarily on their posterior surfaces. The tissue of the thyroid gland is composed mostly of thyroid follicles. The follicles are made up of a central cavity filled with a sticky fluid called colloid. Surrounded by a wall of epithelial follicle cells, the colloid is the center of thyroid hormone production, and that production is dependent on the hormones' essential and unique component which is iodine.

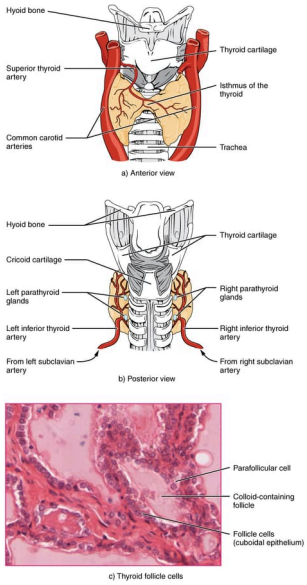


Figure 1.7.1: The thyroid gland is located in the neck where it wraps around the trachea. (Micrograph provided by the Regents of University of Michigan Medical School © 2012). (CC BY 4.0; via The Thyroid Gland). Detailed text description of the Figure 1.7.1.

Synthesis and Release of Thyroid Hormones

Hormones are produced in the colloid when atoms of the mineral iodine attach to a glycoprotein, called thyroglobulin, that is secreted into the colloid by the follicle cells. The following steps outline the hormones' assembly:

1. Binding of TSH to its receptors in the follicle cells of the thyroid gland causes the cells to actively transport iodide ions (I^-) across their cell membrane, from the bloodstream into the cytosol. As a result, the concentration of iodide ions "trapped" in the follicular cells is many times higher than the concentration in the bloodstream.
2. Iodide ions then move to the lumen of the follicle cells that border the colloid. There, the ions undergo oxidation (their negatively charged electrons are removed). The oxidation of two iodide ions ($2\ I^-$) results in iodine (I_2), which passes through the follicle cell membrane into the colloid.
3. In the colloid, peroxidase enzymes link the iodine to the tyrosine amino acids in thyroglobulin to produce two intermediaries: a tyrosine attached to one iodine and a tyrosine attached to two iodines. When one of each of these intermediaries is linked by covalent bonds, the resulting compound is triiodothyronine (T_3), a thyroid hormone with three iodines. Much more commonly, two copies of the second intermediary bond, forming tetraiodothyronine, also known as thyroxine (T_4), a thyroid hormone with four iodines.

These hormones remain in the colloid center of the thyroid follicles until TSH stimulates endocytosis of colloid back into the follicle cells. There, lysosomal enzymes break apart the thyroglobulin colloid, releasing free T_3 and T_4, which diffuse across the follicle cell membrane and enter the bloodstream.

In the bloodstream, less than one percent of the circulating T_3 and T_4 remains unbound. This free T_3 and T_4 can cross the lipid bilayer of cell membranes and be taken up by cells. The remaining 99 percent of circulating T_3 and T_4 is bound to specialized transport proteins called thyroxine-binding globulins (TBGs), to albumin, or to other plasma proteins. This "packaging" prevents their free diffusion into body cells. When blood levels of T_3 and T_4 begin to decline, bound T_3 and T_4 are released from these plasma proteins and readily cross the membrane of target cells. T_3 is more potent than T_4, and many cells convert T_4 to T_3 through the removal of an iodine atom.

Regulation of TH Synthesis

The release of T_3 and T_4 from the thyroid gland is regulated by thyroid-stimulating hormone (TSH). As shown in Figure 1.7.2, low blood levels of T_3 and T_4 stimulate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus, which triggers secretion of TSH from the anterior pituitary. In turn, TSH stimulates the thyroid gland to secrete T_3 and T_4. The levels of TRH, TSH, T_3, and T_4 are regulated by a negative feedback system in which increasing levels of T_3 and T_4 decrease the production and secretion of TSH.

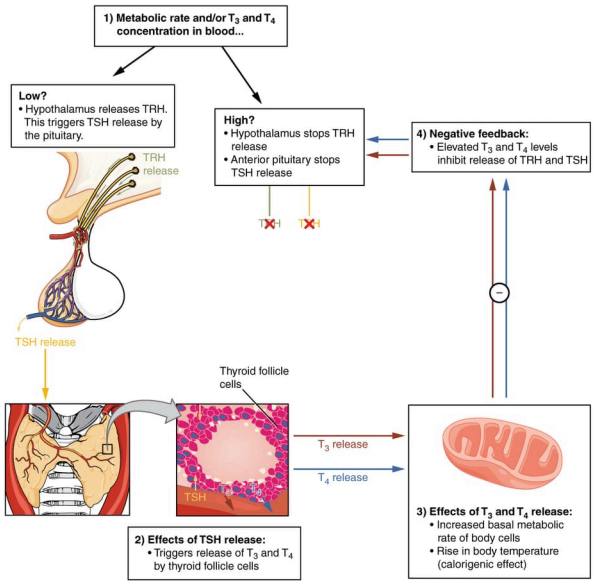


Figure 1.7.2: A classic negative feedback loop controls the regulation of thyroid hormone levels. (CC BY 4.0; via The Thyroid Gland). Detailed text description of the Figure 1.7.2.

Functions of Thyroid Hormones

The thyroid hormones, T_3 and T_4, are often referred to as metabolic hormones because their levels influence the body's basal metabolic rate, the amount of energy used by the body at rest. When T_3 and T_4 bind to intracellular receptors located on the mitochondria, they cause an increase in nutrient breakdown and the use of oxygen to produce ATP. In addition, T_3 and T_4 initiate the transcription of genes involved in glucose oxidation. Although these mechanisms prompt cells to produce more ATP, the process is inefficient, and an abnormally increased level of heat is released as a byproduct of these reactions. This so-called calorigenic effect (calor- = "heat") raises body temperature.

Adequate levels of thyroid hormones are also required for protein synthesis and for fetal and childhood tissue development and growth. They are especially critical for normal development of the nervous system both in utero and in early childhood, and they continue to support neurological function in adults. As noted earlier, these thyroid hormones have a complex interrelationship with reproductive hormones, and deficiencies can influence libido, fertility, and other aspects of reproductive function. Finally, thyroid hormones increase the body's sensitivity to catecholamines (epinephrine and norepinephrine) from the adrenal medulla by Upregulation of receptors in the blood vessels. When levels of T_3 and T_4 hormones are excessive, this effect accelerates the heart rate, strengthens the heartbeat, and increases blood pressure. Because thyroid hormones regulate metabolism, heat production, protein synthesis, and many other body functions, thyroid disorders can have severe and widespread consequences.

Disorders of the...

Endocrine System: Iodine Deficiency, Hypothyroidism, and Hyperthyroidism

As discussed above, dietary iodine is required for the synthesis of T_3 and T_4. But for much of the world's population, foods do not provide adequate levels of this mineral, because the amount varies according to the level in the soil in which the food was grown, as well as the irrigation and fertilizers used. Marine fish and shrimp tend to have high levels because they concentrate iodine from seawater, but many people in landlocked regions lack access to seafood. Thus, the primary source of dietary iodine in many countries is iodized salt. Fortification of salt with iodine began in the United States in 1924, and international efforts to iodize salt in the world's poorest nations continue today.

Dietary iodine deficiency can result in the impaired ability to synthesize T_3 and T_4, leading to a variety of severe disorders. When T_3 and T_4 cannot be produced, TSH is secreted in increasing amounts. As a result of this hyperstimulation, thyroglobulin accumulates in the thyroid gland follicles, increasing their deposits of colloid. The accumulation of colloid increases the overall size of the thyroid gland, a condition called a goiter (Figure 1.7.3). A goiter is only a visible indication of the deficiency. Other iodine deficiency disorders include impaired growth and development, decreased fertility, and prenatal and infant death. Moreover, iodine deficiency is the primary cause of preventable intellectual disabilities worldwide. Neonatal hypothyroidism (cretinism) is characterized by cognitive deficits, short stature, and sometimes deafness and muteness in children and adults born to mothers who were iodine-deficient during pregnancy.



Figure 1.7.3: Enlargement of the thyroid region visible as a pronounced swelling on the front of the neck. (CC BY 4.0; via The Thyroid Gland). Detailed text description of the Figure 1.7.3.

In areas of the world with access to iodized salt, dietary deficiency is rare. Instead, inflammation of the thyroid gland is the more common cause of low blood levels of thyroid hormones. Called hypothyroidism, the condition is characterized by a low metabolic rate, weight gain, cold extremities, constipation, reduced libido, menstrual irregularities, and reduced mental activity. In contrast, hyperthyroidism—an abnormally elevated blood level of thyroid hormones—is often caused by a pituitary or thyroid tumor. In Graves' disease, the hyperthyroid state results from an autoimmune reaction in which antibodies overstimulate the follicle cells of the thyroid gland. Hyperthyroidism can lead to an increased metabolic rate, excessive body heat and sweating, diarrhea, weight loss, tremors, and increased heart rate. The person's eyes may bulge (called exophthalmos) as antibodies produce inflammation in the soft tissues of the orbits. The person may also develop a goiter.

Calcitonin

The thyroid gland also secretes a hormone called calcitonin that is produced by the parafollicular cells (also called C cells) that stud the tissue between distinct follicles. Calcitonin is released in response to a rise in blood calcium levels. It appears to have a

function in decreasing blood calcium concentrations by:

- Inhibiting the activity of osteoclasts, bone cells that release calcium into the circulation by degrading bone matrix
- Increasing osteoblastic activity
- Decreasing calcium absorption in the intestines
- Increasing calcium loss in the urine

However, these functions are usually not significant in maintaining calcium homeostasis, so the importance of calcitonin is not entirely understood. Pharmaceutical preparations of calcitonin are sometimes prescribed to reduce osteoclast activity in people with osteoporosis and to reduce the degradation of cartilage in people with osteoarthritis. The hormones secreted by thyroid are summarized in Table 1.7.1.

Table 1.7.1*: Thyroid Hormones*

Associated hormones	Chemical class	Effect
Thyroxine (T_4), triiodothyronine (T_3)	Amine	Stimulate basal metabolic rate
Calcitonin	Peptide	Reduces blood Ca^{2+} levels

Of course, calcium is critical for many other biological processes. It is a second messenger in many signaling pathways, and is essential for muscle contraction, nerve impulse transmission, and blood clotting. Given these roles, it is not surprising that blood calcium levels are tightly regulated by the endocrine system. The organs involved in the regulation are the parathyroid glands.

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1.8: The Parathyroid Glands

Parathyroid Hormone and Blood Calcium Regulation

The parathyroid glands are tiny, round structures usually found embedded in the posterior surface of the thyroid gland (Figure 1.8.1). A thick connective tissue capsule separates the glands from the thyroid tissue. Most people have four parathyroid glands, but occasionally there are more in tissues of the neck or chest. The function of one type of parathyroid cells, the oxyphil cells, is not clear. The primary functional cells of the parathyroid glands are the chief cells. These epithelial cells produce and secrete the parathyroid hormone (PTH), the major hormone involved in the regulation of blood calcium levels.

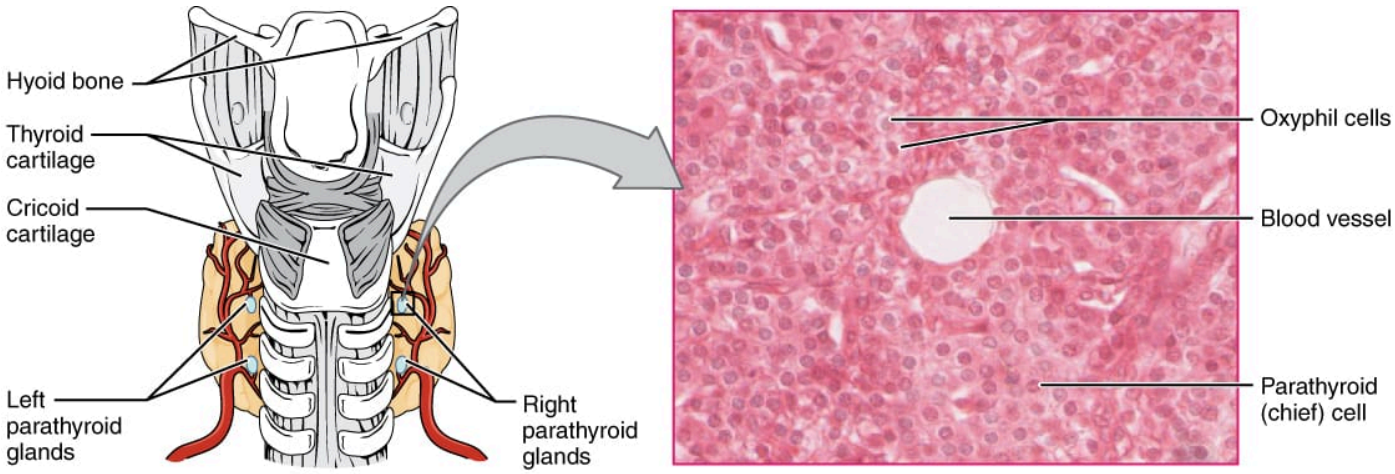


Figure 1.8.1: The small parathyroid glands are embedded in the posterior surface of the thyroid gland. LM × 760. (Micrograph provided by the Regents of University of Michigan Medical School © 2012). (CC BY 4.0; via The Parathyroid Gland). Detailed text description of the Figure 1.8.1.

The parathyroid glands produce and secrete PTH, a peptide hormone, in response to low blood calcium levels (Figure 1.8.2). PTH secretion causes the release of calcium from the bones by stimulating osteoclasts, which secrete enzymes that degrade bone and release calcium into the interstitial fluid. PTH also inhibits osteoblasts, the cells involved in bone deposition, thereby sparing blood calcium. PTH causes increased reabsorption of calcium (and magnesium) in the kidney tubules from the urine filtrate. In addition, PTH initiates the production of the steroid hormone calcitriol (also known as 1,25-dihydroxyvitamin D), which is the active form of vitamin D_3, in the kidneys. Calcitriol then stimulates increased absorption of dietary calcium by the intestines. A negative feedback loop regulates the levels of PTH, with rising blood calcium levels inhibiting further release of PTH.

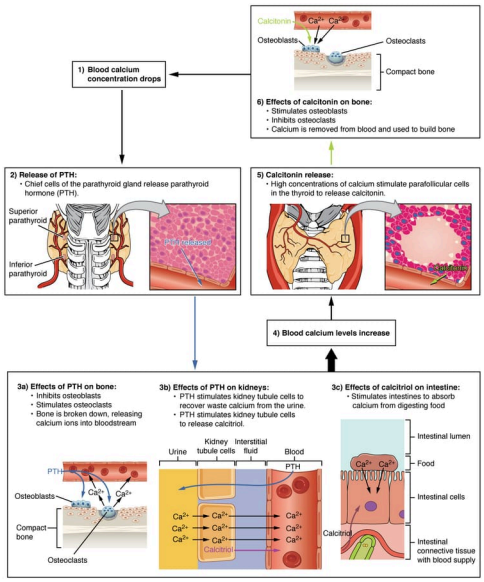


Figure 1.8.2: Parathyroid hormone increases blood calcium levels when they drop too low. Conversely, calcitonin, which is released from the thyroid gland, decreases blood calcium levels when they become too high. These two mechanisms constantly maintain blood calcium concentration at homeostasis. (CC BY 4.0; via The Parathyroid Gland). Detailed text description of the Figure 1.8.2.

Abnormally high activity of the parathyroid gland can cause hyperparathyroidism, a disorder caused by an overproduction of PTH that results in excessive calcium reabsorption from bone. Hyperparathyroidism can significantly decrease bone density, leading to spontaneous fractures or deformities. As blood calcium levels rise, cell membrane permeability to sodium is decreased, and the responsiveness of the nervous system is reduced. At the same time, calcium deposits may collect in the body's tissues and organs, impairing their functioning.

In contrast, abnormally low blood calcium levels may be caused by parathyroid hormone deficiency, called hypoparathyroidism, which may develop following injury or surgery involving the thyroid gland. Low blood calcium increases membrane permeability to sodium, resulting in muscle twitching, cramping, spasms, or convulsions. Severe deficits can paralyze muscles, including those involved in breathing, and can be fatal.

When blood calcium levels are high, calcitonin is produced and secreted by the parafollicular cells of the thyroid gland. As discussed earlier, calcitonin inhibits the activity of osteoclasts, reduces the absorption of dietary calcium in the intestine, and signals the kidneys to reabsorb less calcium, resulting in larger amounts of calcium excreted in the urine.

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1.9: The Adrenal Glands

Structure and Function of the Adrenal Glands

The adrenal glands are wedges of glandular and neuroendocrine tissue adhering to the top of the kidneys by a fibrous capsule (Figure 1.9.1). The adrenal glands have a rich blood supply and experience one of the highest rates of blood flow in the body. They are served by several arteries branching off the aorta, including the suprarenal and renal arteries. Blood flows to each adrenal gland at the adrenal cortex and then drains into the adrenal medulla. Adrenal hormones are released into the circulation via the left and right suprarenal veins.

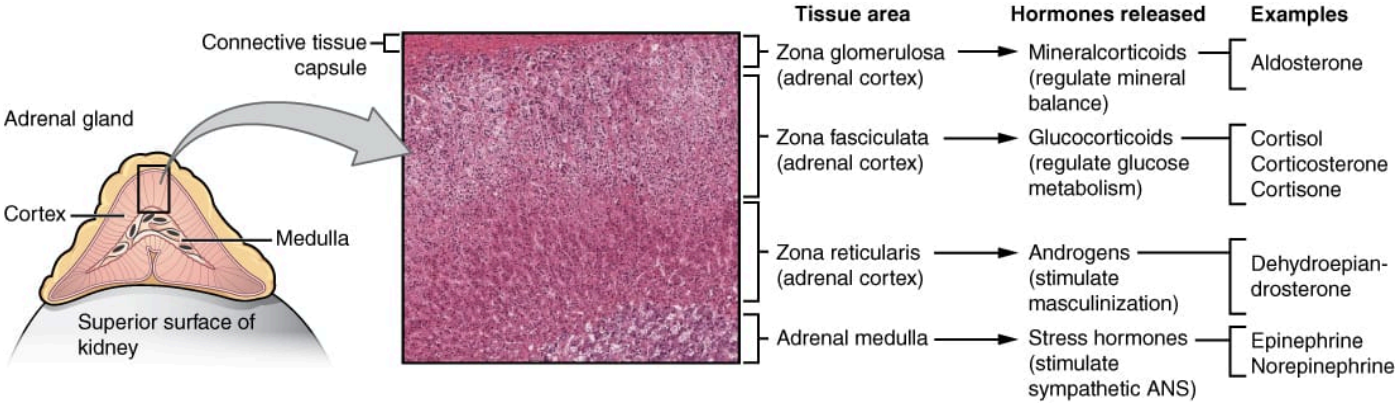


Figure 1.9.1: Both adrenal glands sit atop the kidneys and are composed of an outer cortex and an inner medulla, all surrounded by a connective tissue capsule. The cortex can be subdivided into additional zones, all of which produce different types of hormones. LM × 204. (Micrograph provided by the Regents of University of Michigan Medical School © 2012). (CC BY 4.0; via Adrenal Glands). Detailed text description of the Figure 1.9.1.

The adrenal cortex, as a component of the hypothalamic-pituitary-adrenal (HPA) axis, secretes steroid hormones important for the regulation of the long-term stress response, blood pressure and blood volume, nutrient uptake and storage, fluid and electrolyte balance, and inflammation. The HPA axis involves the stimulation of hormone release of adrenocorticotropic hormone (ACTH) from the pituitary by the hypothalamus. ACTH then stimulates the adrenal cortex to produce the hormone cortisol. This pathway will be discussed in more detail below.

The adrenal medulla is neuroendocrine tissue composed of postganglionic sympathetic nervous system (SNS) neurons. It is really an extension of the autonomic nervous system, which regulates homeostasis in the body. The sympathomedullary (SAM) pathway involves the stimulation of the medulla by impulses from the hypothalamus via neurons from the thoracic spinal cord. The medulla is stimulated to secrete the amine hormones epinephrine and norepinephrine.

One of the major functions of the adrenal gland is to respond to stress. Stress can be either physical or psychological or both. Physical stresses include exposing the body to injury, walking outside in cold and wet conditions without a coat on, or malnutrition. Psychological stresses include the perception of a physical threat, a fight with a loved one, or just a bad day at school.

The body responds in different ways to short-term stress and long-term stress following a pattern known as the general adaptation syndrome (GAS). Stage one of GAS is called the alarm reaction. This is short-term stress, the fight-or-flight response, mediated by the hormones epinephrine and norepinephrine from the adrenal medulla via the SAM pathway. Their function is to prepare the body for extreme physical exertion. Once this stress is relieved, the body quickly returns to normal. The section on the adrenal medulla covers this response in more detail.

If the stress is not soon relieved, the body adapts to the stress in the second stage called the stage of resistance. If a person is starving for example, the body may send signals to the gastrointestinal tract to maximize the absorption of nutrients from food.

If the stress continues for a longer term however, the body responds with symptoms quite different than the fight-or-flight response. During the stage of exhaustion, individuals may begin to suffer depression, the suppression of their immune response,

severe fatigue, or even a fatal heart attack. These symptoms are mediated by the hormones of the adrenal cortex, especially cortisol, released as a result of signals from the HPA axis.

Adrenal hormones also have several non–stress-related functions, including the increase of blood sodium and glucose levels, which will be described in detail below.

Adrenal Cortex

The adrenal cortex consists of multiple layers of lipid-storing cells that occur in three structurally distinct regions. Each of these regions produces different hormones.

Hormones of the Zona Glomerulosa

The most superficial region of the adrenal cortex is the zona glomerulosa, which produces a group of hormones collectively referred to as mineralocorticoids because of their effect on body minerals, especially sodium and potassium. These hormones are essential for fluid and electrolyte balance.

Aldosterone is the major mineralocorticoid. It is important in the regulation of the concentration of sodium and potassium ions in urine, sweat, and saliva. For example, it is released in response to elevated blood K^+, low blood Na^+, low blood pressure, or low blood volume. In response, aldosterone increases the excretion of K^+ and the retention of Na^+, which in turn increases blood volume and blood pressure. Its secretion is prompted when CRH from the hypothalamus triggers ACTH release from the anterior pituitary.

Aldosterone is also a key component of the renin-angiotensin-aldosterone system (RAAS) in which specialized cells of the kidneys secrete the enzyme renin in response to low blood volume or low blood pressure. Renin then catalyzes the conversion of the blood protein angiotensinogen, produced by the liver, to the hormone angiotensin I. Angiotensin I is converted in the lungs to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II has three major functions:

1. Initiating vasoconstriction of the arterioles, decreasing blood flow
2. Stimulating kidney tubules to reabsorb NaCl and water, increasing blood volume
3. Signaling the adrenal cortex to secrete aldosterone, the effects of which further contribute to fluid retention, restoring blood pressure and blood volume

For individuals with hypertension, or high blood pressure, drugs are available that block the production of angiotensin II. These drugs, known as ACE inhibitors, block the ACE enzyme from converting angiotensin I to angiotensin II, thus mitigating the latter's ability to increase blood pressure.

Hormones of the Zona Fasciculata

The intermediate region of the adrenal cortex is the zona fasciculata, named as such because the cells form small fascicles (bundles) separated by tiny blood vessels. The cells of the zona fasciculata produce hormones called glucocorticoids because of their role in glucose metabolism. The most important of these is cortisol, some of which the liver converts to cortisone. A glucocorticoid produced in much smaller amounts is corticosterone. In response to long-term stressors, the hypothalamus secretes CRH, which in turn triggers the release of ACTH by the anterior pituitary. ACTH triggers the release of the glucocorticoids. Their overall effect is to inhibit tissue building while stimulating the breakdown of stored nutrients to maintain adequate fuel supplies. In conditions of long-term stress, for example, cortisol promotes the catabolism of glycogen to glucose, the catabolism of stored triglycerides into fatty acids and glycerol, and the catabolism of muscle proteins into amino acids. These raw materials can then be used to synthesize additional glucose and ketones for use as body fuels. The hippocampus, which is part of the temporal lobe of the cerebral cortices and important in memory formation, is highly sensitive to stress levels because of its many glucocorticoid receptors.

You are probably familiar with prescription and over-the-counter medications containing glucocorticoids, such as cortisone injections into inflamed joints, prednisone tablets and steroid-based inhalers used to manage severe asthma, and hydrocortisone creams applied to relieve itchy rashes. These drugs reflect another role of cortisol—the Downregulation of the immune system, which inhibits the inflammatory response.

Hormones of the Zona Reticularis

The deepest region of the adrenal cortex is the zona reticularis, which produces small amounts of a class of steroid sex hormones called androgens. During puberty and most of adulthood, androgens are produced in the gonads. The androgens produced in the zona reticularis supplement the gonadal androgens. They are produced in response to ACTH from the anterior pituitary and are converted in the tissues to testosterone or estrogens. In adult females, they may contribute to the sex drive, but their function in adult males is not well understood. In post-menopausal people, as the functions of the ovaries decline, the main source of estrogens becomes the androgens produced by the zona reticularis.

Adrenal Medulla

As noted earlier, the adrenal cortex releases glucocorticoids in response to long-term stress such as severe illness. In contrast, the adrenal medulla releases its hormones in response to acute, short-term stress mediated by the sympathetic nervous system (SNS).

The medullary tissue is composed of unique postganglionic SNS neurons called chromaffin cells, which are large and irregularly shaped, and produce the neurotransmitters epinephrine (also called adrenaline) and norepinephrine (or noradrenaline). Epinephrine is produced in greater quantities—approximately a 4 to 1 ratio with norepinephrine—and is the more powerful hormone. Because the chromaffin cells release epinephrine and norepinephrine into the systemic circulation, where they travel widely and exert effects on distant cells, they are considered hormones. Derived from the amino acid tyrosine, they are chemically classified as catecholamines.

The secretion of medullary epinephrine and norepinephrine is controlled by a neural pathway that originates from the hypothalamus in response to danger or stress (the SAM pathway). Both epinephrine and norepinephrine signal the liver and skeletal muscle cells to convert glycogen into glucose, resulting in increased blood glucose levels. These hormones increase the heart rate, pulse, and blood pressure to prepare the body to fight the perceived threat or flee from it. In addition, the pathway dilates the airways, raising blood oxygen levels. It also prompts vasodilation, further increasing the oxygenation of important organs such as the lungs, brain, heart, and skeletal muscle. At the same time, it triggers vasoconstriction to blood vessels serving less essential organs such as the gastrointestinal tract, kidneys, and skin, and downregulates some components of the immune system. Other effects include a dry mouth, loss of appetite, pupil dilation, and a loss of peripheral vision. The major hormones of the adrenal glands are summarized in Table 1.9.1.

Table 1.9.1: Hormones of the Adrenal Glands

Adrenal gland	Associated hormones	Chemical class	Effect
Adrenal cortex	Aldosterone	Steroid	Increases blood Na^+ levels
Adrenal cortex	Cortisol, corticosterone, cortisone	Steroid	Increase blood glucose levels
Adrenal medulla	Epinephrine, norepinephrine	Amine	Stimulate fight-or-flight response

Disorders Involving the Adrenal Glands

Several disorders are caused by the dysregulation of the hormones produced by the adrenal glands. For example, Cushing's disease is a disorder characterized by high blood glucose levels and the accumulation of lipid deposits on the face and neck. It is caused by hypersecretion of cortisol. The most common source of Cushing's disease is a pituitary tumor that secretes cortisol or ACTH in abnormally high amounts. Other common signs of Cushing's disease include the development of a moon-shaped face, a buffalo hump on the back of the neck, rapid weight gain, and hair loss. Chronically elevated glucose levels are also associated with an elevated risk of developing type 2 diabetes. In addition to hyperglycemia, chronically elevated glucocorticoids compromise immunity, resistance to infection, and memory, and can result in rapid weight gain and hair loss.

In contrast, the hyposecretion of corticosteroids can result in Addison's disease, a rare disorder that causes low blood glucose levels and low blood sodium levels. The signs and symptoms of Addison's disease are vague and are typical of other disorders as well, making diagnosis difficult. They may include general weakness, abdominal pain, weight loss, nausea, vomiting, sweating, and cravings for salty food.

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1.10: The Pineal Gland

Structure and Function of the Pineal Gland

Recall that the hypothalamus, part of the diencephalon of the brain, sits inferior and somewhat anterior to the thalamus. Inferior but somewhat posterior to the thalamus is the pineal gland, a tiny endocrine gland whose functions are not entirely clear. The pinealocyte cells that make up the pineal gland are known to produce and secrete the amine hormone melatonin, which is derived from serotonin.

The secretion of melatonin varies according to the level of light received from the environment. When photons of light stimulate the retinas of the eyes, a nerve impulse is sent to a region of the hypothalamus called the suprachiasmatic nucleus (SCN), which is important in regulating biological rhythms. From the SCN, the nerve signal is carried to the spinal cord and eventually to the pineal gland, where the production of melatonin is inhibited. As a result, blood levels of melatonin fall, promoting wakefulness. In contrast, as light levels decline—such as during the evening—melatonin production increases, boosting blood levels and causing drowsiness.

The secretion of melatonin may influence the body's circadian rhythms, the dark-light fluctuations that affect not only sleepiness and wakefulness, but also appetite and body temperature. Interestingly, children have higher melatonin levels than adults, which may prevent the release of gonadotropins from the anterior pituitary, thereby inhibiting the onset of puberty. Finally, an antioxidant role of melatonin is the subject of current research.

Jet lag occurs when a person travels across several time zones and feels sleepy during the day or wakeful at night. Traveling across multiple time zones significantly disturbs the light-dark cycle regulated by melatonin. It can take up to several days for melatonin synthesis to adjust to the light-dark patterns in the new environment, resulting in jet lag. Some air travelers take melatonin supplements to induce sleep.

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1.11: Gonadal and Placental Hormones

Hormonal Functions of the Gonads and Placenta

This section briefly discusses the hormonal role of the gonads—the testes and ovaries—which produce the sex cells (sperm and ova) and secrete the gonadal hormones. The roles of the gonadotropins released from the anterior pituitary (FSH and LH) were discussed earlier.

The primary hormone produced by the testes is testosterone, a steroid hormone important in the development of the testicular reproductive system, the maturation of sperm cells, and the development of secondary sex characteristics such as a deepened voice, body hair, and increased muscle mass. Interestingly, testosterone is also produced in the ovaries, but at a much reduced level. In addition, the testes produce the peptide hormone inhibin, which inhibits the secretion of FSH from the anterior pituitary gland. FSH stimulates spermatogenesis.

The primary hormones produced by the ovaries are estrogens, which include estradiol, estriol, and estrone. Estrogens play an important role in a larger number of physiological processes, including the development of the ovarian reproductive system, regulation of the menstrual cycle, the development of secondary sex characteristics such as increased adipose tissue and the development of breast tissue, and the maintenance of pregnancy. Another significant ovarian hormone is progesterone, which contributes to regulation of the menstrual cycle and is important in preparing the body for pregnancy as well as maintaining pregnancy. In addition, the granulosa cells of the ovarian follicles produce inhibin, which inhibits the secretion of FSH.During the initial stages of pregnancy, an organ called the placenta develops within the uterus. The placenta supplies oxygen and nutrients to the fetus, excretes waste products, and produces and secretes estrogens and progesterone. The placenta produces human chorionic gonadotropin (hCG) as well. The hCG hormone promotes progesterone synthesis and reduces the mother's immune function to protect the fetus from immune rejection. It also secretes human placental lactogen (hPL), which plays a role in preparing the breasts for lactation, and relaxin, which is thought to help soften and widen the pubic symphysis in preparation for childbirth. The hormones controlling reproduction are summarized in Table 1.11.1.

Table 1.11.1: Reproductive Hormones

Gonad	Associated hormones	Chemical class	Effect
Testes	Testosterone	Steroid	Stimulates development of secondary sex characteristics and sperm production
Testes	Inhibin	Protein	Inhibits FSH release from pituitary
Ovaries	Estrogens and progesterone	Steroid	Stimulate development of secondary sex characteristics and prepare the body for childbirth
Placenta	Human chorionic gonadotropin	Protein	Promotes progesterone synthesis during pregnancy and inhibits immune response against fetus

Everyday Connection

Anabolic Steroids

The endocrine system can be exploited for illegal or unethical purposes. A prominent example of this is the use of steroid drugs by professional athletes.

Commonly used for performance enhancement, anabolic steroids are synthetic versions of the sex hormone, testosterone. By boosting natural levels of this hormone, athletes experience increased muscle mass. Synthetic versions of human growth hormone are also used to build muscle mass.

The use of performance-enhancing drugs is banned by all major collegiate and professional sports organizations in the United States because they impart an unfair advantage to athletes who take them. In addition, the drugs can cause significant and dangerous side effects. For example, anabolic steroid use can increase cholesterol levels, raise blood pressure, and damage the liver. Altered testosterone levels (both too low or too high) have been implicated in causing structural damage to the heart, and increasing the risk for cardiac arrhythmias, heart attacks, congestive heart failure, and sudden death. Paradoxically, steroids can have effects, including shriveled testicles and enlarged breast tissue. In females, their use can cause effects such as an enlarged clitoris and growth of facial hair. In all people, their use can promote increased aggression (commonly known as “roid-rage”), depression, sleep disturbances, severe acne, and infertility.

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1.12: Development and Aging of the Endocrine System

Embryonic Origins of the Endocrine System

The endocrine system arises from all three embryonic germ layers. The endocrine glands that produce the steroid hormones, such as the gonads and adrenal cortex, arise from the mesoderm. In contrast, endocrine glands that arise from the endoderm and ectoderm produce the amine, peptide, and protein hormones. The pituitary gland arises from two distinct areas of the ectoderm: the anterior pituitary gland arises from the oral ectoderm, whereas the posterior pituitary gland arises from the neural ectoderm at the base of the hypothalamus. The pineal gland also arises from the ectoderm. The two structures of the adrenal glands arise from two different germ layers: the adrenal cortex from the mesoderm and the adrenal medulla from ectoderm neural cells. The endoderm gives rise to the thyroid and parathyroid glands, as well as the pancreas and the thymus.

As the body ages, changes occur that affect the endocrine system, sometimes altering the production, secretion, and catabolism of hormones. For example, the structure of the anterior pituitary gland changes as vascularization decreases and the connective tissue content increases with increasing age. This restructuring affects the gland's hormone production. For example, the amount of human growth hormone that is produced declines with age, resulting in the reduced muscle mass commonly observed in the elderly.

The adrenal glands also undergo changes as the body ages; as fibrous tissue increases, the production of cortisol and aldosterone decreases. Interestingly, the production and secretion of epinephrine and norepinephrine remain normal throughout the aging process.

A well-known example of the aging process affecting an endocrine gland is menopause and the decline of ovarian function. With increasing age, the ovaries decrease in both size and weight and become progressively less sensitive to gonadotropins. This gradually causes a decrease in estrogen and progesterone levels, leading to menopause and the inability to reproduce. Low levels of estrogens and progesterone are also associated with some disease states, such as osteoporosis, atherosclerosis, and hyperlipidemia, or abnormal blood lipid levels.

Testosterone levels also decline with age, a condition called andropause (or viropause); however, this decline is much less dramatic than the decline of estrogens, and much more gradual, rarely affecting sperm production until very old age. Although this means that males maintain their ability to produce offspring for decades longer than females, the quantity, quality, and motility of their sperm is often reduced.

As the body ages, the thyroid gland produces less of the thyroid hormones, causing a gradual decrease in the basal metabolic rate. The lower metabolic rate reduces the production of body heat and increases levels of body fat. Parathyroid hormones, on the other hand, increase with age. This may be because of reduced dietary calcium levels, causing a compensatory increase in parathyroid hormone. However, increased parathyroid hormone levels combined with decreased levels of calcitonin (and estrogens in females) can lead to osteoporosis as PTH stimulates demineralization of bones to increase blood calcium levels. Notice that osteoporosis is common in all elderly people regardless of sex.

Increasing age also affects glucose metabolism, as blood glucose levels spike more rapidly and take longer to return to normal in the elderly. In addition, increasing glucose intolerance may occur because of a gradual decline in cellular insulin sensitivity. Almost 27 percent of Americans aged 65 and older have diabetes.

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1.13: Terms and Definitions

Key Terms

Select to View Definition

Acromegaly
disorder in adults caused when abnormally high levels of GH trigger growth of bones in the face, hands, and feet

Adenylyl cyclase
membrane-bound enzyme that converts ATP to cyclic AMP, creating cAMP, as a result of G-protein activation

Adrenal cortex
outer region of the adrenal glands consisting of multiple layers of epithelial cells and capillary networks that produces mineralocorticoids and glucocorticoids

Adrenal glands
endocrine glands located at the top of each kidney that are important for the regulation of the stress response, blood pressure and blood volume, water homeostasis, and electrolyte levels

Adrenal medulla
inner layer of the adrenal glands that plays an important role in the stress response by producing epinephrine and norepinephrine

Adrenocorticotropic hormone (ACTH)
anterior pituitary hormone that stimulates the adrenal cortex to secrete corticosteroid hormones (also called corticotropin)

Alarm reaction
the short-term stress, or the fight-or-flight response, of stage one of the general adaptation syndrome mediated by the hormones epinephrine and norepinephrine

Aldosterone
hormone produced and secreted by the adrenal cortex that stimulates sodium and fluid retention and increases blood volume and blood pressure

Alpha cell
pancreatic islet cell type that produces the hormone glucagon

Angiotensin-converting enzyme
the enzyme that converts angiotensin I to angiotensin II

Antidiuretic hormone (ADH)
hypothalamic hormone that is stored by the posterior pituitary and that signals the kidneys to reabsorb water

Atrial natriuretic peptide (ANP)
peptide hormone produced by the walls of the atria in response to high blood pressure, blood volume, or blood sodium that reduces the reabsorption of sodium and water in the kidneys and promotes vasodilation

Aautocrine
chemical signal that elicits a response in the same cell that secreted it

Beta cell
pancreatic islet cell type that produces the hormone insulin

Calcitonin
peptide hormone produced and secreted by the parafollicular cells (C cells) of the thyroid gland that functions to

decrease blood calcium levels

Chromaffin
neuroendocrine cells of the adrenal medulla

Colloid
viscous fluid in the central cavity of thyroid follicles, containing the glycoprotein thyroglobulin

Cortisol
glucocorticoid important in gluconeogenesis, the catabolism of glycogen, and downregulation of the immune system

Cyclic adenosine monophosphate (cAMP)
second messenger that, in response to adenylyl cyclase activation, triggers a phosphorylation cascade

Delta cell
minor cell type in the pancreas that secretes the hormone somatostatin

Diabetes mellitus
condition caused by destruction or dysfunction of the beta cells of the pancreas or cellular resistance to insulin that results in abnormally high blood glucose levels

Diacylglycerol (DAG)
molecule that, like cAMP, activates protein kinases, thereby initiating a phosphorylation cascade

Downregulation
decrease in the number of hormone receptors, typically in response to chronically excessive levels of a hormone

Endocrine gland
tissue or organ that secretes hormones into the blood and lymph without ducts such that they may be transported to organs distant from the site of secretion

Endocrine system
cells, tissues, and organs that secrete hormones as a primary or secondary function and play an integral role in normal bodily processes

Epinephrine
primary and most potent catecholamine hormone secreted by the adrenal medulla in response to short-term stress; also called adrenaline

Erythropoietin (EPO)
protein hormone secreted in response to low oxygen levels that triggers the bone marrow to produce red blood cells

Estrogens
class of predominantly female sex hormones important for the development and growth of the female reproductive tract, secondary sex characteristics, the female reproductive cycle, and the maintenance of pregnancy

Exocrine system
cells, tissues, and organs that secrete substances directly to target tissues via glandular ducts

First messenger
hormone that binds to a cell membrane hormone receptor and triggers activation of a second messenger system

Follicle-stimulating hormone (FSH)
anterior pituitary hormone that stimulates the production and maturation of sex cells

G protein
protein associated with a cell membrane hormone receptor that initiates the next step in a second messenger system upon activation by hormone–receptor binding

General adaptation syndrome (GAS)
the human body's three-stage response pattern to short- and long-term stress

Gigantism
disorder in children caused when abnormally high levels of GH prompt excessive growth

Glucagon
pancreatic hormone that stimulates the catabolism of glycogen to glucose, thereby increasing blood glucose levels

Glucocorticoids
hormones produced by the zona fasciculata of the adrenal cortex that influence glucose metabolism

Goiter
enlargement of the thyroid gland either as a result of iodine deficiency or hyperthyroidism

Gonadotropins
hormones that regulate the function of the gonads

Growth hormone (GH)
anterior pituitary hormone that promotes tissue building and influences nutrient metabolism (also called somatotropin)

Hormone
secretion of an endocrine organ that travels via the bloodstream or lymphatics to induce a response in target cells or tissues in another part of the body

Hormone receptor
protein within a cell or on the cell membrane that binds a hormone, initiating the target cell response

Hyperglycemia
abnormally high blood glucose levels

Hyperparathyroidism
disorder caused by overproduction of PTH that results in abnormally elevated blood calcium

Hyperthyroidism
clinically abnormal, elevated level of thyroid hormone in the blood; characterized by an increased metabolic rate, excess body heat, sweating, diarrhea, weight loss, and increased heart rate

Hypoparathyroidism
disorder caused by underproduction of PTH that results in abnormally low blood calcium

Hypophyseal portal system
network of blood vessels that enables hypothalamic hormones to travel into the anterior lobe of the pituitary without entering the systemic circulation

Hypothalamus
region of the diencephalon inferior to the thalamus that functions in neural and endocrine signaling

Hypothyroidism
clinically abnormal, low level of thyroid hormone in the blood; characterized by low metabolic rate, weight gain, cold extremities, constipation, and reduced mental activity

Infundibulum
stalk containing vasculature and neural tissue that connects the pituitary gland to the hypothalamus (also called the pituitary stalk)

Inhibin
hormone secreted by the male and female gonads that inhibits FSH production by the anterior pituitary

Inositol triphosphate (IP_3)
molecule that initiates the release of calcium ions from intracellular stores

Insulin
pancreatic hormone that enhances the cellular uptake and utilization of glucose, thereby decreasing blood glucose levels

Insulin-like growth factors (IGF)
protein that enhances cellular proliferation, inhibits apoptosis, and stimulates the cellular uptake of amino acids for protein synthesis

Leptin
protein hormone secreted by adipose tissues in response to food consumption that promotes satiety

Luteinizing hormone (LH)
anterior pituitary hormone that triggers ovulation and the production of ovarian hormones, and the production of testosterone

Melatonin
amino acid–derived hormone that is secreted in response to low light and causes drowsiness

Mineralocorticoids
hormones produced by the zona glomerulosa cells of the adrenal cortex that influence fluid and electrolyte balance

Neonatal hypothyroidism
condition characterized by cognitive deficits, short stature, and other signs and symptoms in people born to people who were iodine-deficient during pregnancy

Norepinephrine
secondary catecholamine hormone secreted by the adrenal medulla in response to short-term stress; also called noradrenaline

Osmoreceptor
hypothalamic sensory receptor that is stimulated by changes in solute concentration (osmotic pressure) in the blood

Oxytocin
hypothalamic hormone stored in the posterior pituitary gland and important in stimulating uterine contractions in labor, milk ejection during breastfeeding, and feelings of attachment (produced by males and females)

Pancreas
organ with both exocrine and endocrine functions located posterior to the stomach that is important for digestion and the regulation of blood glucose

Pancreatic islets
specialized clusters of pancreatic cells that have endocrine functions; also called islets of Langerhans

Paracrine
chemical signal that elicits a response in neighboring cells; also called paracrine factor

Parathyroid glands
small, round glands embedded in the posterior thyroid gland that produce parathyroid hormone (PTH)

Parathyroid hormone (PTH)
peptide hormone produced and secreted by the parathyroid glands in response to low blood calcium levels

Phosphodiesterase (PDE)
cytosolic enzyme that deactivates and degrades cAMP

Phosphorylation cascade
signaling event in which multiple protein kinases phosphorylate the next protein substrate by transferring a phosphate group from ATP to the protein

Pineal gland
endocrine gland that secretes melatonin, which is important in regulating the sleep-wake cycle

Pinealocyte
cell of the pineal gland that produces and secretes the hormone melatonin

Pituitary dwarfism
disorder in children caused when abnormally low levels of GH result in growth retardation

Pituitary gland
bean-sized organ suspended from the hypothalamus that produces, stores, and secretes hormones in response to hypothalamic stimulation (also called hypophysis)

PP cell
minor cell type in the pancreas that secretes the hormone pancreatic polypeptide

Progesterone
predominantly female sex hormone important in regulating the female reproductive cycle and the maintenance of pregnancy

Prolactin (PRL)
anterior pituitary hormone that promotes development of the mammary glands and the production of breast milk

Protein kinase
enzyme that initiates a phosphorylation cascade upon activation

Second messenger
molecule that initiates a signaling cascade in response to hormone binding on a cell membrane receptor and activation of a G protein

Stage of exhaustion
stage three of the general adaptation syndrome; the body's long-term response to stress mediated by the hormones of the adrenal cortex

Stage of resistance
stage two of the general adaptation syndrome; the body's continued response to stress after stage one diminishes

Testosterone
steroid hormone secreted by the testes and important in the maturation of sperm cells, growth and development of the reproductive system, and the development of secondary sex characteristics

Thymosins
hormones produced and secreted by the thymus that play an important role in the development and differentiation of T cells

Thymus
organ that is involved in the development and maturation of T-cells and is particularly active during infancy and childhood

Thyroid gland
large endocrine gland responsible for the synthesis of thyroid hormones

Thyroid-stimulating hormone (TSH)
anterior pituitary hormone that triggers secretion of thyroid hormones by the thyroid gland (also called thyrotropin)

Thyroxine
(also, tetraiodothyronine, T_4) amino acid–derived thyroid hormone that is more abundant but less potent than T_3 and often converted to T_3 by target cells

Triiodothyronine
(also, T_3) amino acid–derived thyroid hormone that is less abundant but more potent than T_4

Upregulation
increase in the number of hormone receptors, typically in response to chronically reduced levels of a hormone

Zona fasciculata
intermediate region of the adrenal cortex that produce hormones called glucocorticoids

Zona glomerulosa
most superficial region of the adrenal cortex, which produces the hormones collectively referred to as mineralocorticoids

Zona reticularis
deepest region of the adrenal cortex, which produces the steroid sex hormones called androgens

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1.14: Chapter Review Questions

Multiple-Choice Section

- Use the end-of-chapter multiple-choice section as a regular self-check tool, not just before exams.
- Read each item carefully, think about what is really being tested (concept, definition, application, or calculation), and choose the option (A, B, C, or D) that best reflects what you have learned in this chapter.
  - After you read through the chapter, attempt all items without looking at your notes; then return to the chapter to review any you missed or felt unsure about.
  - Explain why the correct option is right and why the others are not. Repeat the multiple-choice section a few days later to reinforce learning.
- Students who consistently use these prompts typically perform better because they turn reading into active practice.

1. Which statement best describes endocrine glands?
   A. They secrete hormones that travel through a duct to the target organs.
   B. They release neurotransmitters into a synaptic cleft.
   C. They secrete chemical messengers that travel in the bloodstream.
   D. They include sebaceous glands and sweat glands.
2. Chemical signaling that affects neighboring cells in the same tissue is called:
   A. Autocrine signaling.
   B. Paracrine signaling.
   C. Endocrine signaling.
   D. Neuronal signaling.
3. A newly developed pesticide is found to bind to intracellular hormone receptors. If a person ingests this pesticide, it could most directly disrupt the actions of which hormone?
   A. Melatonin.
   B. Growth hormone.
   C. Thyroid hormone.
   D. Insulin.
4. A small molecule binds to a G protein and prevents its activation. What direct effect will this have on a signaling pathway that normally uses cAMP as a second messenger?
   A. The hormone will not be able to bind to its receptor.
   B. Adenylyl cyclase will not be activated.
   C. Excessive amounts of cyclic AMP (cAMP) will be produced.
   D. The phosphorylation cascade will be initiated.
5. A college student is in a car accident. Although uninjured, within seconds they experience pupil dilation, increased heart rate, and rapid breathing. What type of endocrine stimulus most directly triggered these responses?
   A. Humoral stimulus.
   B. Hormonal stimulus.
   C. Neural stimulus.
   D. Positive feedback.
6. A 24-year-old man suffers a severe head injury in a motor vehicle accident. Imaging shows damage to the infundibulum (pituitary stalk). In the weeks following the injury, he develops excessive thirst and excretes large volumes of dilute urine. His laboratory tests reveal low antidiuretic hormone (ADH) levels, despite normal hypothalamic nuclei that produce ADH. Which anatomical structure that normally connects the hypothalamus to the posterior pituitary has most likely been disrupted?
   A. A specialized capillary network (hypophyseal portal veins).
   B. A bundle of unmyelinated nerve axons in the pituitary stalk.
   C. A cartilaginous bridge between the hypothalamus and pituitary.
   D. A fibrous band of connective tissue attaching the pituitary to the sphenoid bone.
7. Which of the following is secreted by the anterior pituitary gland?
   A. Antidiuretic hormone (ADH)
   B. Oxytocin
   C. Thyroid-stimulating hormone (TSH)
   D. Cortisol
8. How many hormones are produced (synthesized) by the posterior pituitary gland itself?

A. 0
B. 1
C. 2
D. 6

9. Which hormone directly contributes to regulating the body's fluid and electrolyte balance?
   A. Adrenocorticotropic hormone (ACTH)
   B. Antidiuretic hormone (ADH)
   C. Luteinizing hormone (LH)
   D. All of the above
10. Which of the following statements about the thyroid gland is true?
   A. It is located anterior to the trachea and inferior to the larynx.
   B. The parathyroid glands are typically embedded in its posterior surface.
   C. It manufactures the hormones T3, T4, and calcitonin.
   D. All of the above.
11. Secretion of thyroid hormones (T3 and T4) is directly controlled by:
   A. Thyroid-stimulating hormone (TSH) from the hypothalamus.
   B. Thyroid-stimulating hormone (TSH) from the anterior pituitary.
   C. Thyroxine from the anterior pituitary.
   D. Thyroglobulin from parafollicular cells of the thyroid.
12. The development of a goiter (enlarged thyroid gland) most commonly indicates that:
   A. The anterior pituitary is abnormally enlarged.
   B. There is hypertrophy of the thyroid's follicular cells.
   C. There is excessive accumulation of colloid in the thyroid follicles.
   D. The anterior pituitary is secreting excessive growth hormone.
13. Iodide ions move from the bloodstream into thyroid follicular cells via:
   A. Simple diffusion.
   B. Facilitated diffusion.
   C. Active transport.
   D. Osmosis.
14. When blood calcium levels are low, parathyroid hormone (PTH) stimulates:
   A. Increased urinary excretion of calcium by the kidneys.
   B. Reduced calcium absorption from the intestines.
   C. Increased activity of osteoblasts.
   D. Increased activity of osteoclasts.
15. Which of the following can result from hyperparathyroidism?
   A. Increased bone deposition.
   B. Bone fractures.
   C. Convulsions due to low calcium.
   D. All of the above.
16. The adrenal glands are attached superiorly to which organs?
   A. Thyroid glands.
   B. Liver.
   C. Kidneys.
   D. Hypothalamus.
17. Which secretory cell type is found in the adrenal medulla?
   A. Chromaffin cells
   B. Neuroglial cells
   C. Follicular cells
   D. Oxyphil cells
18. Cushing's disease is most commonly caused by:
   A. Abnormally low cortisol levels
   B. Abnormally high cortisol levels
   C. Abnormally low aldosterone levels
   D. Abnormally high aldosterone levels
19. Which of the following is NOT typically part of the fight-or-flight response?
   A. Pupil dilation
   B. Increased oxygen delivery to the lungs and muscles
   C. Suppressed digestion

D. Reduced mental alertness

20. Melatonin is primarily secreted by:
    A. Melanocytes
    B. Pinealocytes
    C. Cells in the suprachiasmatic nucleus
    D. Retinal photoreceptor cells
21. The production of melatonin is inhibited by:
    A. Declining levels of light
    B. Exposure to bright light
    C. Secretion of serotonin
    D. Activity of pinealocytes
22. The gonads (ovaries and testes) primarily produce which class of hormones?
    A. Amine hormones
    B. Peptide hormones
    C. Steroid hormones
    D. Catecholamines
23. Production of follicle-stimulating hormone (FSH) by the anterior pituitary is reduced by which hormone?
    A. Estrogens
    B. Progesterone
    C. Relaxin
    D. Inhibin
24. The primary function of the placental hormone human placental lactogen (hPL) is to:
    A. Prepare the breasts for lactation and alter maternal metabolism to support fetal growth
    B. Directly nourish the placenta
    C. Regulate the menstrual cycle in non-pregnant women
    D. Stimulate uterine contractions during labor
25. If an autoimmune disorder selectively destroys the alpha cells of the pancreatic islets, production of which hormone will be directly affected?
    A. Somatostatin
    B. Pancreatic polypeptide
    C. Insulin
    D. Glucagon
26. Which statement about insulin is true?
    A. Insulin acts as a carrier protein transporting glucose across the cell membrane by itself
    B. Insulin triggers movement of intracellular glucose transporters (e.g., GLUT4) to the cell membrane
    C. Insulin stimulates breakdown of glycogen into glucose in the liver
    D. Insulin stimulates the kidneys to reabsorb more glucose into the blood
27. The walls of the atria of the heart produce which hormone?
    A. Cholecystokinin
    B. Atrial natriuretic peptide (ANP)
    C. Renin
    D. Calcitriol
28. The overall effect of activation of the renin-angiotensin-aldosterone system (RAAS) is to:
    A. Reduce blood volume
    B. Increase blood glucose
    C. Reduce blood pressure
    D. Increase blood pressure
29. Athletes who take synthetic erythropoietin (EPO) are attempting to increase their:
    A. Blood calcium levels
    B. Secretion of growth hormone
    C. Blood oxygen-carrying capacity
    D. Skeletal muscle fiber number
30. Hormones produced by the thymus gland are important for:
    A. Development and maturation of T lymphocytes
    B. Preparing the body for childbirth
    C. Regulating appetite
    D. Stimulating gastric acid secretion
31. A 35-year-old woman reports fatigue, weight gain, cold intolerance, and constipation. Her TSH level is elevated, and her T3/

T4 levels are low. Which of the following best describes the feedback relationship in this patient?

A. Low T3/T4 causes increased TSH secretion by the anterior pituitary
B. High T3/T4 causes increased TSH secretion by the anterior pituitary
C. Low T3/T4 causes decreased TSH secretion by the anterior pituitary
D. TSH has no relationship to T3/T4 secretion

32. A 28-year-old patient presents with low blood pressure, weight loss, and hyperpigmentation of the skin. Laboratory tests show low cortisol and high ACTH. Which structure is most likely failing?

A. Hypothalamus
B. Anterior pituitary
C. Adrenal cortex
D. Adrenal medulla

33. A 60-year-old woman presents with bone pain and frequent fractures. Laboratory tests show elevated blood calcium and elevated parathyroid hormone levels. Which of the following is most likely occurring in her bones?

A. Increased activity of osteoclasts
B. Increased activity of osteoblasts
C. Increased deposition of calcium in bone
D. No change in bone turnover

34. A 14-year-old boy presents with excessive thirst, frequent urination, and weight loss. Blood glucose is markedly elevated, and he requires lifelong insulin injections. Which of the following best describes the underlying endocrine problem?

A. Decreased tissue responsiveness to insulin (insulin resistance)
B. Autoimmune destruction of pancreatic beta cells
C. Excessive secretion of glucagon by alpha cells
D. Excess production of cortisol by the adrenal cortex

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1.15: Applied Thinking Self - Assessment

Challenge Yourself

- Extended response questions are assessment items that require students to construct written answers of substantial length - typically several sentences to multiple paragraphs - rather than selecting from predefined options. They represent a form of constructed response assessment designed to measure complex, higher-order thinking skills.
- First, try answering without using your notes. Then review reliable resources and revise your response if needed. Make a note of any areas where you felt unsure and revisit those topics.

Writing Guidelines

- Answer each question in your own words.
- Write 4–8 clear, complete sentences per question, organized into short paragraphs (not bullet points).
- Focus on explaining your reasoning, not just stating the answer.
- Use correct scientific vocabulary, and briefly define terms when needed.
- For questions that ask you to compare, contrast, or explain why/how:
  - Clearly state similarities or differences
  - Support your ideas with a brief explanation or example

General Principles of Endocrine Physiology

1. Endocrine vs. Nervous System Communication

   - Describe several major differences in the communication methods used by the endocrine system and the nervous system. In your answer, compare:
     - Speed of response
     - Duration of effect
     - Chemical messengers used
     - Specificity of target cells
     - How signals are delivered (e.g., synapses vs. bloodstream)

2. Endocrine vs. Exocrine Glands

   - Compare and contrast endocrine and exocrine glands. Be sure to address:
     - How each type secretes its products (into ducts vs. into blood)
     - Typical secretory products (e.g., hormones vs. enzymes)
     - One example of each type of gland.

3. Neurotransmitters and Paracrines

   - True or false: “Neurotransmitters are a special class of paracrines.”
   - Explain your answer using:
     - Definitions of paracrine signaling and synaptic signaling
     - At least one similarity and one difference between them.

4. Hormone Signaling Pathways: cAMP vs. Intracellular Receptors

   - Compare and contrast:
     - (a) The signaling events involved in a hormone that acts via the second messenger cAMP
     - (b) The mechanism of hormone response resulting from binding to an intracellular receptor (e.g., steroid or thyroid hormone).
   - Include:
     - Where the receptor is located

- The speed of onset
- Whether gene transcription is directly affected
- Typical duration of the response

5. Hormone Classes and Receptors

   - Choose one peptide hormone and one steroid hormone. For each:
     - State where its receptor is located (membrane vs. intracellular)
     - Briefly describe how that receptor type influences the time course and type of response.

Hypothalamus–Pituitary Axis

1. Anatomical Relationship: Anterior vs. Posterior Pituitary

   - Compare and contrast the anatomical and functional relationships of the anterior and posterior lobes of the pituitary gland to the hypothalamus. In your answer, discuss:
     - Blood supply and portal system vs. neural connections
     - Where the hormones are synthesized vs. released
     - How hypothalamic control differs for each lobe.

2. Prolactin Targets and Regulation

   - Name the main target tissues for prolactin. Briefly describe:
     - Its primary physiological effect
     - How prolactin secretion is regulated by the hypothalamus (including the unusual role of dopamine).

3. Integration Question: Pituitary Tumor

   - A benign pituitary tumor secretes excess prolactin.
     - Predict two potential clinical signs or symptoms and explain the mechanisms behind them.

Thyroid and Parathyroid

1. Iodine Deficiency and Fetal Brain Development

   - Explain why maternal iodine deficiency might lead to neurological impairment in the fetus. Include:
     - The role of thyroid hormones in nervous system development
     - How iodine deficiency alters maternal and fetal thyroid hormone levels.

2. Hyperthyroidism and Weight Loss

   - Define hyperthyroidism.
   - Explain why one of its common symptoms is weight loss, even when appetite may be normal or increased.
   - Refer to at least two effects of thyroid hormone on metabolism.

3. Negative Feedback and the Parathyroid Glands

   - Describe the role of negative feedback in the regulation of parathyroid hormone (PTH) secretion. In your answer, explain:
     - How plasma Ca^{2+} levels influence PTH release
     - How PTH then alters Ca^{2+} levels to complete the feedback loop.

4. Parathyroid Tumor and Kidney Stones

   - Explain why someone with a PTH-secreting parathyroid gland tumor (hyperparathyroidism) might develop kidney stones.

     Be sure to link:
     - Changes in blood Ca^{2+} and phosphate
     - Effects on bone and kidney
     - How these changes favor stone formation.

5. Calcium Homeostasis Integration
    - Compare the roles of PTH and calcitonin in calcium homeostasis.
    - Which hormone is more critical in day-to-day regulation in adults, and why?

Adrenal Glands and Stress Response

1. Regions of the Adrenal Cortex and Their Hormones
    - Name the three histologically defined regions (zones) of the adrenal cortex.
    - For each zone, list the primary class of hormones produced and one major function for that hormone class.
2. Loss of Adrenal Medulla Innervation
    - If innervation to the adrenal medulla were disrupted, what would be the physiological outcome? Focus on:
        - Changes in epinephrine/norepinephrine release
        - Effects on the acute stress (“fight or flight”) response.
3. Short-Term vs. Long-Term Stress Response
    - Compare and contrast the short-term (acute) and long-term (chronic) stress responses. Include:
        - Primary hormones involved (e.g., catecholamines vs. glucocorticoids/mineralocorticoids)
        - Main physiological effects (on cardiovascular system, metabolism, immune function, etc.)
        - One possible health consequence of prolonged activation of the long-term stress response.

Pineal Gland and Melatonin

1. Melatonin and Seasonal Affective Disorder
    - Seasonal affective disorder (SAD) is associated with increased appetite, sluggishness, and increased sleepiness in winter, especially in regions with long nights.
    - Propose a role for melatonin in SAD and suggest a possible non-drug therapy.
    - Explain how your proposed therapy might alter melatonin secretion patterns.
2. Retinitis Pigmentosa and Melatonin Levels
    - Retinitis pigmentosa (RP) causes deterioration of the retina.
    - Describe how this might impact melatonin levels and circadian rhythms. In your answer, consider:
        - How light information normally reaches the pineal gland
        - What happens when the retina cannot detect light properly.

Reproductive Hormones and Pregnancy

1. Roles of Estrogens vs. Progesterone

- Compare and contrast the roles of estrogens and progesterone in the female reproductive system.
- Discuss effects on:
    - The menstrual cycle
    - The endometrium
    - Secondary sex characteristics
    - Pregnancy maintenance.

2. Placental Relaxin and Childbirth Preparation

- Describe the role of placental secretion of relaxin in preparation for childbirth. Include:
  - Its effects on the cervix and pelvic ligaments
  - Why these changes are important for delivery.

3. Pregnancy Test Hormones

- Identify the hormone commonly measured in pregnancy tests and describe:
  - Which organ secretes it
  - Its role in maintaining early pregnancy.

Pancreas, Diabetes, and Metabolic Regulation

1. Loss of Pancreatic Beta Cells

- What would be the physiological consequence of a disease that destroyed the beta cells of the pancreas?
- Explain how this affects:
  - Blood glucose levels
  - Use of fats and proteins for energy
  - Potential long-term complications.

2. Foot Care in Diabetes Mellitus

- Explain why foot care is extremely important for people with diabetes mellitus. In your answer, address:
  - Effects of chronic hyperglycemia on blood vessels and nerves
  - How these changes increase the risk of foot ulcers and serious infections.

3. GI Tract Hormones After a Meal

- Summarize the role of GI tract hormones (such as gastrin, secretin, CCK, incretins) following a meal. Include:
  - Effects on digestion and absorption
  - Interactions with pancreatic endocrine function (e.g., insulin release).

4. Metabolic Hormone Balance

- Compare and contrast the actions of insulin and glucagon on:
  - Liver
  - Muscle
  - Adipose tissue
- Describe how they work together to maintain blood glucose.

Thymus and Lifespan Changes

1. Thymus in Infancy vs. Adulthood

- Compare and contrast the thymus gland in infancy and adulthood. Be sure to mention:
  - Relative size and activity level
  - Its role in T-lymphocyte development
  - How changes in the thymus may relate to immune function later in life.

2. Endocrine Aging Overview

- Choose one endocrine gland (e.g., ovaries, testes, pineal, thyroid, or thymus) and briefly describe:
  - How its function changes with age
  - One clinical or physiological consequence of that change.

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1.16: Alternate Text Descriptions

Figure 1.1: Hypothalamic-Pituitary-Gonadal (HPG) Axis

The figure illustrates the hypothalamic-pituitary-gonadal (HPG) axis, a hormone signaling pathway that regulates reproductive function.

At the top of the pathway, the hypothalamus releases gonadotropin-releasing hormone (GnRH). An arrow points downward from the hypothalamus to the anterior pituitary gland, indicating that GnRH stimulates the pituitary.

The anterior pituitary then releases the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). A second downward arrow shows these hormones acting on the gonads, represented by a testis and an ovary.

The gonads produce sex steroids, shown at the bottom of the pathway. Curved arrows extending from the sex steroids back toward both the hypothalamus and anterior pituitary are marked with negative (–) symbols. These arrows indicate negative feedback, meaning that increasing levels of sex steroids inhibit hormone release from both the hypothalamus and anterior pituitary.

The function of the figure is to show how hormone production by the gonads is regulated through a feedback loop that maintains hormonal balance within the reproductive system.

Figure 1.1.1: The Pancreas

This image is a labeled diagram of the pancreas and associated structures, showing both digestive and hormone functions. The structure labeled “Pancreas” contains two main functional components:

1. Exocrine function (digestion):
    - The “Acinar cells secrete digestive enzymes” label indicates that these cells produce digestive enzymes.
    - These enzymes move through the “Pancreatic duct.”
    - The pancreatic duct connects to the “Common bile duct” and the “Bile duct (from gall bladder).”
    - These ducts empty into the “Duodenum of small intestine.”
    - The label “Digestive enzymes” indicates that enzymes are delivered into the duodenum to help break down food.
2. Endocrine function (hormones):
    - The pancreas contains clusters labeled “Pancreatic islets.”
    - These islets produce hormones listed as “Pancreatic hormones: Insulin, Glucagon.”
    - In the inset labeled “Pancreatic islet,” the following cell types are identified:
        - “Alpha cells” – function: produce glucagon
        - “Beta cells” – function: produce insulin
        - “Exocrine acinus” – surrounding tissue involved in enzyme production

Additional labeled structures:

- “Splenic artery” – supplies blood to the pancreas and spleen
- “Spleen” – organ connected near the pancreas (not directly involved in pancreatic secretion)

Figure 1.1.2: High Blood Glucose Pathway

This image illustrates the homeostatic regulation of blood glucose by the hormones insulin and glucagon. At the center is the normal blood glucose range, labeled “START: Homeostasis (70–110 mg/dL)”, represented by a glucose meter reading 90 mg/dL.

High blood glucose pathway: When blood glucose rises above the normal range (hyperglycemia), a glucose meter shows a reading of 160 mg/dL. Beta cells in the pancreas release insulin into the splenic artery, where the hormone enters the bloodstream and is transported throughout the body. Insulin lowers blood glucose concentration through three major actions:

- Body cells increase glucose uptake and use glucose for cellular respiration.

- The liver removes glucose from the blood and stores it as glycogen.
- Gluconeogenesis is inhibited, so amino acids and glycerol are not converted into glucose.

These actions reduce blood glucose concentration and return it toward the normal homeostatic range.

Low blood glucose pathway: When blood glucose falls below the normal range (hypoglycemia), a glucose meter shows a reading of 50 mg/dL. Alpha cells in the pancreas release glucagon into the splenic artery, where the hormone enters the bloodstream and is transported throughout the body. Glucagon raises blood glucose concentration through three major actions:

- Many body cells decrease glucose uptake and utilization.
- Glycogen stored in the liver is broken down into glucose and released into the blood.
- Gluconeogenesis is stimulated, causing amino acids and glycerol to be converted into glucose and released into the blood.

These actions increase blood glucose concentration and return it toward the normal homeostatic range.

The diagram emphasizes a negative feedback system in which insulin and glucagon are released into the bloodstream from the pancreas through the splenic artery and act on body tissues to maintain blood glucose levels within the normal range of 70–110 mg/dL.

Figure 1.4.1: The Endocrine System

This is a labeled diagram of the endocrine system. It identifies the major hormone-producing glands and shows their locations in the body.

1. Brain structures: An inset of the brain labels the pineal gland, thalamus, and pituitary gland. The pineal gland secretes hormones involved in biological rhythms. The pituitary gland releases hormones that regulate other endocrine glands. The thalamus is shown as a nearby brain structure for anatomical reference.
2. Neck region: A magnified inset of the neck labels the thyroid gland, parathyroid glands, thyroid cartilage of the larynx, and trachea. The thyroid gland regulates metabolism through hormone secretion. The parathyroid glands, located on the posterior side of the thyroid, regulate calcium levels. The thyroid cartilage and trachea are included as surrounding anatomical landmarks.
3. Chest region: The thymus is labeled in the upper chest. It contributes to immune system development, especially the maturation of certain immune cells.
4. Abdominal region: The adrenal glands are shown above the kidneys. They produce hormones involved in stress response and metabolism. The pancreas is also labeled and is shown in the abdomen. It has both digestive and endocrine functions, including hormone production that helps regulate blood glucose.
5. Reproductive structures: The image labels the ovaries in the female body and the testes in the male body. The ovaries produce hormones such as estrogen and progesterone. The testes produce hormones such as testosterone. The uterus is also labeled as a reproductive organ for anatomical reference.

Overall, the figure shows that endocrine glands are distributed throughout the body and work together to regulate homeostasis, metabolism, growth, reproduction, and other body functions.

Figure 1.5.1: Major Hormone Classes

This image presents a three-column table comparing four classes of hormones. The column headings are Hormone Class, Components, and Example(s). The figure demonstrates how hormones are classified according to their chemical composition and shows representative molecular structures for each class.

Amine Hormones

- Components: Amino acids with modified groups (for example, norepinephrine's carboxyl group is replaced with a benzene ring).
- Example: Norepinephrine.
- The example is shown as a chemical structure consisting of a benzene ring with hydroxyl groups and an attached amino-containing side chain.

Peptide Hormones

- Components: Short chains of linked amino acids.
- Example: Oxytocin.
- The example is shown as a peptide composed of linked amino acids labeled Gly, Leu, Pro, Cys, Cys, Tyr, Ile, Asp, and Glu. The amino acids are connected in a chain and ring arrangement, illustrating the structure of a peptide hormone.

Protein Hormones

- Components: Long chains of linked amino acids.
- Example: Human Growth Hormone.
- The example is shown as a complex folded three-dimensional protein structure composed of multiple loops, coils, and sheet-like regions, illustrating how large protein hormones fold into specific shapes.

Steroid Hormones

- Components: Derived from the lipid cholesterol.
- Examples: Testosterone and Progesterone.
- Both examples are shown as chemical structures with the characteristic four interconnected carbon rings that distinguish steroid hormones. Small differences in the attached chemical groups distinguish testosterone from progesterone.

The figure emphasizes that hormones can be grouped into four major classes based on their chemical makeup. Amine hormones are modified amino acids, peptide hormones are short amino acid chains, protein hormones are long amino acid chains folded into complex structures, and steroid hormones are derived from cholesterol and share a characteristic four-ring structure.

Figure 1.5.2: Mechanism of Action of Lipid-Soluble Hormones

This image illustrates how a lipid-soluble hormone affects gene expression inside a target cell.

The figure shows a capillary above the cell containing lipid-soluble hormone molecules. Below the capillary is the extracellular fluid surrounding the cell. The large cell is divided into a cytoplasm surrounding a central nucleus.

Step 1: A lipid-soluble hormone leaves the capillary, passes through the extracellular fluid, and diffuses across the plasma membrane into the cytoplasm.

Step 2: Within the cytoplasm, the hormone binds to an intracellular receptor, forming a receptor-hormone complex.

Step 3: The receptor-hormone complex enters the nucleus. Inside the nucleus, the complex interacts with DNA, shown as a double-helix structure, and initiates transcription. During transcription, messenger RNA (mRNA) is produced from the DNA template. The DNA and newly formed mRNA are both shown within the nucleus.

Step 4: The mRNA leaves the nucleus and moves into the cytoplasm, where translation occurs. Translation produces proteins, represented at the bottom of the cell. The resulting activated protein alters cellular activity.

Additional labels identify:

- Capillary, located above the cell and containing hormone molecules.
- Extracellular fluid, surrounding the outside of the cell.
- Cytoplasm, the region between the plasma membrane and the nucleus.
- Nucleus, the central organelle that contains the DNA.
- DNA, located within the nucleus as the genetic material involved in transcription.
- mRNA, shown first within the nucleus after transcription and then in the cytoplasm before translation.
- Translation, located in the cytoplasm where proteins are produced.
- Activated protein, shown at the bottom right of the cell as the product of translation that changes cell function.

The figure demonstrates that lipid-soluble hormones can enter cells, bind intracellular receptors, influence gene transcription in the nucleus, and ultimately alter cellular activity through the production of proteins.

Figure 1.5.3: Mechanism of Action of Water-Soluble Hormones

This image illustrates how a water-soluble hormone affects a target cell through membrane receptors, G proteins, and intracellular signaling molecules.

The figure shows a capillary above the cell containing water-soluble hormone molecules. Below the capillary is the extracellular fluid surrounding the cell. The hormone remains outside the cell because it cannot pass through the plasma membrane. The cell contains a cytoplasm surrounding a central nucleus that contains DNA.

Step 1: A water-soluble hormone leaves the capillary, enters the extracellular fluid, and binds to a receptor located on the cell membrane. Because the hormone is membrane-insoluble, it does not enter the cell.

Step 2: Hormone binding activates a G protein located on the inner surface of the cell membrane. The activated G protein is shown adjacent to the membrane receptor within the cytoplasm.

Step 3: The activated G protein activates adenylyl cyclase, an enzyme embedded in the cell membrane.

Step 4: Adenylyl cyclase converts ATP into cyclic AMP (cAMP). The cAMP molecules are shown within the cytoplasm and act as secondary messengers that transmit the signal inside the cell.

Step 5: cAMP activates protein kinases located in the cytoplasm. An inactive protein kinase is shown being converted into an activated protein kinase.

Step 6: Activated protein kinases phosphorylate proteins in the cytoplasm. During this process, ATP is converted to ADP as phosphate groups are transferred to target proteins. The figure shows an inactive protein becoming an activated protein after phosphorylation. These activated proteins alter cellular activity and produce the cell's response to the hormone.

Additional labeled structures include:

- Capillary, located above the cell and containing water-soluble hormone molecules.
- Extracellular fluid, surrounding the outside of the cell.
- Cell membrane receptor, located on the plasma membrane where hormone binding occurs.
- G protein, located on the inner surface of the cell membrane and activated after hormone binding.
- Adenylyl cyclase, an enzyme embedded in the plasma membrane that produces cAMP.
- cAMP, located in the cytoplasm and functioning as a secondary messenger.
- Protein kinase and activated protein kinase, located in the cytoplasm where signaling is amplified.
- Cytoplasm, the area between the cell membrane and nucleus where most signaling events occur.
- Nucleus, located near the center of the cell and containing DNA.
- DNA, shown within the nucleus but not directly involved in the signaling steps illustrated.
- Inactive protein and activated protein, located in the cytoplasm and representing the final targets of the signaling pathway.

The figure demonstrates that water-soluble hormones do not enter target cells directly. Instead, they bind to membrane receptors and activate intracellular signaling pathways involving G proteins, adenylyl cyclase, cAMP, and protein kinases, ultimately changing cellular activity through protein activation.

Figure 1.5.4: Negative Feedback Loop of Glucocorticoid Secretion

This image illustrates a negative feedback loop that maintains homeostasis of glucocorticoid levels in the blood through interactions between the hypothalamus and adrenal glands.

The diagram is organized into four stages: Imbalance, Hormone Release, Correction, and Negative Feedback, which together return glucocorticoid levels to the normal range.

Step 1: Imbalance

The process begins when glucocorticoid levels in the blood become too low. A blood vessel contains only a small number of glucocorticoid molecules. The figure shows a hypothalamic glucocorticoid sensor monitoring hormone levels within the blood

vessel. The hypothalamus detects the decreased concentration of glucocorticoids and recognizes that homeostasis has been disrupted.

Step 2: Hormone Release

In response to the low glucocorticoid concentration, the hypothalamus releases corticotropin-releasing hormone (CRH). The figure shows CRH secretion from the hypothalamus into the bloodstream. The released CRH initiates a hormone cascade that stimulates the adrenal glands to produce and release glucocorticoids into the blood.

Step 3: Correction

The adrenal gland responds by releasing glucocorticoids into the bloodstream. The figure shows increased numbers of glucocorticoid molecules circulating in a blood vessel. As glucocorticoid levels rise, the hormone imbalance is corrected and blood concentrations move back toward the normal homeostatic range.

Step 4: Negative Feedback

Once glucocorticoid concentrations have returned to normal, the hypothalamus detects the restored hormone level through the same blood-borne sensing mechanism. The figure shows CRH release being stopped, indicated by a crossed-out CRH label. Reduced CRH secretion prevents further stimulation of the adrenal glands and limits additional glucocorticoid release.

Homeostasis

At the center of the diagram is a box labeled Homeostasis, representing the stable state achieved when glucocorticoid levels are maintained within the normal range. The negative feedback loop continually adjusts hormone secretion to keep blood glucocorticoid concentrations near this equilibrium.

The figure demonstrates how low blood glucocorticoid levels stimulate CRH release from the hypothalamus, which ultimately increases glucocorticoid secretion by the adrenal glands. As blood glucocorticoid concentrations rise and return to normal, they inhibit further CRH release, completing a negative feedback loop that maintains hormonal homeostasis.

Figure 1.6.1: ADH and Oxytocin Release from the Posterior Pituitary

This image shows a magnified sagittal section of the brain focusing on the hypothalamus, infundibulum, and pituitary gland, with emphasis on the posterior pituitary hormone pathway. A smaller sagittal image of the brain on the left highlights the region being enlarged. In this inset, the thalamus is located near the center of the brain, superior to the hypothalamus. The highlighted region lies beneath the thalamus and includes the hypothalamus, infundibulum, and pituitary gland. An arrow points to a detailed diagram on the right.

At the top of the enlarged diagram, within the region labeled hypothalamus, are two groups of neurosecretory cells. One group is labeled neurosecretory cells of the supraoptic nucleus and is associated with antidiuretic hormone (ADH) production. The other group is labeled neurosecretory cells of the paraventricular nucleus and is associated with oxytocin (OT) production.

Axons extend downward from these neurosecretory cells through the structure labeled infundibulum. The bundle of axons is identified as the hypothalamohypophyseal tract, which connects the hypothalamus to the posterior pituitary.

The axons terminate in the region labeled posterior pituitary, which forms part of the pituitary gland. Near the axon terminals, ADH and oxytocin are released into a nearby capillary plexus within the posterior pituitary and enter the bloodstream. The diagram shows ADH release from axons originating in the supraoptic nucleus and oxytocin release from axons originating in the paraventricular nucleus.

Adjacent to the posterior pituitary is the anterior pituitary, labeled separately to distinguish it from the posterior pituitary. The capillary plexus is shown surrounding the posterior pituitary tissue where hormone release occurs.

The figure emphasizes that ADH and oxytocin are synthesized in neurosecretory cells of the hypothalamus, transported along axons through the hypothalamohypophyseal tract, and stored and released from the posterior pituitary into the bloodstream. This

pathway differs from anterior pituitary hormone regulation because the hormones are produced by hypothalamic neurons rather than by pituitary cells.

Figure 1.6.2: Posterior Pituitary

This image shows a magnified sagittal section of the brain focusing on the hypothalamus, infundibulum, and pituitary gland, with emphasis on the posterior pituitary hormone pathway. A smaller brain image on the left highlights the region being enlarged. An arrow points to a detailed diagram on the right.

At the top of the enlarged diagram, two groups of labeled cells are shown: “neurosecretory cells of supraoptic nucleus” and “neurosecretory cells of paraventricular nucleus.” These cells are located in the region labeled “hypothalamus.” One group is associated with “ADH release,” and the other with “OT release.”

Axons extend downward from these neurosecretory cells through a structure labeled “infundibulum.” This bundle of axons is labeled “hypothalamohypophyseal tract.”

The axons terminate in the region labeled “posterior pituitary,” which is part of the “pituitary gland.” Near these endings, arrows labeled “ADH release” and “OT release” indicate that the hormones are released from axon terminals into nearby blood vessels.

Adjacent to the posterior pituitary is the “anterior pituitary,” labeled separately. A vascular network labeled “capillary plexus” is shown near the pituitary, indicating entry of hormones into circulation.

Arrows throughout the diagram indicate downward transport of hormones from hypothalamic neurons to the posterior pituitary, followed by release into blood. The diagram emphasizes that ADH and oxytocin are produced in hypothalamic neurons and transported along axons for release at the posterior pituitary.

Figure 1.6.3: Anterior Pituitary

This image shows a side view of a human head with the brain, highlighting a small region near the base of the brain. A large arrow points from this overview to a detailed anatomical diagram of the hypothalamus, infundibulum, and pituitary gland.

At the top of the detailed diagram is the hypothalamus. It contains neurosecretory cells that release regulatory hormones. Below the hypothalamus is the infundibulum, a narrow stalk that connects the hypothalamus to the pituitary gland and serves as a pathway for blood vessels and nerve fibers.

The pituitary gland is divided into two parts. The anterior pituitary is the front portion and is shown with a dense network of blood vessels. The posterior pituitary is the rear portion and is connected more directly to nerve fibers.

The diagram highlights the hypophyseal portal system, a specialized blood supply between the hypothalamus and anterior pituitary. The superior hypophyseal artery brings blood to the hypothalamus region. Hormones released by the hypothalamus enter the primary capillary plexus. These hormones then travel through the hypophyseal portal veins to the secondary capillary plexus in the anterior pituitary.

The numbered sequence shows the hormone pathway:

1. The hypothalamus releases regulatory hormones.
2. These hormones travel through the portal system and stimulate the anterior pituitary.
3. The anterior pituitary releases its own hormones into the bloodstream.

The diagram emphasizes how the hypothalamus communicates directly with the anterior pituitary through the hypophyseal portal system to regulate endocrine function.

Figure 1.6.4: Regulation of Growth Hormone Secretion and Effects of GH and IGF-1

This image is a flow chart showing how growth hormone (GH) is released, how it promotes growth and metabolism, and how

negative feedback regulates its secretion. The process is divided into three major stages: (1) Release of growth hormone, (2) Effects of growth hormone, and (3) Inhibition of growth hormone.

Step 1: Release of Growth Hormone

The process begins in the hypothalamus, which releases growth hormone-releasing hormone (GHRH). GHRH travels to the anterior pituitary and stimulates it to release growth hormone (GH) into the bloodstream.

Step 2: Effects of Growth Hormone

After being released from the anterior pituitary, GH produces three major effects.

Step 2a: Glucose-Sparing Effect

GH stimulates adipose (fat) cells to break down stored fat. Fatty acids released from adipose tissue can be used by many tissues as an energy source, reducing their dependence on glucose. This glucose-sparing effect helps preserve blood glucose for other tissues.

The figure illustrates this effect using a large adipose cell.

Step 2b: Growth Effects

GH promotes growth by increasing cellular uptake of amino acids from the blood, enhancing protein synthesis, stimulating cellular proliferation, and reducing apoptosis (programmed cell death).

The figure identifies several target tissues that respond to GH and growth-promoting signals:

- Bone cells
- Muscle cells
- Nervous system cells
- Immune system cells

The diagram also indicates that the liver releases insulin-like growth factor 1 (IGF-1), which further stimulates these growth effects. IGF-1 enhances cellular growth and protein synthesis and serves as an important mediator of many GH actions.

Step 2c: Diabetogenic Effect

GH stimulates the liver to break down glycogen into glucose. The liver releases both glucose and IGF-1 into the bloodstream. Increased glucose production raises blood glucose concentration and contributes to the diabetogenic effect of GH.

The figure represents this process with an illustration of the liver and a label indicating IGF-1 release.

Step 3: Inhibition of Growth Hormone

As IGF-1 levels rise in the blood, the hypothalamus detects the increased concentration. In response, the hypothalamus releases growth hormone-inhibiting hormone (GHIH).

GHIH acts on the anterior pituitary and inhibits further GH release. The figure shows a crossed-out GH label to indicate suppression of growth hormone secretion.

This negative feedback loop helps regulate growth hormone activity and prevents excessive GH production.

The figure demonstrates that the hypothalamus controls GH secretion through GHRH and GHIH. GH released from the anterior pituitary produces glucose-sparing effects, growth-promoting effects, and diabetogenic effects. Many of the growth-promoting actions occur through stimulation of IGF-1 production by the liver. Rising IGF-1 levels then inhibit further GH release through negative feedback, helping maintain hormonal homeostasis.

Figure 1.6.5: Summary of the Pituitary Hormones

This image presents the relationships between hypothalamic releasing hormones, pituitary hormones, their target organs, and their physiological effects.

The posterior pituitary stores and releases hormones produced by the hypothalamus. Antidiuretic hormone (ADH) acts on the kidneys, sweat glands, and circulatory system to regulate water balance. Oxytocin (OT), also produced by the hypothalamus, acts on the female reproductive system to trigger uterine contractions during childbirth.

The anterior pituitary produces hormones in response to signals from the hypothalamus. Gonadotropin-releasing hormone (GnRH) stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), both of which act on the reproductive system. LH stimulates the production of sex hormones by the gonads, while FSH stimulates the production of sperm and eggs.

Thyrotropin-releasing hormone (TRH) stimulates the release of thyroid-stimulating hormone (TSH), which acts on the thyroid gland to regulate metabolism through thyroid hormone release.

Prolactin-releasing hormone (PRH), when not inhibited by prolactin-inhibiting hormone (PIH), stimulates the release of prolactin (PRL), which promotes milk production in the mammary glands.

Growth hormone–releasing hormone (GHRH), when not inhibited by growth hormone–inhibiting hormone (GHIH), stimulates the release of growth hormone (GH). GH acts on the liver, bones, and muscles to promote the production of insulin-like growth factors (IGFs), which support growth and increase metabolic activity.

Corticotropin-releasing hormone (CRH) stimulates the release of adrenocorticotropic hormone (ACTH), which acts on the adrenal glands to promote the release of glucocorticoids involved in metabolism and the stress response.

This diagram emphasizes the pathway of hormonal communication from the hypothalamus to the pituitary gland and then to target organs, illustrating how endocrine signaling regulates multiple body systems.

Figure 1.7.1: The Thyroid Gland

This image includes three panels showing the thyroid gland from the anterior view, posterior view, and microscopic level.

1. Panel A: Anterior view - The thyroid gland is shown as a butterfly-shaped structure positioned in front of the trachea and below the thyroid cartilage. The two lobes are connected by a narrow middle region labeled the isthmus of the thyroid. The hyoid bone appears above the thyroid cartilage. The common carotid arteries run vertically on both sides of the trachea, along the outer edges of the thyroid gland. A superior thyroid artery enters the upper portion of the thyroid and branches through the gland.
2. Panel B: Posterior view - The posterior panel shows that the thyroid gland does not completely encircle the back of the trachea. The hyoid bone, thyroid cartilage, and cricoid cartilage are labeled above the gland. On the posterior side of each thyroid lobe are small parathyroid glands embedded in the tissue. The left side is labeled left parathyroid glands, and the right side is labeled right parathyroid glands. The inferior thyroid arteries approach the gland from below. One vessel is labeled left inferior thyroid artery from the left subclavian artery, and the other is labeled right inferior thyroid artery from the right subclavian artery.
3. Panel C: Microscopic view - The micrograph shows thyroid tissue composed of follicles. Each follicle contains colloid in the center. The follicle walls are formed by follicle cells labeled as cuboidal epithelium. A parafollicular cell is labeled near the edge of a follicle, positioned between surrounding cells.

The figure shows the thyroid gland's location in the neck, its relationship to nearby arteries and airway structures, the position of the parathyroid glands on the posterior thyroid surface, and the microscopic organization of thyroid follicles, colloid, follicle cells, and parafollicular cells.

Figure 1.7.2: Negative Feedback Regulation of Thyroid Hormone Secretion

This image illustrates the regulation of thyroid hormone levels through a negative feedback loop involving the hypothalamus, anterior pituitary gland, thyroid gland, and target body cells. The process is presented as a four-step flowchart.

Step 1: Metabolic Rate and/or T_3 and T_4 Concentration in Blood

The process begins when the body's metabolic rate and/or blood concentrations of the thyroid hormones triiodothyronine (T_3) and thyroxine (T_4) are monitored.

If T_3 and T_4 levels are low, the hypothalamus releases thyrotropin-releasing hormone (TRH). TRH stimulates the anterior pituitary gland to release thyroid-stimulating hormone (TSH).

If T_3 and T_4 levels are high, the hypothalamus stops releasing TRH and the anterior pituitary stops releasing TSH.

Step 2: Effects of TSH Release

TSH travels through the bloodstream to the thyroid gland and acts on the thyroid follicle cells.

The figure shows TSH stimulating the thyroid follicle cells to synthesize and release T_3 and T_4 into the bloodstream.

Step 3: Effects of T_3 and T_4 Release

Released T_3 and T_4 circulate throughout the body and act on target cells.

The figure identifies two major physiological effects:

- Increased basal metabolic rate of body cells
- Increased body temperature through the calorigenic effect, which increases heat production

A mitochondrion is shown to represent increased cellular metabolic activity.

Step 4: Negative Feedback

As blood concentrations of T_3 and T_4 rise, the elevated hormone levels exert negative feedback on both the hypothalamus and the anterior pituitary gland.

This feedback reduces or inhibits the release of:

- TRH from the hypothalamus
- TSH from the anterior pituitary gland

Reduced TRH and TSH secretion decreases stimulation of the thyroid gland and limits further production and release of T_3 and T_4.

The figure demonstrates a negative feedback system that regulates thyroid hormone production. Low T_3 and T_4 levels stimulate TRH release from the hypothalamus and TSH release from the anterior pituitary, causing the thyroid gland to secrete T_3 and T_4. These hormones increase cellular metabolism and heat production. As T_3 and T_4 concentrations rise, they inhibit further TRH and TSH release, helping maintain stable thyroid hormone levels and metabolic homeostasis.

Figure 1.7.3: Enlargement of the Thyroid Region

This image shows the lower face, neck, and upper chest of an adult. The focus of the image is the neck area. A large, rounded swelling is visible at the front of the neck, extending from just below the jawline to the upper chest. The swelling appears centered along the midline of the neck. The skin over the area looks smooth, and no wounds or discoloration are visible. The person is wearing patterned clothing and a shawl that frames the sides of the neck but does not cover the enlarged area. The background is plain and does not contain additional relevant features.

Figure 1.8.1: Location and Histology of the Parathyroid Glands

This image presents the location and microscopic structure of the parathyroid glands. The figure is divided into two labeled

panels.

Panel A: Thyroid Gland, Posterior View

The first panel shows the anatomical position of the parathyroid glands in relation to the thyroid gland and nearby structures of the neck. The thyroid gland occupies the central region of the image and wraps around the upper portion of the trachea. Four small parathyroid glands, shown as embedded structures on the posterior surface of the thyroid gland, are present as left and right pairs.

Several neighboring structures help orient the viewer:

- The hyoid bone is located superior to the thyroid gland near the top of the neck.
- The thyroid cartilage is positioned inferior to the hyoid bone and forms the prominent anterior cartilage of the larynx.
- The cricoid cartilage lies inferior to the thyroid cartilage and superior to the trachea.
- Major blood vessels run along both sides of the thyroid gland, supplying blood to the thyroid and parathyroid tissues.

This panel emphasizes that the parathyroid glands are small endocrine glands embedded within the posterior surface of the much larger thyroid gland.

Panel B: Micrograph of Parathyroid Tissue

The second panel shows a microscopic view of parathyroid tissue.

The tissue is composed primarily of densely packed parathyroid (chief) cells, which make up most of the tissue and are responsible for producing and secreting parathyroid hormone (PTH).

Scattered among the chief cells are larger oxyphil cells. These cells appear larger and more strongly stained than the surrounding chief cells. Their precise physiological role remains unclear.

A blood vessel is visible within the tissue. This vessel provides a pathway for parathyroid hormone released by the chief cells to enter the bloodstream and be transported throughout the body.

Together, the two panels show both the anatomical location of the parathyroid glands on the posterior surface of the thyroid gland and the microscopic structure of the cells responsible for producing parathyroid hormone.

Figure 1.8.2: Regulation of Blood Calcium Levels by Parathyroid Hormone and Calcitonin

This image illustrates the regulation of blood calcium levels through the opposing actions of parathyroid hormone (PTH) and calcitonin. The process is presented as a six-step flowchart.

Step 1: Blood Calcium Concentration Drops

The process begins when the concentration of calcium ions (Ca2+\text{Ca}^{2+}Ca2+) in the blood decreases below the normal range.

Step 2: Release of PTH

In response to low blood calcium levels, the chief cells of the superior and inferior parathyroid glands release parathyroid hormone (PTH) into the bloodstream.

Step 3a: Effects of PTH on Bone

PTH acts on bone tissue and produces three effects:

- Inhibits osteoblasts
- Stimulates osteoclasts
- Causes bone breakdown, releasing calcium ions into the bloodstream

The figure shows osteoclast activity increasing while calcium ions move from compact bone into the blood.

Step 3b: Effects of PTH on the Kidneys

PTH acts on kidney tubule cells and produces two effects:

- Stimulates kidney tubule cells to recover calcium that would otherwise be lost in the urine
- Stimulates kidney tubule cells to produce and release calcitriol (the active form of vitamin D)

The figure shows calcium ions being reabsorbed from the filtrate back into the blood and calcitriol being produced within kidney tubule cells.

Step 3c: Effects of Calcitriol on the Intestine

Calcitriol acts on the intestines and:

- Stimulates intestinal cells to absorb calcium from digested food

The figure shows calcium ions moving from the intestinal lumen through intestinal cells and into the intestinal connective tissue and blood supply.

Step 4: Blood Calcium Levels Increase

The combined actions of PTH on bone and kidneys, together with calcitriol's effects on the intestines, increase the concentration of calcium ions in the blood.

Step 5: Calcitonin Release

As blood calcium concentrations become elevated, parafollicular cells of the thyroid gland respond by releasing calcitonin.

Step 6: Effects of Calcitonin on Bone

Calcitonin acts on bone tissue and produces three effects:

- Stimulates osteoblasts
- Inhibits osteoclasts
- Removes calcium from the blood and incorporates it into bone

The figure shows calcium ions leaving the bloodstream and being deposited into compact bone by osteoblast activity.

The figure demonstrates two opposing hormonal pathways that maintain calcium homeostasis. When blood calcium levels fall, PTH is released from the parathyroid glands. PTH stimulates calcium release from bone, calcium reabsorption by the kidneys, and calcitriol production, which increases intestinal calcium absorption. These actions raise blood calcium levels. When blood calcium levels become elevated, the thyroid gland releases calcitonin, which promotes calcium deposition in bone and lowers blood calcium concentrations. Together, PTH and calcitonin maintain stable calcium levels through negative feedback regulation.

Figure 1.9.1: Adrenal Glands

This image shows the adrenal gland, a micrograph of adrenal tissue, and a labeled summary of tissue areas, hormones released, and examples.

1. The adrenal gland sits on the superior surface of the kidney. It has an outer cortex and an inner medulla, surrounded by a connective tissue capsule.
2. The micrograph shows the layered structure of the adrenal gland. The labeled tissue areas are:
    - zona glomerulosa, adrenal cortex
    - zona fasciculata, adrenal cortex
    - zona reticularis, adrenal cortex
    - adrenal medulla
3. The labeled hormones released and examples are:
    - zona glomerulosa: mineralocorticoids, which regulate mineral balance; example: aldosterone
    - zona fasciculata: glucocorticoids, which regulate glucose metabolism; examples: cortisol, corticosterone, cortisone
    - zona reticularis: androgens, which stimulate masculinization; example: dehydroepiandrosterone
    - adrenal medulla: stress hormones, which stimulate sympathetic ANS; examples: epinephrine and norepinephrine

The adrenal cortex is divided into three hormone-producing zones. The outermost zone, the zona glomerulosa, releases mineralocorticoids such as aldosterone, which help regulate mineral balance. Beneath it, the zona fasciculata produces glucocorticoids including cortisol, corticosterone, and cortisone. These hormones help regulate glucose metabolism.

The next layer, the zona reticularis, releases androgens, such as dehydroepiandrosterone, which contribute to masculinizing effects. At the center of the gland is the adrenal medulla. This region releases stress hormones, including epinephrine and norepinephrine, which support the sympathetic division of the autonomic nervous system.

The adrenal gland consists of an outer cortex of glandular tissue and an inner medulla of nervous tissue. The cortex itself is divided into three zones: the zona glomerulosa, the zona fasciculata, and the zona reticularis. Each region secretes its own set of hormones.

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2: THE LYMPHATIC AND IMMUNE SYSTEM

Chapter Overview

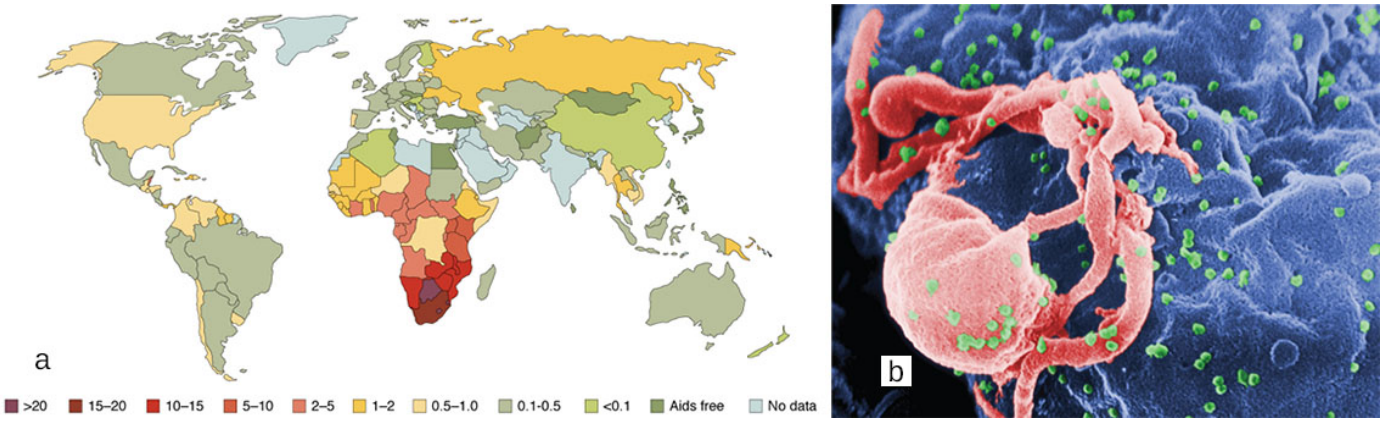


Figure 2.1: The Worldwide AIDS Epidemic (a) As of 2008, more than 15 percent of adults were infected with HIV in certain African countries. This grim picture had changed little by 2012. (b) In this scanning electron micrograph, HIV virions (green particles) are budding off the surface of a macrophage. (CC BY 4.0; C. Goldsmith via The Lymphatic and Immune System). Detailed text description of the Figure 2.1.

This chapter briefly introduces the importance of the lymphatic and immune systems in health and disease, using real-world examples (e.g., infections, vaccinations, HIV/AIDS).

The Lymphatic System: Structure and Basic Functions

Outlines lymphatic vessels, ducts, and trunks; movement of lymph; and the roles of the lymphatic system in fluid balance, lipid absorption, and immune cell transport.

Lymphoid Organs: Primary and Secondary

Defines and contrasts primary lymphoid organs (bone marrow, thymus) where lymphocytes develop and mature, with secondary lymphoid organs (lymph nodes, spleen, MALT = Mucosa Associated Lymphatic Tissue) where immune responses are initiated. Many immune system cells use the lymphatic and circulatory systems for transport throughout the body to search for and then protect against pathogens.

Innate Immunity: The First Line of Defense

Physical and chemical barriers are the body's first line of defense against infection and are part of innate immunity. Skin acts as a tough physical barrier. Its outer keratinized layer prevents most microbes from entering, and its slightly acidic pH plus antimicrobial peptides (like defensins) inhibit microbial growth on the surface. Intact skin is one of the most effective protections against infection. Mucous membranes lining the respiratory, gastrointestinal, and genitourinary tracts trap microbes in mucus. Structures like cilia in the airways move mucus (and trapped particles) out of the body. Stomach acidity provides a strong chemical barrier. Gastric acid has a very low pH (around 1–3), which destroys many ingested pathogens before they can reach the intestines. Additional chemical barriers include lysozyme in tears and saliva (which breaks down bacterial cell walls) and the slightly acidic environment of the vagina, which inhibits many pathogens.

The first line of physiological defense explains barrier defenses and innate responses, including phagocytes, natural killer cells, complement, interferons, and inflammation, emphasizing that innate immunity provides rapid, non-specific protection and generates signals (cytokines, co-stimulatory molecules, antigen presentation) that activate and shape the adaptive immune response.

Adaptive Immunity: Specific, Memory-Based, and Shaped by Innate Signals

The adaptive immune response is a slow-acting, highly specific, and long-lasting defense system that targets specific pathogens and creates lasting memory. Key characteristics include specificity (tailored to recognize specific pieces of a pathogen called antigens); memory (remembers past infections to fight future exposures faster and delay (takes days to activate fully during a first-time infection).

Understanding adaptive immunity does indeed start with two key definitions:

- Antigen: An antigen is any molecule that can be specifically recognized by the receptors of B cells or T cells and can trigger an adaptive immune response. Antigens are often proteins or large polysaccharides (for example, components of bacteria, viruses, or pollen), but can also include other molecules. A small part of the antigen that is actually recognized by an antibody or T cell receptor is called an epitope.
- Antibody: An antibody (also called an immunoglobulin, Ig) is a Y-shaped protein produced by activated B cells (plasma cells) in response to an antigen. Antibodies bind specifically to their matching antigen/epitope. Once bound, they help neutralize pathogens, mark them for destruction (opsonization), or activate other immune components such as complement.

Main players (Lymphocytes) are B Cells (mature in the bone marrow and drive humoral immunity by making antibodies. and T Cells (mature in the thymus and drive cell-mediated immunity. There are several functional types of T lymphocytes, the major ones being Helper T Cells (CD4⊕): coordinate the immune response and activate other cells. and Cytotoxic T Cells (CD8⊕): identify and destroy infected or cancerous host cells. Two Types of Responses:

- Humoral/ Antibody-mediated Response: B cells turn into plasma cells that release Y-shaped antibodies into the blood to tag and neutralize floating pathogens.
- Cell-Mediated Response: T cells directly attack infected cells or signal other cells to destroy the threat.

Immunological Memory, Pathogen Targets, and Evasion

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.

Immune Dysregulation: Immunodeficiency, Hypersensitivity, and Autoimmunity

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 their 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.

Transfusion, Transplantation, and Cancer Immunology

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.

Opportunistic Infection as a Clue to Immune Failure

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?

HIV and AIDS: A New Disease Highlighting Immune Function

Acquired immune deficiency syndrome, or AIDS, turned out to be a condition 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.

Chapter Objectives

To achieve these chapter objectives, actively engage with the material. Learning tissues is not a passive process. Your understanding will grow as you interact with the content, peers, and your instructor. Regularly check your thinking against feedback. Revisit complex concepts until you can confidently explain and apply them on your own.

By the end of this chapter, you will be able to:

- Describe the major functions of the lymphatic system: fluid recovery (returning excess interstitial fluid to the blood), immunity (filtering pathogens), and lipid absorption from the digestive tract.
- Identify and describe the structure and function of lymphatic vessels, lymph nodes, thymus, and spleen.
- Explain how tissue fluid is formed and how lymph is transported back to the cardiovascular system (via lymphatic capillaries, ducts, and valves).
- Distinguish between innate (nonspecific) and adaptive (specific) defenses, including the role of lymphocytes and antibody production.
- Describe the power of the adaptive immune response to cure disease.
- Explain immunological deficiencies and over-reactions of the immune system.
- Discuss the role of the immune response in transplantation and cancer.

2.1: Anatomy of the Lymphatic and Immune Systems

2.2: First Line of Defense- Barriers and the Innate Immune Responses

2.3: The Adaptive Immune Response - Role of T Lymphocytes

2.4: The Adaptive Immune Response - B Lymphocytes and Antibodies

2.5: Defending the Body- Immune Responses to Pathogens

2.6: Diseases Associated with Depressed or Overactive Immune Responses

2.7: Transplantation and Cancer Immunology

2.8: Terms and Definitions

2.9: Chapter Review Questions

2.10: Applied Thinking Self - Assessment

2.11: Alternate Text Descriptions

2.12: Applied Thinking Self - Assessment

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2.1: Anatomy of the Lymphatic and Immune Systems

Organization of 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.

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.

Structure of the Lymphatic System

The lymphatic vessels begin as a blind ending, or closed at one end, 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 2.1.1).

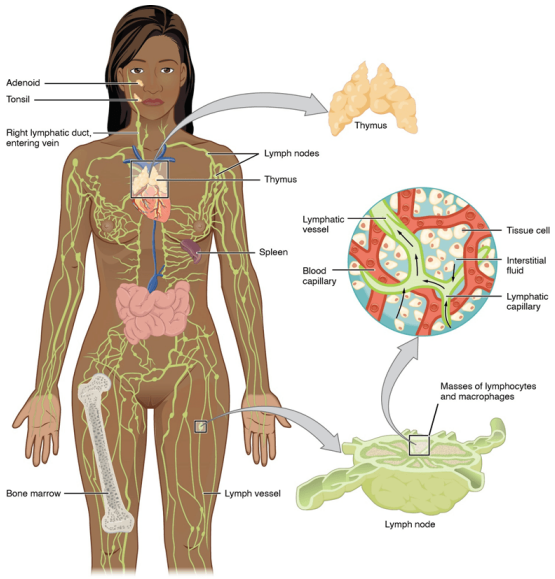


Figure 2.1.1: Lymphatic vessels in the arms and legs convey lymph to the larger lymphatic vessels in the torso. (CC BY 4.0; via Anatomy of the Lymphatic and Immune Systems). Detailed text description of the Figure 2.1.1.

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 2.1.2). Exceptions are the central nervous system, bone marrow, bones, teeth, and the cornea of the eye, which do not contain lymph vessels.

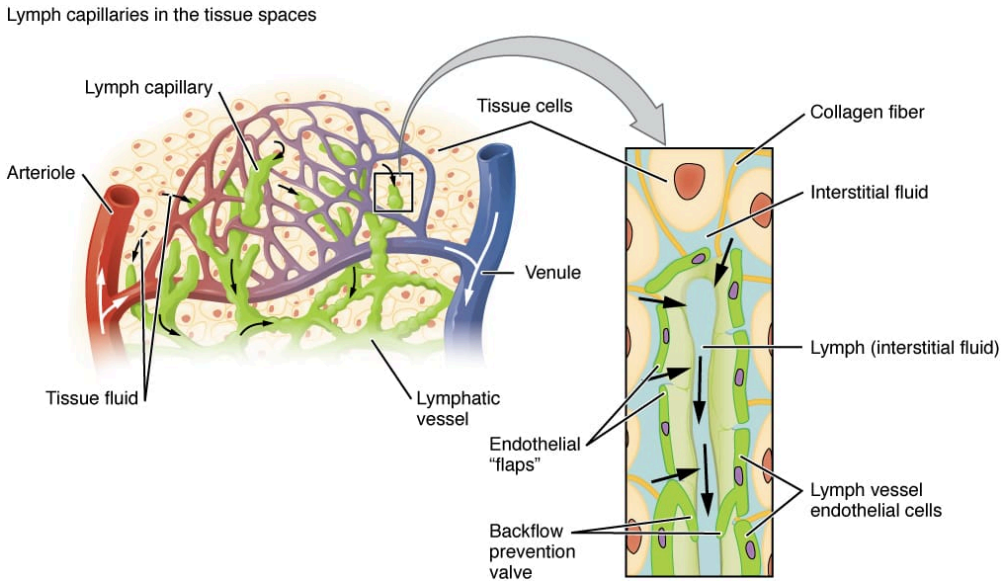


Figure 2.1.2: Lymphatic capillaries are interlaced with the arterioles and venules of the cardiovascular system. Collagen fibers anchor a lymphatic capillary in the tissue (inset). Interstitial fluid slips through spaces between the overlapping endothelial cells that compose the lymphatic capillary. (CC BY 4.0; via Anatomy of the Lymphatic and Immune Systems). Detailed text description of the Figure 2.1.2.

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 (Figure 2.1.2). 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 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 (Figure 2.1.2).

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 2.1.3). 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.

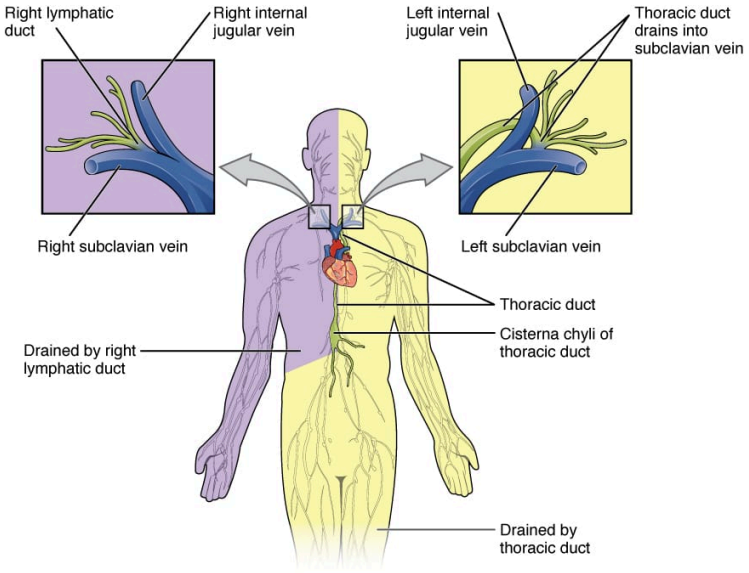


Figure 2.1.3: The thoracic duct drains a much larger portion of the body than does the right lymphatic duct. (CC BY 4.0; via Anatomy of the Lymphatic and Immune Systems). Detailed text description of the Figure 2.1.3.

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 2.1.4). 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

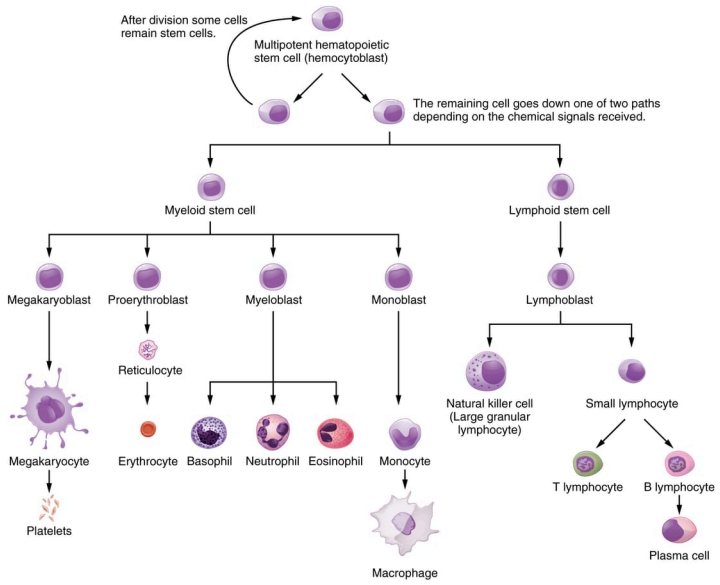


Figure 2.1.4: All the cells of the immune response as well as of the blood arise by differentiation from hematopoietic stem cells. Platelets are cell fragments involved in the clotting of blood. (CC BY 4.0; via Anatomy of the Lymphatic and Immune Systems). Detailed text description of the Figure 2.1.4.

Lymphocytes: B Cells, T Cells, Plasma Cells, and Natural Killer Cells

As stated above, lymphocytes are the primary cells of adaptive immune responses (Table 2.1.1). 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.

Table 2.1.1: 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

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 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 2.1.5). 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.

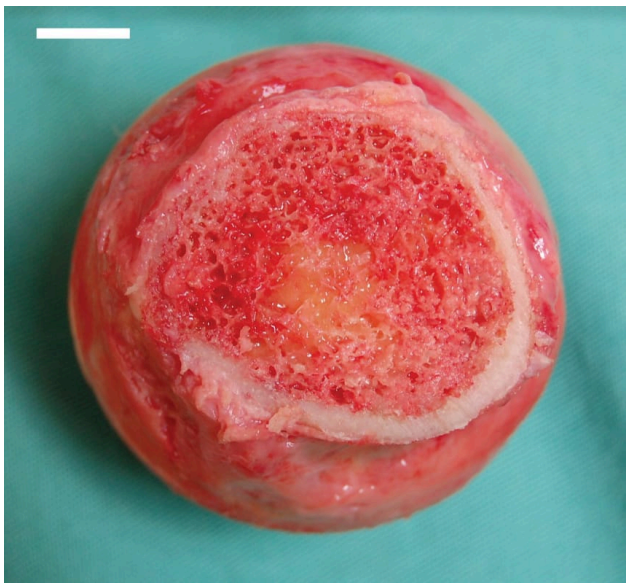


Figure 2.1.5: Red bone marrow fills the head of the femur, and a spot of yellow bone marrow is visible in the center. The white reference bar is 1 cm. (CC BY 4.0; via Anatomy of the Lymphatic and Immune Systems). Detailed text description of the Figure 2.1.5.

Thymus

The thymus gland is a bilobed organ found in the space between the sternum and the aorta of the heart (Figure 2.1.6). Connective tissue holds the lobes closely together but also separates them and forms a capsule.

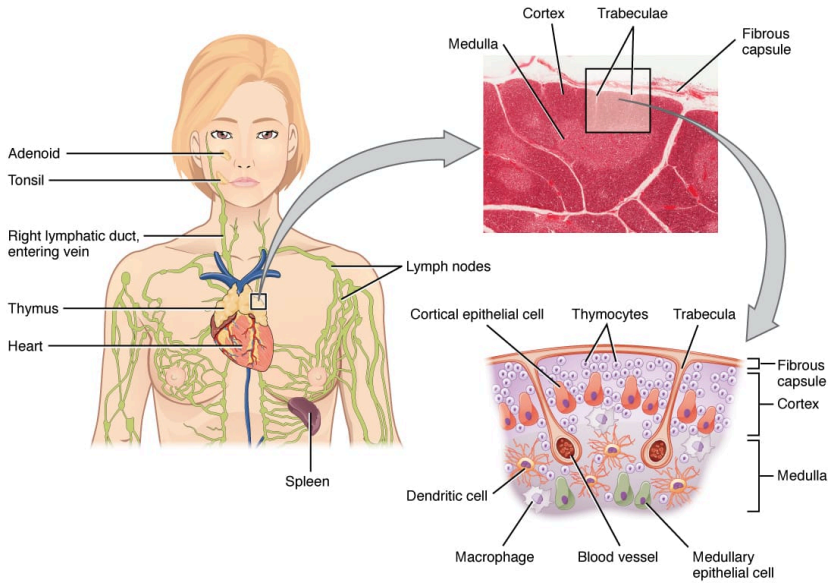


Figure 2.1.6: The thymus lies above the heart. The trabeculae and lobules, including the darkly staining cortex and the lighter staining medulla of each lobule, are clearly visible in the light micrograph of the thymus of a newborn. LM × 100. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012). (CC BY 4.0; via Anatomy of the Lymphatic and Immune Systems). Detailed text description of the Figure 2.1.6.

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. 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 people 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 and differentiating B lymphocytes
- 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 2.1.7). 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.

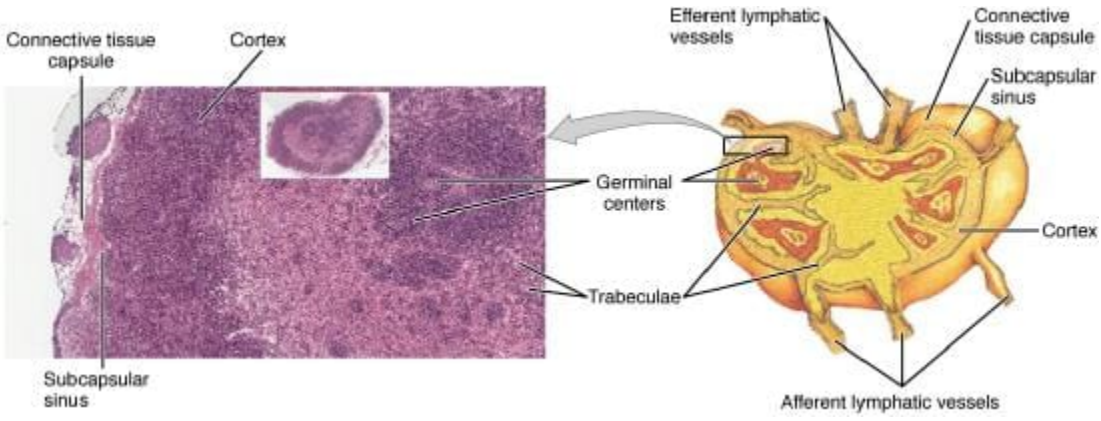


Figure 2.1.7: Lymph nodes are masses of lymphatic tissue located along the larger lymph vessels. The micrograph of the lymph nodes shows a germinal center, which consists of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. LM × 128. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012). (CC BY 4.0; via Anatomy of the Lymphatic and Immune Systems). Detailed text description of the Figure 2.1.7.

The major routes into the lymph node are via afferent lymphatic vessels (Figure 2.1.7). 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 2.1.8). 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.

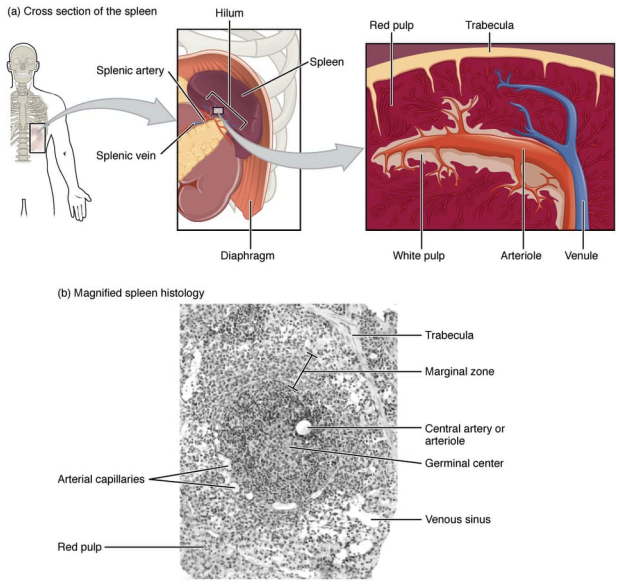


Figure 2.1.8: (a) The spleen is attached to the stomach. (b) A micrograph of spleen tissue shows the germinal center. The marginal zone is the region between the red pulp and white pulp, which sequesters particulate antigens from the circulation and presents these antigens to lymphocytes in the white pulp. EM × 660. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012). (CC BY 4.0; via Anatomy of the Lymphatic and Immune Systems). Detailed text description of the Figure 2.1.8.

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 2.1.9). 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.

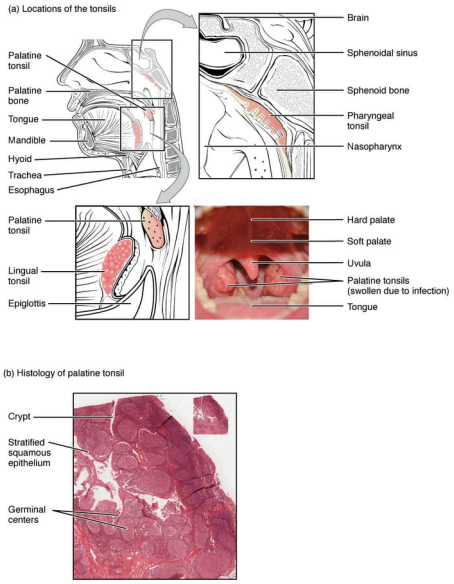


Figure 2.1.9: Locations and Histology of the Tonsils (a) The pharyngeal tonsil is located on the roof of the posterior superior wall of the nasopharynx. The palatine tonsils lay on each side of the pharynx. (b) A micrograph shows the palatine tonsil tissue. LM × 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012). (CC BY 4.0; via Anatomy of the Lymphatic and Immune Systems). Detailed text description of the Figure 2.1.9.

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 2.1.10). 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. A similar process occurs involving MALT in the mucosa and submucosa of the appendix. A blockage of the lumen triggers these cells to elicit an inflammatory response that can lead to appendicitis.

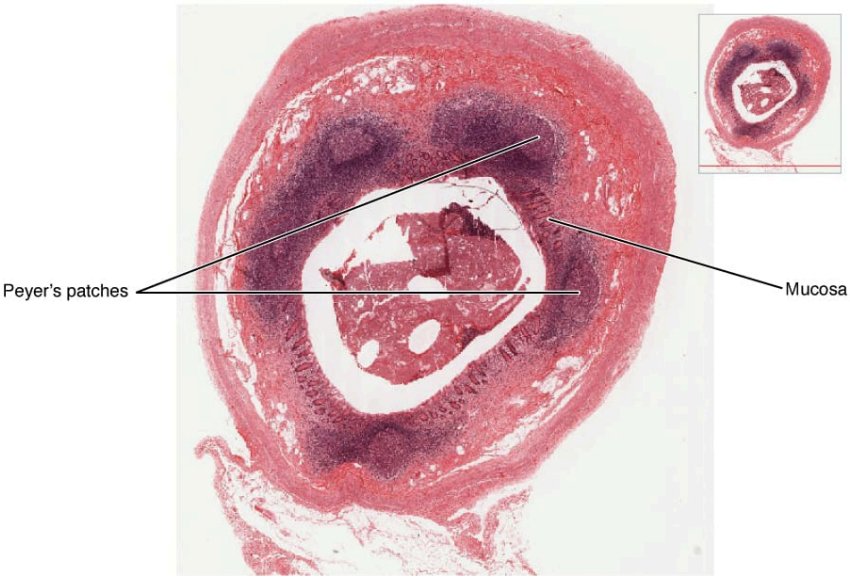


Figure 2.1.10: Mucosa-associated Lymphoid Tissue (MALT) Nodule LM × 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012). (CC BY 4.0; via Anatomy of the Lymphatic and Immune Systems). Detailed text description of the Figure 2.1.10.

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2.2: First Line of Defense- Barriers and the Innate Immune Responses

Mechanisms of Innate Immunity

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 2.2.1).

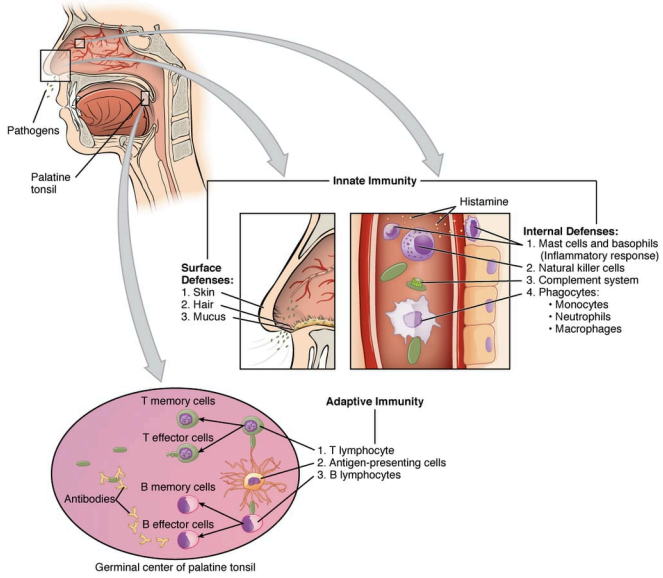


Figure 2.2.1: The innate immune system enhances adaptive immune responses so they can be more effective. (CC BY 4.0; via Barrier Defenses and the Innate Immune Response). Detailed text description of the Figure 2.2.1.

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 2.2.1). 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.

Table 2.2.1: 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

Site	Specific defense	Protective aspect
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 2.2.2). 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.

Table 2.2.2: 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.

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 2.2.2 shows the classical pathway, which requires antibodies of the adaptive immune response. The alternate pathway does not require an antibody to become activated.

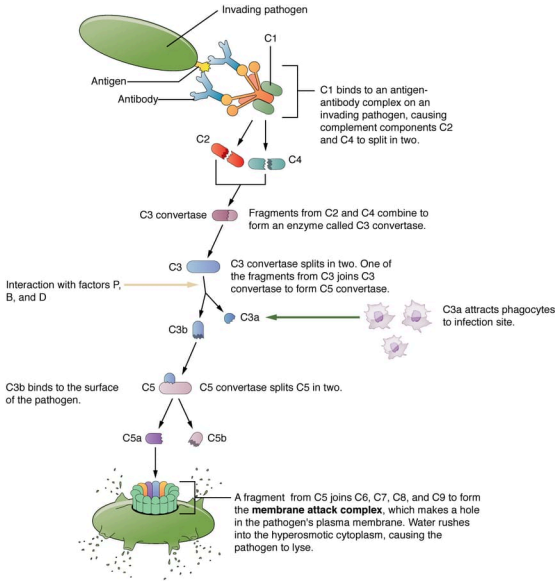


Figure 2.2.2: The classical pathway, used during adaptive immune responses, occurs when C1 reacts with antibodies that have bound an antigen. (CC BY 4.0; via Barrier Defenses and the Innate Immune Response). Detailed text description of the Figure 2.2.2.

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 2.2.3).

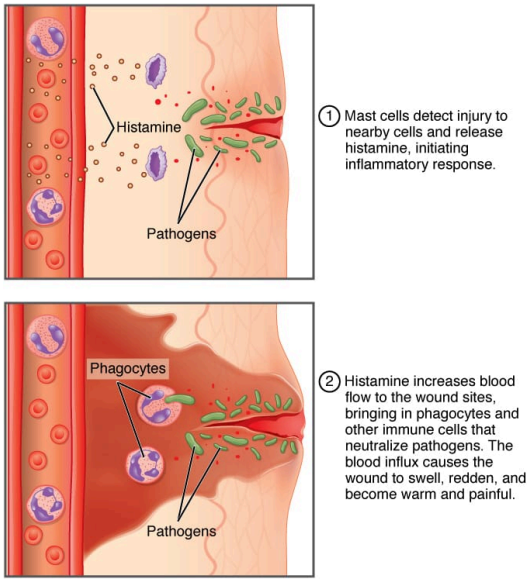


Figure 2.2.3: Events resulting in warmth, redness, pain, and swelling, as well as the recruitment of phagocytes. (CC BY 4.0; via Barrier Defenses and the Innate Immune Response). Detailed text description of the Figure 2.2.3.

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.

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2.3: The Adaptive Immune Response - Role of T Lymphocytes

Adaptive Immunity and T Cell Function

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 than 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 2.3.1).

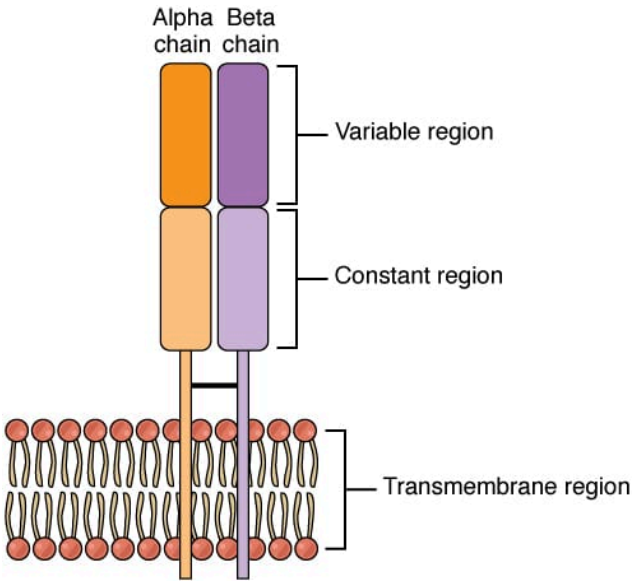


Figure 2.3.1: Notice the constant and variable regions of each chain, anchored by the transmembrane region. (CC BY 4.0 ; via The Adaptive Immune Response - T Lymphocytes and Their Functional Types). Detailed text description of the Figure 2.3.1.

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 2.3.2).

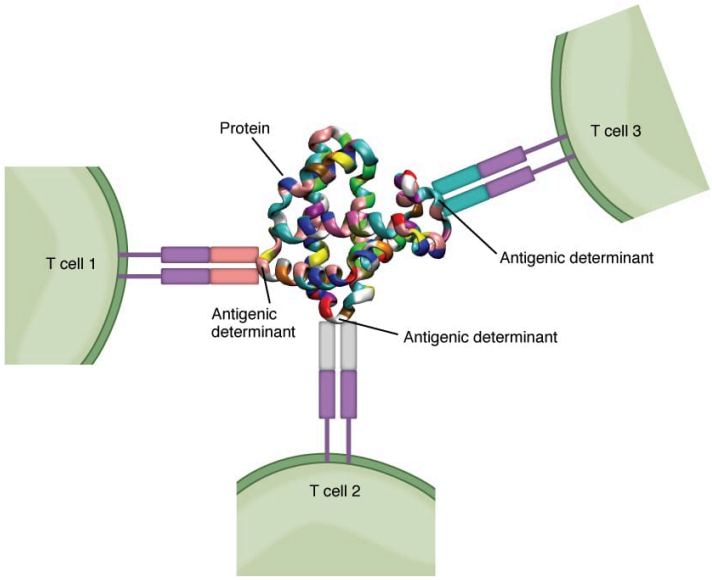


Figure 2.3.2: A typical protein antigen has multiple antigenic determinants, shown by the ability of T cells with three different specificities to bind to different parts of the same antigen. (CC BY 4.0 ; via The Adaptive Immune Response - T Lymphocytes and Their Functional Types).
Detailed text description of the Figure 2.3.2.

Antigen Processing and Presentation

Although Figure 2.3.2 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 2.3.3).

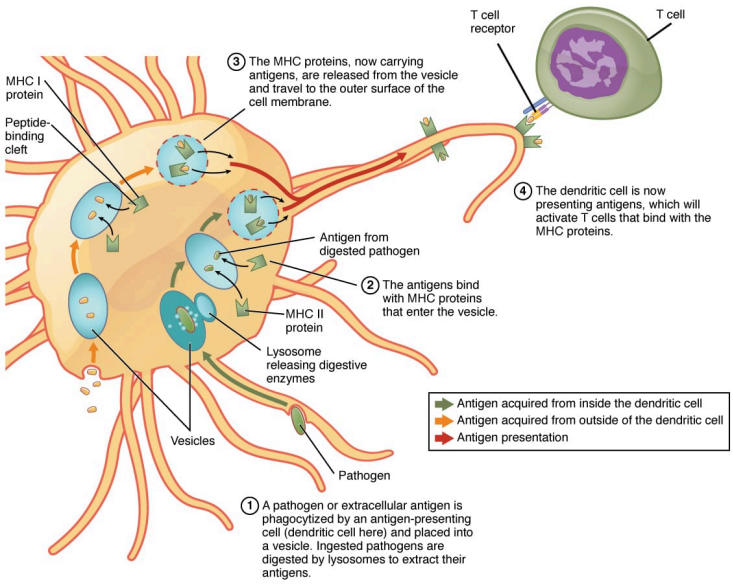


Figure 2.3.3: Antigen Processing and Presentation. (CC BY 4.0 ; via The Adaptive Immune Response - T Lymphocytes and Their Functional Types). Detailed text description of the Figure 2.3.3.

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 2.3.1).Macrophages stimulate T cells to release cytokines that enhance phagocytosis. Dendritic cells also kill pathogens by phagocytosis (Figure 2.3.3), 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.

Table 2.3.1: 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 2.3.4). 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.

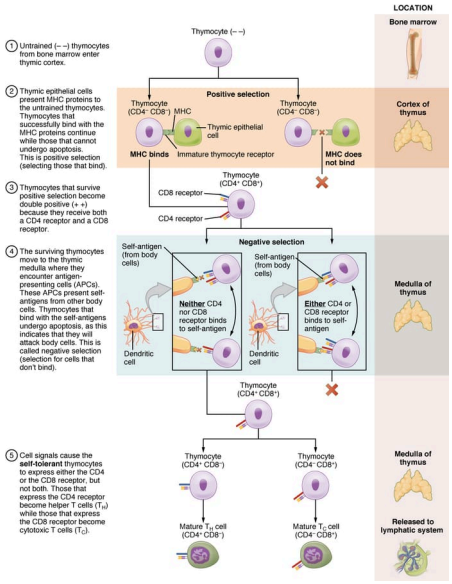


Figure 2.3.4: Immature T-cells, called thymocytes, enter the thymus and go through a series of developmental stages that ensures both function and tolerance before they leave and become functional components of the adaptive immune response. (CC BY 4.0 ; via The Adaptive Immune Response - T Lymphocytes and Their Functional Types). Detailed text description of the Figure 2.3.4.

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. 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 2.3.5). 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.

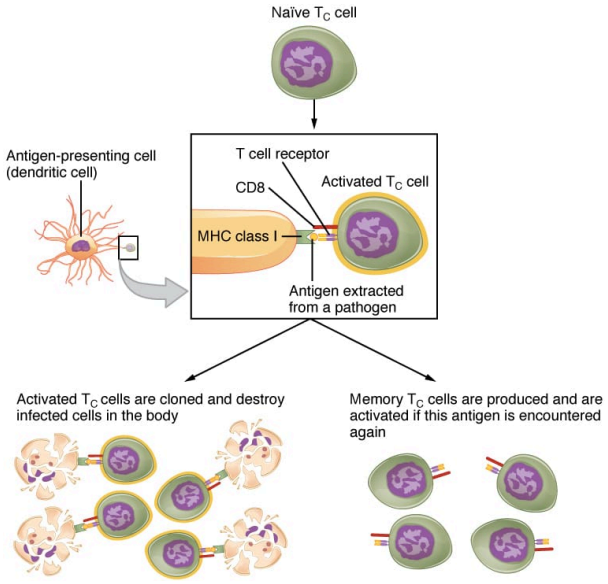


Figure 2.3.5: Stem cells differentiate into T cells with specific receptors, called clones. The clones with receptors specific for antigens on the pathogen are selected for and expanded. (CC BY 4.0; via The Adaptive Immune Response - T Lymphocytes and Their Functional Types).
Detailed text description of the Figure 2.3.5.

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.

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 2.3.6).

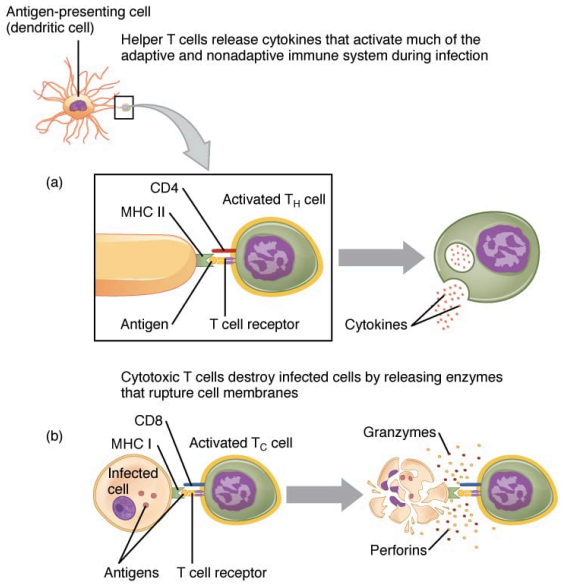


Figure 2.3.6: Pathogen Presentation. (a) CD4 is associated with helper and regulatory T cells. An extracellular pathogen is processed and presented in the binding cleft of a class II MHC molecule, and this interaction is strengthened by the CD4 molecule. (b) CD8 is associated with cytotoxic T cells. An intracellular pathogen is presented by a class I MHC molecule, and CD8 interacts with it. (CC BY 4.0 ; via The Adaptive Immune Response - T Lymphocytes and Their Functional Types). Detailed text description of the Figure 2.3.6.

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 2.3.2).

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 (Table 2.3.2).

Table 2.3.2:Functions of T Cell Types and Their Cytokines

T cell	Main target	Function	Pathogen	Surface marker	MHC	Cytokines or mediators
T_C	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

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2.4: The Adaptive Immune Response - B Lymphocytes and Antibodies

B Cells and Antibody-Mediated Immunity

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 induce their own destruction 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 2.4.1). 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.

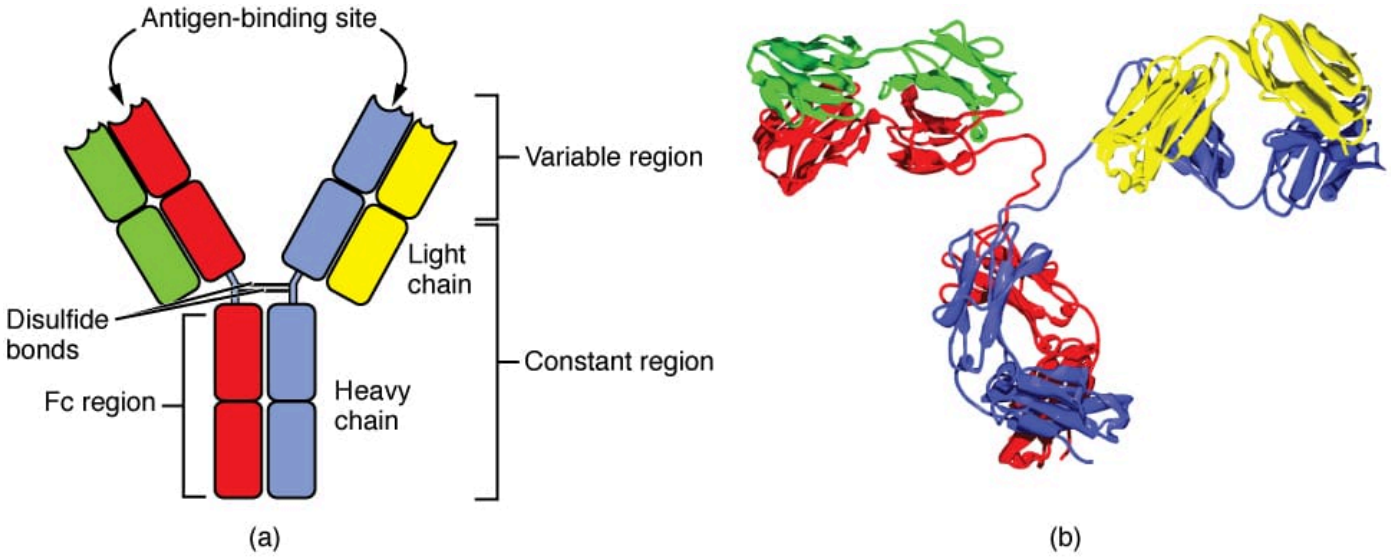


Figure 2.4.1: The typical four chain structure of a generic antibody and the corresponding three-dimensional structure of the antibody IgG2. (CC BY 4.0; via The Adaptive Immune Response). Detailed text description of the Figure 2.4.1.

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 2.4.2). 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.

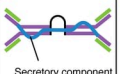
The Five Immunoglobulin (Ig) Classes					
	IgM pentamer	IgG monomer	Secretory IgA dimer	IgE monomer	IgD monomer
					
Heavy chains	μ	γ	α	ε	δ
Number of antigen binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000
Percentage of total antibody in serum	6%	80%	13%	0.002%	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 2.4.2: Comparison of the five immunoglobulin classes by structure, heavy chain type, antigen-binding sites, molecular weight, serum percentage, placental transfer, complement fixation, Fc binding, and primary immune function. (CC BY 4.0; via The Adaptive Immune Response). Detailed text description of the Figure 2.4.2.

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 their 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 2.4.3). 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.

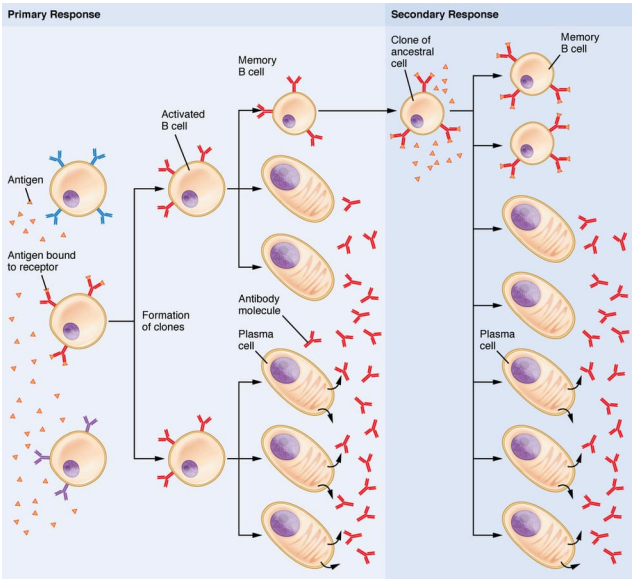


Figure 2.4.3: During a primary B cell immune response, both antibody-secreting plasma cells and memory B cells are produced. These memory cells lead to the differentiation of more plasma cells and memory B cells during secondary responses. (CC BY 4.0; via The Adaptive Immune Response). Detailed text description of the Figure 2.4.3.

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 2.4.4). 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.

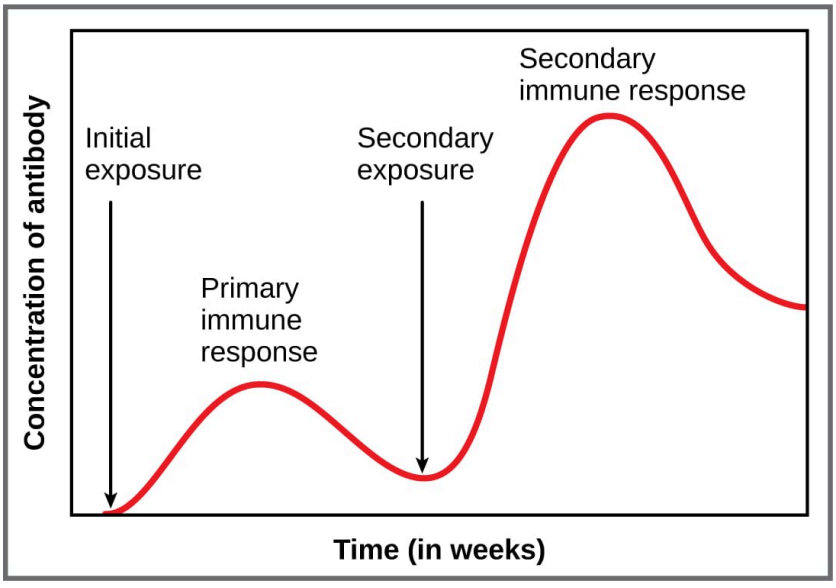


Figure 2.4.4: Antigen A is given once to generate a primary response and later to generate a secondary response. When a different antigen is given for the first time, a new primary response is made. (CC BY 4.0; via The Adaptive Immune Response). Detailed text description of the Figure 2.4.4.

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 2.4.1). 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.

Table 2.4.1: 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 based on the pathogens to which the pregnant person 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.

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 2.4.5). 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.

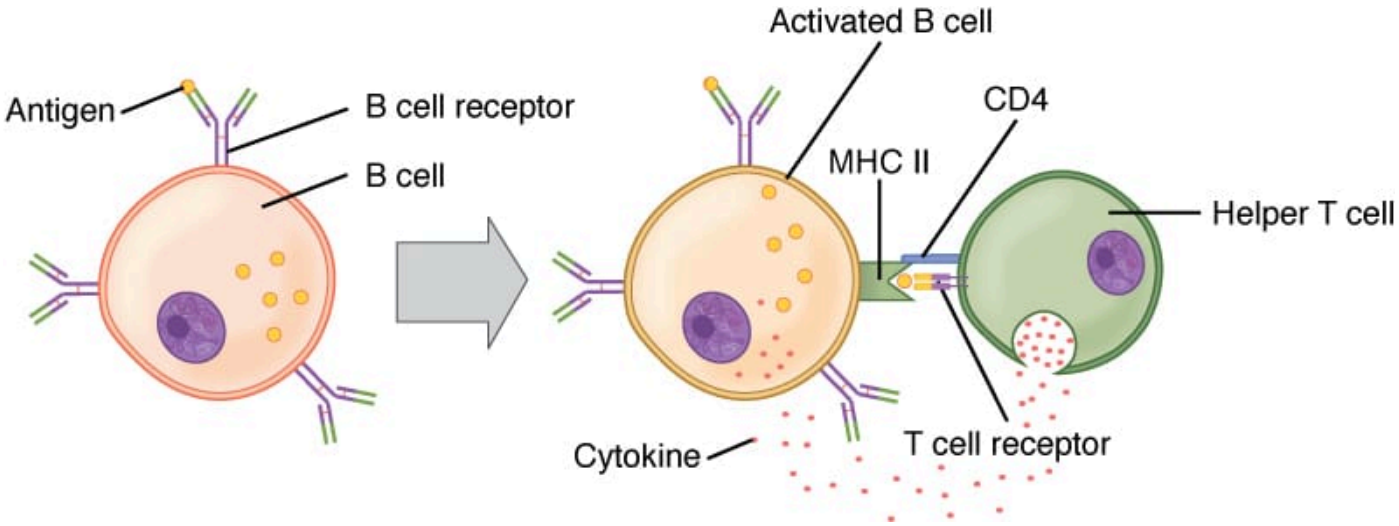


Figure 2.4.5: To elicit a response to a T cell-dependent antigen, the B and T cells must come close together. To become fully activated, the B cell must receive two signals from the native antigen and the T cell's cytokines. (CC BY 4.0; via The Adaptive Immune Response). Detailed text description of the Figure 2.4.5.

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2.5: Defending the Body- Immune Responses to Pathogens

How the Immune System Responds to Pathogens?

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 2.5.1). 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.

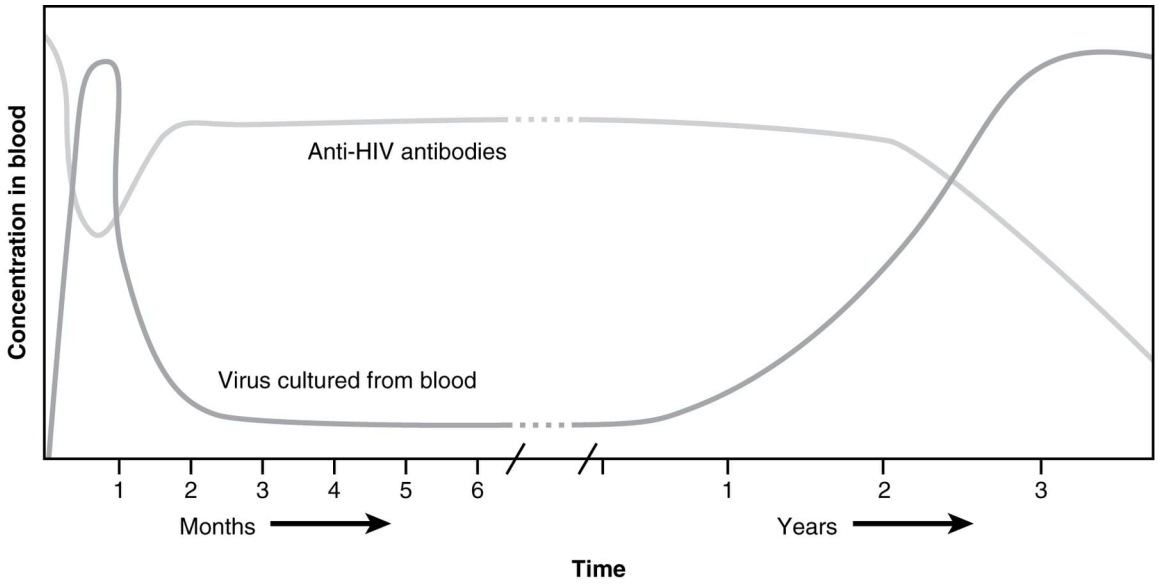


Figure 2.5.1: Graph showing how HIV virus levels and anti-HIV antibodies change over time, with an early spike in virus, a stable phase where antibodies control the virus, and a later increase in virus as antibody levels decline. (CC BY 4.0; via The Immune Response Against Pathogens). Detailed text description of the Figure 2.5.1.

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 (Figure 2.5.2) in the small intestine take up particulate antigens by specialized cells known as microfold or M cells. 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.

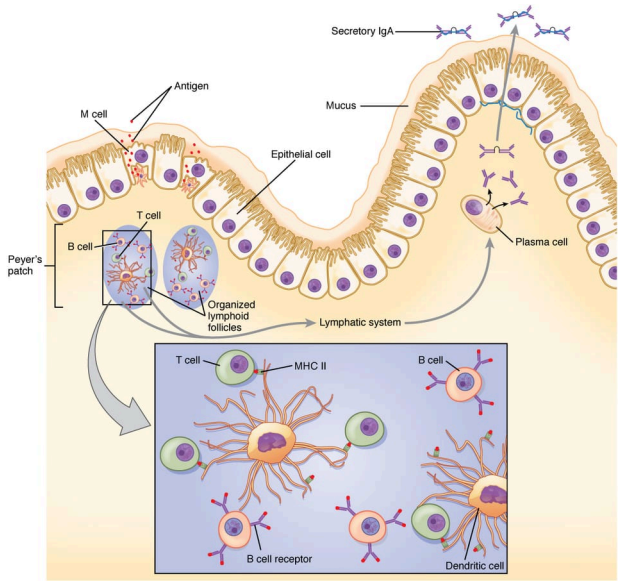


Figure 2.5.2: The nasal-associated lymphoid tissue and Peyer's patches of the small intestine generate IgA immunity. Both use M cells to transport antigen inside the body so that immune responses can be mounted. (CC BY 4.0; via The Immune Response Against Pathogens). Detailed text description of the Figure 2.5.2.

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 Mycobacterium 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.

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2.6: Diseases Associated with Depressed or Overactive Immune Responses

Immunodeficiencies

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.

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

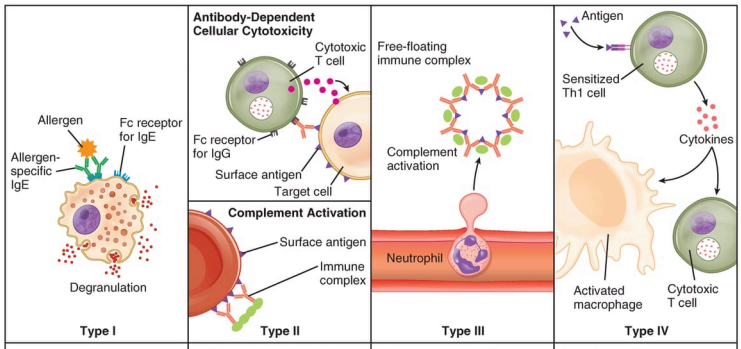
Although many viruses cause suppression of the immune system, only one wipes it out completely, and that is the previously mentioned HIV. It is worth discussing the biology of this virus, which can lead to the well-known AIDS, so that its full effects on the immune system can be understood. The virus 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. HIV uses CD4 as the receptor to get inside cells, but it also needs a co-receptor, such as CCR5 or CXCR4. These co-receptors, which usually bind to chemokines, present another target for anti-HIV drug development. Although other antigen-presenting cells are infected with HIV, given that $CD4^+$ helper T cells play an important role 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 2.6.1).



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 2.6.1: 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. (CC BY 4.0; via Diseases Associated with Depressed or Overactive Immune Responses). Detailed text description of the Figure 2.6.1.

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 2.6.2).

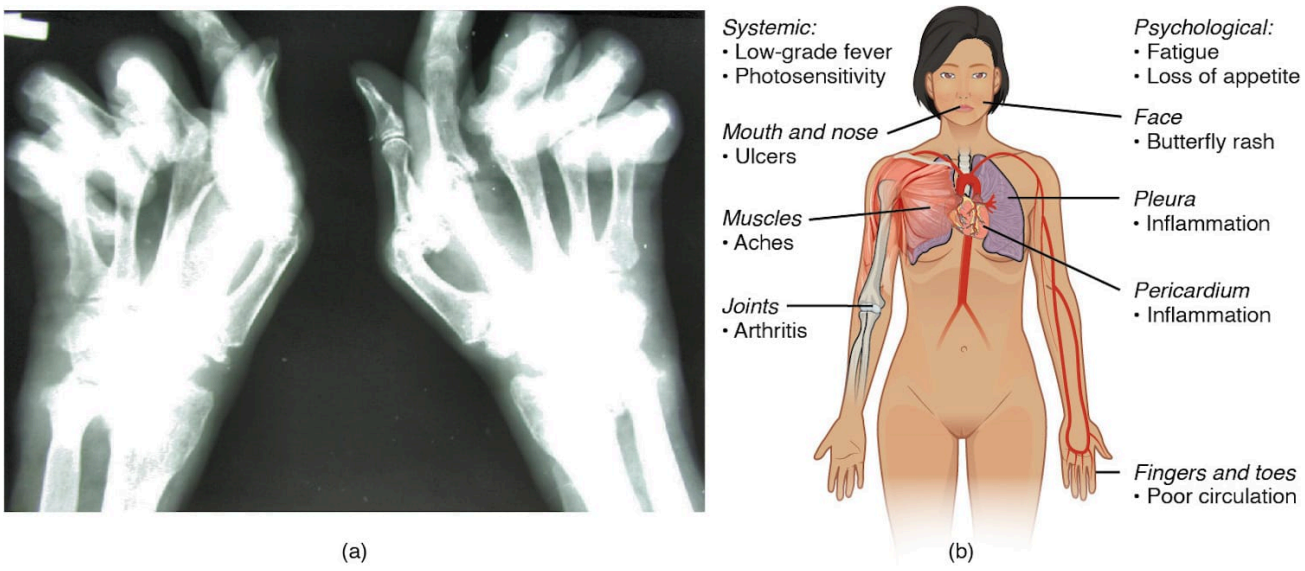


Figure 2.6.2: Rheumatoid Arthritis and Lupus. (a) Extensive damage to the right hand of a rheumatoid arthritis sufferer is shown in the x-ray. (b) The diagram shows a variety of possible symptoms of systemic lupus erythematosus. (CC BY 4.0; via Diseases Associated with Depressed or Overactive Immune Responses). Detailed text description of the Figure 2.6.2.

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 2.6.1 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.

Table 2.6.1: 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

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2.7: Transplantation and Cancer Immunology

The Rh (Rhesus) Factor

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.

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 2.7.1). This disease occurs when people negative for Rh antigen have multiple Rh-positive children. During the birth of a first Rh-positive child, the birth parent makes a primary anti-Rh antibody response to the fetal blood cells that enter the pregnant person's bloodstream. If the same parent 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 birth parent, and thus the parent is capable of mounting an immune response against it. This disease is treated with antibodies specific for Rh factor. These are given to the pregnant person during the first and subsequent births, destroying any fetal blood that might enter their system and preventing the immune response.

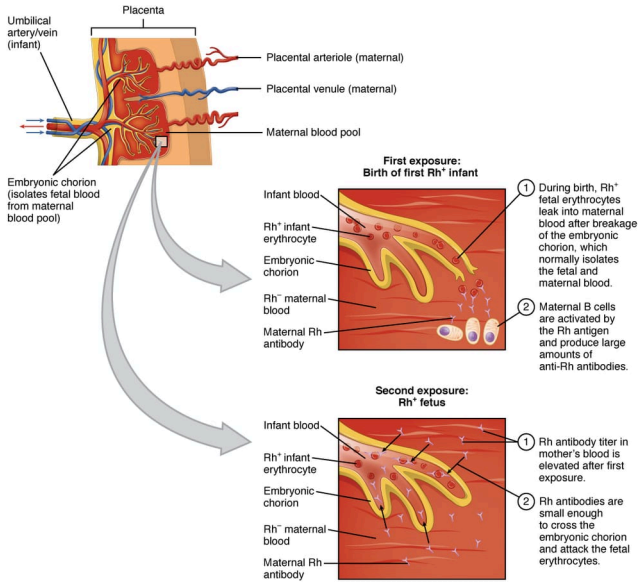


Figure 2.7.1: Rh incompatibility between mother and fetus. The diagram shows the placenta separating maternal and fetal blood, sensitization of an Rh-negative mother after exposure to Rh-positive fetal red blood cells during a first birth, and destruction of fetal red blood cells in a later Rh-positive pregnancy when maternal anti-Rh antibodies cross the placenta.Tissue Transplantation. (CC BY 4.0; via Transplantation and Cancer Immunology). Detailed text description of the Figure 2.7.1.

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 2.7.1 and Table 2.7.2). 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.

Table 2.7.1: Partial Table of Alleles of the Human MHC (Class I)

Gene	Number of alleles	Number of possible MHC I protein components
A	2132	1527
B	2798	2110
C	1672	1200
E	11	3
F	22	4
G	50	16

Table 2.7.2: Partial Table of Alleles of the Human MHC (Class II)

Gene	Number of alleles	Number 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 2.7.2). 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.

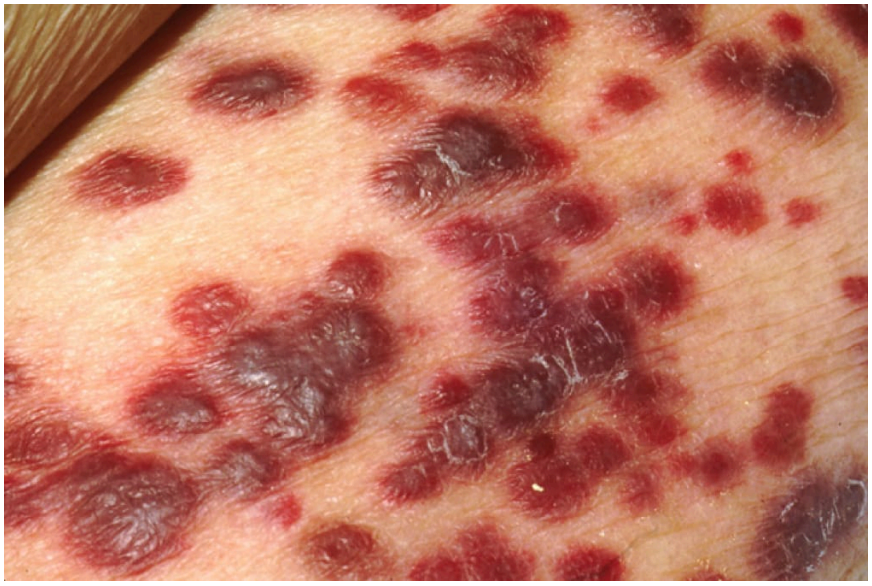


Figure 2.7.2: Close-up image of human skin showing numerous clustered lesions of varying size and shape, including raised red-purple spots and larger irregular dark patches. (CC BY 4.0; via Transplantation and Cancer Immunology). Detailed text description of the Figure 2.7.2.

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 2.7.3).

Table 2.7.3: Effects of Stress on Body Systems

System	Stress-related illness
Integumentary system	Acne, 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.

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2.8: Terms and Definitions

Key Terms

Select to View Definition

Active immunity
immunity developed from an individual's own immune system

Acute inflammation
inflammation occurring for a limited time period; rapidly developing

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

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

Antigenic determinant
(also, epitope) one of the chemical groups recognized by a single type of lymphocyte antigen receptor

B cells
lymphocytes that act by differentiating into an antibody-secreting plasma cell

Barrier defenses
antipathogen defenses deriving from a barrier that physically prevents pathogens from entering the body to establish an infection

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

Central tolerance
B cell tolerance induced in immature B cells of the bone marrow

Chemokine
soluble, long-range, cell-to-cell communication molecule

Chronic inflammation
inflammation occurring for long periods of time

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

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

Clonal expansion
growth of a clone of selected lymphocytes

Clonal selection
stimulating growth of lymphocytes that have specific receptors

Clone
group of lymphocytes sharing the same antigen receptor

Complement
enzymatic cascade of constitutive blood proteins that have antipathogen effects, including the direct killing of bacteria

Constant region domain
part of a lymphocyte antigen receptor that does not vary much between different receptor types

Cytokine
soluble, short-range, cell-to-cell communication molecule

Cytotoxic T cells (Tc)
T lymphocytes with the ability to induce apoptosis in target cells

Delayed hypersensitivity
(type IV) T cell-mediated immune response against pathogens infiltrating interstitial tissues, causing cellular infiltrate

Early induced immune response
includes antimicrobial proteins stimulated during the first several days of an infection

Effector T cells
immune cells with a direct, adverse effect on a pathogen

Efferent lymphatic vessels
lead out of a lymph node

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

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

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

Germinal centers
clusters of rapidly proliferating B cells found in secondary lymphoid tissues

Graft-versus-host disease
in bone marrow transplants; occurs when the transplanted cells mount an immune response against the recipient

Granzyme
apoptosis-inducing substance contained in granules of NK cells and cytotoxic T cells

Heavy chain
larger protein chain of an antibody

Helper T cells (Th)
T cells that secrete cytokines to enhance other immune responses, involved in activation of both B and T cell lymphocytes

High endothelial venules
vessels containing unique endothelial cells specialized to allow migration of lymphocytes from the blood to the lymph node

Histamine
vasoactive mediator in granules of mast cells and is the primary cause of allergies and anaphylactic shock

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 carrier 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

Immediate hypersensitivity
(type I) IgE-mediated mast cell degranulation caused by crosslinking of surface IgE by antigen

Immune system
series of barriers, cells, and soluble mediators that combine to response to infections of the body with pathogenic organisms

Immunoglobulin
protein antibody; occurs as one of five main classes

Immunological memory
ability of the adaptive immune response to mount a stronger and faster immune response upon re-exposure to a pathogen

Inflammation
basic innate immune response characterized by heat, redness, pain, and swelling

Innate immune response
rapid but relatively nonspecific immune response

Interferons
early induced proteins made in virally infected cells that cause nearby cells to make antiviral proteins

Light chain
small protein chain of an antibody

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

Macrophage
ameboid phagocyte found in several tissues throughout the body

Macrophage oxidative metabolism
metabolism turned on in macrophages by T cell signals that help destroy intracellular bacteria

Major histocompatibility complex (MHC)
gene cluster whose proteins present antigens to T cells

Mast cell
cell found in the skin and the lining of body cells that contains cytoplasmic granules with vasoactive mediators such as histamine

Memory T cells
long-lived immune cell reserved for future exposure to a 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

MHC polygeny
multiple MHC genes and their proteins found in body cells

MHC polymorphism
multiple alleles for each individual MHC locus

Monocyte
precursor to macrophages and dendritic cells seen in the blood

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

Neutralization
inactivation of a virus by the binding of specific antibody

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

Passive immunity
transfer of immunity to a pathogen to an individual that lacks immunity to this pathogen usually by the injection of antibodies

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

Peripheral tolerance
mature B cell made tolerant by lack of T cell help

Phagocytosis
movement of material from the outside to the inside of the cells via vesicles made from invaginations of the plasma membrane

Plasma cell
differentiated B cell that is actively secreting antibody

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

Primary lymphoid organ
site where lymphocytes mature and proliferate; red bone marrow and thymus gland

Psychoneuroimmunology
study of the connections between the immune, nervous, and endocrine systems

Regulatory T cells (Treg)
(also, suppressor T cells) class of CD4 T cells that regulates other T cell responses

Right lymphatic duct
drains lymph fluid from the upper right side of body into the right subclavian vein

Secondary adaptive response
immune response observed upon re-exposure to a pathogen, which is stronger and faster than a primary response

Secondary lymphoid organs
sites where lymphocytes mount adaptive immune responses; examples include lymph nodes and spleen

Sensitization
first exposure to an antigen

Seroconversion
clearance of pathogen in the serum and the simultaneous rise of serum antibody

Severe combined immunodeficiency disease (SCID)
genetic mutation that affects both T cell and B cell arms of the immune response

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

T cell tolerance
process during T cell differentiation where most T cells that recognize antigens from one's own body are destroyed

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

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

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

Tissue typing
typing of MHC molecules between a recipient and donor for use in a potential transplantation procedure

Tonsils
lymphoid nodules associated with the nasopharynx

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

Variable region domain
part of a lymphocyte antigen receptor that varies considerably between different receptor types

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2.9: Chapter Review Questions

Multiple-Choice Section

- Use the end-of-chapter multiple-choice section as a regular self-check tool, not just before exams.
- Read each item carefully, think about what is really being tested (concept, definition, application, or calculation), and choose the option (A, B, C, or D) that best reflects what you have learned in this chapter.
  - After you read through the chapter, attempt all items without looking at your notes; then return to the chapter to review any you missed or felt unsure about.
  - Afterward, explain to yourself why the correct option is right and why the others are not. Finally, repeat the multiple-choice section a few days later to see what you truly remember and understand.
- Students who consistently use these prompts in this way typically perform better across the course because they turn reading into active practice

1. A 68-year-old man with chronic lung disease presents with fever and shortness of breath. A sputum sample shows many large cells that have engulfed bacteria and cell debris. Which of the following cell types is performing this phagocytic function?
   A. Plasma cell
   B. Macrophage
   C. B cell
   D. Natural killer (NK) cell

2. A 52-year-old woman develops severe lymphedema of the right leg after surgery for melanoma. Which structure normally allows lymph from the lower right limb to return to the bloodstream?
   A. Thoracic duct
   B. Right lymphatic duct
   C. Right lymphatic trunk
   D. Left lymphatic trunk

3. A previously healthy adult cuts their finger while cooking. Within a few hours, the site becomes red, warm, and swollen. Which of the following cell types is most important in the early innate immune response at this site of injury?
   A. B cells
   B. T cells
   C. Macrophages
   D. Plasma cells

4. A 30-year-old nurse is exposed for the first time to a novel respiratory virus. In the first 24–48 hours before an adaptive response develops, which of the following cells would be most active in controlling the early viral infection?
   A. Macrophage
   B. T cell
   C. Neutrophil
   D. Natural killer (NK) cell

5. A 7-year-old child swallows a small amount of contaminated food. Which lymphoid structure is most likely to encounter these food antigens first?
   A. Tonsils
   B. Peyer's patches
   C. Bronchus-associated lymphoid tissue (BALT)
   D. Mucosa-associated lymphoid tissue (MALT) of the nasal cavity

6. A patient presents with a warm, painful, swollen, and red area on the lower leg after an insect bite. Which of the following findings would NOT be characteristic of acute inflammation at the site?
   A. Redness
   B. Pain
   C. Cold skin over the affected area

D. Swelling

7. A 40-year-old man is infected with an enveloped RNA virus. His innate immune system responds before antibodies are produced. Which of the following components is LEAST important in this early antiviral innate response?
   A. Interferons
   B. Natural killer (NK) cells
   C. Complement system
   D. Microphages

8. A 65-year-old woman has a bacterial infection. Certain plasma proteins bind to the surface of the bacteria and make them easier for phagocytes to recognize and ingest. What is this enhanced phagocytosis called?
   A. Endocytosis
   B. Opsonization
   C. Anaphylaxis
   D. Complement activation

9. A patient sustains a cut that becomes inflamed. Which of the following changes is primarily responsible for the redness at the inflamed site?
   A. Increased vascular permeability
   B. Anaphylactic shock
   C. Increased local blood flow
   D. Complement activation

10. A 23-year-old patient has a parasitic infection and mounts a strong antibody response. Which subset of T cells is most directly involved in secreting cytokines that help B cells produce antibodies?
    A. Th1 cells
    B. Th2 cells
    C. Regulatory T cells
    D. Thymocytes

11. A dendritic cell engulfs a bacterium, digests it into smaller fragments, and later displays those fragments on its surface with MHC molecules. The digestion step is best described as:
    A. Antigen presentation
    B. Antigen processing
    C. Endocytosis
    D. Exocytosis

12. A person is exposed to a new pathogen. After activation of a specific B cell, many identical copies of that B cell are produced. Why is this 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 antigen-specific cells

13. During T cell development in the thymus, thymocytes that strongly recognize self-antigen are eliminated. This process is called:
    A. Positive selection
    B. Negative selection
    C. Tolerance
    D. Clonal selection

14. A patient with chronic hepatitis B infection requires a strong T cell response to clear infected hepatocytes. Which type of T cell is most effective at directly killing virus-infected cells?
    A. Th1 cells
    B. Th2 cells
    C. Cytotoxic T cells
    D. Regulatory T cells

15. A self-reactive B cell survives development but receives signals that permanently inactivate it without killing it. This loss of

function is called:
A. Clonal selection
B. Clonal expansion
C. Clonal deletion
D. Clonal anergy

16. A pregnant person is found to have certain protective antibodies against measles that are also detected in the fetal circulation. Which class of antibody has crossed the placenta?
A. IgM
B. IgA
C. IgE
D. IgG

17. A researcher studies a B cell receptor on naïve B cells that is membrane-bound and has no well-defined role in secreted form. Which class of antibody fits this description?
A. IgM
B. IgA
C. IgE
D. IgD

18. A 5-year-old child with recurrent sinus and ear infections has low levels of the antibody class that predominates in secretions such as saliva, tears, and mucus. Which antibody class is primarily found in these mucosal secretions?
A. IgM
B. IgA
C. IgE
D. IgD

19. A 56-year-old patient with chronic intracellular bacterial infection (e.g., Mycobacterium) relies on macrophages to kill these organisms. Which enzymes in macrophages are most important for degrading these intracellular bacteria?
A. Metabolic enzymes in the cytosol
B. Mitochondrial enzymes
C. Nuclear enzymes
D. Lysosomal enzymes

20. A 45-year-old man has chronic cough, night sweats, weight loss, and cavitary lesions on chest X-ray. Sputum culture grows an acid-fast bacillus. Which chronic lung disease caused by a Mycobacterium best matches this presentation?
A. Asthma
B. Emphysema
C. Tuberculosis
D. Leprosy

21. A 72-year-old woman develops a serious bacterial pneumonia. Which of the following immune mechanisms is most directly effective at killing free bacteria in the bloodstream?
A. Natural killer (NK) cells
B. Complement activation
C. Cytotoxic T cells
D. Helper T cells

22. A patient asks why they receive a new influenza vaccine each year. Which of the following is the primary reason for the need for annual influenza immunization?
A. The vaccine is only protective for one year
B. Frequent viral mutation alters surface antigens
C. Macrophage oxidative metabolism declines each year
D. Memory responses are lost after one year

23. A 40-year-old man with chronic hepatitis C has liver cells infected with the virus. Which type of innate immune response works together with cytotoxic T cells to kill these virally infected cells?
A. Natural killer (NK) cell activity
B. Complement-mediated lysis

C. Antibodies alone
D. Immunologic memory alone

24. A 25-year-old woman develops serum sickness after receiving antiserum derived from animals. This reaction is mediated by immune complexes deposited in tissues. Which type of hypersensitivity involves soluble antigen–antibody complexes?
A. Type I
B. Type II
C. Type III
D. Type IV

25. A patient undergoes a tuberculin skin test (PPD). Induration appears 48–72 hours later. What causes the delay in this type of delayed (Type IV) hypersensitivity reaction?
A. Immediate inflammation at the site
B. Rapid cytokine release within minutes
C. Time required for recruitment and activation of T cells and macrophages
D. Rapid histamine release from mast cells

26. A 19-year-old student has a severe allergic reaction within minutes of eating peanuts, including hives and difficulty breathing. Which of the following is a critical feature of this immediate (Type I) hypersensitivity reaction?
A. General inflammation only
B. Cytotoxic T cell activation
C. Slow recruitment of immune cells over days
D. Rapid histamine release from mast cells and basophils

27. A 10-year-old child recently recovered from untreated streptococcal throat infection and now develops fever, joint pain, and carditis. Which of the following is an autoimmune disease that can affect the heart valves after a strep infection?
A. Rheumatoid arthritis
B. Systemic lupus erythematosus
C. Rheumatic fever
D. Hashimoto's thyroiditis

28. A 30-year-old woman with a known peanut allergy accidentally eats peanut-containing food and develops anaphylactic shock. What drug is given as first-line treatment to counteract the life-threatening effects of anaphylaxis?
A. Epinephrine
B. Antihistamines
C. Antibiotics
D. Aspirin

29. A researcher studies "natural antibodies" that are present in individuals without known prior exposure to the antigen. Why are these natural antibodies thought to be important?
A. Their function is completely unknown
B. They provide early immunity to common environmental bacteria
C. They provide "immunity" to organ transplants
D. They arise only after clonal selection by specific antigens

30. A 36-year-old man with advanced HIV infection presents with purple-red skin lesions on his legs and oral mucosa. Biopsy reveals a vascular tumor associated with human herpesvirus 8. Which type of cancer is characteristically associated with HIV disease?
A. Kaposi's sarcoma
B. Melanoma
C. Lymphoma of the kidney
D. Renal cell carcinoma

31. A 50-year-old kidney transplant recipient is started on cyclosporine A to prevent rejection. How does cyclosporine A primarily work as an immunosuppressive drug?
A. Suppresses antibody production directly
B. Suppresses activation and function of T cells
C. Suppresses macrophage phagocytic activity
D. Suppresses neutrophil production in the bone marrow

32. A patient who received an allogeneic bone marrow transplant develops a widespread rash, diarrhea, and liver dysfunction several weeks later. Donor immune cells are attacking the recipient's tissues. What is this complication called?
A. Diabetes mellitus type I
B. Melanoma
C. Severe headache
D. Graft-versus-host disease

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2.10: Applied Thinking Self - Assessment

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2.11: Alternate Text Descriptions

Figure 2.1: Global HIV/AIDS Prevalence and HIV Interaction with an Immune Cell

This image is a two-panel image. Panel (a) shows a world map of HIV/AIDS prevalence by country, and Panel (b) shows a color-enhanced microscopic image of HIV particles interacting with a human immune cell.

Panel (a): World Map of HIV/AIDS Prevalence

This panel displays a global map in which countries are color-coded according to the percentage of the population living with HIV/AIDS.

- Dark red indicates the highest prevalence, greater than 20%, concentrated primarily in southern Africa.
- Red and orange shades indicate prevalence levels between approximately 5% and 20%, also concentrated largely in sub-Saharan Africa.
- Yellow indicates prevalence levels between approximately 0.5% and 2%.
- Light green indicates prevalence levels between approximately 0.1% and 0.5%.
- Yellow-green indicates prevalence levels below 0.1%.
- Gray-green indicates countries categorized as AIDS-free. Examples include Australia, New Zealand, and Japan.
- Pale blue-gray indicates No data available. An example shown on the map is Greenland.

Overall, the map highlights that HIV/AIDS prevalence is substantially higher in parts of Africa than in most other regions of the world. Southern Africa contains the highest concentrations of countries with prevalence rates above 15% and 20%, while much of North America, Europe, Asia, South America, and Oceania have substantially lower prevalence rates.

Panel (b): Microscopic Image of HIV Virus and Immune Cell

This panel is a color-enhanced microscopic image showing HIV particles interacting with a human immune cell.

- A large blue structure represents a human immune cell, likely a T lymphocyte.
- Pink, irregular structures extend from the cell surface and represent portions of the cell membrane and membrane projections.
- Numerous small green spherical particles surrounding the cell represent HIV virions.

The image illustrates HIV particles attaching to and interacting with immune cells, an important step in viral infection. HIV targets immune system cells and uses them to reproduce, ultimately impairing the body's ability to fight infections. Together, the two panels emphasize both the global impact of HIV/AIDS and the cellular interactions that occur during HIV infection.

Figure 2.1.1: Major Components and Functions of the Lymphatic System

This image illustrates the major structures of the human lymphatic system and includes three enlarged views showing the thymus, the formation of lymph, and the internal structure of a lymph node.

Main Body: Lymphatic System Overview

The central image shows a full-body view of the lymphatic system. A network of lymphatic vessels extends throughout the body from the head to the feet. Small lymph nodes are distributed along these vessels, particularly in the neck, armpits, chest, abdomen, and groin.

Several major lymphatic organs are identified:

- The adenoids are located at the back of the nasal cavity in the upper throat.
- The tonsils are located at the back of the mouth and throat.
- The thymus is located in the upper chest, directly above the heart and behind the sternum.
- The spleen is located in the upper left side of the abdomen beneath the rib cage.
- Bone marrow is shown within a long bone of the leg, illustrating the location where many blood and immune cells are produced.
- The right lymphatic duct is shown emptying lymph into a large vein near the base of the neck, where lymph re-enters the bloodstream.

The figure emphasizes that lymphatic vessels collect fluid from tissues throughout the body and return it to the circulatory system.

Enlarged View: Thymus

An enlarged image of the thymus is shown adjacent to the body. This view highlights the thymus as a lobed organ located in the upper chest. The thymus is a primary lymphatic organ where T lymphocytes mature before entering circulation and participating in immune responses.

Enlarged View: Formation and Movement of Lymph

A circular magnified view shows the relationship between tissue cells, blood capillaries, interstitial fluid, lymphatic capillaries, and lymphatic vessels.

Blood capillaries are located among body tissues and release fluid into the spaces surrounding tissue cells. This fluid becomes interstitial fluid, which bathes and nourishes the cells. Excess interstitial fluid enters nearby lymphatic capillaries, where it is then called lymph. The lymph is collected into larger lymphatic vessels and transported through the lymphatic system before eventually returning to the bloodstream.

This view illustrates the pathway:

Blood capillaries → interstitial fluid surrounding tissue cells → lymphatic capillaries → lymphatic vessels

Enlarged View: Lymph Node

A second enlarged view shows a cross-section of a lymph node connected to lymphatic vessels.

The lymph node contains dense collections of lymphocytes and macrophages, concentrated within the interior of the node. These immune cells monitor and filter lymph as it passes through the node, helping remove pathogens, abnormal cells, and foreign material.

This view emphasizes the immune function of lymph nodes as filtration and surveillance sites within the lymphatic system.

The figure demonstrates how the lymphatic system collects excess fluid from body tissues, transports that fluid through lymphatic vessels and lymph nodes, and ultimately returns it to the bloodstream. It also highlights several major lymphatic organs, including the adenoids, tonsils, thymus, spleen, and bone marrow, which contribute to immune system function and the production, maturation, or storage of immune cells. Unlike the cardiovascular system, the lymphatic system does not have a central pump; lymph movement depends on body movement, skeletal muscle contraction, breathing, and one-way valves that prevent backflow and help direct lymph toward the veins of the neck.

Figure 2.1.2: Formation of Lymph and Entry into Lymphatic Capillaries

This image illustrates how interstitial fluid is collected by lymphatic capillaries and becomes lymph. The figure consists of a tissue-level view and an enlarged microscopic view of a lymphatic capillary wall.

Tissue-Level View

The left portion of the figure shows tissue spaces located between body cells. An arteriole supplies blood to a network of blood

capillaries within the tissue, and a venule collects blood leaving the capillary bed.

As blood passes through the capillaries, some fluid leaves the bloodstream and enters the spaces between tissue cells. This fluid is called interstitial fluid or tissue fluid. The interstitial fluid surrounds and bathes the tissue cells, providing nutrients and removing wastes.

Interspersed throughout the tissue spaces are branching lymphatic capillaries, which collect excess interstitial fluid. These capillaries merge into larger lymphatic vessels, which transport the collected fluid through the lymphatic system toward the bloodstream.

This portion of the figure demonstrates the pathway:

Blood capillaries → interstitial fluid surrounding tissue cells → lymphatic capillaries → lymphatic vessels

Enlarged View of a Lymphatic Capillary

The enlarged view shows the wall of a lymphatic capillary and the mechanism by which interstitial fluid enters the lymphatic system.

The lymphatic capillary is located among tissue cells and is surrounded by interstitial fluid. The wall of the capillary is composed of overlapping lymph vessel endothelial cells that form flexible endothelial flaps.

Collagen fibers anchor the lymphatic capillary to the surrounding tissue. These fibers help prevent collapse of the capillary and assist in opening the endothelial flaps when tissue pressure rises.

Excess interstitial fluid moves from the spaces between tissue cells through openings between the endothelial flaps and enters the lymphatic capillary. Once the fluid enters the capillary, it is called lymph.

Within the lymphatic capillary, the overlapping endothelial flaps function as one-way entry points. The structure identified as a backflow prevention valve helps prevent lymph from moving back into the surrounding tissues, ensuring that lymph continues to move in one direction through the lymphatic system.

The figure demonstrates how excess fluid that leaves blood capillaries is collected from body tissues and returned to circulation through the lymphatic system. Interstitial fluid becomes lymph after entering lymphatic capillaries through specialized endothelial openings. Collagen fibers, endothelial flaps, and one-way valves help ensure efficient fluid collection and directional movement of lymph from tissues into larger lymphatic vessels.

Figure 2.1.3: Major Trunks and Ducts of the Lymphatic System

This image illustrates how lymph from different regions of the body is collected and returned to the bloodstream through the two major lymphatic drainage pathways: the right lymphatic duct and the thoracic duct.

Main Body: Lymphatic Drainage Regions

The central figure shows a human body divided into two drainage territories.

The right lymphatic duct drains lymph from:

- The right side of the head and neck
- The right upper limb
- The right side of the thorax

The remaining regions of the body drain into the thoracic duct, including:

- The left side of the head and neck
- The left upper limb
- The left side of the thorax
- The abdomen

- The pelvis
- Both lower limbs

The thoracic duct begins in the abdomen at an enlarged sac-like structure called the cisterna chyli, which collects lymph from the lower body before the lymph travels superiorly through the thoracic duct toward the neck.

Right Lymphatic Duct

An enlarged view of the right side of the neck shows the right lymphatic duct near the junction of the right internal jugular vein and the right subclavian vein.

The right internal jugular vein descends from the head and neck, while the right subclavian vein drains blood from the right upper limb. The right lymphatic duct empties lymph into the bloodstream where these veins join, allowing lymph collected from the upper right quadrant of the body to re-enter circulation.

Thoracic Duct

A second enlarged view shows the termination of the thoracic duct on the left side of the neck.

The thoracic duct ascends through the thorax and empties lymph into the venous circulation near the junction of the left internal jugular vein and the left subclavian vein. The left internal jugular vein drains blood from the head and neck, and the left subclavian vein drains blood from the left upper limb.

Through this connection, lymph collected from most of the body is returned to the bloodstream.

The figure demonstrates that lymph collected from tissues throughout the body is ultimately returned to the venous circulation through one of two major lymphatic ducts. The right lymphatic duct drains only the upper right portion of the body, whereas the thoracic duct drains the remainder of the body. The cisterna chyli serves as a collection reservoir for lymph from the lower body before it enters the thoracic duct and is transported to the veins of the neck.

Figure 2.1.4: Hematopoietic System of the Bone Marrow

This image shows hematopoiesis, the process by which blood cells develop from a multipotent hematopoietic stem cell, also called a hemocytoblast. At the top, the multipotent hematopoietic stem cell is shown dividing. One note explains that after division, some cells remain stem cells. Another note explains that the remaining cell follows one of two developmental paths depending on the chemical signals received. These two major pathways are:

1. Myeloid stem cell pathway - The myeloid stem cell gives rise to four precursor cell types:

- Megakaryoblast
- Proerythroblast
- Myeloblast
- Monoblast

These develop as follows:

- Megakaryoblast → Megakaryocyte → Platelets
- Proerythroblast → Reticulocyte → Erythrocyte
- Myeloblast → Basophil
- Myeloblast → Neutrophil
- Myeloblast → Eosinophil
- Monoblast → Monocyte → Macrophage

2. Lymphoid stem cell pathway - The lymphoid stem cell develops into a lymphoblast. The lymphoblast gives rise to:

- Natural killer cell, also labeled large granular lymphocyte
- Small lymphocyte

The small lymphocyte then develops into:

- T lymphocyte
- B lymphocyte → Plasma cell

Figure 2.1.5: Bone Marrow

This image shows a cross-section of bone marrow.

The outer edge forms a denser, lighter-colored ring that represents compact bone. Inside this outer layer is a porous, lattice-like region that represents spongy bone. Near the center is a lighter-colored area that may represent marrow or internal bone tissue.

The image emphasizes the structural contrast between the solid outer compact bone and the more open, trabecular interior of spongy bone. A small scale bar appears in the upper left, indicating magnification or size reference.

Figure 2.1.6: Location, Structure, and Histology of the Thymus

This image shows the location and internal structure of the thymus within the lymphatic system. On the left, a body-wide lymphatic system diagram includes labeled structures such as adenoid, tonsil, right lymphatic duct entering vein, thymus, heart, spleen, and lymph nodes. A highlighted box in the upper chest marks the thymus, and a large arrow points from this region to enlarged views on the right. The upper right panel shows a tissue view of the thymus. Labels identify:

- medulla
- cortex
- trabeculae
- fibrous capsule

This panel emphasizes the outer fibrous capsule, the internal trabeculae extending inward, and the division between the cortex and medulla. A curved arrow leads from this tissue view to a lower right schematic showing a more detailed internal organization of the thymus. The lower right panel labels:

- fibrous capsule
- cortex
- medulla
- trabecula
- cortical epithelial cell
- thymocytes
- dendritic cell
- macrophage
- blood vessel
- medullary epithelial cell

This detailed view shows the thymus as a layered structure. The outer fibrous capsule surrounds the cortex. Below the cortex is the medulla. Trabeculae extend inward from the capsule. The cortex contains many thymocytes and cortical epithelial cells. The medulla contains medullary epithelial cells, dendritic cells, macrophages, and blood vessels.

Figure 2.1.7: Structure and Histology of a Lymph Node

This image shows the structure of a lymph node using two linked views: a schematic cross-section on the right and a magnified tissue image on the left.

On the right, the lymph node cross-section is labeled with the following structures:

- connective tissue capsule
- subcapsular sinus
- cortex
- trabeculae

- germinal centers
- afferent lymphatic vessels
- efferent lymphatic vessels

The connective tissue capsule forms the outer covering of the lymph node. Just beneath it is the subcapsular sinus. The cortex lies below the capsule and contains germinal centers. Trabeculae extend inward from the capsule into the node. Multiple afferent lymphatic vessels enter the lymph node, while efferent lymphatic vessels leave it. A large arrow points from the schematic view to the tissue image on the left, indicating that the left panel is a magnified view of part of the lymph node.

On the left, the tissue image labels:

- connective tissue capsule
- subcapsular sinus
- cortex

The tissue image also highlights germinal centers within the cortex. An inset image near the top provides an additional magnified view of one of these germinal centers.

Figure 2.1.8: Anatomy and Histology of the Spleen

This image illustrates the anatomical location, internal organization, and microscopic structure of the spleen. The figure consists of two panels: an anatomical cross-section of the spleen and a magnified histological view of splenic tissue.

Panel A: Cross Section of the Spleen

A body reference image shows the spleen located in the upper left region of the abdomen, beneath the diaphragm and protected by the lower rib cage. The enlarged anatomical view shows the spleen adjacent to the diaphragm.

The hilum is located on the medial surface of the spleen and serves as the entry and exit point for blood vessels. The splenic artery enters the spleen through the hilum and supplies oxygenated blood, while the splenic vein exits through the hilum and carries blood away from the organ.

An internal cross-sectional view of the spleen shows two major tissue regions:

- White pulp, which consists of dense lymphatic tissue organized around small arteries and is involved in immune surveillance and immune responses.
- Red pulp, which occupies most of the spleen and is responsible for filtering blood, removing aged or damaged red blood cells, and storing blood components.

Fibrous trabeculae extend inward from the capsule of the spleen, providing structural support and carrying blood vessels through the organ.

Within the splenic tissue, small arterioles deliver blood into the spleen, while venules collect blood that has passed through the organ.

Panel B: Magnified Spleen Histology

The lower panel provides a microscopic view of splenic tissue, illustrating the detailed organization of the white pulp and red pulp.

A central artery (arteriole) runs through the white pulp region. Surrounding the central artery is a germinal center, which contains proliferating lymphocytes involved in immune responses. Encircling the germinal center is the marginal zone, a transition area where blood-borne antigens encounter immune cells.

The surrounding red pulp occupies most of the tissue and contains networks of blood-filled spaces and immune cells. Within the red pulp are venous sinuses, which collect and transport filtered blood, and arterial capillaries, which distribute blood throughout the splenic tissue.

A trabecula is visible extending through the tissue, providing structural support and serving as a pathway for blood vessels.

The figure demonstrates the relationship between the gross anatomy and microscopic organization of the spleen. The spleen receives blood through the splenic artery, filters that blood through the white pulp and red pulp, supports immune responses through lymphocyte-rich regions of the white pulp, removes aged or damaged blood cells within the red pulp, and returns filtered blood to circulation through venous pathways and the splenic vein.

Figure 2.1.9: Locations and Histology of the Tonsils

This image shows the anatomical locations of the major tonsils and the microscopic structure of a palatine tonsil. The figure is divided into two panels.

Panel A: Locations of the Tonsils

The upper portion of the figure illustrates the locations of the pharyngeal, palatine, and lingual tonsils within the head and throat.

A sagittal section of the head and neck shows the palatine tonsil located on each side of the oropharynx, between the oral cavity and the throat. Nearby anatomical structures include:

- The palatine bone, which forms part of the roof of the mouth and separates the oral and nasal cavities.
- The tongue, located on the floor of the oral cavity anterior to the pharynx.
- The mandible, which forms the lower jaw and supports the lower teeth.
- The hyoid bone, located inferior to the tongue and superior to the larynx.
- The trachea, located anteriorly and carrying air toward the lungs.
- The esophagus, located posterior to the trachea and carrying food toward the stomach.

An enlarged view of the upper pharynx shows the pharyngeal tonsil located in the roof and posterior wall of the nasopharynx, behind the nasal cavity. Surrounding structures include:

- The brain, located superior to the nasopharynx.
- The sphenoidal sinus, located within the sphenoid bone above the nasopharynx.
- The sphenoid bone, located at the base of the skull.

A second enlarged view compares the positions of the palatine tonsil and lingual tonsil within the throat. The palatine tonsil is located along the lateral walls of the oropharynx, whereas the lingual tonsil is located at the base of the tongue. The epiglottis is positioned posterior to the tongue and superior to the larynx.

A clinical photograph shows the visible structures of the oral cavity. The hard palate forms the anterior roof of the mouth, while the soft palate forms the posterior roof. The uvula hangs from the posterior edge of the soft palate. The palatine tonsils, shown enlarged because of infection, are located on either side of the back of the throat. The tongue occupies the floor of the oral cavity.

Panel B: Histology of the Palatine Tonsil

The lower panel shows a microscopic view of palatine tonsil tissue.

The outer surface is lined by stratified squamous epithelium, which forms a protective covering exposed to the oral cavity.

Deep folds of the epithelial surface extend inward to form crypts. These crypts increase the surface area of the tonsil and help trap microorganisms and foreign material that enter through the mouth or throat.

Beneath the epithelium are numerous germinal centers, which are regions of densely packed lymphocytes. These germinal centers are sites of immune-cell proliferation and activation during immune responses.

The figure demonstrates the locations of the major tonsils that form part of the body's first line of immune defense against inhaled or ingested pathogens. The pharyngeal tonsil is located in the nasopharynx, the palatine tonsils are located on either side of the oropharynx, and the lingual tonsil is located at the base of the tongue. The histology of the palatine tonsil shows crypts and germinal centers that increase exposure to foreign material and support immune surveillance and immune responses.

Figure 2.1.10:Mucosa-associated Lymphoid Tissue

This image shows a histological cross-section of intestinal tissue labeled to highlight Peyer's patches and mucosa.

The section is circular with a central open lumen. Surrounding the lumen is the mucosa, labeled along the inner lining of the intestinal wall. Within the wall are several large, darkly stained oval regions labeled Peyer's patches. These clustered lymphatic nodules are positioned beneath the mucosal surface.

A small inset in the upper right shows a reduced overview of the same tissue section, providing orientation for the larger labeled image.

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.

Figure 2.2.1: Cooperation between Innate and Adaptive Immune Responses

This image shows how pathogens entering through the upper airway or oral region can encounter both innate immunity and adaptive immunity, with the palatine tonsil highlighted as a site of immune activity. Starting point

- Pathogens are shown entering near the upper airway or oral cavity.
- The palatine tonsil is labeled as one important lymphatic structure in this region.

Innate immunity - Arrows from the entry region point to the section labeled Innate Immunity, which is divided into surface defenses and internal defenses.

- Surface defenses structures act as physical or chemical barriers that help block or trap pathogens before they enter deeper tissues:
  1. Skin
  2. Hair
  3. Mucus
- Internal defenses - A label for histamine appears near the internal defense panel, indicating inflammatory signaling involved in innate immune responses.
  1. Mast cells and basophils, associated with the inflammatory response
  2. Natural killer cells
  3. Complement system
  4. Phagocytes:
     - Monocytes
     - Neutrophils
     - Macrophages

Adaptive immunity - Another arrow leads to the section labeled Adaptive Immunity, shown in the germinal center of the palatine tonsil. Key components listed:

1. T lymphocyte
2. Antigen-presenting cells
3. B lymphocytes

Within the germinal center, labels identify:

- T memory cells
- T effector cells
- B memory cells
- B effector cells
- antibodies

This shows that adaptive immunity includes activation and differentiation of lymphocytes, formation of memory cells, and antibody production.

Figure 2.2.2: Complement Cascade and Function

This image shows the complement cascade, beginning when complement protein C1 binds to an antigen–antibody complex on an invading pathogen and ending with formation of the membrane attack complex.

Initiation: An invading pathogen has an antigen on its surface. An antibody binds to the antigen, forming an antigen–antibody complex. Complement protein C1 binds to this complex, triggering complement components C2 and C4 to split.

Formation of C3 convertase: Fragments of C2 and C4 combine to form an enzyme called C3 convertase.

Splitting of C3: C3 convertase splits C3 into two fragments: C3a and C3b. Interaction with additional factors P, B, and D is also indicated.

- C3a attracts phagocytes to the infection site.
- C3b binds to the pathogen surface.

Formation of C5 convertase: A fragment from C3 joins C3 convertase to form C5 convertase. This enzyme splits C5 into C5a and C5b.

Formation of the membrane attack complex: C5b combines with complement proteins C6, C7, C8, and C9 to form the membrane attack complex. This complex creates a pore in the pathogen's membrane, allowing water to enter and causing the pathogen to lyse.

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.

Figure 2.2.3: Inflammatory Response

This image shows two stages of the inflammatory response after tissue injury and pathogen entry.

1. Detection and histamine release is the first stage which shows the signal that inflammation starts.
    - Mast cells detect injury in nearby tissue.
    - In response, they release histamine.
    - Pathogens are shown at the wound site.
    - Histamine initiates the inflammatory response.
2. Increased blood flow and immune cell response is the second stage which shows how inflammation recruits immune defenses to the injured tissue.
    - Histamine increases blood flow to the wound site.
    - This brings phagocytes and other immune cells into the area.
    - Phagocytes move toward the pathogens and help neutralize them.
3. Visible effects of inflammation - The increased blood flow causes the wound area to:
    - swell
    - redden
    - become warm
    - become painful

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.

Figure 2.3.1: Alpha-beta T Cell Receptor

This image shows the structure of a T-cell receptor embedded in a cell membrane.

1. Main receptor chains are made of two protein chains. These two chains are positioned side by side and together form the receptor.
    - alpha chain
    - beta chain
2. Variable region
    - The top portion of the receptor is labeled variable region.
    - This region is the part involved in recognizing specific antigens.
3. Constant region
    - Below the variable region is the constant region.
    - This portion provides structural support and remains more similar across receptors of the same type.
4. Transmembrane region
    - The lower part of the receptor passes through the cell membrane.
    - This portion is labeled transmembrane region.
    - It anchors the receptor in the membrane.
5. Membrane
    - The receptor is shown extending through a phospholipid bilayer.
    - This indicates that the T-cell receptor is attached to the cell surface.

Figure 2.3.2: Antigenic Determinants

This image shows a protein with multiple antigenic determinants interacting with three different T cells.

1. Central protein
    - A protein is shown in the center as a folded ribbon structure.
    - This protein contains multiple labeled antigenic determinants.
2. Antigenic determinants
    - Three separate antigenic determinants are labeled on different parts of the same protein.
    - These represent distinct regions of the protein that can be recognized by immune cells.
3. T cell 1
    - T cell 1 is shown on the left.
    - Its receptor is positioned to recognize one antigenic determinant on the protein.
4. T cell 2
    - T cell 2 is shown at the bottom.
    - Its receptor is positioned to recognize a different antigenic determinant on the same protein.
5. T cell 3
    - T cell 3 is shown on the right.
    - Its receptor is positioned to recognize another antigenic determinant on the protein.

Figure 2.3.3: Antigen Processing and Presentation by a Dendritic Cell

This image shows how a dendritic cell processes an external pathogen and presents antigen to a T cell using MHC proteins.

- Step 1: Pathogen uptake
    1. A pathogen or extracellular antigen is taken into the dendritic cell by phagocytosis.

2. The material is enclosed in a vesicle.
3. A lysosome releases digestive enzymes that break down the pathogen and extract antigen fragments.

- Step 2: Antigen binding to MHC proteins
  - Antigen fragments from the digested pathogen enter vesicles inside the dendritic cell.
  - MHC proteins enter these vesicles and bind the antigen fragments.
  - The diagram labels:
    - MHC I protein
    - MHC II protein
    - peptide-binding cleft
    - antigen from digested pathogen
- Step 3: Transport to the cell surface
  - The MHC proteins, now carrying antigen fragments, leave the vesicle.
  - They move to the outer surface of the dendritic cell membrane.
- Step 4: Antigen presentation
  - At the cell surface, the dendritic cell presents antigen fragments on MHC proteins.
  - A T cell receptor on a nearby T cell binds to the antigen-MHC complex.
  - This interaction activates T cells that recognize the displayed antigen.

Figure 2.3.4: T-Cell Development and Selection in the Thymus

This image illustrates the development and selection of T lymphocytes in the thymus, beginning with untrained thymocytes from the bone marrow and ending with mature helper and cytotoxic T cells that are released to the lymphatic system. The process is organized into five numbered steps and occurs as cells move from the thymic cortex to the medulla.

Step 1

Untrained (−−) thymocytes from bone marrow enter the thymic cortex.

The process begins with immature thymocytes that originate in the bone marrow. These cells enter the cortex of the thymus and are identified as CD4− CD8−, meaning they express neither the CD4 receptor nor the CD8 receptor.

Step 2

Thymic epithelial cells present MHC proteins to the untrained thymocytes. Thymocytes that successfully bind with the MHC proteins continue while those that cannot undergo apoptosis. This is positive selection (selecting those that bind).

In the cortex of the thymus, thymic epithelial cells display MHC proteins. The figure shows an MHC molecule on a thymic epithelial cell interacting with an immature thymocyte receptor.

- If the immature thymocyte receptor successfully binds the MHC protein, the thymocyte survives.
- If the MHC protein does not bind the thymocyte receptor, the thymocyte undergoes apoptosis and is eliminated.

This process is called positive selection because cells capable of recognizing self-MHC molecules are selected to survive.

Step 3

Thymocytes that survive positive selection become double positive (+ +) because they receive both a CD4 receptor and a CD8 receptor.

The surviving thymocytes now express both CD4 and CD8 receptors and are identified as CD4+ CD8+. The figure shows both receptors on the cell surface as the thymocytes move from the cortex toward the medulla of the thymus.

Step 4

The surviving thymocytes move to the thymic medulla where they encounter antigen-presenting cells (APCs). These APCs present self-antigens from other body cells. Thymocytes that bind with the self-antigens undergo apoptosis, as this indicates that they will

attack body cells. This is called negative selection (selection for cells that don't bind).

In the medulla of the thymus, dendritic cells functioning as antigen-presenting cells display self-antigens derived from body tissues.

The figure shows two possible outcomes:

- If neither the CD4 receptor nor the CD8 receptor binds the self-antigen, the thymocyte survives.
- If either the CD4 receptor or the CD8 receptor binds the self-antigen, the thymocyte undergoes apoptosis.

This process is known as negative selection because self-reactive cells are eliminated, promoting self-tolerance and helping prevent autoimmunity.

Step 5

Cell signals cause the self-tolerant thymocytes to express either the CD4 or the CD8 receptor, but not both. Those that express the CD4 receptor become helper T cells (TH) while those that express the CD8 receptor become cytotoxic T cells (TC).

The surviving self-tolerant thymocytes lose one of the two receptors and become single-positive cells:

- CD4+ CD8– thymocytes differentiate into mature helper T cells (TH).
- CD4– CD8+ thymocytes differentiate into mature cytotoxic T cells (TC).

After maturation, these cells leave the thymus and enter the lymphatic system, where they circulate and participate in adaptive immune responses.

The figure demonstrates how developing T cells are selected for two critical properties. Through positive selection in the thymic cortex, T cells must be able to recognize the body's own MHC molecules. Through negative selection in the medulla, T cells that react strongly to self-antigens are eliminated. The remaining self-tolerant T cells mature into either helper T cells or cytotoxic T cells and are released into the lymphatic system to participate in immune defense.

Figure 2.3.5: Clonal Selection and Expansion of T Lymphocytes

This image shows activation of a naïve cytotoxic T cell by an antigen-presenting cell and the two main outcomes of that activation.

1. Activation of the naïve cytotoxic T cell - shows how a cytotoxic T cell is activated by recognition of a specific antigen presented on MHC class I.
   - A naïve T_C cell is shown at the top.
   - An antigen-presenting cell, identified as a dendritic cell, displays an antigen fragment on MHC class I.
   - The naïve cytotoxic T cell binds to this antigen-MHC class I complex through its T cell receptor and CD8.
   - After binding, the cell becomes an activated T_C cell.
2. Clonal expansion and effector function - represents production of multiple effector cytotoxic T cells that respond to infected target cells.
   1. One pathway from the activated T_C cell shows that activated cytotoxic T cells are cloned.
   2. These cloned cells destroy infected cells in the body.
3. Memory cell formation - represents immunological memory and a faster response during future exposure to the same antigen.
   - A second pathway shows that memory T_C cells are produced.
   - These memory cells are activated if the same antigen is encountered again.

Figure 2.3.6: Pathogen Presentation

This image compares helper T-cell activation and cytotoxic T-cell activation and shows the different responses each cell type produces.

1. Helper T-cell pathway - The cytokines activate much of the adaptive and nonadaptive immune system during infection.
   - An antigen-presenting cell, identified as a dendritic cell, displays an antigen on MHC II.

    - An activated T helper cell (T_H cell) binds to this antigen-MHC II complex through its T cell receptor and CD4.
    - After activation, the helper T cell releases cytokines.
2. Cytotoxic T-cell pathway - These enzymes and proteins damage the infected cell membrane and contribute to destruction of the infected cell.
    1. An infected cell displays antigens on MHC I.
    2. An activated cytotoxic T cell (T_C cell) binds to this antigen-MHC I complex through its T cell receptor and CD8.
    3. After activation, the cytotoxic T cell releases granzymes and perforins.

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.

Figure 2.4.1: Antibody and IgG2 Structures

This image is a two-panel antibody image showing a labeled structure diagram and a 3D antibody model.

Panel (a) - This panel shows a simplified diagram of an antibody shaped like the letter Y. Labeled antibody structure diagram:

- The top arms of the Y are labeled antigen-binding sites, where the antibody attaches to foreign substances.
- These upper portions are called the variable regions, which can differ in shape to bind to different antigens.
- The lower stem is labeled the constant region, which has a more stable structure.
- The antibody is made of two types of protein chains:
    - Heavy chains, which form the inner and longer parts of the structure
    - Light chains, which are shorter and attached to the outer sides
- The chains are connected by disulfide bonds, shown as links between segments.
- The lower stem is also labeled the Fc region, which helps activate immune system responses.

Panel (b) - This panel shows a three-dimensional ribbon model of an antibody protein. 3D antibody structure model:

- The structure keeps the same general Y shape shown in the diagram.
- Different colors distinguish sections of the protein chains.
- The folded ribbon form shows how the protein is arranged in three-dimensional space.
- The two upper arms correspond to the antigen-binding regions.
- The lower portion corresponds to the constant region.

Figure 2.4.2: The Five Immunoglobulin (Ig) Classes

This image compares the five major classes of immunoglobulins (antibodies): IgM, IgG, Secretory IgA, IgE, and IgD. The figure presents both the molecular structure of each antibody class and a comparison of their major characteristics and functions.

At the top of the figure, each antibody class is represented by a simplified structural diagram.

- IgM is shown as a pentamer, consisting of five antibody units joined together in a circular arrangement.
- IgG is shown as a monomer, consisting of a single Y-shaped antibody unit.
- Secretory IgA is shown as a dimer, consisting of two joined antibody units connected by a secretory component.
- IgE is shown as a monomer, consisting of a single Y-shaped antibody unit.
- IgD is shown as a monomer, consisting of a single Y-shaped antibody unit.

The figure compares the five antibody classes using the following characteristics.

IgM (Pentamer)

- Heavy chain: μ (mu)
- Number of antigen-binding sites: 10
- Molecular weight: 900,000 daltons
- Percentage of total antibody in serum: 6%
- Crosses placenta: No

- Fixes complement: Yes
- Fc region binds to: None Shown
- Function:
  - Main antibody of the primary immune response
  - Most effective antibody for complement activation
  - Monomer form of IgM functions as a B-cell receptor

IgG (Monomer)

- Heavy chain: γ (gamma)
- Number of antigen-binding sites: 2
- Molecular weight: 150,000 daltons
- Percentage of total antibody in serum: 80%
- Crosses placenta: Yes
- Fixes complement: Yes
- Fc region binds to: Phagocytes
- Function:
  - Main antibody of secondary immune responses
  - Neutralizes toxins
  - Promotes phagocytosis through opsonization

Secretory IgA (Dimer)

- Heavy chain: α (alpha)
- Number of antigen-binding sites: 4
- Molecular weight: 385,000 daltons
- Percentage of total antibody in serum: 13%
- Crosses placenta: No
- Fixes complement: No
- Fc region binds to: None Shown
- Function:
  - Secreted into mucus, tears, saliva, and colostrum
  - Provides protection at mucosal surfaces and in body secretions

IgE (Monomer)

- Heavy chain: ε (epsilon)
- Number of antigen-binding sites: 2
- Molecular weight: 200,000 daltons
- Percentage of total antibody in serum: 0.002%
- Crosses placenta: No
- Fixes complement: No
- Fc region binds to: Mast cells and basophils
- Function:
  - Antibody involved in allergic reactions
  - Participates in defense against parasitic infections

IgD (Monomer)

- Heavy chain: δ (delta)
- Number of antigen-binding sites: 2
- Molecular weight: 180,000 daltons
- Percentage of total antibody in serum: 1%
- Crosses placenta: No
- Fixes complement: No
- Fc region binds to: None Shown

- Function:
  - Functions as a B-cell receptor

The figure demonstrates that the five immunoglobulin classes differ in structure, abundance, and function. IgG is the most abundant antibody in serum and is the only class shown crossing the placenta. IgM has the greatest number of antigen-binding sites and is the strongest activator of complement. Secretory IgA is specialized for protection of mucosal surfaces and body secretions. IgE is associated with allergic responses and antiparasitic immunity, while IgD primarily functions as a receptor on B lymphocytes.

Figure 2.4.3: Clonal Selection of B Cells

This image compares the primary immune response (first exposure to an antigen) and the secondary immune response (later exposure to the same antigen).

Left Side - Primary Response (First Exposure):

- Small particles labeled antigens enter the body.
- A B cell recognizes and binds to the antigen using receptors on its surface.
- The B cell becomes an activated B cell.
- The activated B cell undergoes clonal expansion, meaning it makes many identical copies of itself.

These copies develop into two types of cells:

1. Plasma cells
   - These cells produce and release antibodies (shown as small Y-shaped molecules).
   - Antibody production is relatively slow during the first exposure.
2. Memory B cells
   - These cells remain in the body long after the infection.
   - They “remember” the specific antigen for future responses.

Right Side - Secondary Response (Second Exposure):

- When the same antigen enters the body again, memory B cells quickly recognize it.
- Memory B cells rapidly form a clone of cells, much faster than during the primary response.

These cells again differentiate into:

1. Plasma cells
   - They produce large amounts of antibodies very quickly.
2. Memory B cells
   - They are replenished to maintain long-term immunity.

Figure 2.4.4: Primary and Secondary Antibody Responses

This image is a graph comparing the primary immune response and the secondary immune response.

Axes (What the graph shows):

- The horizontal axis (x-axis) represents time in weeks.
- The vertical axis (y-axis) represents the concentration of antibodies in the blood.
- A red curve shows how antibody levels change over time.

Primary Response (First Exposure):

- The graph begins with an initial exposure to an antigen (a foreign substance).
- There is a delay (lag phase) before antibodies start to appear.
- Antibody levels then increase slowly, forming a small peak.
- After reaching this peak, antibody levels gradually decrease.

This response is slow and relatively weak because the immune system is encountering the antigen for the first time and must learn how to respond.

Secondary Response (Second Exposure):

- Later on the graph, there is a second exposure to the same antigen.
- This time, antibody levels rise much more quickly, with little or no delay.
- The graph shows a much higher peak, meaning many more antibodies are produced.
- The response is also longer-lasting compared to the primary response.

This happens because memory cells for med during the first exposure allow the immune system to respond faster and more effectively

Figure 2.4.5: T and B Cell Binding

This image shows the activation of a B cell, including how it recognizes an antigen and receives help from a helper T cell.

Step 1: Antigen Recognition by B Cell

- On the left, a B cell is shown with B cell receptors on its surface.
- Small particles labeled antigens bind to these receptors.
- This step represents the B cell recognizing a foreign substance.

Step 2: Antigen Processing and Presentation

- After binding the antigen, the B cell processes it internally.
- The B cell then displays a piece of the antigen on its surface using a molecule called MHC class II (MHC II).

Step 3: Interaction with Helper T Cell

- On the right, a helper T cell is shown interacting with the B cell.
- The helper T cell uses its T cell receptor to recognize the antigen presented on MHC II.
- The helper T cell also uses a surface molecule called CD4 to stabilize this interaction.

Step 4: Activation Through Cytokines

- The helper T cell releases cytokines (chemical signaling molecules).
- These cytokines send signals that activate the B cell.

Step 5: Activated B Cell

- The B cell is now labeled as an activated B cell.
- Once activated, the B cell can divide and later develop into:
  - Plasma cells, which produce antibodies
  - Memory B cells, which help respond faster in future infections

Figure 2.5.1: HIV Disease Progression Seroconversion

This image is a graph showing how HIV virus concentration and anti-HIV antibody levels change over time in the blood.

1. Axes
   - The horizontal axis (x-axis) represents time, starting with months and continuing into years.
   - The vertical axis (y-axis) represents the concentration in blood, meaning how much virus or antibody is present.
2. Two lines are shown:
   - One represents HIV virus levels
   - The other represents anti-HIV antibodies
3. Early Stage (Initial Infection)
   - Soon after infection, the virus level rises very quickly to a high peak.

    - At this point, antibody levels are low because the immune system is just starting to respond.
    - As time progresses, antibody levels increase, which causes the virus level to drop sharply.
4. Middle Stage (Chronic Phase)
    - During the following months and years, the virus remains at a low but steady level.
    - Antibody levels remain relatively high and stable.
    - This stage represents a long period where the infection is present but partially controlled by the immune system.
5. Late Stage (Disease Progression)
    - After several years, the graph shows the virus level rising again.
    - At the same time, antibody levels begin to decline.
    - This indicates that the immune system is weakening and is less able to control the infection.

Figure 2.5.2: IgA Immunity

This image shows how the immune system in the intestine responds to antigens and produces secretory IgA antibodies for protection.

Top Section: Intestinal Surface

- The upper part shows a lining of epithelial cells forming the intestinal wall.
- A layer of mucus covers these cells.
- Specialized cells called M cells take in antigens (small foreign particles) from the intestinal lumen and transport them across the epithelial layer.

Left Side: Peyer's Patch (Immune Activation Area)

- Beneath the epithelial layer is a region labeled Peyer's patch, which contains organized lymphoid follicles.
- Inside this region are:
    - B cells
    - T cells
    - Dendritic cells, which present antigens to T cells using MHC class II molecules
- B cells use their B cell receptors to recognize antigens.
- With help from T cells, B cells become activated.

Middle Section: Lymphatic System

- Activated immune cells move through the lymphatic system, shown as arrows leading away from the Peyer's patch.
- This step represents the circulation and distribution of immune cells.

Right Side: Antibody Production

- Activated B cells differentiate into plasma cells.
- Plasma cells produce IgA antibodies.
- These antibodies are transported back toward the epithelial surface.

Top Right: Secretion into Mucus

- Secretory IgA antibodies are released into the mucus layer.
- These antibodies bind to antigens and help prevent pathogens from attaching to or invading epithelial cells.

Figure 2.6.1: Immune Hypersensitivity

The figure compares the four major types of hypersensitivity reactions: Type I (IgE-mediated hypersensitivity), Type II (IgG-mediated cytotoxic hypersensitivity), Type III (immune complex-mediated hypersensitivity), and Type IV (cell-mediated hypersensitivity). Each column illustrates the immune mechanism responsible for tissue damage and provides representative disorders or conditions associated with that reaction type.

Type I: IgE-Mediated Hypersensitivity

An allergen binds to allergen-specific IgE antibodies attached to the surface of a mast cell through Fc receptors. Crosslinking of the IgE antibodies triggers mast-cell degranulation, resulting in the release of inflammatory mediators.

The figure states: IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.

Examples shown include localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as shellfish and peanut allergies, hives, and eczema.

Type II: IgG-Mediated Cytotoxic Hypersensitivity

IgG antibodies bind to antigens located on the surface of a target cell. The figure shows two mechanisms by which the target cell can be damaged.

Antibody-dependent cellular cytotoxicity (ADCC): A cytotoxic cell bearing Fc receptors recognizes antibody-coated target cells and destroys them.

Complement activation: Binding of antibodies to surface antigens activates the complement system, resulting in cell damage.

The figure states: 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).

Example shown: Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis.

Type III: Immune Complex-Mediated Hypersensitivity

Circulating antigen-antibody complexes, shown as free-floating immune complexes, become deposited in tissues. These deposits activate the complement system and attract neutrophils, resulting in inflammation and tissue injury.

The figure states: Antigen-antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site.

Examples shown include glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.

Type IV: Cell-Mediated Hypersensitivity

Unlike the other hypersensitivity types, Type IV reactions do not involve antibodies. A sensitized Th1 cell recognizes antigen and releases cytokines. These cytokines activate macrophages and cytotoxic T cells, leading to inflammation and tissue damage. An activated macrophage is depicted as a major effector cell in the reaction.

The figure states: Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site.

Examples shown include contact dermatitis, tuberculin reaction, and autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis.

The figure compares four distinct mechanisms of hypersensitivity. Type I reactions involve IgE-mediated mast-cell degranulation. Type II reactions involve IgG antibodies that destroy antibody-coated cells through complement activation or ADCC. Type III reactions involve deposition of antigen-antibody complexes in tissues, causing complement activation and neutrophil recruitment. Type IV reactions are mediated by Th1 cells, macrophages, and cytotoxic T cells through cytokine signaling without antibody involvement. Together, the four pathways illustrate the major mechanisms by which immune responses can cause allergic, autoimmune, and inflammatory tissue damage.

Figure 2.6.2: Autoimmune Disorders

This two-panel figure compares characteristic physical effects of autoimmune disorders. Panel (a) focuses on severe joint damage associated with rheumatoid arthritis, while Panel (b) illustrates multiple body systems that may be affected by systemic lupus erythematosus (SLE).

Panel (a): Hand X-Ray Showing Rheumatoid Arthritis

The left panel is an X-ray image of both hands. The bones of the wrists, palms, and fingers are visible. The joints of multiple fingers show significant deformity, including joint narrowing, displacement, and abnormal angulation of the fingers. Several fingers appear bent away from their normal alignment, and the joint spaces are irregular. The changes are most pronounced in the small joints of the hands and fingers.

The image demonstrates the destructive effects of chronic rheumatoid arthritis on synovial joints. Persistent autoimmune inflammation damages cartilage, bone, and supporting connective tissues, leading to pain, loss of joint function, stiffness, and visible deformities of the hands.

Panel (b): Systemic Effects of Systemic Lupus Erythematosus (SLE)

The right panel shows a full-body anatomical illustration highlighting multiple organs and body systems affected by lupus. Labels identify common signs and symptoms throughout the body.

Systemic Effects

- Low-grade fever
- Photosensitivity (increased sensitivity to sunlight)

These symptoms reflect widespread immune activation and inflammation.

Psychological Effects

- Fatigue
- Loss of appetite

These generalized symptoms are common in chronic autoimmune disease and may affect quality of life and daily functioning.

Mouth and Nose

- Ulcers

The figure indicates ulcer formation within the oral or nasal mucosa.

Face

- Butterfly rash

A characteristic butterfly-shaped rash extends across the cheeks and bridge of the nose. This is a common clinical sign of lupus.

Muscles

- Aches

Muscle pain and discomfort may occur due to systemic inflammation.

Joints

- Arthritis

Inflammation of the joints may cause pain, swelling, stiffness, and reduced mobility.

Pleura

- Inflammation

The pleura, the membranes surrounding the lungs, may become inflamed, causing pleuritis and chest discomfort.

Pericardium

- Inflammation

The pericardium, the sac surrounding the heart, may become inflamed, resulting in pericarditis.

Fingers and Toes

- Poor circulation

Blood flow to the extremities may be reduced, resulting in color changes, numbness, or discomfort.

Together, the two panels illustrate that autoimmune diseases can affect the body in different ways. Rheumatoid arthritis primarily targets joints, producing progressive joint destruction and deformity, especially in the hands. Systemic lupus erythematosus affects multiple organ systems throughout the body, producing a wide range of symptoms involving the skin, joints, muscles, circulatory system, respiratory system, cardiovascular system, and mucous membranes. The figure emphasizes that autoimmune disorders result from immune responses directed against the body's own tissues and can cause both localized and systemic disease.

Figure 2.7.1: Rh Incompatibility and Maternal Sensitization During Pregnancy

This image illustrates how Rh incompatibility can develop between an Rh-negative mother and an Rh-positive fetus. The figure consists of three parts: a diagram of the placenta and two enlarged panels showing the first and second exposures to Rh-positive fetal red blood cells.

Placenta Structure

The left side of the figure shows the placenta connecting the fetal and maternal circulations.

The umbilical artery and vein carry blood between the fetus and the placenta. Within the placenta, branches of the fetal circulation are enclosed by the embryonic chorion, a membrane that normally separates fetal blood from maternal blood.

Surrounding the chorion is the maternal blood pool, which receives blood from a placental arteriole (maternal) and drains into a placental venule (maternal). Although nutrients, gases, and wastes are exchanged across the placental barrier, fetal and maternal blood are normally kept separate by the embryonic chorion.

First Exposure: Birth of First Rh⍰ Infant

The upper-right panel illustrates the first exposure of an Rh-negative mother to Rh-positive fetal blood.

The panel identifies:

- Infant blood
- Rh⦰ infant erythrocytes
- Embryonic chorion
- Rh⦰ maternal blood
- Maternal Rh antibody

Step 1: During birth, Rh⦰ fetal erythrocytes leak into maternal blood after breakdown of the embryonic chorion, which normally isolates fetal and maternal blood.

The figure shows fetal red blood cells crossing from the infant circulation into the maternal circulation.

Step 2: Maternal B cells are activated by the Rh antigen and produce large amounts of anti-Rh antibodies.

The figure shows activated maternal B cells releasing antibodies directed against the Rh antigen. Because this antibody production occurs after fetal blood enters the maternal circulation, the first Rh-positive infant is usually not harmed.

Second Exposure: Rh⦰ Fetus

The lower-right panel illustrates a later pregnancy involving another Rh-positive fetus.

The panel identifies:

- Infant blood
- Rh⦰ infant erythrocytes
- Embryonic chorion
- Rh⦰ maternal blood
- Maternal Rh antibody

Step 1: Rh antibody titer in the mother's blood is elevated after the first exposure.

The figure shows numerous anti-Rh antibodies already present within the maternal circulation as a result of immune memory from the first pregnancy.

Step 2: Rh antibodies are small enough to cross the embryonic chorion and attack the fetal erythrocytes.

Unlike fetal red blood cells, maternal antibodies can pass through the placental barrier. The figure shows anti-Rh antibodies crossing the embryonic chorion, binding to Rh-positive fetal erythrocytes, and targeting them for destruction.

The figure demonstrates the development of Rh incompatibility. During the first pregnancy, exposure to Rh-positive fetal erythrocytes sensitizes an Rh-negative mother and stimulates production of anti-Rh antibodies. During a subsequent pregnancy with an Rh-positive fetus, preexisting maternal anti-Rh antibodies cross the placenta and attack fetal red blood cells, potentially causing hemolytic disease of the newborn (erythroblastosis fetalis). The figure emphasizes the role of maternal immune memory and the ability of antibodies, but not fetal red blood cells, to cross the placental barrier.

Figure 2.7.2: Karposi's Sarcoma Lesions

This image shows a close-up view of human skin with multiple visible lesions.

- The skin surface contains numerous spots and patches of varying sizes.
- The lesions are mostly red to dark purple in color, with some appearing darker in the center.
- Many of the spots are raised and irregular in shape, while others are flatter.
- The lesions are spread unevenly across the skin and appear in clusters.
- Some areas show larger patches where smaller spots have merged together.
- The surrounding skin appears lighter in color, creating contrast with the darker lesions.

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2.12: Applied Thinking Self - Assessment

Challenge Yourself

- Extended response questions are assessment items that require students to construct written answers of substantial length - typically several sentences to multiple paragraphs - rather than selecting from predefined options. They represent a form of constructed response assessment designed to measure complex, higher-order thinking skills.
- First, try answering without using your notes. Then review reliable resources and revise your response if needed. Make a note of any areas where you felt unsure and revisit those topics.

Writing Guidelines

- Answer each question in your own words.
- Write 4–8 clear, complete sentences per question, organized into short paragraphs (not bullet points).
- Focus on explaining your reasoning, not just stating the answer.
- Use correct scientific vocabulary, and briefly define terms when needed.
- For questions that ask you to compare, contrast, or explain why/how:
  - Clearly state similarities or differences
  - Support your ideas with a brief explanation or example

Lymphatic Vessels and Flow

1. Lymphatic Capillaries: Structure and Function
   a. Discuss the unique structural features of lymphatic capillaries (e.g., flap-like mini valves, lack of a basement membrane, anchoring filaments).
   b. Explain how each of these features helps in:
      i. Absorbing interstitial fluid
      ii. Allowing entry of proteins and cells
      iii. Maintaining one-way lymph flow.
2. Types of Lymphatic Vessels and Drainage Territories
   a. Describe the major types of lymphatic vessels: lymphatic capillaries, collecting vessels, lymphatic trunks, and ducts.
   b. For each of the main lymphatic trunks (e.g., lumbar, intestinal, bronchomediastinal, subclavian, jugular), state which general body regions they drain.
3. Pathway of Lymph to the Heart
   a. Create a flow chart that traces the path of lymph from a specific tissue bed to the heart. Do this for:
      i. Lymph from the right upper limb
      ii. Lymph from the left lower limb
   b. Start with “interstitial fluid” and end with “return to venous circulation at the subclavian veins,” naming key vessels and ducts along the way.
4. Mechanisms of Lymph Circulation
   i. Beyond the structure of lymph vessels, describe three physiological mechanisms that help propel lymph (e.g., skeletal muscle pump, respiratory pump, valves, smooth muscle in vessel walls).
   ii. Explain why lymph flow is slower than blood flow and why this is functionally important.

Lymphatic Organs and Immune Surveillance

1. Primary vs. Secondary Lymphatic Organs
   a. Describe the structure (gross and basic histology), location, and functions of the primary and secondary lymphatic organs. In your answer, include:
      i. Primary: red bone marrow and thymus
      ii. Secondary: lymph nodes, spleen, mucosa-associated lymphoid tissue (MALT), and tonsils

   b. For each, state:
      i. Main cell types present
      ii. Major immune function (e.g., site of lymphocyte maturation vs. site of antigen encounter).
2. Lymphatic System and Cancer: Double-Edged Sword
   a. The lymphatic system helps keep us healthy by identifying and destroying cancer cells, but it can also help spread malignant cancer.
   b. Explain this statement by describing:
      i. How lymph nodes and immune cells can attack tumor cells
      ii. How tumor cells can use lymphatic vessels and nodes as pathways for metastasis
      iii. The clinical relevance of “sentinel lymph nodes” in cancer staging.
   c. Effect of Lymph Node Removal
      i. After breast cancer surgery, some axillary lymph nodes are removed.
      ii. Predict two consequences this might have for:
         - Local immune defense in the arm
         - Fluid balance in the affected limb.

Inflammation and Innate (Non-Specific) Defenses

1. Outline the classic signs of inflammation (redness, heat, swelling, pain, loss of function) and explain the underlying vascular and cellular events.
2. Innate vs. Adaptive Immunity; Properties of Antigens
   a. Distinguish between innate and adaptive immunity with respect to:
      i. Specificity
      ii. Memory
      iii. Response time
      iv. Major cell types involved
   b. Then describe key properties of an antigen (e.g., foreignness, size, complexity, epitopes) that make it capable of eliciting an adaptive immune response.
3. Physical and Chemical Barriers in Innate Defense
   a. Explain how physical barriers and secretions contribute to innate (non-specific) defenses.
   b. For each of the following, describe its protective role and mechanism:
      i. Keratinized epithelia
      ii. Sweat
      iii. Sebum
      iv. Saliva
      v. Gastric juice
      vi. Mucus
      vii. Cilia
      viii. Vomiting and diarrhea
4. Cellular and Systemic Innate Defenses
   a. Describe the characteristics and roles of these innate defenses:
      i. Phagocytes (neutrophils and macrophages)
      ii. Natural killer (NK) cells
      iii. Interferons
      iv. Complement (optional if covered)
      v. Inflammation
      vi. Fever
   b. For each, briefly indicate:
      i. Main targets (e.g., viruses, bacteria, tumor cells)
      ii. How they help contain or eliminate the threat.

Adaptive Immunity and Antigen Presentation

1. Antibody-Mediated vs. Cell-Mediated Immunity

a. Differentiate between antibody-mediated (humoral) immunity and cell-mediated immunity. In your answer, include:
   i. Main cell types involved (e.g., B cells, helper T cells, cytotoxic T cells)
   ii. Main targets (e.g., extracellular vs. intracellular pathogens)
   iii. The role of antibodies vs. direct cell killing.

2. Histocompatibility Antigens and MHC Molecules (the questions and the answers are provided as an example)
   a. Define histocompatibility antigens.
   b. Explain the importance of Class I and Class II MHC molecules in T-cell function by addressing:
      i. Where Class I and Class II MHC molecules are found
      ii. Which T-cell subsets (CD8⁺ vs CD4⁺) recognize each class
      iii. How this influences the type of response generated (kill infected cells vs. coordinate immune responses).
3. Antigen Recognition and CD Markers
   a. Describe the events of antigen recognition by T cells.
   b. Include the roles of:
      i. T-cell receptor (TCR)
      ii. MHC–antigen complex on antigen-presenting cells
      iii. CD4 and CD8 coreceptors
      iv. Costimulation and subsequent T-cell activation and differentiation (into helper, cytotoxic, or memory cells).
4. Immunoglobulin Classes and Key Functions
   a. Name the five classes of immunoglobulins discussed in class.
   b. For each, state one distinctive feature or function, and then answer:
      i. Which immunoglobulin is most abundant in blood plasma?
      ii. Which is most associated with allergic responses and parasitic infections?
      iii. Which is the first major immunoglobulin released during a primary immune response?
      iv. Which can cross the placenta to provide passive immunity to the fetus?
5. Immunologic Memory
   a. Explain how primary and secondary immune responses differ in terms of:
      i. Speed of onset
      ii. Magnitude of antibody production
      iii. Predominant immunoglobulin classes
   b. Describe the role of memory B and T cells in these differences.

Types of Immunity and Clinical Reactions

1. Active vs. Passive Immunity; Natural vs. Artificial
   a. Compare active and passive immunity in terms of:
      i. How each is acquired
      ii. Whether immunologic memory develops
      iii. Duration of protection
   b. Then classify each of the following as natural/active, artificial/active, natural/passive, or artificial/passive, and give an example of each:
      i. Immunity from recovering from an infection
      ii. Immunity from vaccination
      iii. Maternal antibodies transferred across placenta or in breast milk
      iv. Antibody injection (e.g., anti-venom, immunoglobulin therapy)
2. Anaphylactic Shock and Peanut Allergy
   a. Describe anaphylactic shock in someone sensitive to peanuts.
   b. Explain:
      i. What happens during the sensitization (first exposure) phase
      ii. What happens during subsequent exposures (role of IgE, mast cells, histamine, and other mediators)
      iii. The major physiological changes (e.g., vasodilation, bronchoconstriction, drop in blood pressure) and why this can be life-threatening.
3. Stress and Immune Responses

a. Describe how chronic stress affects immune responses.
b. In your answer, discuss:
    i. The roles of cortisol and sympathetic activation
    ii. Effects on innate vs. adaptive immunity (e.g., changes in inflammation, lymphocyte function)
    iii. One potential clinical consequence (e.g., increased infection risk, slower wound healing).

4. Autoimmunity and Tolerance
    i. Briefly explain the concept of self-tolerance.
    ii. Describe how failure of self-tolerance can lead to autoimmune disease, giving one example of such a disease and the tissue it targets.

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3: THE DIGESTIVE SYSTEM

Chapter Overview



Figure 3.1: Eating may be one of the simple pleasures in life, but digesting even one apple requires the coordinated work of many organs. (CC BY 4.0; via Overview of the Digestive System).

Introduces the continuous, largely unnoticed work of the digestive system using a simple example (eating an apple). Emphasizes that this chapter will describe the structures and functions of digestive organs, and the mechanics and chemistry of digestion.

Organization of the Digestive System: Alimentary Canal and Accessory Organs

Defines the alimentary canal as a continuous tube open at both ends (mouth, pharynx, esophagus, stomach, small intestine, large intestine). Lists accessory structures (teeth, tongue, salivary glands, liver, pancreas, gallbladder) and their supportive roles.

Histology and Neural Control of the Gut Wall

Describes the four basic layers of the alimentary canal (mucosa, submucosa, muscularis, serosa). Introduces the enteric nervous system as intrinsic innervation and the autonomic nervous system as extrinsic innervation.

Core Functions of the Digestive System

Summarizes the six key activities: ingestion, motility, mechanical digestion, chemical digestion, absorption, and defecation. Notes that these processes are regulated by neural and hormonal mechanisms.

Mouth, Tongue, and Teeth: Beginning of Digestion

Explains mechanical digestion by teeth and tongue, and chemical digestion initiated by saliva. Introduces the mouth as the entry point for food and site of early processing.

Pharynx and Esophagus: Swallowing and Food Transport

Describes the pharynx as a shared passageway for breathing, vocalization, and digestion. Outlines the phases of swallowing (deglutition), including soft palate elevation and epiglottis closure. Explains upper and lower esophageal sphincters and mucus

secretion that eases passage of the food bolus.

Stomach: Storage, Mixing, and Early Chemical Digestion

Describes churning, secretion of gastric juice, initial protein digestion, continuation of carbohydrate and fat digestion, limited absorption (e.g., aspirin, alcohol), formation of acidic chyme, and controlled release through the pyloric sphincter.

Small Intestine: Structure and Specializations for Absorption

Introduces the three main regions - duodenum, jejunum, ileum. Emphasizes that digestion is completed and virtually all absorption occurs here. Describes circular folds, villi, and microvilli (brush border) and their 600-fold increase in surface area.

Small Intestine: Motility and Secretions

Explains brush border enzymes that complete digestion of carbohydrates and proteins. Outlines the contribution of intestinal juice and pancreatic juice as the liquid medium for digestion and absorption. Describes segmentation (mixing, back-and-forth movement) and migrating motility complexes (propulsion toward the large intestine).

Large Intestine: Water Absorption and Feces Formation

Defines main regions - cecum, colon, rectum. Describes water absorption, feces formation, and defecation. Explains the role of bacterial flora in breaking down residual carbohydrates and synthesizing some vitamins. Notes abundant goblet cells and mucus secretion, and the defecation reflex.

Liver and Gallbladder: Bile Production, Storage, and Lipid Emulsification

Describes liver production of bile and delivery to the common hepatic duct. Explains bile components (bile salts, phospholipids) and their role in emulsifying large lipid globules. Describes gallbladder storage and concentration of bile and its release into the small intestine when needed.

Pancreas: Digestive Enzymes and Bicarbonate Secretion

Explains production of pancreatic juice rich in enzymes and bicarbonate. Describes delivery to the small intestine, buffering of acidic chyme, inactivation of pepsin, and creation of optimal pH for digestive enzymes.

Chemical Digestion: From Macromolecules to Absorbable Units

Summarizes how chemical digestion in the small intestine breaks down large food molecules into their building blocks. Highlights the central roles of brush border enzymes, pancreatic enzymes, and bile in nutrient breakdown.

Nutrient Absorption and Transport Pathways

Describes how most nutrients are absorbed across the apical surface of enterocytes via specific transport mechanisms. Explains exceptions for lipids and vitamins, and outlines the hepatic portal pathway for absorbed monomers traveling to the liver.

Lipid Digestion and Absorption: Micelles and Chylomicrons

Details how bile salts and lecithin emulsify dietary fats into micelles. Explains how micelles deliver fats to enterocyte membranes, where they diffuse in, are reassembled into triglycerides, and packaged with other lipids and proteins into chylomicrons that enter lacteals. Notes that other monomers enter blood capillaries in villi and then the hepatic portal vein.

Chapter Objectives

To achieve these chapter objectives, actively engage with the material. Learning tissues is not a passive process. Your understanding will grow as you interact with the content, peers, and your instructor. Regularly check your thinking against feedback. Revisit complex concepts until you can confidently explain and apply them on your own.

By the end of this chapter, you will be able to:

- Identify all components of the alimentary canal (from mouth to anus) and accessory organs (liver, gallbladder, pancreas).
- Describe the four fundamental tissue layers of the digestive tract and their respective functions.
- Explain the six main processes: ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation.
- Detail the enzymatic breakdown and absorption mechanisms for macronutrients (carbohydrates, proteins, lipids).
- Contrast the roles of the enteric nervous system, autonomic nervous system, and hormonal control (e.g., gastrin, CCK, secretin) in digestion.
- Analyze the specific roles of the liver (detoxification, bile production), gallbladder (bile storage), and pancreas (enzyme secretion).
- Discuss common diseases, disorders, and diagnostic procedures related to the digestive system.
- Analyze how the digestive system works as a whole, including the integration of neural and hormonal signals.
- Explain how specific organ structures (e.g., intestinal villi) are adapted for their function.

3.1: Digestive System Anatomy

3.2: Digestive System Processes and Regulation

3.3: The Mouth, Pharynx, and Esophagus

3.4: The Stomach

3.5: The Small and Large Intestines

3.6: Accessory Organs in Digestion

3.7: Chemical Digestion and Absorption - A Closer Look

3.8: Terms and Definitions

3.9: Chapter Review Questions

3.10: Applied Thinking Self-Assessment

3.11: Alternate Text Description

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3.1: Digestive System Anatomy

Overview of the Digestive System

The function of the digestive system is to break down the foods you eat, release their nutrients, and absorb those nutrients into the body. Although the small intestine is the workhorse of the system, where the majority of digestion occurs, and where most of the released nutrients are absorbed into the blood or lymph, each of the digestive system organs makes a vital contribution to this process (Figure 3.1.1).

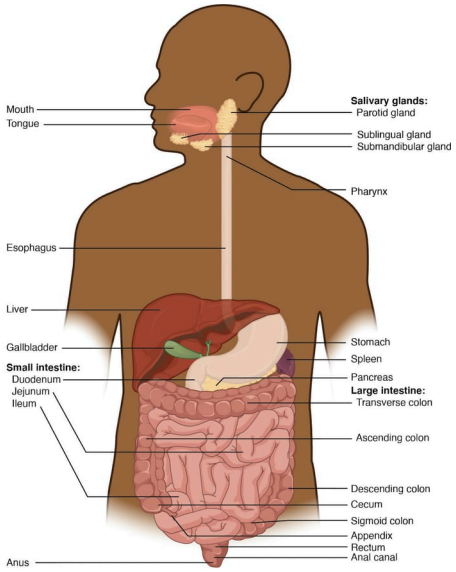


Figure 3.1.1: All digestive organs play integral roles in the life-sustaining process of digestion. (CC BY 4.0; via Overview of the Digestive System). Detailed text description of the Figure 3.1.1.

As is the case with all body systems, the digestive system does not work in isolation; it functions cooperatively with the other systems of the body. Consider for example, the interrelationship between the digestive and cardiovascular systems. Arteries supply the digestive organs with oxygen and processed nutrients, and veins drain the digestive tract. These intestinal veins, constituting the hepatic portal system, are unique; they do not return blood directly to the heart. Rather, this blood is diverted to the liver where its nutrients are off-loaded for processing before blood completes its circuit back to the heart. At the same time, the digestive system provides nutrients to the heart muscle and vascular tissue to support their functioning. The interrelationship of the digestive and endocrine systems is also critical. Hormones secreted by several endocrine glands, as well as endocrine cells of the pancreas, the stomach, and the small intestine, contribute to the control of digestion and nutrient metabolism. In turn, the digestive system provides the nutrients to fuel endocrine function. Table 3.1.1 gives a quick glimpse at how these other systems contribute to the functioning of the digestive system.

Table 3.1.1: Contribution of Other Body Systems to the Digestive System

Body system	Benefits received by the digestive system
Cardiovascular	Blood supplies digestive organs with oxygen and processed nutrients
Endocrine	Endocrine hormones help regulate secretion in digestive glands and accessory organs
Integumentary	Skin helps protect digestive organs and synthesizes vitamin D for calcium absorption
Lymphatic	Mucosa-associated lymphoid tissue and other lymphatic tissue defend against entry of pathogens; lacteals absorb lipids; and lymphatic vessels transport lipids to bloodstream
Muscular	Skeletal muscles support and protect abdominal organs

Body system	Benefits received by the digestive system
Nervous	Sensory and motor neurons help regulate secretions and muscle contractions in the digestive tract
Respiratory	Respiratory organs provide oxygen and remove carbon dioxide
Skeletal	Bones help protect and support digestive organs
Urinary	Kidneys convert vitamin D into its active form, allowing calcium absorption in the small intestine

Digestive System Organs

The easiest way to understand the digestive system is to divide its organs into two main categories. The first group is the organs that make up the alimentary canal. Accessory digestive organs comprise the second group and are critical for orchestrating the breakdown of food and the assimilation of its nutrients into the body. Accessory digestive organs, despite their name, are critical to the function of the digestive system.

Alimentary Canal Organs

Also called the gastrointestinal (GI) tract or gut, the alimentary canal (aliment- = "to nourish") is a one-way tube about 7.62 meters (25 feet) in length during life and closer to 10.67 meters (35 feet) in length when measured after death, once smooth muscle tone is lost. The main function of the organs of the alimentary canal is to nourish the body. This tube begins at the mouth and terminates at the anus. Between those two points, the canal is modified as the pharynx, esophagus, stomach, and small and large intestines to fit the functional needs of the body. Both the mouth and anus are open to the external environment; thus, food and wastes within the alimentary canal are technically considered to be outside the body. Only through the process of absorption do the nutrients in food enter into and nourish the body's "inner space."

Accessory Structures

Each accessory digestive organ aids in the breakdown of food. Within the mouth, the teeth and tongue begin mechanical digestion, whereas the salivary glands begin chemical digestion. Once food products enter the small intestine, the gallbladder, liver, and pancreas release secretions—such as bile and enzymes—essential for digestion to continue. Together, these are called accessory organs because they sprout from the lining cells of the developing gut (mucosa) and augment its function; indeed, you could not live without their vital contributions, and many significant diseases result from their malfunction. Even after development is complete, they maintain a connection to the gut by way of ducts.

Histology of the Alimentary Canal

Throughout its length, the alimentary tract is composed of the same four tissue layers; the details of their structural arrangements vary to fit their specific functions. Starting from the lumen and moving outwards, these layers are the mucosa, submucosa, muscularis, and serosa, which is continuous with the mesentery (Figure 3.1.2).

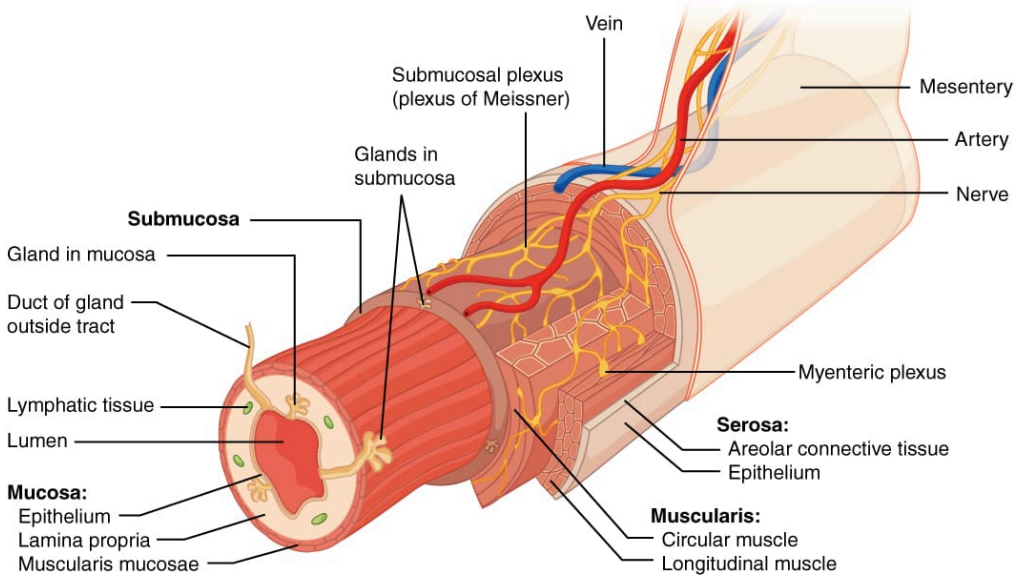


Figure 3.1.2: The wall of the alimentary canal has four basic tissue layers: the mucosa, submucosa, muscularis, and serosa. (CC BY 4.0; via Overview of the Digestive System). Detailed text description of the Figure 3.1.2.

The mucosa is referred to as a mucous membrane, because mucus production is a characteristic feature of gut epithelium. The membrane consists of epithelium, which is in direct contact with ingested food, and the lamina propria, a layer of connective tissue analogous to the dermis. In addition, the mucosa has a thin, smooth muscle layer, called the muscularis mucosae (not to be confused with the muscularis layer, described below).

Epithelium—In the mouth, pharynx, esophagus, and anal canal, the epithelium is primarily a non-keratinized, stratified squamous epithelium. In the stomach and intestines, it is a simple columnar epithelium. Notice that the epithelium is in direct contact with the lumen, the space inside the alimentary canal. Interspersed among its epithelial cells are goblet cells, which secrete mucus and fluid into the lumen, and enteroendocrine cells, which secrete hormones into the interstitial spaces between cells. Epithelial cells have a very brief lifespan, averaging from only a couple of days (in the mouth) to about a week (in the gut). This process of rapid renewal helps preserve the health of the alimentary canal, despite the wear and tear resulting from continued contact with foodstuffs.

Lamina propria—In addition to loose connective tissue, the lamina propria contains numerous blood and lymphatic vessels that transport nutrients absorbed through the alimentary canal to other parts of the body. The lamina propria also serves an immune function by housing clusters of lymphocytes, making up the mucosa-associated lymphoid tissue (MALT). These lymphocyte clusters are particularly substantial in the distal ileum where they are known as Peyer's patches. When you consider that the alimentary canal is exposed to foodborne bacteria and other foreign matter, it is not hard to appreciate why the immune system has evolved a means of defending against the pathogens encountered within it.

Muscularis mucosae—This thin layer of smooth muscle is in a constant state of tension, pulling the mucosa of the stomach and small intestine into undulating folds. These folds dramatically increase the surface area available for digestion and absorption.

As its name implies, the submucosa lies immediately beneath the mucosa. A broad layer of dense connective tissue, it connects the overlying mucosa to the underlying muscularis. It includes blood and lymphatic vessels (which transport absorbed nutrients), and a scattering of submucosal glands that release digestive secretions. Additionally, it serves as a conduit for a dense branching network of nerves, the submucosal plexus, which functions as described below.

The third layer of the alimentary canal is the muscularis (also called the muscularis externa). The muscularis in the small intestine is made up of a double layer of smooth muscle: an inner circular layer and an outer longitudinal layer. The contractions of these layers promote mechanical digestion, expose more of the food to digestive chemicals, and move the food along the canal. In the most proximal and distal regions of the alimentary canal, including the mouth, pharynx, anterior part of the esophagus, and external anal sphincter, the muscularis is made up of skeletal muscle, which gives you voluntary control over swallowing and defecation. The basic two-layer structure found in the small intestine is modified in the organs proximal and distal to it. The stomach is equipped for its churning function by the addition of a third layer, the oblique muscle. While the colon has two layers like the small intestine, its longitudinal layer is segregated into three narrow parallel bands, the tenia coli, which make it look like

a series of pouches rather than a simple tube.

The serosa is the portion of the alimentary canal superficial to the muscularis. Present only in the region of the alimentary canal within the abdominal cavity, it consists of a layer of visceral peritoneum overlying a layer of loose connective tissue. Instead of serosa, the mouth, pharynx, and esophagus have a dense sheath of collagen fibers called the adventitia. These tissues serve to hold the alimentary canal in place near the ventral surface of the vertebral column.

Nerve Supply

As soon as food enters the mouth, it is detected by receptors that send impulses along the sensory neurons of cranial nerves. Without these nerves, not only would your food be without taste, but you would also be unable to feel either the food or the structures of your mouth, and you would be unable to avoid biting yourself as you chew, an action enabled by the motor branches of cranial nerves.

Intrinsic innervation of much of the alimentary canal is provided by the enteric nervous system, which runs from the esophagus to the anus, and contains approximately 100 million motor, sensory, and interneurons (unique to this system compared to all other parts of the peripheral nervous system). These enteric neurons are grouped into two plexuses. The myenteric plexus (plexus of Auerbach) lies in the muscularis layer of the alimentary canal and is responsible for motility, especially the rhythm and force of the contractions of the muscularis. The submucosal plexus (plexus of Meissner) lies in the submucosal layer and is responsible for regulating digestive secretions and reacting to the presence of food.

Extrinsic innervations of the alimentary canal are provided by the autonomic nervous system, which includes both sympathetic and parasympathetic nerves. In general, sympathetic activation (the fight-or-flight response) restricts the activity of enteric neurons, thereby decreasing GI secretion and motility. In contrast, parasympathetic activation (the rest-and-digest response) increases GI secretion and motility by stimulating neurons of the enteric nervous system.

Blood Supply

The blood vessels serving the digestive system have two functions. They transport the protein and carbohydrate nutrients absorbed by mucosal cells after food is digested in the lumen. Lipids are absorbed via lacteals, tiny structures of the lymphatic system. The blood vessels' second function is to supply the organs of the alimentary canal with the nutrients and oxygen needed to drive their cellular processes.

Specifically, the more anterior parts of the alimentary canal are supplied with blood by arteries branching off the aortic arch and thoracic aorta. Below this point, the alimentary canal is supplied with blood by arteries branching from the abdominal aorta. The celiac trunk services the liver, stomach, and duodenum, whereas the superior and inferior mesenteric arteries supply blood to the remaining small and large intestines.

The veins that collect nutrient-rich blood from the small intestine (where most absorption occurs) empty into the hepatic portal system. This venous network takes the blood into the liver where the nutrients are either processed or stored for later use. Only then does the blood drained from the alimentary canal viscera circulate back to the heart. To appreciate just how demanding the digestive process is on the cardiovascular system, consider that while you are "resting and digesting," about one-fourth of the blood pumped with each heartbeat enters arteries serving the intestines.

The Peritoneum

The digestive organs within the abdominal cavity are held in place by the peritoneum, a broad serous membranous sac made up of squamous epithelial tissue surrounded by connective tissue. It is composed of two different regions: the parietal peritoneum, which lines the abdominal wall, and the visceral peritoneum, which envelopes the abdominal organs (Figure 3.1.3). The peritoneal cavity is the space bounded by the visceral and parietal peritoneal surfaces. A few milliliters of watery fluid act as a lubricant to minimize friction between the serosal surfaces of the peritoneum.

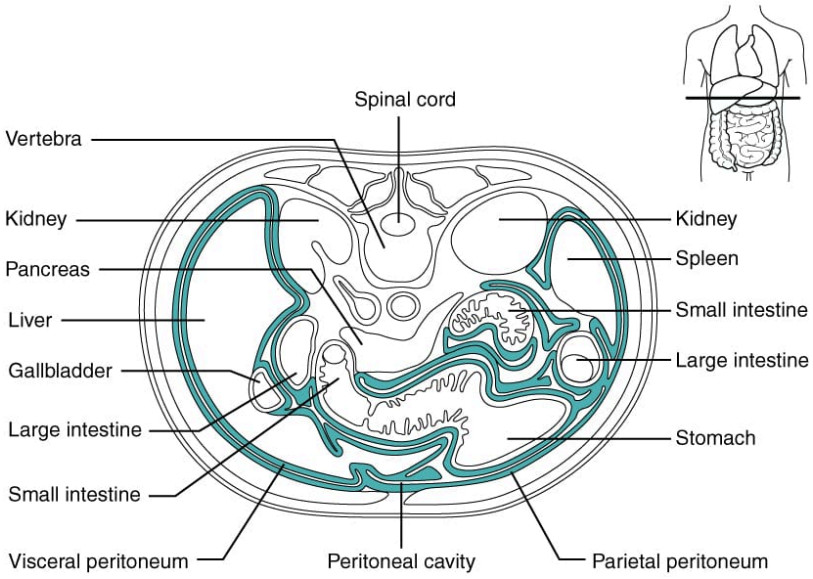


Figure 3.1.3: A cross-section of the abdomen shows the relationship between abdominal organs and the peritoneum. (CC BY 4.0; via Overview of the Digestive System). Detailed text description of the Figure 3.1.3.

Disorders of the...

Digestive System: Peritonitis

Inflammation of the peritoneum is called peritonitis. Chemical peritonitis can develop any time the wall of the alimentary canal is breached, allowing the contents of the lumen entry into the peritoneal cavity. For example, when an ulcer perforates the stomach wall, gastric juices spill into the peritoneal cavity. Hemorrhagic peritonitis occurs after a ruptured tubal pregnancy or traumatic injury to the liver or spleen fills the peritoneal cavity with blood. Even more severe peritonitis is associated with bacterial infections seen with appendicitis, colonic diverticulitis, and pelvic inflammatory disease (infection of uterine tubes, usually by sexually transmitted bacteria). Peritonitis is life threatening and often results in emergency surgery to correct the underlying problem and intensive antibiotic therapy. When your great grandparents and even your parents were young, the mortality from peritonitis was high. Aggressive surgery, improvements in anesthesia safety, the advance of critical care expertise, and antibiotics have greatly improved the mortality rate from this condition. Even so, the mortality rate still ranges from 30 to 40 percent.

The visceral peritoneum includes multiple large folds that envelope various abdominal organs, holding them to the dorsal surface of the body wall. Within these folds are blood vessels, lymphatic vessels, and nerves that innervate the organs with which they are in contact, supplying their adjacent organs. The five major peritoneal folds are described in Table 3.1.2. Note that during fetal development, certain digestive structures, including the first portion of the small intestine (called the duodenum), the pancreas, and portions of the large intestine (the ascending and descending colon, and the rectum) remain completely or partially posterior to the peritoneum. Thus, the location of these organs is described as retroperitoneal.

Table 3.1.2: The Five Major Peritoneal Folds

Fold	Description
Greater omentum	Apron-like structure that lies superficial to the small intestine and transverse colon; a site of fat deposition in people who are overweight
Falciform ligament	Anchors the liver to the anterior abdominal wall and inferior border of the diaphragm
Lesser omentum	Suspends the stomach from the inferior border of the liver; provides a pathway for structures connecting to the liver
Mesentery	Vertical band of tissue anterior to the lumbar vertebrae and anchoring all of the small intestine except the initial portion (the duodenum)

Fold	Description
Mesocolon	Attaches two portions of the large intestine (the transverse and sigmoid colon) to the posterior abdominal wall

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3.2: Digestive System Processes and Regulation

Digestive Organ Functions

The digestive system uses mechanical and chemical activities to break food down into absorbable substances during its journey through the digestive system. Table 3.2.1 provides an overview of the basic functions of the digestive organs.

Table 3.2.1: Functions of the Digestive Organs

Organ	Major functions	Other functions
Mouth	• Ingests food • Chews and mixes food • Begins chemical breakdown of carbohydrates • Moves food into the pharynx • Begins breakdown of lipids via lingual lipase	• Moistens and dissolves food, allowing you to taste it • Cleans and lubricates the teeth and oral cavity • Has some antimicrobial activity
Pharynx	• Propels food from the oral cavity to the esophagus	• Lubricates food and passageways
Esophagus	• Propels food to the stomach	• Lubricates food and passageways
Stomach	• Mixes and churns food with gastric juices to form chyme • Begins chemical breakdown of proteins • Releases food into the duodenum as chyme • Absorbs some fat-soluble substances (for example, alcohol, aspirin) • Possesses antimicrobial functions	• Stimulates protein-digesting enzymes • Secretes intrinsic factor required for vitamin B_{12} absorption in small intestine
Small intestine	• Mixes chyme with digestive juices • Propels food at a rate slow enough for digestion and absorption • Absorbs breakdown products of carbohydrates, proteins, lipids, and nucleic acids, along with vitamins, minerals, and water • Performs physical digestion via segmentation	• Provides optimal medium for enzymatic activity
Accessory organs	• Liver: produces bile salts, which emulsify lipids, aiding their digestion and absorption • Gallbladder: stores, concentrates, and releases bile • Pancreas: produces digestive enzymes and bicarbonate	• Bicarbonate-rich pancreatic juices help neutralize acidic chyme and provide optimal environment for enzymatic activity

Organ	Major functions	Other functions
Large intestine	• Further breaks down food residues • Absorbs most residual water, electrolytes, and vitamins produced by enteric bacteria • Propels feces toward rectum • Eliminates feces	• Food residue is concentrated and temporarily stored prior to defecation • Mucus eases passage of feces through colon

Digestive Processes

The processes of digestion include six activities: ingestion, propulsion, mechanical or physical digestion, chemical digestion, absorption, and defecation.

The first of these processes, ingestion, refers to the entry of food into the alimentary canal through the mouth. There, the food is chewed and mixed with saliva, which contains enzymes that begin breaking down the carbohydrates in the food plus some lipid digestion via lingual lipase. Chewing increases the surface area of the food and allows an appropriately sized bolus to be produced.

Food leaves the mouth when the tongue and pharyngeal muscles propel it into the esophagus. This act of swallowing, the last voluntary act until defecation, is an example of propulsion, which refers to the movement of food through the digestive tract. It includes both the voluntary process of swallowing and the involuntary process of peristalsis. Peristalsis consists of sequential, alternating waves of contraction and relaxation of alimentary wall smooth muscles, which act to propel food along (Figure 3.2.1). These waves also play a role in mixing food with digestive juices. Peristalsis is so powerful that foods and liquids you swallow enter your stomach even if you are standing on your head.

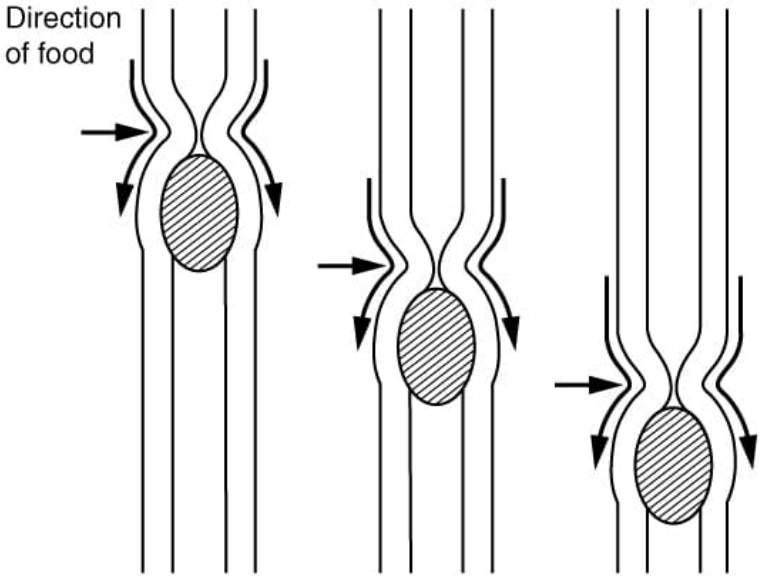


Figure 3.2.1: Peristalsis moves food through the digestive tract with alternating waves of muscle contraction and relaxation. (CC BY 4.0; via Digestive System Process and Regulation). Detailed text description of the Figure 3.2.1.

Digestion includes both mechanical and chemical processes. Mechanical digestion is a purely physical process that does not change the chemical nature of the food. Instead, it makes the food smaller to increase both surface area and mobility. It includes mastication, or chewing, as well as tongue movements that help break food into smaller bits and mix food with saliva. Although there may be a tendency to think that mechanical digestion is limited to the first steps of the digestive process, it occurs after the food leaves the mouth, as well. The mechanical churning of food in the stomach serves to further break it apart and expose more of its surface area to digestive juices, creating an acidic “soup” called chyme. Segmentation, which occurs mainly in the small intestine, consists of localized contractions of circular muscle of the muscularis layer of the alimentary canal. These contractions isolate small sections of the intestine, moving their contents back and forth while continuously subdividing, breaking up, and

mixing the contents. By moving food back and forth in the intestinal lumen, segmentation mixes food with digestive juices and facilitates absorption.

In chemical digestion, starting in the mouth, digestive secretions break down complex food molecules into their chemical building blocks (for example, proteins into separate amino acids). These secretions vary in composition, but typically contain water, various enzymes, acids, and salts. The process is completed in the small intestine.

Food that has been broken down is of no value to the body unless it enters the bloodstream and its nutrients are put to work. This occurs through the process of absorption, which takes place primarily within the small intestine. There, most nutrients are absorbed from the lumen of the alimentary canal into the bloodstream through the epithelial cells that make up the mucosa. Lipids are absorbed into lacteals and are transported via the lymphatic vessels to the bloodstream (the subclavian veins near the heart). The details of these processes will be discussed later.

In defecation, the final step in digestion, undigested materials are removed from the body as feces.

Aging and the...

Digestive System: From Appetite Suppression to Constipation

Age-related changes in the digestive system begin in the mouth and can affect virtually every aspect of the digestive system. Taste buds become less sensitive, so food isn't as appetizing as it once was. A slice of pizza is a challenge, not a treat, when you have lost teeth, your gums are diseased, and your salivary glands aren't producing enough saliva. Swallowing can be difficult, and ingested food moves slowly through the alimentary canal because of reduced strength and tone of muscular tissue. Neurosensory feedback is also dampened, slowing the transmission of messages that stimulate the release of enzymes and hormones.

Pathologies that affect the digestive organs—such as hiatal hernia, gastritis, and peptic ulcer disease—can occur at greater frequencies as you age. Problems in the small intestine may include duodenal ulcers, maldigestion, and malabsorption. Problems in the large intestine include hemorrhoids, diverticular disease, and constipation. Conditions that affect the function of accessory organs—and their abilities to deliver pancreatic enzymes and bile to the small intestine—include jaundice, acute pancreatitis, cirrhosis, and gallstones.

In some cases, a single organ is in charge of a digestive process. For example, ingestion occurs only in the mouth and defecation only in the anus. However, most digestive processes involve the interaction of several organs and occur gradually as food moves through the alimentary canal (Figure 3.2.2).

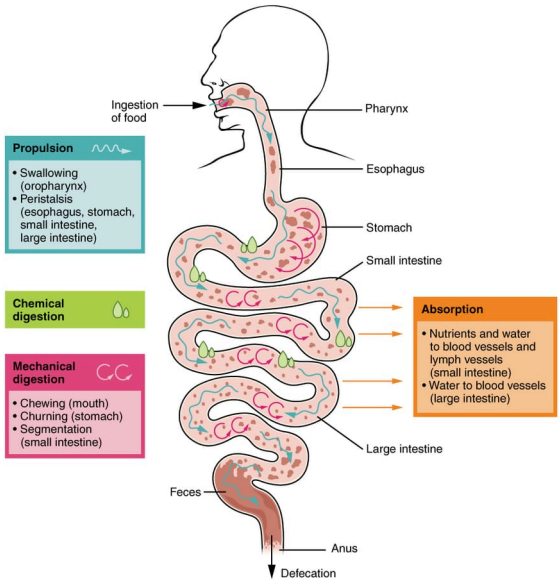


Figure 3.2.2: The digestive processes are ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation. (CC BY 4.0; via Digestive System Process and Regulation). Detailed text description of the Figure 3.2.2.

Regulatory Mechanisms

Neural and endocrine regulatory mechanisms work to maintain the optimal conditions in the lumen needed for digestion and absorption. These regulatory mechanisms, which stimulate digestive activity through mechanical and chemical activity, are controlled both extrinsically and intrinsically.

Neural Controls

The walls of the alimentary canal contain a variety of sensors that help regulate digestive functions. These include mechanoreceptors, chemoreceptors, and osmoreceptors, which are capable of detecting mechanical, chemical, and osmotic stimuli, respectively. For example, these receptors can sense when the presence of food has caused the stomach to expand, whether food particles have been sufficiently broken down, how much liquid is present, and the type of nutrients in the food (lipids, carbohydrates, and/or proteins). Stimulation of these receptors provokes an appropriate reflex that furthers the process of digestion. This may entail sending a message that activates the glands that secrete digestive juices into the lumen, or it may mean the stimulation of muscles within the alimentary canal, thereby activating peristalsis and segmentation that move food along the intestinal tract.

The walls of the entire alimentary canal are embedded with nerve plexuses that interact with the central nervous system and other nerve plexuses—either within the same digestive organ or in different ones. These interactions prompt several types of reflexes. Extrinsic nerve plexuses orchestrate long reflexes, which involve the central and autonomic nervous systems and work in response to stimuli from outside the digestive system. Short reflexes, on the other hand, are orchestrated by intrinsic nerve plexuses within the alimentary canal wall. These two plexuses and their connections were introduced earlier as the enteric nervous system. Short reflexes regulate activities in one area of the digestive tract and may coordinate local peristaltic movements and stimulate digestive secretions. For example, the sight, smell, and taste of food initiate long reflexes that begin with a sensory neuron delivering a signal to the medulla oblongata. The response to the signal is to stimulate cells in the stomach to begin secreting digestive juices in preparation for incoming food. In contrast, food that distends the stomach initiates short reflexes that cause cells in the stomach wall to increase their secretion of digestive juices.

Hormonal Controls

A variety of hormones are involved in the digestive process. The main digestive hormone of the stomach is gastrin, which is secreted in response to the presence of food. Gastrin stimulates the secretion of gastric acid by the parietal cells of the stomach mucosa. Other GI hormones are produced and act upon the gut and its accessory organs. Hormones produced by the duodenum include secretin, which stimulates a watery secretion of bicarbonate by the pancreas; cholecystokinin (CCK), which stimulates the secretion of pancreatic enzymes and bile from the liver and release of bile from the gallbladder; and gastric inhibitory peptide, which inhibits gastric secretion and slows gastric emptying and motility. These GI hormones are secreted by specialized epithelial cells, called endocrinocytes, located in the mucosal epithelium of the stomach and small intestine. These hormones then enter the bloodstream, through which they can reach their target organs.

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3.3: The Mouth, Pharynx, and Esophagus

Overview of the Upper Alimentary Canal

In this section, you will examine the anatomy and functions of the three main organs of the upper alimentary canal—the mouth, pharynx, and esophagus—as well as three associated accessory organs—the tongue, salivary glands, and teeth

The Mouth

The cheeks, tongue, and palate frame the mouth, which is also called the oral cavity (or buccal cavity). The structures of the mouth are illustrated in Figure 3.3.1.

At the entrance to the mouth are the lips, or labia (singular = labium). Their outer covering is skin, which transitions to a mucous membrane in the mouth proper. Lips are very vascular with a thin layer of keratin; hence, the reason they are "red." They have a huge representation on the cerebral cortex, which probably explains the human fascination with kissing! The lips cover the orbicularis oris muscle, which regulates what comes in and goes out of the mouth. The labial frenulum is a midline fold of mucous membrane that attaches the inner surface of each lip to the gum. The cheeks make up the oral cavity's sidewalls. While their outer covering is skin, their inner covering is mucous membrane. This membrane is made up of non-keratinized, stratified squamous epithelium. Between the skin and mucous membranes are connective tissue and buccinator muscles. The next time you eat some food, notice how the buccinator muscles in your cheeks and the orbicularis oris muscle in your lips contract, helping you keep the food from falling out of your mouth. Additionally, notice how these muscles work when you are speaking.

The pocket-like part of the mouth that is framed on the inside by the gums and teeth, and on the outside by the cheeks and lips is called the oral vestibule. Moving farther into the mouth, the opening between the oral cavity and throat (oropharynx) is called the fauces (like the kitchen "faucet"). The main open area of the mouth, or oral cavity proper, runs from the gums and teeth to the fauces.

When you are chewing, you do not find it difficult to breathe simultaneously. The next time you have food in your mouth, notice how the arched shape of the roof of your mouth allows you to handle both digestion and respiration at the same time. This arch is called the palate. The anterior region of the palate serves as a wall (or septum) between the oral and nasal cavities as well as a rigid shelf against which the tongue can push food. It is created by the maxillary and palatine bones of the skull and, given its bony structure, is known as the hard palate. If you run your tongue along the roof of your mouth, you'll notice that the hard palate ends in the posterior oral cavity, and the tissue becomes fleshier. This part of the palate, known as the soft palate, is composed mainly of skeletal muscle. You can therefore manipulate, subconsciously, the soft palate—for instance, to yawn, swallow, or sing (Figure 3.3.1).

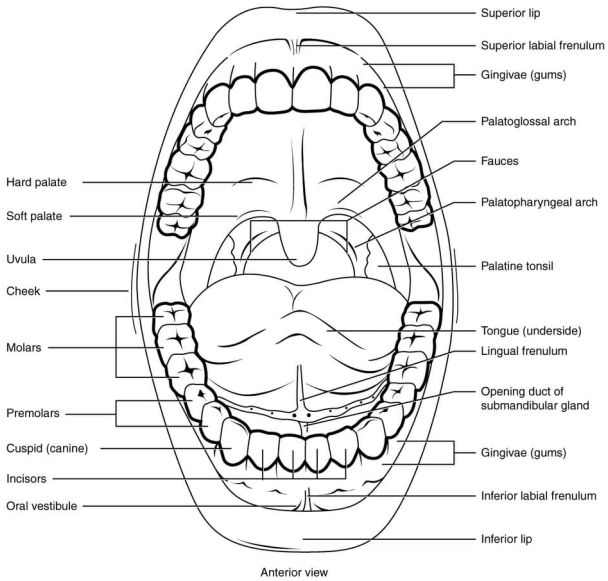


Figure 3.3.1: The mouth includes the lips, tongue, palate, gums, and teeth. (CC BY 4.0; via The mouth, Pharynx, and Esophagus). Detailed text description of the Figure 3.3.1.

The Tongue

Perhaps you have heard it said that the tongue is the strongest muscle in the body. Those who stake this claim cite its strength proportionate to its size. Although it is difficult to quantify the relative strength of different muscles, it remains indisputable that the tongue is a workhorse, facilitating ingestion, mechanical digestion, chemical digestion (lingual lipase), sensation (of taste, texture, and temperature of food), swallowing, and vocalization.

The tongue is attached to the mandible, the styloid processes of the temporal bones, and the hyoid bone. The hyoid is unique in that it only distantly/indirectly articulates with other bones. The tongue is positioned over the floor of the oral cavity. A medial septum extends the entire length of the tongue, dividing it into symmetrical halves.

Beneath its mucous membrane covering, each half of the tongue is composed of the same number and type of intrinsic and extrinsic skeletal muscles. The intrinsic muscles (those within the tongue) are the longitudinalis inferior, longitudinalis superior, transversus linguae, and verticalis linguae muscles. These allow you to change the size and shape of your tongue, as well as to stick it out, if you wish. Having such a flexible tongue facilitates both swallowing and speech.

As you learned in your study of the muscular system, the extrinsic muscles of the tongue are the palatoglossus, hyoglossus, styloglossus, and genioglossus muscles. These muscles originate outside the tongue and insert into connective tissues within the tongue. The mylohyoid is responsible for raising the tongue, the hyoglossus pulls it down and back, the styloglossus pulls it up and back, and the genioglossus pulls it forward. Working in concert, these muscles perform three important digestive functions in the mouth:

1. position food for optimal chewing
2. gather food into a bolus (rounded mass)
3. position food so it can be swallowed.

The top and sides of the tongue are studded with papillae, extensions of lamina propria of the mucosa, which are covered in stratified squamous epithelium (Figure 3.3.2). Fungiform papillae, which are mushroom shaped, cover a large area of the tongue; they tend to be larger toward the rear of the tongue and smaller on the tip and sides. In contrast, filiform papillae are long and thin. Fungiform papillae contain taste buds, and filiform papillae have touch receptors that help the tongue move food around in the mouth. The filiform papillae create an abrasive surface that performs mechanically, much like a cat's rough tongue that is used for grooming. Lingual glands in the lamina propria of the tongue secrete mucus and a watery serous fluid that contains the enzyme lingual lipase, which plays a minor role in breaking down triglycerides but does not begin working until it is activated in the stomach. A fold of mucous membrane on the underside of the tongue, the lingual frenulum, tethers the tongue to the floor of the mouth. People with the congenital anomaly ankyloglossia, also known by the non-medical term "tongue tie," have a lingual frenulum that is too short or otherwise malformed. Severe ankyloglossia can impair speech and must be corrected with surgery.

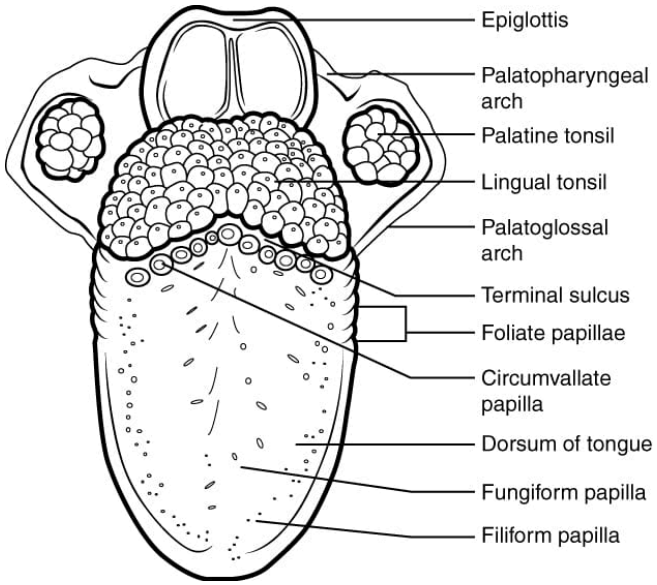


Figure 3.3.2: This superior view of the tongue shows the locations and types of lingual papillae. (CC BY 4.0; via The mouth, Pharynx, and Esophagus). Detailed text description of the Figure 3.3.2.

The Salivary Glands

Many small salivary glands are housed within the mucous membranes of the mouth and tongue. These minor exocrine glands are constantly secreting saliva, either directly into the oral cavity or indirectly through ducts, even while you sleep. In fact, an average of 1 to 1.5 liters of saliva is secreted each day. Usually just enough saliva is present to moisten the mouth and teeth. Secretion increases when you eat, because saliva is essential to moisten food and initiate the chemical breakdown of carbohydrates. Small amounts of saliva are also secreted by the labial glands in the lips. In addition, the buccal glands in the cheeks, palatal glands in the palate, and lingual glands in the tongue help ensure that all areas of the mouth are supplied with adequate saliva.

The Major Salivary Glands

Outside the oral mucosa are three pairs of major salivary glands, which secrete the majority of saliva into ducts that open into the mouth:

- The submandibular glands, which are in the floor of the mouth, secrete saliva into the mouth through the submandibular ducts.
- The sublingual glands, which lie below the tongue, use the lesser sublingual ducts to secrete saliva into the oral cavity.
- The parotid glands lie between the skin and the masseter muscle, near the ears. They secrete saliva into the mouth through the parotid duct, which is located near the second upper molar tooth (Figure 3.3.3).

Saliva

Saliva is essentially (99.4 percent) water. The remaining 0.6 percent is a complex mixture of ions, glycoproteins, enzymes, growth factors, and waste products. Perhaps the most important ingredient in saliva from the perspective of digestion is the enzyme salivary amylase, which initiates the breakdown of carbohydrates. Food does not spend enough time in the mouth to allow all the carbohydrates to break down, but salivary amylase continues acting until it is inactivated by stomach acids. Bicarbonate and phosphate ions function as chemical buffers, maintaining saliva at a pH between 6.35 and 6.85. Salivary mucus helps lubricate food, facilitating movement in the mouth, bolus formation, and swallowing. Saliva contains immunoglobulin A, which prevents microbes from penetrating the epithelium, and lysozyme, which makes saliva antimicrobial. Saliva also contains epidermal growth factor, which might have given rise to the adage “a mother’s kiss can heal a wound.”

Each of the major salivary glands secretes a unique formulation of saliva according to its cellular makeup. For example, the parotid glands secrete a watery solution that contains salivary amylase. The submandibular glands have cells similar to those of the parotid glands, as well as mucus-secreting cells. Therefore, saliva secreted by the submandibular glands also contains amylase

but in a liquid thickened with mucus. The sublingual glands contain mostly mucous cells, and they secrete the thickest saliva with the least amount of salivary amylase.

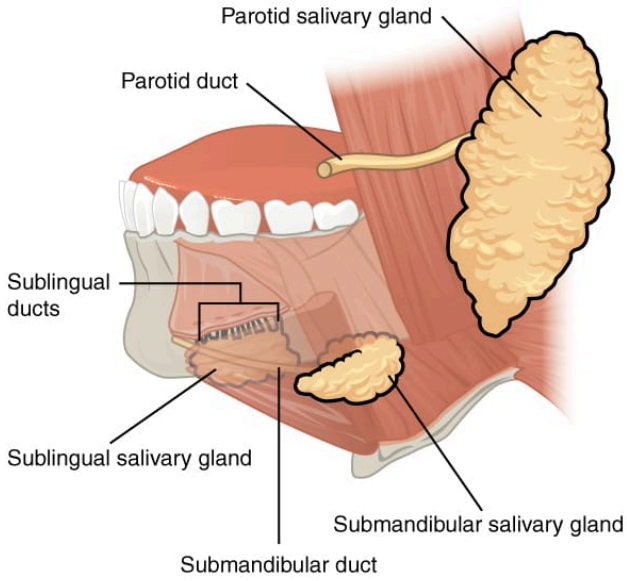


Figure 3.3.3: The major salivary glands are located outside the oral mucosa and deliver saliva into the mouth through ducts. (CC BY 4.0; via The mouth, Pharynx, and Esophagus). Detailed text description of the Figure 3.3.3.

Homeostatic Imbalances

The Parotid Glands: Mumps

Infections of the nasal passages and pharynx can attack any salivary gland. The parotid glands are the usual site of infection with the virus that causes mumps (paramyxovirus). Mumps manifests by enlargement and inflammation of the parotid glands, causing a characteristic swelling between the ears and the jaw. Symptoms include fever and throat pain, which can be severe when swallowing acidic substances such as orange juice.

In about one-third of males who are past puberty, mumps also causes testicular inflammation, typically affecting only one testis and rarely resulting in sterility. With the increasing use and effectiveness of mumps vaccines, the incidence of mumps has decreased dramatically. According to the U.S. Centers for Disease Control and Prevention (CDC), the number of mumps cases dropped from more than 150,000 in 1968 to fewer than 1700 in 1993 to only 11 reported cases in 2011.

Regulation of Salivation

The autonomic nervous system regulates salivation (the secretion of saliva). In the absence of food, parasympathetic stimulation keeps saliva flowing at just the right level for comfort as you speak, swallow, sleep, and generally go about life. Over-salivation can occur, for example, if you are stimulated by the smell of food, but that food is not available for you to eat. Drooling is an extreme instance of the overproduction of saliva. During times of stress, such as before speaking in public, sympathetic stimulation takes over, reducing salivation and producing the symptom of dry mouth often associated with anxiety. When you are dehydrated, salivation is reduced, causing the mouth to feel dry and prompting you to take action to quench your thirst.

Salivation can be stimulated by the sight, smell, and taste of food. It can even be stimulated by thinking about food. You might notice whether reading about food and salivation right now has had any effect on your production of saliva.

How does the salivation process work while you are eating? Food contains chemicals that stimulate taste receptors on the tongue, which send impulses to the superior and inferior salivatory nuclei in the brain stem. These two nuclei then send back parasympathetic impulses through fibers in the glossopharyngeal and facial nerves, which stimulate salivation. Even after you swallow food, salivation is increased to cleanse the mouth and to water down and neutralize any irritating chemical remnants, such as that hot sauce in your burrito. Most saliva is swallowed along with food and is reabsorbed, so that fluid is not lost.

The Teeth

The teeth, or dentes (singular = dens), are organs similar to bones that you use to tear, grind, and otherwise mechanically break down food.

Types of Teeth

During the course of your lifetime, you have two sets of teeth (one set of teeth is a dentition). Your 20 deciduous teeth, or baby teeth, first begin to appear at about 6 months of age. Between approximately age 6 and 12, these teeth are replaced by 32 permanent teeth. Moving from the center of the mouth toward the side, these are as follows (Figure 3.3.4):

- The eight incisors, four top and four bottom, are the sharp front teeth you use for biting into food.
- The four cuspids (or canines) flank the incisors and have a pointed edge (cusp) to tear up food. These fang-like teeth are superb for piercing tough or fleshy foods.
- Posterior to the cuspids are the eight premolars (or bicuspids), which have an overall flatter shape with two rounded cusps useful for mashing foods.
- The most posterior and largest are the 12 molars, which have several pointed cusps used to crush food so it is ready for swallowing. The third members of each set of three molars, top and bottom, are commonly referred to as the wisdom teeth, because their eruption is commonly delayed until early adulthood. It is not uncommon for wisdom teeth to fail to erupt; that is, they remain impacted. In these cases, the teeth are typically removed by orthodontic surgery.

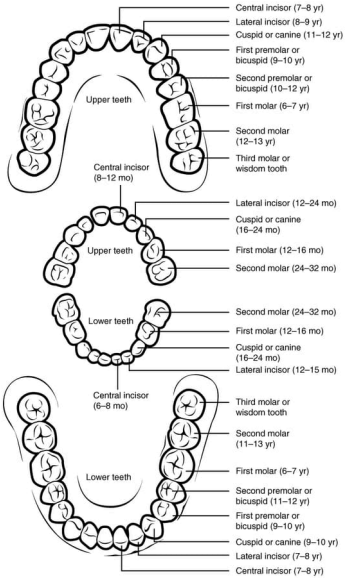


Figure 3.3.4: This figure of two human dentitions shows the arrangement of teeth in the maxilla and mandible, and the relationship between the deciduous and permanent teeth. (CC BY 4.0; via The mouth, Pharynx, and Esophagus). Detailed text description of the Figure 3.3.4.

Anatomy of a Tooth

The teeth are secured in the alveolar processes (sockets) of the maxilla and the mandible. Gingivae (commonly called the gums) are soft tissues that line the alveolar processes and surround the necks of the teeth. Teeth are also held in their sockets by a connective tissue called the periodontal ligament.

The two main parts of a tooth are the crown, which is the portion projecting above the gum line, and the root, which is embedded within the maxilla and mandible. Both parts contain an inner pulp cavity, containing loose connective tissue through which run nerves and blood vessels. The region of the pulp cavity that runs through the root of the tooth is called the root canal. Surrounding the pulp cavity is dentin, a bone-like tissue. In the root of each tooth, the dentin is covered by an even harder bone-like layer called cementum. In the crown of each tooth, the dentin is covered by an outer layer of enamel, the hardest substance in the body (Figure 3.3.5).

Although enamel protects the underlying dentin and pulp cavity, it is still nonetheless susceptible to mechanical and chemical erosion, or what is known as tooth decay. The most common form, dental caries (cavities) develops when colonies of bacteria feeding on sugars in the mouth release acids that cause soft tissue inflammation and degradation of the calcium crystals of the enamel. The digestive functions of the mouth are summarized in Table 3.3.1.

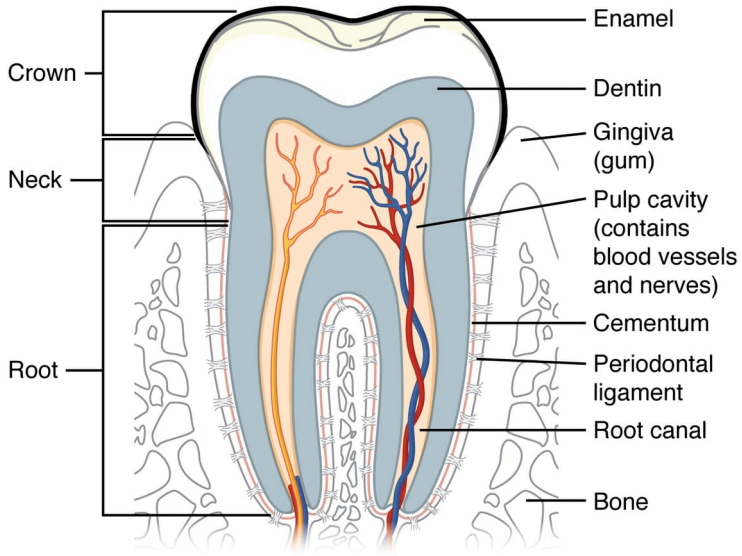


Figure 3.3.5: This longitudinal section through a molar in its alveolar socket shows the relationships between enamel, dentin, and pulp. (CC BY 4.0; via The mouth, Pharynx, and Esophagus). Detailed text description of the Figure 3.3.5.

Table 3.3.1: Digestive Functions of the Mouth

Structure	Action	Outcome
Lips and cheeks	Confine food between teeth	• Food is chewed evenly during mastication
Salivary glands	Secrete saliva	• Moisten and lubricate the lining of the mouth and pharynx • Moisten, soften, and dissolve food • Clean the mouth and teeth • Salivary amylase breaks down starch
Tongue's extrinsic muscles	Move tongue sideways, and in and out	• Manipulate food for chewing • Shape food into a bolus • Manipulate food for swallowing
Tongue's intrinsic muscles	Change tongue shape	• Manipulate food for swallowing
Taste buds	Sense food in mouth and sense taste	• Nerve impulses from taste buds are conducted to salivary nuclei in the brain stem and then to salivary glands, stimulating saliva secretion

Structure	Action	Outcome
Lingual glands	Secrete lingual lipase	• Activated in the stomach • Break down triglycerides into fatty acids and diglycerides
Teeth	Shred and crush food	• Break down solid food into smaller particles for deglutition

The Pharynx

The pharynx (throat) is involved in both digestion and respiration. It receives food and air from the mouth, and air from the nasal cavities. When food enters the pharynx, involuntary muscle contractions close off the air passageways.

A short tube of skeletal muscle lined with a mucous membrane, the pharynx runs from the posterior oral and nasal cavities to the opening of the esophagus and larynx. It has three subdivisions. The most superior, the nasopharynx, is involved only in breathing and speech. The other two subdivisions, the oropharynx and the laryngopharynx, are used for both breathing and digestion. The oropharynx begins inferior to the nasopharynx and is continuous below with the laryngopharynx (Figure 3.3.6). The inferior border of the laryngopharynx connects to the esophagus, whereas the anterior portion connects to the larynx, allowing air to flow into the bronchial tree.

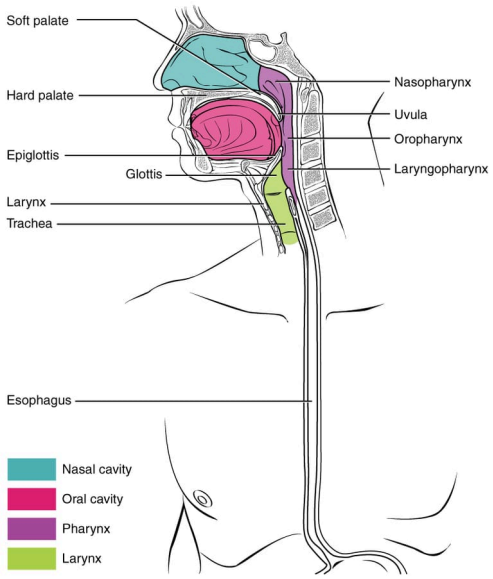


Figure 3.3.6: The pharynx runs from the nostrils to the esophagus and the larynx. (CC BY 4.0; via The mouth, Pharynx, and Esophagus). Detailed text description of the Figure 3.3.6.

Histologically, the wall of the oropharynx is similar to that of the oral cavity. The mucosa includes a stratified squamous epithelium that is endowed with mucus-producing glands. During swallowing, the elevator skeletal muscles of the pharynx contract, raising and expanding the pharynx to receive the bolus of food. Once received, these muscles relax and the constrictor muscles of the pharynx contract, forcing the bolus into the esophagus and initiating peristalsis.

Usually during swallowing, the soft palate and uvula rise reflexively to close off the entrance to the nasopharynx. At the same time, the larynx is pulled superiorly and the cartilaginous epiglottis, its most superior structure, folds inferiorly, covering the glottis (the opening to the larynx); this process effectively blocks access to the trachea and bronchi. When the food "goes down the wrong way," it goes into the trachea. When food enters the trachea, the reaction is to cough, which usually forces the food up and out of the trachea, and back into the pharynx.

The Esophagus

The esophagus is a muscular tube that connects the pharynx to the stomach. It is approximately 25.4 cm (10 in) in length, located posterior to the trachea, and remains in a collapsed form when not engaged in swallowing. As illustrated in Figure 3.3.7, the esophagus runs a mainly straight route through the mediastinum of the thorax. To enter the abdomen, the esophagus penetrates the diaphragm through an opening called the esophageal hiatus.

Passage of Food through the Esophagus

The upper esophageal sphincter, which is continuous with the inferior pharyngeal constrictor, controls the movement of food from the pharynx into the esophagus. The upper two-thirds of the esophagus consists of both smooth and skeletal muscle fibers, with the latter fading out in the bottom third of the esophagus. Rhythmic waves of peristalsis, which begin in the upper esophagus, propel the bolus of food toward the stomach. Meanwhile, secretions from the esophageal mucosa lubricate the esophagus and food. Food passes from the esophagus into the stomach at the lower esophageal sphincter (also called the gastroesophageal or cardiac sphincter). Recall that sphincters are muscles that surround tubes and serve as valves, closing the tube when the sphincters contract and opening it when they relax. The lower esophageal sphincter relaxes to let food pass into the stomach, and then contracts to prevent stomach acids from backing up into the esophagus. Surrounding this sphincter is the muscular diaphragm, which helps close off the sphincter when no food is being swallowed. When the lower esophageal sphincter does not completely close, the stomach's contents can reflux (that is, back up into the esophagus), causing heartburn or gastroesophageal reflux disease (GERD).

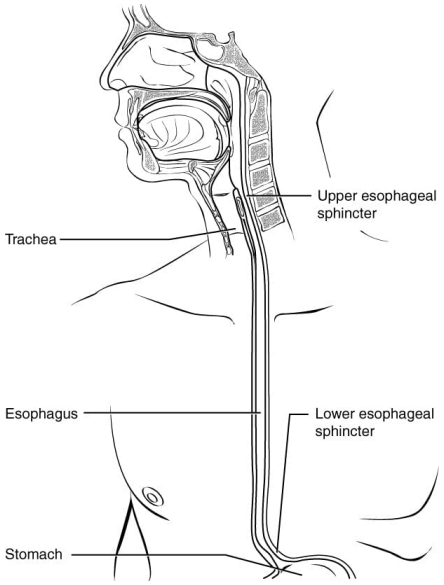


Figure 3.3.7: The upper esophageal sphincter controls the movement of food from the pharynx to the esophagus. The lower esophageal sphincter controls the movement of food from the esophagus to the stomach. (CC BY 4.0; via The mouth, Pharynx, and Esophagus). Detailed text description of the Figure 3.3.7.

Histology of the Esophagus

The mucosa of the esophagus is made up of an epithelial lining that contains non-keratinized, stratified squamous epithelium, with a layer of basal and parabasal cells. This epithelium protects against erosion from food particles. The mucosa's lamina propria contains mucus-secreting glands. The muscularis layer changes according to location: In the upper third of the esophagus, the muscularis is skeletal muscle. In the middle third, it is both skeletal and smooth muscle. In the lower third, it is smooth muscle. As mentioned previously, the most superficial layer of the esophagus is called the adventitia, not the serosa. In contrast to the stomach and intestines, the loose connective tissue of the adventitia is not covered by a fold of visceral peritoneum. The digestive functions of the esophagus are identified in Table 3.3.2.

Table 3.3.2: Digestive Functions of the Esophagus

Action	Outcome
Upper esophageal sphincter relaxation	Allows the bolus to move from the laryngopharynx to the esophagus
Peristalsis	Propels the bolus through the esophagus
Lower esophageal sphincter relaxation	Allows the bolus to move from the esophagus into the stomach and prevents chyme from entering the esophagus
Mucus secretion	Lubricates the esophagus, allowing easy passage of the bolus

Deglutition

Deglutition is another word for swallowing—the movement of food from the mouth to the stomach. The entire process takes about 4 to 8 seconds for solid or semisolid food, and about 1 second for very soft food and liquids. Although this sounds quick and effortless, deglutition is, in fact, a complex process that involves both the skeletal muscle of the tongue and the muscles of the pharynx and esophagus. It is aided by the presence of mucus and saliva. There are three stages in deglutition: the voluntary phase, the pharyngeal phase, and the esophageal phase (Figure 3.3.8). The autonomic nervous system controls the latter two phases.

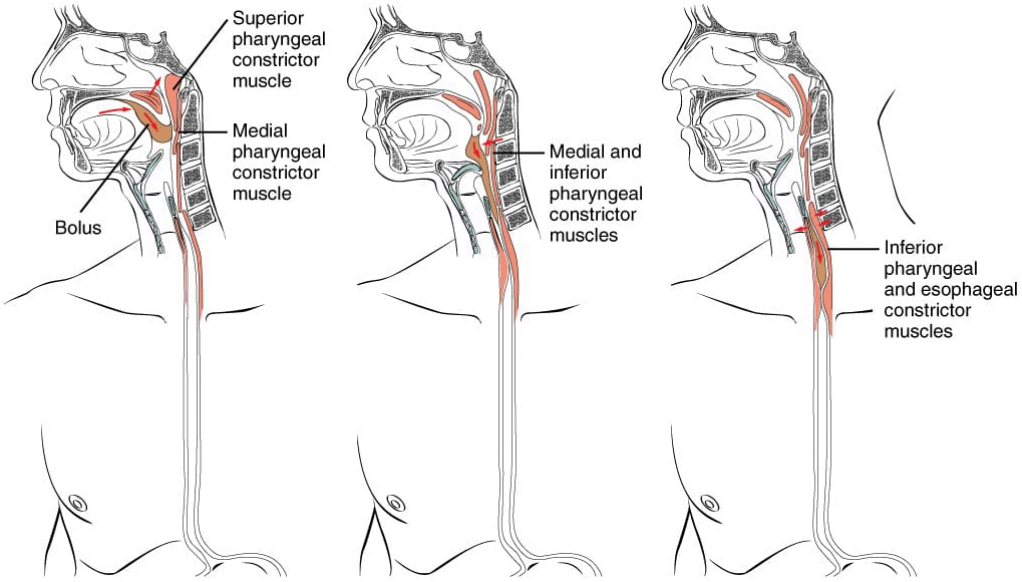


Figure 3.3.8: Deglutition includes the voluntary phase and two involuntary phases: the pharyngeal phase and the esophageal phase. (CC BY 4.0; via The mouth, Pharynx, and Esophagus). Detailed text description of the Figure 3.3.8.

The Voluntary Phase

The voluntary phase of deglutition (also known as the oral or buccal phase) is so called because you can control when you swallow food. In this phase, chewing has been completed and swallowing is set in motion. The tongue moves upward and backward against the palate, pushing the bolus to the back of the oral cavity and into the oropharynx. Other muscles keep the mouth closed and prevent food from falling out. At this point, the two involuntary phases of swallowing begin.

The Pharyngeal Phase

In the pharyngeal phase, stimulation of receptors in the oropharynx sends impulses to the deglutition center (a collection of neurons that controls swallowing) in the medulla oblongata. Impulses are then sent back to the uvula and soft palate, causing them to move upward and close off the nasopharynx. The laryngeal muscles also constrict to prevent aspiration of food into the trachea. At this point, deglutition apnea takes place, which means that breathing ceases for a very brief time. Contractions of the pharyngeal constrictor muscles move the bolus through the oropharynx and laryngopharynx. Relaxation of the upper esophageal

sphincter then allows food to enter the esophagus.

The Esophageal Phase

The entry of food into the esophagus marks the beginning of the esophageal phase of deglutition and the initiation of peristalsis. As in the previous phase, the complex neuromuscular actions are controlled by the medulla oblongata. Peristalsis propels the bolus through the esophagus and toward the stomach. The circular muscle layer of the muscularis contracts, pinching the esophageal wall and forcing the bolus forward. At the same time, the longitudinal muscle layer of the muscularis also contracts, shortening this area and pushing out its walls to receive the bolus. In this way, a series of contractions keeps moving food toward the stomach. When the bolus nears the stomach, distention of the esophagus initiates a short reflex relaxation of the lower esophageal sphincter that allows the bolus to pass into the stomach. During the esophageal phase, esophageal glands secrete mucus that lubricates the bolus and minimizes friction.

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3.4: The Stomach

Structure and Functions of the Stomach

Although a minimal amount of carbohydrate digestion occurs in the mouth, chemical digestion really gets underway in the stomach. An expansion of the alimentary canal that lies immediately inferior to the esophagus, the stomach links the esophagus to the first part of the small intestine (the duodenum) and is relatively fixed in place at its esophageal and duodenal ends. In between, however, it can be a highly active structure, contracting and continually changing position and size. These contractions provide mechanical assistance to digestion. The empty stomach is only about the size of your fist, but can stretch to hold as much as 4 liters of food and fluid, or more than 75 times its empty volume, and then return to its resting size when empty. Although you might think that the size of a person's stomach is related to how much food that individual consumes, body weight does not correlate with stomach size. Rather, when you eat greater quantities of food—such as at holiday dinner—you stretch the stomach more than when you eat less.

Popular culture tends to refer to the stomach as the location where all digestion takes place. Of course, this is not true. An important function of the stomach is to serve as a temporary holding chamber. You can ingest a meal far more quickly than it can be digested and absorbed by the small intestine. Thus, the stomach holds food and parses only small amounts into the small intestine at a time. Foods are not processed in the order they are eaten; rather, they are mixed together with digestive juices in the stomach until they are converted into chyme, which is released into the small intestine.

As you will see in the sections that follow, the stomach plays several important roles in chemical digestion, including the continued digestion of carbohydrates and the initial digestion of proteins and triglycerides. Little if any nutrient absorption occurs in the stomach, with the exception of the negligible amount of nutrients in alcohol.

Structure

There are four main regions in the stomach: the cardia, fundus, body, and pylorus (Figure 3.4.1). The cardia (or cardiac region) is the point where the esophagus connects to the stomach and through which food passes into the stomach. Located inferior to the diaphragm, above and to the left of the cardia, is the dome-shaped fundus. Below the fundus is the body, the main part of the stomach. The funnel-shaped pylorus connects the stomach to the duodenum. The wider end of the funnel, the pyloric antrum, connects to the body of the stomach. The narrower end is called the pyloric canal, which connects to the duodenum. The smooth muscle pyloric sphincter is located at this latter point of connection and controls stomach emptying. In the absence of food, the stomach deflates inward, and its mucosa and submucosa fall into a large fold called a ruga.

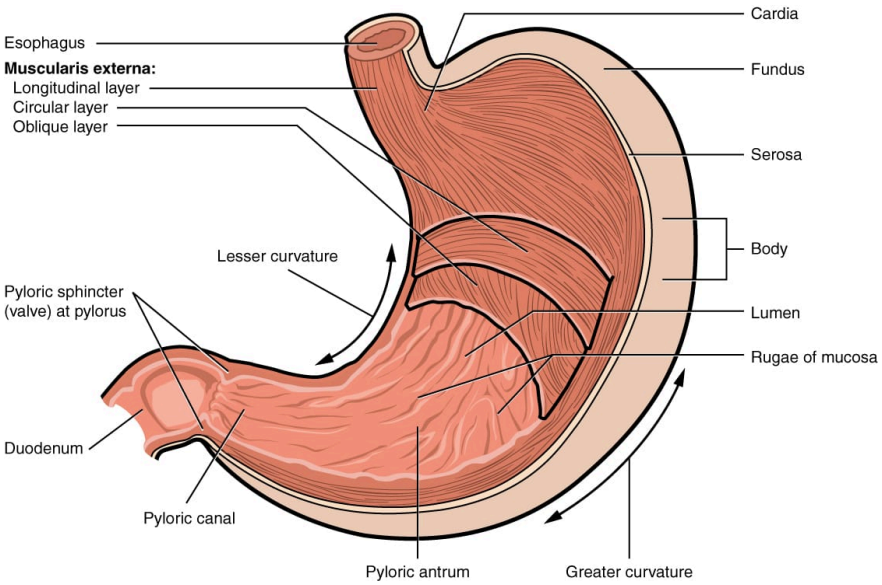


Figure 3.4.1: The stomach has four major regions: the cardia, fundus, body, and pylorus. The addition of an inner oblique smooth muscle layer gives the muscularis the ability to vigorously churn and mix food. (CC BY 4.0; via The Stomach). Detailed text description of the Figure 3.4.1.

Histology

The wall of the stomach is made of the same four layers as most of the rest of the alimentary canal, but with adaptations to the mucosa and muscularis for the unique functions of this organ. In addition to the typical circular and longitudinal smooth muscle layers, the muscularis has an inner oblique smooth muscle layer (Figure 3.4.2). As a result, in addition to moving food through the canal, the stomach can vigorously churn food, mechanically breaking it down into smaller particles.

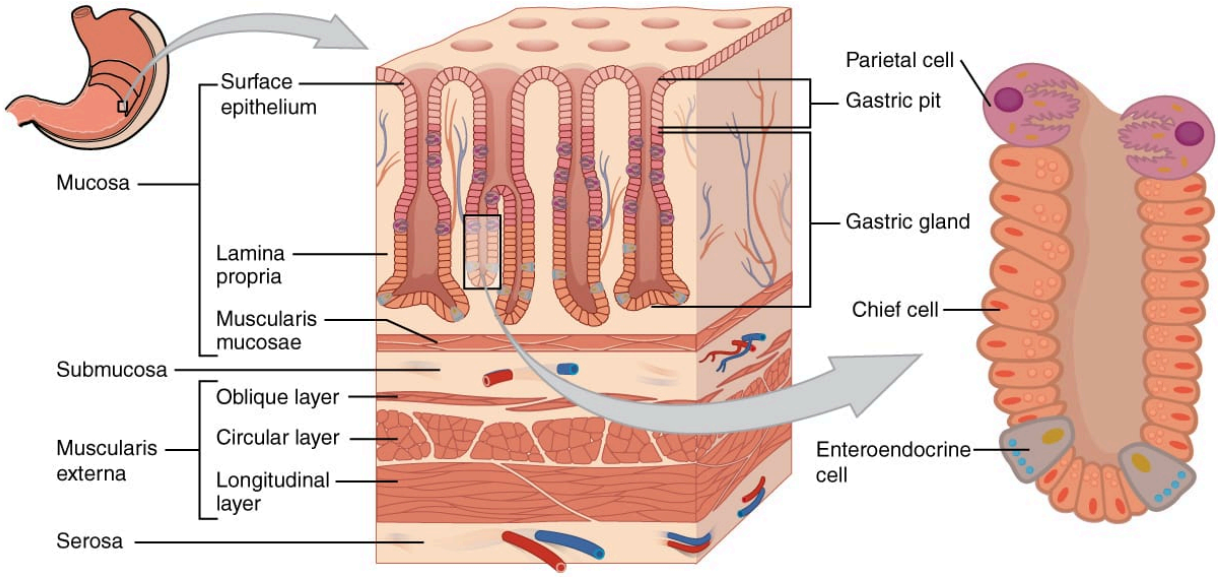


Figure 3.4.2: The stomach wall is adapted for the functions of the stomach. In the epithelium, gastric pits lead to gastric glands that secrete gastric juice. The gastric glands (one gland is shown enlarged on the right) contain different types of cells that secrete a variety of enzymes, including hydrochloride acid, which activates the protein-digesting enzyme pepsin. (CC BY 4.0; via The Stomach). Detailed text description of the Figure 3.4.2.

The stomach mucosa's epithelial lining consists only of surface mucus cells, which secrete a protective coat of alkaline mucus. A vast number of gastric pits dot the surface of the epithelium, giving it the appearance of a well-used pincushion, and mark the entry to each gastric gland, which secretes a complex digestive fluid referred to as gastric juice.

Although the walls of the gastric pits are made up primarily of mucus cells, the gastric glands are made up of different types of cells. The glands of the cardia and pylorus are composed primarily of mucus-secreting cells. Cells that make up the pyloric antrum secrete mucus and a number of hormones, including the majority of the stimulatory hormone, gastrin. The much larger glands of the fundus and body of the stomach, the site of most chemical digestion, produce most of the gastric secretions. These glands are made up of a variety of secretory cells. These include parietal cells, chief cells, mucous neck cells, and enteroendocrine cells.

Parietal cells—Located primarily in the middle region of the gastric glands are parietal cells, which are among the most highly differentiated of the body's epithelial cells. These relatively large cells produce both hydrochloric acid (HCl) and intrinsic factor. HCl is responsible for the high acidity (pH 1.5 to 3.5) of the stomach contents and is needed to activate the protein-digesting enzyme, pepsin. The acidity also kills much of the bacteria you ingest with food and helps to denature proteins, making them more available for enzymatic digestion. Intrinsic factor is a glycoprotein necessary for the absorption of vitamin B_{12} in the small intestine.

Chief cells—Located primarily in the basal regions of gastric glands are chief cells, which secrete pepsinogen, the inactive proenzyme form of pepsin. HCl is necessary for the conversion of pepsinogen to pepsin.

Mucous neck cells—Gastric glands in the upper part of the stomach contain mucous neck cells that secrete thin, acidic mucus that is much different from the mucus secreted by the goblet cells of the surface epithelium. The role of this mucus is not currently known.

Enteroendocrine cells—Finally, enteroendocrine cells found in the gastric glands secrete various hormones into the interstitial fluid of the lamina propria. These include gastrin, which is released mainly by enteroendocrine G cells.

Table 3.4.1: Hormones Secreted by the Stomach

Hormone	Production site	Production stimulus	Target organ	Action
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Stomach	Increases secretion by gastric glands; promotes gastric emptying
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Small intestine	Promotes intestinal muscle contraction
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Ileocecal valve	Relaxes valve
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Large intestine	Triggers mass movements
Ghrelin	Stomach mucosa, mainly fundus	Fasting state (levels increase just prior to meals)	Hypothalamus	Regulates food intake, primarily by stimulating hunger and satiety
Histamine	Stomach mucosa	Presence of food in the stomach	Stomach	Stimulates parietal cells to release HCl
Serotonin	Stomach mucosa	Presence of food in the stomach	Stomach	Contracts stomach muscle
Somatostatin	Mucosa of stomach, especially pyloric antrum; also duodenum	Presence of food in the stomach; sympathetic axon stimulation	Stomach	Restricts all gastric secretions, gastric motility, and emptying
Somatostatin	Mucosa of stomach, especially pyloric antrum; also duodenum	Presence of food in the stomach; sympathetic axon stimulation	Pancreas	Restricts pancreatic secretions
Somatostatin	Mucosa of stomach, especially pyloric antrum; also duodenum	Presence of food in the stomach; sympathetic axon stimulation	Small intestine	Reduces intestinal absorption by reducing blood flow

Gastric Secretion

The secretion of gastric juice is controlled by both nerves and hormones. Stimuli in the brain, stomach, and small intestine activate or inhibit gastric juice production. This is why the three phases of gastric secretion are called the cephalic, gastric, and intestinal phases (Figure 3.4.3). However, once gastric secretion begins, all three phases can occur simultaneously.

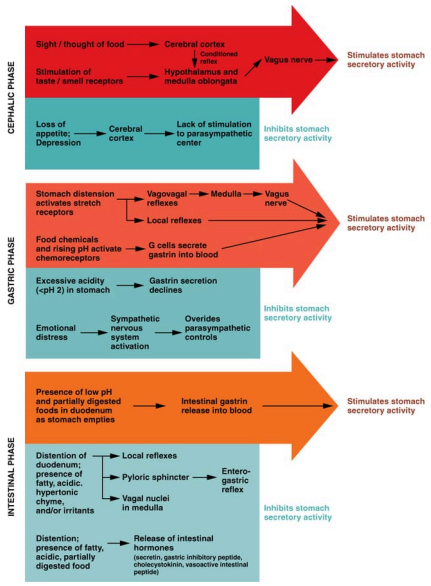


Figure 3.4.3: The three phases of gastric secretion occurs in three phases: cephalic, gastric, and intestinal. During each phase, the secretion of gastric juice can be stimulated or inhibited. (CC BY 4.0; via The Stomach). Detailed text description of the Figure 3.4.3.

The cephalic phase (reflex phase) of gastric secretion, which is relatively brief, takes place before food enters the stomach. The smell, taste, sight, or thought of food triggers this phase. For example, when you bring a piece of sushi to your lips, impulses from receptors in your taste buds or the nose are relayed to your brain, which returns signals that increase gastric secretion to prepare your stomach for digestion. This enhanced secretion is a conditioned reflex, meaning it occurs only if you like or want a particular food. Depression and loss of appetite can suppress the cephalic reflex.

The gastric phase of secretion lasts 3 to 4 hours, and is set in motion by local neural and hormonal mechanisms triggered by the entry of food into the stomach. For example, when your sushi reaches the stomach, it creates distention that activates the stretch receptors. This stimulates parasympathetic neurons to release acetylcholine, which then provokes increased secretion of gastric juice. Partially digested proteins, caffeine, and rising pH stimulate the release of gastrin from enteroendocrine G cells, which in turn induces parietal cells to increase their production of HCl, which is needed to create an acidic environment for the conversion of pepsinogen to pepsin, and protein digestion. Additionally, the release of gastrin activates vigorous smooth muscle contractions. However, it should be noted that the stomach does have a natural means of avoiding excessive acid secretion and potential heartburn. Whenever pH levels drop too low, cells in the stomach react by suspending HCl secretion and increasing mucous secretions.

The intestinal phase of gastric secretion has both excitatory and inhibitory elements. The duodenum has a major role in regulating the stomach and its emptying. When partially digested food fills the duodenum, intestinal mucosal cells release a hormone called intestinal (enteric) gastrin, which further excites gastric juice secretion. This stimulatory activity is brief, however, because when the intestine distends with chyme, the enterogastric reflex inhibits secretion. One of the effects of this reflex is to close the pyloric sphincter, which blocks additional chyme from entering the duodenum.

The Mucosal Barrier

The mucosa of the stomach is exposed to the highly corrosive acidity of gastric juice. Gastric enzymes that can digest protein can also digest the stomach itself. The stomach is protected from self-digestion by the mucosal barrier. This barrier has several components. First, the stomach wall is covered by a thick coating of bicarbonate-rich mucus. This mucus forms a physical barrier, and its bicarbonate ions neutralize acid. Second, the epithelial cells of the stomach's mucosa meet at tight junctions, which block gastric juice from penetrating the underlying tissue layers. Finally, stem cells located where gastric glands join the gastric pits

quickly replace damaged epithelial mucosal cells, when the epithelial cells are shed. In fact, the surface epithelium of the stomach is completely replaced every 3 to 6 days.

Homeostatic Imbalances

Ulcers: When the Mucosal Barrier Breaks Down

As effective as the mucosal barrier is, it is not a "fail-safe" mechanism. Sometimes, gastric juice eats away at the superficial lining of the stomach mucosa, creating erosions, which mostly heal on their own. Deeper and larger erosions are called ulcers.

Why does the mucosal barrier break down? A number of factors can interfere with its ability to protect the stomach lining. The majority of all ulcers are caused by either excessive intake of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, or *Helicobacter pylori* infection.

Antacids help relieve symptoms of ulcers such as "burning" pain and indigestion. When ulcers are caused by NSAID use, switching to other classes of pain relievers allows healing. When caused by *H. pylori* infection, antibiotics are effective.

A potential complication of ulcers is perforation: Perforated ulcers create a hole in the stomach wall, resulting in peritonitis (inflammation of the peritoneum). These ulcers must be repaired surgically.

Digestive Functions of the Stomach

The stomach participates in virtually all the digestive activities with the exception of ingestion and defecation. Although almost all absorption takes place in the small intestine, the stomach does absorb some drugs, such as alcohol and aspirin.

Mechanical Digestion

Within a few moments after food enters your stomach, mixing waves begin to occur at intervals of approximately 20 seconds. A mixing wave is a unique type of peristalsis that mixes and softens the food with gastric juices to create chyme. The initial mixing waves are relatively gentle, but these are followed by more intense waves, starting at the body of the stomach and increasing in force as they reach the pylorus. It is fair to say that long before your sushi exits through the pyloric sphincter, it bears little resemblance to the sushi you ate.

The pylorus, which holds around 30 mL (1 fluid ounce) of chyme, acts as a filter, permitting only liquids and small food particles to pass through the mostly, but not fully, closed pyloric sphincter. In a process called gastric emptying, rhythmic mixing waves force about 3 mL of chyme at a time through the pyloric sphincter and into the duodenum. Release of a greater amount of chyme at one time would overwhelm the capacity of the small intestine to handle it. The rest of the chyme is pushed back into the body of the stomach, where it continues mixing. This process is repeated when the next mixing waves force more chyme into the duodenum.

Gastric emptying is regulated by both the stomach and the duodenum. The presence of chyme in the duodenum activates receptors that inhibit gastric secretion. This prevents additional chyme from being released by the stomach before the duodenum is ready to process it.

Chemical Digestion

The fundus plays an important role, because it stores both undigested food and gases that are released during the process of chemical digestion. Food may sit in the fundus of the stomach for a while before being mixed with the chyme. While the food is in the fundus, the digestive activities of salivary amylase continue until the food begins mixing with the acidic chyme. Ultimately, mixing waves incorporate this food with the chyme, the acidity of which inactivates salivary amylase and activates lingual lipase. Lingual lipase then begins breaking down triglycerides into free fatty acids, and mono- and diglycerides.

The breakdown of protein begins in the stomach through the actions of HCl and the enzyme pepsin.

Its numerous digestive functions notwithstanding, there is only one stomach function necessary to life: the production of intrinsic factor. The intestinal absorption of vitamin B_{12}, which is necessary for both the production of mature red blood cells and normal neurological functioning, cannot occur without intrinsic factor. People who undergo total gastrectomy (stomach removal)—for life-

threatening stomach cancer, for example—can survive with minimal digestive dysfunction if they receive vitamin B_{12} injections.

The contents of the stomach are completely emptied into the duodenum within 2 to 4 hours after you eat a meal. Different types of food take different amounts of time to process. Foods heavy in carbohydrates empty fastest, followed by high-protein foods. Meals with a high triglyceride content remain in the stomach the longest. Since enzymes in the small intestine digest fats slowly, food can stay in the stomach for 6 hours or longer when the duodenum is processing fatty chyme. However, note that this is still a fraction of the 24 to 72 hours that full digestion typically takes from start to finish.

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3.5: The Small and Large Intestines

The Intestines

The word intestine is derived from a Latin root meaning “internal,” and indeed, the two organs together nearly fill the interior of the abdominal cavity. In addition, called the small and large bowel, or colloquially the “guts,” they constitute the greatest mass and length of the alimentary canal and, with the exception of ingestion, perform all digestive system functions.

The Small Intestine

Chyme released from the stomach enters the small intestine, which is the primary digestive organ in the body. Not only is this where most digestion occurs, it is also where practically all absorption occurs. The longest part of the alimentary canal, the small intestine is about 3.05 meters (10 feet) long in a living person (but about twice as long in a cadaver due to the loss of muscle tone). Since this makes it about five times longer than the large intestine, you might wonder why it is called “small.” In fact, its name derives from its relatively smaller diameter of only about 2.54 cm (1 in), compared with 7.62 cm (3 in) for the large intestine. As we’ll see shortly, in addition to its length, the folds and projections of the lining of the small intestine work to give it an enormous surface area, which is approximately 200 m^2, more than 100 times the surface area of your skin. This large surface area is necessary for complex processes of digestion and absorption that occur within it.

Structure

The coiled tube of the small intestine is subdivided into three regions. From proximal (at the stomach) to distal, these are the duodenum, jejunum, and ileum (Figure 3.5.1).

The shortest region is the 25.4-cm (10-in) duodenum, which begins at the pyloric sphincter. Just past the pyloric sphincter, it bends posteriorly behind the peritoneum, becoming retroperitoneal, and then makes a C-shaped curve around the head of the pancreas before ascending anteriorly again to return to the peritoneal cavity and join the jejunum. The duodenum can therefore be subdivided into four segments: the superior, descending, horizontal, and ascending duodenum.

Of particular interest is the hepatopancreatic ampulla (ampulla of Vater). Located in the duodenal wall, the ampulla marks the transition from the anterior portion of the alimentary canal to the mid-region, and is where the bile duct (through which bile passes from the liver) and the main pancreatic duct (through which pancreatic juice passes from the pancreas) join. This ampulla opens into the duodenum at a tiny volcano-shaped structure called the major duodenal papilla. The hepatopancreatic sphincter (sphincter of Oddi) regulates the flow of both bile and pancreatic juice from the ampulla into the duodenum.

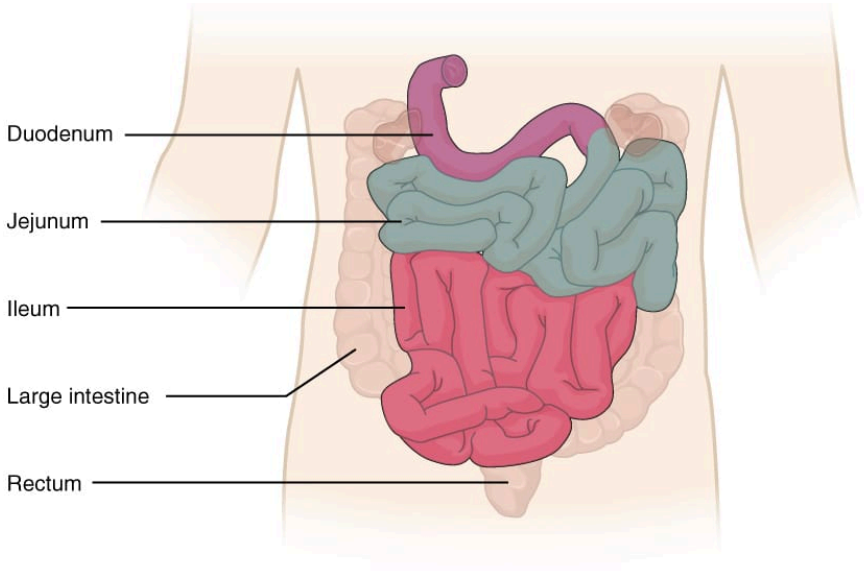


Figure 3.5.1: The three regions of the small intestine are the duodenum, jejunum, and ileum. (CC BY 4.0; via The Small and Large Intestine). Detailed text description of the Figure 3.5.1.

The jejunum is about 0.9 meters (3 feet) long (in life) and runs from the duodenum to the ileum. Jejunum means “empty” in Latin and supposedly was so named by the ancient Greeks who noticed it was always empty at death. No clear demarcation exists between the jejunum and the final segment of the small intestine, the ileum.

The ileum is the longest part of the small intestine, measuring about 1.8 meters (6 feet) in length. It is thicker, more vascular, and has more developed mucosal folds than the jejunum. The ileum joins the cecum, the first portion of the large intestine, at the ileocecal sphincter (or valve). The jejunum and ileum are tethered to the posterior abdominal wall by the mesentery. The large intestine frames these three parts of the small intestine.

Parasympathetic nerve fibers from the vagus nerve and sympathetic nerve fibers from the thoracic splanchnic nerve provide extrinsic innervation to the small intestine. The superior mesenteric artery is its main arterial supply. Veins run parallel to the arteries and drain into the superior mesenteric vein. Nutrient-rich blood from the small intestine is then carried to the liver via the hepatic portal vein.

Histology

The wall of the small intestine is composed of the same four layers typically present in the alimentary system. However, three features of the mucosa and submucosa are unique. These features, which increase the absorptive surface area of the small intestine more than 600-fold, include circular folds, villi, and microvilli (Figure 3.5.2). These adaptations are most abundant in the proximal two-thirds of the small intestine, where the majority of absorption occurs.

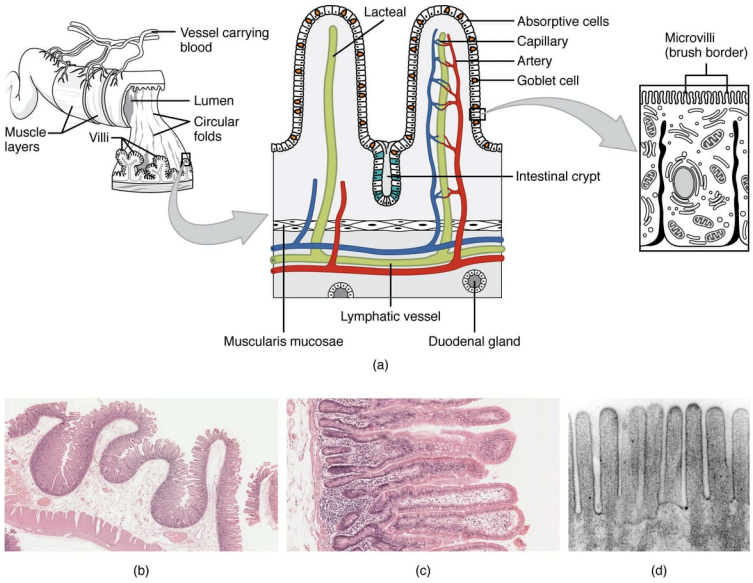


Figure 3.5.2: (a) The absorptive surface of the small intestine is vastly enlarged by the presence of circular folds, villi, and microvilli. (b) Micrograph of the circular folds. (c) Micrograph of the villi. (d) Electron micrograph of the microvilli. From left to right, LM x 56, LM x 508, EM x 196,000. (CC BY 4.0; via The Small and Large Intestine). Detailed text description of the Figure 3.5.2.

Circular folds

Also called a plica circulare, a circular fold is a deep ridge in the mucosa and submucosa. Beginning near the proximal part of the duodenum and ending near the middle of the ileum, these folds facilitate absorption. Their shape causes the chyme to spiral, rather than move in a straight line, through the small intestine. Spiraling slows the movement of chyme and provides the time needed for nutrients to be fully absorbed.

Villi

Within the circular folds are small (0.5–1 mm long) hairlike vascularized projections called villi (singular = villus) that give the mucosa a furry texture. There are about 20 to 40 villi per square millimeter, increasing the surface area of the epithelium tremendously. The mucosal epithelium, primarily composed of absorptive cells, covers the villi. In addition to muscle and connective tissue to support its structure, each villus contains a capillary bed composed of one arteriole and one venule, as well as a lymphatic capillary called a lacteal. The breakdown products of carbohydrates and proteins (sugars and amino acids) can enter the bloodstream directly, but lipid breakdown products are absorbed by the lacteals and transported to the bloodstream via the lymphatic system.

Microvilli

As their name suggests, microvilli (singular = microvillus) are much smaller (1 μm) than villi. They are cylindrical apical surface extensions of the plasma membrane of the mucosa's epithelial cells, and are supported by microfilaments within those cells. Although their small size makes it difficult to see each microvillus, their combined microscopic appearance suggests a mass of bristles, which is termed the brush border. Fixed to the surface of the microvilli membranes are enzymes that finish digesting carbohydrates and proteins. There are an estimated 200 million microvilli per square millimeter of small intestine, greatly expanding the surface area of the plasma membrane and thus greatly enhancing absorption.

Intestinal Glands

In addition to the three specialized absorptive features just discussed, the mucosa between the villi is dotted with deep crevices that each lead into a tubular intestinal gland (crypt of Lieberkühn), which is formed by cells that line the crevices. These produce intestinal juice, a slightly alkaline (pH 7.4 to 7.8) mixture of water and mucus. Each day, about 0.95 to 1.9 liters (1 to 2 quarts) are secreted in response to the distention of the small intestine or the irritating effects of chyme on the intestinal mucosa.

The submucosa of the duodenum is the only site of the complex mucus-secreting duodenal glands (Brunner's glands), which produce a bicarbonate-rich alkaline mucus that buffers the acidic chyme as it enters from the stomach. The roles of the cells in the small intestinal mucosa are detailed in Table 3.5.1.

Table 3.5.1: Cells of the Small Intestinal Mucosa

Cell type	Location in the mucosa	Function
Absorptive	Epithelium/intestinal glands	Digestion and absorption of nutrients in chyme
Goblet	Epithelium/intestinal glands	Secretion of mucus
Paneth	Intestinal glands	Secretion of the bactericidal enzyme lysozyme; phagocytosis
G cells	Intestinal glands of duodenum	Secretion of the hormone intestinal gastrin
I cells	Intestinal glands of duodenum	Secretion of the hormone cholecystokinin, which stimulates release of pancreatic juices and bile
K cells	Intestinal glands	Secretion of the hormone glucose-dependent insulinotropic peptide, which stimulates the release of insulin
M cells	Intestinal glands of duodenum and jejunum	Secretion of the hormone motilin, which accelerates gastric emptying, stimulates intestinal peristalsis, and stimulates the production of pepsin
S cells	Intestinal glands	Secretion of the hormone secretin

Intestinal MALT

The lamina propria of the small intestine mucosa is studded with quite a bit of MALT. In addition to solitary lymphatic nodules, aggregations of intestinal MALT, which are typically referred to as Peyer's patches, are concentrated in the distal ileum, and serve to keep bacteria from entering the bloodstream. Peyer's patches are most prominent in young people and become less distinct as you age, which coincides with the general activity of our immune system.

Mechanical Digestion in the Small Intestine

The movement of intestinal smooth muscles includes both segmentation and a form of peristalsis called migrating motility complexes. The kind of peristaltic mixing waves seen in the stomach are not observed here.

If you could see into the small intestine when it was going through segmentation, it would look as if the contents were being shoved incrementally back and forth, as the rings of smooth muscle repeatedly contract and then relax. Segmentation in the small intestine does not force chyme through the tract. Instead, it combines the chyme with digestive juices and pushes food particles against the mucosa to be absorbed. The duodenum is where the most rapid segmentation occurs, at a rate of about 12 times per minute. In the ileum, segmentations are only about eight times per minute (Figure 3.5.3).

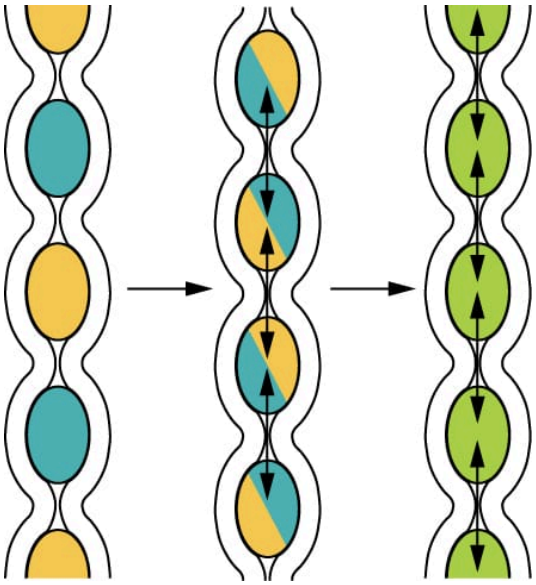


Figure 3.5.3: Segmentation separates chyme and then pushes it back together, mixing it and providing time for digestion and absorption. (CC BY 4.0; via The Small and Large Intestine). Detailed text description of the Figure 3.5.3.

When most of the chyme has been absorbed, the small intestinal wall becomes less distended. At this point, the localized segmentation process is replaced by transport movements. The duodenal mucosa secretes the hormone motilin, which initiates peristalsis in the form of a migrating motility complex. These complexes, which begin in the duodenum, force chyme through a short section of the small intestine and then stop. The next contraction begins a little bit farther down than the first, forces chyme a bit farther through the small intestine, then stops. These complexes move slowly down the small intestine, forcing chyme on the way, taking around 90 to 120 minutes to finally reach the end of the ileum. At this point, the process is repeated, starting in the duodenum.

The ileocecal valve, a sphincter, is usually in a constricted state, but when motility in the ileum increases, this sphincter relaxes, allowing food residue to enter the first portion of the large intestine, the cecum. Relaxation of the ileocecal sphincter is controlled by both nerves and hormones. First, digestive activity in the stomach provokes the gastroileal reflex, which increases the force of ileal segmentation. Second, the stomach releases the hormone gastrin, which enhances ileal motility, thus relaxing the ileocecal sphincter. After chyme passes through, backward pressure helps close the sphincter, preventing backflow into the ileum. Because of this reflex, your lunch is completely emptied from your stomach and small intestine by the time you eat your dinner. It takes about 3 to 5 hours for all chyme to leave the small intestine.

Chemical Digestion in the Small Intestine

The digestion of proteins and carbohydrates, which partially occurs in the stomach, is completed in the small intestine with the aid of intestinal and pancreatic juices. Lipids arrive in the intestine largely undigested, so much of the focus here is on lipid digestion, which is facilitated by bile and the enzyme pancreatic lipase.

Moreover, intestinal juice combines with pancreatic juice to provide a liquid medium that facilitates absorption. The intestine is also where most water is absorbed, via osmosis. The small intestine's absorptive cells also synthesize digestive enzymes and then place them in the plasma membranes of the microvilli. This distinguishes the small intestine from the stomach; that is, enzymatic digestion occurs not only in the lumen, but also on the luminal surfaces of the mucosal cells.

For optimal chemical digestion, chyme must be delivered from the stomach slowly and in small amounts. This is because chyme from the stomach is typically hypertonic, and if large quantities were forced all at once into the small intestine, the resulting osmotic water loss from the blood into the intestinal lumen would result in potentially life-threatening low blood volume. In addition, continued digestion requires an upward adjustment of the low pH of stomach chyme, along with rigorous mixing of the chyme with bile and pancreatic juices. Both processes take time, so the pumping action of the pylorus must be carefully controlled to prevent the duodenum from being overwhelmed with chyme.

Disorders of the...

Small Intestine: Lactose Intolerance

Lactose intolerance is a condition characterized by indigestion caused by dairy products. It occurs when the absorptive cells of the small intestine do not produce enough lactase, the enzyme that digests the milk sugar lactose. In most mammals, lactose intolerance increases with age. In contrast, some human populations are able to maintain the ability to produce lactase as adults.

In people with lactose intolerance, the lactose in chyme is not digested. Bacteria in the large intestine ferment the undigested lactose, a process that produces gas. In addition to gas, symptoms include abdominal cramps, bloating, and diarrhea. Symptom severity ranges from mild discomfort to severe pain; however, symptoms resolve once the lactose is eliminated in feces.

The hydrogen breath test is used to help diagnose lactose intolerance. Lactose-tolerant people have very little hydrogen in their breath. Those with lactose intolerance exhale hydrogen, which is one of the gases produced by the bacterial fermentation of lactose in the colon. After the hydrogen is absorbed from the intestine, it is transported through blood vessels into the lungs. There are a number of lactose-free dairy products available in grocery stores. In addition, dietary supplements are available. Taken with food, they provide lactase to help digest lactose.

The Large Intestine

The large intestine is the terminal part of the alimentary canal. The primary function of this organ is to finish absorption of nutrients and water, synthesize certain vitamins, form feces, and eliminate feces from the body.

Structure

The large intestine runs from the appendix to the anus. It frames the small intestine on three sides. Despite its being about one-half as long as the small intestine, it is called large because it is more than twice the diameter of the small intestine, about 3 inches.

Subdivisions

The large intestine is subdivided into four main regions: the cecum, the colon, the rectum, and the anus. The ileocecal valve, located at the opening between the ileum and the large intestine, controls the flow of chyme from the small intestine to the large intestine.

Cecum

The first part of the large intestine is the cecum, a sac-like structure that is suspended inferior to the ileocecal valve. It is about 6 cm (2.4 in) long, receives the contents of the ileum, and continues the absorption of water and salts. The appendix (or vermiform appendix) is a winding tube that attaches to the cecum. Although the 7.6-cm (3-in) long appendix contains lymphoid tissue, suggesting an immunologic function, this organ is generally considered vestigial. However, at least one recent report postulates a survival advantage conferred by the appendix: In diarrheal illness, the appendix may serve as a bacterial reservoir to repopulate the enteric bacteria for those surviving the initial phases of the illness. Moreover, its twisted anatomy provides a haven for the accumulation and multiplication of enteric bacteria. The mesoappendix, the mesentery of the appendix, tethers it to the mesentery of the ileum.

Colon

The cecum blends seamlessly with the colon. Upon entering the colon, the food residue first travels up the ascending colon on the right side of the abdomen. At the inferior surface of the liver, the colon bends to form the right colic flexure (hepatic flexure) and becomes the transverse colon. The region defined as hindgut begins with the last third of the transverse colon and continues on. Food residue passing through the transverse colon travels across to the left side of the abdomen, where the colon angles

sharply immediately inferior to the spleen, at the left colic flexure (splenic flexure). From there, food residue passes through the descending colon, which runs down the left side of the posterior abdominal wall. After entering the pelvis inferiorly, it becomes the s-shaped sigmoid colon, which extends medially to the midline (Figure 3.5.4). The ascending and descending colon, and the rectum are located in the retroperitoneum. The transverse and sigmoid colon are tethered to the posterior abdominal wall by the mesocolon.

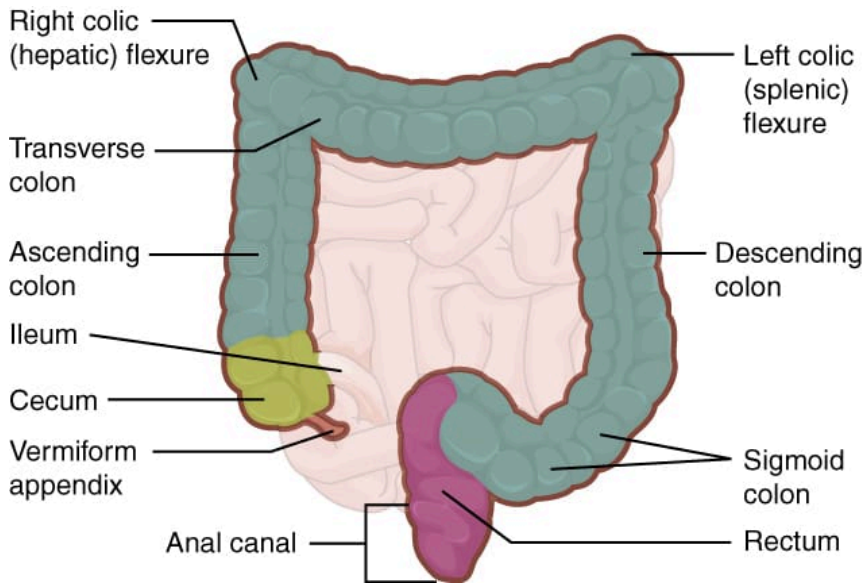


Figure 3.5.4: The large intestine includes the cecum, colon, and rectum. (CC BY 4.0; via The Small and Large Intestine). Detailed text description of the Figure 3.5.4.

Homeostatic Imbalances

Colorectal Cancer

Each year, approximately 140,000 Americans are diagnosed with colorectal cancer, and another 49,000 die from it, making it one of the most deadly malignancies. People with a family history of colorectal cancer are at increased risk. Smoking, excessive alcohol consumption, and a diet high in animal fat and protein also increase the risk. Despite popular opinion to the contrary, studies support the conclusion that dietary fiber and calcium do not reduce the risk of colorectal cancer.

Colorectal cancer may be signaled by constipation or diarrhea, cramping, abdominal pain, and rectal bleeding. Bleeding from the rectum may be either obvious or occult (hidden in feces). Since most colon cancers arise from benign mucosal growths called polyps, cancer prevention is focused on identifying these polyps. The colonoscopy is both diagnostic and therapeutic. Colonoscopy not only allows identification of precancerous polyps, the procedure also enables them to be removed before they become malignant. Screening for fecal occult blood tests and colonoscopy is recommended for those over 50 years of age.

Rectum

Food residue leaving the sigmoid colon enters the rectum in the pelvis, near the third sacral vertebra. The final 20.3 cm (8 in) of the alimentary canal, the rectum extends anterior to the sacrum and coccyx. Even though rectum is Latin for “straight,” this structure follows the curved contour of the sacrum and has three lateral bends that create a trio of internal transverse folds called the rectal valves. These valves help separate the feces from gas to prevent the simultaneous passage of feces and gas.

Anal Canal

Finally, food residue reaches the last part of the large intestine, the anal canal, which is located in the perineum, completely outside of the abdominopelvic cavity. This 3.8–5 cm (1.5–2 in) long structure opens to the exterior of the body at the anus. The anal canal includes two sphincters. The internal anal sphincter is made of smooth muscle, and its contractions are involuntary.

The external anal sphincter is made of skeletal muscle, which is under voluntary control. Except when defecating, both usually remain closed.

Histology

There are several notable differences between the walls of the large and small intestines (Figure 3.5.5). For example, few enzyme-secreting cells are found in the wall of the large intestine, and there are no circular folds or villi. Other than in the anal canal, the mucosa of the colon is simple columnar epithelium made mostly of enterocytes (absorptive cells) and goblet cells. In addition, the wall of the large intestine has far more intestinal glands, which contain a vast population of enterocytes and goblet cells. These goblet cells secrete mucus that eases the movement of feces and protects the intestine from the effects of the acids and gases produced by enteric bacteria. The enterocytes absorb water and salts as well as vitamins produced by your intestinal bacteria.

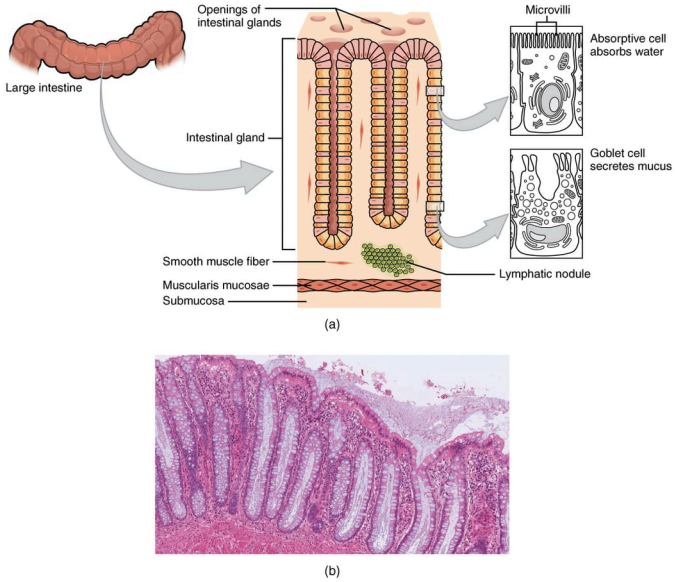


Figure 3.5.5: (a) The histologies of the large intestine and small intestine (not shown) are adapted for the digestive functions of each organ. (b) This micrograph shows the colon's simple columnar epithelium and goblet cells. LM x 464. (CC BY 4.0; via The Small and Large Intestine). Detailed text description of the Figure 3.5.5.

Unlike the small intestine, the large intestine does not rely on villi. Instead, it uses straight tubular glands, numerous goblet cells, and absorptive cells with microvilli to support its role in waste processing.

Anatomy

Three features are unique to the large intestine: teniae coli, haustra, and epiploic appendages (Figure 3.5.6). The teniae coli are three bands of smooth muscle that make up the longitudinal muscle layer of the muscularis of the large intestine, except at its terminal end. Tonic contractions of the teniae coli bunch up the colon into a succession of pouches called haustra (singular = haustrum), which are responsible for the wrinkled appearance of the colon. Attached to the teniae coli are small, fat-filled sacs of visceral peritoneum called epiploic appendages. The purpose of these is unknown. Although the rectum and anal canal have neither teniae coli nor haustra, they do have well-developed layers of muscularis that create the strong contractions needed for defecation.

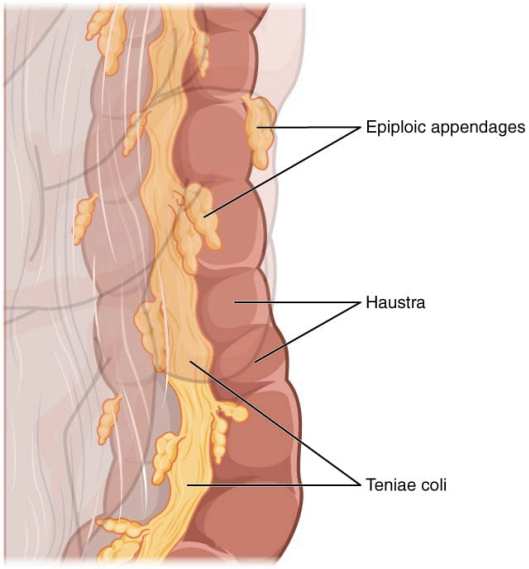


Figure 3.5.6: Teniae Coli, Haustra, and Epiploic Appendage. (CC BY 4.0; via The Small and Large Intestine). Detailed text description of the Figure 3.5.6.

The stratified squamous epithelial mucosa of the anal canal connects to the skin on the outside of the anus. This mucosa varies considerably from that of the rest of the colon to accommodate the high level of abrasion as feces pass through. The anal canal's mucous membrane is organized into longitudinal folds, each called an anal column, which house a grid of arteries and veins. Two superficial venous plexuses are found in the anal canal: one within the anal columns and one at the anus.

Depressions between the anal columns, each called an anal sinus, secrete mucus that facilitates defecation. The pectinate line (or dentate line) is a horizontal, jagged band that runs circumferentially just below the level of the anal sinuses, and represents the junction between the hindgut and external skin. The mucosa above this line is fairly insensitive, whereas the area below is very sensitive. The resulting difference in pain threshold is due to the fact that the upper region is innervated by visceral sensory fibers, and the lower region is innervated by somatic sensory fibers.

Bacterial Flora

Most bacteria that enter the alimentary canal are killed by lysozyme, defensins, HCl, or protein-digesting enzymes. However, trillions of bacteria live within the large intestine and are referred to as the bacterial flora. Most of the more than 700 species of these bacteria are nonpathogenic commensal organisms that cause no harm as long as they stay in the gut lumen. In fact, many facilitate chemical digestion and absorption, and some synthesize certain vitamins, mainly biotin, pantothenic acid, and vitamin K. Some are linked to increased immune response. A refined system prevents these bacteria from crossing the mucosal barrier. First, peptidoglycan, a component of bacterial cell walls, activates the release of chemicals by the mucosa's epithelial cells, which draft immune cells, especially dendritic cells, into the mucosa. Dendritic cells open the tight junctions between epithelial cells and extend probes into the lumen to evaluate the microbial antigens. The dendritic cells with antigens then travel to neighboring lymphoid follicles in the mucosa where T cells inspect for antigens. This process triggers an IgA-mediated response, if warranted, in the lumen that blocks the commensal organisms from infiltrating the mucosa and setting off a far greater, widespread systematic reaction.

Digestive Functions of the Large Intestine

The residue of chyme that enters the large intestine contains few nutrients except water, which is reabsorbed as the residue lingers in the large intestine, typically for 12 to 24 hours. Thus, it may not surprise you that the large intestine can be completely removed without significantly affecting digestive functioning. For example, in severe cases of inflammatory bowel disease, the large intestine can be removed by a procedure known as a colectomy. Often, a new fecal pouch can be crafted from the small intestine and sutured to the anus, but if not, an ileostomy can be created by bringing the distal ileum through the abdominal wall, allowing the watery chyme to be collected in a bag-like adhesive appliance.

Mechanical Digestion

In the large intestine, mechanical digestion begins when chyme moves from the ileum into the cecum, an activity regulated by the ileocecal sphincter. Right after you eat, peristalsis in the ileum forces chyme into the cecum. When the cecum is distended with chyme, contractions of the ileocecal sphincter strengthen. Once chyme enters the cecum, colon movements begin.

Mechanical digestion in the large intestine includes a combination of three types of movements. The presence of food residues in the colon stimulates a slow-moving haustral contraction. This type of movement involves sluggish segmentation, primarily in the transverse and descending colons. When a haustrum is distended with chyme, its muscle contracts, pushing the residue into the next haustrum. These contractions occur about every 30 minutes, and each last about 1 minute. These movements also mix the food residue, which helps the large intestine absorb water. The second type of movement is peristalsis, which, in the large intestine, is slower than in the more proximal portions of the alimentary canal. The third type is a mass movement. These strong waves start midway through the transverse colon and quickly force the contents toward the rectum. Mass movements usually occur three or four times per day, either while you eat or immediately afterward. Distension in the stomach and the breakdown products of digestion in the small intestine provoke the gastrocolic reflex, which increases motility, including mass movements, in the colon. Fiber in the diet both softens the stool and increases the power of colonic contractions, optimizing the activities of the colon.

Chemical Digestion

Although the glands of the large intestine secrete mucus, they do not secrete digestive enzymes. Therefore, chemical digestion in the large intestine occurs exclusively because of bacteria in the lumen of the colon. Through the process of saccharolytic fermentation, bacteria break down some of the remaining carbohydrates. This results in the discharge of hydrogen, carbon dioxide, and methane gases that create flatus (gas) in the colon; flatulence is excessive flatus. Each day, up to 1500 mL of flatus is produced in the colon. More is produced when you eat foods such as beans, which are rich in otherwise indigestible sugars and complex carbohydrates like soluble dietary fiber.

Absorption, Feces Formation, and Defecation

The small intestine absorbs about 90 percent of the water you ingest (either as liquid or within solid food). The large intestine absorbs most of the remaining water, a process that converts the liquid chyme residue into semisolid feces (“stool”). Feces is composed of undigested food residues, unabsorbed digested substances, millions of bacteria, old epithelial cells from the GI mucosa, inorganic salts, and enough water to let it pass smoothly out of the body. Of every 500 mL (17 ounces) of food residue that enters the cecum each day, about 150 mL (5 ounces) become feces.

Feces are eliminated through contractions of the rectal muscles. You help this process by a voluntary procedure called Valsalva’s maneuver, in which you increase intra-abdominal pressure by contracting your diaphragm and abdominal wall muscles, and closing your glottis.

The process of defecation begins when mass movements force feces from the colon into the rectum, stretching the rectal wall and provoking the defecation reflex, which eliminates feces from the rectum. This parasympathetic reflex is mediated by the spinal cord. It contracts the sigmoid colon and rectum, relaxes the internal anal sphincter, and initially contracts the external anal sphincter. The presence of feces in the anal canal sends a signal to the brain, which gives you the choice of voluntarily opening the external anal sphincter (defecating) or keeping it temporarily closed. If you decide to delay defecation, it takes a few seconds for the reflex contractions to stop and the rectal walls to relax. The next mass movement will trigger additional defecation reflexes until you defecate.

If defecation is delayed for an extended time, additional water is absorbed, making the feces firmer and potentially leading to constipation. On the other hand, if the waste matter moves too quickly through the intestines, not enough water is absorbed, and diarrhea can result. This can be caused by the ingestion of foodborne pathogens. In general, diet, health, and stress determine the frequency of bowel movements. The number of bowel movements varies greatly between individuals, ranging from two or three per day to three or four per week.

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3.6: Accessory Organs in Digestion

The Liver, Pancreas, and Gallbladder

Chemical digestion in the small intestine relies on the activities of three accessory digestive organs: the liver, pancreas, and gallbladder (Figure 3.6.1). The digestive role of the liver is to produce bile and export it to the duodenum. The gallbladder primarily stores, concentrates, and releases bile. The pancreas produces pancreatic juice, which contains digestive enzymes and bicarbonate ions, and delivers it to the duodenum.

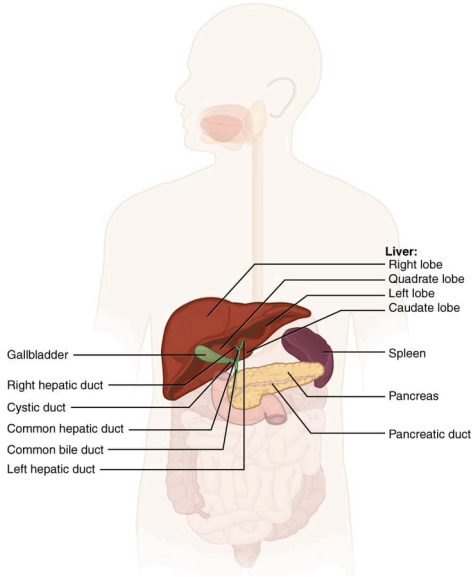


Figure 3.6.1: The liver, pancreas, and gallbladder are considered accessory digestive organs, but their roles in the digestive system are vital. (CC BY 4.0; via Accessory Organs in Digestion- The Liver, Pancreas, and Gallbladder). Detailed text description of the Figure 3.6.1.

The Liver

The liver is the largest gland in the body, weighing about three pounds in an adult. It is also one of the most important organs. In addition to being an accessory digestive organ, it plays a number of roles in metabolism and regulation. The liver lies inferior to the diaphragm in the right upper quadrant of the abdominal cavity and receives protection from the surrounding ribs.

The liver is divided into two primary lobes: a large right lobe and a much smaller left lobe. In the right lobe, some anatomists also identify an inferior quadrate lobe and a posterior caudate lobe, which are defined by internal features. The liver is connected to the abdominal wall and diaphragm by five peritoneal folds referred to as ligaments. These are the falciform ligament, the coronary ligament, two lateral ligaments, and the ligamentum teres hepatis. The falciform ligament and ligamentum teres hepatis are actually remnants of the umbilical vein, and separate the right and left lobes anteriorly. The lesser omentum tethers the liver to the lesser curvature of the stomach.

The porta hepatis (“gate to the liver”) is where the hepatic artery and hepatic portal vein enter the liver. These two vessels, along with the common hepatic duct, run behind the lateral border of the lesser omentum on the way to their destinations. As shown in Figure 3.6.2, the hepatic artery delivers oxygenated blood from the heart to the liver. The hepatic portal vein delivers partially deoxygenated blood containing nutrients absorbed from the small intestine and actually supplies more oxygen to the liver than do the much smaller hepatic arteries. In addition to nutrients, drugs and toxins are also absorbed. After processing the bloodborne nutrients and toxins, the liver releases nutrients needed by other cells back into the blood, which drains into the central vein and then through the hepatic vein to the inferior vena cava. With this hepatic portal circulation, all blood from the alimentary canal passes through the liver. This largely explains why the liver is the most common site for the metastasis of cancers that originate in the alimentary canal.

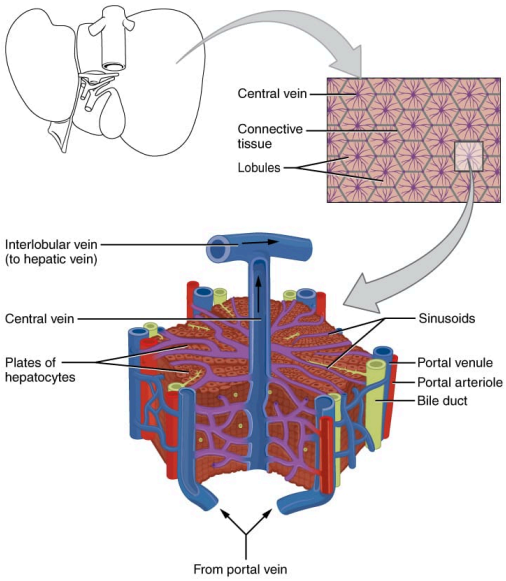


Figure 3.6.2: The liver receives oxygenated blood from the hepatic artery and nutrient-rich deoxygenated blood from the hepatic portal vein. (CC BY 4.0; via Accessory Organs in Digestion- The Liver, Pancreas, and Gallbladder). Detailed text description of the Figure 3.6.2.

Histology

The liver has three main components: hepatocytes, bile canaliculi, and hepatic sinusoids. A hepatocyte is the liver's main cell type, accounting for around 80 percent of the liver's volume. These cells play a role in a wide variety of secretory, metabolic, and endocrine functions. Plates of hepatocytes called hepatic laminae radiate outward from the portal vein in each hepatic lobule.

Between adjacent hepatocytes, grooves in the cell membranes provide room for each bile canaliculus (plural = canaliculi). These small ducts accumulate the bile produced by hepatocytes. From here, bile flows first into bile ductules and then into bile ducts. The bile ducts unite to form the larger right and left hepatic ducts, which themselves merge and exit the liver as the common hepatic duct. This duct then joins with the cystic duct from the gallbladder, forming the common bile duct through which bile flows into the small intestine.

A hepatic sinusoid is an open, porous blood space formed by fenestrated capillaries from nutrient-rich hepatic portal veins and oxygen-rich hepatic arteries. Hepatocytes are tightly packed around the fenestrated endothelium of these spaces, giving them easy access to the blood. From their central position, hepatocytes process the nutrients, toxins, and waste materials carried by the blood. Materials such as bilirubin are processed and excreted into the bile canaliculi. Other materials including proteins, lipids, and carbohydrates are processed and secreted into the sinusoids or just stored in the cells until called upon. The hepatic sinusoids combine and send blood to a central vein. Blood then flows through a hepatic vein into the inferior vena cava. This means that blood and bile flow in opposite directions. The hepatic sinusoids also contain star-shaped reticuloendothelial cells (Kupffer cells), phagocytes that remove dead red and white blood cells, bacteria, and other foreign material that enter the sinusoids. The portal triad is a distinctive arrangement around the perimeter of hepatic lobules, consisting of three basic structures: a bile duct, a hepatic artery branch, and a hepatic portal vein branch.

Bile

Recall that lipids are hydrophobic, that is, they do not dissolve in water. Thus, before they can be digested in the watery environment of the small intestine, large lipid globules must be broken down into smaller lipid globules, a process called emulsification. Bile is a mixture secreted by the liver to accomplish the emulsification of lipids in the small intestine.

Hepatocytes secrete about one liter of bile each day. A yellow-brown or yellow-green alkaline solution (pH 7.6 to 8.6), bile is a mixture of water, bile salts, bile pigments, phospholipids (such as lecithin), electrolytes, cholesterol, and triglycerides. The components most critical to emulsification are bile salts and phospholipids, which have a nonpolar (hydrophobic) region as well as a polar (hydrophilic) region. The hydrophobic region interacts with the large lipid molecules, whereas the hydrophilic region interacts with the watery chyme in the intestine. This results in the large lipid globules being pulled apart into many tiny lipid fragments of about 1 μm in diameter. This change dramatically increases the surface area available for lipid-digesting enzyme

activity. This is the same way dish soap works on fats mixed with water.

Bile salts act as emulsifying agents, so they are also important for the absorption of digested lipids. While most constituents of bile are eliminated in feces, bile salts are reclaimed by the enterohepatic circulation. Once bile salts reach the ileum, they are absorbed and returned to the liver in the hepatic portal blood. The hepatocytes then excrete the bile salts into newly formed bile. Thus, this precious resource is recycled.

Bilirubin, the main bile pigment, is a waste product produced when the spleen removes old or damaged red blood cells from the circulation. These breakdown products, including proteins, iron, and toxic bilirubin, are transported to the liver via the splenic vein of the hepatic portal system. In the liver, proteins and iron are recycled, whereas bilirubin is excreted in the bile. It accounts for the green color of bile. Bilirubin is eventually transformed by intestinal bacteria into stercobilin, a brown pigment that gives your stool its characteristic color! In some disease states, bile does not enter the intestine, resulting in white ('acholic') stool with a high fat content, since virtually no fats are broken down or absorbed.

Hepatocytes work non-stop, but bile production increases when fatty chyme enters the duodenum and stimulates the secretion of the gut hormone secretin. Between meals, bile is produced but conserved. The valve-like hepatopancreatic ampulla closes, allowing bile to divert to the gallbladder, where it is concentrated and stored until the next meal.

The Pancreas

The soft, oblong, glandular pancreas lies transversely in the retroperitoneum behind the stomach. Its head is nestled into the "c-shaped" curvature of the duodenum with the body extending to the left about 15.2 cm (6 in) and ending as a tapering tail in the hilum of the spleen. It is a curious mix of exocrine (secreting digestive enzymes) and endocrine (releasing hormones into the blood) functions (Figure 3.6.3).

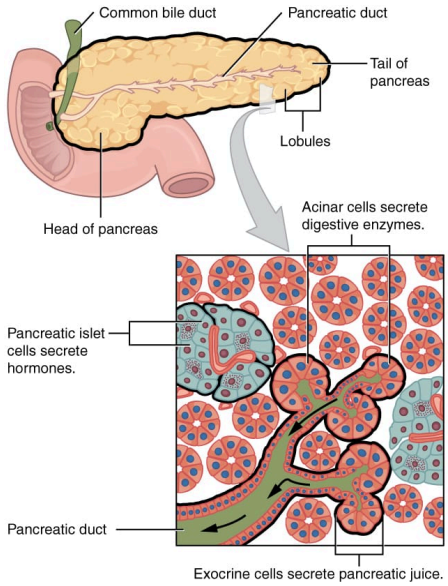


Figure 3.6.3: The pancreas has a head, a body, and a tail. It delivers pancreatic juice to the duodenum through the pancreatic duct. (CC BY 4.0; via Accessory Organs in Digestion- The Liver, Pancreas, and Gallbladder). Detailed text description of the Figure 3.6.3.

The exocrine part of the pancreas arises as little grape-like cell clusters, each called an acinus (plural = acini), located at the terminal ends of pancreatic ducts. These acinar cells secrete enzyme-rich pancreatic juice into tiny merging ducts that form two dominant ducts. The larger duct fuses with the common bile duct (carrying bile from the liver and gallbladder) just before entering the duodenum via a common opening (the hepatopancreatic ampulla). The smooth muscle sphincter of the hepatopancreatic ampulla controls the release of pancreatic juice and bile into the small intestine. The second and smaller pancreatic duct, the accessory duct (duct of Santorini), runs from the pancreas directly into the duodenum, approximately 1 inch above the hepatopancreatic ampulla. When present, it is a persistent remnant of pancreatic development.

Scattered through the sea of exocrine acini are small islands of endocrine cells, the islets of Langerhans. These vital cells produce the hormones pancreatic polypeptide, insulin, glucagon, and somatostatin.

Pancreatic Juice

The pancreas produces over a liter of pancreatic juice each day. Unlike bile, it is clear and composed mostly of water along with some salts, sodium bicarbonate, and several digestive enzymes. Sodium bicarbonate is responsible for the slight alkalinity of pancreatic juice (pH 7.1 to 8.2), which serves to buffer the acidic gastric juice in chyme, inactivate pepsin from the stomach, and create an optimal environment for the activity of pH-sensitive digestive enzymes in the small intestine. Pancreatic enzymes are active in the digestion of sugars, proteins, and fats.

The pancreas produces protein-digesting enzymes in their inactive forms. These enzymes are activated in the duodenum. If produced in an active form, they would digest the pancreas (which is exactly what occurs in the disease, pancreatitis). The intestinal brush border enzyme enteropeptidase stimulates the activation of trypsin from trypsinogen of the pancreas, which in turn changes the pancreatic enzymes procarboxypeptidase and chymotrypsinogen into their active forms, carboxypeptidase and chymotrypsin.

The enzymes that digest starch (amylase), fat (lipase), and nucleic acids (nuclease) are secreted in their active forms, since they do not attack the pancreas as do the protein-digesting enzymes.

Pancreatic Secretion

Regulation of pancreatic secretion is the job of hormones and the parasympathetic nervous system. The entry of acidic chyme into the duodenum stimulates the release of secretin, which in turn causes the duct cells to release bicarbonate-rich pancreatic juice. The presence of proteins and fats in the duodenum stimulates the secretion of CCK, which then stimulates the acini to secrete enzyme-rich pancreatic juice and enhances the activity of secretin. Parasympathetic regulation occurs mainly during the cephalic and gastric phases of gastric secretion, when vagal stimulation prompts the secretion of pancreatic juice.

Usually, the pancreas secretes just enough bicarbonate to counterbalance the amount of HCl produced in the stomach. Hydrogen ions enter the blood when bicarbonate is secreted by the pancreas. Thus, the acidic blood draining from the pancreas neutralizes the alkaline blood draining from the stomach, maintaining the pH of the venous blood that flows to the liver.

The Gallbladder

The gallbladder is 8–10 cm (~3–4 in) long and is nested in a shallow area on the posterior aspect of the right lobe of the liver. This muscular sac stores, concentrates, and, when stimulated, propels the bile into the duodenum via the common bile duct. It is divided into three regions. The fundus is the widest portion and tapers medially into the body, which in turn narrows to become the neck. The neck angles slightly superiorly as it approaches the hepatic duct. The cystic duct is 1–2 cm (less than 1 in) long and turns inferiorly as it bridges the neck and hepatic duct.

The simple columnar epithelium of the gallbladder mucosa is organized in rugae, similar to those of the stomach. There is no submucosa in the gallbladder wall. The wall's middle, muscular coat is made of smooth muscle fibers. When these fibers contract, the gallbladder's contents are ejected through the cystic duct and into the bile duct (Figure 3.6.4). Visceral peritoneum reflected from the liver capsule holds the gallbladder against the liver and forms the outer coat of the gallbladder. The gallbladder's mucosa absorbs water and ions from bile, concentrating it by up to 10-fold.

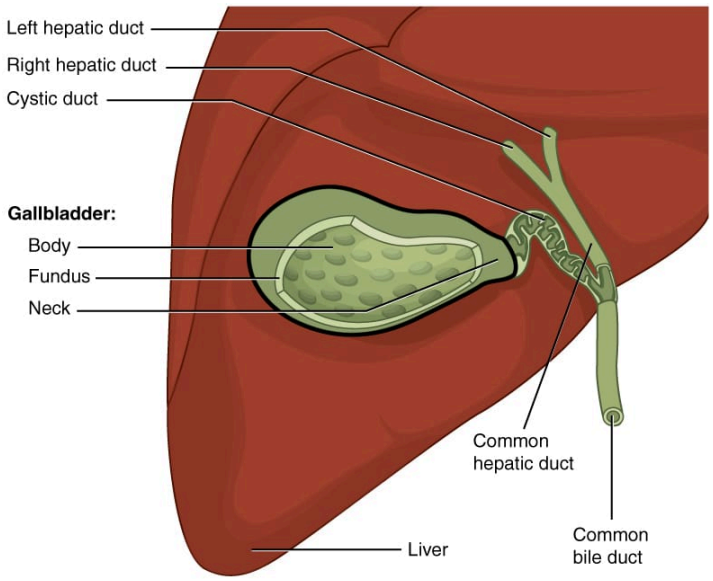


Figure 3.6.4: The gallbladder stores and concentrates bile, and releases it into the two-way cystic duct when it is needed by the small intestine. (CC BY 4.0; via Accessory Organs in Digestion- The Liver, Pancreas, and Gallbladder). Detailed text description of the Figure 3.6.4.

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3.7: Chemical Digestion and Absorption - A Closer Look

Chemical Digestion and Absorption>

As you have learned, the process of mechanical digestion is relatively simple. It involves the physical breakdown of food but does not alter its chemical makeup. Chemical digestion, on the other hand, is a complex process that reduces food into its chemical building blocks, which are then absorbed to nourish the cells of the body (Figure 3.7.1). In this section, you will look more closely at the processes of chemical digestion and absorption.

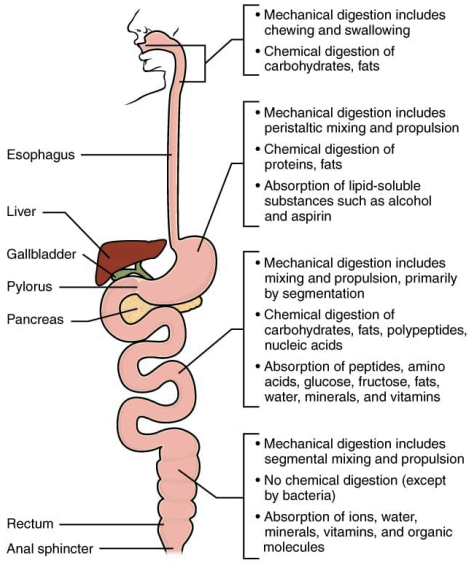


Figure 3.7.1: Digestion begins in the mouth and continues as food travels through the small intestine. Most absorption occurs in the small intestine. (CC BY 4.0; via Chemical Digestion and Absorption). Detailed text description of the Figure 3.7.1.

Chemical Digestion

Large food molecules (for example, proteins, lipids, nucleic acids, and starches) must be broken down into subunits that are small enough to be absorbed by the lining of the alimentary canal. This is accomplished by enzymes through hydrolysis. The many enzymes involved in chemical digestion are summarized in Table 3.7.1.

Table 3.7.1: The Digestive Enzymes

Enzyme Category	Enzyme Name	Source	Substrate	Product
Salivary Enzymes	Lingual lipase	Lingual glands	Triglycerides	Free fatty acids, and mono- and diglycerides
Salivary Enzymes	Salivary amylase	Salivary glands	Polysaccharides	Disaccharides and trisaccharides
Gastric enzymes	Gastric lipase	Chief cells	Triglycerides	Fatty acids and monoacylglycerides
Gastric enzymes	Pepsin*	Chief cells	Proteins	Peptides
Brush border enzymes	α-Dextrinase	Small intestine	α-Dextrins	Glucose

Enzyme Category	Enzyme Name	Source	Substrate	Product
Brush border enzymes	Enteropeptidase	Small intestine	Trypsinogen	Trypsin
Brush border enzymes	Lactase	Small intestine	Lactose	Glucose and galactose
Brush border enzymes	Maltase	Small intestine	Maltose	Glucose
Brush border enzymes	Nucleosidases and phosphatases	Small intestine	Nucleotides	Phosphates, nitrogenous bases, and pentoses
Brush border enzymes	Peptidases	Small intestine	• Aminopeptidase: amino acids at the amino end of peptides • Dipeptidase: dipeptides	• Aminopeptidase: amino acids and peptides • Dipeptidase: amino acids
Brush border enzymes	Sucrase	Small intestine	Sucrose	Glucose and fructose
Pancreatic enzymes	Carboxy-peptidase*	Pancreatic acinar cells	Amino acids at the carboxyl end of peptides	Amino acids and peptides
Pancreatic enzymes	Chymotrypsin*	Pancreatic acinar cells	Proteins	Peptides
Pancreatic enzymes	Elastase*	Pancreatic acinar cells	Proteins	Peptides
Pancreatic enzymes	Nucleases	Pancreatic acinar cells	• Ribonuclease: ribonucleic acids • Deoxyribonuclease: deoxyribonucleic acids	Nucleotides
Pancreatic enzymes	Pancreatic amylase	Pancreatic acinar cells	Polysaccharides (starches)	α-Dextrins, disaccharides (maltose), trisaccharides (maltotriose)
Pancreatic enzymes	Pancreatic lipase	Pancreatic acinar cells	Triglycerides that have been emulsified by bile salts	Fatty acids and monoacylglycerides
Pancreatic enzymes	Trypsin*	Pancreatic acinar cells	Proteins	Peptides

Carbohydrate Digestion

The average American diet is about 50 percent carbohydrates, which may be classified according to the number of monomers they contain of simple sugars (monosaccharides and disaccharides) and/or complex sugars (polysaccharides). Glucose, galactose, and fructose are the three monosaccharides that are commonly consumed and are readily absorbed. Your digestive system is also able to break down the disaccharide sucrose (regular table sugar: glucose + fructose), lactose (milk sugar: glucose + galactose), and maltose (grain sugar: glucose + glucose), and the polysaccharides glycogen and starch (chains of monosaccharides). Your bodies do not produce enzymes that can break down most fibrous polysaccharides, such as cellulose. While indigestible polysaccharides do not provide any nutritional value, they do provide dietary fiber, which helps propel food through the alimentary canal.

The chemical digestion of starches begins in the mouth and has been reviewed above.

In the small intestine, pancreatic amylase does the 'heavy lifting' for starch and carbohydrate digestion (Figure 3.7.2). After amylases break down starch into smaller fragments, the brush border enzyme α-dextrinase starts working on α-dextrin, breaking off one glucose unit at a time. Three brush border enzymes hydrolyze sucrose, lactose, and maltose into monosaccharides. Sucrase splits sucrose into one molecule of fructose and one molecule of glucose; maltase breaks down maltose and maltotriose into two and three glucose molecules, respectively; and lactase breaks down lactose into one molecule of glucose and one molecule of galactose. Insufficient lactase can lead to lactose intolerance.

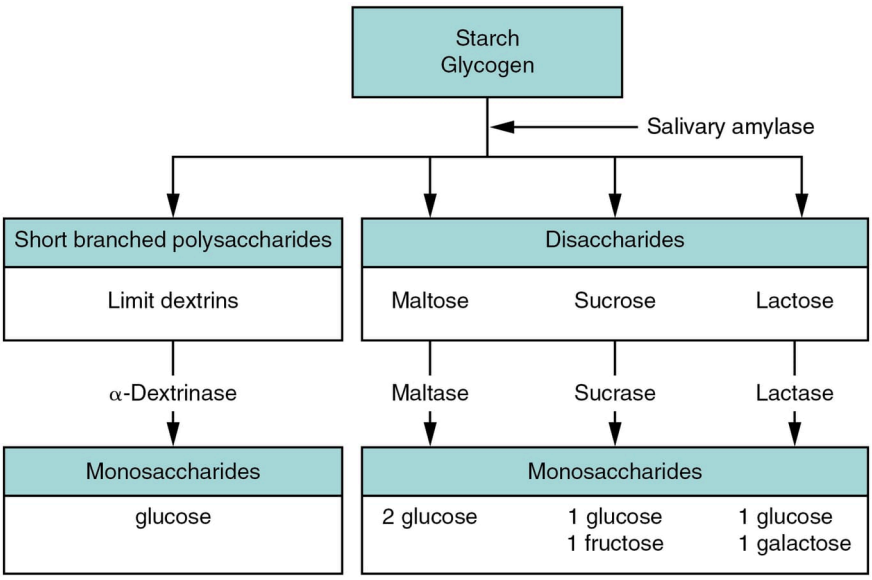


Figure 3.7.2: Carbohydrates are broken down into their monomers in a series of steps. (CC BY 4.0; via Chemical Digestion and Absorption). Detailed text description of the Figure 3.7.2.

Protein Digestion

Proteins are polymers composed of amino acids linked by peptide bonds to form long chains. Digestion reduces them to their constituent amino acids. You usually consume about 15 to 20 percent of your total calorie intake as protein.

The digestion of protein starts in the stomach, where HCl and pepsin break proteins into smaller polypeptides, which then travel to the small intestine (Figure 3.7.3). Chemical digestion in the small intestine is continued by pancreatic enzymes, including chymotrypsin and trypsin, each of which act on specific bonds in amino acid sequences. At the same time, the cells of the brush border secrete enzymes such as aminopeptidase and dipeptidase, which further break down peptide chains. This results in molecules small enough to enter the bloodstream (Figure 3.7.4).

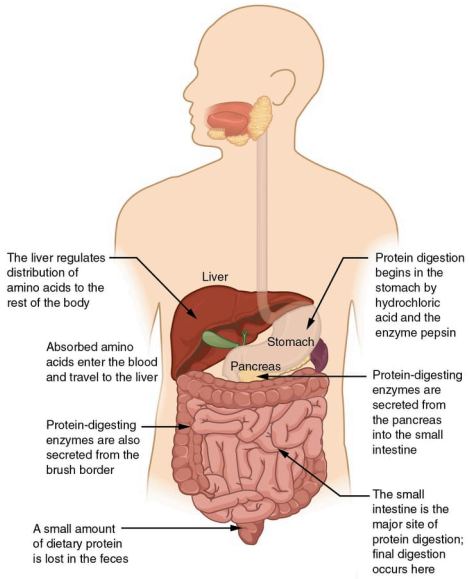


Figure 3.7.3: The digestion of protein begins in the stomach and is completed in the small intestine. (CC BY 4.0; via Chemical Digestion and Absorption). Detailed text description of the Figure 3.7.3.

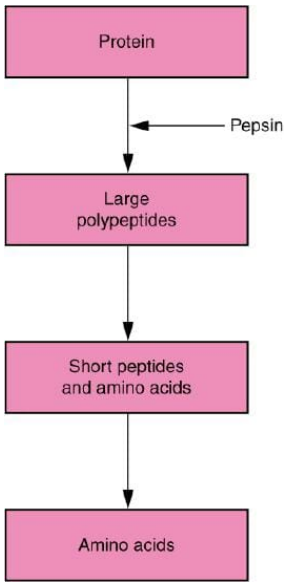


Figure 3.7.4: Proteins are successively broken down into their amino acid components. (CC BY 4.0; via Chemical Digestion and Absorption). Detailed text description of the Figure 3.7.4.

Lipid Digestion

A healthy diet limits lipid intake to 35 percent of total calorie intake. The most common dietary lipids are triglycerides, which are made up of a glycerol molecule bound to three fatty acid chains. Small amounts of dietary cholesterol and phospholipids are also consumed.

The three lipases responsible for lipid digestion are lingual lipase, gastric lipase, and pancreatic lipase. However, because the pancreas is the only consequential source of lipase, virtually all lipid digestion occurs in the small intestine. Pancreatic lipase breaks down each triglyceride into two free fatty acids and a monoglyceride. The fatty acids include both short-chain (less than 10 to 12 carbons) and long-chain fatty acids.

Nucleic Acid Digestion

The nucleic acids DNA and RNA are found in most of the foods you eat. Two types of pancreatic nuclease are responsible

for their digestion: deoxyribonuclease, which digests DNA, and ribonuclease, which digests RNA. The nucleotides produced by this digestion are further broken down by two intestinal brush border enzymes (nucleosidase and phosphatase) into pentoses, phosphates, and nitrogenous bases, which can be absorbed through the alimentary canal wall. The large food molecules that must be broken down into subunits are summarized Table 3.7.2.

Table 3.7.2: Absorbable Food Substances

Source	Substance
Carbohydrates	Monosaccharides: glucose, galactose, and fructose
Proteins	Single amino acids, dipeptides, and tripeptides
Triglycerides	Monoacylglycerides, glycerol, and free fatty acids
Nucleic acids	Pentose sugars, phosphates, and nitrogenous bases

Absorption

The mechanical and digestive processes have one goal: to convert food into molecules small enough to be absorbed by the epithelial cells of the intestinal villi. The absorptive capacity of the alimentary canal is almost endless. Each day, the alimentary canal processes up to 10 liters of food, liquids, and GI secretions, yet less than one liter enters the large intestine. Almost all ingested food, 80 percent of electrolytes, and 90 percent of water are absorbed in the small intestine. Although the entire small intestine is involved in the absorption of water and lipids, most absorption of carbohydrates and proteins occurs in the jejunum. Notably, bile salts and vitamin B_{12} are absorbed in the terminal ileum. By the time chyme passes from the ileum into the large intestine, it is essentially indigestible food residue (mainly plant fibers like cellulose), some water, and millions of bacteria (Figure 3.7.5).

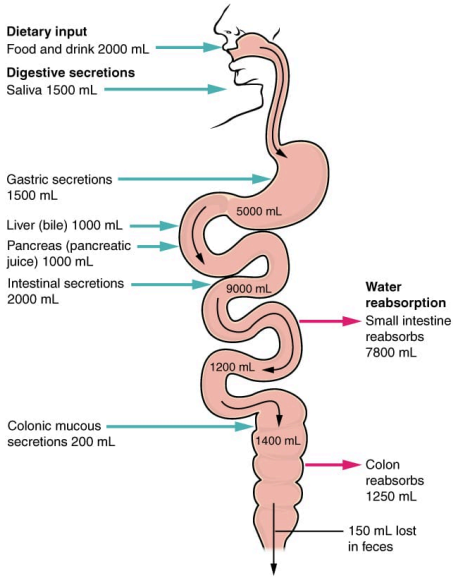


Figure 3.7.5: Absorption is a complex process, in which nutrients from digested food are harvested. (CC BY 4.0; via Chemical Digestion and Absorption). Detailed text description of the Figure 3.7.5.

Absorption can occur through five mechanisms: (1) active transport, (2) passive diffusion, (3) facilitated diffusion, (4) co-transport (or secondary active transport), and (5) endocytosis. As studied previously, active transport refers to the movement of a substance across a cell membrane going from an area of lower concentration to an area of higher concentration (up the concentration gradient). In this type of transport, proteins within the cell membrane act as “pumps,” using cellular energy (ATP) to move the substance. Passive diffusion refers to the movement of substances from an area of higher concentration to an area of lower concentration, while facilitated diffusion refers to the movement of substances from an area of higher to an area of lower concentration using a carrier protein in the cell membrane. Co-transport uses the movement of one molecule through the membrane from higher to lower concentration to power the movement of another from lower to higher. Finally, endocytosis is a transportation process in which the cell membrane engulfs material. It requires energy, generally in the form of ATP.

Because the cell's plasma membrane is made up of hydrophobic phospholipids, water-soluble nutrients must use transport molecules embedded in the membrane to enter cells. Moreover, substances cannot pass between the epithelial cells of the intestinal mucosa because these cells are bound together by tight junctions. Thus, substances can only enter blood capillaries by passing through the apical surfaces of epithelial cells and into the interstitial fluid. Water-soluble nutrients enter the capillary blood in the villi and travel to the liver via the hepatic portal vein.

In contrast to the water-soluble nutrients, lipid-soluble nutrients can diffuse through the plasma membrane. Once inside the cell, they are packaged for transport via the base of the cell and then enter the lacteals of the villi to be transported by lymphatic vessels to the systemic circulation via the thoracic duct. The absorption of most nutrients through the mucosa of the intestinal villi requires active transport fueled by ATP. The routes of absorption for each food category are summarized in Table 3.7.3.

Table 3.7.3: Absorption in the Alimentary Canal

Food	Breakdown products	Absorption mechanism	Entry to bloodstream	Destination
Carbohydrates	Glucose	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Carbohydrates	Galactose	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Carbohydrates	Fructose	Facilitated diffusion	Capillary blood in villi	Liver via hepatic portal vein
Protein	Amino acids	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Lipids	Long-chain fatty acids	Diffusion into intestinal cells, where they are combined with proteins to create chylomicrons	Lacteals of villi	Systemic circulation via lymph entering thoracic duct
Lipids	Monoacylglycerides	Diffusion into intestinal cells, where they are combined with proteins to create chylomicrons	Lacteals of villi	Systemic circulation via lymph entering thoracic duct
Lipids	Short-chain fatty acids	Simple diffusion	Capillary blood in villi	Liver via hepatic portal vein
Lipids	Glycerol	Simple diffusion	Capillary blood in villi	Liver via hepatic portal vein
Nucleic Acids	Nucleic acid digestion products	Active transport via membrane carriers	Capillary blood in villi	Liver via hepatic portal vein

Carbohydrate Absorption

All carbohydrates are absorbed in the form of monosaccharides. The small intestine is highly efficient at this, absorbing monosaccharides at an estimated rate of 120 grams per hour. All normally digested dietary carbohydrates are absorbed; indigestible fibers are eliminated in the feces. The monosaccharides glucose and galactose are transported into the epithelial cells by common protein carriers via secondary active transport (that is, co-transport with sodium ions). The monosaccharides leave these cells via facilitated diffusion and enter the capillaries through intercellular clefts. The monosaccharide fructose (which is in fruit) is absorbed and transported by facilitated diffusion alone. The monosaccharides combine with the transport proteins immediately after the disaccharides are broken down.

Protein Absorption

Active transport mechanisms, primarily in the duodenum and jejunum, absorb most proteins as their breakdown products, amino acids. Almost all (95 to 98 percent) protein is digested and absorbed in the small intestine. The type of carrier that transports an amino acid varies. Most carriers are linked to the active transport of sodium. Short chains of two amino acids (dipeptides) or three amino acids (tripeptides) are also transported actively. However, after they enter the absorptive epithelial cells, they are broken down into their amino acids before leaving the cell and entering the capillary blood via diffusion.

Lipid Absorption

About 95 percent of lipids are absorbed in the small intestine. Bile salts not only speed up lipid digestion, they are also essential to the absorption of the end products of lipid digestion. Short-chain fatty acids are relatively water soluble and can enter the absorptive cells (enterocytes) directly. The small size of short-chain fatty acids enables them to be absorbed by enterocytes via simple diffusion, and then take the same path as monosaccharides and amino acids into the blood capillary of a villus.

The large and hydrophobic long-chain fatty acids and monoacylglycerides are not so easily suspended in the watery intestinal chyme. However, bile salts and lecithin resolve this issue by enclosing them in a micelle, which is a tiny sphere with polar (hydrophilic) ends facing the watery environment and hydrophobic tails turned to the interior, creating a receptive environment for the long-chain fatty acids. The core also includes cholesterol and fat-soluble vitamins. Without micelles, lipids would sit on the surface of chyme and never come in contact with the absorptive surfaces of the epithelial cells. Micelles can easily squeeze between microvilli and get very near the luminal cell surface. At this point, lipid substances exit the micelle and are absorbed via simple diffusion.

The free fatty acids and monoacylglycerides that enter the epithelial cells are reincorporated into triglycerides. The triglycerides are mixed with phospholipids and cholesterol, and surrounded with a protein coat. This new complex, called a chylomicron, is a water-soluble lipoprotein. After being processed by the Golgi apparatus, chylomicrons are released from the cell (Figure 3.7.6). Too big to pass through the basement membranes of blood capillaries, chylomicrons instead enter the large pores of lacteals. The lacteals come together to form the lymphatic vessels. The chylomicrons are transported in the lymphatic vessels and empty through the thoracic duct into the subclavian vein of the circulatory system. Once in the bloodstream, the enzyme lipoprotein lipase breaks down the triglycerides of the chylomicrons into free fatty acids and glycerol. These breakdown products then pass through capillary walls to be used for energy by cells or stored in adipose tissue as fat. Liver cells combine the remaining chylomicron remnants with proteins, forming lipoproteins that transport cholesterol in the blood.

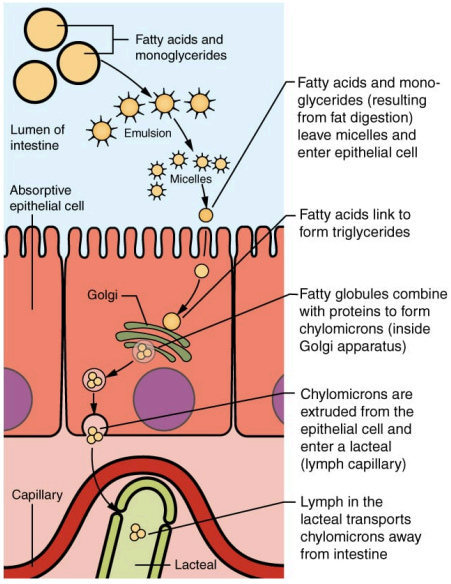


Figure 3.7.6: Unlike amino acids and simple sugars, lipids are transformed as they are absorbed through epithelial cells. (CC BY 4.0; via Chemical Digestion and Absorption). Detailed text description of the Figure 3.7.6.

Nucleic Acid Absorption

The products of nucleic acid digestion—pentose sugars, nitrogenous bases, and phosphate ions—are transported by carriers across the villus epithelium via active transport. These products then enter the bloodstream.

Mineral Absorption

The electrolytes absorbed by the small intestine are from both GI secretions and ingested foods. Since electrolytes dissociate into ions in water, most are absorbed via active transport throughout the entire small intestine. During absorption, co-transport

mechanisms result in the accumulation of sodium ions inside the cells, whereas anti-port mechanisms reduce the potassium ion concentration inside the cells. To restore the sodium-potassium gradient across the cell membrane, a sodium-potassium pump requiring ATP pumps sodium out and potassium in.

In general, all minerals that enter the intestine are absorbed, whether you need them or not. Iron and calcium are exceptions; they are absorbed in the duodenum in amounts that meet the body's current requirements, as follows:

Iron—The ionic iron needed for the production of hemoglobin is absorbed into mucosal cells via active transport. Once inside mucosal cells, ionic iron binds to the protein ferritin, creating iron-ferritin complexes that store iron until needed. When the body has enough iron, most of the stored iron is lost when worn-out epithelial cells slough off. When the body needs iron because, for example, it is lost during acute or chronic bleeding, there is increased uptake of iron from the intestine and accelerated release of iron into the bloodstream. Since females experience significant iron loss during menstruation, they have around four times as many iron transport proteins in their intestinal epithelial cells as do males.

Calcium—Blood levels of ionic calcium determine the absorption of dietary calcium. When blood levels of ionic calcium drop, parathyroid hormone (PTH) secreted by the parathyroid glands stimulates the release of calcium ions from bone matrices and increases the reabsorption of calcium by the kidneys. PTH also upregulates the activation of vitamin D in the kidney, which then facilitates intestinal calcium ion absorption.

Vitamin Absorption

The small intestine absorbs the vitamins that occur naturally in food and supplements. Fat-soluble vitamins (A, D, E, and K) are absorbed along with dietary lipids in micelles via simple diffusion. This is why you are advised to eat some fatty foods when you take fat-soluble vitamin supplements. Most water-soluble vitamins (including most B vitamins and vitamin C) also are absorbed by simple diffusion. An exception is vitamin B_{12}, which is a very large molecule. Intrinsic factor secreted in the stomach binds to vitamin B_{12}, preventing its digestion and creating a complex that binds to mucosal receptors in the terminal ileum, where it is taken up by endocytosis.

Water Absorption

Each day, about nine liters of fluid enter the small intestine. About 2.3 liters are ingested in foods and beverages, and the rest is from GI secretions. About 90 percent of this water is absorbed in the small intestine. Water absorption is driven by the concentration gradient of the water: The concentration of water is higher in chyme than it is in epithelial cells. Thus, water moves down its concentration gradient from the chyme into cells. As noted earlier, much of the remaining water is then absorbed in the colon.

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3.8: Terms and Definitions

Key Terms

Select to View Definition

Absorption
passage of digested products from the intestinal lumen through mucosal cells and into the bloodstream or lacteals

Accessory digestive organ
includes teeth, tongue, salivary glands, gallbladder, liver, and pancreas

Accessory duct
(also, duct of Santorini) duct that runs from the pancreas into the duodenum

Acinus
cluster of glandular epithelial cells in the pancreas that secretes pancreatic juice in the pancreas

Alimentary canal
continuous muscular digestive tube that extends from the mouth to the anus

Aminopeptidase
brush border enzyme that acts on proteins

Anal canal
final segment of the large intestine

Anal column
long fold of mucosa in the anal canal

Anal sinus
recess between anal columns

Appendix
(vermiform appendix) coiled tube attached to the cecum

Ascending colon
first region of the colon

Bacterial flora
bacteria in the large intestine

Bile
alkaline solution produced by the liver and important for the emulsification of lipids

Bile canaliculus
small duct between hepatocytes that collects bile

Bilirubin
main bile pigment, which is responsible for the brown color of feces

Body
mid-portion of the stomach

Bolus
mass of chewed food

Brush border
fuzzy appearance of the small intestinal mucosa created by microvilli

Cardia
(also, cardiac region) part of the stomach surrounding the cardiac orifice (esophageal hiatus)

Cecum
pouch forming the beginning of the large intestine

Cementum
bone-like tissue covering the root of a tooth

Central vein
vein that receives blood from hepatic sinusoids

Cephalic phase
(also, reflex phase) initial phase of gastric secretion that occurs before food enters the stomach

Chemical digestion
enzymatic breakdown of food

Chief cell
gastric gland cell that secretes pepsinogen

Chylomicron
large lipid-transport compound made up of triglycerides, phospholipids, cholesterol, and proteins

Chyme
soupy liquid created when food is mixed with digestive juices

Circular fold
(also, plica circulare) deep fold in the mucosa and submucosa of the small intestine

Colon
part of the large intestine between the cecum and the rectum

Common bile duct
structure formed by the union of the common hepatic duct and the gallbladder's cystic duct

Common hepatic duct
duct formed by the merger of the two hepatic ducts

Crown
portion of tooth visible superior to the gum line

Cuspid
(also, canine) pointed tooth used for tearing and shredding food

Cystic duct
duct through which bile drains and enters the gallbladder

Deciduous tooth
one of 20 "baby teeth"

Defecation
elimination of undigested substances from the body in the form of feces

Deglutition
three-stage process of swallowing

Dentin
bone-like tissue immediately deep to the enamel of the crown or cementum of the root of a tooth

Dentition
set of teeth

Deoxyribonuclease
pancreatic enzyme that digests DNA

Descending colon
part of the colon between the transverse colon and the sigmoid colon

Dipeptidase
brush border enzyme that acts on proteins

Duodenal gland
(also, Brunner's gland) mucous-secreting gland in the duodenal submucosa

Duodenum
first part of the small intestine, which starts at the pyloric sphincter and ends at the jejunum

Enamel
covering of the dentin of the crown of a tooth

Enteroendocrine cell
gastric gland cell that releases hormones

Enterohepatic circulation
recycling mechanism that conserves bile salts

Enteropeptidase
intestinal brush-border enzyme that activates trypsinogen to trypsin

Epiploic appendage
small sac of fat-filled visceral peritoneum attached to teniae coli

Esophagus
muscular tube that runs from the pharynx to the stomach

External anal sphincter
voluntary skeletal muscle sphincter in the anal canal

Fauces
opening between the oral cavity and the oropharynx

Feces
semisolid waste product of digestion

Flatus
gas in the intestine

Fundus
dome-shaped region of the stomach above and to the left of the cardia

G cell
gastrin-secreting enteroendocrine cell

Gallbladder
accessory digestive organ that stores and concentrates bile

Gastric emptying
process by which mixing waves gradually cause the release of chyme into the duodenum

Gastric gland
gland in the stomach mucosal epithelium that produces gastric juice

Gastric phase
phase of gastric secretion that begins when food enters the stomach

Gastric pit
narrow channel formed by the epithelial lining of the stomach mucosa

Gastrin
peptide hormone that stimulates secretion of hydrochloric acid and gut motility

Gastrocolic reflex
propulsive movement in the colon activated by the presence of food in the stomach

Gastroileal reflex
long reflex that increases the strength of segmentation in the ileum

Gingiva
gum

Haustral contraction
slow segmentation in the large intestine

Haustrum
small pouch in the colon created by tonic contractions of teniae coli

Hepatic artery
artery that supplies oxygenated blood to the liver

Hepatic lobule
hexagonal-shaped structure composed of hepatocytes that radiate outward from a central vein

Hepatic portal vein
vein that supplies deoxygenated nutrient-rich blood to the liver

Hepatic sinusoid
blood capillaries between rows of hepatocytes that receive blood from the hepatic portal vein and the branches of the hepatic artery

Hepatic vein
vein that drains into the inferior vena cava

Hepatocytes
major functional cells of the liver

Hepatopancreatic ampulla
(also, ampulla of Vater) bulb-like point in the wall of the duodenum where the bile duct and main pancreatic duct unite

Hepatopancreatic sphincter
(also, sphincter of Oddi) sphincter regulating the flow of bile and pancreatic juice into the duodenum

Hydrochloric acid (HCl)
digestive acid secreted by parietal cells in the stomach

Ileocecal sphincter
sphincter located where the small intestine joins with the large intestine

Ileum
end of the small intestine between the jejunum and the large intestine

Incisor
midline, chisel-shaped tooth used for cutting into food

Ingestion
taking food into the GI tract through the mouth

Internal anal sphincter
involuntary smooth muscle sphincter in the anal canal

Intestinal gland
(also, crypt of Lieberkühn) gland in the small intestinal mucosa that secretes intestinal juice

Intestinal juice
mixture of water and mucus that helps absorb nutrients from chyme

Intestinal phase
phase of gastric secretion that begins when chyme enters the intestine

Intrinsic factor
glycoprotein required for vitamin B_{12} absorption in the small intestine

Jejunum
middle part of the small intestine between the duodenum and the ileum

Labial frenulum
midline mucous membrane fold that attaches the inner surface of the lips to the gums

Labium
lip

Lactase
brush border enzyme that breaks down lactose into glucose and galactose

Lacteal
lymphatic capillary in the villi

Large intestine
terminal portion of the alimentary canal

Laryngopharynx
part of the pharynx that functions in respiration and digestion

Left colic flexure
(also, splenic flexure) point where the transverse colon curves below the inferior end of the spleen

Lingual frenulum
mucous membrane fold that attaches the bottom of the tongue to the floor of the mouth

Lingual lipase
digestive enzyme from glands in the tongue that acts on triglycerides

Lipoprotein lipase
enzyme that breaks down triglycerides in chylomicrons into fatty acids and monoglycerides

Liver
largest gland in the body whose main digestive function is the production of bile

Lower esophageal sphincter
smooth muscle sphincter that regulates food movement from the esophagus to the stomach

Main pancreatic duct
(also, duct of Wirsung) duct through which pancreatic juice drains from the pancreas

Major duodenal papilla
point at which the hepatopancreatic ampulla opens into the duodenum

Maltase
brush border enzyme that breaks down maltose and maltotriose into two and three molecules of glucose, respectively

Mass movement
long, slow, peristaltic wave in the large intestine

Mastication
chewing

Mechanical digestion
chewing, mixing, and segmentation that prepares food for chemical digestion

Mesoappendix
mesentery of the appendix

Micelle
tiny lipid-transport compound composed of bile salts and phospholipids with a fatty acid and monoacylglyceride core

Microvillus
small projection of the plasma membrane of the absorptive cells of the small intestinal mucosa

Migrating motility complex
form of peristalsis in the small intestine

Mixing wave
unique type of peristalsis that occurs in the stomach

Molar
tooth used for crushing and grinding food

Motilin
hormone that initiates migrating motility complexes

Motility
movement of food through the GI tract

Mucosa
innermost lining of the alimentary canal

Mucosal barrier
protective barrier that prevents gastric juice from destroying the stomach itself

Mucous neck cell
gastric gland cell that secretes a uniquely acidic mucus

Muscularis
muscle (skeletal or smooth) layer of the alimentary canal wall

Myenteric plexus
(plexus of Auerbach) major nerve supply to alimentary canal wall; controls motility

Nucleosidase
brush border enzyme that digests nucleotides

Oral cavity
(also, buccal cavity) mouth

Oral vestibule
part of the mouth bounded externally by the cheeks and lips, and internally by the gums and teeth

Oropharynx
part of the pharynx continuous with the oral cavity that functions in respiration and digestion

Palatoglossal arch
muscular fold that extends from the lateral side of the soft palate to the base of the tongue

Palatopharyngeal arch
muscular fold that extends from the lateral side of the soft palate to the side of the pharynx

Pancreas
accessory digestive organ that secretes pancreatic juice

Pancreatic amylase
enzyme secreted by the pancreas that completes the chemical digestion of carbohydrates in the small intestine

Pancreatic juice
secretion of the pancreas containing digestive enzymes and bicarbonate

Pancreatic lipase
enzyme secreted by the pancreas that participates in lipid digestion

Pancreatic nuclease
enzyme secreted by the pancreas that participates in nucleic acid digestion

Parietal cell
gastric gland cell that secretes hydrochloric acid and intrinsic factor

Parotid gland
one of a pair of major salivary glands located inferior and anterior to the ears

Pectinate line
horizontal line that runs like a ring, perpendicular to the inferior margins of the anal sinuses

Pepsinogen
inactive form of pepsin

Peristalsis
muscular contractions and relaxations that propel food through the GI tract

Permanent tooth
one of 32 adult teeth

Pharynx
throat

Phosphatase
brush border enzyme that digests nucleotides

Porta hepatis
“gateway to the liver” where the hepatic artery and hepatic portal vein enter the liver

Portal triad
bile duct, hepatic artery branch, and hepatic portal vein branch

Premolar
(also, bicuspid) transitional tooth used for mastication, crushing, and grinding food

Propulsion
voluntary process of swallowing and the involuntary process of peristalsis that moves food through the digestive tract

Pulp cavity
deepest portion of a tooth, containing nerve endings and blood vessels

Pyloric antrum
wider, more superior part of the pylorus

Pyloric canal
narrow, more inferior part of the pylorus

Pyloric sphincter
sphincter that controls stomach emptying

Pylorus
lower, funnel-shaped part of the stomach that is continuous with the duodenum

Rectal valve
one of three transverse folds in the rectum where feces is separated from flatus

Rectum
part of the large intestine between the sigmoid colon and anal canal

Reticuloendothelial cell
(also, Kupffer cell) phagocyte in hepatic sinusoids that filters out material from venous blood from the alimentary canal

Retroperitoneal
located posterior to the peritoneum

Ribonuclease
pancreatic enzyme that digests RNA

Right colic flexure
(also, hepatic flexure) point, at the inferior surface of the liver, where the ascending colon turns abruptly to the left

Root
portion of a tooth embedded in the alveolar processes beneath the gum line

Ruga
fold of alimentary canal mucosa and submucosa in the empty stomach and other organs

Saccharolytic fermentation
anaerobic decomposition of carbohydrates

Saliva
aqueous solution of proteins and ions secreted into the mouth by the salivary glands

Salivary amylase
digestive enzyme in saliva that acts on starch

Salivary gland
an exocrine gland that secretes a digestive fluid called saliva

Salivation
secretion of saliva

Segmentation
alternating contractions and relaxations of non-adjacent segments of the intestine that move food forward and backward, breaking it apart and mixing it with digestive juices

Serosa
outermost layer of the alimentary canal wall present in regions within the abdominal cavity

Sigmoid colon
: end portion of the colon, which terminates at the rectum

Small intestine
: section of the alimentary canal where most digestion and absorption occurs

Soft palate
: posterior region of the bottom portion of the nasal cavity that consists of skeletal muscle

Stomach
: alimentary canal organ that contributes to chemical and mechanical digestion of food from the esophagus before releasing it, as chyme, to the small intestine

Sublingual gland
: one of a pair of major salivary glands located beneath the tongue

Submandibular gland
: one of a pair of major salivary glands located in the floor of the mouth

Submucosa
: layer of dense connective tissue in the alimentary canal wall that binds the overlying mucosa to the underlying muscularis

Submucosal plexus
: (plexus of Meissner) nerve supply that regulates activity of glands and smooth muscle

Sucrase
: brush border enzyme that breaks down sucrose into glucose and fructose

Tenia coli
: one of three smooth muscle bands that make up the longitudinal muscle layer of the muscularis in all of the large intestine except the terminal end

Tongue
: accessory digestive organ of the mouth, the bulk of which is composed of skeletal muscle

Transverse colon
: part of the colon between the ascending colon and the descending colon

Upper esophageal sphincter
: skeletal muscle sphincter that regulates food movement from the pharynx to the esophagus

Valsalva's maneuver
: voluntary contraction of the diaphragm and abdominal wall muscles and closing of the glottis, which increases intra-abdominal pressure and facilitates defecation

Villus
: projection of the mucosa of the small intestine

Voluntary phase
: initial phase of deglutition, in which the bolus moves from the mouth to the oropharynx

α-dextrin
: breakdown product of starch

α-dextrinase
: brush border enzyme that acts on α-dextrins

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3.9: Chapter Review Questions

Multiple-Choice Section

- Use the end-of-chapter multiple-choice section as a regular self-check tool, not just before exams.
- Read each item carefully, think about what is really being tested (concept, definition, application, or calculation), and choose the option (A, B, C, or D) that best reflects what you have learned in this chapter.
  - After you read through the chapter, attempt all items without looking at your notes; then return to the chapter to review any you missed or felt unsure about.
  - Afterward, explain to yourself why the correct option is right and why the others are not. Finally, repeat the multiple-choice section a few days later to see what you truly remember and understand.
- Students who consistently use these prompts in this way typically perform better across the course because they turn reading into active practice

1. A 40-year-old man with gallstones has normal liver function but cannot store or concentrate bile properly. His physician explains that bile and pancreatic enzymes are not part of the main food pathway through the gut but enter via ducts. Which of these organs is NOT considered an accessory digestive structure?
   A. Mouth
   B. Salivary glands
   C. Pancreas
   D. Liver

2. A 65-year-old man with chronic reflux has an upper endoscopy. The gastroenterologist notes that a portion of his gastrointestinal tract is retroperitoneal and covered externally by a fibrous connective tissue layer rather than a serous membrane. Which of the following organs is supported by a layer of adventitia rather than serosa?
   A. Esophagus
   B. Stomach
   C. Small intestine
   D. Large intestine

3. During laparoscopic surgery, a surgeon identifies a shiny, serous membrane directly covering the external surface of the stomach. Which of the following membranes covers the stomach itself?
   A. Falciform ligament
   B. Mesocolon
   C. Parietal peritoneum
   D. Visceral peritoneum

4. A 17-year-old student eats a sandwich quickly between classes. Which of these digestive processes are occurring in his mouth while he chews and mixes the food with saliva?
   A. Ingestion only
   B. Mechanical digestion only
   C. Chemical digestion only
   D. All of the above

5. A patient reports that food seems to move normally through their digestive tract once swallowed. Which of these processes occurs throughout most of the length of the alimentary canal to move its contents forward?
   A. Ingestion
   B. Propulsion
   C. Segmentation
   D. Absorption

6. A 32-year-old woman eats a large meal and later feels abdominal distension. Stretch receptors and chemoreceptors in her stomach wall become activated. Which of the following types of stimuli can activate these sensory receptors in the walls of digestive organs?

A. Breakdown products of digestion
B. Distension (stretch)
C. pH of chyme
D. All of the above

7. A researcher is studying neural control of gut motility. Which of these statements about reflexes in the gastrointestinal (GI) tract is FALSE?
A. Short reflexes are provoked by stimuli near or within the GI tract wall
B. Short reflexes are mediated by the enteric nervous system
C. Food that distends the stomach can initiate long reflexes
D. Long reflexes cannot be provoked by stimuli originating outside the GI tract

8. A physiologist examines saliva composition. Which of these components is responsible for creating the optimal ionic environment to activate salivary amylase?
A. Mucus
B. Phosphate ions
C. Chloride ions
D. Urea

9. A 10-year-old child presents with a sore throat and difficulty swallowing. On exam, the physician reviews the anatomy of the pharynx with a medical student. Which of the following statements about the pharynx is TRUE?
A. It extends from the nasal and oral cavities superiorly to the esophagus anteriorly
B. The oropharynx is continuous superiorly with the nasopharynx
C. The nasopharynx is a major structure involved in digestion
D. The laryngopharynx is composed primarily of cartilage

10. A hiatal hernia is diagnosed in a 58-year-old woman, where part of the stomach protrudes through the diaphragm. This involves the opening in the diaphragm through which the esophagus passes. Which structure is located where the esophagus penetrates the diaphragm?
A. Esophageal hiatus
B. Cardiac orifice
C. Upper esophageal sphincter
D. Lower esophageal sphincter

11. A speech therapist is explaining the stages of swallowing (deglutition) to a patient after stroke. During which phase does contraction of the longitudinal muscle layer of the esophageal muscularis help move the food bolus toward the stomach?
A. Voluntary (oral) phase
B. Buccal phase
C. Pharyngeal phase
D. Esophageal phase

12. A biopsy from the gastric mucosa shows cells at the base of gastric glands that release regulatory peptides such as gastrin and somatostatin into the bloodstream. Which of these gastric cell types secretes hormones?
A. Parietal cells
B. Mucous neck cells
C. Enteroendocrine cells
D. Chief cells

13. A radiologist reviews a barium swallow study and notes the regions of the stomach most involved in secretion and mixing of gastric juice. Where does the majority of chemical digestion within the stomach occur?
A. Fundus and body
B. Cardia and fundus
C. Body and pylorus
D. Body alone

14. During gastric emptying, partially digested food (chyme) passes from the stomach into the duodenum. Through which structure is chyme released into the duodenum?
A. Esophageal hiatus
B. Pyloric antrum

C. Pyloric canal
D. Pyloric sphincter

15. A patient with severe gastric ulcers is found to have greatly reduced stomach acid. Which gastric cells have likely been damaged, leading to decreased secretion of this substance? Parietal cells normally secrete:
A. Gastrin
B. Hydrochloric acid
C. Pepsin
D. Pepsinogen

16. A 54-year-old man with celiac disease has damage to the mucosa of the proximal small intestine. He is at high risk for malabsorption because this is the main site of digestion and absorption. In which part of the alimentary canal does most digestion occur?
A. Stomach
B. Proximal small intestine
C. Distal small intestine
D. Ascending colon

17. A pathologist examines a section of small intestine and notes fingerlike projections that greatly increase surface area. Within each projection is a lymphatic capillary important for fat absorption. Which of the following is most closely associated with these villi?
A. Haustra
B. Lacteals
C. Bacterial flora
D. Intestinal glands

18. A 6-year-old child has an infection with intestinal bacteria. Lymphoid tissue in the wall of the small intestine helps prevent these microbes from entering the bloodstream. What is the primary role of the small intestine's mucosa-associated lymphoid tissue (MALT)?
A. Secreting mucus
B. Buffering acidic chyme
C. Activating pepsin
D. Preventing bacteria and pathogens from entering the bloodstream

19. A surgeon removes an inflamed appendix from a 12-year-old patient. The appendix arises from a blind pouch located at the beginning of the large intestine. Which part of the large intestine directly attaches to the appendix?
A. Cecum
B. Ascending colon
C. Transverse colon
D. Descending colon

20. A 55-year-old has gallbladder disease. The doctor explains how bile made in the liver helps digest dietary fats and is reused multiple times. Which of these statements about bile is TRUE?
A. About 500 mL is secreted daily in adults
B. Its main function is denaturation of proteins
C. It is synthesized in the gallbladder
D. Bile salts are recycled via enterohepatic circulation

21. A patient with a duodenal ulcer is prescribed a medication to reduce the acidity of the contents leaving the stomach. Pancreatic secretions are important in neutralizing this acid. Pancreatic juice primarily:
A. Deactivates bile
B. Is secreted by pancreatic islet cells
C. Buffers acidic chyme
D. Is released into the cystic duct

22. A 9-year-old child eats a piece of bread. Soon after chewing, an enzyme begins to break down starch into simpler sugars. In which region of the alimentary canal does the chemical digestion of starch begin?
A. Mouth
B. Esophagus

C. Stomach
D. Small intestine

23. A biochemistry student studies digestive enzymes and their substrates. Which of the following is directly involved in the chemical digestion of proteins into smaller peptides in the small intestine?
A. Pancreatic amylase
B. Trypsin
C. Sucrase
D. Pancreatic nuclease

24. A 47-year-old man has difficulty digesting fats after his pancreas is damaged in an accident. Most of the lipases and other enzymes that break down fats come from one accessory organ. Where are most fat-digesting enzymes produced?
A. Small intestine
B. Gallbladder
C. Liver
D. Pancreas

25. A 30-year-old patient experiences burning chest pain after meals. Tests show delayed gastric emptying and poor mixing of food with gastric secretions, but normal mouth and esophageal function. Which of the following regions is MOST responsible for churning food and mixing it with acid and enzymes before release into the duodenum, and therefore is likely contributing to his symptoms?
A. Cardia of the stomach
B. Fundus of the stomach
C. Body and pyloric region of the stomach
D. Ascending colon

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3.10: Applied Thinking Self-Assessment

Challenge Yourself

- Extended response questions are assessment items that require students to construct written answers of substantial length - typically several sentences to multiple paragraphs - rather than selecting from predefined options. They represent a form of constructed response assessment designed to measure complex, higher-order thinking skills.
- First, try answering without using your notes. Then review reliable resources and revise your response if needed. Make a note of any areas where you felt unsure and revisit those topics.

Writing Guidelines

- Answer each question in your own words.
- Write 4–8 clear, complete sentences per question, organized into short paragraphs (not bullet points).
- Focus on explaining your reasoning, not just stating the answer.
- Use correct scientific vocabulary, and briefly define terms when needed.
- For questions that ask you to compare, contrast, or explain why/how:
  - Clearly state similarities or differences
  - Support your ideas with a brief explanation or example

Enteric vs. Autonomic Nervous System and Digestion

1. Explain how the enteric nervous system (ENS) supports and regulates digestive system function.
2. Describe a situation in which the autonomic nervous system (sympathetic or parasympathetic) could negatively affect digestion, and explain the mechanism.

Defense in the Alimentary Canal Wall

1. Which layer of the alimentary canal provides protection against pathogens, and by what specific mechanisms (cells, structures, or secretions) does it help defend the body?

Segmentation vs. Peristalsis in the Small Intestine

1. Propose a theory for why segmentation contractions are prominent and peristalsis is relatively slower or weaker in the small intestine.
2. How does this pattern of motility benefit digestion and absorption?

Cephalic Reflex and the Smell of Food

1. Several hours after your last meal, you walk past a bakery and smell freshly baked bread.
   a. What type of reflex is triggered?
   b. Which nervous pathways are involved, and what are the main digestive responses that occur?

Differences in Saliva from Major Salivary Glands

1. Compare the saliva produced by the parotid gland with the saliva produced by the sublingual gland in terms of:
   a. Composition (e.g., serous vs. mucous)
   b. Primary actions in the oral cavity (e.g., digestion, lubrication, protection).

Loss of Anterior Teeth and Ingestion

1. A hockey player is struck in the mouth and loses all eight of their most anterior teeth.
    a. Identify which teeth were lost (by name and/or position).
    b. Explain how this loss would affect the mechanical aspects of food ingestion/digestion.

Protection of the Airway During Swallowing

1. What anatomical structures and coordinated actions prevent swallowed food and liquid from entering the airways during deglutition?

Mechanism of Gastroesophageal Reflux

1. Explain the mechanism responsible for gastroesophageal reflux (GERD).
    a. Include the role of the lower esophageal sphincter and pressure differences between the stomach and esophagus.

Esophageal Phase of Swallowing

1. Describe the three major processes that occur during the esophageal phase of deglutition, from entry of the bolus into the esophagus to its arrival in the stomach.

Protection of the Stomach from Self-Digestion

1. Explain how the stomach protects its own tissues from digestion by acid and enzymes.
    a. Why is this protection essential for normal function?

Anatomical Specializations of the Stomach

1. Describe unique anatomical features of the stomach (e.g., muscle layers, mucosa, sphincters) that enable it to perform its mechanical and chemical digestive functions.

Absorbed Nutrients and General Circulation

1. Explain how nutrients absorbed in the small intestine (carbohydrates, proteins, and lipids) are transported from the intestinal mucosa into the general circulation.
2. Distinguish between venous (portal) and lymphatic pathways.

Rate of Chyme Delivery to the Small Intestine

1. Why must chyme be delivered from the stomach to the small intestine slowly and in small amounts?
2. What problems might occur if chyme entered the duodenum too quickly or in large quantities?

Inactive Pancreatic Enzymes

1. Why does the pancreas secrete some digestive enzymes in inactive (zymogen) forms?
2. Where and how are these enzymes activated in the digestive tract?

Organization and Function of Hepatocytes

1. Describe the arrangement of hepatocytes within the liver (e.g., in lobules, around central veins).
2. Explain how this organization enhances their roles in metabolism, detoxification, and bile production.

Role of Bile Salts in Fat Digestion

1. Explain how bile salts contribute to the emulsification of dietary lipids.
2. How does this process improve the efficiency of lipid digestion and absorption?

Villi and Microvilli in Nutrient Absorption

1. Describe how villi and microvilli increase absorptive efficiency in the small intestine.
2. Relate their structure to their function.

Large Intestine: Water and Electrolyte Balance

1. Explain the main roles of the large intestine in digestion and homeostasis, particularly in water and electrolyte balance.

Hormonal Control of Digestion

1. Choose one digestive hormone (e.g., gastrin, secretin, CCK) and explain its source, major stimuli for release, and main effects on the digestive organs.

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3.11: Alternate Text Description

Figure 3.1.1: Components of the Digestive System

This image shows the human digestive system arranged vertically from the head to the lower torso, with labels identifying each structure and its role in the pathway food follows through the body. At the top, the mouth is shown as the entry point where food enters the digestive system. Inside the mouth, the tongue is labeled, indicating its role in positioning food during chewing and swallowing. Three sets of salivary glands are labeled near the mouth:

- The parotid gland, located near the cheek area
- The sublingual gland, located beneath the tongue
- The submandibular gland, located below the jaw

These glands produce saliva that begins chemical digestion and lubricates food. From the mouth, the pathway continues to the pharynx, which serves as a passage guiding swallowed food toward the esophagus. The esophagus is shown as a long vertical tube descending through the chest region, transporting food from the pharynx to the stomach through muscular contractions. In the upper abdominal region, the stomach is labeled. The stomach acts as a holding chamber where food is mixed with digestive secretions for further breakdown. Surrounding the stomach are accessory digestive organs:

- The liver, located above and to one side of the stomach, produces substances that aid digestion
- The gallbladder, positioned beneath the liver, stores and releases bile needed for fat digestion
- The pancreas, located behind the stomach, releases enzymes that support chemical digestion

Below the stomach begins the small intestine, which is divided into three segments:

- The duodenum, the first section where digestion continues
- The jejunum, the middle section where nutrient absorption occurs
- The ileum, the final section that completes absorption and connects to the large intestine

The large intestine surrounds the small intestine and is labeled in several parts:

- The ascending colon, which carries material upward
- The transverse colon, which runs horizontally
- The descending colon, which moves downward
- The sigmoid colon, which curves toward the rectum
- The cecum, located at the beginning of the large intestine
- The appendix, attached to the cecum

At the end of the digestive tract, the rectum stores waste before elimination, and the anal canal and anus serve as the exit point for waste removal.

Figure 3.1.2: Layers of the Alimentary Canal

This figure illustrates the organization of the gastrointestinal tract wall and the function of its layers. Food and digestive contents travel through the central lumen, which is surrounded by four major tissue layers that work together to support digestion, absorption, secretion, movement of food, immune defense, and communication with the nervous system.

The innermost layer is the mucosa, which is composed of the epithelium, lamina propria, and muscularis mucosae. The epithelium lines the lumen directly and serves as the primary site of secretion and absorption. The lamina propria supports the epithelium and contains blood vessels, lymphatic tissue, and immune cells that help transport absorbed nutrients and protect against pathogens. The muscularis mucosae is a thin smooth muscle layer that produces small movements of the mucosal surface, increasing contact between digested material and the absorptive lining.

Surrounding the mucosa is the submucosa, a connective tissue layer that contains blood vessels, lymphatic vessels, glands, and the submucosal plexus. This nerve network helps regulate secretion and local blood flow. Glands located within the submucosa

contribute digestive secretions, and ducts allow secretions from glands outside the tract to enter the lumen.

Outside the submucosa is the muscularis, which consists of an inner circular muscle layer and an outer longitudinal muscle layer. The circular muscle narrows the lumen when it contracts, while the longitudinal muscle shortens the digestive tract. Working together, these layers generate mixing and propulsion movements that move food through the gastrointestinal tract. Between them lies the myenteric plexus, a network of nerves that coordinates muscle contractions and controls gastrointestinal motility.

The outermost layer is the serosa, which consists of areolar connective tissue covered by a thin epithelial layer. The serosa protects the digestive tract and reduces friction between abdominal organs. Attached to the serosa is the mesentery, which anchors the intestine within the abdominal cavity and provides pathways for blood vessels, lymphatic vessels, and nerves.

The figure also shows how supporting structures enter the intestinal wall. An artery enters through the mesentery and branches toward the submucosa to supply oxygen and nutrients. A vein located near the muscularis carries blood away from the intestinal tissues. A nerve enters through the mesentery and connects with the submucosal plexus, helping regulate secretion, blood flow, and digestive activity.

Overall, the image demonstrates how the layers of the gastrointestinal tract function together to digest food, absorb nutrients, transport materials through the digestive system, provide immune protection, and coordinate activity through the enteric nervous system.

Figure 3.1.3: The Peritoneum

This image shows a horizontal cross-section of the abdomen, as if the body has been sliced across the midsection. The organs are arranged within a circular body outline, with labels identifying both digestive organs and surrounding structures. At the center top of the image is the vertebra, with the spinal cord located just in front of it. These structures provide support and protection for the central nervous system.

On both sides of the spinal cord are the kidneys, positioned toward the back of the abdominal cavity. Near one kidney, the spleen is labeled, and on the opposite side, the liver is shown as a large organ occupying significant space in the upper abdomen. Beneath the liver is the gallbladder, which stores bile.

Near the middle of the abdomen is the pancreas, positioned behind the stomach and extending across the midline. The stomach is located toward the front portion of the abdominal cavity. From the stomach, the digestive tract continues into the small intestine, shown as coiled loops occupying the central region of the abdomen.

Surrounding the small intestine is the large intestine, which forms a thicker tube that frames the smaller loops of the small intestine. The diagram highlights the peritoneum, a continuous membrane that lines and supports the abdominal organs. It is divided into:

- The parietal peritoneum, which lines the inner surface of the body wall
- The visceral peritoneum, which covers the surfaces of the organs

Between these two layers is the peritoneal cavity, a space that allows movement of the organs while reducing friction. The diagram uses a highlighted boundary to show how the peritoneum wraps around and encloses the organs, forming a supportive and protective structure that helps maintain the organization of the abdominal contents.

Figure 3.2.1: Digestive Processes

This image consists of three side-by-side diagrams showing a sequence of events in peristalsis, the process that moves food through the digestive tract. Each diagram shows a vertical tube representing a section of the digestive tract. Inside the tube is an oval-shaped mass representing a bolus of food. Arrows indicate both the direction of food movement and the actions of the surrounding muscles.

1. Left Diagram: Start of Movement - The bolus is located near the upper part of the tube. The text “direction of food” and a downward arrow indicate that movement occurs from top to bottom. The tube is narrowed just above the bolus, showing contraction of circular muscles behind the bolus. Below the bolus, the tube is wider, indicating relaxation of muscles ahead of the bolus.
2. Middle Diagram: Progression - The bolus has moved downward. The region of contraction has also shifted downward to

remain just behind the bolus. Arrows on the sides of the tube indicate inward pressure behind the bolus and reduced pressure ahead of it. This demonstrates that muscle contraction follows the bolus, continuing to push it forward.

3. Right Diagram: Continued Movement - The bolus is now positioned further down the tube. The same pattern continues: contraction occurs behind the bolus, and relaxation occurs ahead of the bolus, maintaining a one-directional push. Arrows indicate the continued downward movement.

Figure 3.2.2: The Human Digestive Tract

The image is the human digestive tract from the head to the lower body, with arrows tracing the movement of food and labels identifying the key processes that occur at each stage.

At the top, the mouth is labeled with ingestion of food, indicating the entry point where food is taken into the digestive system. From the mouth, a continuous pathway leads through the pharynx and into the esophagus. A labeled section titled Propulsion explains how food moves through the digestive tract. Two mechanisms are listed:

- Swallowing, which moves food from the mouth through the oropharynx and into the esophagus
- Peristalsis, which occurs in the esophagus, stomach, small intestine, and large intestine, pushing food forward through coordinated muscle contractions

The pathway continues into the stomach, where arrows inside the organ indicate mixing movements. A labeled section titled Mechanical digestion explains that physical breakdown occurs through:

- chewing in the mouth
- churning in the stomach
- segmentation in the small intestine, which mixes contents

Another labeled section titled Chemical digestion shows that digestive substances act throughout the tract to break down food into smaller components suitable for absorption. From the stomach, the pathway continues into the small intestine, shown as a long, coiled tube. Arrows along this region indicate both movement and mixing. A labeled section titled Absorption explains that:

- nutrients and water move into blood vessels and lymphatic vessels in the small intestine
- water is absorbed into blood vessels in the large intestine

The pathway then continues into the large intestine, shown as a broader tube surrounding the end of the small intestine. Near the bottom, the remaining material is labeled feces, indicating the waste left after digestion and absorption. The final section shows the anus, labeled with defecation, where waste is eliminated from the body. Some chemical digestion occurs in the mouth. Some absorption can occur in the mouth and stomach, for example, alcohol and aspirin.

Figure 3.3.1: Anatomy of the Oral Cavity

This image shows an anterior view of the open mouth, with the lips parted and the internal structures of the oral cavity clearly labeled.

At the top are the superior lip and the superior labial frenulum, a thin fold of tissue connecting the upper lip to the gum. The gingivae (gums) surround the upper teeth and provide support. The roof of the mouth is divided into two regions:

- The hard palate, located toward the front, provides a firm surface that helps press food during chewing.
- The soft palate, located toward the back, is more flexible and helps direct food toward the throat during swallowing.

Hanging from the soft palate is the uvula, a small projection that helps close off the nasal passage during swallowing. At the back of the oral cavity are the palatoglossal arch and palatopharyngeal arch, which form the boundaries of the fauces, the opening between the mouth and the pharynx. Between these arches is the palatine tonsil, which helps with immune defense. On the sides of the mouth are the cheeks, which form the lateral walls of the oral cavity.

The lower portion of the diagram shows the tongue (underside), which is lifted to reveal structures beneath it. The lingual frenulum is the fold of tissue connecting the tongue to the floor of the mouth. Near this area is the opening of the duct of the submandibular gland, where saliva enters the oral cavity. The diagram also labels different types of teeth, arranged from front to back:

- Incisors, used for cutting food
- Cuspids (canines), used for tearing
- Premolars, used for crushing
- Molars, used for grinding

The oral vestibule, the space between the lips or cheeks and the teeth, is labeled along the lower outer region. At the bottom are the inferior lip and the inferior labial frenulum, which connects the lower lip to the gum.

A fleshy bead of tissue called the uvula drops down from the center of the posterior edge of the soft palate. Although some have suggested that the uvula is a vestigial organ, it serves an important purpose. When you swallow, the soft palate and uvula move upward, helping to keep foods and liquid from entering the nasal cavity. Unfortunately, it can also contribute to the sound produced by snoring. Two muscular folds extend downward from the soft palate, on either side of the uvula. Toward the front, the palatoglossal arch lies next to the base of the tongue; behind it, the palatopharyngeal arch forms the superior and lateral margins of the fauces. Between these two arches are the palatine tonsils, clusters of lymphoid tissue that protect the pharynx. The lingual tonsils are located at the base of the tongue.

Figure 3.3.2: Surface Anatomy of the Tongue and Associated Oral Structures

This image shows a superior view of the tongue and adjacent throat structures, with the tongue extended forward and the back of the oral cavity visible. At the top of the image is the epiglottis, positioned behind the tongue. It helps close the airway during swallowing.

On both sides of the upper region are the palatopharyngeal arches and palatoglossal arches, which form the boundaries of the passage between the oral cavity and the pharynx. Between these arches are the palatine tonsils, which help support immune defense by detecting pathogens. At the base of the tongue is the lingual tonsil, another area of immune tissue.

Across the surface of the tongue is a V-shaped groove called the terminal sulcus, which separates the anterior portion of the tongue from the posterior portion. The surface of the tongue, labeled as the dorsum of the tongue, contains several types of papillae, which contribute to both mechanical processing and taste:

- Circumvallate papillae are large, rounded structures arranged in a row along the terminal sulcus. They contain taste buds and play a major role in detecting taste.
- Foliate papillae are located along the sides of the tongue near the posterior region and also contain taste receptors.
- Fungiform papillae are scattered across the surface of the tongue, especially toward the front, and contain taste buds.
- Filiform papillae are the most numerous and cover much of the tongue surface. Unlike the other papillae, they do not contain taste buds. Instead, they provide friction and help move food.

Figure 3.3.3: Salivary glands

This image shows a side view of the lower face and oral cavity, focusing on the three major salivary glands and the ducts that transport saliva into the mouth.

Near the upper cheek region is the parotid salivary gland, the largest of the salivary glands. Extending forward from this gland is the parotid duct, which travels across the cheek and opens into the oral cavity near the upper teeth. This duct delivers saliva into the mouth to begin chemical digestion and lubrication.

Beneath the jaw is the submandibular salivary gland, positioned along the lower part of the face. The submandibular duct extends from this gland and opens into the floor of the mouth. This gland produces a large portion of saliva and contributes both fluid and enzymes.

Located in the floor of the mouth is the sublingual salivary gland, which is smaller and positioned beneath the tongue. Multiple sublingual ducts extend from this gland and open directly into the oral cavity. These ducts release saliva continuously to help maintain moisture and assist in digestion.

All three glands are connected to the oral cavity through ducts, which are shown as narrow channels directing secretions into the mouth. The diagram emphasizes that:

- The parotid gland secretes saliva through a single long duct into the cheek area.
- The submandibular gland releases saliva through a duct into the floor of the mouth.
- The sublingual gland releases saliva through multiple small ducts under the tongue.

Figure 3.3.4: Permanent and Deciduous Teeth

This image shows three views of human dentition, focusing on tooth types and their eruption timelines. The views include an upper jaw for permanent teeth, a smaller upper and lower jaw for primary teeth, and a lower jaw for permanent teeth. Each tooth is labeled by type and typical age of eruption.

1. Upper Permanent Teeth - The upper dental arch is shown from a top view and labeled upper teeth. Teeth are arranged from front to back as follows:
    - Central incisors: 7 to 8 years
    - Lateral incisors: 8 to 9 years
    - Cuspids or canines: 11 to 12 years
    - First premolars: 9 to 10 years
    - Second premolars: 10 to 12 years
    - First molars: 6 to 7 years
    - Second molars: 12 to 13 years
    - Third molars or wisdom teeth: shown without a specific age
2. Primary Teeth - Smaller upper and lower arches represent the primary dentition, with eruption ages listed in months.
    a. Upper Primary Teeth
        - Central incisors: 8 to 12 months
        - Lateral incisors: 12 to 24 months
        - Cuspids or canines: 16 to 24 months
        - First molars: 12 to 16 months
        - Second molars: 24 to 32 months
    b. Lower Primary Teeth
        - Central incisors: 6 to 8 months
        - Lateral incisors: 12 to 15 months
        - Cuspids or canines: 16 to 24 months
        - First molars: 12 to 16 months
        - Second molars: 24 to 32 months
3. Lower Permanent Teeth - A larger lower dental arch is shown with eruption ages in years:
    - Central incisors: 7 to 8 years
    - Lateral incisors: 7 to 8 years
    - Cuspids or canines: 9 to 10 years
    - First premolars: 9 to 10 years
    - Second premolars: 11 to 12 years
    - First molars: 6 to 7 years
    - Second molars: 11 to 13 years
    - Third molars or wisdom teeth: shown without a specific age

Figure 3.3.5: The Structure of the Tooth

This image shows a cross-sectional view of a single tooth embedded in the jaw, with labels identifying its major structural regions and internal components.

The tooth is divided into three main regions:

- The crown, which is the visible portion above the gum line and is involved in chewing
- The neck, which is the narrow region at the gum line where the crown meets the root
- The root, which extends below the gum and anchors the tooth in the jawbone

The outermost layer of the crown is enamel, which forms a hard protective covering that resists wear from chewing. Beneath the enamel is dentin, a dense tissue that forms most of the tooth structure and supports the outer layer while transmitting forces from chewing.

At the center of the tooth is the pulp cavity, which contains blood vessels and nerves. These structures provide nourishment to the tooth and allow it to respond to stimuli. The pulp cavity extends downward into the root as the root canal, carrying blood vessels and nerves toward the base of the tooth.

Surrounding the root is cementum, a layer that covers the outer surface of the root and helps anchor the tooth.

Between the cementum and the surrounding bone is the periodontal ligament, a connective tissue that secures the tooth within the socket while allowing slight movement during chewing.

The gingiva (gum) surrounds the tooth at the level of the neck, providing protection and support where the tooth meets the oral cavity. The tooth is embedded in bone, which forms the socket that holds the root in place.

Figure 3.3.6: Pharynx

This image shows a side (sagittal) view of the head and neck, showing the pathways for both air and food and how these pathways intersect and separate.

At the upper front of the diagram is the nasal cavity, located above the roof of the mouth. It connects to the nasopharynx, the upper part of the throat behind the nasal cavity, which serves as a passageway for air. Below the nasal cavity is the oral cavity, which extends from the lips to the back of the mouth. The roof of the oral cavity is divided into two regions:

- The hard palate at the front, which provides a rigid surface
- The soft palate at the back, which is flexible and helps direct substances during swallowing

Extending downward from the soft palate is the uvula, which helps close off the nasal passage during swallowing so food does not enter the nasal cavity. Behind the oral cavity is the oropharynx, which serves as a shared pathway for both air and food. Below this region is the laryngopharynx, which directs air toward the trachea and food toward the esophagus.

At the lower front of the throat is the larynx, which is part of the airway and leads into the trachea. The trachea carries air to and from the lungs. Located above the larynx is the epiglottis, which acts as a movable flap. During swallowing, the epiglottis folds downward to cover the airway opening and helps prevent food from entering the trachea.

The glottis is also labeled as the opening within the larynx through which air passes. Behind the trachea is the esophagus, the tube that carries food from the pharynx to the stomach. It lies posterior to the airway and functions only in food movement. A legend identifies the major regions:

- Nasal cavity, the upper air passage
- Oral cavity, an entry point for both food and air
- Pharynx, the shared passage with three regions: nasopharynx, oropharynx, and laryngopharynx
- Larynx, the airway structure leading to the trachea

Figure 3.3.7: Anatomy of the Esophagus and Esophageal Sphincters

This image shows a side (sagittal) view of the head, neck, and upper torso, focusing on the esophagus and the structures that control the movement of food between the throat and the stomach.

At the upper portion of the image, the pathway from the mouth leads to the pharynx and then into the esophagus, a long muscular tube that descends vertically through the chest.

At the upper end of the esophagus is the upper esophageal sphincter, located near the transition between the throat and the esophagus. This sphincter acts as a controlled opening that relaxes to allow swallowed material to enter the esophagus and then contracts to help prevent air from entering and material from moving back upward.

The esophagus is shown as a continuous tube extending downward behind the airway. Adjacent to it and positioned in front is the trachea, which carries air to the lungs. The separation between these two tubes helps ensure that food and air follow different pathways. At the lower end of the esophagus is the lower esophageal sphincter, located just before the stomach. This sphincter helps:

- allow food to enter the stomach
- prevent backflow of stomach contents into the esophagus

The stomach is shown at the bottom as the receiving organ where food is delivered after passing through the esophagus.

Figure 3.3.8: Pharyngeal Contractions During Swallowing

This image consists of three side-by-side sagittal views of the head and neck, showing the pharyngeal phase of swallowing and how muscles contract in sequence to move a bolus downward. Each panel shows a vertical pathway from the mouth to the esophagus. A rounded mass labeled bolus represents food. Arrows and highlighted muscle regions show the direction of movement and the sequence of muscle activity.

1. Left Panel: Initiation of Swallowing - The bolus is located in the back of the mouth near the entrance to the pharynx. The superior pharyngeal constrictor muscle is labeled and shown contracting around the upper pharynx. The medial pharyngeal constrictor muscle is also labeled just below it. This contraction narrows the passage behind the bolus and begins to push it downward from the oral cavity into the pharynx.
2. Middle Panel: Progression Through the Pharynx - The bolus has moved farther down into the pharynx. The labeled region shows the medial and inferior pharyngeal constrictor muscles contracting in sequence. The contraction now occurs lower than in the first panel, showing that muscle activity follows the bolus downward and continues to push it through the pharyngeal passage.
3. Right Panel: Entry Into the Esophagus - The bolus is positioned at the lower end of the pharynx near the esophagus. The diagram labels the inferior pharyngeal constrictor muscles and esophageal constrictor muscles. These muscles contract to push the bolus into the esophagus, completing the pharyngeal phase of swallowing. The contraction is now at the lowest level in the sequence.

Figure 3.4.1: The Stomach

This image shows a cutaway view of the stomach, connected to the esophagus above and the duodenum below, with labels identifying its regions, internal folds, and muscle layers. At the top, the esophagus enters the stomach at a region labeled the cardia, which serves as the entry point for food into the stomach.

Above and to the left of this entry is the fundus, a dome-shaped region that functions as a storage area for ingested material. The largest portion of the stomach is the body, located centrally, where mixing and digestion primarily occur.

The inner space of the stomach is labeled the lumen, which contains partially digested material. The internal surface of the stomach lining forms folds called rugae of the mucosa, which allow the stomach to expand as it fills and also help mix contents. Along the outer shape of the stomach are two borders:

- The lesser curvature, a shorter inner curve
- The greater curvature, a longer outer curve

Arrows along these curves indicate the general direction of movement and mixing within the stomach. Toward the lower end of the stomach is the pyloric region, which includes:

- The pyloric antrum, where food is further processed
- The pyloric canal, a narrowing passage
- The pyloric sphincter, which regulates the movement of stomach contents into the next structure

Beyond the sphincter is the duodenum, the first part of the small intestine, which receives partially digested material from the stomach. The wall of the stomach is labeled muscularis externa, consisting of three layers of muscle:

- An outer longitudinal layer, which shortens the stomach
- A middle circular layer, which constricts the lumen
- An inner oblique layer, unique to the stomach, which enhances mixing

Together, these layers generate strong mixing movements that mechanically break down food. The outermost covering of the stomach is the serosa, which provides protection and reduces friction with surrounding structures.

The convex lateral surface of the stomach is called the greater curvature; the concave medial border is the lesser curvature. The stomach is held in place by the lesser omentum, which extends from the liver to the lesser curvature, and the greater omentum, which runs from the greater curvature to the posterior abdominal wall.

Figure 3.4.2: Layers of the Stomach Wall and Gastric Glands

This image combines a cross-sectional view of the stomach wall with progressively magnified views of the gastric mucosa and a gastric gland. The figure illustrates how the layers of the stomach wall relate to the structures responsible for gastric secretion.

On the left, a small stomach diagram identifies the region being enlarged. The enlarged cross-sectional view shows the four major layers of the stomach wall arranged from the lumen outward.

Mucosa

The innermost layer is the mucosa, which contains the surface epithelium, lamina propria, and muscularis mucosae. The surface epithelium lines the stomach lumen and forms numerous downward invaginations called gastric pits. These pits extend from the surface into the underlying tissue and serve as openings into the gastric glands. Beneath the epithelium is the lamina propria, a connective tissue layer that surrounds and supports the gastric glands. The muscularis mucosae forms a thin layer of smooth muscle at the base of the mucosa.

Submucosa

Immediately beneath the mucosa is the submucosa, a connective tissue layer that contains blood vessels and provides structural support for the overlying mucosa.

Muscularis Externa

Outside the submucosa is the muscularis externa, which is composed of three smooth-muscle layers characteristic of the stomach. From inner to outer, these layers are:

- Oblique layer
- Circular layer
- Longitudinal layer

Together, these muscle layers generate the powerful mixing, churning, and propulsive movements that mechanically process food within the stomach.

Serosa

The outermost layer is the serosa, which forms the external covering of the stomach and helps reduce friction between abdominal organs.

Gastric Pits and Gastric Glands

The center of the figure enlarges the mucosal region to show multiple gastric pits extending downward into the stomach lining. Each gastric pit opens into one or more gastric glands, which are tubular structures embedded within the lamina propria. The figure emphasizes the close relationship between the gastric pits and the underlying gastric glands, through which secretions produced by glandular cells are released into the stomach lumen.

Cell Types in a Gastric Gland

The panel on the right further magnifies a single gastric gland and identifies three major cell types found within the gland.

Parietal cells are located primarily in the upper and middle portions of the gland. These cells secrete hydrochloric acid and

intrinsic factor, substances that support protein digestion and vitamin B12 absorption.

Chief cells are concentrated deeper within the gland. These cells produce pepsinogen, the inactive precursor of the protein-digesting enzyme pepsin.

Enteroendocrine cells are located near the base of the gland. These cells release hormones and signaling molecules that help regulate digestive activity and coordinate stomach function.

The figure demonstrates the hierarchical organization of the stomach wall, from the large-scale tissue layers of the stomach to the microscopic gastric glands and specialized secretory cells. It shows how gastric pits connect the stomach lumen to gastric glands and how different cell types within those glands contribute to digestion through the production of acid, digestive enzymes, and regulatory hormones.

Figure 3.4.3: Neural and Hormonal Regulation of Gastric Secretion

This image is a flowchart divided into three major sections: the cephalic phase, gastric phase, and intestinal phase. Each section shows pathways that either stimulate or inhibit stomach secretory activity. Arrows connect the steps and show the direction of signals and responses.

Cephalic Phase

This phase occurs before food enters the stomach.

Stimulation Pathway

Stomach secretory activity is stimulated.

- Sight or thought of food sends signals to the cerebral cortex.
- Stimulation of taste and smell receptors sends signals to the hypothalamus and medulla oblongata.
- A conditioned reflex connects the cerebral cortex to the hypothalamus and medulla.
- Signals travel through the vagus nerve.

Inhibition Pathway

Stomach secretory activity is inhibited.

- Loss of appetite or depression affects the cerebral cortex.
- Reduced signaling to the parasympathetic center occurs.

Gastric Phase

This phase occurs when food is present in the stomach.

Stimulation Pathways

Stomach secretory activity is stimulated.

Two main mechanisms increase stomach secretion.

Mechanical Stimulation

- Stomach distension activates stretch receptors.
- Signals trigger vagovagal reflexes and local reflexes.
- These pathways involve the medulla and vagus nerve.

Chemical Stimulation

- Food chemicals and rising pH activate chemoreceptors.
- G cells secrete gastrin into the blood.
- Gastrin increases gastric secretion.

Inhibition Pathways

Stomach activity decreases.

- Excessive acidity in the stomach, with pH less than 2, reduces gastrin secretion.

A second inhibitory pathway also appears.

- Stomach secretory activity is inhibited.
- Emotional distress activates the sympathetic nervous system.
- Sympathetic activity overrides parasympathetic control.

Intestinal Phase

This phase begins when food enters the small intestine.

Stimulation Pathway

Stomach secretory activity is stimulated.

- Low pH and partially digested foods in the duodenum are present.
- This causes release of intestinal gastrin into the blood.

Inhibition Pathways

Two major mechanisms decrease stomach activity.

Neural Reflexes

Stomach secretory activity is inhibited.

- Distention of the duodenum or the presence of fatty, acidic, hypertonic chyme, or irritants triggers signals.
- These signals involve local reflexes, vagal nuclei in the medulla, and pyloric sphincter activity.
- Together, these form the enterogastric reflex.

Hormonal Inhibition

Stomach secretory activity is inhibited.

- Distention and the presence of fatty, acidic, or partially digested food trigger intestinal hormone release.

These hormones include:

- secretin
- gastric inhibitory peptide (GIP)
- cholecystokinin (CCK)
- vasoactive intestinal peptide (VIP)

The figure demonstrates that gastric secretion is regulated by both neural and hormonal mechanisms across three phases of

digestion. The cephalic phase prepares the stomach before food arrives, the gastric phase responds to food within the stomach, and the intestinal phase adjusts stomach activity after chyme enters the small intestine. Some pathways stimulate gastric secretion, while others inhibit it to prevent excessive acidity and coordinate digestion with the small intestine.

Figure 3.5.1: Anatomy of the Small Intestine and Large Intestine

This image shows a front view of the abdomen with the digestive organs simplified and labeled, focusing on the small intestine and large intestine. The small intestine appears as tightly folded loops in the center of the abdomen. It is divided into three labeled sections:

- The duodenum, located at the top, receives material from the stomach and begins further digestion.
- The jejunum, located in the middle, continues digestion and is a major site of nutrient absorption.
- The ileum, located in the lower portion, completes absorption and connects to the large intestine.

Surrounding the small intestine is the large intestine, shown as a thicker tube forming an outer frame around the smaller loops. At the bottom, the large intestine narrows into the rectum, which stores waste before elimination.

Figure 3.5.2: Structural Adaptations of the Small Intestine for Absorption

This image shows three levels of structural detail of the small intestine, along with matching microscopic images, to explain how the intestinal lining is specialized for absorption.

In the image, at the broadest level, the small intestine is shown as a tube with a central space labeled the lumen. The inner lining forms large ridges called circular folds that project into the lumen. Covering these folds are many small, finger-like projections called villi. Together, the folds and villi greatly increase the surface area available for absorption. The outer wall also includes muscle layers that move intestinal contents, and a labeled blood vessel indicates circulation involved in nutrient transport.

The middle level enlarges the villi to show their internal structure. Each villus is covered by absorptive cells that form the outer surface. Between these cells are goblet cells, which secrete mucus to lubricate and protect the lining. Inside each villus is a capillary network connected to an artery and vein, which carries absorbed nutrients into the bloodstream. Each villus also contains a central lacteal, a lymphatic vessel that absorbs certain nutrients. Between the villi are intestinal crypts, which are downward extensions of the lining that contain cells involved in secretion and renewal. At the base of the mucosa is the muscularis mucosae, a thin muscle layer that helps move the villi slightly. Below this are larger lymphatic vessels and a labeled duodenal gland, showing additional support structures.

The most magnified view in Figure $3.11.2$ shows a single absorptive cell. Its apical surface is covered with tiny projections called microvilli, together known as the brush border. These structures increase surface area even further at the cellular level and contain enzymes that support the final stages of digestion and absorption.

A row of three microscope images corresponds to these same levels of structure. The first shows large folds with villi projecting outward. The second shows a closer view of densely packed villi lining the intestinal surface. The third shows the brush border at very high magnification, revealing the closely spaced microvilli.

Figure 3.5.3: Segmentation

This image shows three vertical panels arranged from left to right, illustrating segmentation, a mixing movement that occurs in the small intestine. Each panel shows a long, narrow intestinal tube divided into repeated segments. Inside the tube are rounded portions of chyme arranged along its length.

In the left panel, the intestinal tube is relaxed. The chyme is arranged in alternating segments, with different portions separated along the tube. There are no arrows yet, indicating that active mixing has not started.

In the middle panel, localized contractions appear at several points along the intestinal wall. These contractions divide the chyme into smaller portions and push it in opposite directions in neighboring segments. Arrows inside the tube point both upward and downward, showing that the contents are moving back and forth rather than in a single forward direction.

In the right panel, the chyme has become more evenly mixed. The contents that were previously separated are now more uniformly distributed within the segments. Arrows continue to show localized movement, but there is still no overall forward progression along the tube.

Overall, the figure demonstrates that segmentation involves alternating contraction and relaxation of intestinal segments. These contractions occur in non-adjacent regions, dividing and recombining chyme. The movement is bidirectional within short sections rather than one-way. The main function of segmentation is to mix chyme with digestive secretions and increase contact with the absorptive surface of the small intestine, which supports digestion and absorption.

Figure 3.5.4: The Large Intestine

This image shows a front view of the large intestine, with labeled sections showing its structure and its connection to the small intestine and the anal canal.

The large intestine forms a broad outer frame around the central abdominal area. At the lower right side of the figure, the ileum, which is the last part of the small intestine, connects to the cecum, a pouch-like structure that marks the beginning of the large intestine. Attached to the cecum is the vermiform appendix, shown as a narrow, finger-like extension.

From the cecum, the pathway continues through the colon in sequence. The ascending colon extends upward along one side of the abdomen. At the top, it bends at the right colic (hepatic) flexure and continues across the abdomen as the transverse colon. On the opposite side, it turns at the left colic (splenic) flexure and then travels downward as the descending colon.

At the lower end, the large intestine narrows into the sigmoid colon, which follows a curved, S-shaped path. The sigmoid colon connects to the rectum, which stores waste material before elimination. The rectum continues into the anal canal, the final segment through which waste leaves the body.

Overall, the figure shows the continuous pathway of the large intestine from the ileum to the anal canal. It also shows the major functions of the large intestine: receiving undigested material from the small intestine, absorbing water and electrolytes, compacting waste into feces, storing feces in the rectum, and eliminating waste through the anal canal.

Figure 3.5.5: Histology and Functional Organization of the Large Intestine Mucosa

This image combines a labeled diagram and a matching microscopic image to show the structure and function of the large intestine mucosa.

In the top portion, a simplified image of the large intestine is shown with an arrow pointing to a magnified view of its inner lining. The lining appears relatively flat and contains many straight, vertical intestinal glands, also called crypts, which open at the surface and extend downward into the tissue.

Two main cell types are shown in the lining. Absorptive cells line the surface and are responsible for absorbing water from intestinal contents. A magnified view shows that these cells have microvilli, small projections that increase surface area for absorption. Goblet cells are scattered among the absorptive cells and secrete mucus, which lubricates the intestinal contents and helps move waste through the colon.

Beneath the glands is the lamina propria, a connective tissue layer that contains support structures and a labeled lymphatic nodule, indicating immune activity. Below this is the muscularis mucosae, a thin layer of smooth muscle that allows minor movement of the mucosa. Beneath that lies the submucosa, a deeper supportive connective tissue layer. A label for smooth muscle fiber indicates contractile tissue involved in movement through the colon.

The lower portion shows a microscopic image of the large intestine lining. It shows closely packed, straight intestinal glands extending downward and many pale spaces representing goblet cells filled with mucus. The surface is relatively even and lacks large finger-like projections, confirming that the large intestine does not have villi.

Overall, the figure demonstrates that the large intestine mucosa is specialized for:

- absorption of water and electrolytes, mainly by absorptive cells

- secretion of mucus, by goblet cells to lubricate and protect the lining
- immune support, through lymphatic tissue
- compaction and movement of waste, supported by smooth muscle activity

Figure 3.5.6: External Features of the Large Intestine

This image shows a close-up view of the outer surface of the large intestine, highlighting three external features that distinguish it from the small intestine: haustra, teniae coli, and epiploic appendages.

The large intestine appears as a thick, segmented tube with an uneven outer surface. Instead of being smooth, it is divided into a series of rounded pouch-like sections.

These bulging sections are labeled haustra. Haustra are sac-like compartments formed by uneven contraction and tension in the intestinal wall. They divide the colon into segments, slow the movement of contents, and allow more time for water and electrolyte absorption.

Running lengthwise along the surface are narrow bands labeled teniae coli. These are thickened bands of longitudinal smooth muscle. They help maintain tension along the colon, contribute to the formation of the haustra, and assist with the movement and mixing of contents through coordinated contractions.

Attached along the outer surface are small, rounded structures labeled epiploic appendages. These are fat-filled pouches that project from the colon wall. They serve as characteristic external features of the large intestine and provide fat storage, cushioning, and support.

Overall, the figure shows how these three structures are related:

- teniae coli create longitudinal tension
- that tension helps form the haustra
- epiploic appendages provide external support

Together, these features help regulate the mixing, movement, and compaction of waste material as it travels through the large intestine.

Figure 3.6.1: Liver, Gallbladder, Pancreas, and Biliary Duct System

This image shows a front view of the upper abdominal region, highlighting the liver, gallbladder, pancreas, spleen, and the duct system that connects the liver, gallbladder, and pancreas to the small intestine.

The liver is the largest structure in the image and occupies the upper right portion of the abdomen. It is divided into four labeled regions: the right lobe, left lobe, quadrate lobe, and caudate lobe. The liver produces bile, which helps digest fats.

Beneath the liver is the gallbladder, a small sac that stores bile. A branching network of ducts connects the liver and gallbladder. The right hepatic duct and left hepatic duct carry bile from the liver and join to form the common hepatic duct. The cystic duct connects the gallbladder to this pathway. These ducts then combine to form the common bile duct, which carries bile toward the small intestine.

Below the liver is the pancreas, shown as an elongated organ extending horizontally. Running through it is the pancreatic duct, which carries digestive enzymes produced by the pancreas. These enzymes help digest carbohydrates, proteins, and fats in the small intestine.

The spleen is shown near the pancreas to indicate its anatomical position, although it is not directly involved in digestion.

Figure 3.6.2: Microscopic Structure of a Liver Lobule

This image shows both a macro-to-micro view of the liver and a three-dimensional view of a single liver lobule, illustrating how liver tissue is organized to process blood. A simplified outline of the liver appears at the upper left, with one region highlighted to show where the enlarged tissue view comes from.

At the upper right, the liver tissue is shown as a repeating pattern of lobules separated by connective tissue. Each lobule contains a central vein at its center. The main image shows one liver lobule in three dimensions. At the center is the central vein, which collects blood after it has passed through the lobule. Surrounding it are plates of hepatocytes arranged like spokes radiating outward. These cells carry out key liver functions such as metabolism, detoxification, and bile production.

Between the hepatocyte plates are irregular blood channels called sinusoids. Blood flows through these channels from the outer edge of the lobule toward the central vein. This arrangement allows close contact between the blood and the hepatocytes so that nutrients, toxins, and other substances can be processed efficiently. At the outer corners of the lobule are groups of structures called the portal triads. Each portal triad includes:

- a portal venule
- a portal arteriole
- a bile duct

Blood enters the lobule from the portal venule and portal arteriole, then passes through the sinusoids toward the central vein. An interlobular vein is also shown, indicating how blood leaving the lobule joins larger venous pathways in the liver.

This organization allows the liver to continuously filter blood, process nutrients, detoxify substances, and regulate blood composition before the blood returns to the general circulation

Figure 3.6.3: Anatomy and Histology of the Pancreas

This image combines a gross anatomical view of the pancreas with a magnified view of pancreatic tissue to illustrate how the pancreas functions as both an exocrine digestive organ and an endocrine gland.

Gross Anatomy of the Pancreas

At the top of the figure, the pancreas is shown as an elongated organ extending horizontally across the upper abdomen. The wider head of the pancreas lies adjacent to the first part of the small intestine, while the narrower tail of the pancreas extends toward the left side of the body. The pancreas is organized into multiple lobules, visible as small clusters throughout the organ.

Running through the center of the pancreas is the pancreatic duct, which collects secretions from pancreatic tissue and carries them toward the small intestine. Adjacent to it is the common bile duct, which passes near the head of the pancreas. These ducts deliver digestive secretions into the same general region of the small intestine, allowing bile and pancreatic secretions to participate together in digestion.

Microscopic Organization of Pancreatic Tissue

The lower portion of the figure enlarges a region of pancreatic tissue and shows its two major functional components: the exocrine pancreas and the endocrine pancreas.

Exocrine Portion

Most of the tissue consists of the exocrine portion of the pancreas. This region is composed of many clusters of acinar cells arranged around small ducts. The acinar cells produce digestive enzymes that become part of pancreatic juice. The figure shows the enzymes moving from the acinar cells into progressively larger ducts, which merge and drain into the pancreatic duct. Through this duct system, pancreatic juice is transported to the small intestine, where it contributes to the digestion of carbohydrates, proteins, fats, and nucleic acids.

Endocrine Portion

Scattered among the exocrine tissue are lighter-colored clusters labeled pancreatic islets (islets of Langerhans). These structures represent the endocrine portion of the pancreas. Unlike the acinar cells, the pancreatic islet cells are not connected to the duct system. Instead, they release hormones directly into nearby blood vessels. These hormones help regulate blood glucose and other aspects of metabolism.

Key Functional Distinctions

The figure emphasizes the distinction between the two functional regions of the pancreas:

- Acinar cells produce digestive enzymes.
- Exocrine cells secrete pancreatic juice into ducts that carry secretions to the small intestine.
- Pancreatic islet cells secrete hormones directly into the bloodstream.

Overall, the figure demonstrates how the pancreas links the digestive and endocrine systems. Its exocrine tissue supports digestion through the production and delivery of digestive enzymes, while its endocrine tissue regulates metabolism through hormone secretion.

Figure 3.6.4: The Gallbladder

This image shows a close-up view of the liver and gallbladder, highlighting the structure of the gallbladder and the duct system that carries bile from the liver toward the small intestine.

The liver occupies the upper part of the figure. Two ducts emerge from it: the left hepatic duct and the right hepatic duct. These ducts drain bile produced in the liver and join to form the common hepatic duct, which carries bile downward.

Attached to the underside of the liver is the gallbladder, shown as a pear-shaped organ. It is divided into three labeled regions:

- the fundus, the rounded wider end
- the body, the central portion
- the neck, the narrowed end that connects to the duct system

These regions show how the gallbladder is shaped to store and concentrate bile before release. The fundus and body serve mainly as the storage area, while the neck forms the connection to the outflow pathway.

The cystic duct extends from the neck of the gallbladder and joins the common hepatic duct. Together they form the common bile duct, which carries bile toward the small intestine.

Overall, the figure shows the pathway of bile movement:

- bile is produced in the liver
- it travels through the right and left hepatic ducts
- enters the common hepatic duct
- may be diverted into the gallbladder for storage and concentration through the cystic duct
- and then passes into the common bile duct for delivery to the small intestine

The diagram emphasizes that the gallbladder functions as a storage and concentration organ for bile, while the duct system provides a continuous route for bile to move from the liver to the digestive tract, where it helps with the digestion of fats.

Figure 3.7.1: The Digestive Tract

This image shows a vertical view of the digestive tract from the mouth to the anus, with labeled organs on the left and text boxes on the right summarizing the main digestive functions that occur in each region.

At the top is the mouth and oral cavity, which leads into the esophagus. The text for this region explains that mechanical digestion begins with chewing and swallowing, while chemical digestion begins with the breakdown of carbohydrates and fats.

Below this, the esophagus is shown as a vertical tube leading to the stomach. The liver and gallbladder are also shown nearby as accessory digestive organs. The text associated with this region explains that mechanical digestion includes peristaltic mixing and propulsion, while chemical digestion includes the digestion of proteins and fats. It also notes that the stomach carries out limited absorption of lipid-soluble substances, including alcohol and aspirin.

Below the stomach is the small intestine, shown as a coiled tube connected near the pancreas. The pylorus marks the exit from

the stomach into the small intestine. The text for this region explains that mechanical digestion includes mixing and propulsion, mainly through segmentation. It also states that chemical digestion of carbohydrates, fats, polypeptides, and nucleic acids occurs here. In addition, this region is identified as the main site for absorption, including peptides, amino acids, glucose, fructose, fats, water, minerals, and vitamins. The large intestine appears below as a wider tube leading downward to the rectum and anal sphincter. The text for this region explains that mechanical digestion includes segmental mixing and propulsion. It states that there is no chemical digestion except by bacteria. It also identifies this region as a site of absorption of ions, water, minerals, vitamins, and organic molecules.

Figure 3.7.2: Digestion of Carbohydrates

This image is a flowchart showing the step-by-step digestion of carbohydrates, beginning with large polysaccharides and ending with absorbable monosaccharides. Arrows indicate the direction of chemical breakdown, and each step is labeled with the enzyme responsible for the change.

At the top, the process begins with starch and glycogen, which are large carbohydrate molecules found in food. An arrow labeled salivary amylase shows that digestion starts in the mouth, where this enzyme begins breaking these polysaccharides into smaller carbohydrate fragments.

From this first step, the pathway continues into two main groups of intermediate products. One branch leads to short branched polysaccharides, including limit dextrins. These partially digested carbohydrate fragments are further broken down by the enzyme alpha-dextrinase, producing glucose. A second branch leads to disaccharides, which are pairs of sugar units. Three disaccharides are shown:

- maltose
- sucrose
- lactose

Each disaccharide is paired with a specific enzyme:

- maltase breaks down maltose
- sucrase breaks down sucrose
- lactase breaks down lactose

The final products at the bottom of the flowchart are monosaccharides, which are the simple sugars that can be absorbed in the small intestine:

- limit dextrins, broken down by alpha-dextrinase, produce glucose
- maltose, broken down by maltase, produces two glucose molecules
- sucrose, broken down by sucrase, produces one glucose and one fructose
- lactose, broken down by lactase, produces one glucose and one galactose

Overall, the figure shows that carbohydrate digestion occurs in a stepwise sequence. Large polysaccharides are broken into smaller fragments and disaccharides, and these are then reduced to monosaccharides such as glucose, fructose, and galactose. These final products are the forms that can be absorbed into the bloodstream and used by body cells.

Figure 3.7.3: Protein Digestion, Absorption, and Distribution of Amino Acids

This image shows a front view of the digestive system with labeled organs and explanatory text describing how proteins are digested, absorbed, and distributed through the body. At the top, the oral cavity and esophagus are shown as the pathway that food follows into the digestive tract. No protein digestion is identified in this region.

The stomach is labeled as the site where protein digestion begins. A text note explains that digestion starts here through the action of hydrochloric acid and the enzyme pepsin. The acid creates the environment needed for pepsin to begin breaking proteins into smaller fragments.

Next to the stomach, the pancreas is identified as a source of protein-digesting enzymes. These enzymes are released into

the small intestine, where they continue the breakdown of protein. The small intestine is shown as the major site of protein digestion and absorption. The labels explain that:

- the small intestine is the primary location where protein digestion is completed
- protein-digesting enzymes are secreted from the brush border
- the final products of digestion are amino acids
- these amino acids are absorbed into the blood and then carried to the liver

The liver is labeled as the organ that regulates the distribution of absorbed amino acids to the rest of the body. This indicates that amino acids do not simply circulate unchanged, but are processed and directed as needed after absorption.

In the lower part of the figure, the large intestine is shown with a note indicating that a small amount of dietary protein is lost in the feces. This shows that most protein is digested and absorbed before the remaining waste reaches the end of the digestive tract.

Figure 3.7.4: Stages of Protein Digestion

This image is a vertical flowchart showing the step-by-step digestion of proteins from large food molecules to absorbable amino acids. Rectangular boxes are connected by downward arrows, indicating the direction of chemical breakdown.

At the top is a box labeled protein, representing large, complex protein molecules from food. An arrow labeled pepsin indicates that this enzyme begins the digestion process by acting on proteins at the first stage.

The next box is labeled large polypeptides. This shows that proteins are first broken into smaller chains of amino acids called polypeptides. In this diagram, pepsin is the enzyme responsible for that initial breakdown.

Below that is a box labeled short peptides and amino acids. This indicates that the large polypeptides are digested further into smaller peptide fragments and some individual amino acids by additional digestive enzymes.

At the bottom is a box labeled amino acids, which are the final end products of protein digestion. These are the small molecules that can be absorbed through the lining of the small intestine and carried into the bloodstream.

Figure 3.7.5: The Digestive Tract

This image shows a front view of the digestive tract from the mouth to the rectum, with arrows and labeled volumes showing how fluid moves, is added, and is reabsorbed throughout the digestive system. At the top, fluid enters the digestive tract through the mouth. Two sources are shown:

- dietary intake: 2000 mL
- saliva: 1500 mL

These combine as the initial fluid entering the digestive tract. As contents move downward into the stomach, additional fluid is added through gastric secretions: 1500 mL. The total fluid volume at this stage is labeled 5000 mL. When the contents enter the small intestine, three more sources of digestive fluid are added:

- liver bile: 1000 mL
- pancreatic juice: 1000 mL
- intestinal secretions: 2000 mL

These additions bring the total fluid volume in the small intestine to 9000 mL. A labeled arrow shows that the small intestine reabsorbs 7800 mL of this fluid. After that absorption, the remaining volume entering the large intestine is labeled 1200 mL. In the colon, another fluid source is added:

- colonic mucus secretions: 200 mL

This increases the volume in the large intestine to 1400 mL. Another labeled arrow shows that the colon reabsorbs 1250 mL. After this reabsorption, the remaining 150 mL is labeled as lost in feces.

Figure 3.7.6: Absorption and Transport of Lipids in the Small Intestine

This image shows a cross-sectional view of the intestinal lining, illustrating how the products of lipid digestion are absorbed by epithelial cells and transported away through the lymphatic system.

At the top is the lumen of the intestine, which contains digested lipid materials. Below the lumen is a layer of absorptive epithelial cells that line the intestinal surface. Beneath these cells are two transport structures: a blood capillary and a lacteal, which is a lymphatic vessel. Arrows show the movement of substances from the lumen, through the epithelial cells, and into the transport vessels.

In the lumen, lipid digestion produces fatty acids and monoglycerides. These molecules are shown combining into emulsified droplets and then into micelles. The micelles carry lipid components to the surface of the epithelial cells.

At the epithelial surface, the diagram shows that fatty acids and monoglycerides leave the micelles and enter the epithelial cell. The micelles themselves do not enter the cell. Instead, they deliver the lipid components to the membrane, where those components pass inward.

Inside the epithelial cell, the fatty acids and monoglycerides are reassembled into triglycerides. Near a labeled Golgi apparatus, these triglycerides combine with proteins to form chylomicrons, which are lipid transport particles.

The diagram then shows chylomicrons leaving the epithelial cell and entering the lacteal. A final label indicates that lymph in the lacteal transports chylomicrons away from the intestine.

Although both a capillary and a lacteal are shown, the figure emphasizes that lipids follow the lymphatic pathway rather than entering the blood capillary directly.

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4: METABOLISM AND NUTRITION

Chapter Overview



Figure 4.1: Metabolism is the sum of all energy-requiring and energy-consuming processes of the body. Many factors contribute to overall metabolism, including lean muscle mass, the amount and quality of food consumed, and the physical demands placed on the human body. (CC BY 4.0; via Introduction).

Nutrition and metabolism are words that are often used together—but what do they mean? Nutrition refers to the foods that we eat and the nutrients they contain. The Council on Food and Nutrition of the American Medical Association defines nutrition broadly as "the science of food; the nutrients and the substances therein; their action, interaction, and balance in relation to health and disease; and the process by which the organism (i.e., body) ingests, digests, absorbs, transports, utilizes, and excretes food substances. Metabolism refers to the complex, interactive set of chemical processes that make life possible. A good phrase to remember in connection with the word metabolism is "use of foods" because basically this is what metabolism is—the use the body makes of foods after they have been digested, absorbed, and circulated to cells.

Defining Metabolism, Catabolism, and Anabolism

Defines metabolism as the sum of all catabolic (breakdown) and anabolic (synthesis) reactions. Introduces metabolic rate as the energy used to maintain life, and explains that survival requires sufficient food intake to support this rate.

Catabolic Reactions: Releasing Energy from Nutrients

Describes how catabolic reactions break down carbohydrates, lipids, and proteins from food, and how ATP breakdown provides energy for cellular work throughout the body.

Anabolic Reactions and Redox Chemistry: Building and Powering the Body

Explains anabolic (biosynthetic) reactions that build bone, muscle, proteins, lipids, and nucleic acids using ATP. Introduces oxidation–reduction reactions as the basis for energy capture in ATP, and notes that metabolic errors in these pathways can cause disease.

Carbohydrate Metabolism: From Food to ATP

Outlines digestion and absorption of carbohydrates, the role of salivary amylase, and cellular processing of glucose. Introduces

glycolysis, pyruvate, NADH, and ATP production, and distinguishes anaerobic (lactate formation) from aerobic pathways (entry of pyruvate into the Krebs/citric acid/TCA cycle and oxidative phosphorylation).

Anaerobic vs Aerobic ATP Production

Clarifies ATP yield under anaerobic conditions (net 2 ATP per glucose via glycolysis) versus aerobic respiration (up to ~36 ATP per glucose), and why oxygen availability is critical for efficient energy production.

Gluconeogenesis: Making Glucose in Low-Carbohydrate States

Describes synthesis of glucose from lactate, pyruvate, glycerol, alanine, or glutamate during fasting, starvation, or low-carbohydrate diets, emphasizing its importance for glucose-dependent organs such as the brain.

Lipid Metabolism: Storage, Mobilization, and Oxidation

Explains dietary, stored, and hepatic sources of lipids; intestinal digestion and absorption of triglycerides; re-synthesis and transport to liver and adipose tissue. Describes β-oxidation of fatty acids to acetyl CoA, entry into the Krebs cycle, and ATP production.

Ketone Bodies and Lipogenesis: Handling Excess or Limited Fuel

Describes ketone body formation when acetyl CoA exceeds Krebs cycle capacity or when glucose is limited, and their use as alternative fuels. Explains lipogenesis (fatty acid and triglyceride synthesis) from excess acetyl CoA, including roles in making steroid hormones, cholesterol, and bile salts. Defines lipolysis as triglyceride breakdown.

Protein Metabolism: Digestion, Use, and Nitrogen Disposal

Outlines protein digestion by HCl and pepsin in the stomach and by pancreatic and intestinal enzymes in the small intestine. Explains amino acid absorption, use for new protein synthesis, conversion of excess amino acids to glucose or ketones, urea formation and excretion, and use of amino acids as fuel (especially during starvation).

Metabolic States: Fed, Fasting, and Starvation

Introduces absorptive (fed), postabsorptive (fasting), and starvation states. Explains how metabolism shifts between these daily, and how fuel use changes in prolonged food deprivation.

Hormonal Regulation of Fuel Use: Insulin and Glucagon

Describes how rising blood glucose in the absorptive state stimulates insulin release, promoting uptake and storage of glucose as glycogen and fat. Explains how falling glucose in the postabsorptive state lowers insulin and raises glucagon, stimulating glycogen breakdown and alternative fuel use (fatty acids and proteins) when glycogen is depleted.

Long-Term Fasting and Starvation: Fuel Priorities and Tissue Survival

Details the progression from short-term fasting to starvation: continued gluconeogenesis for brain fuel, later shift to ketone bodies as preferred fuel for many organs, and eventual catabolism of body proteins, with initial preservation of muscle and later muscle breakdown when other stores are exhausted.

Energy Balance and Thermoregulation

Explains that much dietary energy is released as heat and used to maintain core temperature (~36.5–37.5 °C / 97.7–99.5 °F). Introduces hypothalamic control of temperature (sweating, shivering) and mechanisms of heat exchange: conduction, convection, radiation, and evaporation.

Nutrition, Caloric Balance, and Health

Links dietary intake to metabolism, noting that all excess calories (from carbohydrate, fat, or protein) are stored as fat. Discusses typical daily energy needs (about 1500–2000 kcal, higher with exercise) and consequences of chronic over- or under-eating, including obesity, cardiovascular disease, cancer, and diabetes.

Vitamins and Minerals: Micronutrients for Metabolic Pathways

Explains that vitamins and minerals are essential for proper function of metabolic pathways. Notes that most vitamins must be obtained regularly from the diet (limited storage), whereas many minerals are stored, especially in bone.

Factors Affecting Metabolic Rate

Describes how age, sex, activity level, fuel intake, and lean body mass influence metabolic rate. Explains that males typically have higher basal metabolic rates due to greater lean mass, that aging reduces metabolic rate, and that genetic factors (enzymes, regulatory proteins) help determine individual metabolic differences.

Modifying Metabolism: Diet, Exercise, and Body Composition

Discusses how changes in diet and exercise can alter lean body mass and metabolic rate, and how these changes impact muscle mass and overall health.

Integrating Metabolism: Oxygen, Mitochondria, Hormones, and Vitamins

Previews key themes explored in detail: why oxygen is required, how mitochondria transfer energy via oxidative phosphorylation, and the roles of “metabolic” hormones and vitamins in coordinating anabolic and catabolic reactions.

Chapter Objectives

To achieve these chapter objectives, actively engage with the material. Learning tissues is not a passive process. Your understanding will grow as you interact with the content, peers, and your instructor. Regularly check your thinking against feedback. Revisit complex concepts until you can confidently explain and apply them on your own.

By the end of this chapter, you will be able to:

- Distinguish between metabolism, catabolism, and anabolism, and relate each to the body’s energy use and storage.
- Describe how carbohydrates are digested and metabolized, including glycolysis, anaerobic vs. aerobic ATP production, the Krebs (citric acid) cycle, oxidative phosphorylation, and gluconeogenesis.
- Explain how lipids are digested, transported, stored, and used for energy, including β-oxidation, lipogenesis, lipolysis, and ketone body formation and use.
- Outline protein digestion, absorption, and metabolic fates of amino acids, including protein synthesis, conversion to glucose or ketones, and nitrogen disposal via the urea cycle.
- Compare the absorptive (fed), postabsorptive (fasting), and starvation states, including the primary fuel sources, hormone regulation (insulin and glucagon), and shifts between carbohydrate, fat, and protein use.
- Describe how the body regulates core temperature (thermoregulation), including the role of the hypothalamus and the mechanisms of heat exchange: conduction, convection, radiation, and evaporation.
- Relate dietary intake (calories, macronutrient balance) to energy balance, fat storage, and the risk of metabolic and diet-related diseases.
- Explain the roles of vitamins and minerals in metabolism and why adequate dietary intake is necessary for proper function of metabolic pathways.
- Identify major factors that influence metabolic rate (age, sex, activity level, lean body mass, and genetics) and how lifestyle can modify metabolic rate and body composition.
- Recognize the central importance of oxygen, mitochondrial energy transfer, and key metabolic hormones and vitamins in sustaining life through anabolic and catabolic reactions.

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4.1: Chemical Reactions Underlying Metabolism

Metabolism and Energy Transfer

Metabolic processes are constantly taking place in the body. Metabolism is the sum of all of the chemical reactions that are involved in catabolism and anabolism. The reactions governing the breakdown of food to obtain energy are called catabolic reactions. Conversely, anabolic reactions use the energy produced by catabolic reactions to synthesize larger molecules from smaller ones, such as when the body forms proteins by stringing together amino acids. Both sets of reactions are critical to maintaining life.

Because catabolic reactions produce energy and anabolic reactions use energy, ideally, energy usage would balance the energy produced. If the net energy change is positive (catabolic reactions release more energy than the anabolic reactions use), then the body stores the excess energy by building fat molecules for long-term storage. On the other hand, if the net energy change is negative (catabolic reactions release less energy than anabolic reactions use), the body uses stored energy to compensate for the deficiency of energy released by catabolism.

Catabolic Reactions

Catabolic reactions break down large organic molecules into smaller molecules, releasing the energy contained in the chemical bonds. These energy releases (conversions) are not 100 percent efficient. The amount of energy released is less than the total amount contained in the molecule. Approximately 40 percent of energy yielded from catabolic reactions is directly transferred to the high-energy molecule adenosine triphosphate (ATP). ATP, the energy currency of cells, can be used immediately to power molecular machines that support cell, tissue, and organ function. This includes building new tissue and repairing damaged tissue. ATP can also be stored to fulfill future energy demands. The remaining 60 percent of the energy released from catabolic reactions is given off as heat, which tissues and body fluids absorb.

Structurally, ATP molecules consist of an adenine, a ribose, and three phosphate groups (Figure 4.1.1). The chemical bond between the second and third phosphate groups, termed a high-energy bond, represents the greatest source of energy in a cell. It is the first bond that catabolic enzymes break when cells require energy to do work. The products of this reaction are a molecule of adenosine diphosphate (ADP) and a lone phosphate group (P_i). ATP, ADP, and P_i are constantly being cycled through reactions that build ATP and store energy, and reactions that break down ATP and release energy.

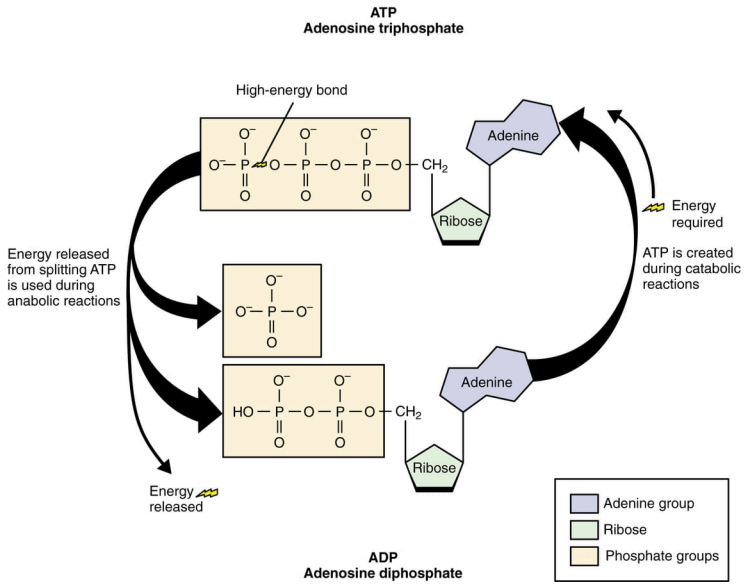


Figure 4.1.1: Adenosine triphosphate (ATP) is the energy molecule of the cell. During catabolic reactions, ATP is created and energy is stored until needed during anabolic reactions. (CC BY 4.0; via Overview of Metabolic Reactions). Detailed text description of the Figure 4.1.1.

The energy from ATP drives all bodily functions, such as contracting muscles, maintaining the electrical potential of nerve cells, and absorbing food in the gastrointestinal tract. The metabolic reactions that produce ATP come from various sources (Figure 4.1.2).

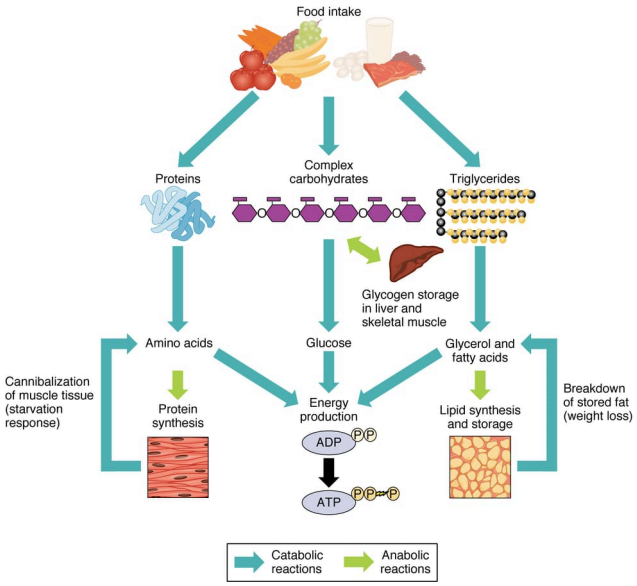


Figure 4.1.2: During catabolic reactions, proteins are broken down into amino acids, lipids are broken down into fatty acids, and polysaccharides are broken down into monosaccharides. These building blocks are then used for the synthesis of molecules in anabolic reactions. (CC BY 4.0; via Overview of Metabolic Reactions). Detailed text description of the Figure 4.1.2.

Of the four major macromolecular groups (carbohydrates, lipids, proteins, and nucleic acids) that are processed by digestion, carbohydrates are considered the most common source of energy to fuel the body. They take the form of either complex carbohydrates, polysaccharides like starch and glycogen, or simple sugars (monosaccharides) like glucose and fructose. Sugar catabolism breaks polysaccharides down into their individual monosaccharides. Among the monosaccharides, glucose is the most common fuel for ATP production in cells, and as such, there are a number of endocrine control mechanisms to regulate glucose concentration in the bloodstream. Excess glucose is either stored as an energy reserve in the liver and skeletal muscles as the complex polymer glycogen, or it is converted into fat (triglyceride) in adipose cells (adipocytes). Among the lipids (fats), triglycerides are most often used for energy via a metabolic process called β-oxidation. About one-half of excess fat is stored in adipocytes that accumulate in the subcutaneous tissue under the skin, whereas the rest is stored in adipocytes in other tissues and organs.

Proteins, which are polymers, can be broken down into their monomers, individual amino acids. Amino acids can be used as building blocks of new proteins or broken down further for the production of ATP. When one is chronically starving, this use of amino acids for energy production can lead to a wasting away of the body, as more and more proteins are broken down.

Nucleic acids are present in most of the foods you eat. During digestion, nucleic acids including DNA and various RNAs are broken down into their constituent nucleotides. These nucleotides are readily absorbed and transported throughout the body to be used by individual cells during nucleic acid metabolism.

Anabolic Reactions

In contrast to catabolic reactions, anabolic reactions involve the joining of smaller molecules into larger ones. Anabolic reactions combine monosaccharides to form polysaccharides, fatty acids to form triglycerides, amino acids to form proteins, and nucleotides to form nucleic acids. These processes require energy in the form of ATP molecules generated by catabolic reactions. Anabolic reactions, also called biosynthesis reactions, create new molecules that form new cells and tissues, and revitalize organs.

Hormonal Regulation of Metabolism

Catabolic and anabolic hormones in the body help regulate metabolic processes. Catabolic hormones stimulate the breakdown

of molecules and the production of energy. These include cortisol, glucagon, adrenaline/epinephrine, and cytokines. All of these hormones are mobilized at specific times to meet the needs of the body. Anabolic hormones are required for the synthesis of molecules and include growth hormone, insulin-like growth factor, insulin, testosterone, and estrogen. Table 4.1.1 summarizes the function of each of the catabolic hormones and Table 4.1.2 summarizes the functions of the anabolic hormones.

Table 4.1.1: Catabolic Hormones

Hormone	Function
Cortisol	Released from the adrenal gland in response to stress; its main role is to increase blood glucose levels by gluconeogenesis (breaking down fats and proteins)
Glucagon	Released from alpha cells in the pancreas either when starving or when the body needs to generate additional energy; it stimulates the breakdown of glycogen in the liver to increase blood glucose levels; its effect is the opposite of insulin; glucagon and insulin are a part of a negative-feedback system that stabilizes blood glucose levels
Adrenaline/ epinephrine	Released in response to the activation of the sympathetic nervous system; increases heart rate and heart contractility, constricts blood vessels, is a bronchodilator that opens (dilates) the bronchi of the lungs to increase air volume in the lungs, and stimulates gluconeogenesis

Table 4.1.2: Anabolic Hormones

Hormone	Function
Growth hormone (GH)	Synthesized and released from the pituitary gland; stimulates the growth of cells, tissues, and bones
Insulin-like growth factor (IGF)	Stimulates the growth of muscle and bone while also inhibiting cell death (apoptosis)
Insulin	Produced by the beta cells of the pancreas; plays an essential role in carbohydrate and fat metabolism, controls blood glucose levels, and promotes the uptake of glucose into body cells; causes cells in muscle, adipose tissue, and liver to take up glucose from the blood and store it in the liver and muscle as glycogen; its effect is the opposite of glucagon; glucagon and insulin are a part of a negative-feedback system that stabilizes blood glucose levels
Testosterone	Produced by the testes in males and the ovaries in females; stimulates an increase in muscle mass and strength as well as the growth and strengthening of bone
Estrogen	Produced primarily by the ovaries, it is also produced by the liver and adrenal glands; its anabolic functions include increasing metabolism and fat deposition

Disorders of the...

Metabolic Processes: Cushing Syndrome and Addison's Disease

As might be expected for a fundamental physiological process like metabolism, errors or malfunctions in metabolic processing lead to a pathophysiology or—if uncorrected—a disease state. Metabolic diseases are most commonly the result of malfunctioning proteins or enzymes that are critical to one or more metabolic pathways. Protein or enzyme malfunction can be the consequence of a genetic alteration or mutation. However, normally functioning proteins and enzymes can also have deleterious effects if their availability is not appropriately matched with metabolic need. For example, excessive production of the hormone cortisol gives rise to Cushing syndrome. Clinically, Cushing syndrome is characterized by rapid weight gain, especially in the trunk and face region, depression, and anxiety. It is worth mentioning that tumors of the pituitary that produce adrenocorticotropic hormone (ACTH), which subsequently stimulates the adrenal cortex to release excessive cortisol, produce similar effects. This indirect mechanism of cortisol overproduction is referred to as Cushing disease.

Patients with Cushing syndrome can exhibit high blood glucose levels and are at an increased risk of becoming obese. They also show slow growth, accumulation of fat between the shoulders, weak muscles, bone pain (because cortisol causes proteins to be broken down to make glucose via gluconeogenesis), and fatigue. Other symptoms include excessive sweating (hyperhidrosis), capillary dilation, and thinning of the skin, which can lead to easy bruising. The treatments for Cushing syndrome are all focused on reducing excessive cortisol levels. Depending on the cause of the excess, treatment may be as simple as discontinuing the use of cortisol ointments. In cases of tumors, surgery is often used to remove the offending tumor. Where surgery is inappropriate, radiation therapy can be used to reduce the size of a tumor or ablate portions of the adrenal cortex. Finally, medications are available that can help to regulate the amounts of cortisol.

Insufficient cortisol production is equally problematic. Adrenal insufficiency, or Addison's disease, is characterized by the reduced production of cortisol from the adrenal gland. It can result from malfunction of the adrenal glands—they do not produce enough cortisol—or it can be a consequence of decreased ACTH availability from the pituitary. Patients with Addison's disease may have low blood pressure, paleness, extreme weakness, fatigue, slow or sluggish movements, lightheadedness, and salt cravings due to the loss of sodium and high blood potassium levels (hyperkalemia). Victims also may suffer from loss of appetite, chronic diarrhea, vomiting, mouth lesions, and patchy skin color. Diagnosis typically involves blood tests and imaging tests of the adrenal and pituitary glands. Treatment involves cortisol replacement therapy, which usually must be continued for life.

Oxidation-Reduction Reactions

The chemical reactions underlying metabolism involve the transfer of electrons from one compound to another by processes catalyzed by enzymes. The electrons in these reactions commonly come from hydrogen atoms, which consist of an electron and a proton. A molecule gives up a hydrogen atom, in the form of a hydrogen ion (H^+) and an electron, breaking the molecule into smaller parts. The loss of an electron, or oxidation, releases a small amount of energy; both the electron and the energy are then passed to another molecule in the process of , or the gaining of an electron. These two reactions always happen together in an oxidation-reduction reaction (also called a redox reaction)—when an electron is passed between molecules, the donor is oxidized and the recipient is reduced. Oxidation-reduction reactions often happen in a series, so that a molecule that is reduced is subsequently oxidized, passing on not only the electron it just received but also the energy it received. As the series of reactions progresses, energy accumulates that is used to combine P_i and ADP to form ATP, the high-energy molecule that the body uses for fuel. Oxidation-reduction reactions are catalyzed by enzymes that trigger the removal of hydrogen atoms. Coenzymes work with enzymes and accept hydrogen atoms. The two most common coenzymes of oxidation-reduction reactions are nicotinamide adenine dinucleotide (NAD)and flavin adenine dinucleotide (FAD). Their respective reduced coenzymes are and FADH , which are energy-containing molecules used to transfer energy during the creation of ATP.

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4.2: Carbohydrate Metabolism

Carbohydrate Metabolism and Cellular Respiration

Carbohydrates are organic molecules composed of carbon, hydrogen, and oxygen atoms. The family of carbohydrates includes both simple and complex sugars. Glucose and fructose are examples of simple sugars, and starch, glycogen, and cellulose are all examples of complex sugars. The complex sugars are also called polysaccharides and are made of multiple monosaccharide molecules. Polysaccharides serve as energy storage (e.g., starch and glycogen) and as structural components (e.g., chitin in insects and cellulose in plants)

During digestion, carbohydrates are broken down into simple, soluble sugars that can be transported across the intestinal wall into the circulatory system to be transported throughout the body. Carbohydrate digestion begins in the mouth with the action of salivary amylase on starches and ends with monosaccharides being absorbed across the epithelium of the small intestine. Once the absorbed monosaccharides are transported to the tissues, the process of cellular respiration begins (Figure 4.2.1). This section will focus first on glycolysis, a process where the monosaccharide glucose is oxidized, releasing the energy stored in its bonds to produce ATP.

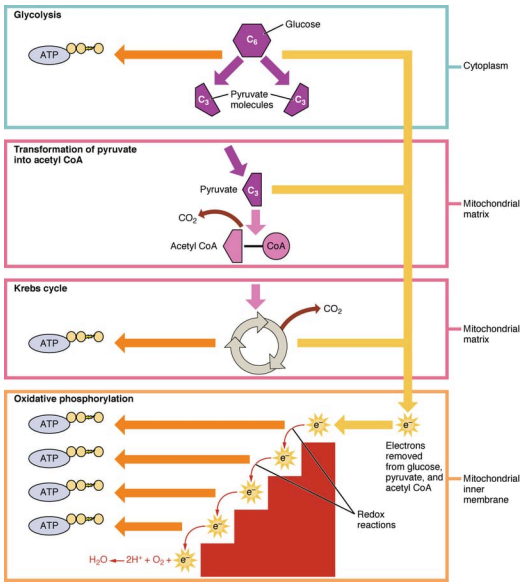


Figure 4.2.1: Cellular respiration oxidizes glucose molecules through glycolysis, the Krebs cycle, and oxidative phosphorylation to produce ATP. (CC BY 4.0; via Carbohydrate Metabolism). Detailed text description of the Figure 4.2.1.

Glycolysis

Glucose is the body's most readily available source of energy. After digestive processes break polysaccharides down into monosaccharides, including glucose, the monosaccharides are transported across the wall of the small intestine and into the circulatory system, which transports them to the liver. In the liver, hepatocytes either pass the glucose on through the circulatory system or store excess glucose as glycogen. Cells in the body take up the circulating glucose in response to insulin and, through a series of reactions called glycolysis, transfer some of the energy in glucose to ADP to form ATP (Figure 4.2.2). The last step in glycolysis produces the product pyruvate.

Glycolysis begins with the phosphorylation of glucose by hexokinase to form glucose-6-phosphate. This step uses one ATP, which is the donor of the phosphate group. Under the action of phosphofructokinase, glucose-6-phosphate is converted into fructose-6-phosphate. At this point, a second ATP donates its phosphate group, forming fructose-1,6-bisphosphate. This six-carbon sugar is split to form two phosphorylated three-carbon molecules, glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, which are both converted into glyceraldehyde-3-phosphate. The glyceraldehyde-3-phosphate is further phosphorylated with groups donated by dihydrogen phosphate present in the cell to form the three-carbon molecule

1,3-bisphosphoglycerate. The energy of this reaction comes from the oxidation of (removal of electrons from) glyceraldehyde-3-phosphate. In a series of reactions leading to pyruvate, the two phosphate groups are then transferred to two ADPs to form two ATPs. Thus, glycolysis uses two ATPs but generates four ATPs, yielding a net gain of two ATPs and two molecules of pyruvate. In the presence of oxygen, pyruvate continues on to the Krebs cycle (also called the citric acid cycle or tricarboxylic acid cycle (TCA), where additional energy is extracted and passed on.

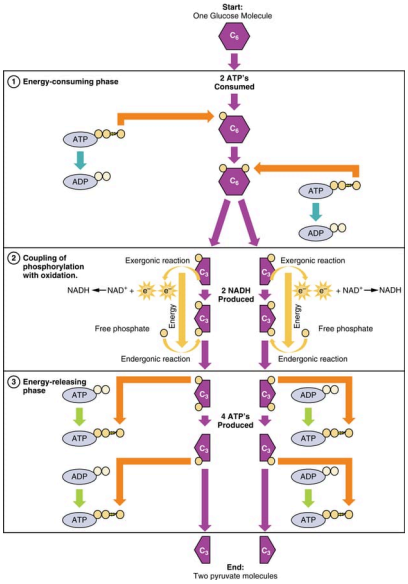


Figure 4.2.2: During the energy-consuming phase of glycolysis, two ATPs are consumed, transferring two phosphates to the glucose molecule. The glucose molecule then splits into two three-carbon compounds, each containing a phosphate. During the second phase, an additional phosphate is added to each of the three-carbon compounds. The energy for this endergonic reaction is provided by the removal (oxidation) of two electrons from each three-carbon compound. During the energy-releasing phase, the phosphates are removed from both three-carbon compounds and used to produce four ATP molecules. (CC BY 4.0; via Carbohydrate Metabolism). Detailed text description of the Figure 4.2.2.

Glycolysis can be divided into two phases: energy consuming (also called chemical priming) and energy yielding. The first phase is the energy-consuming phase, so it requires two ATP molecules to start the reaction for each molecule of glucose. However, the end of the reaction produces four ATPs, resulting in a net gain of two ATP energy molecules.

Glycolysis can be expressed as the following equation:

$$\mathrm{Glucose} + 2\,\mathrm{ATP} + 2\,\mathrm{NAD^+} + 4\,\mathrm{ADP} + 2\,\mathrm{P_i} \longrightarrow 2\,\mathrm{Pyruvate} + 4\,\mathrm{ATP} + 2\,\mathrm{NADH} + 2\,\mathrm{H^+}$$

This equation states that glucose, in combination with ATP (the energy source), $\mathrm{NAD^+}$ (a coenzyme that serves as an electron acceptor), and inorganic phosphate, breaks down into two pyruvate molecules, generating four ATP molecules—for a net yield of two ATP—and two energy-containing NADH coenzymes. The NADH that is produced in this process will be used later to produce ATP in the mitochondria. Importantly, by the end of this process, one glucose molecule generates two pyruvate molecules, two high-energy ATP molecules, and two electron-carrying NADH molecules.

The following discussions of glycolysis include the enzymes responsible for the reactions. When glucose enters a cell, the enzyme hexokinase (or glucokinase, in the liver) rapidly adds a phosphate to convert it into glucose-6-phosphate. A kinase is a type of enzyme that adds a phosphate molecule to a substrate (in this case, glucose, but it can be true of other molecules also). This conversion step requires one ATP and essentially traps the glucose in the cell, preventing it from passing back through the plasma membrane, thus allowing glycolysis to proceed. It also functions to maintain a concentration gradient with higher glucose levels in the blood than in the tissues. By establishing this concentration gradient, the glucose in the blood will be able to flow from an area of high concentration (the blood) into an area of low concentration (the tissues) to be either used or stored. Hexokinase is found in nearly every tissue in the body. Glucokinase, on the other hand, is expressed in tissues that are active when blood glucose levels are high, such as the liver. Hexokinase has a higher affinity for glucose than glucokinase and therefore is able to convert glucose at a faster rate than glucokinase. This is important when levels of glucose are very low in the body, as it allows glucose to travel preferentially to those tissues that require it more.

In the next step of the first phase of glycolysis, the enzyme glucose-6-phosphate isomerase converts glucose-6-phosphate

into fructose-6-phosphate. Like glucose, fructose is also a six carbon-containing sugar. The enzyme phosphofructokinase-1 then adds one more phosphate to convert fructose-6-phosphate into fructose-1-6-bisphosphate, another six-carbon sugar, using another ATP molecule. Aldolase then breaks down this fructose-1-6-bisphosphate into two three-carbon molecules, glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. The triosephosphate isomerase enzyme then converts dihydroxyacetone phosphate into a second glyceraldehyde-3-phosphate molecule. Therefore, by the end of this chemical-priming or energy-consuming phase, one glucose molecule is broken down into two glyceraldehyde-3-phosphate molecules.

The second phase of glycolysis, the energy-yielding phase, creates the energy that is the product of glycolysis. Glyceraldehyde-3-phosphate dehydrogenase converts each three-carbon glyceraldehyde-3-phosphate produced during the energy-consuming phase into 1,3-bisphosphoglycerate. This reaction releases an electron that is then picked up by NAD^+ to create an NADH molecule. NADH is a high-energy molecule, like ATP, but unlike ATP, it is not used as energy currency by the cell. Because there are two glyceraldehyde-3-phosphate molecules, two NADH molecules are synthesized during this step. Each 1,3-bisphosphoglycerate is subsequently dephosphorylated (i.e., a phosphate is removed) by phosphoglycerate kinase into 3-phosphoglycerate. Each phosphate released in this reaction can convert one molecule of ADP into one high-energy ATP molecule, resulting in a gain of two ATP molecules.

The enzyme phosphoglycerate mutase then converts the 3-phosphoglycerate molecules into 2-phosphoglycerate. The enolase enzyme then acts upon the 2-phosphoglycerate molecules to convert them into phosphoenolpyruvate molecules. The last step of glycolysis involves the dephosphorylation of the two phosphoenolpyruvate molecules by pyruvate kinase to create two pyruvate molecules and two ATP molecules.

In summary, one glucose molecule breaks down into two pyruvate molecules, and creates two net ATP molecules and two NADH molecules by glycolysis. Therefore, glycolysis generates energy for the cell and creates pyruvate molecules that can be processed further through the aerobic Krebs cycle (also called the citric acid cycle or tricarboxylic acid cycle); converted into lactic acid or alcohol (in yeast) by fermentation; or used later for the synthesis of glucose through gluconeogenesis.

Anaerobic Respiration

When oxygen is limited or absent, pyruvate enters an anaerobic pathway called fermentation. In these reactions, pyruvate can be converted into lactic acid. In addition to generating an additional ATP, this pathway serves to keep the pyruvate concentration low so glycolysis continues, and it oxidizes NADH into the NAD^+ needed by glycolysis. In this reaction, lactic acid replaces oxygen as the final electron acceptor. Anaerobic respiration occurs in most cells of the body when oxygen is limited or mitochondria are absent or nonfunctional. For example, because erythrocytes (red blood cells) lack mitochondria, they must produce their ATP from anaerobic respiration. This is an effective pathway of ATP production for short periods of time, ranging from seconds to a few minutes. The lactic acid produced diffuses into the plasma and is carried to the liver, where it is converted back into pyruvate or glucose via the Cori cycle. Similarly, when a person exercises, muscles use ATP faster than oxygen can be delivered to them. They depend on glycolysis and lactic acid production for rapid ATP production.

Aerobic Respiration

In the presence of oxygen, pyruvate can enter the Krebs cycle where additional energy is extracted as electrons are transferred from the pyruvate to the receptors NAD^+, GDP, and FAD, with carbon dioxide being a “waste product” (Figure 4.2.3). The NADH and $FADH_2$ pass electrons on to the electron transport chain, which uses the transferred energy to produce ATP. As the terminal step in the electron transport chain, oxygen is the terminal electron acceptor and creates water inside the mitochondria.

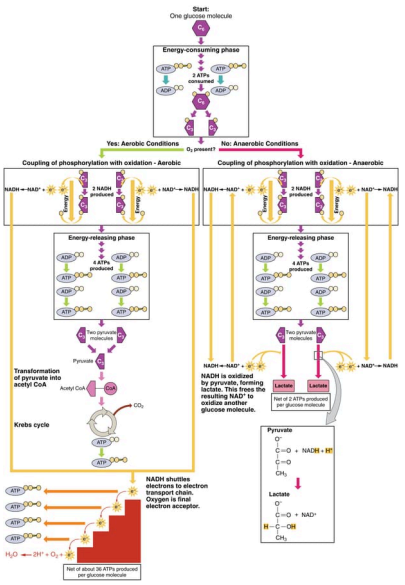


Figure 4.2.3: The process of anaerobic respiration converts glucose into two lactate molecules in the absence of oxygen or within erythrocytes that lack mitochondria. During aerobic respiration, glucose is oxidized into two pyruvate molecules. (CC BY 4.0; via Carbohydrate Metabolism). Detailed text description of the Figure 4.2.3.

Krebs Cycle/Citric Acid Cycle/Tricarboxylic Acid Cycle

The pyruvate molecules generated during glycolysis are transported across the mitochondrial membrane into the inner mitochondrial matrix, where they are metabolized by enzymes in a pathway called the Krebs cycle (Figure 4.2.4). The Krebs cycle is also commonly called the citric acid cycle or the tricarboxylic acid (TCA) cycle. During the Krebs cycle, high-energy molecules, including ATP, NADH, and $FADH_2$, are created. NADH and $FADH_2$ then pass electrons through the electron transport chain in the mitochondria to generate more ATP molecules.

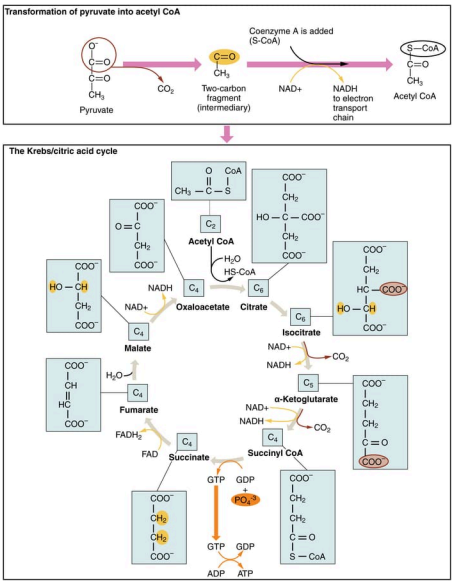


Figure 4.2.4: During the Krebs cycle, each pyruvate that is generated by glycolysis is converted into a two-carbon acetyl CoA molecule. The acetyl CoA is systematically processed through the cycle and produces high-energy NADH, $FADH_2$, and ATP molecules. (CC BY 4.0; via Carbohydrate Metabolism). Detailed text description of the Figure 4.2.4.

The three-carbon pyruvate molecule generated during glycolysis moves from the cytoplasm into the mitochondrial matrix, where it is converted by the enzyme pyruvate dehydrogenase into a two-carbon acetyl coenzyme A (acetyl CoA) molecule. This reaction

is an oxidative decarboxylation reaction. It converts the three-carbon pyruvate into a two-carbon acetyl CoA molecule, releasing carbon dioxide and transferring two electrons that combine with NAD^+ to form NADH. Acetyl CoA enters the Krebs cycle by combining with a four-carbon molecule, oxaloacetate, to form the six-carbon molecule citrate, or citric acid, at the same time releasing the coenzyme A molecule.

The six-carbon citrate molecule is systematically converted to a five-carbon molecule and then a four-carbon molecule, ending with oxaloacetate, the beginning of the cycle. Along the way, each citrate molecule will produce one ATP, one $FADH_2$, and three NADH. The $FADH_2$ and NADH will enter the oxidative phosphorylation system located in the inner mitochondrial membrane. In addition, the Krebs cycle supplies the starting materials to process and break down proteins and fats.

To start the Krebs cycle, citrate synthase combines acetyl CoA and oxaloacetate to form a six-carbon citrate molecule; CoA is subsequently released and can combine with another pyruvate molecule to begin the cycle again. The aconitase enzyme converts citrate into isocitrate. In two successive steps of oxidative decarboxylation, two molecules of CO_2 and two NADH molecules are produced when isocitrate dehydrogenase converts isocitrate into the five-carbon α-ketoglutarate, which is then catalyzed and converted into the four-carbon succinyl CoA by α-ketoglutarate dehydrogenase. The enzyme succinyl CoA dehydrogenase then converts succinyl CoA into succinate and forms the high-energy molecule GTP, which transfers its energy to ADP to produce ATP. Succinate dehydrogenase then converts succinate into fumarate, forming a molecule of $FADH_2$. Fumarase then converts fumarate into malate, which malate dehydrogenase then converts back into oxaloacetate while reducing NAD^+ to NADH. Oxaloacetate is then ready to combine with the next acetyl CoA to start the Krebs cycle again (Figure $4.2.4$). For each turn of the cycle, three NADH, one ATP (through GTP), and one $FADH_2$ are created. Each carbon of pyruvate is converted into CO_2, which is released as a byproduct of oxidative (aerobic) respiration.

Oxidative Phosphorylation and the Electron Transport Chain

The electron transport chain (ETC) uses the NADH and $FADH_2$ produced by the Krebs cycle to generate ATP. Electrons from NADH and $FADH_2$ are transferred through protein complexes embedded in the inner mitochondrial membrane by a series of enzymatic reactions. The electron transport chain consists of a series of four enzyme complexes (Complex I – Complex IV) and two coenzymes (ubiquinone and Cytochrome c), which act as electron carriers and proton pumps used to transfer H^+ ions into the space between the inner and outer mitochondrial membranes (Figure $4.2.5$). The ETC couples the transfer of electrons between a donor (like NADH) and an electron acceptor (like O_2) with the transfer of protons (H^+ ions) across the inner mitochondrial membrane, enabling the process of oxidative phosphorylation. In the presence of oxygen, energy is passed, stepwise, through the electron carriers to collect gradually the energy needed to attach a phosphate to ADP and produce ATP. The role of molecular oxygen, O_2, is as the terminal electron acceptor for the ETC. This means that once the electrons have passed through the entire ETC, they must be passed to another, separate molecule. These electrons, O_2, and H^+ ions from the matrix combine to form new water molecules. This is the basis for your need to breathe in oxygen. Without oxygen, electron flow through the ETC ceases.

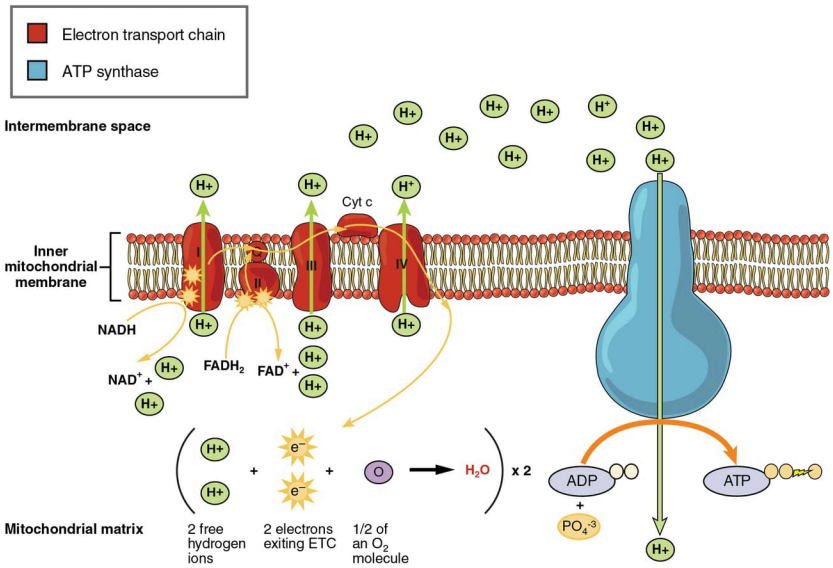


Figure 4.2.5: The electron transport chain is a series of electron carriers and ion pumps that are used to pump H^+ ions out of the inner mitochondrial matrix. (CC BY 4.0; via Carbohydrate Metabolism). Detailed text description of the Figure 4.2.5.

The electrons released from NADH and $FADH_2$ are passed along the chain by each of the carriers, which are reduced when they receive the electron and oxidized when passing it on to the next carrier. Each of these reactions releases a small amount of energy, which is used to pump H^+ ions across the inner membrane. The accumulation of these protons in the space between the membranes creates a proton gradient with respect to the mitochondrial matrix.

Also embedded in the inner mitochondrial membrane is an amazing protein pore complex called ATP synthase. Effectively, it is a turbine that is powered by the flow of H^+ ions across the inner membrane down a gradient and into the mitochondrial matrix. As the H^+ ions traverse the complex, the shaft of the complex rotates. This rotation enables other portions of ATP synthase to encourage ADP and P_i to create ATP. In accounting for the total number of ATP produced per glucose molecule through aerobic respiration, it is important to remember the following points:

- A net of two ATP are produced through glycolysis (four produced and two consumed during the energy-consuming stage). However, these two ATP are used for transporting the NADH produced during glycolysis from the cytoplasm into the mitochondria. Therefore, the net production of ATP during glycolysis is zero.
- In all phases after glycolysis, the number of ATP, NADH, and $FADH_2$ produced must be multiplied by two to reflect how each glucose molecule produces two pyruvate molecules.
- In the ETC, about three ATP are produced for every oxidized NADH. However, only about two ATP are produced for every oxidized $FADH_2$. The electrons from $FADH_2$ produce less ATP, because they start at a lower point in the ETC (Complex II) compared to the electrons from NADH (Complex I) (Figure 4.2.5).

Therefore, for every glucose molecule that enters aerobic respiration, a net total of 36 ATPs are produced (Figure 4.2.6).

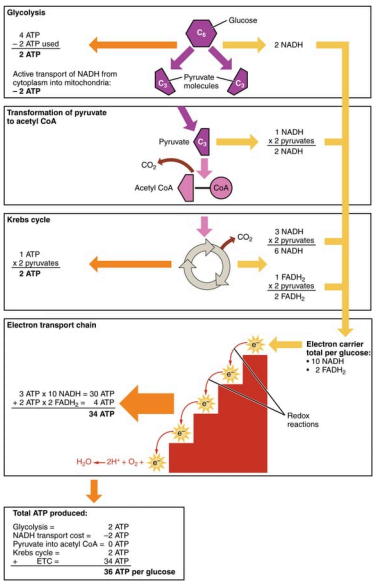


Figure 4.2.6: Carbohydrate metabolism involves glycolysis, the Krebs cycle, and the electron transport chain. (CC BY 4.0; via Carbohydrate Metabolism). Detailed text description of the Figure 4.2.7.

Gluconeogenesis

Gluconeogenesis is the synthesis of new glucose molecules from pyruvate, lactate, glycerol, or the amino acids alanine or glutamine. This process takes place primarily in the liver during periods of low glucose, that is, under conditions of fasting, starvation, and low carbohydrate diets. So, the question can be raised as to why the body would create something it has just spent a fair amount of effort to break down? Certain key organs, including the brain, can use only glucose as an energy source; therefore, it is essential that the body maintain a minimum blood glucose concentration. When the blood glucose concentration falls below that certain point, new glucose is synthesized by the liver to raise the blood concentration to normal.

Gluconeogenesis is not simply the reverse of glycolysis. There are some important differences (Figure 4.2.7). Pyruvate is a common starting material for gluconeogenesis. First, the pyruvate is converted into oxaloacetate. Oxaloacetate then serves as a substrate for the enzyme phosphoenolpyruvate carboxykinase (PEPCK), which transforms oxaloacetate into phosphoenolpyruvate (PEP). From this step, gluconeogenesis is nearly the reverse of glycolysis. PEP is converted back into 2-phosphoglycerate, which is converted into 3-phosphoglycerate. Then, 3-phosphoglycerate is converted into 1,3 bisphosphoglycerate and then into glyceraldehyde-3-phosphate. Two molecules of glyceraldehyde-3-phosphate then combine to form fructose-1-6-bisphosphate, which is converted into fructose 6-phosphate and then into glucose-6-phosphate. Finally, a series of reactions generates glucose itself. In gluconeogenesis (as compared to glycolysis), the enzyme hexokinase is replaced by glucose-6-phosphatase, and the enzyme phosphofructokinase-1 is replaced by fructose-1,6-bisphosphatase. This helps the cell to regulate glycolysis and gluconeogenesis independently of each other.

As will be discussed as part of lipolysis, fats can be broken down into glycerol, which can be phosphorylated to form dihydroxyacetone phosphate or DHAP. DHAP can either enter the glycolytic pathway or be used by the liver as a substrate for gluconeogenesis.

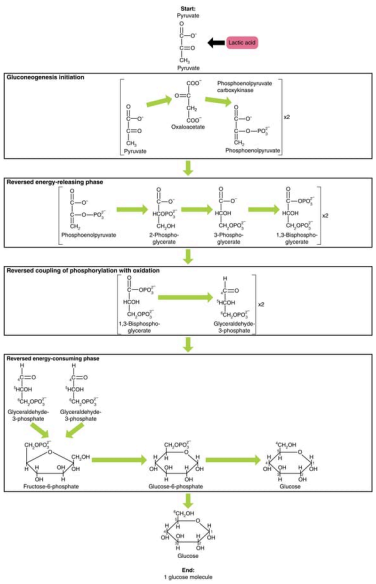


Figure 4.2.7: Gluconeogenesis is the synthesis of glucose from pyruvate, lactate, glycerol, alanine, or glutamate. (CC BY 4.0; via Carbohydrate Metabolism). Detailed text description of the Figure 4.2.7.

Aging and the...

Body's Metabolic Rate

The human body's metabolic rate decreases nearly 2 percent per decade after age 30. Changes in body composition, including reduced lean muscle mass, are mostly responsible for this decrease. The most dramatic loss of muscle mass, and consequential decline in metabolic rate, occurs between 50 and 70 years of age. Loss of muscle mass is the equivalent of reduced strength, which tends to inhibit seniors from engaging in sufficient physical activity. This results in a positive-feedback system where the reduced physical activity leads to even more muscle loss, further reducing metabolism.

There are several things that can be done to help prevent general declines in metabolism and to fight back against the cyclic nature of these declines. These include eating breakfast, eating small meals frequently, consuming plenty of lean protein, drinking water to remain hydrated, exercising (including strength training), and getting enough sleep. These measures can help keep energy levels from dropping and curb the urge for increased calorie consumption from excessive snacking. While these strategies are not guaranteed to maintain metabolism, they do help prevent muscle loss and may increase energy levels. Some experts also suggest avoiding sugar, which can lead to excess fat storage. Spicy foods and green tea might also be beneficial. Because stress activates cortisol release, and cortisol slows metabolism, avoiding stress, or at least practicing relaxation techniques, can also help.

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4.3: Lipid Metabolism

Lipid Metabolism

Fats (or triglycerides) within the body are ingested as food or synthesized by adipocytes or hepatocytes from carbohydrate precursors (Figure 4.3.1). Lipid metabolism entails the oxidation of fatty acids to either generate energy or synthesize new lipids from smaller constituent molecules. Lipid metabolism is associated with carbohydrate metabolism, as products of glucose (such as acetyl CoA) can be converted into lipids.

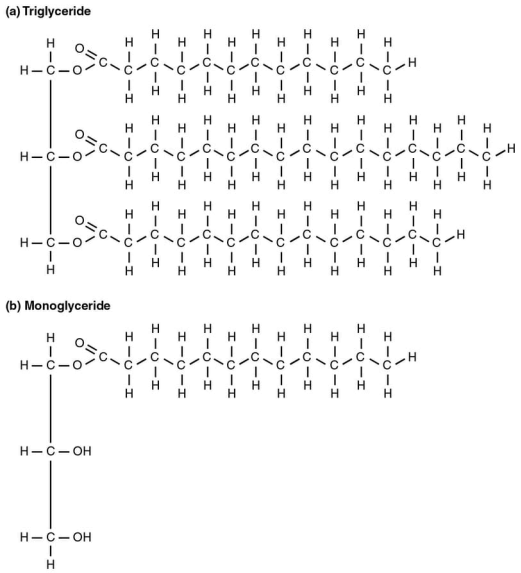


Figure 4.3.1: A triglyceride consists of a glycerol backbone attached to three fatty acid chains through ester bonds, whereas a monoglyceride contains a glycerol backbone attached to a single fatty acid chain and two hydroxyl groups. Triglycerides serve as the primary storage form of fat, while monoglycerides are intermediate products formed during lipid digestion and absorption. (CC BY 4.0; via Lipid Metabolism). Detailed text description of the Figure 4.3.1.

Lipid metabolism begins in the intestine where ingested triglycerides are broken down into smaller chain fatty acids and subsequently into monoglyceride molecules (Figure 4.3.1*b*) by pancreatic lipases, enzymes that break down fats after they are emulsified by bile salts. When food reaches the small intestine in the form of chyme, a digestive hormone called cholecystokinin (CCK) is released by intestinal cells in the intestinal mucosa. CCK stimulates the release of pancreatic lipase from the pancreas and stimulates the contraction of the gallbladder to release stored bile salts into the intestine. CCK also travels to the brain, where it can act as a hunger suppressant.

Together, the pancreatic lipases and bile salts break down triglycerides into free fatty acids. These fatty acids can be transported across the intestinal membrane. However, once they cross the membrane, they are recombined to again form triglyceride molecules. Within the intestinal cells, these triglycerides are packaged along with cholesterol molecules in phospholipid vesicles called chylomicrons (Figure 4.3.2). The chylomicrons enable fats and cholesterol to move within the aqueous environment of your lymphatic and circulatory systems. Chylomicrons leave the enterocytes by exocytosis and enter the lymphatic system via lacteals in the villi of the intestine. From the lymphatic system, the chylomicrons are transported to the circulatory system. Once in the circulation, they can either go to the liver or be stored in fat cells (adipocytes) that comprise adipose (fat) tissue found throughout the body.

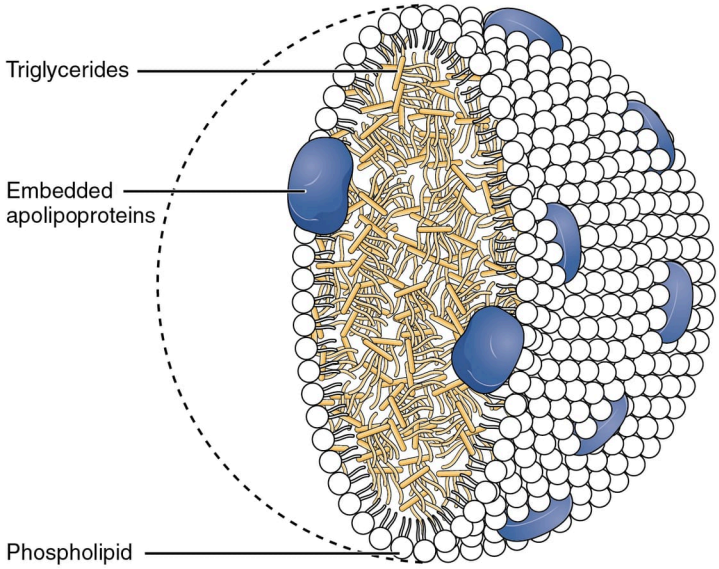


Figure 4.3.2: Chylomicrons contain triglycerides, cholesterol molecules, and other apolipoproteins (protein molecules). They function to carry these water-insoluble molecules from the intestine, through the lymphatic system, and into the bloodstream, which carries the lipids to adipose tissue for storage. (CC BY 4.0; via Lipid Metabolism). Detailed text description of the Figure 4.3.2.

Lipolysis

To obtain energy from fat, triglycerides must first be broken down by hydrolysis into their two principal components, fatty acids and glycerol. This process, called lipolysis, takes place in the cytoplasm. The resulting fatty acids are oxidized by β-oxidation into acetyl CoA, which is used by the Krebs cycle. The glycerol that is released from triglycerides after lipolysis directly enters the glycolysis pathway as DHAP. Because one triglyceride molecule yields three fatty acid molecules with as much as 16 or more carbons in each one, fat molecules yield more energy than carbohydrates and are an important source of energy for the human body. Triglycerides yield more than twice the energy per unit mass when compared to carbohydrates and proteins. Therefore, when glucose levels are low, triglycerides can be converted into acetyl CoA molecules and used to generate ATP through aerobic respiration.

The breakdown of fatty acids, called fatty acid oxidation or beta (β)-oxidation, begins in the cytoplasm, where fatty acids are converted into fatty acyl CoA molecules. This fatty acyl CoA combines with carnitine to create a fatty acyl carnitine molecule, which helps to transport the fatty acid across the mitochondrial membrane. Once inside the mitochondrial matrix, the fatty acyl carnitine molecule is converted back into fatty acyl CoA and then into acetyl CoA (Figure 4.3.3). The newly formed acetyl CoA enters the Krebs cycle and is used to produce ATP in the same way as acetyl CoA derived from pyruvate.

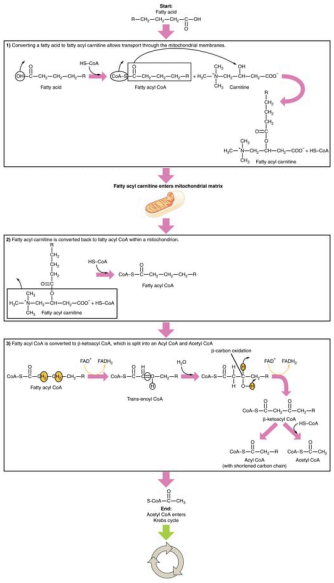


Figure 4.3.3: During fatty acid oxidation, triglycerides can be broken down into acetyl CoA molecules and used for energy when glucose levels are low. (CC BY 4.0; via Lipid Metabolism). Detailed text description of the Figure 4.3.3.

Ketogenesis

If excessive acetyl CoA is created from the oxidation of fatty acids and the Krebs cycle is overloaded and cannot handle it, the acetyl CoA is diverted to create ketone bodies. These ketone bodies can serve as a fuel source if glucose levels are too low in the body. Ketones serve as fuel in times of prolonged starvation or when patients suffer from uncontrolled diabetes and cannot utilize most of the circulating glucose. In both cases, fat stores are liberated to generate energy through the Krebs cycle and will generate ketone bodies when too much acetyl CoA accumulates.

In this ketone synthesis reaction, excess acetyl CoA is converted into hydroxymethylglutaryl CoA (HMG CoA). HMG CoA is a precursor of cholesterol and is an intermediate that is subsequently converted into β-hydroxybutyrate, the primary ketone body in the blood (Figure 4.3.4).

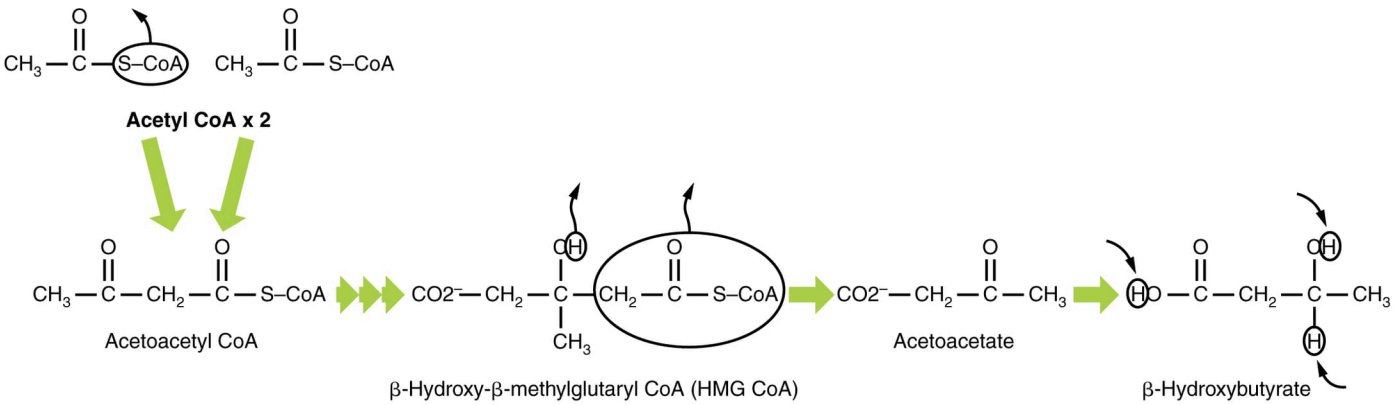


Figure 4.3.4: Aacetyl CoA is diverted from the Krebs cycle to the ketogenesis pathway. This reaction occurs in the mitochondria of liver cells. The result is the production of β-hydroxybutyrate, the primary ketone body found in the blood. (CC BY 4.0; via Lipid Metabolism). Detailed text description of the Figure 4.3.4.

Ketone Body Oxidation

Organs that have classically been thought to be dependent solely on glucose, such as the brain, can actually use ketones as an alternative energy source. This keeps the brain functioning when glucose is limited. When ketones are produced faster than they can be used, they can be broken down into CO_2 and acetone. The acetone is removed by exhalation. One symptom of ketogenesis is that the patient's breath smells sweet like alcohol. This effect provides one way of telling if a person with

diabetes is properly controlling the disease. The carbon dioxide produced can acidify the blood, leading to diabetic ketoacidosis, a dangerous condition in people with diabetes.

Ketones oxidize to produce energy for the brain. beta (β)-hydroxybutyrate is oxidized to acetoacetate and NADH is released. An HS-CoA molecule is added to acetoacetate, forming acetoacetyl CoA. The carbon within the acetoacetyl CoA that is not bonded to the CoA then detaches, splitting the molecule in two. This carbon then attaches to another free HS-CoA, resulting in two acetyl CoA molecules. These two acetyl CoA molecules are then processed through the Krebs cycle to generate energy (Figure 4.3.5).

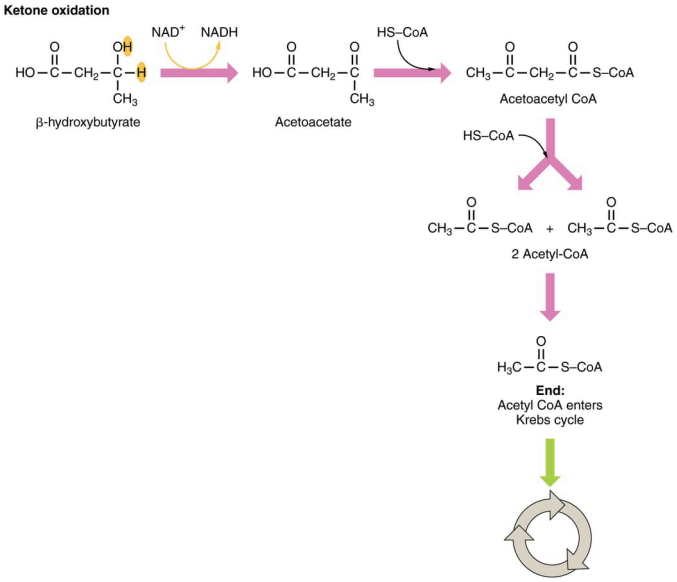


Figure 4.3.5: When glucose is limited, ketone bodies can be oxidized to produce acetyl CoA to be used in the Krebs cycle to generate energy. (CC BY 4.0; via Lipid Metabolism). Detailed text description of the Figure 4.3.5.

Lipogenesis

When glucose levels are plentiful, the excess acetyl CoA generated by glycolysis can be converted into fatty acids, triglycerides, cholesterol, steroids, and bile salts. This process, called lipogenesis, creates lipids (fat) from the acetyl CoA and takes place in the cytoplasm of adipocytes (fat cells) and hepatocytes (liver cells). When you eat more glucose or carbohydrates than your body needs, your system uses acetyl CoA to turn the excess into fat. Although there are several metabolic sources of acetyl CoA, it is most commonly derived from glycolysis. Acetyl CoA availability is significant, because it initiates lipogenesis. Lipogenesis begins with acetyl CoA and advances by the subsequent addition of two carbon atoms from another acetyl CoA; this process is repeated until fatty acids are the appropriate length. Because this is a bond-creating anabolic process, ATP is consumed. However, the creation of triglycerides and lipids is an efficient way of storing the energy available in carbohydrates. Triglycerides and lipids, high-energy molecules, are stored in adipose tissue until they are needed.

Although lipogenesis occurs in the cytoplasm, the necessary acetyl CoA is created in the mitochondria and cannot be transported across the mitochondrial membrane. To solve this problem, pyruvate is converted into both oxaloacetate and acetyl CoA. Two different enzymes are required for these conversions. Oxaloacetate forms via the action of pyruvate carboxylase, whereas the action of pyruvate dehydrogenase creates acetyl CoA. Oxaloacetate and acetyl CoA combine to form citrate, which can cross the mitochondrial membrane and enter the cytoplasm. In the cytoplasm, citrate is converted back into oxaloacetate and acetyl CoA. Oxaloacetate is converted into malate and then into pyruvate. Pyruvate crosses back across the mitochondrial membrane to wait for the next cycle of lipogenesis. The acetyl CoA is converted into malonyl CoA that is used to synthesize fatty acids. Figure 4.3.6 summarizes the pathways of lipid metabolism.

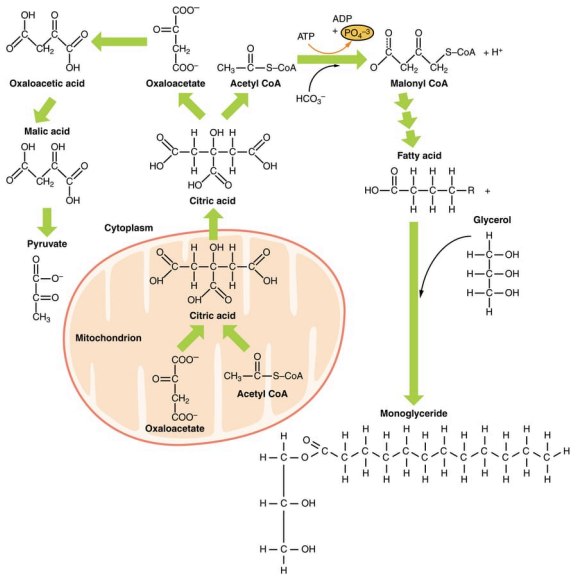


Figure 4.3.6: Lipids may follow one of several pathways during metabolism. Glycerol and fatty acids follow different pathways. (CC BY 4.0; via Lipid Metabolism). Detailed text description of the Figure 4.3.6.

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4.4: Protein Metabolism

Protein Metabolism

Much of the body is made of protein, and these proteins take on a myriad of forms. They represent cell signaling receptors, signaling molecules, structural members, enzymes, intracellular trafficking components, extracellular matrix scaffolds, ion pumps, ion channels, oxygen and CO_2 transporters (hemoglobin). That is not even the complete list! There is protein in bones (collagen), muscles, and tendons; the hemoglobin that transports oxygen; and enzymes that catalyze all biochemical reactions. Protein is also used for growth and repair. Amid all these necessary functions, proteins also hold the potential to serve as a metabolic fuel source. Proteins are not stored for later use, so excess proteins must be converted into glucose or triglycerides, and used to supply energy or build energy reserves. Although the body can synthesize proteins from amino acids, food is an important source of those amino acids, especially because humans cannot synthesize all of the 20 amino acids used to build proteins.

The digestion of proteins begins in the stomach. When protein-rich foods enter the stomach, they are greeted by a mixture of the enzyme pepsin and hydrochloric acid (HCl; 0.5 percent). The latter produces an environmental pH of 1.5–3.5 that denatures proteins within food. Pepsin cuts proteins into smaller polypeptides and their constituent amino acids. When the food-gastric juice mixture (chyme) enters the small intestine, the pancreas releases sodium bicarbonate to neutralize the HCl. This helps to protect the lining of the intestine. The small intestine also releases digestive hormones, including secretin and CCK, which stimulate digestive processes to break down the proteins further. Secretin also stimulates the pancreas to release sodium bicarbonate. The pancreas releases most of the digestive enzymes, including the proteases trypsin, chymotrypsin, and elastase, which aid protein digestion. Together, all of these enzymes break complex proteins into smaller individual amino acids (Figure 4.4.1), which are then transported across the intestinal mucosa to be used to create new proteins, or to be converted into fats or acetyl CoA and used in the Krebs cycle.

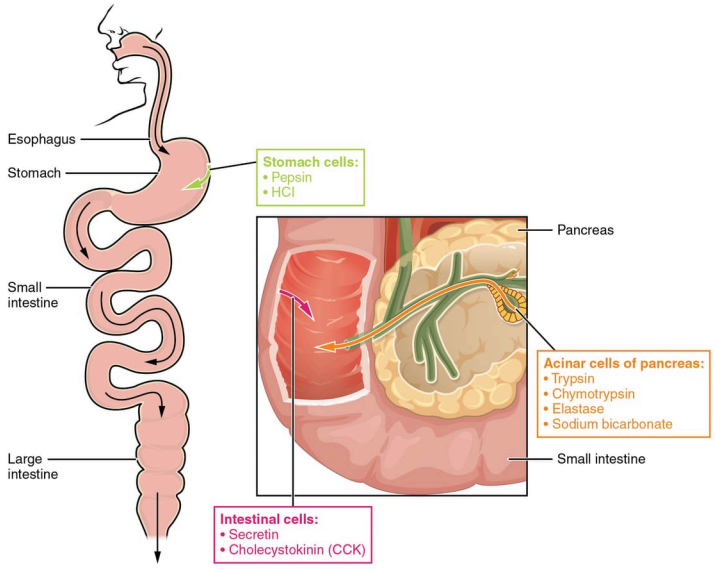


Figure 4.4.1: Enzymes in the stomach and small intestine break down proteins into amino acids. HCl in the stomach aids in proteolysis, and hormones secreted by intestinal cells direct the digestive processes. (CC BY 4.0; via Protein Metabolism). Detailed text description of the Figure 4.4.1.

In order to avoid breaking down the proteins that make up the pancreas and small intestine, pancreatic enzymes are released as inactive proenzymes that are only activated in the small intestine. In the pancreas, vesicles store trypsin and chymotrypsin as trypsinogen and chymotrypsinogen. Once released into the small intestine, an enzyme found in the wall of the small intestine, called enterokinase, binds to trypsinogen and converts it into its active form, trypsin. Trypsin then binds to chymotrypsinogen to convert it into the active chymotrypsin. Trypsin and chymotrypsin break down large proteins into smaller peptides, a process called proteolysis. These smaller peptides are catabolized into their constituent amino acids, which are transported across the apical surface of the intestinal mucosa in a process that is mediated by sodium-amino acid transporters. These transporters bind sodium and then bind the amino acid to transport it across the membrane. At the basal surface of the mucosal cells, the sodium

and amino acid are released. The sodium can be reused in the transporter, whereas the amino acids are transferred into the bloodstream to be transported to the liver and cells throughout the body for protein synthesis.

Freely available amino acids are used to create proteins. If amino acids exist in excess, the body has no capacity or mechanism for their storage; thus, they are converted into glucose or ketones, or they are decomposed. Amino acid decomposition results in hydrocarbons and nitrogenous waste. However, high concentrations of nitrogenous byproducts are toxic. The urea cycle processes nitrogen and facilitates its excretion from the body.

Urea Cycle

The urea cycle is a set of biochemical reactions that produces urea from ammonium ions in order to prevent a toxic level of ammonium in the body. It occurs primarily in the liver and, to a lesser extent, in the kidney. Prior to the urea cycle, ammonium ions are produced from the breakdown of amino acids. In these reactions, an amine group, or ammonium ion, from the amino acid is exchanged with a keto group on another molecule. This transamination event creates a molecule that is necessary for the Krebs cycle and an ammonium ion that enters into the urea cycle to be eliminated.

In the urea cycle, ammonium is combined with CO_2, resulting in urea and water. The urea is eliminated through the kidneys in the urine.

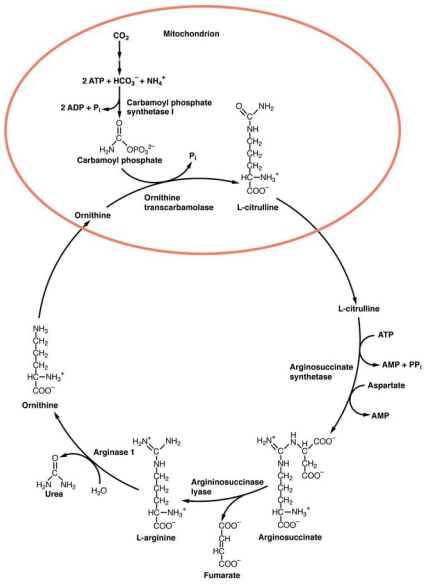


Figure 4.4.2: Nitrogen is transaminated, creating ammonia and intermediates of the Krebs cycle. Ammonia is processed in the urea cycle to produce urea that is eliminated through the kidneys. (CC BY 4.0; via Protein Metabolism). Detailed text description of the Figure 4.4.2.

Amino acids can also be used as a source of energy, especially in times of starvation. Because the processing of amino acids results in the creation of metabolic intermediates, including pyruvate, acetyl CoA, acetoacyl CoA, oxaloacetate, and α-ketoglutarate, amino acids can serve as a source of energy production through the Krebs cycle.

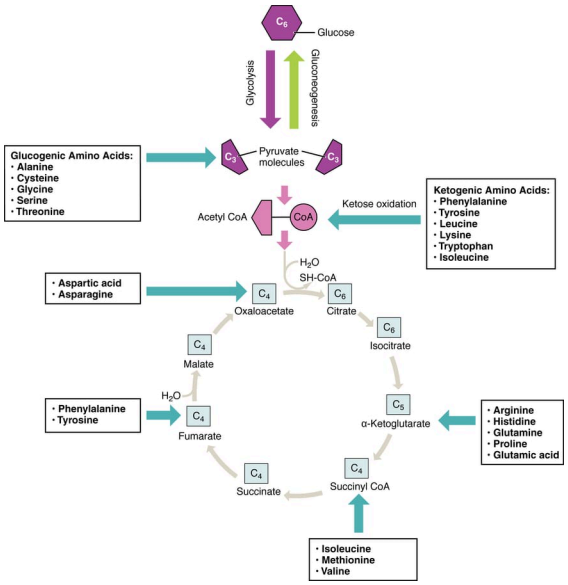


Figure 4.4.3: Amino acids can be broken down into precursors for glycolysis or the Krebs cycle. Amino acids (in bold) can enter the cycle through more than one pathway. (CC BY 4.0; via Protein Metabolism). Detailed text description of the Figure Extra close brace or missing open brace .

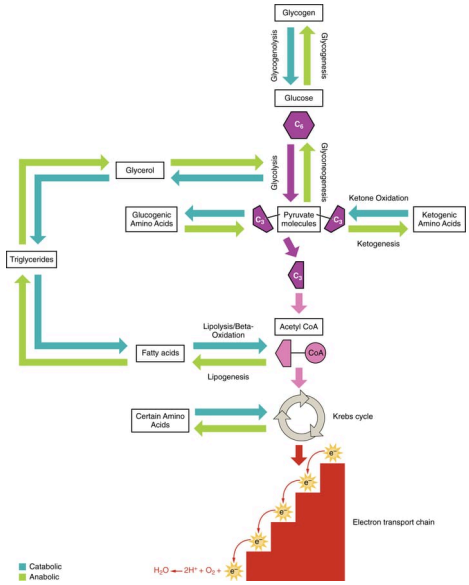


Figure 4.4.4: Nutrients follow a complex pathway from ingestion through anabolism and catabolism to energy production. (CC BY 4.0; via Protein Metabolism). Detailed text description of the Figure 4.4.4.

Disorders of the...

Metabolism: Pyruvate Dehydrogenase Complex Deficiency and Phenylketonuria

Pyruvate dehydrogenase complex deficiency (PDCD) and phenylketonuria (PKU) are genetic disorders. Pyruvate dehydrogenase is the enzyme that converts pyruvate into acetyl CoA, the molecule necessary to begin the Krebs cycle to produce ATP. With low levels of the pyruvate dehydrogenase complex (PDC), the rate of cycling through the Krebs cycle is dramatically reduced. This results in a decrease in the total amount of energy that is produced by the cells of the body. PDC deficiency results in a neurodegenerative disease that ranges in severity, depending on the levels of the PDC enzyme. It may cause developmental defects, muscle spasms, and death. Treatments can include diet modification, vitamin supplementation, and gene therapy; however, damage to the central nervous system usually cannot be reversed.

PKU affects about 1 in every 15,000 births in the United States. People afflicted with PKU lack sufficient activity of the enzyme phenylalanine hydroxylase and are therefore unable to break down phenylalanine into tyrosine adequately. Because of this, levels of phenylalanine rise to toxic levels in the body, which results in damage to the central nervous system and brain. Symptoms include delayed neurological development, hyperactivity, intellectual disability, seizures, rash, tremors, and uncontrolled movements of the arms and legs. Pregnant people with PKU are at a high risk for exposing the fetus to too much phenylalanine, which can cross the placenta and affect fetal development. Babies exposed to excess phenylalanine in utero may present with heart defects, physical and/or intellectual disability, and microcephaly. Every infant in the United States and Canada is tested at birth to determine whether PKU is present. The earlier a modified diet is begun, the less severe the symptoms will be. The person must closely follow a strict diet that is low in phenylalanine to avoid symptoms and damage. Phenylalanine is found in high concentrations in artificial sweeteners, including aspartame. Therefore, these sweeteners must be avoided. Some animal products and certain starches are also high in phenylalanine, and intake of these foods should be carefully monitored.

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4.5: Metabolic States of the Body

The Absorptive State

You eat periodically throughout the day; however, your organs, especially the brain, need a continuous supply of glucose. How does the body meet this constant demand for energy? Your body processes the food you eat both to use immediately and, importantly, to store as energy for later demands. If there were no method in place to store excess energy, you would need to eat constantly in order to meet energy demands. Distinct mechanisms are in place to facilitate energy storage, and to make stored energy available during times of fasting and starvation.

The absorptive state, or the fed state, occurs after a meal when your body is digesting the food and absorbing the nutrients (anabolism exceeds catabolism). Digestion begins the moment you put food into your mouth, as the food is broken down into its constituent parts to be absorbed through the intestine. The digestion of carbohydrates begins in the mouth, whereas the digestion of proteins and fats begins in the stomach and small intestine. The constituent parts of these carbohydrates, fats, and proteins are transported across the intestinal wall and enter the bloodstream (sugars and amino acids) or the lymphatic system (fats). From the intestines, these systems transport them to the liver, adipose tissue, or muscle cells that will process and use, or store, the energy.

Depending on the amounts and types of nutrients ingested, the absorptive state can linger for up to 4 hours. The ingestion of food and the rise of glucose concentrations in the bloodstream stimulate pancreatic beta cells to release insulin into the bloodstream, where it initiates the absorption of blood glucose by liver hepatocytes, and by adipose and muscle cells. Once inside these cells, glucose is immediately converted into glucose-6-phosphate. By doing this, a concentration gradient is established where glucose levels are higher in the blood than in the cells. This allows for glucose to continue moving from the blood to the cells where it is needed. Insulin also stimulates the storage of glucose as glycogen in the liver and muscle cells where it can be used for later energy needs of the body. Insulin also promotes the synthesis of protein in muscle. As you will see, muscle protein can be catabolized and used as fuel in times of starvation.

If energy is exerted shortly after eating, the dietary fats and sugars that were just ingested will be processed and used immediately for energy. If not, the excess glucose is stored as glycogen in the liver and muscle cells, or as fat in adipose tissue; excess dietary fat is also stored as triglycerides in adipose tissues. Figure 4.5.1 summarizes the metabolic processes occurring in the body during the absorptive state.

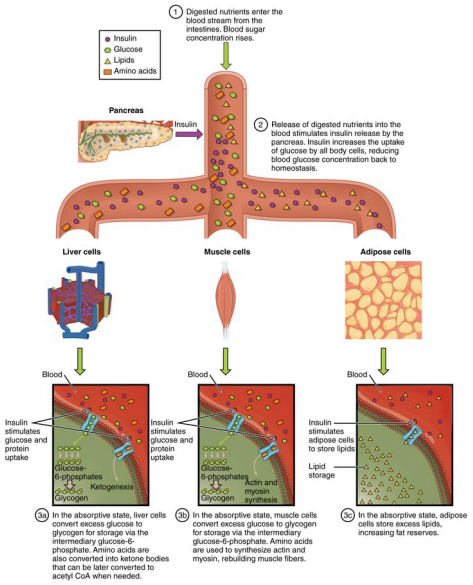


Figure 4.5.1: During the absorptive state, the body digests food and absorbs the nutrients. (CC BY 4.0; via Metabolic States of the Body). Detailed text description of the Figure 4.5.1.

The Postabsorptive State

The postabsorptive state, or the fasting state, occurs when the food has been digested, absorbed, and stored. You commonly fast overnight, but skipping meals during the day puts your body in the postabsorptive state as well. During this state, the body must rely initially on stored glycogen. Glucose levels in the blood begin to drop as it is absorbed and used by the cells. In response to the decrease in glucose, insulin levels also drop. Glycogen and triglyceride storage slows. However, due to the demands of the tissues and organs, blood glucose levels must be maintained in the normal range of 80–120 mg/dL. In response to a drop in blood glucose concentration, the hormone glucagon is released from the alpha cells of the pancreas. Glucagon acts upon the liver cells, where it inhibits the synthesis of glycogen and stimulates the breakdown of stored glycogen back into glucose. This glucose is released from the liver to be used by the peripheral tissues and the brain. As a result, blood glucose levels begin to rise. Gluconeogenesis will also begin in the liver to replace the glucose that has been used by the peripheral tissues.

After ingestion of food, fats and proteins are processed as described previously; however, the glucose processing changes a bit. The peripheral tissues preferentially absorb glucose. The liver, which normally absorbs and processes glucose, will not do so after a prolonged fast. The gluconeogenesis that has been ongoing in the liver will continue after fasting to replace the glycogen stores that were depleted in the liver. After these stores have been replenished, excess glucose that is absorbed by the liver will be converted into triglycerides and fatty acids for long-term storage. Figure 4.5.2 summarizes the metabolic processes occurring in the body during the postabsorptive state.

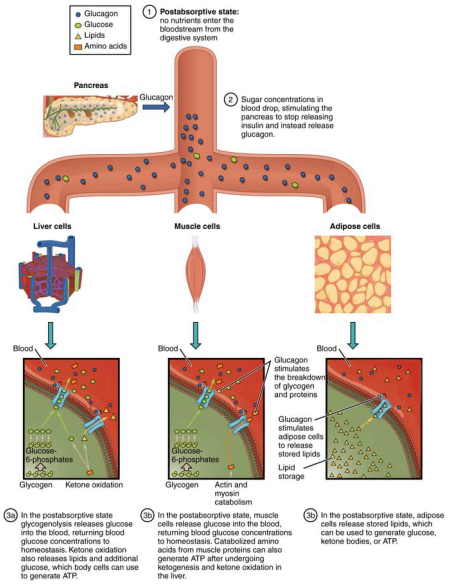


Figure 4.5.2: During the postabsorptive state, the body must rely on stored glycogen for energy. (CC BY 4.0; via Metabolic States of the Body). Detailed text description of the Figure 4.5.2.

Starvation

When the body is deprived of nourishment for an extended period of time, it goes into “survival mode.” The first priority for survival is to provide enough glucose or fuel for the brain. The second priority is the conservation of amino acids for proteins. Therefore, the body uses ketones to satisfy the energy needs of the brain and other glucose-dependent organs, and to maintain proteins in the cells. Because glucose levels are very low during starvation, glycolysis will shut off in cells that can use alternative fuels. For example, muscles will switch from using glucose to fatty acids as fuel. As previously explained, fatty acids can be converted into acetyl CoA and processed through the Krebs cycle to make ATP. Pyruvate, lactate, and alanine from muscle cells are not converted into acetyl CoA and used in the Krebs cycle, but are exported to the liver to be used in the synthesis of glucose. As starvation continues, and more glucose is needed, glycerol from fatty acids can be liberated and used as a source for gluconeogenesis.

After several days of starvation, ketone bodies become the major source of fuel for the heart and other organs. As starvation continues, fatty acids and triglyceride stores are used to create ketones for the body. This prevents the continued breakdown of proteins that serve as carbon sources for gluconeogenesis. Once these stores are fully depleted, proteins from muscles are released and broken down for glucose synthesis. Overall survival is dependent on the amount of fat and protein stored in the body.

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4.6: Energy and Heat Balance

Regulation of Body Temperatures

The body tightly regulates the body temperature through a process called thermoregulation, in which the body can maintain its temperature within certain boundaries, even when the surrounding temperature is very different. The core temperature of the body remains steady at around 36.5–37.5 °C (or 97.7–99.5 °F). In the process of ATP production by cells throughout the body, approximately 60 percent of the energy produced is in the form of heat used to maintain body temperature. Thermoregulation is an example of negative feedback.

The hypothalamus in the brain is the master switch that works as a thermostat to regulate the body's core temperature (Figure 4.6.1). If the temperature is too high, the hypothalamus can initiate several processes to lower it. These include increasing the circulation of the blood to the surface of the body to allow for the dissipation of heat through the skin and initiation of sweating to allow evaporation of water on the skin to cool its surface. Conversely, if the temperature falls below the set core temperature, the hypothalamus can initiate shivering to generate heat. The body uses more energy and generates more heat. In addition, thyroid hormone will stimulate more energy use and heat production by cells throughout the body. An environment is said to be thermoneutral when the body does not expend or release energy to maintain its core temperature. For a naked human, this is an ambient air temperature of around 84 °F. If the temperature is higher, for example, when wearing clothes, the body compensates with cooling mechanisms. The body loses heat through the mechanisms of heat exchange.

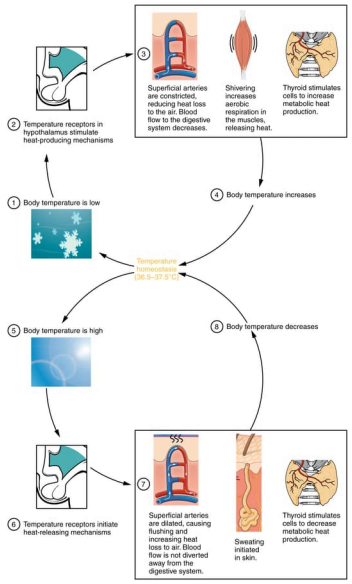


Figure 4.6.1: The hypothalamus controls thermoregulation. (CC BY 4.0; via Energy and Heat Balance). Detailed text description of the Figure 4.6.1.

Mechanisms of Heat Exchange

When the environment is not thermoneutral, the body uses four mechanisms of heat exchange to maintain homeostasis: conduction, convection, radiation, and evaporation. Each of these mechanisms relies on the property of heat to flow from a higher concentration to a lower concentration; therefore, each of the mechanisms of heat exchange varies in rate according to the temperature and conditions of the environment.

Conduction is the transfer of heat by two objects that are in direct contact with one another. It occurs when the skin comes in contact with a cold or warm object. For example, when holding a glass of ice water, the heat from your skin will warm the glass and in turn melt the ice. Alternatively, on a cold day, you might warm up by wrapping your cold hands around a hot mug of coffee. Only about 3 percent of the body's heat is lost through conduction.

Convection is the transfer of heat to the air surrounding the skin. The warmed air rises away from the body and is replaced by

cooler air that is subsequently heated. Convection can also occur in water. When the water temperature is lower than the body's temperature, the body loses heat by warming the water closest to the skin, which moves away to be replaced by cooler water. The convection currents created by the temperature changes continue to draw heat away from the body more quickly than the body can replace it, resulting in hyperthermia. About 15 percent of the body's heat is lost through convection.

Radiation is the transfer of heat via infrared waves. This occurs between any two objects when their temperatures differ. A radiator can warm a room via radiant heat. On a sunny day, the radiation from the sun warms the skin. The same principle works from the body to the environment. About 60 percent of the heat lost by the body is lost through radiation.

Evaporation is the transfer of heat by the evaporation of water. Because it takes a great deal of energy for a water molecule to change from a liquid to a gas, evaporating water (in the form of sweat) takes with it a great deal of energy from the skin. However, the rate at which evaporation occurs depends on relative humidity—more sweat evaporates in lower humidity environments. Sweating is the primary means of cooling the body during exercise, whereas at rest, about 20 percent of the heat lost by the body occurs through evaporation.

Metabolic Rate

The metabolic rate is the amount of energy consumed minus the amount of energy expended by the body. The basal metabolic rate (BMR) describes the amount of daily energy expended by humans at rest, in a neutrally temperate environment, while in the postabsorptive state. It measures how much energy the body needs for normal, basic, daily activity. About 70 percent of all daily energy expenditure comes from the basic functions of the organs in the body. Another 20 percent comes from physical activity, and the remaining 10 percent is necessary for body thermoregulation or temperature control. This rate will be higher if a person is more active or has more lean body mass. As you age, the BMR generally decreases as the percentage of less lean muscle mass decreases.

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4.7: Nutrition and Diet

Food, Energy and Metabolism

The carbohydrates, lipids, and proteins in the foods you eat are used for energy to power molecular, cellular, and organ system activities. Importantly, the energy is stored primarily as fats. The quantity and quality of food that is ingested, digested, and absorbed affects the amount of fat that is stored as excess calories. Diet—both what you eat and how much you eat—has a dramatic impact on your health. Eating too much or too little food can lead to serious medical issues, including cardiovascular disease, cancer, anorexia, and diabetes, among others. Combine an unhealthy diet with unhealthy environmental conditions, such as smoking, and the potential medical complications increase significantly.

The amount of energy that is needed or ingested per day is measured in calories. The nutritional Calorie (C) is the amount of heat it takes to raise 1 kg (1000 g) of water by 1 °C. This is different from the calorie (c) used in the physical sciences, which is the amount of heat it takes to raise 1 g of water by 1 °C. When we refer to "calorie," we are referring to the nutritional Calorie.

On average, a person needs 1500 to 2000 calories per day to sustain (or carry out) daily activities. The total number of calories needed by one person is dependent on their body mass, age, height, gender, activity level, and the amount of exercise per day. If exercise is regular part of one's day, more calories are required. As a rule, people underestimate the number of calories ingested and overestimate the amount they burn through exercise. This can lead to ingestion of too many calories per day. The accumulation of an extra 3500 calories adds one pound of weight. If an excess of 200 calories per day is ingested, one extra pound of body weight will be gained every 18 days. At that rate, an extra 20 pounds can be gained over the course of a year. Of course, this increase in calories could be offset by increased exercise. Running or jogging one mile burns almost 100 calories.

The type of food ingested also affects the body's metabolic rate. Processing of carbohydrates requires less energy than processing of proteins. In fact, the breakdown of carbohydrates requires the least amount of energy, whereas the processing of proteins demands the most energy. In general, the amount of calories ingested and the amount of calories burned determines the overall weight. To lose weight, the number of calories burned per day must exceed the number ingested. Calories are in almost everything you ingest, so when considering calorie intake, beverages must also be considered.

To help provide guidelines regarding the types and quantities of food that should be eaten every day, the USDA has updated their food guidelines from MyPyramid to MyPlate. They have put the recommended elements of a healthy meal into the context of a place setting of food. MyPlate categorizes food into the standard six food groups: fruits, vegetables, grains, protein foods, dairy, and oils. The accompanying website gives clear recommendations regarding quantity and type of each food that you should consume each day, as well as identifying which foods belong in each category. The accompanying graphic (Figure $4.7.1$) gives a clear visual with general recommendations for a healthy and balanced meal. The guidelines recommend to "Make half your plate fruits and vegetables." The other half is grains and protein, with a slightly higher quantity of grains than protein. Dairy products are represented by a drink, but the quantity can be applied to other dairy products as well.

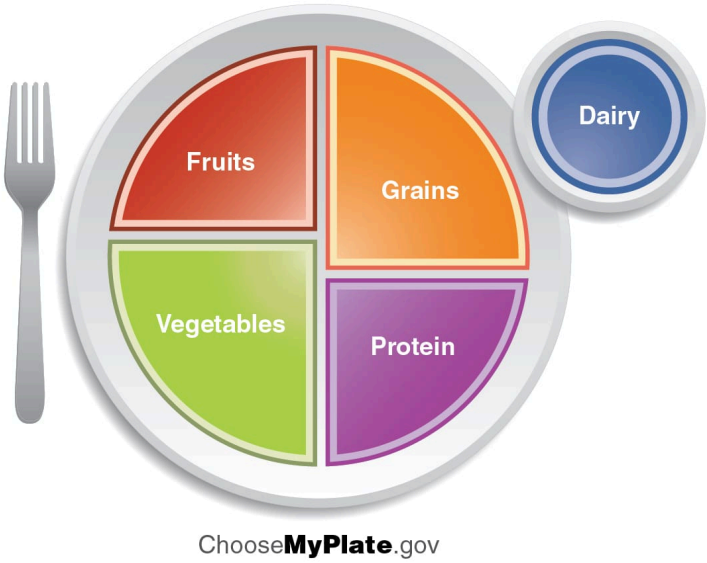


Figure 4.7.1: The U.S. Department of Agriculture developed food guidelines called MyPlate to help demonstrate how to maintain a healthy lifestyle. (CC BY 4.0; via Nutrition and Diet). Detailed text description of the Figure 4.7.1.

Everyday Connection

Metabolism and Obesity

Obesity in the United States is epidemic. The rate of obesity has been steadily rising since the 1980s. In the 1990s, most states reported that less than 10 percent of their populations was obese, and the state with the highest rate reported that only 15 percent of their population was considered obese. By 2010, the U.S. Centers for Disease Control and Prevention reported that nearly 36 percent of adults over 20 years old were obese and an additional 33 percent were overweight, leaving only about 30 percent of the population at a healthy weight. These studies find the highest levels of obesity are concentrated in the southern states. They also find the level of childhood obesity is rising.

Obesity is defined by the body mass index (BMI), which is a measure of a person's weight in kilograms divided by height in meters squared. The normal, or healthy, BMI range is between 18 and 24.9 kg/m^2. Overweight is defined as a BMI of 25 to 29.9 kg/m^2, and obesity is considered to be a BMI greater than 30 kg/m^2. Obesity can arise from a number of factors, including overeating, poor diet, sedentary lifestyle, limited sleep, genetic factors, and even diseases or drugs. Severe obesity (morbid obesity) or long-term obesity can result in serious medical conditions, including coronary heart disease; type 2 diabetes; endometrial, breast, or colon cancer; hypertension (high blood pressure); dyslipidemia (high cholesterol or elevated triglycerides); stroke; liver disease; gall bladder disease; sleep apnea or respiratory diseases; osteoarthritis; and infertility. Research has shown that losing weight can help reduce or reverse the complications associated with these conditions.

To support these dietary recommendations, the U.S. Department of Agriculture provides online resources at ChooseMyPlate.gov, where you can find practical guidance for building a healthy eating pattern and maintaining an active lifestyle. The site includes tools for meal planning, tips for managing body weight, and recommendations for physical activity. It also offers interactive features, such as the SuperTracker, which allows individuals to evaluate and monitor their food choices and physical activity habits

Vitamins

Vitamins are organic compounds found in foods and are a necessary part of the biochemical reactions in the body. They are involved in a number of processes, including mineral and bone metabolism, and cell and tissue growth, and they act as cofactors for energy metabolism. The B vitamins play the largest role of any vitamins in metabolism (Table 4.7.1 and Table 4.7.2).

You get most of your vitamins through your diet, although some can be formed from the precursors absorbed during digestion.

For example, the body synthesizes vitamin A from the β-carotene in orange vegetables like carrots and sweet potatoes. Vitamins are either fat-soluble or water-soluble. Fat-soluble vitamins A, D, E, and K, are absorbed through the intestinal tract with lipids in chylomicrons. Vitamin D is also synthesized in the skin through exposure to sunlight. Because they are carried in lipids, fat-soluble vitamins can accumulate in the lipids stored in the body. If excess vitamins are retained in the lipid stores in the body, hypervitaminosis can result.

Water-soluble vitamins, including the eight B vitamins and vitamin C, are absorbed with water in the gastrointestinal tract. These vitamins move easily through bodily fluids, which are water based, so they are not stored in the body. Excess water-soluble vitamins are excreted in the urine. Therefore, hypervitaminosis of water-soluble vitamins rarely occurs, except with an excess of vitamin supplements.

Table 4.7.1: Fat-soluble Vitamins

Vitamin and alternative name	Sources	Recommended daily allowance	Function	Problems associated with deficiency
A retinal or β-carotene	Yellow and orange fruits and vegetables, dark green leafy vegetables, eggs, milk, liver	700–900 μg	Eye and bone development, immune function	Night blindness, epithelial changes, immune system deficiency
D cholecalciferol	Dairy products, egg yolks; also synthesized in the skin from exposure to sunlight	5–15 μg	Aids in calcium absorption, promoting bone growth	Rickets, bone pain, muscle weakness, increased risk of death from cardiovascular disease, cognitive impairment, asthma in children, cancer
E tocopherols	Seeds, nuts, vegetable oils, avocados, wheat germ	15 mg	Antioxidant	Anemia
K phylloquinone	Dark green leafy vegetables, broccoli, Brussels sprouts, cabbage	90–120 μg	Blood clotting, bone health	Hemorrhagic disease of newborn in infants; uncommon in adults

Table 4.7.2: Water-soluble Vitamins

Vitamin and alternative name	Sources	Recommended daily allowance	Function	Problems associated with deficiency
B_1 thiamine	Whole grains, enriched bread and cereals, milk, meat	1.1–1.2 mg	Carbohydrate metabolism	Beriberi, Wernicke-Korsakoff syndrome
B_2 riboflavin	Brewer's yeast, almonds, milk, organ meats, legumes, enriched breads and cereals, broccoli, asparagus	1.1–1.3 mg	Synthesis of FAD for metabolism, production of red blood cells	Fatigue, slowed growth, digestive problems, light sensitivity, epithelial problems like cracks in the corners of the mouth
B_3 niacin	Meat, fish, poultry, enriched breads and cereals, peanuts	14–16 mg	Synthesis of NAD, nerve function, cholesterol production	Cracked, scaly skin; dementia; diarrhea; also known as pellagra
B_5 pantothenic acid	Meat, poultry, potatoes, oats, enriched breads and cereals, tomatoes	5 mg	Synthesis of coenzyme A in fatty acid metabolism	Rare: symptoms may include fatigue, insomnia, depression, irritability
B_6 pyridoxine	Potatoes, bananas, beans, seeds, nuts, meat, poultry, fish, eggs, dark green leafy vegetables, soy, organ meats	1.3–1.5 mg	Sodium and potassium balance, red blood cell synthesis, protein metabolism	Confusion, irritability, depression, mouth and tongue sores

Vitamin and alternative name	Sources	Recommended daily allowance	Function	Problems associated with deficiency
B_7 biotin	Liver, fruits, meats	30 μg	Cell growth, metabolism of fatty acids, production of blood cells	Rare in developed countries; symptoms include dermatitis, hair loss, loss of muscular coordination
B_9 folic acid	Liver, legumes, dark green leafy vegetables, enriched breads and cereals, citrus fruits	400 μg	DNA/protein synthesis	Poor growth, gingivitis, appetite loss, shortness of breath, gastrointestinal problems, mental deficits
B_{12} cyanocobalamin	Fish, meat, poultry, dairy products, eggs	2.4 μg	Fatty acid oxidation, nerve cell function, red blood cell production	Pernicious anemia, leading to nerve cell damage
C ascorbic acid	Citrus fruits, red berries, peppers, tomatoes, broccoli, dark green leafy vegetables	75–90 mg	Necessary to produce collagen for formation of connective tissue and teeth, and for wound healing	Dry hair, gingivitis, bleeding gums, dry and scaly skin, slow wound healing, easy bruising, compromised immunity; can lead to scurvy

Minerals

Minerals in food are inorganic compounds that work with other nutrients to ensure the body functions properly. Minerals cannot be made in the body; they come from the diet. The amount of minerals in the body is small—only 4 percent of the total body mass—and most of that consists of the minerals that the body requires in moderate quantities: potassium, sodium, calcium, phosphorus, magnesium, and chloride.

The most common minerals in the body are calcium and phosphorous, both of which are stored in the skeleton and necessary for the hardening of bones. Most minerals are ionized, and their ionic forms are used in physiological processes throughout the body. Sodium and chloride ions are electrolytes in the blood and extracellular tissues, and iron ions are critical to the formation of hemoglobin. There are additional trace minerals that are still important to the body's functions, but their required quantities are much lower.

Like vitamins, minerals can be consumed in toxic quantities (although it is rare). A healthy diet includes most of the minerals your body requires, so supplements and processed foods can add potentially toxic levels of minerals. Table 4.7.3 and Table 4.7.4 provide a summary of minerals and their function in the body.

Table 4.7.3: Major Minerals

Mineral	Sources	Recommended daily allowance	Function	Problems associated with deficiency
Potassium	Meats, some fish, fruits, vegetables, legumes, dairy products	4700 mg	Nerve and muscle function; acts as an electrolyte	Hypokalemia: weakness, fatigue, muscle cramping, gastrointestinal problems, cardiac problems
Sodium	Table salt, milk, beets, celery, processed foods	2300 mg	Blood pressure, blood volume, muscle and nerve function	Rare
Calcium	Dairy products, dark green leafy vegetables, blackstrap molasses, nuts, brewer's yeast, some fish	1000 mg	Bone structure and health; nerve and muscle functions, especially cardiac function	Slow growth, weak and brittle bones
Phosphorous	Meat, milk	700 mg	Bone formation, metabolism, ATP production	Rare

Mineral	Sources	Recommended daily allowance	Function	Problems associated with deficiency
Magnesium	Whole grains, nuts, leafy green vegetables	310–420 mg	Enzyme activation, production of energy, regulation of other nutrients	Agitation, anxiety, sleep problems, nausea and vomiting, abnormal heart rhythms, low blood pressure, muscular problems
Chloride	Most foods, salt, vegetables, especially seaweed, tomatoes, lettuce, celery, olives	2300 mg	Balance of body fluids, digestion	Loss of appetite, muscle cramps

Table 4.7.4: Trace Minerals

Mineral	Sources	Recommended daily allowance	Function	Problems associated with deficiency
Iron	Meat, poultry, fish, shellfish, legumes, nuts, seeds, whole grains, dark leafy green vegetables	8–18 mg	Transport of oxygen in blood, production of ATP	Anemia, weakness, fatigue
Zinc	Meat, fish, poultry, cheese, shellfish	8–11 mg	Immunity, reproduction, growth, blood clotting, insulin and thyroid function	Loss of appetite, poor growth, weight loss, skin problems, hair loss, vision problems, lack of taste or smell
Copper	Seafood, organ meats, nuts, legumes, chocolate, enriched breads and cereals, some fruits and vegetables	900 μg	Red blood cell production, nerve and immune system function, collagen formation, acts as an antioxidant	Anemia, low body temperature, bone fractures, low white blood cell concentration, irregular heartbeat, thyroid problems
Iodine	Fish, shellfish, garlic, lima beans, sesame seeds, soybeans, dark leafy green vegetables	150 μg	Thyroid function	Hypothyroidism: fatigue, weight gain, dry skin, temperature sensitivity
Sulfur	Eggs, meat, poultry, fish, legumes	None	Component of amino acids	Protein deficiency
Fluoride	Fluoridated water	3–4 mg	Maintenance of bone and tooth structure	Increased cavities, weak bones and teeth
Manganese	Nuts, seeds, whole grains, legumes	1.8–2.3 mg	Formation of connective tissue and bones, blood clotting, sex hormone development, metabolism, brain and nerve function	Infertility, bone malformation, weakness, seizures
Cobalt	Fish, nuts, leafy green vegetables, whole grains	None	Component of B_{12}	None
Selenium	Brewer's yeast, wheat germ, liver, butter, fish, shellfish, whole grains	55 μg	Antioxidant, thyroid function, immune system function	Muscle pain
Chromium	Whole grains, lean meats, cheese, black pepper, thyme, brewer's yeast	25–35 μg	Insulin function	High blood sugar, triglyceride, and cholesterol levels

Mineral	Sources	Recommended daily allowance	Function	Problems associated with deficiency
Molybdenum	Legumes, whole grains, nuts	45 μg	Cofactor for enzymes	Rare

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4.8: Terms and Definitions

Key Terms

Select to View Definition

Absorptive state
also called the fed state; the metabolic state occurring during the first few hours after ingesting food in which the body is digesting food and absorbing the nutrients

Acetyl coenzyme A (acetyl CoA)
starting molecule of the Krebs cycle

Anabolic hormones
hormones that stimulate the synthesis of new, larger molecules

Anabolic reactions
reactions that build smaller molecules into larger molecules

ATP synthase
protein pore complex that creates ATP

Basal metabolic rate (BMR)
amount of energy expended by the body at rest

Beta (β)-hydroxybutyrate
primary ketone body produced in the body

Beta (β)-oxidation
fatty acid oxidation

Bile salts
salts that are released from the liver in response to lipid ingestion and surround the insoluble triglycerides to aid in their conversion to monoglycerides and free fatty acids

Biosynthesis reactions
reactions that create new molecules, also called anabolic reactions

Body mass index (BMI)
relative amount of body weight compared to the overall height; a BMI ranging from 18–24.9 is considered normal weight, 25–29.9 is considered overweight, and greater than 30 is considered obese

Calorie
amount of heat it takes to raise 1 kg (1000 g) of water by 1 °C

Catabolic hormones
hormones that stimulate the breakdown of larger molecules

Catabolic reactions
reactions that break down larger molecules into their constituent parts

Cellular respiration
production of ATP from glucose oxidation via glycolysis, the Krebs cycle, and oxidative phosphorylation

Cholecystokinin (CCK)
hormone that stimulates the release of pancreatic lipase and the contraction of the gallbladder to release bile salts

Chylomicrons
vesicles containing cholesterol and triglycerides that transport lipids out of the intestinal cells and into the lymphatic and circulatory systems

Chymotrypsin
pancreatic enzyme that digests protein

Chymotrypsinogen
proenzyme that is activated by trypsin into chymotrypsin

Citric acid cycle
also called the Krebs cycle or the tricarboxylic acid cycle; converts pyruvate into CO_2 and high-energy $FADH_2$, NADH, and ATP molecules

Conduction
transfer of heat through physical contact

Convection
transfer of heat between the skin and air or water

Elastase
pancreatic enzyme that digests protein

Electron transport chain (ETC)
ATP production pathway in which electrons are passed through a series of oxidation-reduction reactions that forms water and produces a proton gradient

Energy-consuming phase
first phase of glycolysis, in which two molecules of ATP are necessary to start the reaction

Energy-yielding phase
second phase of glycolysis, during which energy is produced

Enterokinase
enzyme located in the wall of the small intestine that activates trypsin

Evaporation
transfer of heat that occurs when water changes from a liquid to a gas

$FADH_2$
high-energy molecule needed for glycolysis

Fatty acid oxidation
breakdown of fatty acids into smaller chain fatty acids and acetyl CoA

Flavin adenine dinucleotide (FAD)
coenzyme used to produce $FADH_2$

Glucokinase
cellular enzyme, found in the liver, which converts glucose into glucose-6-phosphate upon uptake into the cell

Gluconeogenesis
process of glucose synthesis from pyruvate or other molecules

Glucose-6-phosphate
phosphorylated glucose produced in the first step of glycolysis

Glycogen
form that glucose assumes when it is stored

Glycolysis
series of metabolic reactions that breaks down glucose into pyruvate and produces ATP

Hexokinase
cellular enzyme, found in most tissues, that converts glucose into glucose-6-phosphate upon uptake into the cell

Hydroxymethylglutaryl CoA (HMG CoA)
molecule created in the first step of the creation of ketone bodies from acetyl CoA

Inactive proenzymes
forms in which proteases are stored and released to prevent the inappropriate digestion of the native proteins of the stomach, pancreas, and small intestine

Insulin
hormone secreted by the pancreas that stimulates the uptake of glucose into the cells

Ketone bodies
alternative source of energy when glucose is limited, created when too much acetyl CoA is created during fatty acid oxidation

Krebs cycle
also called the citric acid cycle or the tricarboxylic acid cycle, converts pyruvate into CO_2 and high-energy $FADH_2$, NADH, and ATP molecules

Lipogenesis
synthesis of lipids that occurs in the liver or adipose tissues

Lipolysis
breakdown of triglycerides into glycerol and fatty acids

Metabolic rate
amount of energy consumed minus the amount of energy expended by the body

Metabolism
sum of all catabolic and anabolic reactions that take place in the body

Minerals
inorganic compounds required by the body to ensure proper function of the body

Monoglyceride molecules
lipid consisting of a single fatty acid chain attached to a glycerol backbone

Monosaccharide
smallest, monomeric sugar molecule

NADH
high-energy molecule needed for glycolysis

Nicotinamide adenine dinucleotide (NAD)
coenzyme used to produce NADH

Oxidation
loss of an electron

Oxidation-reduction reaction
(also, redox reaction) pair of reactions in which an electron is passed from one molecule to another, oxidizing one and reducing the other

Oxidative phosphorylation
process that converts high-energy NADH and $FADH_2$ into ATP

Pancreatic lipases
enzymes released from the pancreas that digest lipids in the diet

Pepsin
enzyme that begins to break down proteins in the stomach

Polysaccharides
complex carbohydrates made up of many monosaccharides

Postabsorptive state
also called the fasting state; the metabolic state occurring after digestion when food is no longer the body's source of energy and it must rely on stored glycogen

Proteolysis
process of breaking proteins into smaller peptides

Pyruvate
three-carbon end product of glycolysis and starting material that is converted into acetyl CoA that enters the Krebs cycle

Radiation
transfer of heat via infrared waves

Reduction
gaining of an electron

Salivary amylase
digestive enzyme that is found in the saliva and begins the digestion of carbohydrates in the mouth

Secretin
hormone released in the small intestine to aid in digestion

Sodium bicarbonate
anion released into the small intestine to neutralize the pH of the food from the stomach

Terminal electron acceptor
oxygen, the recipient of the free hydrogen at the end of the electron transport chain

Thermoneutral
external temperature at which the body does not expend any energy for thermoregulation, about 84 °F

Thermoregulation
process of regulating the temperature of the body

Transamination
transfer of an amine group from one molecule to another as a way to turn nitrogen waste into ammonia so that it can enter the urea cycle

Tricarboxylic acid cycle (TCA)
also called the Krebs cycle or the citric acid cycle; converts pyruvate into CO_2 and high-energy $FADH_2$, NADH, and ATP molecules

Triglycerides
lipids, or fats, consisting of three fatty acid chains attached to a glycerol backbone

Trypsin
pancreatic enzyme that activates chymotrypsin and digests protein

Trypsinogen
proenzyme form of trypsin

Urea cycle
process that converts potentially toxic nitrogen waste into urea that can be eliminated through the kidneys

Vitamins

organic compounds required by the body to perform biochemical reactions like metabolism and bone, cell, and tissue growth

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4.9: Chapter Review Questions

Multiple Choice Section

- Use the end-of-chapter multiple-choice section as a regular self-check tool, not just before exams.
- Read each item carefully, think about what is really being tested (concept, definition, application, or calculation), and choose the option (A, B, C, or D) that best reflects what you have learned in this chapter.
  - After you read through the chapter, attempt all items without looking at your notes; then return to the chapter to review any you missed or felt unsure about.
  - Afterward, explain to yourself why the correct option is right and why the others are not. Finally, repeat the multiple-choice section a few days later to see what you truly remember and understand.

1. A 22-year-old athlete drinks a carbohydrate-rich sports drink after a long run. Complex carbohydrates in the drink are broken down into monosaccharides before absorption. A monosaccharide is formed from a polysaccharide in what kind of reaction?
   A. Oxidation–reduction reaction
   B. Anabolic reaction
   C. Catabolic reaction
   D. Biosynthetic reaction

2. A 35-year-old office worker begins a high-calorie diet and stops exercising. Over several months, his body synthesizes more fat and glycogen than it breaks down. If anabolic reactions exceed catabolic reactions, the most likely result will be:
   A. Weight loss
   B. Weight gain
   C. A fixed metabolic rate change without weight change
   D. Immediate development of disease

3. During cellular respiration, the coenzyme NAD accepts high-energy electrons and a proton to become NADH. When NAD becomes NADH, the coenzyme has been:
   A. Reduced
   B. Oxidized
   C. Metabolized
   D. Hydrolyzed

4. A cell is actively building new proteins and storing energy-rich molecules. Anabolic reactions in this cell use energy primarily by:
   A. Converting ADP into ATP
   B. Removing a phosphate group from ATP
   C. Producing heat directly
   D. Breaking down molecules into smaller parts

5. A biochemistry student is tracing glucose metabolism. Glycolysis results in the production of two _____ molecules from a single molecule of glucose. In the absence of sufficient _____, the end product of glycolysis is _____.
   A. Acetyl CoA; pyruvate; lactate
   B. ATP; carbon; pyruvate
   C. Pyruvate; oxygen; lactate
   D. Pyruvate; carbon; acetyl CoA

6. In the mitochondria, a two-carbon molecule derived from pyruvate enters a cyclic series of reactions. The Krebs cycle converts _____ through these reactions. In the process, ATP, _____, and _____ are produced.
   A. Acetyl CoA; FAD; NAD
   B. Acetyl CoA; $FADH_2$; NADH
   C. Pyruvate; NAD; $FADH_2$
   D. Pyruvate; oxygen; oxaloacetate

7. A patient's muscle cells are analyzed to determine how they generate ATP during prolonged aerobic exercise. Which pathway of cellular respiration produces the greatest number of ATP molecules per molecule of glucose?
   A. Lactic acid fermentation
   B. The Krebs cycle
   C. The electron transport chain
   D. Glycolysis

8. A medical student summarizes aerobic cellular respiration as "glucose plus oxygen yields energy and waste products." Aerobic cellular respiration ultimately results in the production of large amounts of ATP and which other primary product?
   A. NADH
   B. $FADH_2$
   C. Glucose
   D. H_2O

9. In oxidative phosphorylation, NAD⁺ accepts electrons and is converted to NADH. When NAD⁺ becomes NADH, the coenzyme has been:
   A. Reduced
   B. Oxidized
   C. Metabolized
   D. Hydrolyzed

10. A dietician counsels a patient about dietary fats. Lipids in the diet can be:
    A. Broken down to provide energy for the body
    B. Stored as triglycerides for later use
    C. Converted into acetyl CoA for entry into metabolic pathways
    D. All of the above

11. After a fatty meal, bile is released into the small intestine from the gallbladder. The gallbladder provides substances that allow lipids to form tiny droplets and cross the intestinal membrane. The gallbladder provides _____ that aid in the transport and absorption of lipids.
    A. Lipases
    B. Cholesterol
    C. Proteins
    D. Bile salts

12. A patient with hyperlipidemia is told that triglycerides absorbed from the intestine travel in large lipoprotein particles called chylomicrons. Triglycerides are transported by chylomicrons primarily because:
    A. They cannot move easily in the blood because they are fat-based and blood is water-based
    B. They are too small to move by themselves
    C. Chylomicrons contain enzymes they need for anabolism
    D. They cannot fit across the intestinal membrane

13. A nutrition scientist compares ATP yield from different fuels. Which of the following provides the greatest ATP yield per molecule when completely oxidized?
    A. Carbohydrates (e.g., glucose)
    B. $FADH_2$
    C. Triglycerides
    D. NADH

14. A two-carbon molecule derived from carbohydrates, fats, or proteins is required for entry into the Krebs cycle. Which molecules can directly enter the Krebs cycle by combining with oxaloacetate?
    A. Chylomicrons
    B. Acetyl CoA
    C. Monoglycerides
    D. Ketone bodies

15. A metabolic report shows that a patient has excess acetyl CoA. It can be diverted into multiple pathways. Acetyl CoA can be converted to all of the following except:
    A. Ketone bodies

B. Fatty acids
C. Polysaccharides
D. Triglycerides

16. A patient begins taking a medication that decreases stomach acid production. The physician warns that this could impair initial protein digestion. Digestion of proteins normally begins in the _____, where _____ and _____ mix with food to break proteins into _____.
A. Stomach; amylase; HCl; amino acids
B. Mouth; pepsin; HCl; fatty acids
C. Stomach; lipase; HCl; amino acids
D. Stomach; pepsin; HCl; amino acids

17. A bodybuilder meets with a nutritionist to plan a high-protein diet. Amino acids from dietary proteins are primarily needed to:
A. Build new proteins in the body
B. Serve as the main fat stores
C. Supply preferred energy for all cells at rest
D. Directly create red blood cells only

18. A person consumes more protein than needed for tissue repair and growth. The excess amino acids are not stored as proteins. If an amino acid is not used to create new proteins, it can be:
A. Converted to acetyl CoA
B. Converted to glucose or ketone bodies
C. Converted directly to nitrogen gas
D. Stored as free amino acids for long-term use

19. Shortly after a carbohydrate-rich meal, a healthy adult has rising blood glucose. During this absorptive state, glucose levels are _____, insulin levels are _____, and glucagon levels are relatively _____.
A. High; low; unchanged
B. Low; low; unchanged
C. High; high; high
D. High; high; low

20. A patient has not eaten for 3–4 days due to illness. Starvation has begun, and blood glucose is falling. Which pair of hormones changes most directly in response to these low glucose levels to help maintain energy supply?
A. Glucagon and insulin
B. Ketones and glucagon
C. Insulin, glucose, and glucagon together
D. Insulin and ketones

21. A person skips meals all day and relies on stored energy to maintain blood glucose. The postabsorptive state relies mainly on stores of _____ in the _____.
A. Insulin; pancreas
B. Glucagon; pancreas
C. Glycogen; liver
D. Glucose; liver

22. A nurse is educating a patient about body temperature regulation. The body's core temperature is regulated by the _____, and in a healthy adult this temperature is normally kept between _____.
A. Pituitary; 36.5–37.5 °C
B. Hypothalamus; 97.7–99.5 °F
C. Hypothalamus; 36.5–37.5 °F
D. Pituitary; 97.7–99.5 °F

23. A 6-year-old child develops a fever during a viral infection and experiences chills and later sweats as the fever resolves. In addition to chills and fever, which mechanisms help the body regulate temperature back toward normal?
A. Shivering only
B. Sweating only
C. Erection of hairs on the arms and legs only

D. All of the above

24. After sitting for a long lecture, a student stands up and notices the seat of the chair is warm. The heat has been transferred from the student's body to the chair mainly via:
A. Conduction
B. Convection
C. Radiation
D. Evaporation

25. A child with poor night vision and dry eyes is found to have a diet very low in leafy vegetables and orange-colored fruits. A deficiency in vitamin A can result in:
A. Improper bone development only
B. Scurvy primarily
C. Improper eye development or impaired vision
D. All of the above

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4.10: Applied Thinking Self - Assessment

Challenge Yourself

- Extended response questions are assessment items that require students to construct written answers of substantial length - typically several sentences to multiple paragraphs - rather than selecting from predefined options. They represent a form of constructed response assessment designed to measure complex, higher-order thinking skills.
- First, try answering without using your notes. Then review reliable resources and revise your response if needed. Make a note of any areas where you felt unsure and revisit those topics.

Writing Guidelines

- Answer each question in your own words.
- Write 4–8 clear, complete sentences per question, organized into short paragraphs (not bullet points).
- Focus on explaining your reasoning, not just stating the answer.
- Use correct scientific vocabulary, and briefly define terms when needed.
- For questions that ask you to compare, contrast, or explain why/how:
  - Clearly state similarities or differences
  - Support your ideas with a brief explanation or example

From Digestion to ATP: Fate of a Glucose Molecule

1. Trace the path of a single glucose molecule from digestion in the GI tract to ATP production in a cell under aerobic conditions.
2. Identify where major oxidation–reduction (redox) reactions occur (glycolysis, pyruvate oxidation, citric acid cycle, electron transport chain).
3. Explain how NADH and $FADH_2$ are generated and how they contribute to ATP synthesis.
4. Explain why the presence of oxygen dramatically increases ATP yield compared with anaerobic glycolysis alone.

Insulin and Glucose Uptake: Maintaining a Concentration Gradient

1. Insulin is released when food is ingested and stimulates the uptake of glucose into cells.
2. Describe the mechanisms cells use to maintain a concentration gradient that allows continuous glucose uptake from the bloodstream (include glucose transporters, phosphorylation of glucose inside the cell, and how this prevents back-diffusion).

Conversion of Carbohydrates to Fat

1. Discuss how excess dietary carbohydrates can be converted into and stored as fat.
   a. Include the major metabolic pathways (e.g., glycolysis, acetyl-CoA formation, fatty acid and triglyceride synthesis) and where they occur in the body.

Diabetes and “Alcohol-Smelling” Breath

1. A person with diabetes has breath that smells like alcohol or nail polish remover.
   a. Explain what this odor most likely indicates, the underlying metabolic changes, and why this situation can be dangerous.

Protection Against Self-Digestion by Pancreatic Enzymes

1. Trypsin and chymotrypsin, if released in their active forms, could digest pancreatic or intestinal tissues. Describe the mechanisms the body uses to prevent self-digestion (include zymogen secretion, activating enzymes, and inhibitors, and where activation occurs).

Type II Diabetes and "Starving in a Sea of Plenty"

1. In type II diabetes, insulin is produced but is ineffective at stimulating normal glucose uptake.
   a. Explain why patients are described as "starving in a sea of plenty," even though their blood glucose levels are high.
   b. Describe how impaired cellular glucose uptake leads to malnutrition at the cellular and tissue level.

Synthesis of Ketone Bodies

1. Ketone bodies can be used as an alternative fuel during fasting or starvation.
   a. Describe where and how ketone bodies are synthesized, including the role of fatty acid oxidation and acetyl-CoA.
   b. Briefly explain how ketones are used by other tissues.

Shivering, Non-Shivering Thermogenesis, and Metabolism

1. On a cold day, a lightly dressed person begins to shiver.
   a. Explain how shivering and non-shivering thermogenesis both increase metabolic rate and energy expenditure.
   b. Discuss the role of the hypothalamus in temperature regulation and the main heat-exchange mechanisms (e.g., radiation, convection, conduction, evaporation).
2. Predict how prolonged exposure to cold might change basal metabolic rate and the types of fuels used.
   a. Explain how vasoconstriction helps increase or preserve core body temperature.

"Non-Fat" Foods and Weight Gain

1. Many "low-fat" or "non-fat" products contain large amounts of added sugar.
   a. Discuss how high sugar intake from these foods can still lead to increased body fat and weight gain.
   b. Include the concepts of energy balance, insulin response, and conversion of excess carbohydrate to fat.

Vitamins and Minerals in Metabolism

1. Choose two vitamins and two minerals that play key roles in metabolic pathways (for example, B-complex vitamins, vitamin C, iron, magnesium, iodine). For each nutrient:
   a. Describe its role as a cofactor, coenzyme, or structural component in metabolism.
   b. Explain how a deficiency would disrupt specific metabolic reactions.
   c. Provide at least one example of clinical symptoms or conditions that might result.

Designing a One-Day Eating Pattern for Metabolic Health

1. Using your understanding of macronutrient metabolism, energy balance, and nutrient quality, design a one-day eating pattern for a sedentary adult aimed at supporting metabolic health and preventing diet-related disease. Include:

   a. Approximate macronutrient distribution (percent of calories from carbohydrates, fats, and proteins).
   b. Example meals and snacks (with a brief description of foods).
   c. Rationale for meal timing (e.g., spacing of meals, handling of evening eating).
   d. Justification for including or limiting certain foods or nutrients (e.g., fiber, added sugars, saturated fats, whole vs. refined grains).
2. Explain how your plan helps prevent or manage conditions such as obesity, type II diabetes, dyslipidemia, and cardiovascular disease.

Glycogen Storage and Mobilization

1. Describe how glycogen is synthesized (glycogenesis) and broken down (glycogenolysis) in liver and muscle.
   a. Explain how these processes help maintain blood glucose and provide energy during exercise.

Basal Metabolic Rate vs. Total Energy Expenditure

1. Define basal metabolic rate (BMR) and total daily energy expenditure (TDEE).
2. Identify the main factors that influence each (e.g., age, sex, body composition, hormones, activity level) and explain how they interact in weight gain or loss.

Metabolic Flexibility

1. Explain the concept of metabolic flexibility (the ability to switch between carbohydrate and fat oxidation).
2. Discuss how diet, physical activity, and insulin sensitivity affect metabolic flexibility and why it is important for long-term health.

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4.11: Alternate Text Descriptions

Figure 4.1.1: Adenosine Triphosphate Cycle

This image shows the ATP–ADP cycle, illustrating how cells store, release, and regenerate energy through a continuous process. At the top is ATP (adenosine triphosphate). ATP is shown as consisting of an adenine group, a ribose sugar, and three phosphate groups linked in a chain. A labeled high-energy bond between phosphate groups identifies the part of the molecule where usable energy is stored.

A curved arrow shows ATP being broken down into ADP (adenosine diphosphate) by losing one phosphate group. The removed phosphate is shown separately. This step is labeled energy released, indicating that breaking the high-energy bond provides energy for cellular work. The diagram notes that this released energy is used in anabolic reactions, which are processes that build larger molecules from smaller ones.

At the bottom, ADP is shown with the same adenine and ribose components but with only two phosphate groups instead of three.

A second curved arrow shows the reverse process, in which a phosphate group is added back to ADP to form ATP again. This step is labeled energy required, showing that energy must be supplied to restore the high-energy phosphate bond. The diagram explains that this energy comes from catabolic reactions, which release energy by breaking down molecules. The circular arrows emphasize that this is a continuous cycle:

- ATP loses a phosphate and releases energy, forming ADP
- ADP gains a phosphate using input energy, forming ATP

A legend identifies the color-coded parts of the molecules, including the adenine group, ribose, and phosphate groups.

Figure 4.1.2: Catabolic and Anabolic Pathways of Nutrient Metabolism

This image presents an integrated overview of metabolism, showing how nutrients from food are either broken down through catabolic reactions or used to build and store molecules through anabolic reactions. The figure uses blue arrows to represent catabolic pathways and green arrows to represent anabolic pathways.

At the top of the diagram, food intake is represented by fruits, vegetables, grains, milk, eggs, and meat. The nutrients from food enter three major macronutrient pathways: proteins, complex carbohydrates, and triglycerides (fats).

Protein Pathway

Proteins are broken down through catabolic reactions into amino acids. The figure also shows a side pathway labeled “Cannibalization of muscle tissue (starvation response)”, indicating that amino acids can be obtained from the breakdown of body proteins during prolonged starvation. Amino acids may be used for energy production or may enter an anabolic pathway labeled protein synthesis, represented by skeletal muscle tissue.

Carbohydrate Pathway

Complex carbohydrates are broken down into glucose. Glucose may be used directly for energy production or may enter an anabolic storage pathway labeled glycogen storage in liver and skeletal muscle. A two-way green arrow connects glucose and glycogen storage, indicating that glycogen can be synthesized from glucose and later broken down to release glucose when needed.

Lipid Pathway

Triglycerides are broken down into glycerol and fatty acids. A side pathway labeled “Breakdown of stored fat (weight loss)” shows that glycerol and fatty acids can also be released from adipose tissue during fat loss. Glycerol and fatty acids may be used for

energy production or may enter an anabolic pathway labeled lipid synthesis and storage, represented by adipose tissue. This pathway shows the storage of excess energy as body fat.

Central Energy Production

At the center of the diagram is energy production, where nutrients from proteins, carbohydrates, and fats converge. The figure shows ADP being converted into ATP by the addition of a phosphate group, illustrating the production of cellular energy. Arrows from amino acids, glucose, and glycerol and fatty acids all point toward this central energy-production pathway, emphasizing that all three macronutrients can serve as fuel for ATP synthesis.

The figure demonstrates the balance between catabolism and anabolism. Catabolic pathways break down proteins, carbohydrates, and fats into smaller molecules that can be used for energy production. Anabolic pathways use those same molecules to build proteins, store glycogen, and synthesize fats. Together, these processes allow the body to obtain energy from food, store excess nutrients, and mobilize stored energy during periods of fasting, starvation, or weight loss.

Figure 4.2.1: Cellular Respiration

This image presents a stepwise overview of cellular respiration, arranged vertically to show four major stages: glycolysis, pyruvate transformation, the Krebs cycle, and oxidative phosphorylation. The figure also labels the cellular location of each stage to show where the reactions occur.

At the top, glycolysis is shown taking place in the cytoplasm. A molecule labeled glucose with six carbons is split into two pyruvate molecules, each with three carbons. This step represents the initial breakdown of glucose and is labeled as producing a small amount of ATP.

The next stage is labeled transformation of pyruvate into acetyl CoA and is shown occurring in the mitochondrial matrix. Each pyruvate molecule is converted into acetyl CoA, and carbon dioxide (CO_2) is released during this process. This step connects glycolysis to the next stage by preparing the carbon molecules for entry into the Krebs cycle.

Below that, the Krebs cycle is shown as a circular pathway, also in the mitochondrial matrix. The circular shape indicates a repeating cycle of reactions. Labels show that carbon dioxide (CO_2) is released here as well, and ATP is produced. This stage represents the continued breakdown of carbon-containing molecules and the generation of energy-rich carriers used in the next stage.

At the bottom, oxidative phosphorylation is shown at the inner mitochondrial membrane. A staircase-like pathway represents a series of electron transfer reactions. Electrons, labeled e-, move step by step through this system. This stage is shown producing the largest amount of ATP in the diagram. A label indicates that electrons removed from glucose, pyruvate, and acetyl CoA ultimately pass through this pathway. At the end of the chain, oxygen, protons (H^+), and electrons combine to form water (H_2O).

A large vertical arrow running through the diagram shows the overall flow of molecules and energy through all four stages. The figure emphasizes:

- the location of each stage in the cell
- the flow of carbon, from glucose to pyruvate to acetyl CoA and then to carbon dioxide
- the progressive production of ATP, with the greatest amount formed during oxidative phosphorylation

Figure 4.2.2: Glycolysis: Energy Investment, Oxidation, and ATP Production

This image is a flowchart illustrating the three major stages of glycolysis, the process by which one glucose molecule is converted into two pyruvate molecules. The diagram is organized into three numbered sections.

Start: One glucose molecule containing six carbon atoms (C6) enters the pathway.

Step 1: Energy-Consuming Phase

A six-carbon glucose molecule undergoes a series of reactions that require an energy investment.

The figure shows:

- 2 ATP consumed
- ATP molecules converted to ADP
- Phosphate groups added to the six-carbon intermediate

Following phosphorylation, the six-carbon molecule is split into two three-carbon molecules (C3), which proceed through parallel pathways for the remainder of glycolysis.

Step 2: Coupling of Phosphorylation with Oxidation

Each three-carbon molecule undergoes oxidation.

The figure shows:

- Exergonic reactions releasing energy
- Electrons transferred to NAD+
- Formation of NADH
- 2 NADH produced in total
- Energy captured from oxidation is used to drive endergonic reactions
- Free phosphate groups added to the three-carbon intermediates

This stage couples the release of energy from oxidation with phosphorylation of the intermediates, storing potential energy in both NADH and phosphorylated molecules.

Step 3: Energy-Releasing Phase

The phosphorylated three-carbon intermediates undergo additional reactions that transfer phosphate groups to ADP.

The figure shows:

- 4 ATP produced
- ADP converted to ATP during multiple substrate-level phosphorylation reactions
- Conversion of the phosphorylated intermediates into final three-carbon products

Each branch of the pathway contributes to ATP generation.

End

The pathway ends with:

- Two pyruvate molecules, each containing three carbon atoms (C3)
- 4 ATP produced
- 2 NADH produced

Because 2 ATP were consumed during Step 1 and 4 ATP were produced during Step 3, glycolysis yields a net gain of 2 ATP per glucose molecule.

The figure demonstrates how glycolysis converts one six-carbon glucose molecule into two three-carbon pyruvate molecules through three sequential stages. Energy is first invested to activate glucose, then captured through oxidation reactions that produce NADH, and finally released through ATP-producing reactions. Glycolysis is the first stage of cellular respiration and provides both ATP and electron carriers that can be used in later metabolic pathways.

Figure 4.2.3: Aerobic and Anaerobic Pathways Following Glycolysis

This image is a flowchart comparing the aerobic and anaerobic fates of glucose after glycolysis. The figure is divided into a shared glycolysis stage followed by two alternative pathways depending on whether oxygen is present.

Start: One glucose molecule containing six carbon atoms (C6) enters the pathway.

Step 1: Energy-Consuming Phase

The first stage of glycolysis is labeled Energy-Consuming Phase.

The figure shows:

- 2 ATPs consumed
- ATP converted to ADP
- Phosphate groups added to the six-carbon glucose molecule

The phosphorylated six-carbon molecule is then split into two three-carbon molecules (C3).

Oxygen Decision Point

The pathway then branches at a decision point labeled:

O2 present?

Two possible pathways follow:

- Yes: Aerobic Conditions
- No: Anaerobic Conditions

Aerobic Conditions

Step 2A: Coupling of Phosphorylation with Oxidation

The two three-carbon molecules undergo oxidation reactions.

The figure shows:

- 2 NADH produced
- NAD+ accepting electrons and becoming NADH
- Energy released by exergonic reactions
- Free phosphate added to the intermediates

Step 3A: Energy-Releasing Phase

The phosphorylated intermediates generate ATP through substrate-level phosphorylation.

The figure shows:

- 4 ATPs produced
- ADP converted to ATP

At the end of glycolysis, two pyruvate molecules (C3) are produced.

Transformation of Pyruvate into Acetyl CoA

Under aerobic conditions, pyruvate enters a pathway labeled:

Transformation of pyruvate into acetyl CoA

Acetyl-CoA is formed and carbon dioxide (CO_2) is released.

Krebs Cycle

Acetyl-CoA enters the Krebs cycle, shown as a circular pathway.

The figure shows:

- Release of CO_2
- Production of ATP
- Generation of electron carriers that continue to the next stage

Electron Transport Chain

The lower portion of the aerobic pathway shows the electron transport chain.

The figure states:

NADH shuttles electrons to electron transport chain. Oxygen is final electron acceptor.

Electrons move through a series of reactions that produce ATP.

At the end of the chain:

- Oxygen (O_2) accepts electrons
- Water (H_2O) is formed
- About 36 ATPs are produced per glucose molecule

Anaerobic Conditions

Step 2B: Coupling of Phosphorylation with Oxidation

The anaerobic pathway undergoes the same glycolytic oxidation stage.

The figure shows:

- 2 NADH produced
- NAD+ converted to NADH
- Energy released and coupled to phosphorylation reactions

Step 3B: Energy-Releasing Phase

The glycolytic ATP-producing reactions proceed as in the aerobic pathway.

The figure shows:

- 4 ATPs produced
- Formation of two pyruvate molecules

Lactate Formation

Without oxygen, pyruvate is converted into lactate.

The figure includes the reaction:

Pyruvate + NADH + H+ → Lactate + NAD+

A boxed explanation states:

NADH is oxidized by pyruvate, forming lactate. This frees the resulting NAD+ to oxidize another glucose molecule.

This regeneration of NAD+ allows glycolysis to continue in the absence of oxygen.

Under anaerobic conditions, the pathway yields a net of 2 ATPs per glucose molecule.

Functional Overview

The figure demonstrates that glycolysis is the common starting point for both aerobic and anaerobic energy production. In both pathways, glucose is converted to pyruvate through an energy-investment phase, an oxidation phase that produces NADH, and an energy-releasing phase that generates ATP.

When oxygen is available, pyruvate is converted to acetyl-CoA, enters the Krebs cycle, and ultimately fuels the electron transport chain, producing approximately 36 ATP per glucose molecule. When oxygen is absent, pyruvate is converted to lactate, regenerating NAD+ and allowing glycolysis to continue, but yielding only 2 ATP per glucose molecule. The figure emphasizes the substantially greater energy yield of aerobic respiration compared with anaerobic metabolism.

Figure 4.2.4: Anaerobic Respiration

This image is divided into two major sections: the transformation of pyruvate into acetyl CoA at the top and the Krebs cycle, also called the citric acid cycle, at the bottom. Arrows show the sequence of reactions and the movement of carbon atoms, energy carriers, and byproducts.

In the top section, a pyruvate molecule with three carbons is shown as the starting material. First, one carbon is removed and released as carbon dioxide (CO2). This leaves a two-carbon fragment. Next, electrons are transferred to nicotinamide adenine dinucleotide (NAD+), forming NADH. A label indicates that this NADH carries energy to the electron transport chain. Finally, coenzyme A (CoA) is added to the two-carbon fragment, forming acetyl CoA. This step prepares the carbon fragment for entry into the Krebs cycle and captures some energy in the form of NADH.

In the bottom section, the Krebs cycle is shown as a circular pathway. The cycle begins when acetyl CoA, which contains two carbons, combines with oxaloacetate, which contains four carbons, to form citrate, a six-carbon molecule. CoA is released during this step.

Next, citrate is rearranged into isocitrate, which still contains six carbons.

In the following step, isocitrate is converted into alpha-ketoglutarate, which contains five carbons. During this reaction, one carbon dioxide (CO2) is released and NAD+ is reduced to NADH.

Next, alpha-ketoglutarate is converted into succinyl CoA, which contains four carbons. Another CO2 is released, and another NADH is produced.

Succinyl CoA is then converted into succinate. During this step, guanosine triphosphate (GTP) is formed and then converted to ATP, representing direct energy capture by substrate-level phosphorylation.

Next, succinate is converted into fumarate, and flavin adenine dinucleotide (FAD) is reduced to FADH2, another energy-carrying molecule.

Fumarate then reacts with water (H2O) to form malate.

Finally, malate is converted back into oxaloacetate, and another NADH is produced. This regenerates the four-carbon starting molecule so that the cycle can repeat.

Overall, the figure shows that:

- pyruvate is converted into acetyl CoA, releasing CO2 and producing NADH
- acetyl CoA enters the Krebs cycle
- carbon atoms are progressively removed as CO2
- energy is captured in NADH, FADH2, and a small amount of ATP
- oxaloacetate is regenerated, allowing the cycle to continue

The diagram emphasizes the central role of the Krebs cycle in cellular respiration by showing how carbon from pyruvate is fully oxidized and how high-energy electron carriers are generated for later ATP production in the electron transport chain.

Figure 4.2.5: The Electron Transport Chain

This image shows a cross-sectional view of the inner mitochondrial membrane, illustrating how the electron transport chain and ATP synthase work together to produce ATP by using a proton gradient. The figure is organized into three labeled regions: the intermembrane space at the top, the inner mitochondrial membrane in the middle, and the mitochondrial matrix at the bottom.

Embedded in the inner mitochondrial membrane are four major electron transport chain complexes, labeled I, II, III, and IV, along with a separate complex labeled ATP synthase. The diagram distinguishes these structures visually, but their identities are also given by text labels rather than color alone.

At the left side of the chain, NADH donates electrons to Complex I and is converted to NAD+. FADH2 donates electrons to Complex II and is converted to FAD. The electrons then move through the chain from Complex I or II to Complex III and then to Complex IV. A small mobile carrier labeled cytochrome c transfers electrons between complexes.

As electrons move through the chain, Complexes I, III, and IV pump hydrogen ions (H+) from the mitochondrial matrix into the intermembrane space. Arrows show this upward movement across the membrane. This pumping creates a difference in hydrogen ion concentration, with a higher concentration in the intermembrane space and a lower concentration in the matrix. The diagram presents this proton gradient as stored energy.

At Complex IV, electrons combine with oxygen (O2) and hydrogen ions (H+) to form water (H2O). A labeled reaction shows this final step, indicating that oxygen is the final electron acceptor in the chain.

On the right side of the figure, ATP synthase spans the membrane. Hydrogen ions flow back down their concentration gradient through ATP synthase and return to the mitochondrial matrix. This movement powers the conversion of adenosine diphosphate (ADP) and phosphate into ATP.

Overall, the figure shows that:

- electrons from NADH and FADH2 enter the electron transport chain
- their movement powers the pumping of H+ ions across the inner mitochondrial membrane
- this creates a proton gradient
- oxygen accepts electrons at the end of the chain and forms water
- the proton gradient drives ATP synthesis through ATP synthase

The central concept illustrated by the diagram is chemiosmosis: energy from electron transfer is first used to create a proton gradient, and that gradient is then used to generate ATP.

Figure 4.2.6: ATP Yield from the Stages of Cellular Respiration

This image summarizes the major stages of cellular respiration and the ATP and electron-carrier yields associated with each stage. The diagram is organized vertically, beginning with glucose at the top and ending with total ATP production at the bottom.

Glycolysis

The process begins with one glucose molecule (C6). During glycolysis, glucose is broken down into two pyruvate molecules (C3).

The figure shows:

- 4 ATP produced
- 2 ATP used
- Net gain: 2 ATP

The figure also includes a note indicating: Active transport of NADH from cytoplasm into mitochondria: –2 ATP

In addition to ATP production, glycolysis generates: 2 NADH

These electron carriers continue to later stages of cellular respiration.

Transformation of Pyruvate to Acetyl CoA

Each pyruvate molecule undergoes a process labeled:

Transformation of pyruvate to acetyl CoA

During this step:

- Pyruvate is converted into acetyl CoA
- CO2 is released
- 1 NADH per pyruvate is produced

For two pyruvate molecules, the figure shows: 2 NADH

No ATP is produced during this stage.

Krebs Cycle

Acetyl CoA enters the Krebs cycle, illustrated as a circular pathway.

The figure shows:

- 1 ATP × 2 pyruvates = 2 ATP
- 3 NADH × 2 pyruvates = 6 NADH
- 1 FADH2 × 2 pyruvates = 2 FADH2

The figure also shows the release of: CO2

Thus, the Krebs cycle contributes both ATP and large numbers of electron carriers.

Electron Transport Chain

The electron transport chain is represented as a series of ascending redox reactions.

The figure summarizes the total electron carriers entering this stage:

- 10 NADH
- 2 FADH2

The ATP calculations shown are:

- 3 ATP × 10 NADH = 30 ATP

- 2 ATP × 2 FADH2 = 4 ATP

Total from the electron transport chain: 34 ATP

The figure identifies oxygen as the final electron acceptor and shows the reaction: $2H+ + O2 \rightarrow H2O$

Water is therefore produced at the end of the electron transport chain.

Total ATP Produced

A summary box at the bottom of the figure lists:

- Glycolysis = 2 ATP
- NADH transport cost = –2 ATP
- Pyruvate into acetyl CoA = 0 ATP
- Krebs cycle = 2 ATP
- Electron transport chain (ETC) = 34 ATP

The figure concludes with: 36 ATP per glucose

The figure demonstrates how the energy stored in one glucose molecule is captured across multiple stages of cellular respiration. Glycolysis provides a small net ATP gain and produces NADH. The transformation of pyruvate to acetyl CoA and the Krebs cycle generate additional NADH and FADH2. These electron carriers then deliver electrons to the electron transport chain, where most ATP production occurs. The figure emphasizes that the majority of ATP generated during cellular respiration comes from the electron transport chain, while earlier stages primarily generate the molecules that fuel this final ATP-producing process.

Figure 4.2.7: Gluconeogenesis: Synthesis of Glucose from Pyruvate

This image is a vertical flowchart illustrating gluconeogenesis, the metabolic pathway that synthesizes glucose from pyruvate. The diagram is organized into four labeled stages: Gluconeogenesis initiation, Reversed energy-releasing phase, Reversed coupling of phosphorylation with oxidation, and Reversed energy-consuming phase.

Start: The pathway begins with pyruvate. A side label indicates that lactic acid can be converted to pyruvate and enter the pathway.

Step 1: Gluconeogenesis Initiation

The first section is labeled Gluconeogenesis initiation.

Pyruvate is converted to oxaloacetate, which is then converted to phosphoenolpyruvate by the enzyme phosphoenolpyruvate carboxykinase. A notation of ×2 indicates that two pyruvate-derived molecules move through this portion of the pathway because two three-carbon molecules are required to produce one glucose molecule.

Step 2: Reversed Energy-Releasing Phase

The second section is labeled Reversed energy-releasing phase.

The pathway proceeds through a series of three-carbon intermediates:

- Phosphoenolpyruvate
- 2-phosphoglycerate
- 3-phosphoglycerate
- 1,3-bisphosphoglycerate

The ×2 notation continues to indicate that two parallel molecules progress through these reactions. This stage reverses the ATP-producing portion of glycolysis.

Step 3: Reversed Coupling of Phosphorylation with Oxidation

The third section is labeled Reversed coupling of phosphorylation with oxidation.

The intermediate 1,3-bisphosphoglycerate is converted into glyceraldehyde-3-phosphate. The figure again indicates ×2, showing that two glyceraldehyde-3-phosphate molecules are produced.

This stage represents the reversal of the glycolytic reactions that couple oxidation with phosphorylation.

Step 4: Reversed Energy-Consuming Phase

The fourth section is labeled Reversed energy-consuming phase.

Two molecules of glyceraldehyde-3-phosphate are combined and rearranged into larger sugar molecules. The pathway proceeds through:

- Fructose-6-phosphate
- Glucose-6-phosphate
- Glucose

The diagram depicts the molecular structures of these sugar intermediates and shows the assembly of a six-carbon glucose molecule from two three-carbon precursors.

End

The pathway ends with: 1 glucose molecule

The figure illustrates gluconeogenesis as a multistep pathway that largely reverses glycolysis. Starting with pyruvate, including pyruvate derived from lactic acid, the pathway proceeds through four labeled stages and ultimately combines two three-carbon molecules to form one six-carbon glucose molecule. The figure emphasizes the sequential reversal of glycolytic stages and the use of specialized reactions, such as the conversion of pyruvate to oxaloacetate and phosphoenolpyruvate, to bypass irreversible glycolytic steps.

Figure 4.3.1: Structural Comparison of a Triglyceride and a Monoglyceride

This image compares the chemical structures of a **t**riglyceride and a monoglyceride.

(a) Triglyceride

The upper diagram shows a triglyceride molecule. A three-carbon glycerol backbone is oriented vertically on the left side of the structure. Each of the three glycerol carbons is connected through an oxygen-containing ester bond to a separate fatty acid chain.

Three fatty acid chains extend horizontally to the right from the glycerol backbone. Each fatty acid begins with a carbonyl group at the point of attachment and continues as a long hydrocarbon chain composed primarily of carbon and hydrogen atoms.

The triglyceride therefore consists of:

- One glycerol molecule
- Three fatty acid chains
- Three ester linkages connecting the fatty acids to glycerol

The overall shape resembles a central backbone with three long hydrocarbon tails extending outward. This structure represents the primary form in which fats are stored in adipose tissue and serves as a major long-term energy reserve.

(b) Monoglyceride

The lower diagram shows a monoglyceride molecule.

As in the triglyceride, a three-carbon glycerol backbone is positioned vertically on the left side. However, only one fatty acid chain is attached. The fatty acid is connected to the upper carbon of glycerol through an ester bond and extends horizontally to the right.

The remaining two glycerol carbons are not attached to fatty acids. Instead, each is bonded to a hydroxyl group (**OH**).

The monoglyceride therefore consists of:

- One glycerol molecule
- One fatty acid chain
- One ester linkage
- Two remaining hydroxyl groups

Compared with the triglyceride, the monoglyceride has only a single hydrocarbon tail instead of three.

The figure illustrates the structural relationship between triglycerides and monoglycerides. Triglycerides are composed of glycerol plus three fatty acids and function primarily in energy storage. During lipid digestion, enzymes break triglycerides into smaller molecules, including monoglycerides and free fatty acids. Monoglycerides can then participate in lipid absorption within the small intestine before being reassembled into triglycerides for transport and storage.

Figure 4.3.2: Chylomicrons

This image shows a cross-sectional view of a spherical lipoprotein particle, such as a chylomicron or very-low-density lipoprotein (VLDL), with its internal lipids surrounded by an outer surface that allows the particle to travel through the watery environment of the body.

At the center of the particle is a core of triglycerides, shown as many tightly packed lipid molecules. These triglycerides form the hydrophobic interior of the particle and are kept away from the surrounding fluid because they do not dissolve in water.

Surrounding the core is a single outer layer of phospholipids. The phospholipid molecules are arranged so that their hydrophilic heads face outward toward the surrounding fluid and their hydrophobic tails face inward toward the triglyceride core. This outer layer makes the particle compatible with transport in blood and lymph.

Embedded within the phospholipid surface are apolipoproteins, shown as large structures partially inserted into the outer layer and exposed at the surface. These proteins help stabilize the particle, support recognition by cell receptors, and assist with lipid transport and metabolism.

Figure 4.3.3: Breakdown of Fatty Acids

This image shows a multi-step pathway of fatty acid breakdown that converts a fatty acid into acetyl CoA, which can then enter the Krebs cycle to support energy production. The pathway is arranged vertically in numbered sections, with arrows showing the sequence of transport and chemical change.

At the top, the starting molecule is a fatty acid, shown as a long hydrocarbon chain ending in a carboxyl group. This is the molecule that will be processed for energy.

In the first section, the fatty acid is first activated by combining with coenzyme A (CoA) to form fatty acyl CoA. The acyl group is then transferred to carnitine, producing fatty acyl carnitine, while CoA is released. This step prepares the fatty acid for movement across the mitochondrial membranes. A central arrow then shows fatty acyl carnitine entering the mitochondrial matrix, indicating transport into the mitochondrion.

In the second section, once inside the mitochondrion, fatty acyl carnitine reacts with coenzyme A again to regenerate fatty acyl CoA. Carnitine is released and can be reused in transport. This restores the fatty acid to its activated form inside the

mitochondrial matrix, where oxidation can occur.

In the third section, the molecule enters beta-oxidation, shown as a repeating cycle. The fatty acyl CoA undergoes a sequence of reactions that includes:

- an oxidation step that produces flavin adenine dinucleotide in its reduced form (FADH2)
- a hydration step in which water is added
- another oxidation step
- a cleavage step that removes a two-carbon unit as acetyl CoA

After cleavage, the remaining fatty acyl CoA is shortened and re-enters the cycle. This repetition continues until the fatty acid chain has been fully broken down into multiple acetyl CoA molecules. At the bottom, the diagram shows acetyl CoA entering the Krebs cycle, linking fatty acid breakdown directly to cellular respiration and ATP production.

Figure 4.3.4: Ketogenesis Excess

This image shows a stepwise biochemical pathway of ketogenesis, in which acetyl CoA molecules are combined and converted into the ketone bodies acetoacetate and beta-hydroxybutyrate. Arrows show the sequence of reactions from left to right.

At the far left, the pathway begins with two acetyl CoA molecules. Each acetyl CoA contains a two-carbon acetyl group attached to coenzyme A (CoA). The diagram shows these two molecules converging, indicating that they combine to begin ketone body synthesis.

The first product formed is acetoacetyl CoA, a four-carbon molecule created by joining the two acetyl units. This molecule still retains a CoA group. This step begins the construction of a larger carbon skeleton from smaller acetyl CoA molecules.

Next, the pathway proceeds to beta-hydroxy-beta-methylglutaryl CoA (HMG CoA). This is a larger intermediate with additional functional groups, including hydroxyl and carbonyl groups. HMG CoA is shown as a key branching intermediate in the pathway and is an important compound in ketone body synthesis.

From HMG CoA, the pathway continues to acetoacetate. In this step, CoA is removed, leaving a free four-carbon ketone body. The structure of acetoacetate includes both a ketone group and a carboxyl group. This molecule is one of the main ketone bodies produced in the liver.

In the final step, acetoacetate is converted into beta-hydroxybutyrate. The diagram shows the addition of hydrogen, indicating a reduction reaction in which the ketone group is converted into a hydroxyl group. Beta-hydroxybutyrate is another major ketone body that circulates in the blood and can be used by other tissues as an energy source.

Figure 4.3.5: Ketone Oxidation

This image shows the stepwise oxidation of the ketone body beta-hydroxybutyrate into acetyl CoA, which then enters the Krebs cycle to support energy production. The pathway progresses from left to right, with arrows indicating the sequence of reactions.

At the far left, the starting molecule is beta-hydroxybutyrate. In the first reaction, nicotinamide adenine dinucleotide (NAD+) is reduced to NADH, indicating that beta-hydroxybutyrate is being oxidized. This reaction converts beta-hydroxybutyrate into acetoacetate, which has a ketone group in place of the hydroxyl group. The production of NADH captures energy that can later be used in the electron transport chain.

Next, acetoacetate reacts with coenzyme A (CoA) to form acetoacetyl CoA. This step activates the molecule and prepares it for further breakdown.

In the following step, acetoacetyl CoA is split into two acetyl CoA molecules. Another CoA molecule is added during this cleavage. Each resulting acetyl CoA contains a two-carbon acetyl group attached to coenzyme A.

At the end of the pathway, the two acetyl CoA molecules are shown entering the Krebs cycle, where they can be further oxidized to generate energy.

Figure 4.3.6: Lipid Metabolism

This image shows how carbon from mitochondrial metabolism is redirected into fatty acid and lipid synthesis in the cytoplasm. It combines part of the Krebs cycle inside the mitochondrion with the cytoplasmic steps of lipogenesis outside the mitochondrion.

Inside the mitochondrion, acetyl CoA combines with oxaloacetate to form citrate. A labeled arrow shows citrate being transported out of the mitochondrion into the cytoplasm. This export step moves carbon units out of the mitochondrion so they can be used for lipid synthesis.

In the cytoplasm, citrate is split back into acetyl CoA and oxaloacetate. The cytoplasmic acetyl CoA becomes the starting material for fatty acid synthesis.

On the left side of the diagram, oxaloacetate is converted to oxaloacetic acid, then to malic acid (malate), and then to pyruvate. This side pathway helps recycle intermediates and supports the synthesis process.

On the right side, acetyl CoA is converted into malonyl CoA. This step uses ATP, which is converted to adenosine diphosphate (ADP) and phosphate, and it also uses bicarbonate (HCO_3^-). Malonyl CoA is shown as the key intermediate used to build a growing fatty acid chain.

Below this step, repeated reactions extend the carbon chain to form a fatty acid, shown as a long hydrocarbon chain with a terminal carboxyl group.

Farther to the right, the diagram shows the fatty acid combining with glycerol, a three-carbon molecule with hydroxyl groups, to form a monoglyceride. This illustrates how newly synthesized fatty acids can be attached to glycerol to begin forming storage lipids such as mono-, di-, and triglycerides.

Overall, the figure shows that:

- acetyl CoA and oxaloacetate form citrate in the mitochondrion
- citrate is exported to the cytoplasm
- citrate is split to regenerate cytoplasmic acetyl CoA
- acetyl CoA is converted to malonyl CoA
- malonyl CoA is used to synthesize fatty acids
- fatty acids combine with glycerol to form lipid molecules

The diagram emphasizes the connection between energy metabolism in the mitochondrion and fat synthesis in the cytoplasm, showing how excess carbon and energy can be redirected into lipid storage pathways.

Figure 4.4.1: Digestive Enzymes and Hormones

This image combines a whole digestive tract overview with a magnified view of the stomach, pancreas, and small intestine to show how protein digestion is coordinated by digestive enzymes, acid, and intestinal hormones.

On the left side, a simplified digestive tract shows the path of food moving downward through the esophagus, stomach, small intestine, and large intestine. Arrows inside the tract indicate the direction of movement and establish the sequence of organs involved in digestion.

Near the stomach, a label identifies substances released by stomach cells: pepsin and hydrochloric acid (HCl). Arrows point from the stomach wall into the stomach contents. This part of the figure shows that hydrochloric acid creates an acidic environment that denatures proteins, while pepsin begins protein digestion by breaking proteins into smaller peptides.

On the right side, a magnified view shows the interaction among the stomach, pancreas, and small intestine. The pancreas is connected to the small intestine by a duct, and arrows show digestive secretions moving from the pancreas into the intestinal lumen. Another arrow shows material leaving the stomach and entering the small intestine.

A label for the acinar cells of the pancreas lists trypsin, chymotrypsin, elastase, and sodium bicarbonate. This indicates that the pancreas releases proteases to continue protein digestion in the small intestine and releases sodium bicarbonate to help neutralize the acidic chyme arriving from the stomach.

A separate label for intestinal cells lists the hormones secretin and cholecystokinin (CCK). These hormones are shown as signals that regulate pancreatic secretion. Secretin stimulates the release of bicarbonate, and CCK stimulates the release of digestive enzymes.

Figure 4.4.2: Urea Cycle

This image shows the urea cycle, a circular metabolic pathway that converts toxic ammonia into urea for excretion. The pathway is divided between the mitochondrion, where the first reactions occur, and the cytoplasm, where the remaining reactions take place. Arrows show the sequence of reactions and the recycling of intermediates.

In the mitochondrial phase, the cycle begins with carbon dioxide (CO_2), ammonium (NH_4^+), and 2 ATP. These react through the enzyme carbamoyl phosphate synthetase I to form carbamoyl phosphate, while producing 2 adenosine diphosphate (ADP) and inorganic phosphate. This step uses energy to incorporate nitrogen from ammonia into a reactive intermediate.

Next, carbamoyl phosphate reacts with ornithine through the enzyme ornithine transcarbamolase to form L-citrulline. A phosphate group is released in the process. Citrulline is then transported out of the mitochondrion into the cytoplasm.

In the cytoplasmic phase, citrulline combines with aspartate through the enzyme argininosuccinate synthetase. This step uses ATP and forms argininosuccinate, along with adenosine monophosphate (AMP) and pyrophosphate (PPi). This reaction introduces the second nitrogen atom that will become part of urea.

Next, argininosuccinate is split by argininosuccinase lyase into L-arginine and fumarate. The production of fumarate shows the connection between the urea cycle and the Krebs cycle.

In the final step, arginine reacts with water through the enzyme arginase 1 to form urea and regenerate ornithine. The urea is the final nitrogen-containing waste product, and ornithine is transported back into the mitochondrion so the cycle can begin again.

Figure 4.4.3: Energy from Amino Acids

This image integrates amino acid metabolism with major energy-producing pathways, showing how different amino acids enter metabolism at different points and are classified as glucogenic or ketogenic based on the products they form.

At the top, glucose is shown as a six-carbon molecule (C6). A downward arrow labeled glycolysis leads from glucose to pyruvate, a three-carbon molecule (C3). An upward arrow labeled gluconeogenesis shows that pyruvate can also be used to regenerate glucose. This top portion highlights the close relationship between carbohydrate metabolism and amino acid metabolism.

Below pyruvate is acetyl CoA, shown as a central branch point. This molecule serves as an important metabolic hub linking amino acid breakdown with energy production and ketone-related pathways.

On the left side, a labeled group of glucogenic amino acids includes alanine, cysteine, glycine, serine, and threonine. Arrows from these amino acids point to pyruvate, indicating that they can be converted into pyruvate and then used in gluconeogenesis to help produce glucose.

On the right side, a labeled group of ketogenic amino acids includes phenylalanine, tyrosine, leucine, lysine, tryptophan, and isoleucine. Arrows point toward acetyl CoA, showing that these amino acids are broken down into products that can form acetyl CoA. These products can contribute to ketone body formation or enter the Krebs cycle for energy production, but they cannot be used to make glucose directly.

The lower portion of the diagram shows the Krebs cycle, also called the citric acid cycle, as a circular pathway with labeled intermediates, including oxaloacetate, citrate, isocitrate, alpha-ketoglutarate, succinyl CoA, succinate, fumarate, and malate. The cycle is shown as a central pathway through which many amino acids enter metabolism.

Additional labeled groups show amino acids feeding into specific Krebs cycle intermediates:

- aspartic acid and asparagine enter at oxaloacetate
- phenylalanine and tyrosine enter at fumarate
- arginine, histidine, glutamine, and glutamic acid enter at alpha-ketoglutarate
- isoleucine, methionine, and valine enter at succinyl CoA

These entry points show that many amino acids are glucogenic because they produce intermediates that can move through the Krebs cycle and eventually support gluconeogenesis.

Figure 4.4.4: Catabolic and Anabolic Pathways

This image presents an integrated metabolic network showing how carbohydrates, lipids, and proteins are connected through shared pathways that support either energy production or energy storage. The diagram uses blue arrows for breakdown pathways and green arrows for synthesis and storage pathways, but the meaning of each pathway is also conveyed by the labels and direction of the arrows rather than by color alone.

At the top, glycogen is connected to glucose. A downward pathway labeled glycogenolysis shows glycogen being broken down into glucose, while an upward pathway labeled glycogenesis shows glucose being stored as glycogen. Below that, glucose is connected to pyruvate. A downward arrow labeled glycolysis shows glucose being broken down into pyruvate, and an upward arrow labeled gluconeogenesis shows pyruvate being used to form glucose. This top section highlights the balance between carbohydrate use and storage.

At the center of the diagram are two pyruvate molecules, which serve as a major metabolic branch point. Pyruvate connects downward to acetyl CoA, linking carbohydrate breakdown to later energy-producing pathways. Pyruvate also connects horizontally with amino acid pathways, showing its role as a central hub between carbohydrates and proteins.

On the left side, triglycerides are shown breaking down into glycerol and fatty acids. The fatty acids are converted to acetyl CoA through lipolysis and beta-oxidation, while the reverse pathways show lipogenesis, in which acetyl CoA is used to synthesize fatty acids and triglycerides for storage. Glycerol is also connected to glucose-related pathways, showing that lipid metabolism can interact with carbohydrate metabolism.

On the right side, amino acids are divided into glucogenic amino acids and ketogenic amino acids. Glucogenic amino acids can be converted into pyruvate, which allows them to support gluconeogenesis and glucose production. Ketogenic amino acids are converted into acetyl CoA and can contribute to ketogenesis. The diagram also shows the reverse process, ketone oxidation, in which ketone bodies are converted back into acetyl CoA.

At the lower center, acetyl CoA enters the Krebs cycle, shown as a circular pathway. A label indicating certain amino acids points to the cycle, showing that some amino acids can also enter metabolism through Krebs cycle intermediates. This part of the figure emphasizes the Krebs cycle as a central pathway for extracting energy from all three macronutrient groups.

At the bottom right, the electron transport chain is shown as a step-like structure receiving electrons from earlier metabolic processes. A chemical expression at the bottom shows oxygen, hydrogen ions, and electrons combining to form water, indicating that oxygen serves as the final electron acceptor. This final stage leads to the production of ATP.

Figure 4.5.1: Metabolic Responses During the Absorptive (Fed) State

This image illustrates how nutrients are processed during the absorptive (fed) state after a meal. The diagram is organized into three numbered steps, followed by three tissue-specific responses labeled 3a, 3b, and 3c.

A key identifies the circulating substances shown in the blood vessel:

- Insulin
- Glucose
- Lipids
- Amino acids

Step 1

Digested nutrients enter the bloodstream from the intestines. Blood sugar concentration rises.

At the top of the diagram, glucose, lipids, and amino acids enter a blood vessel from the digestive tract. This increases the concentration of nutrients, including glucose, in the blood.

Step 2

Release of digested nutrients into the blood stimulates insulin release by the pancreas. Insulin increases the uptake of glucose by all body cells, reducing blood glucose concentration back to homeostasis.

The pancreas is shown releasing insulin into the bloodstream. Insulin circulates together with glucose, amino acids, and lipids and promotes nutrient uptake by target tissues.

The blood vessel then branches toward three major target tissues:

- Liver cells
- Muscle cells
- Adipose cells

Step 3a: Liver Cells

In the absorptive state, liver cells convert excess glucose to glycogen for storage via the intermediary glucose-6-phosphate. Amino acids are also processed through pathways associated with ketogenesis.

The figure shows insulin stimulating glucose uptake and protein uptake by liver cells.

Within the liver cell:

- Glucose enters the cell
- Glucose is converted to glucose-6-phosphates
- Glucose-6-phosphates are converted into glycogen for storage
- Amino acids enter the cell and contribute to metabolic pathways labeled ketogenesis

This panel illustrates the storage of excess glucose and the processing of amino acids during the absorptive state.

Step 3b: Muscle Cells

In the absorptive state, muscle cells convert excess glucose to glycogen for storage via the intermediary glucose-6-phosphate. Amino acids are used to synthesize actin and myosin, rebuilding muscle fibers.

The figure shows insulin stimulating glucose uptake and protein uptake by muscle cells.

Within the muscle cell:

- Glucose enters the cell
- Glucose is converted into glucose-6-phosphates
- Glucose-6-phosphates are converted into glycogen for storage
- Amino acids are used in actin and myosin synthesis

This panel illustrates glycogen storage and protein synthesis in skeletal muscle.

Step 3c: Adipose Cells

In the absorptive state, adipose cells store excess lipids, increasing fat reserves.

The figure shows insulin acting on adipose tissue and stimulating lipid storage.

Within the adipose cell:

- Lipids move from the bloodstream into the cell
- Lipids accumulate as stored fat

This panel illustrates the storage of excess dietary energy as fat.

The figure demonstrates how nutrient metabolism is coordinated during the absorptive state. Following a meal, digested nutrients enter the bloodstream and stimulate insulin release from the pancreas. Insulin promotes nutrient uptake by tissues and directs excess nutrients into storage pathways. The liver stores glucose as glycogen and processes amino acids, muscle cells store glycogen and synthesize proteins, and adipose tissue stores lipids as fat. Together, these responses lower blood glucose concentrations and promote energy storage for later use.

Figure 4.5.2: Metabolic Responses During the Postabsorptive (Fasting) State

This image illustrates the body's metabolic responses during the postabsorptive state, when nutrients are no longer entering the bloodstream from digestion. The diagram is organized into two numbered steps followed by three tissue-specific responses labeled 3a, 3b, and 3c.

A key identifies the circulating substances shown in the blood vessel:

- Glucagon
- Glucose
- Lipids
- Amino acids

Step 1

Postabsorptive state: no nutrients enter the bloodstream from the digestive system.

At the top of the diagram, the bloodstream contains relatively low levels of circulating nutrients. No additional nutrients are entering from the intestines, indicating a fasting condition.

Step 2

Sugar concentrations in blood drop, stimulating the pancreas to stop releasing insulin and instead release glucagon.

The pancreas is shown releasing glucagon into the bloodstream. Glucagon becomes the dominant hormone during fasting and promotes the mobilization of stored energy reserves.

The bloodstream then distributes glucagon to three target tissues:

- Liver cells
- Muscle cells
- Adipose cells

Step 3a: Liver Cells

In the postabsorptive state, glycogenolysis releases glucose into the blood, returning blood glucose concentrations to homeostasis. Ketone oxidation is also shown as part of liver metabolism during fasting.

Within the liver cell:

- Stored glycogen is broken down
- Glycogen is converted into glucose-6-phosphates
- Glucose moves from the liver into the bloodstream
- A pathway labeled ketone oxidation is also shown

This panel illustrates the liver's role in maintaining blood glucose levels during fasting by releasing glucose into circulation.

Step 3b: Muscle Cells

In the postabsorptive state, muscle cells break down stored glycogen and proteins. Actin and myosin catabolism releases amino acids that can contribute to energy-related pathways.

The figure shows:

- Glucagon stimulates the breakdown of glycogen and proteins
- Actin and myosin catabolism releases amino acids from muscle proteins
- Glycogen is converted into glucose-6-phosphates

This panel emphasizes the use of stored muscle glycogen and muscle proteins as fuel sources during prolonged fasting.

Step 3c: Adipose Cells

In the postabsorptive state, adipose cells release stored lipids, which can be used in pathways that support glucose production, ketone body formation, or ATP generation.

The figure shows:

- Glucagon stimulates adipose cells to release stored lipids
- Lipids move from storage sites into the bloodstream

This panel illustrates the mobilization of stored fat during fasting and the use of lipids as alternative fuel sources.

The figure demonstrates how the body maintains energy availability during fasting. When nutrient absorption ceases and blood glucose levels decline, glucagon secretion increases and insulin secretion decreases. Glucagon stimulates the breakdown of glycogen, proteins, and stored lipids. The liver releases glucose into the bloodstream, muscle tissue contributes amino acid substrates through protein catabolism, and adipose tissue releases stored lipids. Together, these responses help maintain blood glucose homeostasis and provide energy to body tissues during the postabsorptive state.

Figure 4.6.1: Negative Feedback Regulation of Body Temperature

Long Description

This image illustrates a negative feedback system that maintains temperature homeostasis between 36.5°C and 37.5°C. The diagram is organized as an eight-step cycle showing how the body responds when temperature becomes too low or too high.

Cold-Response Pathway

Step 1: Body temperature is low.

The pathway begins when body temperature falls below the normal range. A cold environment is shown as the initiating condition.

Step 2: Temperature receptors in the hypothalamus stimulate heat-producing mechanisms.

The hypothalamus detects the decrease in body temperature and activates responses that increase heat production and reduce heat loss.

Step 3: Three heat-producing responses occur:

- Superficial arteries constrict, reducing heat loss to the air. Blood flow to the digestive system decreases.
- Shivering increases aerobic respiration in muscles, generating heat.
- The thyroid stimulates cells to increase metabolic heat production.

Step 4: Body temperature increases.

These responses raise body temperature and return it toward the homeostatic range.

Temperature Homeostasis

At the center of the diagram is the normal temperature range of 36.5–37.5°C, representing temperature homeostasis.

Heat-Response Pathway

Step 5: Body temperature is high.

The second pathway begins when body temperature rises above the normal range. A warm environment is shown as the initiating condition.

Step 6: Temperature receptors initiate heat-releasing mechanisms.

The hypothalamus detects the increase in body temperature and activates responses that promote heat loss and reduce heat production.

Step 7: Three heat-releasing responses occur:

- Superficial arteries dilate, causing flushing and increasing heat loss to the air. Blood flow is not diverted away from the digestive system.
- Sweating is initiated in the skin.
- The thyroid stimulates cells to decrease metabolic heat production.

Step 8: Body temperature decreases.

These responses lower body temperature and return it toward the homeostatic range.

The figure demonstrates a negative feedback mechanism that regulates body temperature. When body temperature falls, the hypothalamus activates vasoconstriction, shivering, and increased metabolic activity to conserve and generate heat. When body temperature rises, the hypothalamus activates vasodilation, sweating, and decreased metabolic activity to promote heat loss. Together, these responses maintain body temperature within the normal range of 36.5–37.5°C.

Figure 4.7.1: MyPlate Food Guide

This image presents the MyPlate food guide as a place setting viewed from above. A large round plate is divided into four labeled sections, and a smaller separate circle to the upper right represents dairy. A fork appears to the left of the plate, reinforcing the idea of meal planning.

The plate is divided into four quadrants labeled Fruits, Vegetables, Grains, and Protein. The left half of the plate contains Fruits and Vegetables, while the right half contains Grains and Protein. A separate small circle labeled Dairy sits beside the plate, indicating a dairy serving that accompanies the meal.

Each section is identified by both text labels and color, so the food groups are not distinguished by color alone. The diagram uses:

- Fruits in the upper left section
- Vegetables in the lower left section
- Grains in the upper right section
- Protein in the lower right section
- Dairy in a separate circle to the right

The arrangement emphasizes that half of the plate should be fruits and vegetables, while the other half should be divided between grains and protein. The separate dairy circle suggests an additional dairy food or beverage as part of a balanced meal.

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5: THE URINARY SYSTEM

Chapter Overview



Figure 5.1: Sewage Treatment Plant. (CC BY 4.0; via Introduction).

This chapter will help you to understand the anatomy of the urinary system and how it enables the physiologic functions critical to homeostasis. It is best to think of the kidney as a regulator of plasma makeup rather than simply a urine producer. As you read each section, ask yourself this question: "What happens if this does not work?" This question will help you to understand how the urinary system maintains homeostasis and affects all the other systems of the body and the quality of one's life.

Why the Urinary System Matters for Whole-Body Health

The urinary system does much more than simply produce urine. It plays central roles in maintaining the internal environment of the body, which is essential for health across the lifespan. The kidneys remove metabolic wastes from the blood, but they also help regulate blood pH together with the lungs and chemical buffers in the blood. They contribute to blood pressure regulation alongside the heart and blood vessels, and they control the concentration of solutes in plasma, including key electrolytes and small molecules.

The kidneys are major endocrine organs. About 85 percent of the hormone erythropoietin (EPO), which stimulates red blood cell production in the bone marrow, is produced in the kidneys. The kidneys also carry out the final activation step for vitamin D by converting calcidiol to calcitriol, the active form. This activated vitamin D is crucial for calcium balance, bone health, and other functions.

Because these functions are essential for homeostasis, it is most accurate to think of the kidney as a regulator of plasma composition rather than just a urine producer. When kidney function is impaired, people can develop anemia, bone disease, blood pressure abnormalities, and acid–base disturbances. As you study each topic in this chapter, asking "What happens if this does not work?" will help you connect structure to function, understand how the urinary system supports other body systems, and appreciate how kidney disease can affect quality of life. It also highlights why equitable access to prevention, diagnosis, and treatment of kidney disease is a public health priority.

Urine Formation and Characteristics

Filtration of blood begins in the glomerulus, a capillary network that filters primarily on the basis of particle size. Normal filtrate contains water, ions, and small molecules, but it does not contain blood cells or large plasma proteins. This filtrate enters the

nephron tubules, where most of its useful components are reclaimed. Almost all of the filtered glucose, amino acids, vitamins, and large amounts of water and electrolytes must be reabsorbed further along the nephron for normal function. The remaining fluid and solutes become urine.

Urine volume and composition vary depending on water intake, physical activity, environmental temperature, and nutrient intake. A minimum of about 400 to 500 mL of urine must be produced each day to safely eliminate metabolic wastes. Excessive urine production can suggest conditions such as diabetes insipidus or uncontrolled diabetes mellitus, in which water handling or glucose regulation is disrupted. Urine pH normally ranges from about 4.5 to 8.0 and is influenced by diet, metabolism, and respiratory status. Urine osmolarity ranges from roughly 50 to 1200 milliosmoles, reflecting how much water has been reabsorbed or excreted by the renal tubules. Urinalysis, which examines urine color, clarity, specific gravity, pH, and solutes, is an important diagnostic tool for kidney disease, infections, diabetes, and other conditions.

Fluid access, work conditions, climate, and diet, which are not evenly distributed in all communities, influence hydration status, urine output, and kidney health. Understanding normal urine characteristics can help in identifying both individual and population-level risks.

Lower Urinary Tract: Ureters, Bladder, and Urethra

The ureters are muscular tubes that carry urine from the renal pelvis of each kidney to the bladder. They are retroperitoneal and have thick walls composed of longitudinal and circular layers of smooth muscle. This muscle uses peristaltic contractions to move urine toward the bladder, allowing transport to continue even when a person is lying down.

The urinary bladder is a largely retroperitoneal, hollow muscular organ that temporarily stores urine. It can typically hold about 500 to 600 mL of urine, although the sensation of fullness occurs at lower volumes. The bladder base contains the trigone, a triangular region defined by the two ureteral openings and the urethral opening. Micturition, or urination, is the process of emptying the bladder. It involves a coordinated sequence of involuntary and voluntary actions. The internal urethral sphincter, composed of smooth muscle, is under involuntary control, while the external urethral sphincter, made of skeletal muscle, is under voluntary control. Effective voluntary control of micturition requires a mature and intact sacral micturition center and spinal cord pathways. Loss of voluntary control, or incontinence, can result from neurologic injury, pelvic floor trauma, congenital conditions, or aging, and often leads to involuntary voiding when the bladder volume reaches about 250 mL. Incontinence can have major social and psychological impacts, especially in communities with limited access to supportive devices or facilities.

The urethra is the only major urinary structure that differs substantially between typical male and typical female anatomy. In most males, the urethra is longer and serves a dual role in carrying both urine and semen. It passes through the prostate and penis and receives secretions from the prostate gland, bulbourethral (Cowper's) glands, and the seminal vesicles (via the ejaculatory ducts), as well as transporting sperm from the testes. In most females, the urethra is shorter and opens into the vestibule anterior to the vaginal opening. The shorter female urethra contributes to a higher incidence of urinary tract infections, especially where access to clean water, hygiene supplies, and timely medical care is limited. Understanding these anatomic differences helps explain sex-based differences in urinary tract disease patterns, while also emphasizing that anyone can experience urinary problems regardless of sex or gender identity.

Gross Anatomy of the Kidneys

The kidneys lie in the retroperitoneal space on either side of the vertebral column. Each kidney is surrounded by a renal fat pad and protected by overlying ribs and back muscles. The two principal internal regions are the outer cortex and the inner medulla. The cortex contains the renal corpuscles and most of the nephron segments, while the medulla consists of renal pyramids, which are cone-shaped structures with their tips (papillae) projecting into minor calyces. Minor calyces join to form major calyces, which join to form the renal pelvis. The renal pelvis narrows to become the ureter.

The kidneys receive a high percentage of cardiac output—about 25 percent. The renal arteries branch directly from the abdominal aorta and subdivide within the kidney, ultimately feeding the glomerular capillaries. Venous blood is collected by the renal veins, which drain directly into the inferior vena cava. At the medial aspect of each kidney is the renal hilum, an opening where ureters, blood vessels, lymphatic vessels, and nerves enter and exit. This rich blood supply and organization underlie the kidneys' ability to continuously filter and regulate the composition of the blood.

The Nephron: Structure and Types

The nephron is the functional unit of the kidney. Each kidney contains roughly 1.3 million nephrons. A nephron consists of a renal corpuscle and a tubular system. The renal corpuscle includes the glomerulus, a capillary tuft, and Bowman's capsule, a surrounding cup-shaped structure that captures the filtrate. The filtration membrane is formed by the fused basement membranes of the glomerular capillary endothelial cells and the specialized epithelial cells called podocytes. This structure allows water and small solutes to pass while retaining blood cells and most proteins. Contractile mesangial cells between capillary loops help regulate the filtration surface area.

From Bowman's capsule, filtrate flows into the proximal convoluted tubule (PCT), which is the primary site of reabsorption and secretion. It then passes into the loop of Henle, which has descending and ascending limbs with thick and thin segments. The descending limb is permeable to water; the ascending limb is relatively impermeable to water but actively transports ions. After the loop, filtrate enters the distal convoluted tubule (DCT), where additional but less extensive reabsorption and secretion occur. Multiple nephrons drain into a shared collecting duct, which carries the forming urine through the medulla toward the renal pelvis. In the collecting ducts, the hormone ADH stimulates insertion of aquaporin channels into the membrane, allowing fine control of water reabsorption. Aldosterone promotes sodium reabsorption in the distal nephron segments, with important effects on volume and potassium balance.

There are two major types of nephrons. Cortical nephrons, which make up the majority, are located primarily in the cortex and have relatively short loops of Henle. Juxtamedullary nephrons, about 15 percent of the total, have long loops of Henle that extend deep into the medulla. These long loops, together with the vasa recta, are essential for establishing the medullary osmotic gradient that allows the production of concentrated urine and conservation of water.

The juxtaglomerular apparatus (JGA) is a specialized structure at the point where the DCT contacts the afferent arteriole of its own glomerulus. Macula densa cells in the DCT sense the concentration of sodium chloride in tubular fluid and send paracrine signals that adjust afferent arteriole tone, thereby influencing filtration. Juxtaglomerular (granular) cells in the arteriole wall secrete renin, a key enzyme in blood pressure regulation. Together with mesangial cells, these elements allow fine control of glomerular filtration and systemic blood pressure.

Glomerular Filtration and Autoregulation

The kidneys filter the entire volume of blood plasma roughly 300 times per day. About 20 percent of the plasma reaching the glomeruli is filtered, and approximately 99 percent of the filtered water is reabsorbed along the nephron. The glomerular filtration rate (GFR) depends on the balance of pressures acting across the filtration membrane. Glomerular hydrostatic pressure, essentially the blood pressure within the glomerular capillaries, favors filtration, while colloid osmotic pressure of plasma proteins and the hydrostatic pressure in Bowman's capsule oppose it. Under normal conditions, hydrostatic pressure predominates, and filtration proceeds continuously.

GFR is regulated to remain relatively stable despite changes in systemic blood pressure. Autoregulatory mechanisms include the myogenic response and tubuloglomerular feedback. In the myogenic mechanism, increased blood pressure stretches the afferent arteriole, causing smooth muscle contraction and narrowing of the vessel, which reduces glomerular pressure. When blood pressure falls, the arteriole relaxes and dilates, maintaining flow and pressure within a functional range. In tubuloglomerular feedback, macula densa cells detect changes in NaCl delivery in the DCT and release signaling molecules that alter the diameter of the afferent arteriole. Increased NaCl delivery, which may indicate high GFR, triggers constriction to reduce filtration; decreased NaCl delivery promotes dilation.

Sympathetic nervous system activity can override autoregulation during severe stress or blood loss, constricting afferent arterioles and reducing renal blood flow to preserve perfusion of essential organs such as the heart and brain. Local paracrine mediators, such as nitric oxide, adenosine, and endothelins, also influence renal vascular tone. Chronic conditions such as long-standing hypertension and diabetes, which are more common in some populations due to structural inequities, can damage glomeruli and interfere with these regulatory mechanisms.

Hormonal Regulation: RAAS, ADH, Natriuretic Hormones, and PTH

The kidneys, adrenal glands, heart, lungs, and liver interact through several hormone systems to regulate blood volume, blood pressure, and electrolyte balance.

The renin–angiotensin–aldosterone system (RAAS) begins with renin secretion by juxtaglomerular cells in response to low blood pressure, low NaCl delivery to the macula densa, or sympathetic stimulation. Renin converts angiotensinogen from the liver to angiotensin I, which is then converted by angiotensin-converting enzyme (ACE), predominantly in the lungs, to angiotensin II. Angiotensin II is a powerful vasoconstrictor that raises blood pressure. It also stimulates aldosterone secretion from the adrenal cortex. Aldosterone acts on the distal tubules and collecting ducts to increase sodium reabsorption and potassium excretion. Because water follows sodium, this promotes water retention, increases blood volume, and helps restore blood pressure.

Antidiuretic hormone (ADH), produced in the hypothalamus and released by the posterior pituitary, acts mainly on the collecting ducts. When plasma osmolarity rises or blood volume falls, ADH release increases. ADH triggers insertion of aquaporin water channels into collecting duct cells, enhancing water reabsorption and concentrating the urine. At high levels, ADH can also cause vasoconstriction, further supporting blood pressure.

Natriuretic peptides, such as atrial natriuretic hormone (ANH or ANP), are released by heart muscle cells when the atria are stretched by increased blood volume or pressure. These hormones promote sodium and water excretion by the kidneys, reduce renin and aldosterone secretion, and cause vasodilation, thereby lowering blood volume and blood pressure.

Endothelins are locally produced peptides that, when elevated—for example in diabetic kidney disease—can increase sodium retention and reduce GFR, contributing to hypertension and kidney damage. Parathyroid hormone (PTH) acts on the kidney to reduce phosphate reabsorption and increase calcium reabsorption. Along with kidney-derived calcitriol, PTH increases circulating calcium levels, which is essential for muscle contraction, nerve function, and bone mineralization. Progesterone, although primarily a reproductive hormone, has a structure similar to aldosterone and can weakly stimulate aldosterone receptors, causing mild sodium retention in some contexts.

Tubular Transport, Countercurrent Mechanisms, and Concentration of Urine

Reabsorption and secretion along the nephron use a variety of transport mechanisms, including active transport, facilitated diffusion, simple diffusion, symporters, antiporters, and ATP-powered pumps. Most filtered substances are reabsorbed to maintain homeostasis. The proximal convoluted tubule is the most metabolically active segment and recovers nearly all filtered glucose, amino acids, and vitamins, as well as substantial amounts of sodium, bicarbonate, and water. Carbonic anhydrase in tubular cells helps reclaim bicarbonate, a key buffer, by catalyzing reversible reactions involving carbon dioxide and carbonic acid. The reabsorption of solutes in the PCT creates an osmotic gradient that drives water reabsorption.

The loop of Henle, particularly in juxtamedullary nephrons, is central to concentrating or diluting urine. The descending limb is permeable to water but not to solutes, so filtrate becomes progressively more concentrated as it descends into the medulla, where the interstitial fluid has high osmolarity. The ascending limb is impermeable to water but actively transports sodium and chloride out of the tubule, making the filtrate more dilute as it ascends. This arrangement, together with the slow, hairpin-shaped flow in the vasa recta, creates a countercurrent multiplier system that maintains a steep osmotic gradient in the medulla.

Collecting ducts run through this osmotic gradient. In the presence of ADH, they become highly permeable to water and, together with urea recycling from the medullary collecting ducts, allow additional water recovery and further concentration of the urine. The vasa recta, a specialized set of capillaries, performs countercurrent exchange, picking up water and solutes from the medulla without dissipating the gradient. By the time filtrate reaches the distal convoluted tubule, about 90 percent of the filtered water has already been reabsorbed. The DCT and collecting ducts adjust the remaining 10 percent of water and significant amounts of electrolytes under hormonal control. For example, PTH and active vitamin D enhance calcium reabsorption in the DCT, while aldosterone increases sodium reabsorption and potassium secretion in the distal nephron.

Autonomic and Local Neural Control of Renal Blood Flow

The kidneys are richly innervated by sympathetic fibers of the autonomic nervous system. During stress, sympathetic stimulation causes vasoconstriction of renal arteries and arterioles, reducing renal blood flow and GFR to preserve blood flow for the brain, heart, and skeletal muscles. This response is adaptive in acute situations but can be harmful if prolonged.

At the local level, the myogenic mechanism and tubuloglomerular feedback provide rapid adjustments to maintain relatively stable blood flow and filtration. In the myogenic response, increased pressure stretches vascular smooth muscle, triggering contraction and vessel narrowing. Decreased pressure allows relaxation and dilation. Tubuloglomerular feedback, mediated by the

juxtaglomerular apparatus, involves sensing the composition and flow of tubular fluid and adjusting afferent arteriole diameter using local signaling molecules. Together, these mechanisms protect glomerular capillaries from damage and help maintain a consistent GFR over a range of blood pressures.

Systemic Fluid, Electrolyte, and pH Regulation

The kidneys play an essential role in controlling body fluid volume, electrolyte concentrations, and acid–base balance, in coordination with the cardiovascular, respiratory, and endocrine systems. Blood pressure, a reflection of blood volume and vascular resistance, is monitored by baroreceptors in the aortic arch and carotid sinuses. When blood pressure rises, baroreceptors send more frequent signals to the central nervous system, which in turn promotes vasodilation and, through hormonal pathways, increases GFR and urine output. Natriuretic peptides released during high pressure further enhance sodium and water excretion. In contrast, when blood pressure drops, RAAS and ADH act to conserve water and sodium, increasing volume and pressure.

Sodium, calcium, and potassium are the most tightly regulated electrolytes. The renin–angiotensin–aldosterone system and ADH largely control sodium, affecting water balance and blood volume. When sodium is retained, potassium is usually excreted; when sodium is lost, potassium is often retained, because aldosterone simultaneously influences both ions. PTH and calcitriol regulate calcium and phosphate handling, ensuring adequate calcium levels for neuromuscular function and bone health while preventing excessive phosphate retention.

Acid–base homeostasis is maintained by three main mechanisms: chemical buffers in the blood (including bicarbonate, proteins, and phosphate), respiratory excretion of carbon dioxide, and renal excretion or reabsorption of hydrogen ions and bicarbonate. The kidneys adjust the excretion of acid and reabsorption of bicarbonate according to the body's needs, complementing the faster but less precise respiratory responses. Proper pH regulation preserves the three-dimensional shapes of proteins and enzymes, which is essential for normal physiological function.

Nitrogenous wastes from protein metabolism are handled primarily by the liver and kidneys. Ammonia produced from amino acid breakdown is converted to urea in the liver, transported in the bloodstream, filtered by the kidneys, and excreted in urine. Many medications are also filtered, secreted, and in some cases reabsorbed by the kidneys; this affects both therapeutic effects and potential toxicity and underscores the importance of adjusting drug doses in people with kidney impairment.

Clinical Consequences and Equity Considerations

Failure or impairment of different parts of the urinary system leads to a wide spectrum of clinical outcomes, from socially disruptive but manageable problems, such as urinary incontinence, to life-threatening conditions, such as complete loss of filtration that requires dialysis or transplantation. The kidneys catalyze the final step in vitamin D activation, so their failure can contribute to bone weakness and deformities. Reduced EPO production in kidney disease leads to anemia and reduced oxygen-carrying capacity. Disordered sodium and water handling can result in hypertension, edema, or dangerous drops in blood pressure. Poor regulation of potassium and calcium can cause arrhythmias, muscle weakness, seizures, and bone disease. Inadequate acid excretion leads to metabolic acidosis, which affects many enzyme systems.

These physiologic roles highlight that kidney health is deeply connected to cardiovascular health, bone health, hematologic status, and more. Because conditions such as diabetes and hypertension, along with environmental toxins and limited access to preventive care, are not evenly distributed, some communities experience a disproportionate burden of chronic kidney disease and its complications. Understanding the anatomy and physiology of the urinary system supports not only individual clinical reasoning but also broader efforts to promote health equity by improving early detection, treatment access, and supportive resources for people at risk of or living with kidney disease.

Learning Objectives

To achieve these chapter objectives, actively engage with the material. Learning tissues is not a passive process. Your understanding will grow as you interact with the content, peers, and your instructor. Regularly check your thinking against feedback. Revisit complex concepts until you can confidently explain and apply them on your own.

By the end of this chapter, you will be able to:

- Describe the composition and characteristics of normal urine.
- Describe the gross and microscopic anatomy of the urinary system (kidneys, ureters, bladder, urethra) and relate structure to function.
- Explain the three basic processes of urine formation—glomerular filtration, tubular reabsorption, and tubular secretion—and how they regulate body fluid composition. List some of the solutes filtered, secreted, and reabsorbed in different parts of the nephron.
- Discuss how the kidneys maintain fluid, electrolyte, and acid–base balance, including regulation of sodium, potassium, and pH.
- Describe hormonal regulation of kidney function, including the roles of ADH, aldosterone, the renin–angiotensin–aldosterone system, and atrial natriuretic peptide.
- Relate normal urinary function to common clinical conditions (e.g., dehydration, edema, hypertension, kidney stones, renal failure) and the diagnostic value of urinalysis.

5.1: Characteristics of Normal Urine

5.2: Gross Anatomy of Urine Transport

5.3: Gross Anatomy of the Kidney

5.4: Microscopic Anatomy of the Kidney

5.5: Physiology of Urine Formation

5.6: Tubular Reabsorption

5.7: Regulation of Renal Blood Flow

5.8: Endocrine Regulation of Kidney Function

5.9: Regulation of Fluid Volume and Composition

5.10: The Urinary System and Homeostasis

5.11: Terms and Definitions

5.12: Chapter Review Questions

5.13: Applied Thinking Self - Assessment

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5.1: Characteristics of Normal Urine

Physical Characteristics of Urine

The urinary system's ability to filter the blood resides in about 2 to 3 million tufts of specialized capillaries—the glomeruli—distributed more or less equally between the two kidneys. Because the glomeruli filter the blood based mostly on particle size, large elements like blood cells, platelets, antibodies, and albumen are excluded. The glomerulus is the first part of the nephron, which then continues as a highly specialized tubular structure responsible for creating the final urine composition. All other solutes, such as ions, amino acids, vitamins, and wastes, are filtered to create a filtrate composition very similar to plasma. The glomeruli create about 200 liters (189 quarts) of this filtrate every day, yet you excrete less than two liters of waste you call urine.

Factors that Influence Urine Characteristics

Characteristics of the urine change, depending on influences such as water intake, exercise, environmental temperature, nutrient intake, and other factors (Table 5.1.1). Some of the characteristics such as color and odor are rough descriptors of your state of hydration. For example, if you exercise or work outside, and sweat a great deal, your urine will turn darker and produce a slight odor, even if you drink plenty of water. Athletes are often advised to consume water until their urine is clear. This is good advice; however, it takes time for the kidneys to process body fluids and store it in the bladder. Another way of looking at this is that the quality of the urine produced is an average over the time it takes to make that urine. Producing clear urine may take only a few minutes if you are drinking a lot of water or several hours if you are working outside and not drinking much.

Table 5.1.1: Normal Urine Characteristics

Characteristic	Normal values
Color	Pale yellow to deep amber
Odor	Odorless
Volume	750–2000 mL/24 hour
pH	4.5–8.0
Specific gravity	1.003–1.032
Osmolarity	40–1350 mOsmol/kg
Urobilinogen	0.2–1.0 mg/100 mL
White blood cells	0–2 HPF (per high-power field of microscope)
Leukocyte esterase	None
Protein	None or trace
Bilirubin	<0.3 mg/100 mL
Ketones	None
Nitrites	None
Blood	None
Glucose	None

Urinalysis and Clinical Significance

Urinalysis (urine analysis) often provides clues to renal disease. Normally, only traces of protein are found in urine, and when higher amounts are found, damage to the glomeruli is the likely basis. Unusually large quantities of urine may point to diseases like diabetes mellitus or hypothalamic tumors that cause diabetes insipidus. The color of urine is determined mostly by the

breakdown products of red blood cell destruction (Figure 5.1.1). The “heme” of hemoglobin is converted by the liver into water-soluble forms that can be excreted into the bile and indirectly into the urine. This yellow pigment is urochrome. Urine color may also be affected by certain foods like beets, berries, and fava beans. A kidney stone or a cancer of the urinary system may produce sufficient bleeding to manifest as pink or even bright red urine. Diseases of the liver or obstructions of bile drainage from the liver impart a dark “tea” or “cola” hue to the urine. Dehydration produces darker, concentrated urine that may also possess the slight odor of ammonia. Most of the ammonia produced from protein breakdown is converted into urea by the liver, so ammonia is rarely detected in fresh urine. The strong ammonia odor you may detect in bathrooms or alleys is due to the breakdown of urea into ammonia by bacteria in the environment. About one in five people detect a distinctive odor in their urine after consuming asparagus; other foods such as onions, garlic, and fish can impart their own aromas! These food-caused odors are harmless.

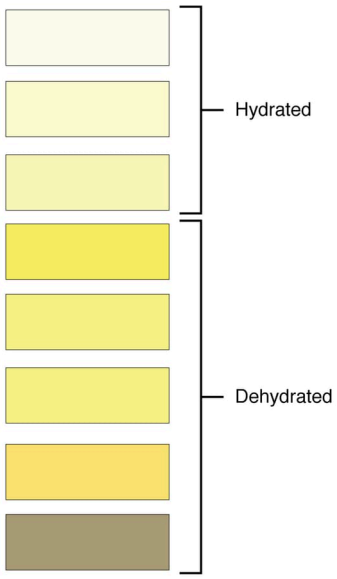


Figure 5.1.1: Urine Color. (CC BY 4.0; via Physical Characteristics of Urine). Detailed text description of the Figure 5.1.1.

Urine Volume

Urine volume varies considerably. The normal range is one to two liters per day (Table 5.1.2). The kidneys must produce a minimum urine volume of about 500 mL/day to rid the body of wastes. Output below this level may be caused by severe dehydration or renal disease and is termed oliguria. The virtual absence of urine production is termed anuria. Excessive urine production is polyuria, which may be due to diabetes mellitus or diabetes insipidus. In diabetes mellitus, blood glucose levels exceed the number of available sodium-glucose transporters in the kidney, and glucose appears in the urine. The osmotic nature of glucose attracts water, leading to its loss in the urine. In the case of diabetes insipidus, insufficient pituitary antidiuretic hormone (ADH) release or insufficient numbers of ADH receptors in the collecting ducts means that too few water channels are inserted into the cell membranes that line the collecting ducts of the kidney. Insufficient numbers of water channels (aquaporins) reduce water absorption, resulting in high volumes of very dilute urine.

Table 5.1.2: Urine Volumes

Volume condition	Volume	Causes
Normal	1–2 L/day	
Polyuria	>2.5 L/day	Diabetes mellitus; diabetes insipidus; excess caffeine or alcohol; kidney disease; certain drugs, such as diuretics; sickle cell anemia; excessive water intake
Oliguria	300–500 mL/day	Dehydration; blood loss; diarrhea; cardiogenic shock; kidney disease; enlarged prostate
Anuria	<50 mL/day	Kidney failure; obstruction, such as kidney stone or tumor; enlarged prostate

Urine pH

The pH (hydrogen ion concentration) of the urine can vary more than 1000-fold, from a normal low of 4.5 to a maximum of 8.0. Diet can influence pH; meats lower the pH, whereas citrus fruits, vegetables, and dairy products raise the pH. Chronically high or low pH can lead to disorders, such as the development of kidney stones or osteomalacia.

Specific gravity is a measure of the quantity of solutes per unit volume of a solution and is traditionally easier to measure than osmolarity. Urine will always have a specific gravity greater than pure water (water = 1.0) due to the presence of solutes. Laboratories can now measure urine osmolarity directly, which is a more accurate indicator of urinary solutes than specific gravity. Remember that osmolarity is the number of osmoles or milliosmoles per liter of fluid (mOsmol/L). Urine osmolarity ranges from a low of 50–100 mOsmol/L to as high as 1200 mOsmol/L H_2O.

Cells are not normally found in the urine. The presence of leukocytes may indicate a urinary tract infection. Leukocyte esterase is released by leukocytes; if detected in the urine, it can be taken as indirect evidence of a urinary tract infection (UTI).

Protein does not normally leave the glomerular capillaries, so only trace amounts of protein should be found in the urine, approximately 10 mg/100 mL in a random sample. If excessive protein is detected in the urine, it usually means that the glomerulus is damaged and is allowing protein to “leak” into the filtrate.

Ketones are byproducts of fat metabolism. Finding ketones in the urine suggests that the body is using fat as an energy source in preference to glucose. In diabetes mellitus when there is not enough insulin (type I diabetes mellitus) or because of insulin resistance (type II diabetes mellitus), there is plenty of glucose, but without the action of insulin, the cells cannot take it up, so it remains in the bloodstream. Instead, the cells are forced to use fat as their energy source, and fat consumed at such a level produces excessive ketones as byproducts. These excess ketones will appear in the urine. Ketones may also appear if there is a severe deficiency of proteins or carbohydrates in the diet.

Nitrates (NO_3^-) occur normally in the urine. Gram-negative bacteria metabolize nitrate into nitrite (NO_2^-), and its presence in the urine is indirect evidence of infection.

There should be no blood found in the urine. It may sometimes appear in urine samples as a result of menstrual contamination, but this is not an abnormal condition. Now that you understand what the normal characteristics of urine are, the next section will introduce you to how you store and dispose of this waste product and how you make it.

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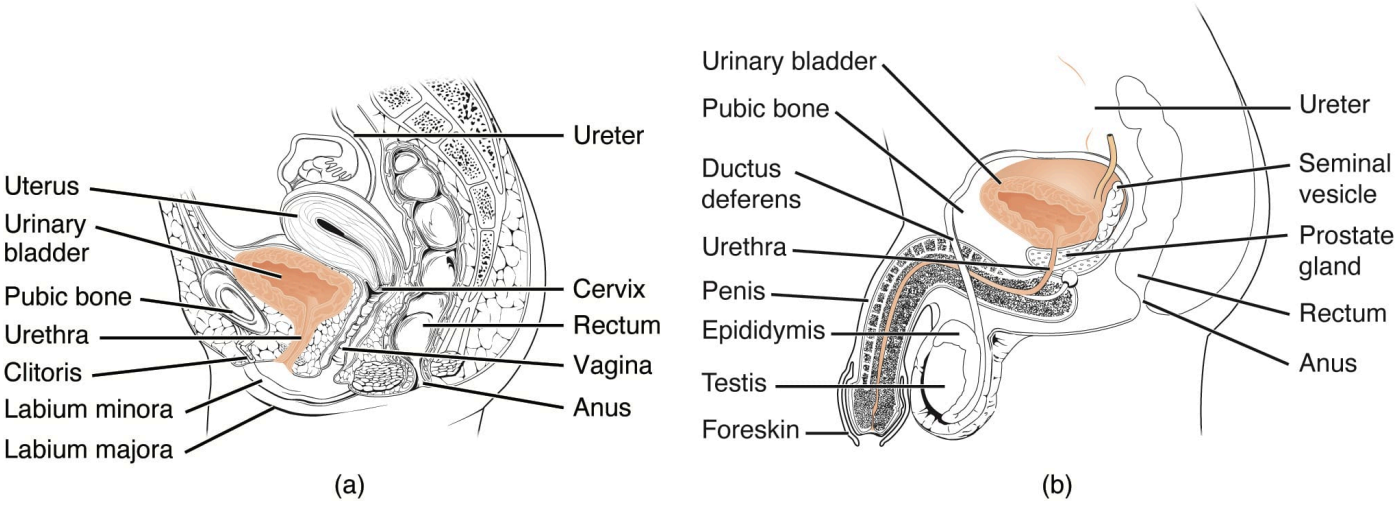
5.2: Gross Anatomy of Urine Transport

Urine Transport and Storage

Rather than start with urine formation, this section will start with urine excretion. Urine is a fluid of variable composition that requires specialized structures to remove it from the body safely and efficiently. Blood is filtered, and the filtrate is transformed into urine at a relatively constant rate throughout the day. This processed liquid is stored until a convenient time for excretion. All structures involved in the transport and storage of the urine are large enough to be visible to the naked eye. This transport and storage system not only stores the waste, but it protects the tissues from damage due to the wide range of pH and osmolarity of the urine, prevents infection by foreign organisms, and for the male, provides reproductive functions.

Urethra

The urethra transports urine from the bladder to the outside of the body for disposal. The urethra is the only urologic organ that shows any significant anatomic difference between males and females; all other urine transport structures are identical (Figure 5.2.1).



Figure

: The urethra transports urine from the bladder to the outside of the body. This image shows (a) a female urethra and (b) a male urethra. (

CC BY 4.0

; via

Gross Anatomy of Urine Transport

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Detailed text description of the Figure 5.2.1

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The urethra in both males and females begins inferior and central to the two ureteral openings forming the three points of a triangular-shaped area at the base of the bladder called the trigone (Greek tri- = “triangle” and the root of the word “trigonometry”). The urethra tracks posterior and inferior to the pubic symphysis (Figure 5.2.1a). In both males and females, the proximal urethra is lined by transitional epithelium, whereas the terminal portion is a nonkeratinized, stratified squamous epithelium. In the male, pseudostratified columnar epithelium lines the urethra between these two cell types. Voiding is regulated by an involuntary autonomic nervous system-controlled internal urinary sphincter, consisting of smooth muscle and voluntary skeletal muscle that forms the external urinary sphincter below it.

Female Urethra

The external urethral orifice is embedded in the anterior vaginal wall inferior to the clitoris, superior to the vaginal opening (introitus), and medial to the labia minora. Its short length, about 4 cm, is less of a barrier to fecal bacteria than the longer male urethra and the best explanation for the greater incidence of UTI in females. Voluntary control of the external urethral sphincter is a function of the pudendal nerve. It arises in the sacral region of the spinal cord, traveling via the S2–S4 nerves of the sacral plexus.

Male Urethra

The male urethra passes through the prostate gland immediately inferior to the bladder before passing below the pubic symphysis (Figure 5.2.1*b*). The length of the male urethra varies between people but averages 20 cm in length. It is divided into four regions: the preprostatic urethra, the prostatic urethra, the membranous urethra, and the spongy or penile urethra. The preprostatic urethra is very short and incorporated into the bladder wall. The prostatic urethra passes through the prostate gland. During sexual intercourse, it receives sperm via the ejaculatory ducts and secretions from the seminal vesicles. Paired Cowper's glands (bulbourethral glands) produce and secrete mucus into the urethra to buffer urethral pH during sexual stimulation. The mucus neutralizes the usually acidic environment and lubricates the urethra, decreasing the resistance to ejaculation. The membranous urethra passes through the deep muscles of the perineum, where it is invested by the overlying urethral sphincters. The spongy urethra exits at the tip (external urethral orifice) of the penis after passing through the corpus spongiosum. Mucous glands are found along much of the length of the urethra and protect the urethra from extremes of urine pH. Innervation is the same in both males and females.

Bladder

The urinary bladder collects urine from both ureters (Figure 5.2.2). The bladder lies anterior to the uterus in females, posterior to the pubic bone and anterior to the rectum. During late pregnancy, its capacity is reduced due to compression by the enlarging uterus, resulting in increased frequency of urination. In males, the anatomy is similar, minus the uterus, and with the addition of the prostate inferior to the bladder. The bladder is a retroperitoneal organ whose "dome" distends superiorly when the bladder is filling with urine.

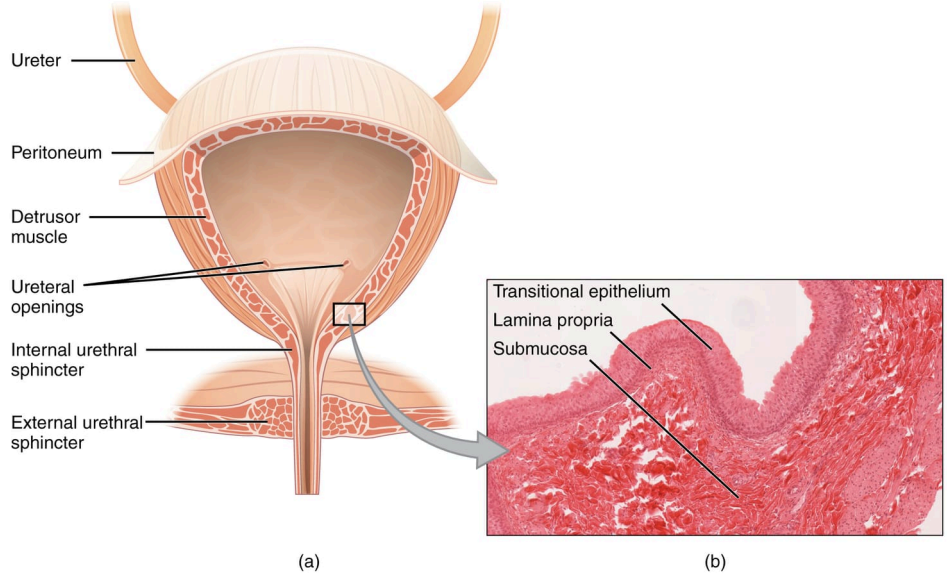


Figure 5.2.2: Bladder (a) Anterior cross section of the bladder. (b) The detrusor muscle of the bladder (source: monkey tissue) LM × 448. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012). (CC BY 4.0; via Gross Anatomy of Urine Transport). Detailed text description of the Figure 5.2.2.

The bladder is a highly distensible organ comprised of irregular crisscrossing bands of smooth muscle collectively called the detrusor muscle. The interior surface is made of transitional cellular epithelium that is structurally suited for the large volume fluctuations of the bladder. When empty, it resembles columnar epithelia, but when stretched, it "transitions" (hence the name) to

a squamous appearance. Volumes in adults can range from nearly zero to 500–600 mL.

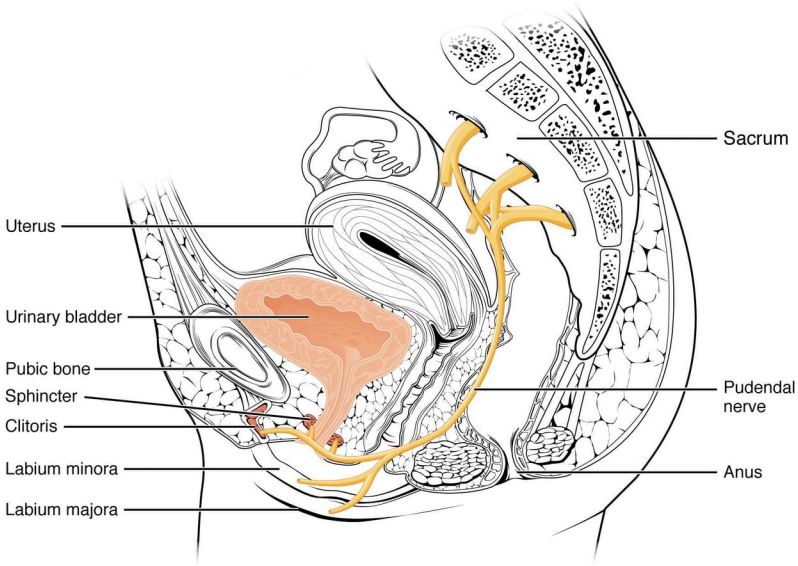
The detrusor muscle contracts with significant force in the young. The bladder's strength diminishes with age, but voluntary contractions of abdominal skeletal muscles can increase intra-abdominal pressure to promote more forceful bladder emptying. Such voluntary contraction is also used in forceful defecation and childbirth.

Micturition Reflex

Micturition is a less-often used, but proper term for urination or voiding. It results from an interplay of involuntary and voluntary actions by the internal and external urethral sphincters. When bladder volume reaches about 150 mL, an urge to void is sensed but is easily overridden. Voluntary control of urination relies on consciously preventing relaxation of the external urethral sphincter to maintain urinary continence. As the bladder fills, subsequent urges become harder to ignore. Ultimately, voluntary constraint fails with resulting incontinence, which will occur as bladder volume approaches 300 to 400 mL.

Normal micturition is a result of stretch receptors in the bladder wall that transmit nerve impulses to the sacral region of the spinal cord to generate a spinal reflex. The resulting parasympathetic neural outflow causes contraction of the detrusor muscle and relaxation of the involuntary internal urethral sphincter. At the same time, the spinal cord inhibits somatic motor neurons, resulting in the relaxation of the skeletal muscle of the external urethral sphincter. The micturition reflex is active in infants but with maturity, children learn to override the reflex by asserting external sphincter control, thereby delaying voiding (potty training). This reflex may be preserved even in the face of spinal cord injury that results in paraplegia or quadriplegia. However, relaxation of the external sphincter may not be possible in all cases, and therefore, periodic catheterization may be necessary for bladder emptying.

Nerves involved in the control of urination include the hypogastric, pelvic, and pudendal (Figure 5.2.3). Voluntary micturition requires an intact spinal cord and functional pudendal nerve arising from the sacral micturition center. Since the external urinary sphincter is voluntary skeletal muscle, actions by cholinergic neurons maintain contraction (and thereby continence) during filling of the bladder. At the same time, sympathetic nervous activity via the hypogastric nerves suppresses contraction of the detrusor muscle. With further bladder stretch, afferent signals traveling over sacral pelvic nerves activate parasympathetic neurons. This activates efferent neurons to release acetylcholine at the neuromuscular junctions, producing detrusor contraction and bladder emptying.



Figure

: Sagittal view illustrating the relationship of the urinary bladder and urethra to the uterus, vagina, rectum, and external genital structures. The pudendal nerve extends from the sacral region to the pelvic floor and external genitalia, highlighting neural pathways involved in urinary continence and pelvic floor function. (

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Detailed text description of the Figure

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Ureters

The kidneys and ureters are completely retroperitoneal, and the bladder has a peritoneal covering only over the dome. As urine is formed, it drains into the calyces of the kidney, which merge to form the funnel-shaped renal pelvis in the hilum of each kidney. The renal pelvis narrows to become the ureter of each kidney. As urine passes through the ureter, it does not passively drain into the bladder but rather is propelled by waves of peristalsis. As the ureters enter the pelvis, they sweep laterally, hugging the pelvic walls. As they approach the bladder, they turn medially and pierce the bladder wall obliquely. This is important because it creates a one-way valve (a physiological sphincter rather than an anatomical sphincter) that allows urine into the bladder but prevents reflux of urine from the bladder back into the ureter. Children born lacking this oblique course of the ureter through the bladder wall are susceptible to “vesicoureteral reflux,” which dramatically increases their risk of serious UTI. Pregnancy also increases the likelihood of reflux and UTI.

The ureters are approximately 30 cm long. The inner mucosa is lined with transitional epithelium (Figure 5.2.4) and scattered goblet cells that secrete protective mucus. The muscular layer of the ureter consists of longitudinal and circular smooth muscles that create the peristaltic contractions to move the urine into the bladder without the aid of gravity. Finally, a loose adventitial layer composed of collagen and fat anchors the ureters between the parietal peritoneum and the posterior abdominal wall.

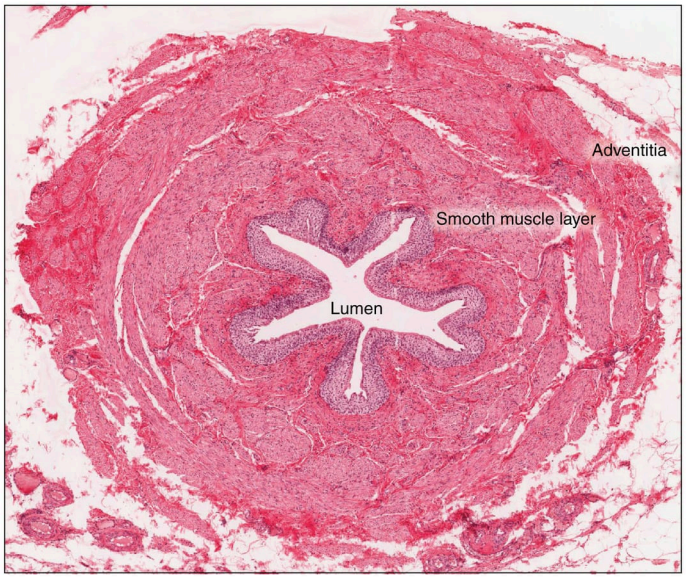


Figure 5.2.4: Contractions help to move urine through the lumen with contributions from fluid pressure and gravity. LM × 128. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012). (CC BY 4.0; via Gross Anatomy of Urine Transport). Detailed text description of the Figure 5.2.4.

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5.3: Gross Anatomy of the Kidney

Kidney Anatomy

The kidneys lie on either side of the spine in the retroperitoneal space between the parietal peritoneum and the posterior abdominal wall, well protected by muscle, fat, and ribs. They are roughly the size of your fist, and the male kidney is typically a bit larger than the female kidney. The kidneys are well vascularized, receiving about 25 percent of the cardiac output at rest.

There have never been sufficient kidney donations to provide a kidney to each person needing one. Watch this video to learn about the TED (Technology, Entertainment, Design) Conference held in March 2011. In this video, Dr. Anthony Atala discusses a cutting-edge technique in which a new kidney is "printed." The successful utilization of this technology is still several years in the future, but imagine a time when you can print a replacement organ or tissue on demand.

External Anatomy

The left kidney is located at about the T12 to L3 vertebrae, whereas the right is lower due to slight displacement by the liver. Upper portions of the kidneys are somewhat protected by the eleventh and twelfth ribs (Figure 5.3.1). Each kidney weighs about 125–175 g in males and 115–155 g in females. They are about 11–14 cm in length, 6 cm wide, and 4 cm thick, and are directly covered by a fibrous capsule composed of dense, irregular connective tissue that helps to hold their shape and protect them. This capsule is covered by a shock-absorbing layer of adipose tissue called the renal fat pad, which in turn is encompassed by a tough renal fascia. The fascia and, to a lesser extent, the overlying peritoneum serve to firmly anchor the kidneys to the posterior abdominal wall in a retroperitoneal position.

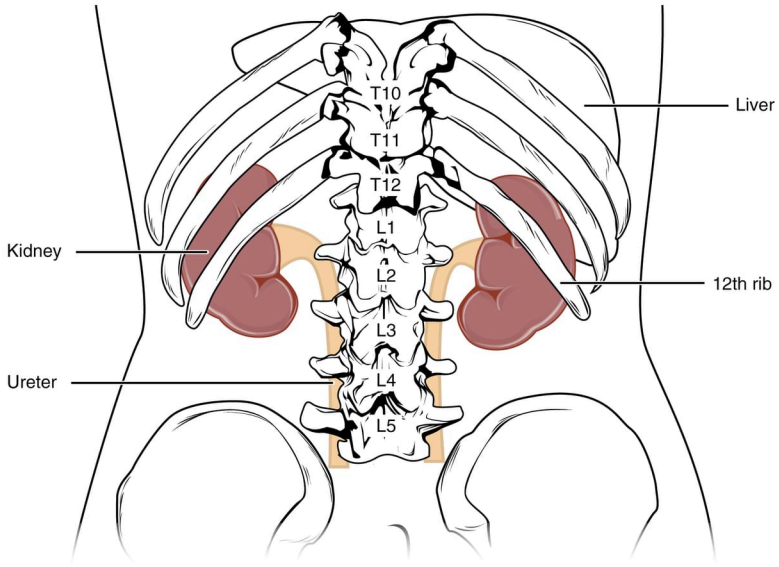


Figure 5.3.1: The kidneys are slightly protected by the ribs and are surrounded by fat for protection (not shown). (CC BY 4.0; via Gross Anatomy of the Kidney). Detailed text description of the Figure 5.3.1.

Internal Anatomy

A frontal section through the kidney reveals an outer region called the renal cortex and an inner region called the medulla (Figure 5.3.2). The renal columns are connective tissue extensions that radiate downward from the cortex through the medulla to separate the most characteristic features of the medulla, the renal pyramids and renal papillae. The papillae are bundles of collecting ducts that transport urine made by nephrons to the calyces of the kidney for excretion. The renal columns also serve to divide the kidney into 6–8 lobes and provide a supportive framework for vessels that enter and exit the cortex. The pyramids and renal columns taken together constitute the kidney lobes.

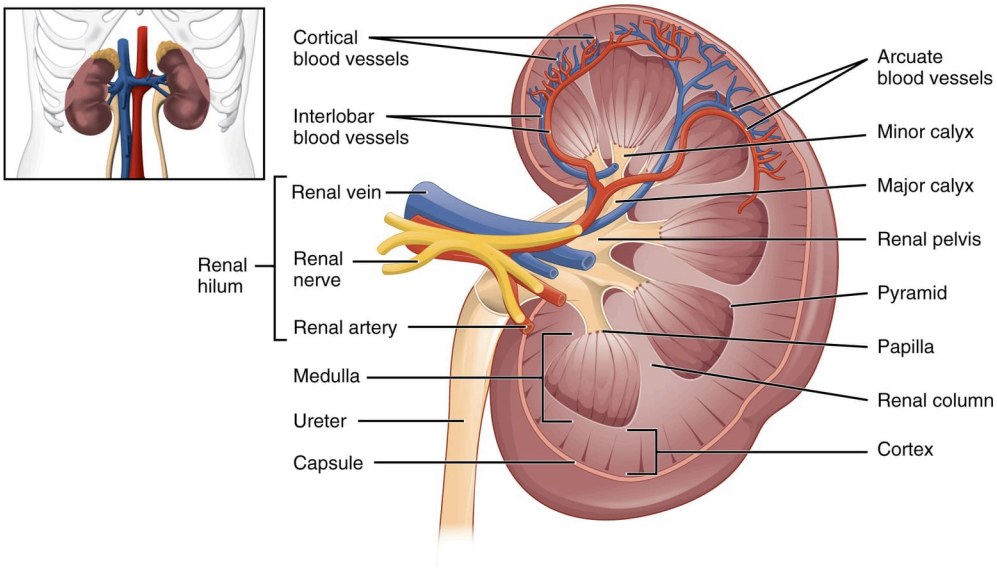


Figure 5.3.2: Left Kidney. (CC BY 4.0; via Gross Anatomy of the Kidney). Detailed text description of the Figure 5.3.2.

Renal Hilum

The renal hilum is the entry and exit site for structures servicing the kidneys: vessels, nerves, lymphatics, and ureters. The medial-facing hila are tucked into the sweeping convex outline of the cortex. Emerging from the hilum is the renal pelvis, which is formed from the major and minor calyxes in the kidney. The smooth muscle in the renal pelvis funnels urine via peristalsis into the ureter. The renal arteries form directly from the descending aorta, whereas the renal veins return cleansed blood directly to the inferior vena cava. The artery, vein, and renal pelvis are arranged in an anterior-to-posterior order.

Nephrons and Vessels

The renal artery first divides into segmental arteries, followed by further branching to form interlobar arteries that pass through the renal columns to reach the cortex (Figure 5.3.3). The interlobar arteries, in turn, branch into arcuate arteries, cortical radiate arteries, and then into afferent arterioles. The afferent arterioles service about 1.3 million nephrons in each kidney.

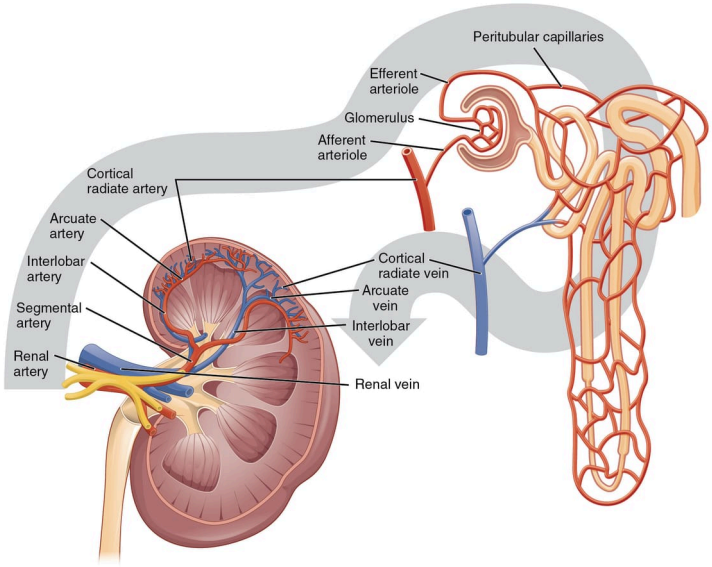
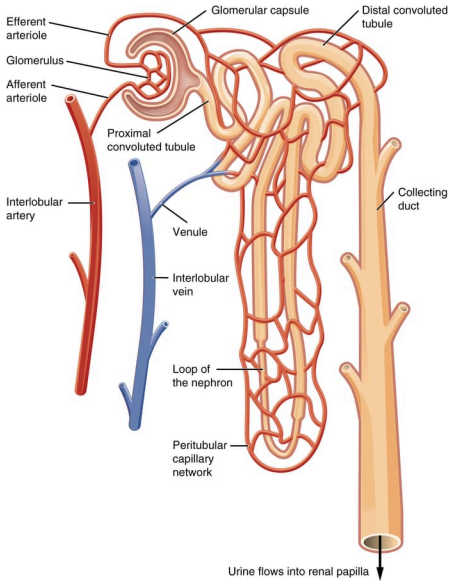


Figure 5.3.3: Blood Flow in the Kidney. (CC BY 4.0; via Gross Anatomy of the Kidney). Detailed text description of the Figure 5.3.3.

Nephrons are the “functional units” of the kidney; they cleanse the blood and balance the constituents of the circulation. The afferent arterioles form a tuft of high-pressure capillaries about 200 µm in diameter, the glomerulus. The rest of the nephron consists of a continuous sophisticated tubule whose proximal end surrounds the glomerulus in an intimate embrace—this is Bowman’s capsule. The glomerulus and Bowman’s capsule together form the renal corpuscle. As mentioned earlier, these glomerular capillaries filter the blood based on particle size. After passing through the renal corpuscle, the capillaries form a second arteriole, the efferent arteriole (Figure 5.3.4). These will next form a capillary network around the more distal portions of the nephron tubule, the peritubular capillaries and vasa recta, before returning to the venous system. As the glomerular filtrate progresses through the nephron, these capillary networks recover most of the solutes and water, and return them to the circulation. Since a capillary bed (the glomerulus) drains into a vessel that in turn forms a second capillary bed, the definition of a portal system is met. This is the only portal system in which an arteriole is found between the first and second capillary beds. (Portal systems also link the hypothalamus to the anterior pituitary, and the blood vessels of the digestive viscera to the liver.)



Figure

: The two capillary beds are clearly shown in this figure. The efferent arteriole is the connecting vessel between the glomerulus and the peritubular capillaries and vasa recta. (

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Detailed text description of the Figure 5.3.4

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Cortex

In a dissected kidney, it is easy to identify the cortex; it appears lighter in color compared to the rest of the kidney. All of the renal corpuscles as well as both the proximal convoluted tubules (PCTs) and distal convoluted tubules are found here. Some nephrons have a short loop of Henle that does not dip beyond the cortex. These nephrons are called cortical nephrons. About 15 percent of nephrons have long loops of Henle that extend deep into the medulla and are called juxtamedullary nephrons.

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5.4: Microscopic Anatomy of the Kidney

Nephrons: The Functional Unit

The renal structures that conduct the essential work of the kidney cannot be seen by the naked eye. Only a light or electron microscope can reveal these structures. Even then, serial sections and computer reconstruction are necessary to give us a comprehensive view of the functional anatomy of the nephron and its associated blood vessels.

Nephrons take a simple filtrate of the blood and modify it into urine. Many changes take place in the different parts of the nephron before urine is created for disposal. The term forming urine will be used hereafter to describe the filtrate as it is modified into true urine. The principle task of the nephron population is to balance the plasma to homeostatic set points and excrete potential toxins in the urine. They do this by accomplishing three principle functions—filtration, reabsorption, and secretion. They also have additional secondary functions that exert control in three areas: blood pressure (via production of renin), red blood cell production (via the hormone EPO), and calcium absorption (via conversion of calcidiol into calcitriol, the active form of vitamin D).

Renal Corpuscle

As discussed earlier, the renal corpuscle consists of a tuft of capillaries called the glomerulus that is largely surrounded by Bowman's (glomerular) capsule. The glomerulus is a high-pressure capillary bed between afferent and efferent arterioles. Bowman's capsule surrounds the glomerulus to form a lumen, and captures and directs this filtrate to the PCT. The outermost part of Bowman's capsule, the parietal layer, is a simple squamous epithelium. It transitions onto the glomerular capillaries in an intimate embrace to form the visceral layer of the capsule. Here, the cells are not squamous, but uniquely shaped cells (podocytes) extending finger-like arms (pedicels) to cover the glomerular capillaries (Figure 5.4.1). These projections interdigitate to form filtration slits, leaving small gaps between the digits to form a sieve. As blood passes through the glomerulus, 10 to 20 percent of the plasma filters between these sieve-like fingers to be captured by Bowman's capsule and funneled to the PCT. Where the fenestrae (windows) in the glomerular capillaries match the spaces between the podocyte "fingers," the only thing separating the capillary lumen and the lumen of Bowman's capsule is their shared basement membrane (Figure 5.4.2). These three features comprise what is known as the filtration membrane. This membrane permits very rapid movement of filtrate from capillary to capsule though pores that are only 70 nm in diameter.

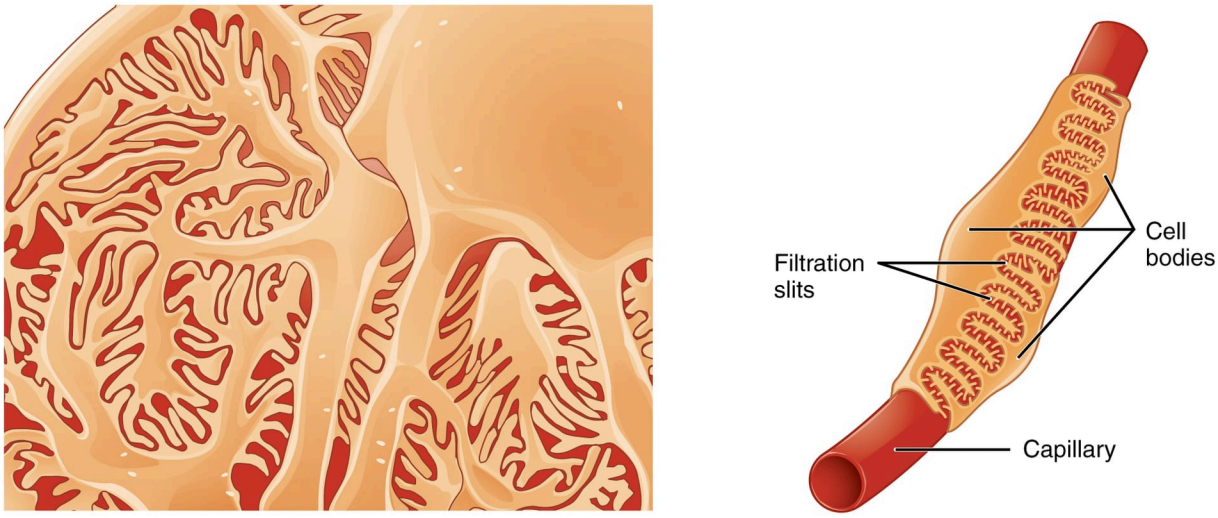


Figure 5.4.1: Podocytes interdigitate with structures called pedicels and filter substances in a way similar to fenestrations. In (a), the large cell body can be seen at the top right corner, with branches extending from the cell body. The smallest finger-like extensions are the pedicels. Pedicels on one podocyte always interdigitate with the pedicels of another podocyte. (b) This capillary has three podocytes wrapped around it. (CC BY 4.0; via Microscopic Anatomy of the Kidney). Detailed text description of the Figure 5.4.1.

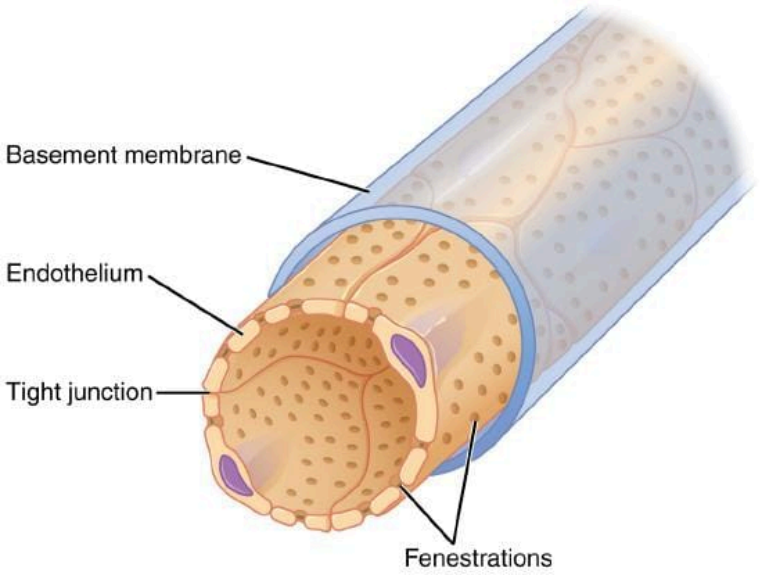


Figure 5.4.2: Fenestrations allow many substances to diffuse from the blood based primarily on size. (CC BY 4.0; via Microscopic Anatomy of the Kidney). Detailed text description of the Figure 5.4.2.

The fenestrations prevent filtration of blood cells or large proteins, but allow most other constituents through. These substances cross readily if they are less than 4 nm in size and most pass freely up to 8 nm in size. An additional factor affecting the ability of substances to cross this barrier is their electric charge. The proteins associated with these pores are negatively charged, so they tend to repel negatively charged substances and allow positively charged substances to pass more readily. The basement membrane prevents filtration of medium-to-large proteins such as globulins. There are also mesangial cells in the filtration membrane that can contract to help regulate the rate of filtration of the glomerulus. Overall, filtration is regulated by fenestrations in capillary endothelial cells, podocytes with filtration slits, membrane charge, and the basement membrane between capillary cells. The result is the creation of a filtrate that does not contain cells or large proteins, and has a slight predominance of positively charged substances.

Lying just outside Bowman's capsule and the glomerulus is the juxtaglomerular apparatus (JGA) (Figure 5.4.3). At the juncture where the afferent and efferent arterioles enter and leave Bowman's capsule, the initial part of the distal convoluted tubule (DCT) comes into direct contact with the arterioles. The wall of the DCT at that point forms a part of the JGA known as the macula densa. This cluster of cuboidal epithelial cells monitors the fluid composition of fluid flowing through the DCT. In response to the concentration of Na^+ in the fluid flowing past them, these cells release paracrine signals. They also have a single, nonmotile cilium that responds to the rate of fluid movement in the tubule. The paracrine signals released in response to changes in flow rate and Na^+ concentration are adenosine triphosphate (ATP) and adenosine.

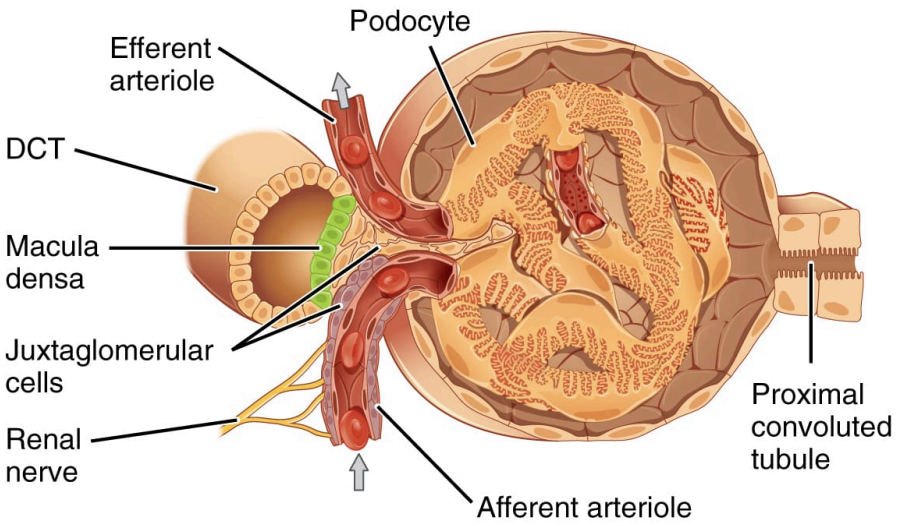


Figure 5.4.3: (a) The JGA allows specialized cells to monitor the composition of the fluid in the DCT and adjust the glomerular filtration rate. (b) This micrograph shows the glomerulus and surrounding structures. LM × 1540. (Micrograph provided by the Regents of University of Michigan Medical School © 2012). (CC BY 4.0; via Microscopic Anatomy of the Kidney). Detailed text description of the Figure 5.4.3.

A second cell type in this apparatus is the juxtaglomerular cell. This is a modified, smooth muscle cell lining the afferent arteriole that can contract or relax in response to ATP or adenosine released by the macula densa. Such contraction and relaxation regulate blood flow to the glomerulus. If the osmolarity of the filtrate is too high (hyperosmotic), the juxtaglomerular cells will contract, decreasing the glomerular filtration rate (GFR) so less plasma is filtered, leading to less urine formation and greater retention of fluid. This will ultimately decrease blood osmolarity toward the physiologic norm. If the osmolarity of the filtrate is too low, the juxtaglomerular cells will relax, increasing the GFR and enhancing the loss of water to the urine, causing blood osmolarity to rise. In other words, when blood osmolarity goes up, filtration and urine formation decrease and water is retained. When blood osmolarity goes down, filtration and urine formation increase and water is lost by way of the urine. The net result of these opposing actions is to keep the rate of filtration relatively constant. A second function of the macula densa cells is to regulate renin release from the juxtaglomerular cells of the afferent arteriole (Figure 5.4.4). Active renin is a protein comprised of 304 amino acids that cleaves several amino acids from angiotensinogen to produce angiotensin I. Angiotensin I is not biologically active until converted to angiotensin II by angiotensin-converting enzyme (ACE) from the lungs. Angiotensin II is a systemic vasoconstrictor that helps to regulate blood pressure by increasing it. Angiotensin II also stimulates the release of the steroid hormone aldosterone from the adrenal cortex. Aldosterone stimulates Na^+ reabsorption by the kidney, which also results in water retention and increased blood pressure.

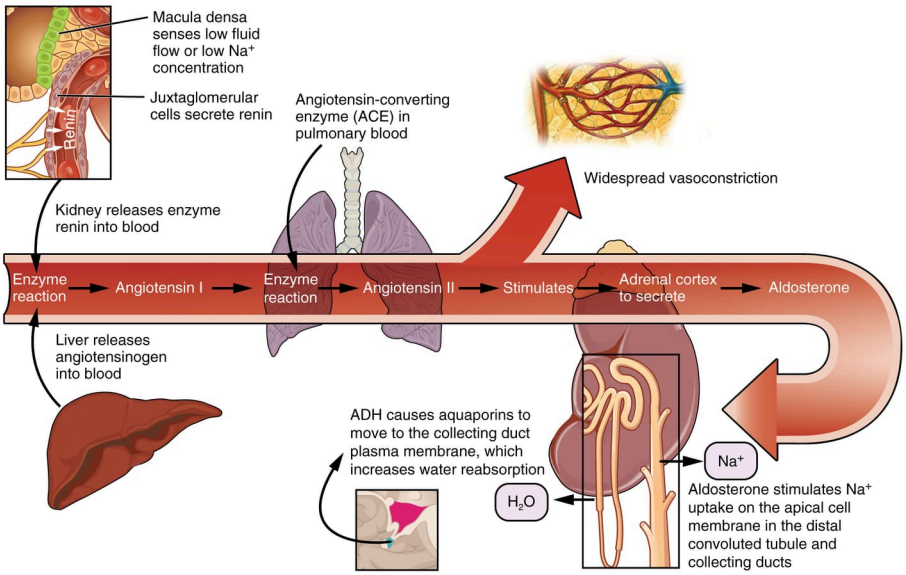


Figure 5.4.4: The enzyme renin converts the pro-enzyme angiotensin I; the lung-derived enzyme ACE converts angiotensin I into active angiotensin II. (CC BY 4.0; via Microscopic Anatomy of the Kidney). Detailed text description of the Figure 5.4.4.

Proximal Convoluted Tubule (PCT)

Filtered fluid collected by Bowman's capsule enters into the PCT. It is called convoluted due to its tortuous path. Simple cuboidal cells form this tubule with prominent microvilli on the luminal surface, forming a brush border. These microvilli create a large surface area to maximize the absorption and secretion of solutes (Na^+, Cl^-, glucose, etc.), the most essential function of this portion of the nephron. These cells actively transport ions across their membranes, so they possess a high concentration of mitochondria in order to produce sufficient ATP.

Loop of Henle

The descending and ascending portions of the loop of Henle (sometimes referred to as the nephron loop) are, of course, just continuations of the same tubule. They run adjacent and parallel to each other after having made a hairpin turn at the deepest point of their descent. The descending loop of Henle consists of an initial short, thick portion and long, thin portion, whereas the ascending loop consists of an initial short, thin portion followed by a long, thick portion. The descending thick portion consists of simple cuboidal epithelium similar to that of the PCT. The descending and ascending thin portions consists of simple squamous epithelium. As you will see later, these are important differences, since different portions of the loop have different permeabilities for solutes and water. The ascending thick portion consists of simple cuboidal epithelium similar to the DCT.

Distal Convoluted Tubule (DCT)

The DCT, like the PCT, is very tortuous and formed by simple cuboidal epithelium, but it is shorter than the PCT. These cells are not as active as those in the PCT; thus, there are fewer microvilli on the apical surface. However, these cells must also pump ions against their concentration gradient, so you will find of large numbers of mitochondria, although fewer than in the PCT.

Collecting Ducts

The collecting ducts are continuous with the nephron but not technically part of it. In fact, each duct collects filtrate from several nephrons for final modification. Collecting ducts merge as they descend deeper in the medulla to form about 30 terminal ducts, which empty at a papilla. They are lined with simple squamous epithelium with receptors for ADH. When stimulated by ADH, these cells will insert aquaporin channel proteins into their membranes, which as their name suggests, allow water to pass from the duct lumen through the cells and into the interstitial spaces to be recovered by the vasa recta. This process allows for the recovery of large amounts of water from the filtrate back into the blood. In the absence of ADH, these channels are not inserted, resulting in the excretion of water in the form of dilute urine. Most, if not all, cells of the body contain aquaporin molecules, whose channels

are so small that only water can pass. At least 10 types of aquaporins are known in humans, and six of those are found in the kidney. The function of all aquaporins is to allow the movement of water across the lipid-rich, hydrophobic cell membrane (Figure 5.4.5).

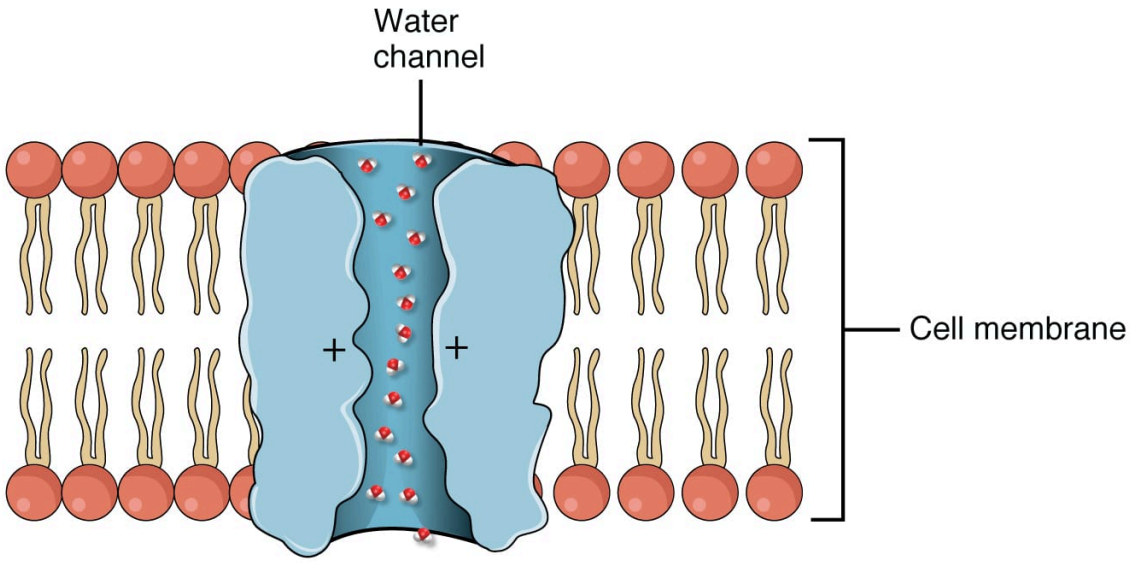


Figure 5.4.5: Positive charges inside the channel prevent the leakage of electrolytes across the cell membrane, while allowing water to move due to osmosis. (CC BY 4.0; via Microscopic Anatomy of the Kidney). Detailed text description of the Figure 5.4.5.

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5.5: Physiology of Urine Formation

Renal Physiology

Having reviewed the anatomy and microanatomy of the urinary system, now is the time to focus on the physiology. You will discover that different parts of the nephron utilize specific processes to produce urine: filtration, reabsorption, and secretion. You will learn how each of these processes works and where they occur along the nephron and collecting ducts. The physiologic goal is to modify the composition of the plasma and, in doing so, produce the waste product urine.

Failure of the renal anatomy and/or physiology can lead suddenly or gradually to renal failure. In this event, a number of symptoms, signs, or laboratory findings point to the diagnosis (Table 5.5.1).

Table 5.5.1: Symptoms of Kidney Failure

Category	Symptoms
General	Weakness, fatigue, lethargy, loss of appetite
Respiratory	Shortness of breath
Fluid balance	Edema, excessive urination, oliguria
Blood/metabolic	Anemia, uremia, metabolic acidosis, metabolic alkalosis
Cardiovascular	Heart arrhythmias

Glomerular Filtration Rate (GFR)

The volume of filtrate formed by both kidneys per minute is termed the glomerular filtration rate (GFR). The heart pumps about 5 L blood per min under resting conditions. Approximately 20 percent or one liter enters the kidneys to be filtered. On average, this liter results in the production of about 125 mL/min filtrate produced in males (range of 90 to 140 mL/min) and 105 mL/min filtrate produced in females (range of 80 to 125 mL/min). This amount equates to a volume of about 180 L/day in males and 150 L/day in females. Ninety-nine percent of this filtrate is returned to the circulation by reabsorption so that only about 1–2 liters of urine are produced per day (Table 5.5.2).

Table 5.5.2: Calculating Urine Formation per Day

Parameter	Flow per minute (mL)	Calculation
Renal blood flow	1050	Cardiac output is about 5000 mL/minute, of which 21 percent flows through the kidney. 5000*0.21 = 1050 mL blood/min
Renal plasma flow	578	Renal plasma flow equals the blood flow per minute times the hematocrit. If a person has a hematocrit of 45, then the renal plasma flow is 55 percent. 1050*0.55 = 578 mL plasma/min
Glomerular filtration rate	110	The GFR is the amount of plasma entering Bowman's capsule per minute. It is the renal plasma flow times the fraction that enters the renal capsule (19 percent). 578*0.19 = 110 mL filtrate/min

Parameter	Flow per minute (mL)	Calculation
Urine	1296 ml/day	The filtrate not recovered by the kidney is the urine that will be eliminated. It is the GFR times the fraction of the filtrate that is not reabsorbed (0.8 percent). 110*.008 = 0.9 mL urine /min Multiply urine/min times 60 minutes times 24 hours to get daily urine production. 0.9*60*24 = 1296 mL/day urine

GFR is influenced by the hydrostatic pressure and colloid osmotic pressure on either side of the capillary membrane of the glomerulus. Recall that filtration occurs as pressure forces fluid and solutes through a semipermeable barrier with the solute movement constrained by particle size. Hydrostatic pressure is the pressure produced by a fluid against a surface. If you have a fluid on both sides of a barrier, both fluids exert a pressure in opposing directions. Net fluid movement will be in the direction of the lower pressure. Osmosis is the movement of solvent (water) across a membrane that is impermeable to a solute in the solution. This creates a pressure, osmotic pressure, which will exist until the solute concentration is the same on both sides of a semipermeable membrane. As long as the concentration differs, water will move. Glomerular filtration occurs when glomerular hydrostatic pressure exceeds the luminal hydrostatic pressure of Bowman's capsule. There is also an opposing force, the osmotic pressure, which is typically higher in the glomerular capillary.

To understand why this is so, look more closely at the microenvironment on either side of the filtration membrane. You will find osmotic pressure exerted by the solutes inside the lumen of the capillary as well as inside of Bowman's capsule. Since the filtration membrane limits the size of particles crossing the membrane, the osmotic pressure inside the glomerular capillary is higher than the osmotic pressure in Bowman's capsule. Recall that cells and the medium-to-large proteins cannot pass between the podocyte processes or through the fenestrations of the capillary endothelial cells. This means that red and white blood cells, platelets, albumins, and other proteins too large to pass through the filter remain in the capillary, creating an average colloid osmotic pressure of 30 mm Hg within the capillary. The absence of proteins in Bowman's space (the lumen within Bowman's capsule) results in an osmotic pressure near zero. Thus, the only pressure moving fluid across the capillary wall into the lumen of Bowman's space is hydrostatic pressure. Hydrostatic (fluid) pressure is sufficient to push water through the membrane despite the osmotic pressure working against it. The sum of all of the influences, both osmotic and hydrostatic, results in a net filtration pressure (NFP) of about 10 mm Hg (Figure 5.5.1).

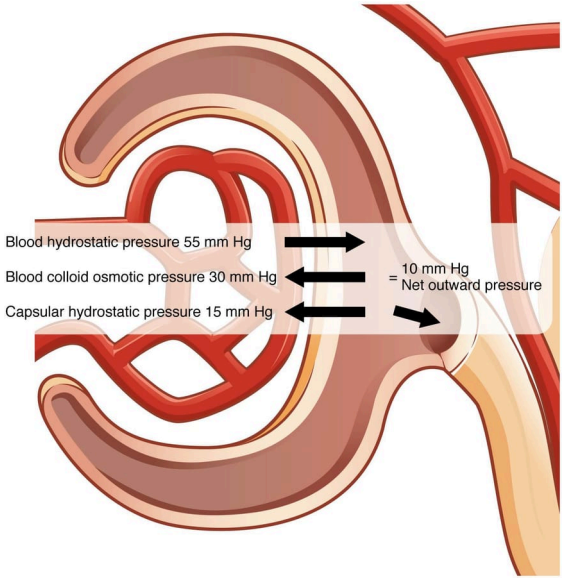


Figure 5.5.1: Net Filtration Pressure. The NFP is the sum of osmotic and hydrostatic pressures. (CC BY 4.0; via Physiology of Urine Formation).

Figure 5.5.1 shows the pressure forces that determine glomerular filtration within the renal corpuscle. It explains how differences in pressure cause fluid to move from the glomerular capillaries into the glomerular capsule, beginning the process of urine formation.

At the center is the glomerulus, a network of capillaries enclosed by the glomerular capsule. Arrows indicate the movement of fluid across the capillary wall and into the capsule. Three pressures are labeled:

- Blood hydrostatic pressure (55 mm Hg) pushes fluid outward from the glomerular capillaries into the capsule.
- Blood colloid osmotic pressure (30 mm Hg) pulls fluid inward toward the capillaries because proteins remaining in the blood attract water.
- Capsular hydrostatic pressure (15 mm Hg) also pushes fluid inward, opposing movement into the capsule.

The diagram shows one outward-directed force and two opposing inward-directed forces. The net filtration pressure is calculated by subtracting the two opposing pressures from the outward blood hydrostatic pressure:

55 mm Hg - 30 mm Hg - 15 mm Hg = 10 mm Hg outward

This means that the total force favoring filtration is 10 mm Hg directed outward.

Overall, the figure shows that:

- blood hydrostatic pressure is the main force driving filtration
- blood colloid osmotic pressure and capsular hydrostatic pressure oppose filtration
- filtration occurs because the outward pressure is greater than the combined opposing pressures
- the result is a net outward movement of fluid from the blood into the glomerular capsule

The diagram emphasizes that glomerular filtration depends on the balance of these pressures and that a positive net filtration pressure is what allows fluid to enter the nephron and begin forming urine.

A proper concentration of solutes in the blood is important in maintaining osmotic pressure both in the glomerulus and systemically. There are disorders in which too much protein passes through the filtration slits into the kidney filtrate. This excess protein in the filtrate leads to a deficiency of circulating plasma proteins. In turn, the presence of protein in the urine increases its osmolarity; this holds more water in the filtrate and results in an increase in urine volume. Because there is less circulating protein, principally albumin, the osmotic pressure of the blood falls. Less osmotic pressure pulling water into the capillaries tips the balance towards hydrostatic pressure, which tends to push it out of the capillaries. The net effect is that water is lost from the circulation to interstitial tissues and cells. This “plumps up” the tissues and cells, a condition termed systemic edema.

Net Filtration Pressure (NFP)

NFP determines filtration rates through the kidney. It is determined as follows:

$$NFP = Glomerular\ blood\ hydrostatic\ pressure\ (GBHP) - [capsular\ hydrostatic\ pressure\ (CHP) + blood\ colloid\ osmotic\ pre$$

That is:

$$NFP = GBHP - [CHP + BCOP] = 10\ mm\ Hg \tag{5.5.2}$$

Or:

$$NFP = 55 - [15 + 30] = 10\ mm\ Hg \tag{5.5.3}$$

As you can see, there is a low net pressure across the filtration membrane. Intuitively, you should realize that minor changes in osmolarity of the blood or changes in capillary blood pressure result in major changes in the amount of filtrate formed at any given point in time. The kidney is able to cope with a wide range of blood pressures. In large part, this is due to the autoregulatory nature of smooth muscle. When you stretch it, it contracts. Thus, when blood pressure goes up, smooth muscle in the afferent capillaries contracts to limit any increase in blood flow and filtration rate. When blood pressure drops, the same capillaries relax to maintain blood flow and filtration rate. The net result is a relatively steady flow of blood into the glomerulus and a relatively steady filtration rate in spite of significant systemic blood pressure changes. Mean arterial blood pressure is calculated by adding 1/3 of the difference between the systolic and diastolic pressures to the diastolic pressure. Therefore, if the blood pressure is 110/80, the difference between systolic and diastolic pressure is 30. One third of this is 10, and when you add this to the diastolic pressure of 80, you arrive at a calculated mean arterial pressure of 90 mm Hg. Therefore, if you use mean arterial pressure for the GBHP in the formula for calculating NFP, you can determine that as long as mean arterial pressure is above approximately 60 mm Hg, the pressure will be adequate to maintain glomerular filtration. Blood pressures below this level will impair renal function

and cause systemic disorders that are severe enough to threaten survival. This condition is called shock.

Determination of the GFR is one of the tools used to assess the kidney's excretory function. This is more than just an academic exercise. Since many drugs are excreted in the urine, a decline in renal function can lead to toxic accumulations. Additionally, administration of appropriate drug dosages for those drugs primarily excreted by the kidney requires an accurate assessment of GFR. GFR can be estimated closely by intravenous administration of inulin. Inulin is a plant polysaccharide that is neither reabsorbed nor secreted by the kidney. Its appearance in the urine is directly proportional to the rate at which it is filtered by the renal corpuscle. However, since measuring inulin clearance is cumbersome in the clinical setting, most often, the GFR is estimated by measuring naturally occurring creatinine, a protein-derived molecule produced by muscle metabolism that is not reabsorbed and only slightly secreted by the nephron.

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5.6: Tubular Reabsorption

Renal Tubular Process

With up to 180 liters per day passing through the nephrons of the kidney, it is quite obvious that most of that fluid and its contents must be reabsorbed. That recovery occurs in the PCT, loop of Henle, DCT, and the collecting ducts (Table 5.6.1 and Figure 5.6.1). Various portions of the nephron differ in their capacity to reabsorb water and specific solutes. While much of the reabsorption and secretion occur passively based on concentration gradients, the amount of water that is reabsorbed or lost is tightly regulated. This control is exerted directly by ADH and aldosterone, and indirectly by renin. Most water is recovered in the PCT, loop of Henle, and DCT. About 10 percent (about 18 L) reaches the collecting ducts. The collecting ducts, under the influence of ADH, can recover almost all of the water passing through them, in cases of dehydration, or almost none of the water, in cases of over-hydration.

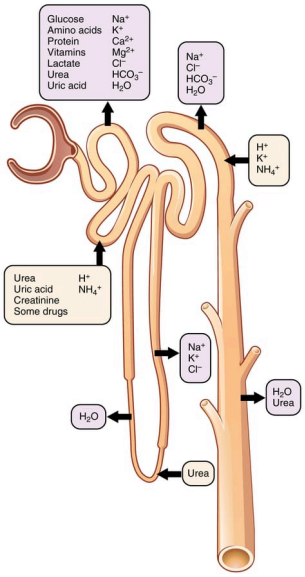


Figure 5.6.1: Locations of Secretion and Reabsorption in the Nephron. (CC BY 4.0; via Tubular Reabsorption). Detailed text description of the Figure 5.6.1.

Table 5.6.1: Substances Secreted or Reabsorbed in the Nephron and Their Locations

Substance	PCT	Loop of Henle	DCT	Collecting ducts
Glucose	Almost 100 percent reabsorbed; secondary active transport with Na^+	No data available	No data available	No data available
Oligopeptides, proteins, amino acids	Almost 100 percent reabsorbed; symport with Na^+	No data available	No data available	No data available
Vitamins	Reabsorbed	No data available	No data available	No data available
Lactate	Reabsorbed	No data available	No data available	No data available
Creatinine	Secreted	No data available	No data available	No data available
Urea	50 percent reabsorbed by diffusion; also secreted	Secretion, diffusion in descending limb	No data available	Reabsorption in medullary collecting ducts; diffusion

Substance	PCT	Loop of Henle	DCT	Collecting ducts
Sodium	65 percent actively reabsorbed	25 percent reabsorbed in thick ascending limb; active transport	5 percent reabsorbed; active	5 percent reabsorbed, stimulated by aldosterone; active
Chloride	Reabsorbed, symport with Na^+, diffusion	Reabsorbed in thin and thick ascending limb; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; symport
Water	67 percent reabsorbed osmotically with solutes	15 percent reabsorbed in descending limb; osmosis	8 percent reabsorbed if ADH; osmosis	Variable amounts reabsorbed, controlled by ADH, osmosis
HCO_3^-	80–90 percent symport reabsorption with Na^+	Reabsorbed, symport with Na^+ and antiport with Cl^-; in ascending limb	No data available	Reabsorbed antiport with Cl^-
H^+	Secreted; diffusion	No data available	Secreted; active	Secreted; active
NH_4^+	Secreted; diffusion	No data available	Secreted; diffusion	Secreted; diffusion
Some drugs	Secreted	No data available	Secreted; active	Secreted; active
Potassium	65 percent reabsorbed; diffusion	20 percent reabsorbed in thick ascending limb; symport	Secreted; active	Secretion controlled by aldosterone; active
Calcium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion	No data available	Reabsorbed if parathyroid hormone present; active
Magnesium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion	Reabsorbed	No data available
Phosphate	85 percent reabsorbed, inhibited by parathyroid hormone, diffusion	No data available	Reabsorbed; diffusion	No data available

Mechanisms of Recovery

Mechanisms by which substances move across membranes for reabsorption or secretion include active transport, diffusion, facilitated diffusion, secondary active transport, and osmosis. These were discussed in an earlier chapter, and you may wish to review them.

Active transport utilizes energy, usually the energy found in a phosphate bond of ATP, to move a substance across a membrane from a low to a high concentration. It is very specific and must have an appropriately shaped receptor for the substance to be transported. An example would be the active transport of Na^+ out of a cell and K^+ into a cell by the Na^+/K^+ pump. Both ions are moved in opposite directions from a lower to a higher concentration.

Simple diffusion moves a substance from a higher to a lower concentration down its concentration gradient. It requires no energy and only needs to be soluble.

Facilitated diffusion is similar to diffusion in that it moves a substance down its concentration gradient. The difference is that it requires specific membrane receptors or channel proteins for movement. The movement of glucose and, in certain situations, Na^+ ions, is an example of facilitated diffusion. In some cases of mediated transport, two different substances share the same channel protein port; these mechanisms are described by the terms symport and antiport.

Symport mechanisms move two or more substances in the same direction at the same time, whereas antiport mechanisms move two or more substances in opposite directions across the cell membrane. Both mechanisms may utilize concentration gradients maintained by ATP pumps. As described previously, when active transport powers the transport of another substance in this way,

it is called “secondary active transport.” Glucose reabsorption in the kidneys is by secondary active transport. Na^+/K^+ ATPases on the basal membrane of a tubular cell constantly pump Na^+ out of the cell, maintaining a strong electrochemical gradient for Na^+ to move into the cell from the tubular lumen. On the luminal (apical) surface, a Na^+/glucose symport protein assists both Na+ and glucose movement into the cell. The cotransporter moves glucose into the cell against its concentration gradient as Na^+ moves down the electrochemical gradient created by the basal membranes Na^+/K^+ ATPases. The glucose molecule then diffuses across the basal membrane by facilitated diffusion into the interstitial space and from there into peritubular capillaries.

Most of the Ca^{++}, Na^+, glucose, and amino acids must be reabsorbed by the nephron to maintain homeostatic plasma concentrations. Other substances, such as urea, K^+, ammonia (NH_3), creatinine, and some drugs are secreted into the filtrate as waste products. Acid–base balance is maintained through actions of the lungs and kidneys: The lungs rid the body of H^+, whereas the kidneys secrete or reabsorb H^+ and HCO_3^- (Table 5.6.2). In the case of urea, about 50 percent is passively reabsorbed by the PCT. More is recovered by in the collecting ducts as needed. ADH induces the insertion of urea transporters and aquaporin channel proteins.

Table 5.6.2: Substances Filtered and Reabsorbed by the Kidney per 24 Hours

Substance	Amount filtered (grams)	Amount reabsorbed (grams)	Amount in urine (grams)
Water	180 L	179 L	1 L
Proteins	10–20	10–20	0
Chlorine	630	625	5
Sodium	540	537	3
Bicarbonate	300	299.7	0.3
Glucose	180	180	0
Urea	53	28	25
Potassium	28	24	4
Uric acid	8.5	7.7	0.8
Creatinine	1.4	0	1.4

Reabsorption and Secretion in the PCT

The renal corpuscle filters the blood to create a filtrate that differs from blood mainly in the absence of cells and large proteins. From this point to the ends of the collecting ducts, the filtrate or forming urine is undergoing modification through secretion and reabsorption before true urine is produced. The first point at which the forming urine is modified is in the PCT. Here, some substances are reabsorbed, whereas others are secreted. Note the use of the term “reabsorbed.” All of these substances were “absorbed” in the digestive tract—99 percent of the water and most of the solutes filtered by the nephron must be reabsorbed. Water and substances that are reabsorbed are returned to the circulation by the peritubular and vasa recta capillaries. It is important to understand the difference between the glomerulus and the peritubular and vasa recta capillaries. The glomerulus has a relatively high pressure inside its capillaries and can sustain this by dilating the afferent arteriole while constricting the efferent arteriole. This assures adequate filtration pressure even as the systemic blood pressure varies. Movement of water into the peritubular capillaries and vasa recta will be influenced primarily by osmolarity and concentration gradients. Sodium is actively pumped out of the PCT into the interstitial spaces between cells and diffuses down its concentration gradient into the peritubular capillary. As it does so, water will follow passively to maintain an isotonic fluid environment inside the capillary. This is called obligatory water reabsorption, because water is “obliged” to follow the Na^+ (Figure 5.6.2).

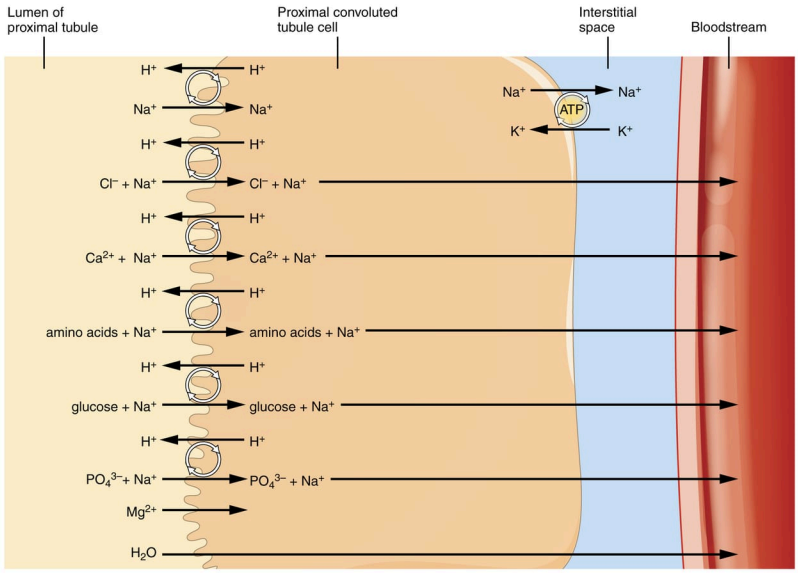


Figure 5.6.2: Substances Reabsorbed and Secreted by the PCT. (CC BY 4.0; via Tubular Reabsorption). Detailed text description of the Figure 5.6.2.

More substances move across the membranes of the PCT than any other portion of the nephron. Many of these substances (amino acids and glucose) use symport mechanisms for transport along with Na^+. Antiport, active transport, diffusion, and facilitated diffusion are additional mechanisms by which substances are moved from one side of a membrane to the other. Recall that cells have two surfaces: apical and basal. The apical surface is the one facing the lumen or open space of a cavity or tube, in this case, the inside of the PCT. The basal surface of the cell faces the connective tissue base to which the cell attaches (basement membrane) or the cell membrane closer to the basement membrane if there is a stratified layer of cells. In the PCT, there is a single layer of simple cuboidal endothelial cells against the basement membrane. The numbers and particular types of pumps and channels vary between the apical and basilar surfaces. A few of the substances that are transported with Na^+ (symport mechanism) on the apical membrane include Cl^-, Ca^{++}, amino acids, glucose, and PO_4^{3-}. Sodium is actively exchanged for K^+ using ATP on the basal membrane. Most of the substances transported by a symport mechanism on the apical membrane are transported by facilitated diffusion on the basal membrane. At least three ions, K^+, Ca^{++}, and Mg^{++}, diffuse laterally between adjacent cell membranes (transcellular).

About 67 percent of the water, Na^+, and K^+ entering the nephron is reabsorbed in the PCT and returned to the circulation. Almost 100 percent of glucose, amino acids, and other organic substances such as vitamins are normally recovered here. Some glucose may appear in the urine if circulating glucose levels are high enough that all the glucose transporters in the PCT are saturated, so that their capacity to move glucose is exceeded (transport maximum, or T_m). In males, the maximum amount of glucose that can be recovered is about 375 mg/min, whereas in females, it is about 300 mg/min. This recovery rate translates to an arterial concentration of about 200 mg/dL. Though an exceptionally high sugar intake might cause sugar to appear briefly in the urine, the appearance of glycosuria usually points to type I or II diabetes mellitus. The transport of glucose from the lumen of the PCT to the interstitial space is similar to the way it is absorbed by the small intestine. Both glucose and Na^+ bind simultaneously to the same symport proteins on the apical surface of the cell to be transported in the same direction, toward the interstitial space. Sodium moves down its electrochemical and concentration gradient into the cell and takes glucose with it. Na^+ is then actively pumped out of the cell at the basal surface of the cell into the interstitial space. Glucose leaves the cell to enter the interstitial space by facilitated diffusion. The energy to move glucose comes from the Na^+/K^+ ATPase that pumps Na^+ out of the cell on the basal surface. Fifty percent of Cl^- and variable quantities of Ca^{++}, Mg^{++}, and HPO_4^{2-} are also recovered in the PCT.

Recovery of bicarbonate (HCO_3^-) is vital to the maintenance of acid–base balance, since it is a very powerful and fast-acting buffer. An important enzyme is used to catalyze this mechanism: carbonic anhydrase (CA). This same enzyme and reaction is used in red blood cells in the transportation of CO_2, in the stomach to produce hydrochloric acid, and in the pancreas to produce HCO_3^- to buffer acidic chyme from the stomach. In the kidney, most of the CA is located within the cell, but a small amount is bound to the brush border of the membrane on the apical surface of the cell. In the lumen of the PCT, HCO_3^- combines with hydrogen ions

to form carbonic acid (H_2CO_3). This is enzymatically catalyzed into CO_2 and water, which diffuse across the apical membrane into the cell. Water can move osmotically across the lipid bilayer membrane due to the presence of aquaporin water channels. Inside the cell, the reverse reaction occurs to produce bicarbonate ions (HCO_3^-). These bicarbonate ions are cotransported with Na^+ across the basal membrane to the interstitial space around the PCT (Figure 5.6.3). At the same time this is occurring, a Na^+/H^+ antiporter excretes H^+ into the lumen, while it recovers Na^+. Note how the hydrogen ion is recycled so that bicarbonate can be recovered. Also, note that a Na^+ gradient is created by the Na^+/K^+ pump.

$$HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2 \tag{5.6.1}$$

The significant recovery of solutes from the PCT lumen to the interstitial space creates an osmotic gradient that promotes water recovery. As noted before, water moves through channels created by the aquaporin proteins. These proteins are found in all cells in varying amounts and help regulate water movement across membranes and through cells by creating a passageway across the hydrophobic lipid bilayer membrane. Changing the number of aquaporin proteins in membranes of the collecting ducts also helps to regulate the osmolarity of the blood. The movement of many positively charged ions also creates an electrochemical gradient. This charge promotes the movement of negative ions toward the interstitial spaces and the movement of positive ions toward the lumen.

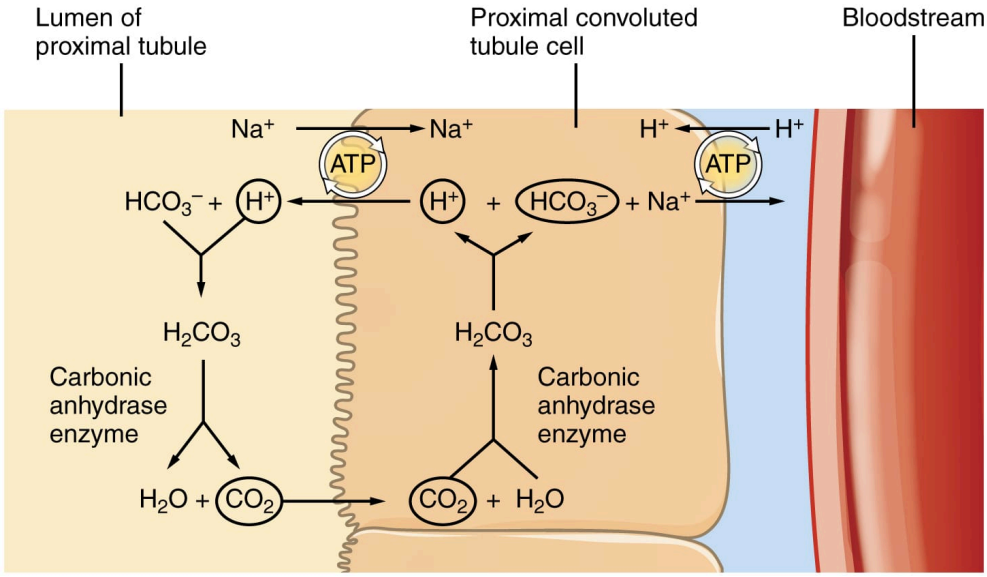


Figure 5.6.3: Reabsorption of Bicarbonate from the PCT. (CC BY 4.0; via Tubular Reabsorption). Detailed text description of the Figure 5.6.3.

Reabsorption and Secretion in the Loop of Henle

The loop of Henle consists of two sections: thick and thin descending and thin and thick ascending sections. The loops of cortical nephrons do not extend into the renal medulla very far, if at all. Juxtamedullary nephrons have loops that extend variable distances, some very deep into the medulla. The descending and ascending portions of the loop are highly specialized to enable recovery of much of the Na^+ and water that were filtered by the glomerulus. As the forming urine moves through the loop, the osmolarity will change from isosmotic with blood (about 278–300 mOsmol/kg) to both a very hypertonic solution of about 1200 mOsmol/kg and a very hypotonic solution of about 100 mOsmol/kg. These changes are accomplished by osmosis in the descending limb and active transport in the ascending limb. Solutes and water recovered from these loops are returned to the circulation by way of the vasa recta.

Descending Loop

The majority of the descending loop is comprised of simple squamous epithelial cells; to simplify the function of the loop, this discussion focuses on these cells. These membranes have permanent aquaporin channel proteins that allow unrestricted movement of water from the descending loop into the surrounding interstitium as osmolarity increases from about 300 mOsmol/

kg to about 1200 mOsmol/kg in the filtrate. This increase results in reabsorption of up to 15 percent of the water entering the nephron. Modest amounts of urea, Na^+, and other ions are also recovered here.

Most of the solutes that were filtered in the glomerulus have now been recovered along with a majority of water, about 82 percent. As the forming urine enters the ascending loop, major adjustments will be made to the concentration of solutes to create what you perceive as urine.

Ascending Loop

The ascending loop is made of very short thin and longer thick portions. Once again, to simplify the function, this section only considers the thick portion. The thick portion is lined with simple cuboidal epithelium without a brush border. It is completely impermeable to water due to the absence of aquaporin proteins, but ions, mainly Na^+ and CL^-, are actively reabsorbed by a cotransport system. This has two significant effects: Removal of NaCl while retaining water leads to a hypoosomotic filtrate by the time it reaches the DCT; pumping NaCl into the interstitial space contributes to the hyperosmotic environment in the kidney medulla.

The $Na^{+/}K^+$ ATPase pumps in the basal membrane create an electrochemical gradient, allowing reabsorption of Cl^- by Na^+/Cl^- symporters in the apical membrane. At the same time that Na^+ is actively pumped from the basal side of the cell into the interstitial fluid, Cl^- follows the Na^+ from the lumen into the interstitial fluid by a paracellular route between cells through leaky tight junctions. These are found between cells of the ascending loop, where they allow certain solutes to move according to their concentration gradient. Most of the K^+ that enters the cell via symporters returns to the lumen (down its concentration gradient) through leaky channels in the apical membrane. Note the environment now created in the interstitial space: With the "back door exiting" K^+, there is one Na^+ and two Cl^- ions left in the interstitium surrounding the ascending loop. Therefore, in comparison to the lumen of the loop, the interstitial space is now a negatively charged environment. This negative charge attracts cations (Na^+, K^+, Ca^{++}, and Mg^{++}) from the lumen via a paracellular route to the interstitial space and vasa recta.

Countercurrent Multiplier System

The structure of the loop of Henle and associated vasa recta create a countercurrent multiplier system (Figure 5.6.4). The countercurrent term comes from the fact that the descending and ascending loops are next to each other and their fluid flows in opposite directions (countercurrent). The multiplier term is due to the action of solute pumps that increase (multiply) the concentrations of urea and Na^+ deep in the medulla.

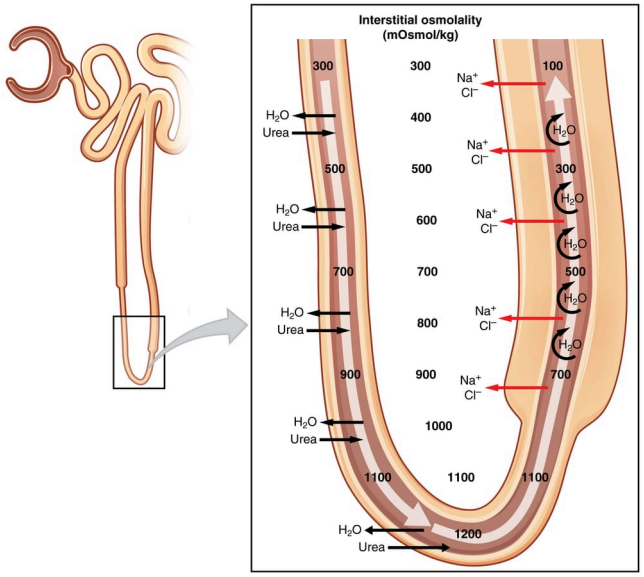


Figure 5.6.4: Countercurrent Multiplier System. (CC BY 4.0; via Tubular Reabsorption). Detailed text description of the Figure 5.6.4.

As discussed above, the ascending loop actively reabsorbs NaCl out of the forming urine into the interstitial spaces. In addition, collecting ducts have urea pumps that actively pump urea into the interstitial spaces. This results in the recovery of NaCl to the circulation via the vasa recta and creates a high osmolar environment in the depths of the medulla.

Ammonia (NH_3) is a toxic byproduct of protein metabolism. It is formed as amino acids are deaminated by liver hepatocytes. That means that the amine group, NH_2, is removed from amino acids as they are broken down. Most of the resulting ammonia is converted into urea by liver hepatocytes. Urea is not only less toxic but is utilized to aid in the recovery of water by the loop of Henle and collecting ducts. At the same time that water is freely diffusing out of the descending loop through aquaporin channels into the interstitial spaces of the medulla, urea freely diffuses into the lumen of the descending loop as it descends deeper into the medulla, much of it to be reabsorbed from the forming urine when it reaches the collecting duct. Thus, the movement of Na^+ and urea into the interstitial spaces by these mechanisms creates the hyperosmotic environment of the medulla. The net result of this countercurrent multiplier system is to recover both water and Na^+ in the circulation.

The amino acid glutamine can be deaminated by the kidney. As NH_2 from the amino acid is converted into NH_3 and pumped into the lumen of the PCT, Na^+ and HCO_3^- are excreted into the interstitial fluid of the renal pyramid via a symport mechanism. When this process occurs in the cells of the PCT, the added benefit is a net loss of a hydrogen ion (complexed to ammonia to form the weak acid NH_4^+) in the urine and a gain of a bicarbonate ion (HCO_3^-) in the blood. Ammonia and bicarbonate are exchanged in a one-to-one ratio. This exchange is yet another means by which the body can buffer and excrete acid. The presence of aquaporin channels in the descending loop allows prodigious quantities of water to leave the loop and enter the hyperosmolar interstitium of the pyramid, where it is returned to the circulation by the vasa recta. As the loop turns to become the ascending loop, there is an absence of aquaporin channels, so water cannot leave the loop. However, in the basal membrane of cells of the thick ascending loop, ATPase pumps actively remove Na^+ from the cell. A $Na^+/K^+/2Cl^-$ symporter in the apical membrane passively allows these ions to enter the cell cytoplasm from the lumen of the loop down a concentration gradient created by the pump. This mechanism works to dilute the fluid of the ascending loop ultimately to approximately 50–100 mOsmol/L.

At the transition from the DCT to the collecting duct, about 20 percent of the original water is still present and about 10 percent of the sodium. If no other mechanism for water reabsorption existed, about 20–25 liters of urine would be produced. Now consider what is happening in the adjacent capillaries, the vasa recta. They are recovering both solutes and water at a rate that preserves the countercurrent multiplier system. In general, blood flows slowly in capillaries to allow time for exchange of nutrients and wastes. In the vasa recta particularly, this rate of flow is important for two additional reasons. The flow must be slow to allow blood cells to lose and regain water without either crenating or bursting. Second, a rapid flow would remove too much Na^+ and urea, destroying the osmolar gradient that is necessary for the recovery of solutes and water. Thus, by flowing slowly to preserve the countercurrent mechanism, as the vasa recta descend, Na^+ and urea are freely able to enter the capillary, while water freely leaves; as they ascend, Na^+ and urea are secreted into the surrounding medulla, while water reenters and is removed.

Reabsorption and Secretion in the Distal Convoluted Tubule

Approximately 80 percent of filtered water has been recovered by the time the dilute forming urine enters the DCT. The DCT will recover another 10–15 percent before the forming urine enters the collecting ducts. Aldosterone increases the amount of Na^+/K^+ ATPase in the basal membrane of the DCT and collecting duct. The movement of Na^+ out of the lumen of the collecting duct creates a negative charge that promotes the movement of Cl^- out of the lumen into the interstitial space by a paracellular route across tight junctions. Peritubular capillaries receive the solutes and water, returning them to the circulation.

Cells of the DCT also recover Ca^{++} from the filtrate. Receptors for parathyroid hormone (PTH) are found in DCT cells and when bound to PTH, induce the insertion of calcium channels on their luminal surface. The channels enhance Ca^{++} recovery from the forming urine. In addition, as Na^+ is pumped out of the cell, the resulting electrochemical gradient attracts Ca^{++} into the cell. Finally, calcitriol (1,25 dihydroxyvitamin D, the active form of vitamin D) is very important for calcium recovery. It induces the production of calcium-binding proteins that transport Ca^{++} into the cell. These binding proteins are also important for the movement of calcium inside the cell and aid in exocytosis of calcium across the basolateral membrane. Any Ca^{++} not reabsorbed at this point is lost in the urine.

Collecting Ducts and Recovery of Water

Solutes move across the membranes of the collecting ducts, which contain two distinct cell types, principal cells and intercalated cells. A principal cell possesses channels for the recovery or loss of sodium and potassium. An intercalated cell secretes or absorbs acid or bicarbonate. As in other portions of the nephron, there is an array of micromachines (pumps and channels) on display in the membranes of these cells.

Regulation of urine volume and osmolarity are major functions of the collecting ducts. By varying the amount of water that is recovered, the collecting ducts play a major role in maintaining the body's normal osmolarity. If the blood becomes hyperosmotic, the collecting ducts recover more water to dilute the blood; if the blood becomes hyposmotic, the collecting ducts recover less of the water, leading to concentration of the blood. Another way of saying this is: If plasma osmolarity rises, more water is recovered and urine volume decreases; if plasma osmolarity decreases, less water is recovered and urine volume increases. This function is regulated by the posterior pituitary hormone ADH (vasopressin). With mild dehydration, plasma osmolarity rises slightly. This increase is detected by osmoreceptors in the hypothalamus, which stimulates the release of ADH from the posterior pituitary. If plasma osmolarity decreases slightly, the opposite occurs.

When stimulated by ADH, aquaporin channels are inserted into the apical membrane of principal cells, which line the collecting ducts. As the ducts descend through the medulla, the osmolarity surrounding them increases (due to the countercurrent mechanisms described above). If aquaporin water channels are present, water will be osmotically pulled from the collecting duct into the surrounding interstitial space and into the peritubular capillaries. Therefore, the final urine will be more concentrated. If less ADH is secreted, fewer aquaporin channels are inserted and less water is recovered, resulting in dilute urine. By altering the number of aquaporin channels, the volume of water recovered or lost is altered. This, in turn, regulates the blood osmolarity, blood pressure, and osmolarity of the urine.

As Na^+ is pumped from the forming urine, water is passively recaptured for the circulation; this preservation of vascular volume is critically important for the maintenance of a normal blood pressure. Aldosterone is secreted by the adrenal cortex in response to angiotensin II stimulation. As an extremely potent vasoconstrictor, angiotensin II functions immediately to increase blood pressure. By also stimulating aldosterone production, it provides a longer-lasting mechanism to support blood pressure by maintaining vascular volume (water recovery).

In addition to receptors for ADH, principal cells have receptors for the steroid hormone aldosterone. While ADH is primarily involved in the regulation of water recovery, aldosterone regulates Na^+ recovery. Aldosterone stimulates principal cells to manufacture luminal Na^+ and K^+ channels as well as Na^+/K^+ ATPase pumps on the basal membrane of the cells. When aldosterone output increases, more Na^+ is recovered from the forming urine and water follows the Na^+ passively. As the pump recovers Na^+ for the body, it is also pumping K^+ into the forming urine, since the pump moves K^+ in the opposite direction. When aldosterone decreases, more Na^+ remains in the forming urine and more K^+ is recovered in the circulation. Symport channels move Na^+ and Cl^- together. Still other channels in the principal cells secrete K^+ into the collecting duct in direct proportion to the recovery of Na^+.

Intercalated cells play significant roles in regulating blood pH. Intercalated cells reabsorb K^+ and HCO_3^- while secreting H^+. This function lowers the acidity of the plasma while increasing the acidity of the urine.

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5.7: Regulation of Renal Blood Flow

Filtration Control

It is vital that the flow of blood through the kidney be at a suitable rate to allow for filtration. This rate determines how much solute is retained or discarded, how much water is retained or discarded, and ultimately, the osmolarity of blood and the blood pressure of the body.

Sympathetic Nerves

The kidneys are innervated by the sympathetic neurons of the autonomic nervous system via the celiac plexus and splanchnic nerves. Reduction of sympathetic stimulation results in vasodilation and increased blood flow through the kidneys during resting conditions. When the frequency of action potentials increases, the arteriolar smooth muscle constricts (vasoconstriction), resulting in diminished glomerular flow, so less filtration occurs. Under conditions of stress, sympathetic nervous activity increases, resulting in the direct vasoconstriction of afferent arterioles (norepinephrine effect) as well as stimulation of the adrenal medulla. The adrenal medulla, in turn, produces a generalized vasoconstriction through the release of epinephrine. This includes vasoconstriction of the afferent arterioles, further reducing the volume of blood flowing through the kidneys. This process redirects blood to other organs with more immediate needs. If blood pressure falls, the sympathetic nerves will also stimulate the release of renin. Additional renin increases production of the powerful vasoconstrictor angiotensin II. Angiotensin II, as discussed above, will also stimulate aldosterone production to augment blood volume through retention of more Na^+ and water. Only a 10 mm Hg pressure differential across the glomerulus is required for normal GFR, so very small changes in afferent arterial pressure significantly increase or decrease GFR.

Autoregulation

The kidneys are very effective at regulating the rate of blood flow over a wide range of blood pressures. Your blood pressure will decrease when you are relaxed or sleeping. It will increase when exercising. Yet, despite these changes, the filtration rate through the kidney will change very little. This is due to two internal autoregulatory mechanisms that operate without outside influence: the myogenic mechanism and the tubuloglomerular feedback mechanism.

Arteriole Myogenic Mechanism

The myogenic mechanism regulating blood flow within the kidney depends upon a characteristic shared by most smooth muscle cells of the body. When you stretch a smooth muscle cell, it contracts; when you stop, it relaxes, restoring its resting length. This mechanism works in the afferent arteriole that supplies the glomerulus. When blood pressure increases, smooth muscle cells in the wall of the arteriole are stretched and respond by contracting to resist the pressure, resulting in little change in flow. When blood pressure drops, the same smooth muscle cells relax to lower resistance, allowing a continued even flow of blood.

Tubuloglomerular Feedback

The tubuloglomerular feedback mechanism involves the JGA and a paracrine signaling mechanism utilizing ATP, adenosine, and nitric oxide (NO). This mechanism stimulates either contraction or relaxation of afferent arteriolar smooth muscle cells (Table 5.7.1). Recall that the DCT is in intimate contact with the afferent and efferent arterioles of the glomerulus. Specialized macula densa cells in this segment of the tubule respond to changes in the fluid flow rate and Na^+ concentration. As GFR increases, there is less time for NaCl to be reabsorbed in the PCT, resulting in higher osmolarity in the filtrate. The increased fluid movement more strongly deflects single nonmotile cilia on macula densa cells. This increased osmolarity of the forming urine, and the greater flow rate within the DCT, activates macula densa cells to respond by releasing ATP and adenosine (a metabolite of ATP). ATP and adenosine act locally as paracrine factors to stimulate the myogenic juxtaglomerular cells of the afferent arteriole to constrict, slowing blood flow and reducing GFR. Conversely, when GFR decreases, less Na^+ is in the forming urine, and most will be reabsorbed before reaching the macula densa, which will result in decreased ATP and adenosine, allowing the afferent arteriole to dilate and increase GFR. NO has the opposite effect, relaxing the afferent arteriole at the same time ATP and adenosine are stimulating it to contract. Thus, NO fine-tunes the effects of adenosine and ATP on GFR.

Table \({5{.}7{.}}\eatSpaces{1} \endSpaces}\: Paracrine Mechanisms Controlling Glomerular Filtration Rate

Change in GFR	NaCl Absorption	Role of ATP and adenosine/Role of NO	Effect on GFR
Increased GFR	Tubular NaCl increases	ATP and adenosine increase, causing vasoconstriction	Vasoconstriction slows GFR
Decreased GFR	Tubular NaCl decreases	ATP and adenosine decrease, causing vasodilation	Vasodilation increases GFR
Increased GFR	Tubular NaCl increases	NO increases, causing vasodilation	Vasodilation increases GFR
Decreased GFR	Tubular NaCl decreases	NO decreases, causing vasoconstriction	Vasoconstriction decreases GFR

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5.8: Endocrine Regulation of Kidney Function

Renin–Angiotensin–Aldosterone

Several hormones have specific, important roles in regulating kidney function. They act to stimulate or inhibit blood flow. Some of these are endocrine, acting from a distance, whereas others are paracrine, acting locally.

Renin is an enzyme that is produced by the juxtaglomerular (JG) cells of the afferent arteriole at the JGA. It enzymatically converts angiotensinogen (made by the liver, freely circulating) into angiotensin I. Its release is stimulated by prostaglandins and NO from the JGA in response to decreased extracellular fluid volume.

ACE is not a hormone but it is functionally important in regulating systemic blood pressure and kidney function. It is produced in the lungs but binds to the surfaces of endothelial cells in the afferent arterioles and glomerulus. It enzymatically converts inactive angiotensin I into active angiotensin II. ACE is important in raising blood pressure. People with high blood pressure are sometimes prescribed ACE inhibitors to lower their blood pressure.

Angiotensin II is a potent vasoconstrictor that plays an immediate role in the regulation of blood pressure. It acts systemically to cause vasoconstriction as well as constriction of both the afferent and efferent arterioles of the glomerulus. In instances of blood loss or dehydration, it reduces both GFR and renal blood flow, thereby limiting fluid loss and preserving blood volume. Its release is usually stimulated by decreases in blood pressure, and so the preservation of adequate blood pressure is its primary role.

Aldosterone, often called the “salt-retaining hormone,” is released from the adrenal cortex in response to angiotensin II or directly in response to increased plasma K^+. It promotes Na^+ reabsorption by the nephron, promoting the retention of water. It is also important in regulating K^+, promoting its excretion. (This dual effect on two minerals and its origin in the adrenal cortex explains its designation as a mineralocorticoid.) As a result, renin has an immediate effect on blood pressure due to angiotensin II–stimulated vasoconstriction and a prolonged effect through Na^+ recovery due to aldosterone. At the same time that aldosterone causes increased recovery of Na^+, it also causes greater loss of K^+. Progesterone is a steroid that is structurally similar to aldosterone. It binds to the aldosterone receptor and weakly stimulates Na^+ reabsorption and increased water recovery. This process is unimportant in males due to low levels of circulating progesterone. It may cause increased retention of water during some periods of the menstrual cycle in females when progesterone levels increase.

Antidiuretic Hormone (ADH)

Diuretics are drugs that can increase water loss by interfering with the recapture of solutes and water from the forming urine. They are often prescribed to lower blood pressure. Coffee, tea, and alcoholic beverages are familiar diuretics. ADH, a 9-amino acid peptide released by the posterior pituitary, works to do the exact opposite. It promotes the recovery of water, decreases urine volume, and maintains plasma osmolarity and blood pressure. It does so by stimulating the movement of aquaporin proteins into the apical cell membrane of principal cells of the collecting ducts to form water channels, allowing the transcellular movement of water from the lumen of the collecting duct into the interstitial space in the medulla of the kidney by osmosis. From there, it enters the vasa recta capillaries to return to the circulation. Water is attracted by the high osmotic environment of the deep kidney medulla.

Endothelin

Endothelins, 21-amino acid peptides, are extremely powerful vasoconstrictors. They are produced by endothelial cells of the renal blood vessels, mesangial cells, and cells of the DCT. Hormones stimulating endothelin release include angiotensin II, bradykinin, and epinephrine. They do not typically influence blood pressure in healthy people. On the other hand, in people with diabetic kidney disease, endothelin is chronically elevated, resulting in sodium retention. They also diminish GFR by damaging the podocytes and by potently vasoconstricting both the afferent and efferent arterioles.

Natriuretic Hormones

Natriuretic hormones are peptides that stimulate the kidneys to excrete sodium—an effect opposite that of aldosterone. Natriuretic hormones act by inhibiting aldosterone release and therefore inhibiting Na^+ recovery in the collecting ducts. If Na^+ remains in the forming urine, its osmotic force will cause a concurrent loss of water. Natriuretic hormones also inhibit ADH release, which of course will result in less water recovery. Therefore, natriuretic peptides inhibit both Na^+ and water recovery. One example from this family of hormones is atrial natriuretic hormone (ANH), a 28-amino acid peptide produced by heart atria in response to over-stretching of the atrial wall. The over-stretching occurs in persons with elevated blood pressure or heart failure. It increases GFR through concurrent vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole. These events lead to an increased loss of water and sodium in the forming urine. It also decreases sodium reabsorption in the DCT. There is also B-type natriuretic peptide (BNP) of 32 amino acids produced in the ventricles of the heart. It has a 10-fold lower affinity for its receptor, so its effects are less than those of ANH. Its role may be to provide "fine tuning" for the regulation of blood pressure. BNP's longer biologic half-life makes it a good diagnostic marker of congestive heart failure (Figure 5.8.1.

Parathyroid Hormone

Parathyroid hormone (PTH) is an 84-amino acid peptide produced by the parathyroid glands in response to decreased circulating Ca^{++} levels. Among its targets is the PCT, where it stimulates the hydroxylation of calcidiol to calcitriol (1,25-hydroxycholecalciferol, the active form of vitamin D). It also blocks reabsorption of phosphate (PO_3^-), causing its loss in the urine. The retention of phosphate would result in the formation of calcium phosphate in the plasma, reducing circulating Ca^{++} levels. By ridding the blood of phosphate, higher circulating Ca^{++} levels are permitted.

Table 5.8.1: Renal Effects of Vasoconstrictors and Vasodilators

Stimulus	Effect on GFR
No data available	**No data available**
Decreased extracellular fluid volume (ECFV) Sympathetic nerves (epinephrine and norepinephrine)	Decrease
Decreased extracellular fluid volume (ECFV) Angiotensin II	Decrease
Endothelin Increased stretch, bradykinin, angiotensin II, epinephrine; decreased extracellular fluid volume (ECFV)	Decrease
No data available	**No data available**
Decreased extracellular fluid volume (ECFV); increased shear stress; angiotensin II Prostaglandins (PGE1, PGE2, and PGI2)	No change or slight increase
Nitric oxide (NO) Increased shear stress, acetylcholine, histamine, bradykinin, ATP, adenosine	Increase
Bradykinin Prostaglandins; decreased ACE activity	Increase
Natriuretic peptides (ANP, B-type) Increased extracellular fluid volume (ECFV)	Increase

Abbreviations: ACE = angiotensin-converting enzyme; ECFV = extracellular fluid volume; GFR = glomerular filtration rate; RBF =

renal blood flow; ANP = atrial natriuretic peptide; B-type = ventricular natriuretic peptide.

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5.9: Regulation of Fluid Volume and Composition

Regulation of Fluid Volume and Composition

The major hormones influencing total body water are ADH, aldosterone, and ANH. Circumstances that lead to fluid depletion in the body include blood loss and dehydration. Homeostasis requires that volume and osmolarity be preserved. Blood volume is important in maintaining sufficient blood pressure, and there are nonrenal mechanisms involved in its preservation, including vasoconstriction, which can act within seconds of a drop in pressure. Thirst mechanisms are also activated to promote the consumption of water lost through respiration, evaporation, or urination. Hormonal mechanisms are activated to recover volume while maintaining a normal osmotic environment. These mechanisms act principally on the kidney.

Volume-sensing Mechanisms

The body cannot directly measure blood volume, but blood pressure can be measured. Blood pressure often reflects blood volume and is measured by baroreceptors in the aorta and carotid sinuses. When blood pressure increases, baroreceptors send more frequent action potentials to the central nervous system, leading to widespread vasodilation. Included in this vasodilation are the afferent arterioles supplying the glomerulus, resulting in increased GFR, and water loss by the kidneys. If pressure decreases, fewer action potentials travel to the central nervous system, resulting in more sympathetic stimulation-producing vasoconstriction, which will result in decreased filtration and GFR, and water loss.

Decreased blood pressure is also sensed by the granular cells in the afferent arteriole of the JGA. In response, the enzyme renin is released. You saw earlier in the chapter that renin activity leads to an almost immediate rise in blood pressure as activated angiotensin II produces vasoconstriction. The rise in pressure is sustained by the aldosterone effects initiated by angiotensin II; this includes an increase in Na^+ retention and water volume. As an aside, late in the menstrual cycle, progesterone has a modest influence on water retention. Due to its structural similarity to aldosterone, progesterone binds to the aldosterone receptor in the collecting duct of the kidney, causing the same, albeit weaker, effect on Na^+ and water retention.

Cardiomyocytes of the atria also respond to greater stretch (as blood pressure rises) by secreting ANH. ANH opposes the action of aldosterone by inhibiting the recovery of Na^+ by the DCT and collecting ducts. More Na^+ is lost, and as water follows, total blood volume and pressure decline. In low-pressure states, ANH does not seem to have much effect.

ADH is also called vasopressin. Early researchers found that in cases of unusually high secretion of ADH, the hormone caused vasoconstriction (vasopressor activity, hence the name). Only later were its antidiuretic properties identified. Synthetic ADH is still used occasionally to stem life-threatening esophagus bleeding in alcoholics.

When blood volume drops 5–10 percent, causing a decrease in blood pressure, there is a rapid and significant increase in ADH release from the posterior pituitary. Immediate vasoconstriction to increase blood pressure is the result. ADH also causes activation of aquaporin channels in the collecting ducts to affect the recovery of water to help restore vascular volume.

Diuretics and Fluid Volume

A diuretic is a compound that increases urine volume. Three familiar drinks contain diuretic compounds: coffee, tea, and alcohol. The caffeine in coffee and tea works by promoting vasodilation in the nephron, which increases GFR. Alcohol increases GFR by inhibiting ADH release from the posterior pituitary, resulting in less water recovery by the collecting duct. In cases of high blood pressure, diuretics may be prescribed to reduce blood volume and, thereby, reduce blood pressure. The most frequently prescribed anti-hypertensive diuretic is hydrochlorothiazide. It inhibits the Na^+/ Cl^- symporter in the DCT and collecting duct. The result is a loss of Na^+ with water following passively by osmosis.

Osmotic diuretics promote water loss by osmosis. An example is the indigestible sugar mannitol, which is most often administered to reduce brain swelling after head injury. However, it is not the only sugar that can produce a diuretic effect. In cases of poorly controlled diabetes mellitus, glucose levels exceed the capacity of the tubular glucose symporters, resulting in glucose in the urine. The unrecovered glucose becomes a powerful osmotic diuretic. Classically, in the days before glucose could be detected in the blood and urine, clinicians identified diabetes mellitus by the three Ps: polyuria (diuresis), polydipsia (increased

thirst), and polyphagia (increased hunger).

Regulation of Extracellular Na^+

Sodium has a very strong osmotic effect and attracts water. It plays a larger role in the osmolarity of the plasma than any other circulating component of the blood. If there is too much Na^+ present, either due to poor control or excess dietary consumption, a series of metabolic problems ensue. There is an increase in total volume of water, which leads to hypertension (high blood pressure). Over a long period, this increases the risk of serious complications such as heart attacks, strokes, and aneurysms. It can also contribute to system-wide edema (swelling).

Mechanisms for regulating Na^+ concentration include the renin–angiotensin–aldosterone system and ADH (see Figure 25.14). Aldosterone stimulates the uptake of Na^+ on the apical cell membrane of cells in the DCT and collecting ducts, whereas ADH helps to regulate Na^+ concentration indirectly by regulating the reabsorption of water.

Regulation of Extracellular K^+

Potassium is present in a 30-fold greater concentration inside the cell than outside the cell. A generalization can be made that K^+ and Na^+ concentrations will move in opposite directions. When more Na^+ is reabsorbed, more K^+ is secreted; when less Na^+ is reabsorbed (leading to excretion by the kidney), more K^+ is retained. When aldosterone causes a recovery of Na^+ in the nephron, a negative electrical gradient is created that promotes the secretion of K^+ and Cl^- into the lumen.

Regulation of Cl^-

Chloride is important in acid–base balance in the extracellular space and has other functions, such as in the stomach, where it combines with hydrogen ions in the stomach lumen to form hydrochloric acid, aiding digestion. Its close association with Na^+ in the extracellular environment makes it the dominant anion of this compartment, and its regulation closely mirrors that of Na^+.

Regulation of Ca^{++} and Phosphate

The parathyroid glands monitor and respond to circulating levels of Ca^{++} in the blood. When levels drop too low, PTH is released to stimulate the DCT to reabsorb Ca^{++} from the forming urine. When levels are adequate or high, less PTH is released and more Ca^{++} remains in the forming urine to be lost. Phosphate levels move in the opposite direction. When Ca^{++} levels are low, PTH inhibits reabsorption of HPO_4^{2-} so that its blood level drops, allowing Ca^{++} levels to rise. PTH also stimulates the renal conversion of calcidiol into calcitriol, the active form of vitamin D. Calcitriol then stimulates the intestines to absorb more Ca^{++} from the diet.

Regulation of H^+, Bicarbonate, and pH

The acid–base homeostasis of the body is a function of chemical buffers and physiologic buffering provided by the lungs and kidneys. Buffers, especially proteins, HCO_3^-, and ammonia have a very large capacity to absorb or release H^+ as needed to resist a change in pH. They can act within fractions of a second. The lungs can rid the body of excess acid very rapidly (seconds to minutes) through the conversion of HCO_3^- into CO_2, which is then exhaled. It is rapid but has limited capacity in the face of a significant acid challenge. The kidneys can rid the body of both acid and base. The renal capacity is large but slow (minutes to hours). The cells of the PCT actively secrete H^+ into the forming urine as Na^+ is reabsorbed. The body rids itself of excess H^+ and raises blood pH. In the collecting ducts, the apical surfaces of intercalated cells have proton pumps that actively secrete H^+ into the luminal, forming urine to remove it from the body.

As hydrogen ions are pumped into the forming urine, it is buffered by bicarbonate (HCO_3^-), $H_2PO_4^-$ (dihydrogen phosphate ion), or ammonia (forming NH_4^+, ammonium ion). Urine pH typically varies in a normal range from 4.5 to 8.0.

Regulation of Nitrogen Wastes

Nitrogen wastes are produced by the breakdown of proteins during normal metabolism. Proteins are broken down into amino acids, which in turn are deaminated by having their nitrogen groups removed. Deamination converts the amino (NH_2) groups into ammonia (NH_3), ammonium ion (NH_4^+), urea, or uric acid (Figure 5.9.1). Ammonia is extremely toxic, so most of it is very rapidly converted into urea in the liver. Human urinary wastes typically contain primarily urea with small amounts of ammonium and very little uric acid.

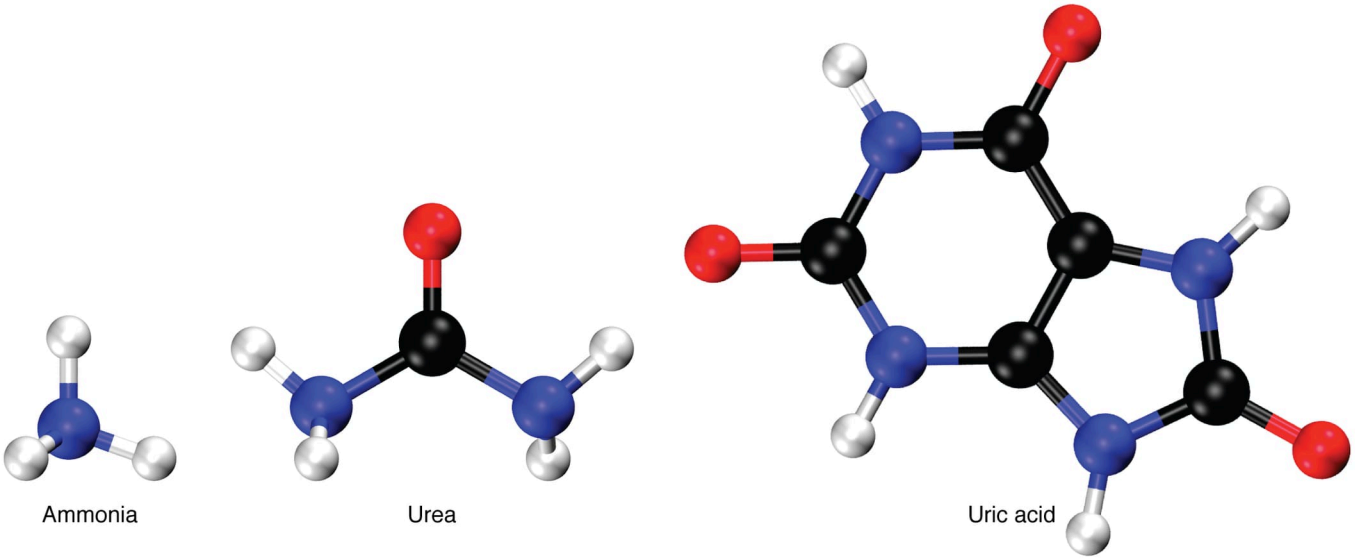


Figure 5.9.1: Nitrogen Wastes. (CC BY 4.0; via Regulation of Fluid Volume Composition). Detailed text description of the Figure 5.9.1.

Elimination of Drugs and Hormones

Water-soluble drugs may be excreted in the urine and are influenced by one or all of the following processes: glomerular filtration, tubular secretion, or tubular reabsorption. Drugs that are structurally small can be filtered by the glomerulus with the filtrate. Large drug molecules such as heparin or those that are bound to plasma proteins cannot be filtered and are not readily eliminated. Some drugs can be eliminated by carrier proteins that enable secretion of the drug into the tubule lumen. There are specific carriers that eliminate basic (such as dopamine or histamine) or acidic drugs (such as penicillin or indomethacin). As is the case with other substances, drugs may be both filtered and reabsorbed passively along a concentration gradient.

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5.10: The Urinary System and Homeostasis

Homeostatic Functions of the Kidney

All systems of the body are interrelated. A change in one system may affect all other systems in the body, with mild to devastating effects. A failure of urinary continence can be embarrassing and inconvenient, but is not life threatening. The loss of other urinary functions may prove fatal. A failure to synthesize vitamin D is one such example.

Vitamin D Synthesis

In order for vitamin D to become active, it must undergo a hydroxylation reaction in the kidney, that is, an –OH group must be added to calcidiol to make calcitriol (1,25-dihydroxycholecalciferol). Activated vitamin D is important for absorption of Ca^{++} in the digestive tract, its reabsorption in the kidney, and the maintenance of normal serum concentrations of Ca^{++} and phosphate. Calcium is vitally important in bone health, muscle contraction, hormone secretion, and neurotransmitter release. Inadequate Ca^{++} leads to disorders like osteoporosis and osteomalacia in adults and rickets in children. Deficits may also result in problems with cell proliferation, neuromuscular function, blood clotting, and the inflammatory response. Recent research has confirmed that vitamin D receptors are present in most, if not all, cells of the body, reflecting the systemic importance of vitamin D. Many scientists have suggested it be referred to as a hormone rather than a vitamin.

Erythropoiesis

EPO is a 193-amino acid protein that stimulates the formation of red blood cells in the bone marrow. The kidney produces 85 percent of circulating EPO; the liver, the remainder. If you move to a higher altitude, the partial pressure of oxygen is lower, meaning there is less pressure to push oxygen across the alveolar membrane and into the red blood cell. One way the body compensates is to manufacture more red blood cells by increasing EPO production. If you start an aerobic exercise program, your tissues will need more oxygen to cope, and the kidney will respond with more EPO. If erythrocytes are lost due to severe or prolonged bleeding, or under produced due to disease or severe malnutrition, the kidneys come to the rescue by producing more EPO. Renal failure (loss of EPO production) is associated with anemia, which makes it difficult for the body to cope with increased oxygen demands or to supply oxygen adequately even under normal conditions. Anemia diminishes performance and can be life threatening.

Blood Pressure Regulation

Due to osmosis, water follows where Na^+ leads. Much of the water the kidneys recover from the forming urine follows the reabsorption of Na^+. ADH stimulation of aquaporin channels allows for regulation of water recovery in the collecting ducts. Normally, all of the glucose is recovered, but loss of glucose control (diabetes mellitus) may result in an osmotic dieresis severe enough to produce severe dehydration and death. A loss of renal function means a loss of effective vascular volume control, leading to hypotension (low blood pressure) or hypertension (high blood pressure), which can lead to stroke, heart attack, and aneurysm formation.

The kidneys cooperate with the lungs, liver, and adrenal cortex through the renin–angiotensin–aldosterone system (Figure 5.10.1). The liver synthesizes and secretes the inactive precursor angiotensinogen. When the blood pressure is low, the kidney synthesizes and releases renin. Renin converts angiotensinogen into angiotensin I, and ACE produced in the lung converts angiotensin I into biologically active angiotensin II. The immediate and short-term effect of angiotensin II is to raise blood pressure by causing widespread vasoconstriction. angiotensin II also stimulates the adrenal cortex to release the steroid hormone aldosterone, which results in renal reabsorption of Na^+ and its associated osmotic recovery of water. The reabsorption of Na^+ helps to raise and maintain blood pressure over a longer term.

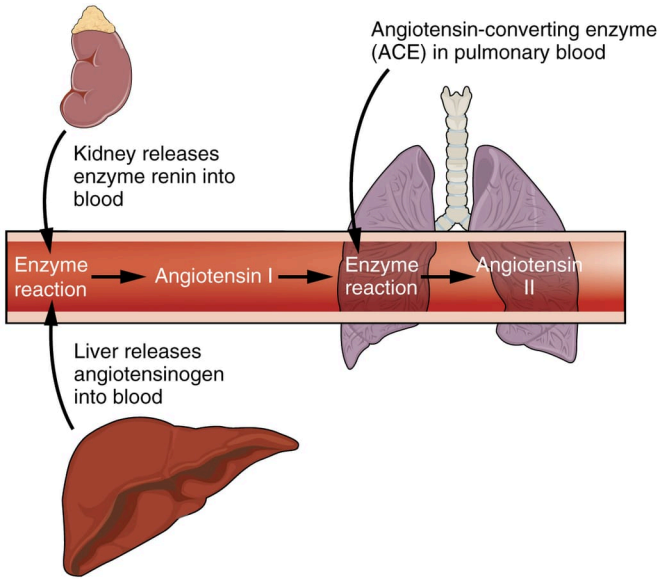


Figure 5.10.1: The Enzyme Renin Converts the Pro-enzyme Angiotensi. (CC BY 4.0; via The Urinary System and Homeostasis). Detailed text description of the Figure 5.10.1.

Regulation of Osmolarity

Blood pressure and osmolarity are regulated in a similar fashion. Severe hypo-osmolarity can cause problems like lysis (rupture) of blood cells or widespread edema, which is due to a solute imbalance. Inadequate solute concentration (such as protein) in the plasma results in water moving toward an area of greater solute concentration, in this case, the interstitial space and cell cytoplasm. If the kidney glomeruli are damaged by an autoimmune illness, large quantities of protein may be lost in the urine. The resultant drop in serum osmolarity leads to widespread edema that, if severe, may lead to damaging or fatal brain swelling. Severe hypertonic conditions may arise with severe dehydration from lack of water intake, severe vomiting, or uncontrolled diarrhea. When the kidney is unable to recover sufficient water from the forming urine, the consequences may be severe (lethargy, confusion, muscle cramps, and finally, death) .

Recovery of Electrolytes

Sodium, calcium, and potassium must be closely regulated. The role of Na^+ and Ca^{++} homeostasis has been discussed at length. Failure of K^+ regulation can have serious consequences on nerve conduction, skeletal muscle function, and most significantly, on cardiac muscle contraction and rhythm.

pH Regulation

Recall that enzymes lose their three-dimensional conformation and, therefore, their function if the pH is too acidic or basic. This loss of conformation may be a consequence of the breaking of hydrogen bonds. Move the pH away from the optimum for a specific enzyme and you may severely hamper its function throughout the body, including hormone binding, central nervous system signaling, or myocardial contraction. Proper kidney function is essential for pH homeostasis.

Everyday Connection

Stem Cells and Repair of Kidney Damage

Stem cell research is transforming our understanding of how the kidney might be protected and repaired after injury. Stem cells are unspecialized cells capable of self-renewal (repeated cell division over long periods) and, under the right conditions, differentiation into specialized, tissue-specific cell types. This dual capacity makes them a promising tool for regenerating damaged organs, including the kidneys.

Several stem and progenitor cell populations are of particular interest in renal repair:

- Mesenchymal stem/stromal cells (MSCs): Found in bone marrow, adipose tissue, and other sites. They can differentiate into multiple mesenchymal lineages and secrete a wide array of bioactive molecules. They are currently the most studied cells in preclinical and early clinical work on acute kidney injury (AKI).
- Endothelial progenitor cells: These contribute to the repair of damaged renal microvasculature, helping restore blood supply to injured kidney tissue.
- Resident renal progenitor cells: Cells within the kidney itself, found for example in the tubular epithelium, that can proliferate and help replace injured tubular cells.
- Induced pluripotent stem cells (iPSCs): Adult cells reprogrammed back to a pluripotent state, which can be directed in the laboratory toward kidney-like cell types and organoids. These are valuable for research and may have future therapeutic applications.

Acute Kidney Injury (AKI) and the Need for New Therapies

Acute kidney injury is a sudden decline in kidney function that can follow major surgery, kidney transplantation, sepsis, shock, severe dehydration, or exposure to nephrotoxic drugs and contrast agents. AKI occurs in about 7–10 percent of hospitalized patients and is associated with high in-hospital mortality rates, often around 35–40 percent in severe cases. Even survivors have an increased risk of chronic kidney disease, cardiovascular events, and long-term mortality.

Current management of AKI is largely supportive. Clinicians optimize blood pressure and fluid status, avoid further kidney toxins, and use dialysis when needed. There is no widely accepted drug therapy that directly reverses the underlying damage. This therapeutic gap is a major reason why stem-cell-based approaches are being explored.

What Have Studies Shown So Far?

Animal studies and small early trials in humans, particularly using mesenchymal stem cells, have suggested several potential benefits:

- Reduced incidence and severity of AKI after high-risk procedures such as cardiac surgery and kidney transplantation.
- Shorter hospital stays and fewer readmissions in some small clinical trials.
- Improved markers of kidney function, such as lower serum creatinine and better urine output, and less structural damage to the kidney on histologic examination in animal models.

These results are encouraging but not yet definitive. Sample sizes are often small, study designs vary, and long-term outcomes and safety profiles are still being clarified. At present, no stem-cell-based therapy for AKI is part of standard clinical care.

Despite promising findings, stem cell therapy for kidney injury is still experimental. Several important issues remain:

- Safety concerns include the potential for unwanted immune reactions (although mesenchymal stem cells are relatively immunoprivileged), theoretical risks of tumor formation or abnormal tissue growth, and complications related to the route of administration.
- Practical challenges include standardizing cell sources (autologous versus donor cells), culture conditions, doses, and timing of treatment; ensuring that cells or vesicles reliably reach and interact with the injured kidney; and scaling up production under clinical-grade conditions.

Future Directions

- Refining cell types by comparing mesenchymal stem cells from different tissues, resident renal progenitor cells, and kidney-like cells derived from induced pluripotent stem cells.
- Developing cell-free therapies using exosomes or conditioned media to capture beneficial paracrine effects with potentially fewer risks than live cell infusion.
- Designing preventive or personalized strategies in which stem-cell-based products are given to patients at high risk of AKI, such as before certain major surgeries or contrast exposure.
- Exploring combination therapies that pair stem cells or their products with drugs, biomaterials such as scaffolds or hydrogels, or engineered kidney tissues and organoids.

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5.11: Terms and Definitions

Key Terms

Select to View Definition

Anatomical sphincter
smooth or skeletal muscle surrounding the lumen of a vessel or hollow organ that can restrict flow when contracted

Angiotensin I
protein produced by the enzymatic action of renin on angiotensinogen; inactive precursor of angiotensin II

Angiotensin II
protein produced by the enzymatic action of ACE on inactive angiotensin I; actively causes vasoconstriction and stimulates aldosterone release by the adrenal cortex

Angiotensin-converting enzyme (ACE)
enzyme produced by the lungs that catalyzes the reaction of inactive angiotensin I into active angiotensin II

Angiotensinogen
inactive protein in the circulation produced by the liver; precursor of angiotensin I; must be modified by the enzymes renin and ACE to be activated

Anuria
absence of urine produced; production of 50 mL or less per day

Aquaporin
protein-forming water channels through the lipid bilayer of the cell; allows water to cross; activation in the collecting ducts is under the control of ADH

Bowman's capsule
cup-shaped sack lined by a simple squamous epithelium (parietal surface) and specialized cells called podocytes (visceral surface) that participate in the filtration process; receives the filtrate which then passes on to the PCTs

Brush border
formed by microvilli on the surface of certain cuboidal cells; in the kidney it is found in the PCT; increases surface area for absorption in the kidney

Calyces
cup-like structures receiving urine from the collecting ducts where it passes on to the renal pelvis and ureter

Cortical nephrons
nephrons with loops of Henle that do not extend into the renal medulla

Countercurrent multiplier system
involves the descending and ascending loops of Henle directing forming urine in opposing directions to create a concentration gradient when combined with variable permeability and sodium pumping

Detrusor muscle
smooth muscle in the bladder wall; fibers run in all directions to reduce the size of the organ when emptying it of urine

Distal convoluted tubules (DCT)
portions of the nephron distal to the loop of Henle that receive hyposmotic filtrate from the loop of Henle and empty into collecting ducts

Diuretic
compound that increases urine output, leading to decreased water conservation

Efferent arteriole
arteriole carrying blood from the glomerulus to the capillary beds around the convoluted tubules and loop of Henle; portion of the portal system

Endothelins
group of vasoconstrictive, 21-amino acid peptides; produced by endothelial cells of the renal blood vessels, mesangial cells, and cells of the DCT

External urinary sphincter
skeletal muscle; must be relaxed consciously to void urine

Fenestrations
small windows through a cell, allowing rapid filtration based on size; formed in such a way as to allow substances to cross through a cell without mixing with cell contents

Filtration slits
formed by pedicels of podocytes; substances filter between the pedicels based on size

Forming urine
filtrate undergoing modifications through secretion and reabsorption before true urine is produced

Glomerular filtration rate (GFR)
rate of renal filtration

Glomerulus
tuft of capillaries surrounded by Bowman's capsule; filters the blood based on size

Glycosuria
presence of glucose in the urine; caused by high blood glucose levels that exceed the ability of the kidneys to reabsorb the glucose; usually the result of untreated or poorly controlled diabetes mellitus

Incontinence
loss of ability to control micturition

Intercalated cell
specialized cell of the collecting ducts that secrete or absorb acid or bicarbonate; important in acid–base balance

Internal urinary sphincter
smooth muscle at the juncture of the bladder and urethra; relaxes as the bladder fills to allow urine into the urethra

Inulin
plant polysaccharide injected to determine GFR; is neither secreted nor absorbed by the kidney, so its appearance in the urine is directly proportional to its filtration rate

Juxtaglomerular apparatus (JGA)
located at the juncture of the DCT and the afferent and efferent arterioles of the glomerulus; plays a role in the regulation of renal blood flow and GFR

Juxtaglomerular cell
modified smooth muscle cells of the afferent arteriole; secretes renin in response to a drop in blood pressure

Juxtamedullary nephrons
nephrons adjacent to the border of the cortex and medulla with loops of Henle that extend into the renal medulla

Leaky tight junctions
tight junctions in which the sealing strands of proteins between the membranes of adjacent cells are fewer in number and incomplete; allows limited intercellular movement of solvent and solutes

Leukocyte esterase
: enzyme produced by leukocytes that can be detected in the urine and that serves as an indirect indicator of urinary tract infection

Loop of Henle
: descending and ascending portions between the proximal and distal convoluted tubules; those of cortical nephrons do not extend into the medulla, whereas those of juxtamedullary nephrons do extend into the medulla

Macula densa
: cells found in the part of the DCT forming the JGA; sense Na^+ concentration in the forming urine

Medulla
: inner region of kidney containing the renal pyramids

Mesangial
: contractile cells found in the glomerulus; can contract or relax to regulate filtration rate

Micturition
: also called urination or voiding

Myogenic mechanism
: mechanism by which smooth muscle responds to stretch by contracting; an increase in blood pressure causes vasoconstriction and a decrease in blood pressure causes vasodilation so that blood flow downstream remains steady

Nephrons
: functional units of the kidney that carry out all filtration and modification to produce urine; consist of renal corpuscles, proximal and distal convoluted tubules, and descending and ascending loops of Henle; drain into collecting ducts

Net filtration pressure (NFP)
: pressure of fluid across the glomerulus; calculated by taking the hydrostatic pressure of the capillary and subtracting the colloid osmotic pressure of the blood and the hydrostatic pressure of Bowman's capsule

Oliguria
: below normal urine production of 400–500 mL/day

Osteomalacia
: softening of bones due to a lack of mineralization with calcium and phosphate; most often due to lack of vitamin D; in children, osteomalacia is termed rickets; not to be confused with osteoporosis

Pedicels
: finger-like projections of podocytes surrounding glomerular capillaries; interdigitate to form a filtration membrane

Peritubular capillaries
: second capillary bed of the renal portal system; surround the proximal and distal convoluted tubules; associated with the vasa recta

Physiological sphincter
: sphincter consisting of circular smooth muscle indistinguishable from adjacent muscle but possessing differential innervations, permitting its function as a sphincter; structurally weak

Podocytes
: cells forming finger-like processes; form the visceral layer of Bowman's capsule; pedicels of the podocytes interdigitate to form a filtration membrane

Polyuria
: urine production in excess of 2.5 L/day; may be caused by diabetes insipidus, diabetes mellitus, or excessive use of diuretics

Principal cell
found in collecting ducts and possess channels for the recovery or loss of sodium and potassium; under the control of aldosterone; also have aquaporin channels under ADH control to regulate recovery of water

Proximal convoluted tubules (PCTs)
tortuous tubules receiving filtrate from Bowman's capsule; most active part of the nephron in reabsorption and secretion

Renal columns
extensions of the renal cortex into the renal medulla; separates the renal pyramids; contains blood vessels and connective tissues

Renal corpuscle
consists of the glomerulus and Bowman's capsule

Renal cortex
outer part of kidney containing all of the nephrons; some nephrons have loops of Henle extending into the medulla

Renal fat pad
adipose tissue between the renal fascia and the renal capsule that provides protective cushioning to the kidney

Renal hilum
recessed medial area of the kidney through which the renal artery, renal vein, ureters, lymphatics, and nerves pass

Renal papillae
medullary area of the renal pyramids where collecting ducts empty urine into the minor calyces

Renal pyramids
six to eight cone-shaped tissues in the medulla of the kidney containing collecting ducts and the loops of Henle of juxtamedullary nephrons

Renin
enzyme produced by juxtaglomerular cells in response to decreased blood pressure or sympathetic nervous activity; catalyzes the conversion of angiotensinogen into angiotensin I

Retroperitoneal
behind the peritoneum; in the case of the kidney and ureters, between the parietal peritoneum and the abdominal wall

Sacral micturition center
group of neurons in the sacral region of the spinal cord that controls urination; acts reflexively unless its action is modified by higher brain centers to allow voluntary urination

Specific gravity
weight of a liquid compared to pure water, which has a specific gravity of 1.0; any solute added to water will increase its specific gravity

Systemic edema
increased fluid retention in the interstitial spaces and cells of the body; can be seen as swelling over large areas of the body, particularly the lower extremities

Trigone
area at the base of the bladder marked by the two ureters in the posterior–lateral aspect and the urethral orifice in the anterior aspect oriented like points on a triangle

Tubuloglomerular feedback
feedback mechanism involving the JGA; macula densa cells monitor Na^+ concentration in the terminal portion of the ascending loop of Henle and act to cause vasoconstriction or vasodilation of afferent and efferent arterioles to alter GFR

Urethra
: transports urine from the bladder to the outside environment

Urinalysis
: analysis of urine to diagnose disease

Urochrome
: heme-derived pigment that imparts the typical yellow color of urine

Vasa recta
: branches of the efferent arterioles that parallel the course of the loops of Henle and are continuous with the peritubular capillaries; with the glomerulus, form a portal system

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5.12: Chapter Review Questions

Multiple Choice Section

- Use the end-of-chapter multiple-choice section as a regular self-check tool, not just before exams.
- Read each item carefully, think about what is really being tested (concept, definition, application, or calculation), and choose the option (A, B, C, or D) that best reflects what you have learned in this chapter.
  - After you read through the chapter, attempt all items without looking at your notes; then return to the chapter to review any you missed or felt unsure about.
  - Afterward, explain to yourself why the correct option is right and why the others are not. Finally, repeat the multiple-choice section a few days later to see what you truly remember and understand.
- Students who consistently use these prompts in this way typically perform better across the course because they turn reading into active practice

1. A 7-year-old child is brought to clinic with a history of excessive thirst and very frequent urination, both day and night. The parent reports the child's urine output is very large in volume. Which finding is most characteristic of diabetes insipidus or uncontrolled diabetes mellitus?
   A. Anuria
   B. Polyuria
   C. Oliguria
   D. None of the above

2. A 60-year-old man notices his urine is consistently yellow, even when his diet does not contain food dyes. The clinician explains that the normal color of urine is determined mainly by:
   A. Diet
   B. Filtration rate
   C. Byproducts of red blood cell breakdown
   D. Filtration efficiency

3. A patient in the intensive care unit produces only 30 mL of urine over the course of a full day. Production of less than 50 mL/day of urine is called:
   A. Normal
   B. Polyuria
   C. Oliguria
   D. Anuria

4. A 45-year-old woman presents with severe flank pain. Imaging shows a kidney stone lodged in the ureter. Which part of the urinary system normally uses peristaltic contractions to propel urine toward the bladder?
   A. Urethra
   B. Bladder
   C. Ureters
   D. All of the above

5. During voluntary urination (micturition), skeletal muscle around the external urethral sphincter must relax. Somatic motor neurons controlling this sphincter must be _____ to allow urination.
   A. Stimulated
   B. Inhibited

6. A 32-year-old pregnant woman has an ultrasound showing that one part of her urinary system lies in the pelvic cavity and is not completely retroperitoneal. Which part of the urinary system is not completely retroperitoneal?
   A. Kidneys
   B. Ureters
   C. Bladder
   D. Nephrons

7. On a coronal section of kidney, a medical student notes triangular renal pyramids separated by extensions of cortical tissue. These cortical extensions are called:
   A. Renal medulla
   B. Minor calyces
   C. Medullary cortices
   D. Renal columns

8. A histology slide of the renal medulla shows long loops that extend deep into the pyramid. The primary nephron structure found within the medulla is the:
   A. Loop of Henle
   B. Minor calyces
   C. Portal system
   D. Ureter

9. On abdominal CT (Computed Tomography) , a radiologist notes that one kidney lies slightly lower than the other. The right kidney is usually slightly lower because:
   A. It is displaced by the liver
   B. It is displaced by the heart
   C. It is slightly smaller
   D. It needs protection from the lower ribs

10. In the renal corpuscle, blood is filtered across a membrane into a surrounding cup-shaped structure. Blood filtrate is captured in the lumen of the:
    A. Glomerulus
    B. Bowman's (glomerular) capsule
    C. Calyces
    D. Renal papillae

11. After blood leaves the glomerulus through the efferent arteriole, it enters a second capillary bed that surrounds the nephron. What are the names of these capillaries?
    A. Arcuate and medullary
    B. Interlobar and interlobular
    C. Peritubular capillaries and vasa recta
    D. Peritubular capillaries and medullary capillaries

12. A nephrologist explains to a patient that each kidney contains about one million microscopic units that filter blood and form urine. The functional unit of the kidney is called:
    A. The renal hilus
    B. The renal corpuscle
    C. The nephron
    D. Bowman's capsule

13. Filtration at the glomerulus depends on pressure differences across the filtration membrane. _____ pressure must be greater on the capillary side of the filtration membrane to drive filtration into Bowman's capsule.
    A. Osmotic
    B. Hydrostatic

14. Modifying the composition of plasma to form urine depends on three basic processes at the nephron. Production of urine that alters plasma makeup is the result of:
    A. Filtration only
    B. Absorption only
    C. Secretion only
    D. Filtration, reabsorption, and secretion

15. A student reading about kidney physiology sees the statement: "Systemic blood pressure must stay above 60 so that the proper amount of filtration occurs." This statement is:
    A. True
    B. False

16. A researcher studies water channels in nephron segments. They note that aquaporin channels are important for water reabsorption in several regions. The statement “Aquaporin channels are only found in the collecting duct” is:
    A. True
    B. False

17. In a patient with early kidney disease, the segment of the nephron responsible for the bulk of solute and water reabsorption is damaged. Most reabsorption and secretion occur in which part of the nephron?
    A. Proximal convoluted tubule
    B. Descending loop of Henle
    C. Ascending loop of Henle
    D. Distal convoluted tubule
    E. Collecting ducts

18. A patient with heart failure is given a drug that enhances the kidney’s ability to adjust water reabsorption precisely, improving fluid balance. The fine-tuning of water recovery or disposal occurs mainly in:
    A. The proximal convoluted tubule
    B. The collecting ducts
    C. The ascending loop of Henle
    D. The distal convoluted tubule

19. A physiologist records sympathetic nerve activity to the renal blood vessels. When the firing rate of these sympathetic nerves decreases, the afferent arterioles dilate. Vasodilation of blood vessels to the kidneys is due to:
    A. More frequent action potentials in sympathetic nerves
    B. Less frequent action potentials in sympathetic nerves

20. When systemic blood pressure suddenly increases, intrinsic autoregulatory mechanisms in the kidney adjust vessel diameter to keep glomerular filtration relatively stable. Blood vessels supplying the kidney will _____ in response to increased blood pressure to maintain a steady rate of filtration.
    A. Contract (constrict)
    B. Relax (dilate)

21. Several local paracrine chemicals influence renal blood flow. Which of these three paracrine substances is a potent vasodilator?
    A. ATP
    B. Adenosine
    C. Nitric oxide

22. A 68-year-old patient with chronic heart failure has high blood volume and pressure. The kidneys and adrenals secrete hormones to adjust sodium and water balance. Which hormone directly opposes the sodium-retaining actions of natriuretic hormones?
    A. Renin
    B. Nitric oxide
    C. Dopamine
    D. Aldosterone

23. A patient with severe hypotension is found to have high levels of a powerful vasoconstrictor peptide that raises systemic blood pressure and stimulates aldosterone release. Which of the following is a vasoconstrictor?
    A. Nitric oxide
    B. Natriuretic hormone
    C. Bradykinin
    D. Angiotensin II

24. A patient with long-standing hypertension has enlarged atria on echocardiogram. The cardiologist explains that stretch of the atrial walls triggers release of atrial natriuretic hormone (ANH). What signal causes the heart to secrete ANH?
    A. Increased blood pressure and volume
    B. Decreased blood pressure
    C. Increased plasma $Na^{\diamondsuit}$ levels only
    D. Decreased plasma $Na^{\diamondsuit}$ levels

25. A rare genetic disorder prevents insertion of aquaporin channels into the collecting duct, even in the presence of antidiuretic hormone (ADH). If there were no aquaporin channels in the collecting duct, which outcome would be expected?
A. You would develop systemic edema
B. You would retain excess Na⊕
C. You would lose large amounts of water-soluble vitamins and electrolytes
D. You would suffer severe dehydration from inability to concentrate urine

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5.13: Applied Thinking Self - Assessment

Challenge Yourself

- Extended response questions are assessment items that require students to construct written answers of substantial length - typically several sentences to multiple paragraphs - rather than selecting from predefined options. They represent a form of constructed response assessment designed to measure complex, higher-order thinking skills.
- First, try answering without using your notes. Then review reliable resources and revise your response if needed. Make a note of any areas where you felt unsure and revisit those topics.

Writing Guidelines

- Answer each question in your own words.
- Write 4–8 clear, complete sentences per question, organized into short paragraphs (not bullet points).
- Focus on explaining your reasoning, not just stating the answer.
- Use correct scientific vocabulary, and briefly define terms when needed.
- For questions that ask you to compare, contrast, or explain why/how:
  - Clearly state similarities or differences
  - Support your ideas with a brief explanation or example

Urinalysis and UTI Inference

1. A 26-year-old presents with fever, dysuria, and increased urinary frequency. Urinalysis shows cloudy urine, positive leukocyte esterase, many white blood cells, and only a trace of protein.
   a. What process is most likely occurring in the urinary tract?
   b. What does the presence of white blood cells in the urine indicate about the underlying condition?
   c. Which regions of the urinary tract are most likely involved?

Diabetes Mellitus vs. Diabetes Insipidus: Comparing Urine

1. Two patients report excessive thirst and very high urine output. One is diagnosed with diabetes mellitus, the other with diabetes insipidus.
   a. Compare the expected characteristics of their urine (glucose content, specific gravity, osmolarity, volume, color).
   b. Explain how these differences reflect the underlying pathophysiology in each disorder.

Anatomical Risk Factors for UTIs

1. A clinician counsels two patients about urinary tract infection prevention: one has a female reproductive system and recurrent bladder infections; the other has a male reproductive system and has never had a UTI. Explain why people with female anatomy generally have a higher risk of bladder infections than those with male anatomy. Include urethral length, proximity to the anus, and any protective factors.

Normal Micturition vs. Neurogenic Bladder

1. In a healthy person, describe how forceful urination is normally accomplished. Include the roles of the detrusor muscle, internal and external urethral sphincters, abdominal pressure, and the autonomic vs. somatic nervous systems.

Protection of the Kidneys from Trauma

1. A car-crash victim sustains a forceful blow to the lower back, raising concern for kidney injury.

a. Identify the anatomical structures that normally protect the kidneys (e.g., ribs, fascia, fat, surrounding muscles).
b. Explain how damage to these protective layers could increase the risk or severity of renal injury.

Structures at the Renal Hilum

1. A radiology report describes a mass at the renal hilum of the right kidney that may be compressing nearby structures.
   a. List the normal structures that pass through the renal hilum.
   b. For each (renal artery, renal vein, ureter, lymphatics, nerves), briefly describe how compression could affect kidney function or produce symptoms.

The Renal Corpuscle and Filtration

1. A biopsy report shows damage localized to the renal corpuscles of several nephrons.
   a. Identify the main structures that make up a renal corpuscle.
   b. Explain how injury to each component (glomerular capillaries, Bowman's capsule, filtration membrane layers) could alter glomerular filtration.

Glomerular Net Filtration Pressure and Edema

1. A patient presents with peripheral edema and rising serum creatinine, and the nephrologist suspects reduced glomerular filtration pressure.
   a. State the formula for net filtration pressure (NFP) at the glomerulus.
   b. Explain how changes in each component (glomerular blood hydrostatic pressure, capsular hydrostatic pressure, blood colloid osmotic pressure) could decrease filtration and contribute to fluid retention.

Clinical Signs of Kidney Failure

1. A middle-aged patient with long-standing high blood pressure and diabetes now reports fatigue, nausea, and swelling of the ankles and around the eyes.For each sign or symptom, briefly explain how reduced kidney function could cause it. In your explanations, refer to at least one of the following:
   a. problems with fluid balance
   b. problems with electrolyte (ion) balance
   c. buildup of wastes in the blood
   d. loss of normal kidney hormone functions (for example, making erythropoietin or activating vitamin D).

Countercurrent Multiplication and the Medullary Gradient

1. Identify which nephron segment and which blood vessels are responsible for countercurrent multiplication and exchange.
2. Explain how this system creates and maintains the corticomedullary osmotic gradient required for urine concentration.

Osmolarity Changes Along the Nephron

1. Describe how the osmolarity (solute concentration) of the tubular fluid changes as it moves through the nephron in a healthy, normally hydrated person. In your answer, briefly compare the tubular fluid in:
   a. the proximal convoluted tubule
   b. the descending limb of the loop of Henle
   c. the ascending limb of the loop of Henle
   d. the distal convoluted tubule
   e. the collecting duct (when ADH is present)

For each region, state whether the fluid is about the same as blood, more concentrated, or more dilute, and explain in one sentence why

Increasing Renal Sodium Excretion

1. Without naming specific drugs, describe at least two physiological strategies/mechanisms by which the kidneys can excrete more Na^+. Include the roles of aldosterone, atrial natriuretic peptide (ANP), changes in glomerular filtration rate, and/or tubular transporters.

Renin–Angiotensin–Aldosterone System (RAAS)

1. Identify the organs and specific cell types that produce renin, angiotensinogen, and angiotensin-converting enzyme (ACE). Explain how their coordinated actions in the RAAS help restore blood pressure and maintain glomerular filtration.

PTH, Calcium, and Phosphate Handling

1. Explain how PTH affects calcium and phosphate:
   a. absorption in the intestines,
   b. reabsorption (or excretion) in the kidney.
2. Describe how these actions help correct low blood calcium levels.

ADH as Vasopressin in Shock

1. An ICU patient with severe hemorrhage develops very low blood pressure and is given vasopressin (ADH). Explain why ADH is also called vasopressin by describing its dual effects on:
   a. the kidneys,
   b. the blood vessels.

Clarify how each effect is beneficial in this clinical scenario.

Low Plasma Proteins, Starling Forces, and Edema

1. A severely malnourished patient with low plasma protein levels presents with generalized edema.
   a. Using Starling forces, explain how reduced plasma proteins lead to fluid accumulation in the interstitial spaces.
   b. Briefly relate how the kidneys may respond in terms of fluid and sodium handling, and why this can worsen edema.

Key Electrolytes in Kidney Regulation and Their Clinical Impact

1. A patient with advanced kidney disease develops dangerous cardiac arrhythmias and muscle weakness. Lab work shows multiple electrolyte abnormalities.
   a. Identify three electrolytes most tightly regulated by the kidneys (e.g., Na^+, K^+, Ca^{2+}, H^+/HCO_3^-).
   b. For each, explain why disturbances are particularly significant for neuromuscular and/or cardiovascular function.

Estimating GFR in Clinical Practice

1. Explain what glomerular filtration rate (GFR) represents and why it is clinically important.
2. Describe how GFR can be estimated using creatinine and outline at least one limitation of this approach.

Acid–Base Balance and the Kidney

1. Describe two major ways the kidneys help maintain acid–base balance.

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5.14: Alternative Text Descriptions

Figure 5.1.1: Urine Color

This image compares hydrated and dehydrated states using two stacked groups of four horizontal bars.

The top group, labeled Hydrated, contains four bars that are similar in appearance and remain light and relatively uniform from top to bottom. This suggests a stable or normal condition with little variation.

The bottom group, labeled Dehydrated, also contains four horizontal bars, but these bars become progressively darker from top to bottom. This indicates increasing concentration or increasing change as dehydration becomes more severe.

A bracket on the right groups the four bars in each section, visually organizing them into the two categories: Hydrated and Dehydrated.

Overall, the graphic shows that:

- in the hydrated state, the measured values remain lighter and more consistent
- in the dehydrated state, the values become darker and more concentrated
- the key comparison is the contrast between stable hydration and progressive concentration during dehydration

Figure 5.2.1: Comparison of the Female and Male Lower Urinary Tracts

This image presents sagittal views of the female pelvis on the left and the male pelvis on the right. The figure compares the anatomical relationships of the urinary bladder, urethra, and ureter to nearby reproductive, digestive, and skeletal structures.

Female Urinary Tract (Panel A)

The female urinary bladder is located in the anterior portion of the pelvis, immediately posterior to the pubic bone. A ureter enters the superior portion of the bladder and carries urine from the kidneys for storage.

The urethra extends inferiorly from the bladder and travels a short distance to the external opening. Because of its short length, the female urethra functions solely as a urinary passageway.

Superior and posterior to the bladder is the uterus. The lower portion of the uterus narrows to form the cervix, which projects into the upper vagina. The vagina extends inferiorly from the cervix and lies posterior to the urethra.

Posterior to both the bladder and reproductive organs is the rectum, which continues inferiorly to the anus. The figure therefore shows the female pelvis arranged from anterior to posterior as:

- Pubic bone
- Urinary bladder and urethra
- Uterus and vagina
- Rectum

External reproductive structures shown near the urethral opening include:

- Clitoris
- Labium minora
- Labium majora

Male Urinary Tract (Panel B)

The male urinary bladder is also positioned posterior to the pubic bone. A ureter enters the bladder superiorly and delivers urine

from the kidneys.

The urethra exits the inferior portion of the bladder and immediately passes through the prostate gland. From there, it continues through the length of the penis before reaching the exterior. Unlike the female urethra, the male urethra functions in both the urinary and reproductive systems.

Posterior to the urinary bladder is the seminal vesicle. The ductus deferens travels upward from the testis and epididymis, passes around the bladder, and joins the reproductive duct system near the prostate. These structures contribute sperm and reproductive secretions to the urethra.

The testis is located within the scrotum inferior to the pelvis. The epididymis lies along the posterior surface of the testis and connects to the ductus deferens. The foreskin surrounds the distal portion of the penis.

The male pelvis is arranged from anterior to posterior as:

- Pubic bone
- Urinary bladder and prostate
- Rectum
- Anus

The figure demonstrates that both sexes possess the same basic urinary structures, including the ureter, urinary bladder, and urethra. However, their anatomical relationships differ. In females, the urethra is short and remains separate from the reproductive tract. In males, the urethra is considerably longer, passes through the prostate and penis, and functions as a common passageway for both urine and reproductive fluids. The figure also illustrates how the urinary system is positioned relative to nearby reproductive organs and the rectum in both sexes.

Figure 5.2.2: Anatomy and Histology of the Urinary Bladder

This two-panel figure illustrates the anatomy of the human urinary bladder, combining an anterior cross-sectional diagram on the left with a magnified histological micrograph on the right.

Panel (a): Anatomical Cross-Section

An anterior cross-sectional view shows the gross anatomy of the bladder and its spatial relationships to connected structures.

- Ureters: Two tube-like channels enter the bladder superiorly from the upper left and upper right sides.
- Peritoneum: A thin membrane-like layer drapes across the rounded superior surface of the bladder.
- Detrusor muscle: A thick muscular wall forms the lateral and superior boundaries of the bladder and surrounds the bladder lumen.
- Ureteral openings: Two slit-like openings are located on the lower posterior floor of the bladder lumen where the ureters empty into the bladder.
- Internal urethral sphincter: Located at the inferior funnel-shaped neck of the bladder where the bladder narrows into the urethra.
- External urethral sphincter: Positioned farther down along the urethra where it passes through the pelvic floor.
- Micrograph callout: A small marked region on the lower right bladder wall is connected by an arrow to the magnified tissue view in Panel (b).

Panel (b): Histological Micrograph

A magnified view shows the microscopic tissue layers of the bladder wall from the innermost luminal surface outward.

- Transitional epithelium: The innermost lining bordering the bladder lumen. It appears folded and allows the bladder to expand.
- Lamina propria: A connective tissue layer directly beneath the transitional epithelium that supports the lining.
- Submucosa: A deeper connective tissue layer beneath the lamina propria.

The figure demonstrates both the gross anatomy and microscopic organization of the urinary bladder. Panel (a) shows how urine

enters through the ureters, is stored in the bladder, and exits through the urethra, with sphincters regulating outflow. Panel (b) shows that the bladder wall contains a transitional epithelial lining supported by connective tissue layers that allow expansion and structural support.

Figure 5.2.3: Female Pelvic Anatomy

This image shows a sagittal view of the female pelvis with emphasis on the pudendal nerve and its role in urinary control and sensory innervation of the external genital region.

At the upper right, the sacrum is shown as the origin of the nerves that contribute to the pudendal nerve. The pudendal nerve travels downward and forward through the pelvis, following a path toward structures involved in continence and external genital sensation.

In the center of the figure, the uterus lies above the urinary bladder. The bladder connects to the urethra, which extends downward toward the external opening. The pubic bone is located at the front of the pelvis, while the rectum and anus are located behind the urinary and reproductive organs. These surrounding structures help orient the path of the nerve within the pelvic region.

In the lower portion of the figure, the pudendal nerve branches toward the external urethral sphincter, clitoris, labium minora, and labium majora. These branches indicate that the nerve provides motor control to the sphincter and sensory input to the external genital structures.

Overall, the figure shows that the pudendal nerve:

- originates from the sacral region
- travels through the female pelvis
- supplies the external urethral sphincter
- provides sensation to the clitoris and labial structures

The diagram emphasizes the importance of the pudendal nerve in voluntary control of urination and in sensory function of the external genital area.

Figure 5.2.4: Ureter Peristaltic

This image shows a histological cross-section of a tubular urinary structure, likely the ureter, viewed under the microscope. The figure highlights the organization of the wall from the central lumen outward to the surrounding tissue layers.

At the center is the lumen, shown as an open star-shaped space. The irregular shape is created by folds in the inner lining, which project inward toward the lumen. This folded inner lining is made of epithelial tissue and allows the tube to expand and contract while still maintaining a passageway for fluid.

Surrounding the lumen is a smooth muscle layer arranged in thick bands around the tube. This muscular wall helps move fluid through the structure by contracting and relaxing, supporting the process of peristalsis.

The outermost layer is the adventitia, a layer of connective tissue that anchors the organ to nearby structures and provides external support.

Overall, the figure shows that this tubular organ has:

- a central lumen for fluid passage
- a folded epithelial lining that creates flexibility
- a smooth muscle wall that helps propel fluid
- an outer adventitia that stabilizes the structure

The diagram emphasizes how the tissue layers work together to support the movement of urine through the urinary tract.

Figure 5.3.1: Anatomical Position of the Kidneys and Ureters

This image shows a posterior view of the upper abdominal and lumbar region with the kidneys, vertebral column, twelfth rib, liver, and ureters labeled to show their relative positions.

At the center, the vertebral column runs vertically and is labeled from thoracic vertebra 10 through thoracic vertebra 12 and lumbar vertebra 1 through lumbar vertebra 5. These labels provide a reference for the location of the kidneys along the posterior body wall.

On each side of the spine is a kidney, positioned approximately from thoracic vertebra 12 to lumbar vertebra 3. The kidneys are shown at similar heights, but the right kidney sits slightly lower than the left kidney because of the liver, which is shown above the right kidney. The twelfth rib crosses the upper part of both kidneys, indicating that the lower rib cage provides partial protection.

From the lower part of each kidney, a ureter extends downward. These tubes carry urine from the kidneys toward the urinary bladder, which is not shown in this figure.

Overall, the diagram shows the following anatomical relationships:

- the kidneys lie on either side of the vertebral column
- the kidneys are located roughly between T12 and L3
- the right kidney is positioned slightly lower because of the liver
- the twelfth rib partially protects the upper kidneys
- the ureters descend from each kidney to transport urine away from the kidneys

This description makes the figure's spatial relationships explicit in text, so the information is not dependent only on visual layout, consistent with WCAG guidance on conveying structure and relationships through text.

On the superior aspect of each kidney is the adrenal gland. The adrenal cortex directly influences renal function through the production of the hormone aldosterone to stimulate sodium reabsorption.

Figure 5.3.2: Left Kidney

This image shows a longitudinal section of a kidney with labeled internal structures, blood vessels, and an inset showing the position of both kidneys in the body.

In the main image, the kidney is opened to reveal its internal organization. The outermost covering is the capsule, which encloses and protects the kidney. Just beneath the capsule is the cortex, the outer region of the kidney. Deeper inside is the medulla, which contains triangular structures called renal pyramids. Between the pyramids are renal columns, which extend inward from the cortex and contain supporting tissue and blood vessels.

Each renal pyramid narrows to a renal papilla. Urine formed in the kidney drains from the papilla into a minor calyx. Several minor calyces join to form major calyces, which then channel urine into the renal pelvis. The renal pelvis narrows to become the ureter, which carries urine away from the kidney toward the bladder.

At the medial indentation of the kidney, the renal hilum is shown as the entry and exit point for major vessels and nerves. The renal artery brings blood into the kidney, the renal vein carries blood away, and the renal nerve provides innervation. Within the kidney, interlobar blood vessels run between the pyramids, and arcuate blood vessels arch along the boundary between the cortex and medulla. Smaller cortical blood vessels branch through the cortex.

The inset image shows the two kidneys located on either side of the spine, with major blood vessels connecting them to the body's circulation. This inset provides body-level context for the position of the kidney shown in section.

Overall, the figure shows two connected pathways:

- the blood pathway, in which blood enters through the renal artery, passes through branching vessels in the cortex and medulla, and exits through the renal vein
- the urine drainage pathway, in which urine flows from the renal pyramids to the papillae, then into the minor calyces, major calyces, renal pelvis, and finally the ureter

Figure 5.3.3: Blood Flow in the Kidney

This image illustrates the pathway of blood flow through the kidney, from entry at the renal artery to filtration in the nephron and return through the renal vein.

In the lower left, blood enters the kidney via the renal artery. The renal artery branches into smaller vessels in a hierarchical sequence: segmental arteries, interlobar arteries (running between kidney structures), arcuate arteries (arching along the boundary between outer and inner regions), and cortical radiate arteries, which extend into the outer cortex.

From the cortical radiate arteries, blood flows into afferent arterioles, each of which leads into a glomerulus, a cluster of capillaries where filtration begins. Within the glomerulus, fluid and small solutes are filtered out of the blood into the nephron.

Blood exits the glomerulus through the efferent arteriole, which leads to a network of peritubular capillaries that surround the nephron tubules. These capillaries enable reabsorption of useful substances and secretion of wastes between the blood and the forming urine.

After passing through the capillaries, blood collects into cortical radiate veins, then flows into arcuate veins, interlobar veins, and finally exits the kidney through the renal vein.

The diagram emphasizes function by showing two connected processes:

- Filtration: blood enters the glomerulus via the afferent arteriole and is filtered.
- Reabsorption and return: blood continues through capillary networks to recover needed substances before leaving the kidney through the venous system.

Figure 5.3.4: Nephron Structure and Blood Supply

This image shows a nephron and its associated blood vessels, illustrating how blood is filtered, how the filtrate is modified, and how urine is carried away from the functional unit of the kidney.

On the left side, an interlobular artery gives rise to an afferent arteriole, which carries blood into the glomerulus. The glomerulus is a cluster of capillaries enclosed by the glomerular capsule. This is the site where filtration occurs, as fluid and small dissolved substances move from the blood into the capsule to begin formation of the filtrate.

Blood leaves the glomerulus through the efferent arteriole. The efferent arteriole then forms a network of peritubular capillaries surrounding the nephron tubules. These capillaries allow exchange between the blood and the tubular fluid. Useful substances such as water, ions, and nutrients can be reabsorbed into the blood, while additional wastes can be secreted from the blood into the tubule. Blood from the peritubular capillaries drains into a venule and then into an interlobular vein.

The nephron tubule begins at the glomerular capsule and continues as the proximal convoluted tubule. This segment is the major site of reabsorption of water, ions, and nutrients. The tubule then extends into the loop of the nephron, which has a descending limb and an ascending limb. This loop helps establish the concentration gradients that regulate water and solute balance in the kidney.

After the loop, the tubule becomes the distal convoluted tubule, where additional regulation of ion balance occurs. The fluid then enters the collecting duct, a larger vertical tube that receives fluid from more than one nephron. An arrow at the bottom shows that fluid in the collecting duct flows toward the renal papilla, where urine leaves the nephron and moves into the next stage of the urinary drainage system.

Overall, the figure shows two coordinated pathways:

- the blood pathway, in which blood enters through the afferent arteriole, is filtered in the glomerulus, passes through the efferent arteriole and peritubular capillaries, and exits through the venous system
- the filtrate and urine pathway, in which filtrate moves from the glomerular capsule through the proximal convoluted tubule, loop of the nephron, distal convoluted tubule, and collecting duct before flowing toward the renal papilla

The diagram emphasizes that the nephron depends on the close relationship between the tubular system and the blood supply to carry out filtration, reabsorption, secretion, and urine formation.

Figure 5.4.1: Microanatomy of the Glomerulus and Filtration Slits

This image has two panels that show the microscopic structure of the glomerulus and the specialized surface where filtration begins in the kidney.

In panel (a), a highly magnified cross-sectional view shows the glomerulus as a dense cluster of looping capillaries. The capillary loops are tightly packed and folded, creating a large surface area for filtration. The glomerulus is surrounded by the beginning of the nephron, where filtered fluid is collected. The many capillary loops and intervening spaces emphasize that filtration occurs across an extensive capillary surface within a compact structure.

In panel (b), an enlarged detail shows part of a glomerular capillary with specialized cells arranged along its outer surface. These cells are shown with larger regions labeled cell bodies and thin extensions that wrap around the capillary. Between adjacent extensions are narrow gaps labeled filtration slits. These slits form part of the filtration barrier and act as selective openings that allow water and small dissolved substances to move out of the blood while restricting blood cells and large proteins.

Together, the two panels show that:

- the glomerulus contains a dense network of capillaries that increases filtration surface area
- specialized cells surrounding the capillaries form filtration slits
- these structures allow fluid and small solutes to leave the blood
- larger components, such as cells and many proteins, are retained in the bloodstream

The figure emphasizes the first step of urine formation: blood is filtered across specialized capillary surfaces into the nephron while larger blood components remain in circulation.

Figure 5.4.2: Structure of the Glomerular Filtration Barrier

This image shows a cross-sectional view of the glomerular capillary wall, highlighting the main structures that form the filtration barrier in the kidney.

At the center is the capillary lumen, the open space through which blood flows. Surrounding the lumen is the endothelium, a thin cellular lining. The endothelial cells contain many small openings labeled fenestrations. These openings allow water and small dissolved substances to move out of the blood while helping prevent the passage of larger blood components.

Outside the endothelium is the basement membrane, shown as a thicker supporting layer around the capillary. This layer provides structural support and acts as an additional selective filter, especially limiting the movement of larger molecules such as proteins.

Connections between neighboring endothelial cells are labeled tight junctions. These junctions help maintain the integrity of the capillary wall and contribute to the regulation of movement across the barrier.

Overall, the figure shows that filtration depends on several coordinated structures:

- the fenestrated endothelium, which permits initial movement of fluid and small solutes
- the basement membrane, which provides support and selective filtering
- the tight junctions, which help preserve barrier integrity

Together, these structures form a specialized filtration barrier that allows fluid and small molecules to leave the bloodstream while retaining larger components within the circulation.

Figure 5.4.3: Renal Corpuscle and Juxtaglomerular Apparatus

This image shows the renal corpuscle and the juxtaglomerular apparatus, emphasizing how blood filtration and regulation of kidney function occur together at the start of the nephron.

At the center is the glomerulus, a cluster of capillaries enclosed by the glomerular capsule. Surrounding the capillaries are podocytes, specialized filtration cells with branching extensions that wrap around the capillary surface and help form the filtration barrier. This is the site where fluid is filtered from the blood into the nephron.

On the left side, blood enters the glomerulus through the afferent arteriole and leaves through the efferent arteriole. The afferent arteriole is shown with a larger diameter than the efferent arteriole, which helps maintain the pressure needed for filtration within the glomerulus.

Near the afferent arteriole is a group of juxtaglomerular cells located in the wall of the arteriole. These cells are involved in the regulation of blood pressure and kidney filtration through the release of signaling substances. Adjacent to them is the macula densa, a specialized group of cells in the wall of the distal convoluted tubule (DCT). The macula densa is positioned where the tubule passes close to the glomerulus and monitors the solute concentration of the tubular fluid.

A renal nerve is also shown near the arteriole, indicating that neural signals can influence renal blood flow and activity.

On the right side, the proximal convoluted tubule extends from the glomerular capsule, showing the next step in filtrate processing after initial filtration has occurred.

Overall, the figure shows the close relationship between filtration and regulation:

- blood enters the glomerulus through the afferent arteriole
- filtration occurs across the glomerular capillaries and podocytes
- blood exits through the efferent arteriole
- the macula densa monitors the composition of tubular fluid
- juxtaglomerular cells help regulate blood flow, filtration rate, and blood pressure

Together, these structures help control how much fluid is filtered and support the regulation of blood pressure, fluid balance, and kidney function.

Figure 5.4.4: Renin-Angiotensin-Aldosterone System (RAAS) and Regulation of Blood Pressure

This image illustrates the renin-angiotensin-aldosterone system (RAAS), a hormonal pathway that helps restore blood pressure, blood volume, and sodium balance when fluid flow or sodium concentration is low.

Step 1

The process begins in the kidney. The macula densa senses low fluid flow or low sodium (Na+) concentration in the distal convoluted tubule.

Step 2

In response, nearby juxtaglomerular cells secrete renin into the bloodstream. Renin is identified as an enzyme released by the kidney.

Step 3

The liver releases angiotensinogen into the blood. Renin acts on angiotensinogen through an enzyme reaction, producing angiotensin I.

Step 4

As blood circulates through the lungs, angiotensin-converting enzyme (ACE) in the pulmonary circulation converts angiotensin I into angiotensin II through a second enzyme reaction.

Step 5

Angiotensin II produces widespread vasoconstriction, causing blood vessels throughout the body to narrow and increasing blood pressure.

Step 6

Angiotensin II also stimulates the adrenal cortex to secrete aldosterone.

Step 7

Aldosterone acts on the distal convoluted tubule and collecting ducts of the kidney. The figure states that aldosterone stimulates Na+ uptake on the apical cell membrane in the distal convoluted tubule and collecting ducts. As sodium is reabsorbed into the bloodstream, water follows by osmosis, helping increase blood volume.

Step 8

The figure also shows the action of antidiuretic hormone (ADH). ADH causes aquaporins to move to the collecting duct plasma membrane, increasing water reabsorption from the tubular fluid into the bloodstream.

The figure demonstrates that low fluid flow or low sodium concentration activates the RAAS pathway. Renin released by the kidney initiates a series of enzyme reactions that produce angiotensin II. Angiotensin II raises blood pressure through widespread vasoconstriction and stimulates aldosterone secretion from the adrenal cortex. Aldosterone increases sodium reabsorption in the distal nephron, while ADH increases water reabsorption through insertion of aquaporin channels in the collecting duct. Together, these responses increase blood pressure, blood volume, and fluid retention, helping restore circulatory homeostasis.

Figure 5.4.5: Aquaporin Water Channel

This image shows a cell membrane with an embedded aquaporin, a specialized water channel protein that allows water to move across the membrane.

The cell membrane is shown as a phospholipid bilayer with two layers of phospholipids arranged back-to-back. Each phospholipid has a round head facing the outer or inner fluid environment and tails oriented toward the center of the membrane. This arrangement creates a hydrophobic barrier that limits the direct movement of water across the membrane.

Embedded within the membrane is a large protein labeled water channel. This channel spans the full thickness of the membrane and forms a narrow passage through the bilayer. The channel is selectively structured so that water molecules move through it in single file.

Small water molecules are shown passing through the channel from one side of the membrane to the other. Their movement occurs down a concentration gradient, meaning water moves from an area with higher water concentration to an area with lower water concentration.

Overall, the figure shows that:

- the phospholipid bilayer forms a barrier to direct water movement
- the aquaporin provides a controlled pathway through the membrane
- water molecules move through the channel in a selective, organized manner
- this process supports rapid and regulated water transport

The diagram emphasizes that aquaporins are essential because they allow cells to regulate water balance efficiently while the membrane itself remains selectively restrictive.

Figure 5.6.1: Reabsorption and Secretion Along the Nephron

This image shows a nephron and identifies specific substances that are reabsorbed from or secreted into the nephron tubule as filtrate is modified into urine. Arrows indicate the direction of movement between the nephron and the surrounding tissues.

The nephron begins at the renal corpuscle on the left and continues into the proximal convoluted tubule (PCT), loop of the nephron, distal convoluted tubule (DCT), and collecting duct.

Proximal Convoluted Tubule

In the proximal convoluted tubule (PCT), an arrow directed outward from the tubule shows reabsorption of:

- Glucose
- Amino acids
- Protein
- Vitamins
- Lactate
- Urea
- Uric acid
- Sodium (Na+)
- Potassium (K+)
- Calcium (Ca2+)
- Magnesium (Mg2+)
- Chloride (Cl–)
- Bicarbonate (HCO3–)
- Water (H2O)

A second arrow directed into the proximal convoluted tubule (PCT) indicates secretion of the following substances:

- Urea
- Uric acid
- Creatinine
- Some drugs
- Hydrogen ions (H+)
- Potassium ions (K+)
- Ammonium ions (NH4+)

Descending Limb of the Loop of the Nephron

As filtrate enters the descending limb of the loop of the nephron, an arrow shows reabsorption of water (H2O) from the tubule.

Near the lower portion of the loop, an arrow shows urea entering the nephron from the surrounding tissues.

Ascending Limb of the Loop of the Nephron

In the ascending limb of the loop of the nephron, an outward arrow indicates reabsorption of:

- Sodium (Na+)
- Potassium (K+)
- Chloride (Cl–)

Distal Convoluted Tubule

In the distal convoluted tubule (DCT), an outward arrow indicates reabsorption of:

- Sodium (Na+)
- Chloride (Cl–)
- Bicarbonate (HCO3–)
- Water (H2O)

A second arrow directed into the DCT shows secretion of:

- Hydrogen ions (H+)
- Potassium ions (K+)
- Ammonium ions (NH4+)

Collecting Duct

In the collecting duct, an outward arrow indicates reabsorption of:

- Water (H2O)
- Urea

The figure demonstrates that different regions of the nephron perform specialized transport functions that together regulate the composition of body fluids and the formation of urine. The proximal convoluted tubule reabsorbs a wide range of filtered substances while also secreting selected wastes and ions. The loop of the nephron contributes to the movement of water, urea, and electrolytes that support urine concentration. The distal convoluted tubule further modifies filtrate through selective reabsorption and secretion, helping regulate electrolyte and acid-base balance. The collecting duct performs final water and urea recovery, influencing the concentration and volume of the urine that leaves the kidney. Together, these transport processes allow the kidneys to conserve needed substances, remove wastes, and maintain fluid and electrolyte homeostasis.

Figure 5.6.2: Reabsorption and Secretion Along the Nephron

This image shows transport processes in a proximal convoluted tubule (PCT) cell, illustrating how substances move from the tubular lumen through the cell and into the interstitial space and bloodstream.

The figure is organized into three regions from left to right:

- lumen of the proximal tubule
- proximal tubule cell
- interstitial space and bloodstream

At the luminal side of the cell, multiple transport proteins move substances from the tubular fluid into the cell. Several substances enter together with sodium (Na+), showing cotransport or symport. These include:

- glucose and Na+
- amino acids and Na+
- chloride and Na+
- calcium and Na+
- phosphate and Na+

Also at the luminal membrane, several arrows show hydrogen ions (H+) moving from the cell into the lumen. This indicates secretion of H+ into the tubular fluid, coupled with sodium uptake.

Inside the proximal tubule cell, sodium movement is the main driving force for many of these transport processes. The diagram emphasizes that sodium gradients support the reabsorption of nutrients and ions through secondary active transport.

At the basolateral side of the cell, facing the interstitial space, a sodium-potassium pump uses ATP to move sodium out of the cell and potassium into the cell. This active transport maintains the low intracellular sodium concentration that makes luminal sodium entry possible. Other arrows show reabsorbed substances such as chloride, calcium, amino acids, glucose, and phosphate moving from the cell into the interstitial space and then into the bloodstream.

The diagram also shows water (H2O) moving from the lumen through the cell and into the interstitial space. This indicates that water follows the reabsorbed solutes by osmosis, allowing a large volume of fluid to return to the blood.

Overall, the figure shows that:

- the proximal convoluted tubule reabsorbs a large amount of filtered material
- sodium transport is the key driving force for many other transport processes
- glucose, amino acids, and several ions are reabsorbed from the lumen into the blood
- hydrogen ions are secreted into the tubular fluid
- water follows solutes, helping recover fluid volume

The diagram emphasizes that the proximal tubule is a major site of bulk reabsorption, where nutrients, electrolytes, and water are

returned to the body while selected substances are secreted into the forming urine.

Figure 5.6.3: Bicarbonate Reabsorption in the Proximal Convoluted Tubule

This image shows how bicarbonate (HCO3-) is reabsorbed in the proximal convoluted tubule (PCT). It illustrates the coordinated movement of substances between the tubular lumen, the PCT cell, and the bloodstream to help maintain acid-base balance.

The figure is organized into three regions from left to right:

- lumen of the proximal tubule
- proximal convoluted tubule cell
- bloodstream

At the luminal side, hydrogen ions (H+) are transported from the tubule cell into the lumen. There, H+ combines with filtered bicarbonate (HCO3-) to form carbonic acid (H2CO3). An enzyme labeled carbonic anhydrase then converts carbonic acid into carbon dioxide (CO2) and water (H2O). The carbon dioxide diffuses across the luminal membrane into the tubule cell.

Inside the proximal tubule cell, carbon dioxide combines again with water to form carbonic acid (H2CO3), with the help of carbonic anhydrase. Carbonic acid then dissociates into hydrogen ions (H+) and bicarbonate (HCO3-).

The hydrogen ions are recycled back into the lumen, where they can participate again in the same reaction sequence. The newly formed bicarbonate remains inside the cell for transport into the blood.

At the basolateral side, bicarbonate (HCO3-) moves out of the cell into the interstitial fluid and then into the bloodstream, often together with sodium (Na+). A sodium pump that uses ATP helps move sodium out of the cell, maintaining the gradient that supports this transport.

Overall, the figure shows that:

- bicarbonate is not directly reabsorbed from the tubular lumen
- in the lumen, bicarbonate combines with H+ and is converted to CO2 and H2O
- CO2 diffuses into the tubule cell
- inside the cell, bicarbonate is re-formed
- the re-formed bicarbonate is then transported into the bloodstream
- H+ is recycled, allowing the process to continue

The diagram emphasizes that this mechanism allows the kidney to reclaim bicarbonate efficiently and plays an important role in regulating the body's acid-base balance.

Figure 5.6.4: Countercurrent Multiplier System

This image shows the loop of the nephron, also called the Loop of Henle, and illustrates how it creates a countercurrent multiplier system that establishes a concentration gradient in the surrounding kidney tissue. This gradient supports later water reabsorption and helps the body produce concentrated urine.

A small inset on the left shows the location of the loop within the nephron. The enlarged main diagram on the right labels the interstitial osmolality of the surrounding tissue, which increases from 300 mOsmol/kg near the top of the loop to 1200 mOsmol/kg at the deepest part of the medulla. This increasing osmolality indicates that the tissue around the loop becomes progressively more concentrated from top to bottom.

The loop has two limbs:

- a descending limb on the left
- an ascending limb on the right

In the descending limb, arrows labeled H2O point outward from the tubule, showing that water leaves the filtrate and enters the surrounding interstitial space. Arrows labeled urea indicate movement of urea into the tubule. As the filtrate moves downward, it becomes progressively more concentrated, matching the increasing interstitial osmolality from 300 to 1200 mOsmol/kg. This

shows that water loss concentrates the filtrate.

In the ascending limb, arrows labeled Na+ and Cl- point outward from the tubule, showing that these ions move from the filtrate into the interstitial space. Circular arrows labeled H2O remain within the tubule, indicating that water does not leave this segment. As the filtrate moves upward, it becomes progressively less concentrated, changing from about 1100 mOsmol/kg to 100 mOsmol/kg. This shows that the ascending limb removes solutes while retaining water, which dilutes the filtrate.

The interstitial space between the two limbs is labeled with increasing osmolality values. These labels show that the concentration gradient is created and maintained by the different transport properties of the two limbs:

- the descending limb allows water to leave
- the ascending limb removes sodium and chloride
- together, these actions build a high-solute environment in the medulla

Overall, the figure shows that:

- the descending limb is permeable to water
- the ascending limb reabsorbs sodium and chloride but does not allow water to leave
- filtrate becomes more concentrated as it descends
- filtrate becomes more dilute as it ascends
- the surrounding interstitial tissue becomes progressively more hyperosmotic toward the bottom of the loop

The diagram emphasizes that the countercurrent multiplier system of the loop of the nephron creates the medullary osmotic gradient needed for regulated water recovery later in the collecting duct and for the formation of concentrated urine.

Figure 5.9.1: Nitrogen Wastes

This image shows three nitrogen-containing waste molecules arranged from left to right: ammonia, urea, and uric acid. The purpose of the figure is to compare these waste products by showing differences in their molecular structure, complexity, and relationship to water use and toxicity.

The molecules are displayed horizontally in order from smallest and simplest to largest and most complex:

- ammonia on the left
- urea in the center
- uric acid on the right

Atoms are represented by colored spheres:

- nitrogen is shown in blue
- oxygen is shown in red
- hydrogen is shown in white
- carbon is shown in black

On the left, ammonia is shown as the smallest molecule. It consists of one nitrogen atom bonded to three hydrogen atoms. Its simple structure reflects that it is the most basic nitrogen waste product. Ammonia is highly toxic and must be excreted with a large amount of water.

In the center, urea is shown as a somewhat larger molecule. It contains a central carbon atom, an oxygen atom, and two nitrogen atoms, each associated with hydrogen atoms. This structure is more complex than ammonia but still relatively simple. Urea is less toxic than ammonia and can be transported in the blood and excreted with moderate water loss.

On the right, uric acid is shown as the largest and most complex molecule. It contains multiple carbon and nitrogen atoms arranged in a ring-like structure with several oxygen atoms attached. This molecule is the least soluble of the three and can be excreted with minimal water, although it requires more energy to produce.

Overall, the figure shows that:

- ammonia is the smallest, simplest, and most toxic

- urea has intermediate complexity and toxicity
- uric acid is the largest, most complex, and least toxic
- the three molecules differ in how much water is needed for excretion

The figure emphasizes that nitrogen waste products vary in structure, toxicity, and water requirements, illustrating different strategies organisms use to remove nitrogen wastes while balancing water conservation.

Figure 5.10.1: Formation of Angiotensin II in the Renin-Angiotensin System

This image shows the early steps of the renin–angiotensin system, illustrating how angiotensin II is produced through a sequence of enzyme reactions involving the kidney, liver, and lungs.

The figure is arranged as a left-to-right pathway within the bloodstream. Arrows indicate the order of the steps, and three organs are shown around the pathway:

- the kidney at the upper left
- the liver at the lower left
- the lungs near the center-right

The process begins when the kidney releases the enzyme renin into the blood. The liver releases angiotensinogen into the blood, where it circulates as the starting substrate for the pathway.

An arrow labeled enzyme reaction shows renin acting on angiotensinogen to produce angiotensin I. This is the first conversion step and takes place in the bloodstream.

As the blood passes through the lung circulation, angiotensin-converting enzyme (ACE) is present in the pulmonary blood vessels. A second arrow labeled enzyme reaction shows ACE converting angiotensin I into angiotensin II. This is the second conversion step.

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6: FLUID, ELECTROLYTES, AND ACID-BASE BALANCE

Chapter Overview



Figure 6.1: Venus Williams Perspiring on the Tennis Court. The body has critically important mechanisms for balancing the intake and output of bodily fluids. An athlete must continuously replace the water and electrolytes lost in sweat. (CC BY-SA 4.0; via Wikimedia Commons).

Homeostasis and the Importance of Fluid Balance

Homeostasis is the process by which the body maintains relatively constant internal conditions despite changes in the external environment. In humans, this is especially crucial for substances that participate in chemical reactions. Many ions, nutrients, and signaling molecules must remain within narrow concentration ranges; too much or too little of a single substance can disrupt cell function. Because metabolic reactions are highly interconnected, a disturbance in one component can affect many organs and even entire organ systems.

Water is central to homeostasis. Most chemical reactions in the body occur in aqueous solutions, where water is the solvent. Body fluids are water-based mixtures that contain dissolved materials called solutes. These fluids differ in solute concentration from one compartment to another (for example, inside cells versus in the blood). The body uses multiple feedback systems to continuously monitor and adjust these concentrations, because healthy physiology depends on them staying within a narrow range. Inequities in access to clean water, safe working conditions, and climate-controlled environments can make it harder for some people to maintain healthy hydration and fluid balance, which has consequences for overall health.

Movement of Water and Solutes Between Compartments

Inside cells, fluid is called cytosol; outside cells, fluid is found in the interstitial space and within blood vessels. If the cytosol becomes too concentrated because the cell loses water, cell functions deteriorate. If the cytosol becomes too dilute because excess water enters the cell, the cell membrane may be damaged and the cell can burst. The body therefore regulates both water and solute movement between fluid compartments.

Hydrostatic pressure is the force that a fluid exerts against the walls of its container, such as blood pressing against vessel walls or filtrate pressing against the walls of capillaries. Differences in hydrostatic pressure drive fluid movement between compartments. Osmotic gradients, created by differences in solute concentrations, also cause water to move: water tends to move from areas of lower solute concentration to areas of higher solute concentration. In addition, many solutes move across membranes via active transport processes, which use ATP to move substances against their concentration gradients, and passive transport processes, which rely on existing gradients and the permeability of membranes. Passive transport includes diffusion and facilitated diffusion from regions of higher to lower concentration.

Because different people may have different exposures to heat, physical workload, and salt intake, the demands placed on these fluid-regulating mechanisms are not the same for everyone. Understanding how water and solutes move between compartments can clarify why some groups are more vulnerable to dehydration, edema, or blood pressure problems.

Balancing Water Intake and Output

Homeostasis requires that water intake and water output be balanced over time. Most water enters the body through the digestive tract, either as liquids or as water contained in foods. A smaller but significant portion (about ten percent) comes from metabolic water produced at the end of aerobic respiration during cellular metabolism. This internal water production is particularly important when access to water is limited.

The kidneys are the primary route for water leaving the body; urine formation accounts for the largest portion of daily water loss. The kidneys can adjust urine concentration based on the body's needs. When the body is dehydrated, the kidneys produce a smaller volume of more concentrated urine to conserve water. When water intake is high, they produce a larger volume of more dilute urine to eliminate the excess. Antidiuretic hormone (ADH) plays a central role in this process by increasing water reabsorption in the kidney's collecting ducts. When ADH levels rise, more water is reclaimed from the filtrate, and urine becomes more concentrated.

Patterns of work, access to fluids, climate, and cultural practices all influence water intake and loss. People working in hot environments, those with limited access to clean drinking water, and those taking certain medications may be at greater risk of imbalance. Recognizing these factors is important for equitable prevention and management of dehydration and overhydration.

Electrolytes and Their Regulation

Electrolytes are ions such as sodium, potassium, calcium, chloride, and phosphate that dissolve in body fluids and carry electrical charge. They are essential for multiple functions. Sodium and potassium gradients across membranes support electrical impulses in neurons and muscle cells. Calcium is necessary for muscle contraction, neurotransmitter release, and blood clotting. Electrolytes also help stabilize the three-dimensional structures of enzymes and facilitate hormone release by endocrine cells. The ions present in plasma contribute to osmotic balance, influencing the movement of water between cells and their environment.

Because of their importance, electrolyte concentrations are tightly regulated. Aldosterone and angiotensin II control the exchange of sodium and potassium in the kidney, especially between the renal filtrate and the cells of the distal nephron and collecting ducts. When aldosterone levels are high, sodium is reabsorbed and potassium is secreted. Calcium and phosphate levels are regulated primarily by parathyroid hormone (PTH), calcitriol (the active form of vitamin D), and calcitonin. PTH and calcitriol tend to increase blood calcium, while calcitonin can help lower it in some contexts.

Electrolyte imbalances can arise from unequal access to nutritious food, differential exposure to heat or physical exertion, varying access to medical care, and use of particular medications. These imbalances may manifest as muscle weakness, cardiac arrhythmias, bone disorders, or seizures. Awareness of these social and environmental determinants is important for equitable diagnosis and treatment.

Buffer Systems and Acid–Base Homeostasis

The pH of blood and other body fluids must be kept within narrow limits for enzymes and cellular processes to function properly. In arterial blood, a normal pH is approximately 7.35 to 7.45. A variety of buffering systems work together to resist abrupt changes in pH. A buffer is a substance that moderates changes in pH by absorbing excess hydrogen ions (H^+) or hydroxyl ions (OH^-). Typically, a weak acid can donate or accept a small number of ions, and a weak base can accept or donate hydrogen ions, helping keep pH within a safe range.

Several substances serve as important buffers in the body. Cell and plasma proteins, including hemoglobin within red blood cells, can bind hydrogen ions due to the chemical groups on their surfaces. Phosphate compounds contribute to buffering, especially inside cells and in the kidney tubules. The bicarbonate–carbonic acid system is the primary buffer in the interstitial fluid and in plasma; bicarbonate ions can accept hydrogen ions, while carbonic acid can release them. The respiratory system contributes to acid–base balance by regulating the exhalation of carbon dioxide, which is in equilibrium with carbonic acid in the blood. When ventilation increases, more CO_2 is lost, reducing carbonic acid and tending to raise pH. When ventilation decreases, CO_2 accumulates, increasing carbonic acid and lowering pH. The kidneys contribute by excreting hydrogen ions and reabsorbing or

generating bicarbonate ions, a slower but more powerful mechanism of long-term pH control.

Access to care, chronic respiratory illnesses, and kidney disease are not evenly distributed, and these conditions can weaken the body's ability to buffer changes in pH. Understanding buffering systems helps explain why some individuals are more vulnerable to acid–base disturbances in the face of infection, medication, or environmental stressors.

Acidosis, Alkalosis, and Compensation

Acidosis and alkalosis refer to conditions in which blood pH falls outside the normal range. Acidosis occurs when blood pH drops below 7.35, making the blood too acidic. Alkalosis occurs when blood pH rises above 7.45, making the blood too alkaline. These changes may result from metabolic disturbances, which primarily affect bicarbonate levels, or from respiratory disturbances, which primarily affect carbon dioxide and carbonic acid levels.

In metabolic acidosis, bicarbonate levels are too low relative to carbonic acid, as can occur with severe diarrhea, uncontrolled diabetes, or kidney failure. In metabolic alkalosis, bicarbonate levels are too high, which can result from excessive loss of gastric acid through prolonged vomiting or certain diuretics. Respiratory acidosis arises when carbon dioxide is not adequately removed from the body, often due to hypoventilation or lung disease such as chronic obstructive pulmonary disease. Respiratory alkalosis occurs when carbon dioxide is exhaled too rapidly, as in hyperventilation due to anxiety, pain, or high altitude exposure.

The body uses several compensatory mechanisms to limit pH shifts. In respiratory disturbances, the kidneys can adjust bicarbonate reabsorption and hydrogen ion excretion over hours to days. In metabolic disturbances, the respiratory system can adjust ventilation to change CO_2 levels within minutes. Buffer systems act immediately to blunt sharp changes. However, these mechanisms have limits, and severe or prolonged imbalances can be life-threatening.

Social and environmental factors, including occupational exposures, air quality, nutrition, and access to medications, influence who is more likely to experience acidosis or alkalosis and how quickly they can receive treatment. Recognizing how acid–base regulation operates, and how it can fail, supports both clinical decision-making and public health efforts to reduce unequal burdens of disease.

Learning Objectives

To achieve these chapter objectives, actively engage with the material. Learning tissues is not a passive process. Your understanding will grow as you interact with the content, peers, and your instructor. Regularly check your thinking against feedback. Revisit complex concepts until you can confidently explain and apply them on your own.

By the end of this chapter, you will be able to:

- Identify the major body fluid compartments (intracellular and extracellular) and describe how water is distributed between them.
- Define plasma osmolality and explain the primary mechanisms that maintain it (thirst/ADH system and renal water reabsorption and excretion)..
- Distinguish between typical intracellular and extracellular concentrations of major electrolytes. Identify the six ions most critical for normal body function (e.g., Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-) and summarize their key physiological roles of each ion in nerve and muscle function, membrane potentials, fluid balance, and acid–base regulation.
- Recognize common clinical disturbances of major electrolytes (e.g., hyponatremia, hyperkalemia, hypocalcemia) and relate them to their principal signs, symptoms, and physiological consequences.
- Define a buffer and explain the general principle of how buffers resist changes in pH.
- Describe the major buffer systems of the body (bicarbonate, phosphate, and protein buffers) and explain how each contributes to stabilizing body pH in different fluid compartments.
- State t.he normal arterial blood pH range and define acidosis and alkalosis. Differentiate between respiratory and metabolic causes of acidosis and alkalosis on a conceptual level
  - Explain how changes in ventilation alter blood CO_2 levels and thus influence pH.
  - Describe how the kidneys regulate acid–base balance by secreting H^+, reabsorbing filtered bicarbonate, and generating new bicarbonate.

6.1: Body Fluids and Fluid Compartment
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6.3: Electrolyte Balance
6.4: Acid-Base Balance
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6.1: Body Fluids and Fluid Compartment

Fluid Shifts Between Body Compartments

The chemical reactions of life take place in aqueous solutions. The dissolved substances in a solution are called solutes. In the human body, solutes vary in different parts of the body, but may include proteins—including those that transport lipids, carbohydrates, and, very importantly, electrolytes. Often in medicine, a mineral dissociated from a salt that carries an electrical charge (an ion) is called an electrolyte. For instance, sodium ions (Na^+) and chloride ions (Cl^-) are often referred to as electrolytes.

In the body, water moves through semi-permeable membranes of cells and from one compartment of the body to another by a process called osmosis. Osmosis is basically the diffusion of water from regions of higher concentration of water to regions of lower concentration of water, along an osmotic gradient across a semi-permeable membrane. As a result, water will move into and out of cells and tissues, depending on the relative concentrations of the water and solutes found there. An appropriate balance of solutes inside and outside of cells must be maintained to ensure normal function.

Body Water Content

Human beings are mostly water, ranging from about 75 percent of body mass in infants to about 50–60 percent in adults, to as low as 45 percent in old age. The percent of body water changes with development, because the proportions of the body given over to each organ and to muscles, fat, bone, and other tissues change from infancy to adulthood (Figure 6.1.1). Your brain and kidneys have the highest proportions of water, which composes 80–85 percent of their masses. In contrast, teeth have the lowest proportion of water, at 8–10 percent.

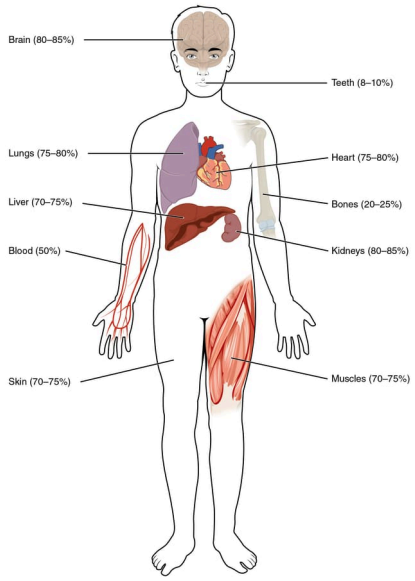


Figure 6.1.1: Water content varies in different body organs and tissues, from as little as 8 percent in the teeth to as much as 85 percent in the brain. (CC BY 4.0 ; via Body Fluids and Fluid Compartment). Detailed text description of the Figure 6.1.1.

Fluid Compartments

Body fluids can be discussed in terms of their specific fluid compartment, a location that is largely separate from another compartment by some form of a physical barrier. The intracellular fluid (ICF) compartment is the system that includes all fluid enclosed in cells by their plasma membranes. Extracellular fluid (ECF) surrounds all cells in the body. Extracellular fluid has two primary constituents: the fluid component of the blood (called plasma) and the interstitial fluid (IF) that surrounds all cells not in the blood (Figure 6.1.2).

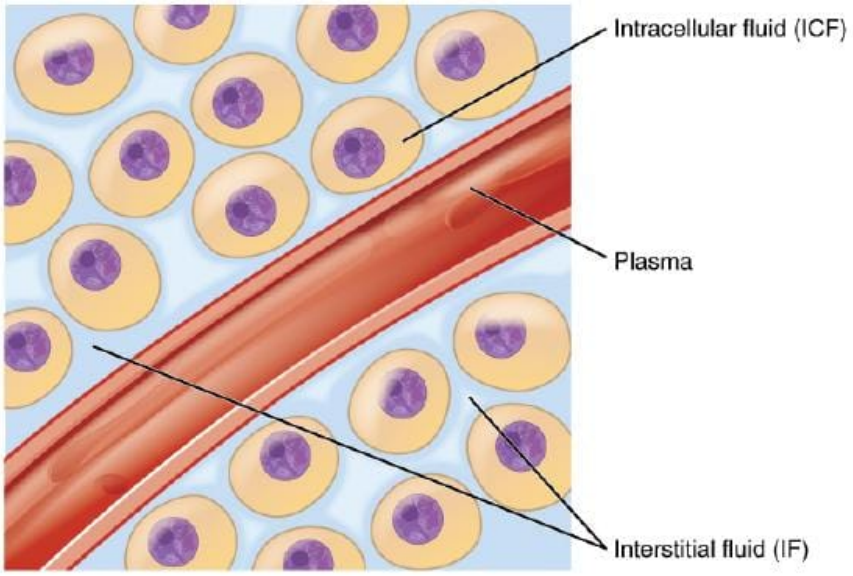


Figure 6.1.2: The intracellular fluid (ICF) is the fluid within cells. The interstitial fluid (IF) is part of the extracellular fluid (ECF) between the cells. Blood plasma is the second part of the ECF. Materials travel between cells and the plasma in capillaries through the IF. (CC BY 4.0 ; via Body Fluids and Fluid Compartment). Detailed text description of the Figure 6.1.2.

Intracellular Fluid

The ICF lies within cells and is the principal component of the cytosol/cytoplasm. The ICF makes up about 60 percent of the total water in the human body, and in an average-size adult male, the ICF accounts for about 25 liters (seven gallons) of fluid (Figure 6.1.3). This fluid volume tends to be very stable, because the amount of water in living cells is closely regulated. If the amount of water inside a cell falls to a value that is too low, the cytosol becomes too concentrated with solutes to carry on normal cellular activities; if too much water enters a cell, the cell may burst and be destroyed.

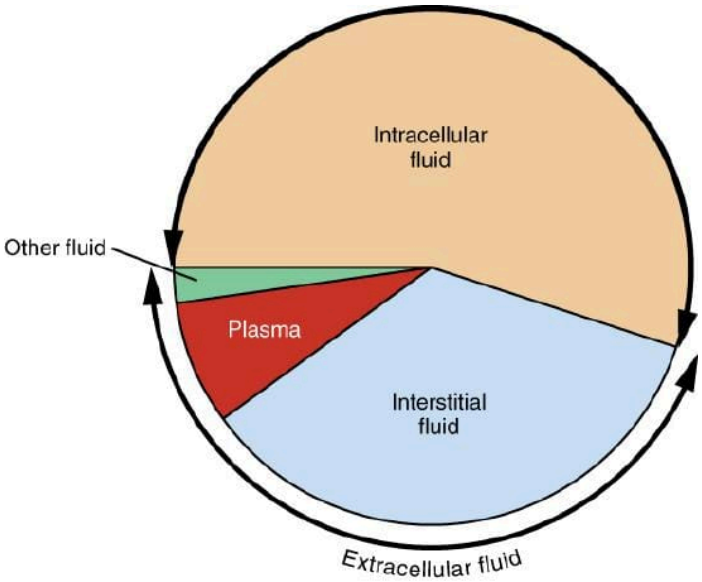


Figure 6.1.3: Intracellular fluid comprises the largest portion of total body fluid, while extracellular fluid is divided into interstitial fluid, plasma, and a smaller “other fluid” component. (CC BY 4.0 ; via Body Fluids and Fluid Compartment). Detailed text description of the Figure 6.1.3.

Extracellular Fluid

The ECF accounts for the other one-third of the body’s water content. Approximately 20 percent of the ECF is found in plasma.

Plasma travels through the body in blood vessels and transports a range of materials, including blood cells, proteins (including clotting factors and antibodies), electrolytes, nutrients, gases, and wastes. Gases, nutrients, and waste materials travel between capillaries and cells through the IF. Cells are separated from the IF by a selectively permeable cell membrane that helps regulate the passage of materials between the IF and the interior of the cell.

The body has other water-based ECF. These include the cerebrospinal fluid that bathes the brain and spinal cord, lymph, the synovial fluid in joints, the pleural fluid in the pleural cavities, the pericardial fluid in the cardiac sac, the peritoneal fluid in the peritoneal cavity, and the aqueous humor of the eye. Because these fluids are outside of cells, these fluids are also considered components of the ECF compartment.

Composition of Body Fluids

The compositions of the two components of the ECF—plasma and IF—are more similar to each other than either is to the ICF (Figure 6.1.4). Blood plasma has high concentrations of sodium, chloride, bicarbonate, and protein. The IF has high concentrations of sodium, chloride, and bicarbonate, but a relatively lower concentration of protein. In contrast, the ICF has elevated amounts of potassium, phosphate, magnesium, and protein. Overall, the ICF contains high concentrations of potassium and phosphate (HPO_4^{2-}), whereas both plasma and the ECF contain high concentrations of sodium and chloride.

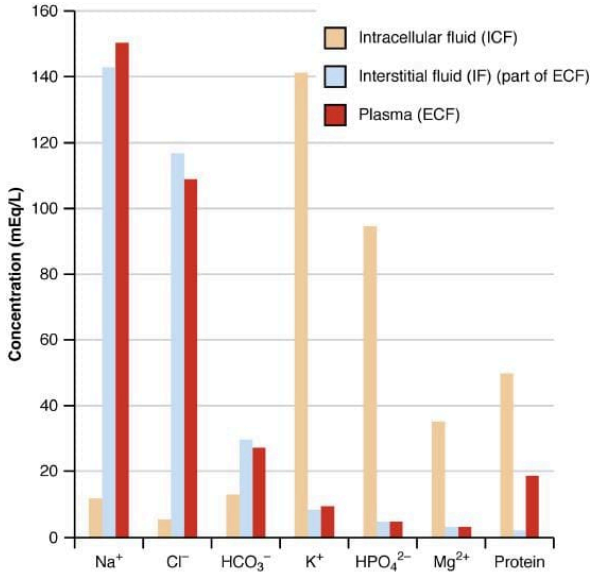


Figure 6.1.4: The graph shows the composition of the ICF, IF, and plasma. The compositions of plasma and IF are similar to one another but are quite different from the composition of the ICF. (CC BY 4.0 ; via Body Fluids and Fluid Compartment). Detailed text description of the Figure 6.1.4.

Most body fluids are neutral in charge. Thus, cations, or positively charged ions, and anions, or negatively charged ions, are balanced in fluids. As seen in the previous graph, sodium (Na^+) ions and chloride (Cl^-) ions are concentrated in the ECF of the body, whereas potassium (K^+) ions are concentrated inside cells. Although sodium and potassium can “leak” through “pores” into and out of cells, respectively, the high levels of potassium and low levels of sodium in the ICF are maintained by sodium-potassium pumps in the cell membranes. These pumps use the energy supplied by ATP to pump sodium out of the cell and potassium into the cell (Figure 6.1.5).

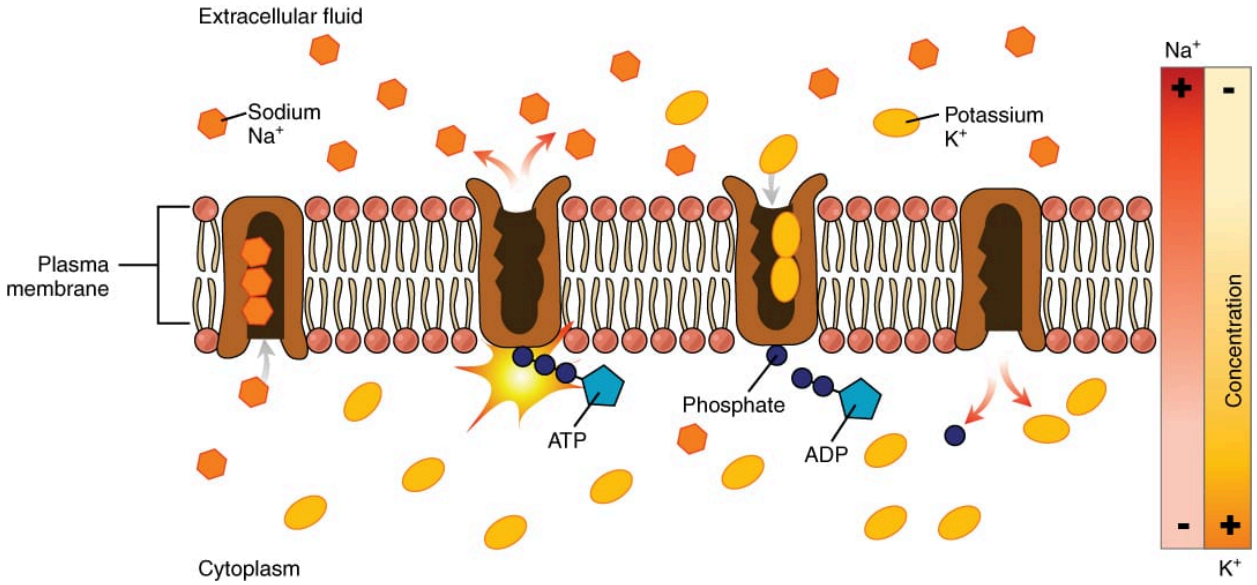


Figure 6.1.5: The sodium-potassium pump is powered by ATP to transfer sodium out of the cytoplasm and into the ECF. The pump also transfers potassium out of the ECF and into the cytoplasm. (CC BY 4.0 ; Mariana Ruiz Villarreal via Body Fluids and Fluid Compartment). Detailed text description of the Figure 6.1.5.

Fluid Movement between Compartments

Hydrostatic pressure, the force exerted by a fluid against a wall, causes movement of fluid between compartments. The hydrostatic pressure of blood is the pressure exerted by blood against the walls of the blood vessels by the pumping action of the heart. In capillaries, hydrostatic pressure (also known as capillary blood pressure) is higher than the opposing "colloid osmotic pressure" in blood—a "constant" pressure primarily produced by circulating albumin—at the arteriolar end of the capillary (Figure 6.1.6). This pressure forces plasma and nutrients out of the capillaries and into surrounding tissues. Fluid and the cellular wastes in the tissues enter the capillaries at the venule end, where the hydrostatic pressure is less than the osmotic pressure in the vessel. Filtration pressure squeezes fluid from the plasma in the blood to the IF surrounding the tissue cells. The surplus fluid in the interstitial space that is not returned directly back to the capillaries is drained from tissues by the lymphatic system, and then re-enters the vascular system at the subclavian veins.

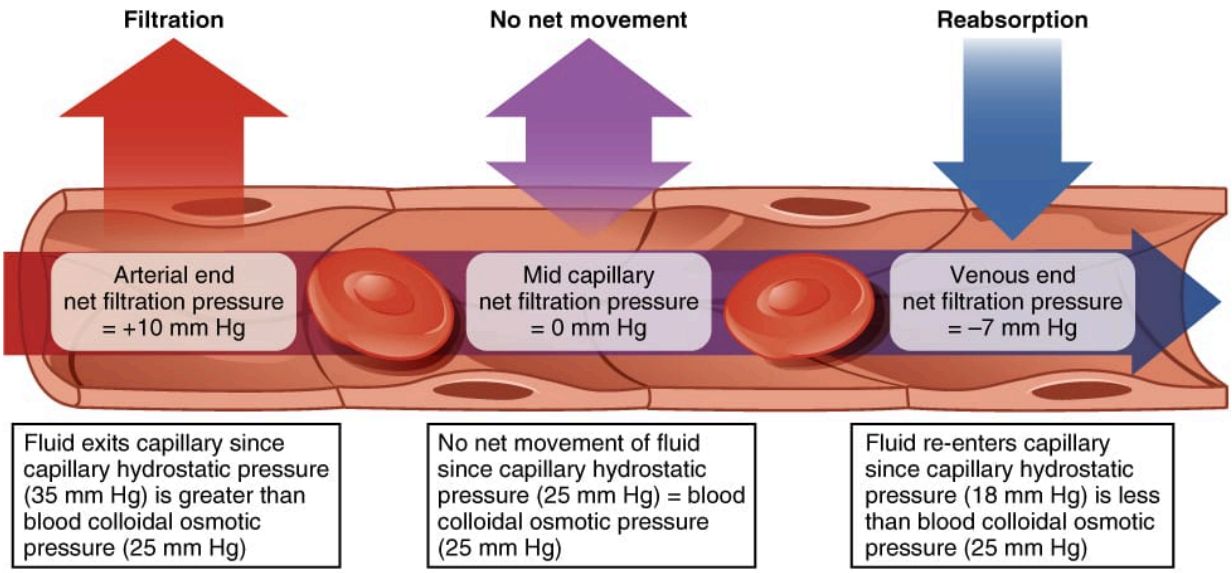


Figure 6.1.6: Net filtration occurs near the arterial end of the capillary since capillary hydrostatic pressure (CHP) is greater than blood colloidal osmotic pressure (BCOP). There is no net movement of fluid near the midpoint of the capillary since CHP = BCOP. Net reabsorption occurs near the venous end of the capillary since BCOP is greater than CHP. (CC BY 4.0 ; via Body Fluids and Fluid Compartment). Detailed text description of the Figure 6.1.6.

Hydrostatic pressure is especially important in governing the movement of water in the nephrons of the kidneys to ensure proper filtering of the blood to form urine. As hydrostatic pressure in the kidneys increases, the amount of water leaving the capillaries also increases, and more urine filtrate is formed. If hydrostatic pressure in the kidneys drops too low, as can happen in dehydration, the functions of the kidneys will be impaired, and less nitrogenous wastes will be removed from the bloodstream. Extreme dehydration can result in kidney failure.

Fluid also moves between compartments along an osmotic gradient. Recall that an osmotic gradient is produced by the difference in concentration of all solutes on either side of a semi-permeable membrane. The magnitude of the osmotic gradient is proportional to the difference in the concentration of solutes on one side of the cell membrane to that on the other side. Water will move by osmosis from the side where its concentration is high (and the concentration of solute is low) to the side of the membrane where its concentration is low (and the concentration of solute is high). In the body, water moves by osmosis from plasma to the IF (and the reverse) and from the IF to the ICF (and the reverse). In the body, water moves constantly into and out of fluid compartments as conditions change in different parts of the body.

For example, if you are sweating, you will lose water through your skin. Sweating depletes your tissues of water and increases the solute concentration in those tissues. As this happens, water diffuses from your blood into sweat glands and surrounding skin tissues that have become dehydrated because of the osmotic gradient. Additionally, as water leaves the blood, it is replaced by the water in other tissues throughout your body that are not dehydrated. If this continues, dehydration spreads throughout the body. When a dehydrated person drinks water and rehydrates, the water is redistributed by the same gradient, but in the opposite direction, replenishing water in all of the tissues.

Solute Movement between Compartments

The movement of some solutes between compartments is active, which consumes energy and is an active transport process, whereas the movement of other solutes is passive, which does not require energy. Active transport allows cells to move a specific substance against its concentration gradient through a membrane protein, requiring energy in the form of ATP. For example, the sodium-potassium pump employs active transport to pump sodium out of cells and potassium into cells, with both substances moving against their concentration gradients.

Passive transport of a molecule or ion depends on its ability to pass through the membrane, as well as the existence of a concentration gradient that allows the molecules to diffuse from an area of higher concentration to an area of lower concentration. Some molecules, like gases, lipids, and water itself (which also utilizes water channels in the membrane called aquaporins), slip fairly easily through the cell membrane; others, including polar molecules like glucose, amino acids, and ions do not. Some of

these molecules enter and leave cells using facilitated transport, whereby the molecules move down a concentration gradient through specific protein channels in the membrane. This process does not require energy. For example, glucose is transferred into cells by glucose transporters that use facilitated transport (Figure 6.1.7).

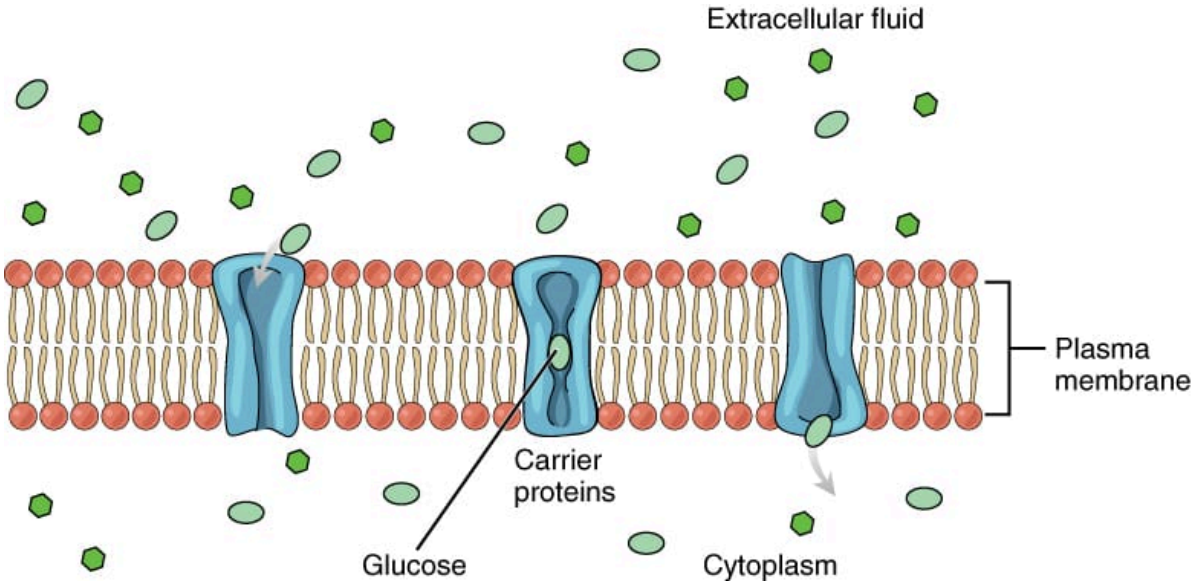


Figure 6.1.7: Glucose molecules use facilitated diffusion to move down a concentration gradient through the carrier protein channels in the membrane. (CC BY 4.0 ; Mariana Ruiz Villarreal via Body Fluids and Fluid Compartment). Detailed text description of the Figure 6.1.7.

Disorders of the...

Fluid Balance: Edema

Edema is the accumulation of excess water in the tissues. It is most common in the soft tissues of the extremities. The physiological causes of edema include water leakage from blood capillaries. Edema is almost always caused by an underlying medical condition, by the use of certain therapeutic drugs, by pregnancy, by localized injury, or by an allergic reaction. In the limbs, the symptoms of edema include swelling of the subcutaneous tissues, an increase in the normal size of the limb, and stretched, tight skin. One quick way to check for subcutaneous edema localized in a limb is to press a finger into the suspected area. Edema is likely if the depression persists for several seconds after the finger is removed (which is called “pitting”).

Pulmonary edema is excess fluid in the air sacs of the lungs, a common symptom of heart and/or kidney failure. People with pulmonary edema likely will experience difficulty breathing, and they may experience chest pain. Pulmonary edema can be life threatening, because it compromises gas exchange in the lungs, and anyone having symptoms should immediately seek medical care.

In pulmonary edema resulting from heart failure, excessive leakage of water occurs because fluids get “backed up” in the pulmonary capillaries of the lungs, when the left ventricle of the heart is unable to pump sufficient blood into the systemic circulation. Because the left side of the heart is unable to pump out its normal volume of blood, the blood in the pulmonary circulation gets “backed up,” starting with the left atrium, then into the pulmonary veins, and then into pulmonary capillaries. The resulting increased hydrostatic pressure within pulmonary capillaries, as blood is still coming in from the pulmonary arteries, causes fluid to be pushed out of them and into lung tissues.

Other causes of edema include damage to blood vessels and/or lymphatic vessels, or a decrease in osmotic pressure in chronic and severe liver disease, where the liver is unable to manufacture plasma proteins (Figure 6.1.8). A decrease in the normal levels of plasma proteins results in a decrease of colloid osmotic pressure (which counterbalances the hydrostatic pressure) in the capillaries. This process causes loss of water from the blood to the surrounding tissues, resulting in edema.



Figure 6.1.8: An allergic reaction can cause capillaries in the hand to leak excess fluid that accumulates in the tissues. (CC BY 4.0 ; via Body Fluids and Fluid Compartment). Detailed text description of the Figure 6.1.8.

Mild, transient edema of the feet and legs may be caused by sitting or standing in the same position for long periods of time, as in the work of a toll collector or a supermarket cashier. This is because deep veins in the lower limbs rely on skeletal muscle contractions to push on the veins and thus "pump" blood back to the heart. Otherwise, the venous blood pools in the lower limbs and can leak into surrounding tissues.

Medications that can result in edema include vasodilators, calcium channel blockers used to treat hypertension, non-steroidal anti-inflammatory drugs, estrogen therapies, and some diabetes medications. Underlying medical conditions that can contribute to edema include congestive heart failure, kidney damage and kidney disease, disorders that affect the veins of the legs, and cirrhosis and other liver disorders.

Therapy for edema usually focuses on elimination of the cause. Activities that can reduce the effects of the condition include appropriate exercises to keep the blood and lymph flowing through the affected areas. Other therapies include elevation of the affected part to assist drainage, massage and compression of the areas to move the fluid out of the tissues, and decreased salt intake to decrease sodium and water retention.

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6.2: Water Balance

Regulation of Water Intake

On a typical day, the average adult will take in about 2500 mL of aqueous fluids. Although most of the intake comes through the digestive tract, about 230 mL (8 ounces) per day is generated metabolically, in the last steps of aerobic respiration. Additionally, each day about the same volume (2500 mL) of water leaves the body by different routes; most of this lost water is removed as urine. The kidneys also can adjust blood volume though mechanisms that draw water out of the filtrate and urine. The kidneys can regulate water levels in the body; they conserve water if you are dehydrated, and they can make urine more dilute to expel excess water if necessary. Water is lost through the skin through evaporation from the skin surface without overt sweating and from air expelled from the lungs. This type of water loss is called insensible water loss because a person is usually unaware of it

Osmolality is the ratio of solutes in a solution to a volume of solvent in a solution. Plasma osmolality is thus the ratio of solutes to water in blood plasma. A person's plasma osmolality value reflects the state of hydration. A healthy body maintains plasma osmolality within a narrow range, by employing several mechanisms that regulate both water intake and output.

Drinking water is considered voluntary. So how is water intake regulated by the body? Consider someone who is experiencing dehydration, a net loss of water that results in insufficient water in blood and other tissues. The water that leaves the body, as exhaled air, sweat, or urine, is ultimately extracted from blood plasma. As the blood becomes more concentrated, the thirst response—a sequence of physiological processes—is triggered (Figure 6.2.1). Osmoreceptors are sensory receptors in the thirst center in the hypothalamus that monitor the concentration of solutes (osmolality) of the blood. If blood osmolality increases above its ideal value, the hypothalamus transmits signals that result in a conscious awareness of thirst. The person should (and normally does) respond by drinking water. The hypothalamus of a dehydrated person also releases antidiuretic hormone (ADH) through the posterior pituitary gland. ADH signals the kidneys to recover water from urine, effectively diluting the blood plasma. To conserve water, the hypothalamus of a dehydrated person also sends signals via the sympathetic nervous system to the salivary glands in the mouth. The signals result in a decrease in watery, serous output (and an increase in stickier, thicker mucus output). These changes in secretions result in a "dry mouth" and the sensation of thirst.

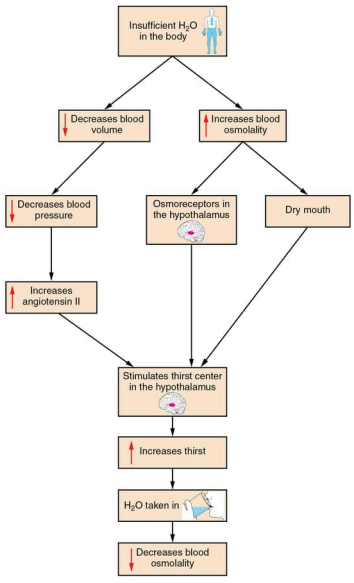


Figure 6.2.1: The thirst response begins when osmoreceptors detect a decrease in water levels in the blood. (CC BY 4.0; via Water Balance). Detailed text description of the Figure 6.2.1.

If adequate fluids are not consumed, dehydration results and a person's body contains too little water to function correctly. A person who repeatedly vomits or who has diarrhea may become dehydrated, and infants, because their body mass is so low, can become dangerously dehydrated very quickly. Endurance athletes such as distance runners often become dehydrated during long races. Dehydration can be a medical emergency, and a dehydrated person may lose consciousness, become comatose, or die, if

their body is not rehydrated quickly.

Regulation of Water Output

Water loss from the body occurs predominantly through the renal system. A person produces an average of 1.5 liters (1.6 quarts) of urine per day. Although the volume of urine varies in response to hydration levels, there is a minimum volume of urine production required for proper bodily functions. The kidney excretes 100 to 1200 milliosmoles of solutes per day to rid the body of a variety of excess salts and other water-soluble chemical wastes, most notably creatinine, urea, and uric acid. Failure to produce the minimum volume of urine means that metabolic wastes cannot be effectively removed from the body, a situation that can impair organ function. The minimum level of urine production necessary to maintain normal function is about 0.47 liters (0.5 quarts) per day.

The kidneys also must make adjustments in the event of ingestion of too much fluid. Diuresis, which is the production of urine in excess of normal levels, begins about 30 minutes after drinking a large quantity of fluid. Diuresis reaches a peak after about 1 hour, and normal urine production is reestablished after about 3 hours.

Role of ADH

Antidiuretic hormone (ADH), also known as vasopressin, controls the amount of water reabsorbed from the collecting ducts and tubules in the kidney. This hormone is produced in the hypothalamus and is delivered to the posterior pituitary for storage and release (Figure 6.2.2). When the osmoreceptors in the hypothalamus detect an increase in the concentration of blood plasma, the hypothalamus signals the release of ADH from the posterior pituitary into the blood.

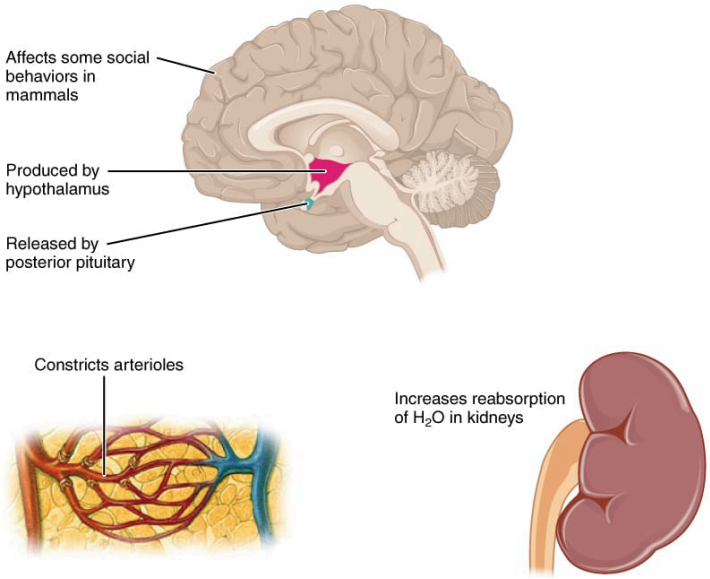


Figure 6.2.2: Antidiuretic hormone (ADH) is produced in the hypothalamus and released by the posterior pituitary gland. It causes the kidneys to retain water, constricts arterioles in the peripheral circulation, and affects some social behaviors in mammals. (CC BY 4.0; via Water Balance). Detailed text description of the Figure 6.2.2.

ADH has two major effects. It constricts the arterioles in the peripheral circulation, which reduces the flow of blood to the extremities and thereby increases the blood supply to the core of the body. ADH also causes the epithelial cells that line the renal collecting tubules to move water channel proteins, called aquaporins, from the interior of the cells to the apical surface, where these proteins are inserted into the cell membrane (Figure 6.2.2). The result is an increase in the water permeability of these cells and, thus, a large increase in water passage from the urine through the walls of the collecting tubules, leading to more reabsorption of water into the bloodstream. When the blood plasma becomes less concentrated and the level of ADH decreases, aquaporins are removed from collecting tubule cell membranes, and the passage of water out of urine and into the blood decreases.

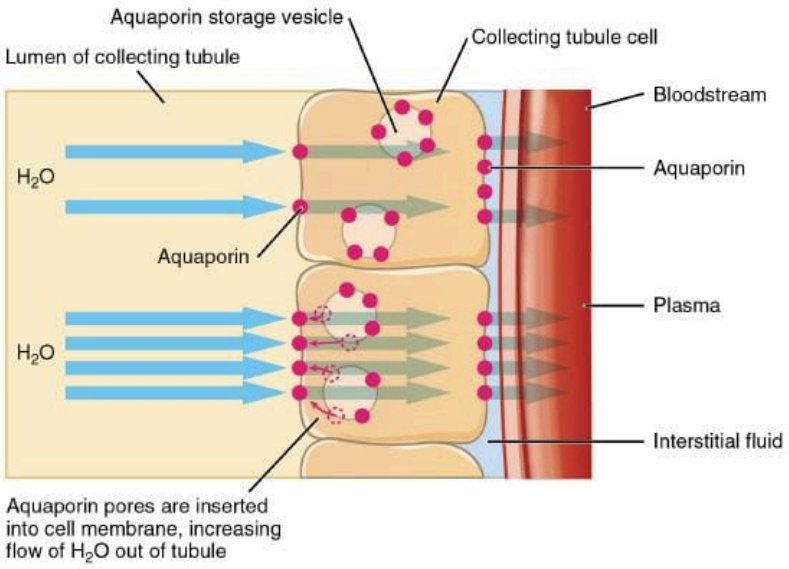


Figure 6.2.3: The binding of ADH to receptors on the cells of the collecting tubule results in aquaporins being inserted into the plasma membrane, shown in the lower cell. This dramatically increases the flow of water out of the tubule and into the bloodstream. (CC BY 4.0; via Water Balance). Detailed text description of the Figure 6.2.3.

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6.3: Electrolyte Balance

Roles of Electrolytes

The body contains a large variety of ions, or electrolytes, which perform a variety of functions. Some ions assist in the transmission of electrical impulses along cell membranes in neurons and muscles. Other ions help to stabilize protein structures in enzymes. Still others aid in releasing hormones from endocrine glands. All of the ions in plasma contribute to the osmotic balance that controls the movement of water between cells and their environment.

Electrolytes in living systems include sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, copper, zinc, iron, manganese, molybdenum, copper, and chromium. In terms of body functioning, six electrolytes are most important: sodium, potassium, chloride, bicarbonate, calcium, and phosphate.

These six ions aid in nerve excitability, endocrine secretion, membrane permeability, buffering body fluids, and controlling the movement of fluids between compartments. These ions enter the body through the digestive tract. More than 90 percent of the calcium and phosphate that enters the body is incorporated into bones and teeth, with bone serving as a mineral reserve for these ions. In the event that calcium and phosphate are needed for other functions, bone tissue can be broken down to supply the blood and other tissues with these minerals. Phosphate is a normal constituent of nucleic acids; hence, blood levels of phosphate will increase whenever nucleic acids are broken down.

Excretion of ions occurs mainly through the kidneys, with lesser amounts lost in sweat and in feces. Excessive sweating may cause a significant loss, especially of sodium and chloride. Severe vomiting or diarrhea will cause a loss of chloride and bicarbonate ions. Adjustments in respiratory and renal functions allow the body to regulate the levels of these ions in the ECF.

Table 6.3.1 lists the reference values for blood plasma, cerebrospinal fluid (CSF), and urine for the six ions addressed in this section. In a clinical setting, sodium, potassium, and chloride are typically analyzed in a routine urine sample. In contrast, calcium and phosphate analysis requires a collection of urine across a 24-hour period, because the output of these ions can vary considerably over the course of a day. Urine values reflect the rates of excretion of these ions. Bicarbonate is the one ion that is not normally excreted in urine; instead, it is conserved by the kidneys for use in the body's buffering systems.

Table 6.3.1: Electrolyte and Ion Reference Values

Name	Chemical symbol	Plasma	CSF	Urine
Sodium	Na^+	136.00–146.00 (mM)	138.00–150.00 (mM)	40.00–220.00 (mM)
Potassium	K^+	3.50–5.00 (mM)	0.35–3.5 (mM)	25.00–125.00 (mM)
Chloride	Cl^-	98.00–107.00 (mM)	118.00–132.00 (mM)	110.00–250.00 (mM)
Bicarbonate	HCO_3^-	22.00–29.00 (mM)	------	------
Calcium	Ca^{++}	2.15–2.55 (mmol/day)	------	Up to 7.49 (mmol/day)
Phosphate	HPO_4^{2-}	0.81–1.45 (mmol/day)	------	12.90–42.00 (mmol/day)

Sodium

Sodium is the major cation of the extracellular fluid. It is responsible for one-half of the osmotic pressure gradient that exists between the interior of cells and their surrounding environment. People eating a typical Western diet, which is very high in NaCl, routinely take in 130 to 160 mmol/day of sodium, but humans require only 1 to 2 mmol/day. This excess sodium appears to be a major factor in hypertension (high blood pressure) in some people. Excretion of sodium is accomplished primarily by the kidneys. Sodium is freely filtered through the glomerular capillaries of the kidneys, and although much of the filtered sodium is reabsorbed in the proximal convoluted tubule, some remains in the filtrate and urine, and is normally excreted.

Hyponatremia is a lower-than-normal concentration of sodium, usually associated with excess water accumulation in the body,

which dilutes the sodium. An absolute loss of sodium may be due to a decreased intake of the ion coupled with its continual excretion in the urine. An abnormal loss of sodium from the body can result from several conditions, including excessive sweating, vomiting, or diarrhea; the use of diuretics; excessive production of urine, which can occur in diabetes; and acidosis, either metabolic acidosis or diabetic ketoacidosis.

A relative decrease in blood sodium can occur because of an imbalance of sodium in one of the body's other fluid compartments, like IF, or from a dilution of sodium due to water retention related to edema or congestive heart failure. At the cellular level, hyponatremia results in increased entry of water into cells by osmosis, because the concentration of solutes within the cell exceeds the concentration of solutes in the now-diluted ECF. The excess water causes swelling of the cells; the swelling of red blood cells—decreasing their oxygen-carrying efficiency and making them potentially too large to fit through capillaries—along with the swelling of neurons in the brain can result in brain damage or even death.

Hypernatremia is an abnormal increase of blood sodium. It can result from water loss from the blood, resulting in the hemoconcentration of all blood constituents. Hormonal imbalances involving ADH and aldosterone may also result in higher-than-normal sodium values.

Potassium

Potassium is the major intracellular cation. It helps establish the resting membrane potential in neurons and muscle fibers after membrane depolarization and action potentials. In contrast to sodium, potassium has very little effect on osmotic pressure. The low levels of potassium in blood and CSF are due to the sodium-potassium pumps in cell membranes, which maintain the normal potassium concentration gradients between the ICF and ECF. The recommendation for daily intake/consumption of potassium is 4700 mg. Potassium is excreted, both actively and passively, through the renal tubules, especially the distal convoluted tubule and collecting ducts. Potassium participates in the exchange with sodium in the renal tubules under the influence of aldosterone, which also relies on basolateral sodium-potassium pumps.

Hypokalemia is an abnormally low potassium blood level. Similar to the situation with hyponatremia, hypokalemia can occur because of either an absolute reduction of potassium in the body or a relative reduction of potassium in the blood due to the redistribution of potassium. An absolute loss of potassium can arise from decreased intake, frequently related to starvation. It can also come about from vomiting, diarrhea, or alkalosis.

Some insulin-dependent diabetic patients experience a relative reduction of potassium in the blood from the redistribution of potassium. When insulin is administered and glucose is taken up by cells, potassium passes through the cell membrane along with glucose, decreasing the amount of potassium in the blood and IF, which can cause hyperpolarization of the cell membranes of neurons, reducing their responses to stimuli.

Hyperkalemia, an elevated potassium blood level, also can impair the function of skeletal muscles, the nervous system, and the heart. Hyperkalemia can result from increased dietary intake of potassium. In such a situation, potassium from the blood ends up in the ECF in abnormally high concentrations. This can result in a partial depolarization (excitation) of the plasma membrane of skeletal muscle fibers, neurons, and cardiac cells of the heart, and can also lead to an inability of cells to repolarize. For the heart, this means that it won't relax after a contraction, and will effectively "seize" and stop pumping blood, which is fatal within minutes. Because of such effects on the nervous system, a person with hyperkalemia may also exhibit mental confusion, numbness, and weakened respiratory muscles.

Chloride

Chloride is the predominant extracellular anion. Chloride is a major contributor to the osmotic pressure gradient between the ICF and ECF, and plays an important role in maintaining proper hydration. Chloride functions to balance cations in the ECF, maintaining the electrical neutrality of this fluid. The paths of secretion and reabsorption of chloride ions in the renal system follow the paths of sodium ions.

Hypochloremia, or lower-than-normal blood chloride levels, can occur because of defective renal tubular absorption. Vomiting, diarrhea, and metabolic acidosis can also lead to hypochloremia. Hyperchloremia, or higher-than-normal blood chloride levels, can occur due to dehydration, excessive intake of dietary salt (NaCl) or swallowing of sea water, aspirin intoxication, congestive heart failure, and the hereditary, chronic lung disease, cystic fibrosis. In people who have cystic fibrosis, chloride levels in sweat are two to five times those of normal levels, and analysis of sweat is often used in the diagnosis of the disease.

Bicarbonate

Bicarbonate is the second most abundant anion in the blood. Its principal function is to maintain your body's acid-base balance by being part of buffer systems. This role will be discussed in a different section.

Bicarbonate ions result from a chemical reaction that starts with carbon dioxide (CO_2) and water, two molecules that are produced at the end of aerobic metabolism. Only a small amount of CO_2 can be dissolved in body fluids. Thus, over 90 percent of the CO_2 is converted into bicarbonate ions, HCO_3^-, through the following reactions:

$$\mathrm{CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+}$$

The bidirectional arrows indicate that the reactions can go in either direction, depending on the concentrations of the reactants and products. Carbon dioxide is produced in large amounts in tissues that have a high metabolic rate. Carbon dioxide is converted into bicarbonate in the cytoplasm of red blood cells through the action of an enzyme called carbonic anhydrase. Bicarbonate is transported in the blood. Once in the lungs, the reactions reverse direction, and CO_2 is regenerated from bicarbonate to be exhaled as metabolic waste.

Calcium

About two pounds of calcium in your body are bound up in bone, which provides hardness to the bone and serves as a mineral reserve for calcium and its salts for the rest of the tissues. Teeth also have a high concentration of calcium within them. A little more than one-half of blood calcium is bound to proteins, leaving the rest in its ionized form. Calcium ions, Ca^{2+}, are necessary for muscle contraction, enzyme activity, and blood coagulation. In addition, calcium helps to stabilize cell membranes and is essential for the release of neurotransmitters from neurons and of hormones from endocrine glands.

Calcium is absorbed through the intestines under the influence of activated vitamin D. A deficiency of vitamin D leads to a decrease in absorbed calcium and, eventually, a depletion of calcium stores from the skeletal system, potentially leading to rickets in children and osteomalacia in adults, contributing to osteoporosis.

Hypocalcemia, or abnormally low calcium blood levels, is seen in hypoparathyroidism, which may follow the removal of the thyroid gland, because the four nodules of the parathyroid gland are embedded in it. Hypercalcemia, or abnormally high calcium blood levels, is seen in primary hyperparathyroidism. Some malignancies may also result in hypercalcemia.

Phosphate

Phosphate is present in the body in three ionic forms: $\mathrm{H_2PO_4}$, $\mathrm{HPO_4^{2-}}$, and $\mathrm{PO_4^{3-}}$. The most common form is $\mathrm{HPO_4^{2-}}$. Bone and teeth bind up 85 percent of the body's phosphate as part of calcium-phosphate salts. Phosphate is found in phospholipids, such as those that make up the cell membrane, and in ATP, nucleotides, and buffers.

Hypophosphatemia, or abnormally low phosphate blood levels, occurs with heavy use of antacids, during alcohol withdrawal, and during malnourishment. In the face of phosphate depletion, the kidneys usually conserve phosphate, but during starvation, this conservation is impaired greatly. Hyperphosphatemia, or abnormally increased levels of phosphates in the blood, occurs if there is decreased renal function or in cases of acute lymphocytic leukemia. Additionally, because phosphate is a major constituent of the ICF, any significant destruction of cells can result in dumping of phosphate into the ECF.

Regulation of Sodium and Potassium

Sodium is reabsorbed from the renal filtrate, and potassium is excreted into the filtrate in the renal collecting tubule. The control of this exchange is governed principally by two hormones—aldosterone and angiotensin II.

Aldosterone

Recall that aldosterone increases the excretion of potassium and the reabsorption of sodium in the distal tubule. Aldosterone is released if blood levels of potassium increase, if blood levels of sodium severely decrease, or if blood pressure decreases. Its net effect is to conserve and increase water levels in the plasma by reducing the excretion of sodium, and thus water, from the kidneys. In a negative feedback loop, increased osmolality of the ECF (which follows aldosterone-stimulated sodium absorption)

inhibits the release of the hormone (Figure 6.3.1).

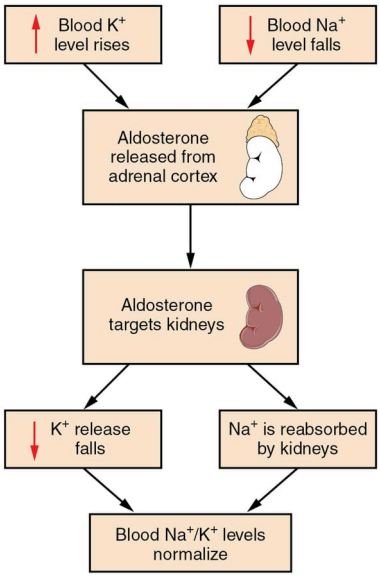


Figure 6.3.1: Aldosterone, which is released by the adrenal gland, facilitates reabsorption of Na+ and thus the reabsorption of water. (CC BY 4.0; via Electrolyte Balance). Detailed text description of the Figure 6.3.1.

Angiotensin II

Angiotensin II causes vasoconstriction and an increase in systemic blood pressure. This action increases the glomerular filtration rate, resulting in more material filtered out of the glomerular capillaries and into Bowman's capsule. Angiotensin II also signals an increase in the release of aldosterone from the adrenal cortex.

In the distal convoluted tubules and collecting ducts of the kidneys, aldosterone stimulates the synthesis and activation of the sodium-potassium pump. Sodium passes from the filtrate, into and through the cells of the tubules and ducts, into the ECF and then into capillaries. Water follows the sodium due to osmosis. Thus, aldosterone causes an increase in blood sodium levels and blood volume. Aldosterone's effect on potassium is the reverse of that of sodium; under its influence, excess potassium is pumped into the renal filtrate for excretion from the body.

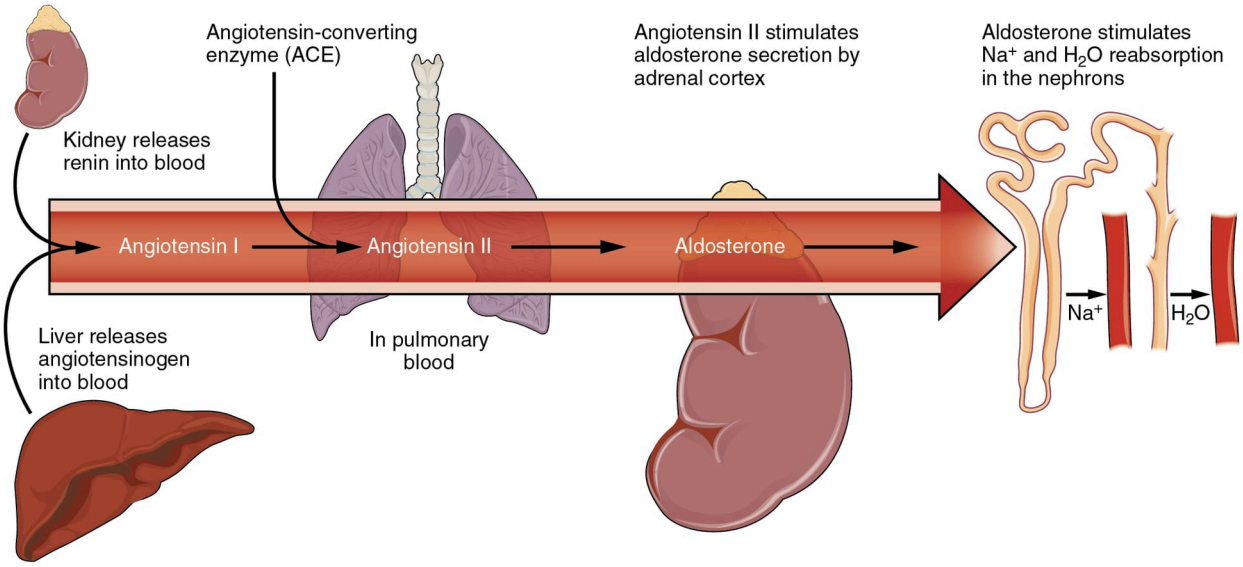


Figure 6.3.2: Angiotensin II stimulates the release of aldosterone from the adrenal cortex. (CC BY 4.0; via Electrolyte Balance). Detailed text description of the Figure 6.3.2.

Regulation of Calcium and Phosphate

Calcium and phosphate are both regulated through the actions of three hormones: parathyroid hormone (PTH), dihydroxyvitamin D (calcitriol), and calcitonin. All three are released or synthesized in response to the blood levels of calcium.

PTH is released from the parathyroid gland in response to a decrease in the concentration of blood calcium. The hormone activates osteoclasts to break down bone matrix and release inorganic calcium-phosphate salts. PTH also increases the gastrointestinal absorption of dietary calcium by converting vitamin D into dihydroxyvitamin D (calcitriol), an active form of vitamin D that intestinal epithelial cells require to absorb calcium.

PTH raises blood calcium levels by inhibiting the loss of calcium through the kidneys. PTH also increases the loss of phosphate through the kidneys.

Calcitonin is released from the thyroid gland in response to elevated blood levels of calcium. The hormone increases the activity of osteoblasts, which remove calcium from the blood and incorporate calcium into the bony matrix.

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6.4: Acid-Base Balance

The pH Scale

Proper physiological functioning depends on a very tight balance between the concentrations of acids and bases in the blood. Acid-Base balance is measured using the pH scale, as shown in Figure 6.4.1. A variety of buffering systems permits blood and other bodily fluids to maintain a narrow pH range, even in the face of perturbations. A buffer is a chemical system that prevents a radical change in fluid pH by dampening the change in hydrogen ion concentrations in the case of excess acid or base. Most commonly, the substance that absorbs the ions is either a weak acid, which takes up hydroxyl ions, or a weak base, which takes up hydrogen ions.

pH	Examples of solutions
0	Battery acid, strong hydrofluoric acid
1	Hydrochloric acid secreted by stomach lining
2	Lemon juice, gastric acid, vinegar
3	Grapefruit juice, orange juice, soda
4	Tomato juice, acid rain
5	Soft drinking water, black coffee
6	Urine, saliva
7	"Pure" water
8	Sea water
9	Baking soda
10	Great Salt Lake, milk of magnesia
11	Ammonia solution
12	Soapy water
13	Bleach, oven cleaner
14	Liquid drain cleaner

Figure 6.4.1: This chart shows where many common substances fall on the pH scale. (CC BY 4.0; via Acid-Base Balance). Detailed text description of the Figure 6.4.1.

Buffer Systems in the Body

The buffer systems in the human body are extremely efficient, and different systems work at different rates. It takes only seconds for the chemical buffers in the blood to make adjustments to pH. The respiratory tract can adjust the blood pH upward in minutes by exhaling CO_2 from the body. The renal system can also adjust blood pH through the excretion of hydrogen ions (H^+) and the conservation of bicarbonate, but this process takes hours to days to have an effect.

The buffer systems functioning in blood plasma include plasma proteins, phosphate, and bicarbonate and carbonic acid buffers. The kidneys help control acid-base balance by excreting hydrogen ions and generating bicarbonate that helps maintain blood plasma pH within a normal range. Protein buffer systems work predominantly inside cells.

Protein Buffers in Blood Plasma and Cells

Nearly all proteins can function as buffers. Proteins are made up of amino acids, which contain positively charged amino groups and negatively charged carboxyl groups. The charged regions of these molecules can bind hydrogen and hydroxyl ions, and thus function as buffers. Buffering by proteins accounts for two-thirds of the buffering power of the blood and most of the buffering within cells.

Hemoglobin as a Buffer

Hemoglobin is the principal protein inside of red blood cells and accounts for one-third of the mass of the cell. During the conversion of CO_2 into bicarbonate, hydrogen ions liberated in the reaction are buffered by hemoglobin, which is reduced by the dissociation of oxygen. This buffering helps maintain normal pH. The process is reversed in the pulmonary capillaries to re-form CO_2, which then can diffuse into the air sacs to be exhaled into the atmosphere. This process is discussed in detail in the chapter on the respiratory system.

Phosphate Buffer

Phosphates are found in the blood in two forms: sodium dihydrogen phosphate (NaH_2PO_4), which is a weak acid, and sodium monohydrogen phosphate (Na_2HPO_4), which is a weak base. When Na_2HPO_4 comes into contact with a strong acid, such as HCl, the base picks up a second hydrogen ion to form the weak acid NaH_2PO_4 and sodium chloride, NaCl. When $NaHPO_4$ (the weak acid) comes into contact with a strong base, such as sodium hydroxide (NaOH), the weak acid reverts back to the weak base and produces water. Acids and bases are still present, but they hold onto the ions.

$$HCl + Na_2HPO_4 \rightarrow NaH_2PO_4 + NaCl \tag{6.4.1}$$

$$(\text{ strong acid }) + (\text{ weak base }) \rightarrow (\text{weak acid }) + (\text{ salt }) \tag{6.4.2}$$

$$NaOH + NaH_2PO_4 \rightarrow Na_2HPO_4 + H_2O \tag{6.4.3}$$

$$(\text{ strong base }) + (\text{ weak acid }) \rightarrow (\text{ weak base }) + (\text{ water }) \tag{6.4.4}$$

Bicarbonate-Carbonic Acid Buffer

The bicarbonate-carbonic acid buffer works in a fashion similar to phosphate buffers. The bicarbonate is regulated in the blood by sodium, as are the phosphate ions. When sodium bicarbonate ($NaHCO_3$), comes into contact with a strong acid, such as HCl, carbonic acid (H_2CO_3), which is a weak acid, and NaCl are formed. When carbonic acid comes into contact with a strong base, such as NaOH, bicarbonate and water are formed.

$$NaHCO_3 + HCl \rightarrow H_2CO_3 + NaCl \tag{6.4.5}$$

$$(\text{ sodium bicarbonate }) + (\text{ strong acid }) \rightarrow (\text{ weak acid }) + (\text{ salt}) \tag{6.4.6}$$

$$H_2CO_3 + NaOH \rightarrow NaHCO_3 + H_2O \tag{6.4.7}$$

$$(\text{ weak acid }) + (\text{ strong base }) \rightarrow (\text{ sodium bicarbonate }) + (\text{ water }) \tag{6.4.8}$$

As with the phosphate buffer, a weak acid or weak base captures the free ions, and a significant change in pH is prevented. Bicarbonate ions and carbonic acid are present in the blood in a 20:1 ratio if the blood pH is within the normal range. With 20 times more bicarbonate than carbonic acid, this capture system is most efficient at buffering changes that would make the blood more acidic. This is useful because most of the body's metabolic wastes, such as lactic acid and ketone bodies, are acids. Carbonic acid levels in the blood are controlled by the expiration of CO_2 through the lungs. In red blood cells, carbonic anhydrase forces the dissociation of the acid, rendering the blood less acidic. Because of this acid dissociation, CO_2 is exhaled (see equations above). The level of bicarbonate in the blood is controlled through the renal system, where bicarbonate ions in the renal filtrate are conserved and passed back into the blood. However, the bicarbonate buffer is the primary buffering system of the IF surrounding the cells in tissues throughout the body.

Respiratory Regulation of Acid-Base Balance

The respiratory system contributes to the balance of acids and bases in the body by regulating the blood levels of carbonic acid (Figure 6.4.2). CO_2 in the blood readily reacts with water to form carbonic acid, and the levels of CO_2 and carbonic acid in the blood are in equilibrium. When the CO_2 level in the blood rises (as it does when you hold your breath), the excess CO_2 reacts with water to form additional carbonic acid, lowering blood pH. Increasing the rate and/or depth of respiration (which you might feel the "urge" to do after holding your breath) allows you to exhale more CO_2. The loss of CO_2 from the body reduces blood levels of carbonic acid and thereby adjusts the pH upward, toward normal levels. As you might have surmised, this process also works in the opposite direction. Excessive deep and rapid breathing (as in hyperventilation) rids the blood of CO_2 and reduces the level of

carbonic acid, making the blood too alkaline. This brief alkalosis can be remedied by rebreathing air that has been exhaled into a paper bag. Rebreathing exhaled air will rapidly bring blood pH down toward normal.

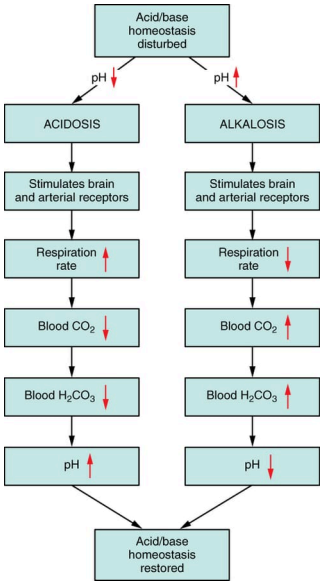


Figure 6.4.2: The respiratory system can reduce blood pH by removing CO_2 from the blood. (CC BY 4.0; via Acid-Base Balance). Detailed text description of the Figure 6.4.2.

The chemical reactions that regulate the levels of CO_2 and carbonic acid occur in the lungs when blood travels through the lung's pulmonary capillaries. Minor adjustments in breathing are usually sufficient to adjust the pH of the blood by changing how much CO_2 is exhaled. In fact, doubling the respiratory rate for less than 1 minute, removing "extra" CO_2, would increase the blood pH by 0.2. This situation is common if you are exercising strenuously over a period of time. To keep up the necessary energy production, you would produce excess CO_2 (and lactic acid if exercising beyond your aerobic threshold). In order to balance the increased acid production, the respiration rate goes up to remove the CO_2. This helps to keep you from developing acidosis.

The body regulates the respiratory rate by the use of chemoreceptors, which primarily use CO_2 as a signal. Peripheral blood sensors are found in the walls of the aorta and carotid arteries. These sensors signal the brain to provide immediate adjustments to the respiratory rate if CO_2 levels rise or fall. Yet other sensors are found in the brain itself. Changes in the pH of CSF affect the respiratory center in the medulla oblongata, which can directly modulate breathing rate to bring the pH back into the normal range.

Hypercapnia, or abnormally elevated blood levels of CO_2, occurs in any situation that impairs respiratory functions, including pneumonia and congestive heart failure. Reduced breathing (hypoventilation) due to drugs such as morphine, barbiturates, or ethanol (or even just holding one's breath) can also result in hypercapnia. Hypocapnia, or abnormally low blood levels of CO_2, occurs with any cause of hyperventilation that drives off the CO_2, such as salicylate toxicity, elevated room temperatures, fever, or hysteria.

Renal Regulation of Acid-Base Balance

The renal regulation of the body's acid-base balance addresses the metabolic component of the buffering system. Whereas the respiratory system (together with breathing centers in the brain) controls the blood levels of carbonic acid by controlling the exhalation of CO_2, the renal system controls the blood levels of bicarbonate. A decrease of blood bicarbonate can result from the inhibition of carbonic anhydrase by certain diuretics or from excessive bicarbonate loss due to diarrhea. Blood bicarbonate levels are also typically lower in people who have Addison's disease (chronic adrenal insufficiency), in which aldosterone levels are reduced, and in people who have renal damage, such as chronic nephritis. Finally, low bicarbonate blood levels can result from elevated levels of ketones (common in unmanaged diabetes mellitus), which bind bicarbonate in the filtrate and prevent its conservation.

Bicarbonate ions, HCO_3^-, found in the filtrate, are essential to the bicarbonate buffer system, yet the cells of the tubule are not permeable to bicarbonate ions. The steps involved in supplying bicarbonate ions to the system are seen in Figure 6.4.3 and are

summarized below:

- Step 1: Sodium ions are reabsorbed from the filtrate in exchange for H^+ by an antiport mechanism in the apical membranes of cells lining the renal tubule.
- Step 2: The cells produce bicarbonate ions that can be shunted to peritubular capillaries.
- Step 3: When CO_2 is available, the reaction is driven to the formation of carbonic acid, which dissociates to form a bicarbonate ion and a hydrogen ion.
- Step 4: The bicarbonate ion passes into the peritubular capillaries and returns to the blood. The hydrogen ion is secreted into the filtrate, where it can become part of new water molecules and be reabsorbed as such, or removed in the urine.

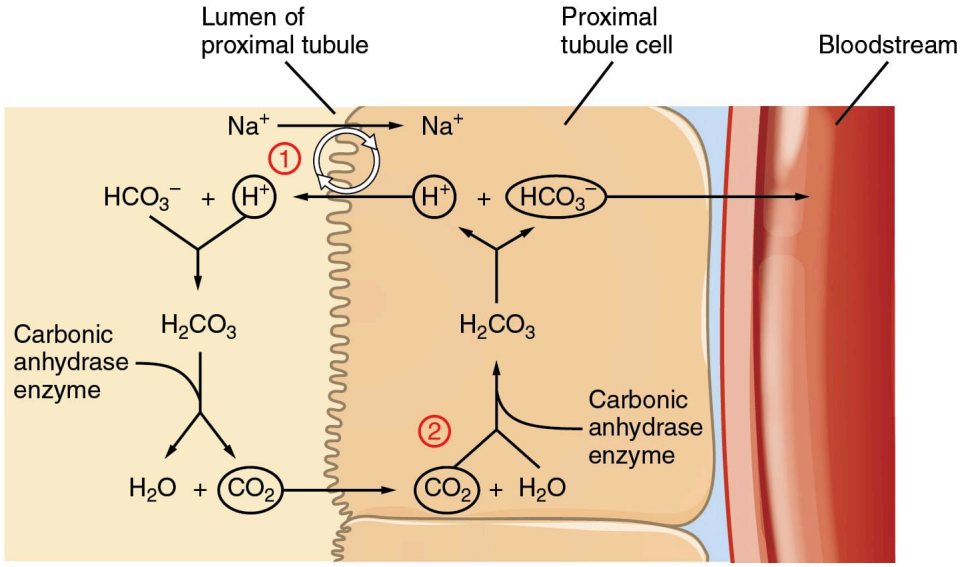


Figure 6.4.3: Tubular cells are not permeable to bicarbonate; thus, bicarbonate is conserved rather than reabsorbed. Steps 1 and 2 of bicarbonate conservation are indicated. (CC BY 4.0; via Acid-Base Balance). Detailed text description of the Figure 6.4.3.

It is also possible that salts in the filtrate, such as sulfates, phosphates, or ammonia, will capture hydrogen ions. If this occurs, the hydrogen ions will not be available to combine with bicarbonate ions and produce CO_2. In such cases, bicarbonate ions are not conserved from the filtrate to the blood, which will also contribute to a pH imbalance and acidosis.

The hydrogen ions also compete with potassium to exchange with sodium in the renal tubules. If more potassium is present than normal, potassium, rather than the hydrogen ions, will be exchanged, and increased potassium enters the filtrate. When this occurs, fewer hydrogen ions in the filtrate participate in the conversion of bicarbonate into CO_2 and less bicarbonate is conserved. If there is less potassium, more hydrogen ions enter the filtrate to be exchanged with sodium and more bicarbonate is conserved.

Chloride ions are important in neutralizing positive ion charges in the body. If chloride is lost, the body uses bicarbonate ions in place of the lost chloride ions. Thus, lost chloride results in an increased reabsorption of bicarbonate by the renal system.

Disorders of the...

Acid-Base Balance: Ketoacidosis

Maria is a 22-year-old college student with type 1 diabetes. She normally takes insulin every day, but during finals week she has been studying late, skipping meals, and forgot to take her evening insulin dose twice. Over the next day, she feels increasingly tired and notices she is very thirsty and urinating more than usual. She assumes it is just stress.

By the second day, Maria's roommate notices that Maria is breathing very deeply and faster than normal, even while resting on the couch. Her skin looks dry and her face is slightly red. When the roommate speaks with her up close, she notices that Maria's breath has a sweet, fruity smell. Maria also complains of nausea, stomach pain, and that she "just doesn't feel right." Worried, the roommate drives her to the emergency room.

In the ER, Maria's blood test shows a very high blood glucose level and a low blood pH. The doctor explains that because Maria missed her insulin, her body's cells could not take in enough glucose from the blood. To get energy, her cells began to break down large amounts of fatty acids. As the fatty acids were broken down, many acetyl groups were produced. These acetyl groups combined to form ketone bodies—acetoacetic acid, beta-hydroxybutyric acid, and acetone. The acids (acetoacetic acid and beta-hydroxybutyric acid) built up in her blood and caused metabolic acidosis (ketoacidosis), lowering her blood pH.

Maria's deep, rapid breathing is her body's way of trying to correct the acid–base imbalance: by breathing faster and deeper, she exhales more CO_2. This helps raise her blood pH slightly (respiratory compensation). The fruity smell on her breath is from acetone, another ketone body, being exhaled. If not treated with fluids and insulin (and sometimes glucose, once insulin is given), this condition can progress to diabetic coma, which can be fatal.

This scenario links:

- Acid–base balance (blood pH falling due to excess organic acids),
- Ketoacidosis (overproduction of acidic ketone bodies from fatty acid breakdown),
- And the body's respiratory compensation (deep, rapid breathing to blow off CO_2 and partially correct the acidosis).

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6.5: Disorders of Acid-Base Balance

Acidosis and Alkalosis

Normal arterial blood pH is restricted to a very narrow range of 7.35 to 7.45. A person who has a blood pH below 7.35 is considered to be in acidosis (actually, "physiological acidosis," because blood is not truly acidic until its pH drops below 7), and a continuous blood pH below 7.0 can be fatal. Acidosis has several symptoms, including headache and confusion, and the individual can become lethargic and easily fatigued (Figure 6.5.1). A person who has a blood pH above 7.45 is considered to be in alkalosis, and a pH above 7.8 is fatal. Some symptoms of alkalosis include cognitive impairment (which can progress to unconsciousness), tingling or numbness in the extremities, muscle twitching and spasm, and nausea and vomiting. Both acidosis and alkalosis can be caused by either metabolic or respiratory disorders.

As discussed earlier in this chapter, the concentration of carbonic acid in the blood is dependent on the level of CO_2 in the body and the amount of CO_2 gas exhaled through the lungs. Thus, the respiratory contribution to acid-base balance is usually discussed in terms of CO_2 (rather than of carbonic acid). Remember that a molecule of carbonic acid is lost for every molecule of CO_2 exhaled, and a molecule of carbonic acid is formed for every molecule of CO_2 retained.

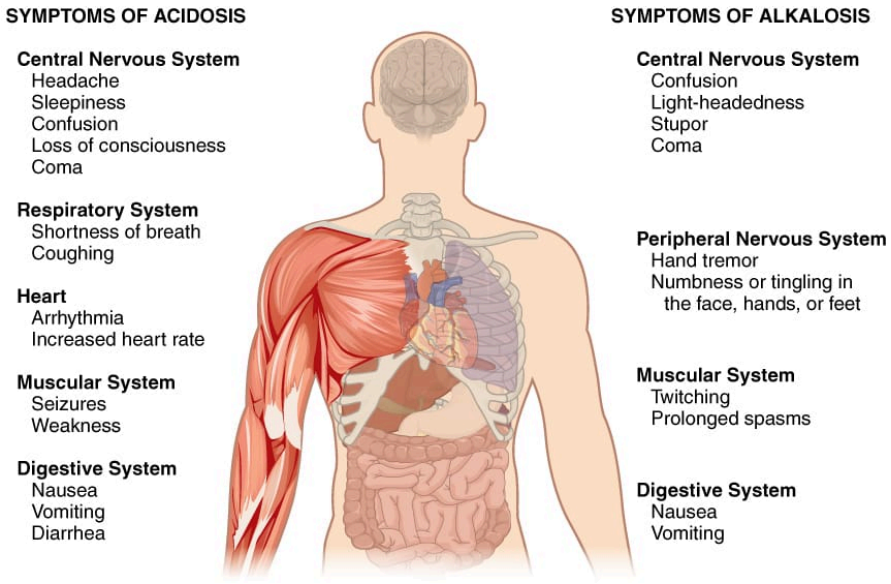


Figure 6.5.1: Symptoms of acidosis affect several organ systems. Both acidosis and alkalosis can be diagnosed using a blood test. (CC BY 4.0; via Disorders of Acis-Base Balance). Detailed text description of the Figure 6.5.1.

Metabolic Acidosis: Primary Bicarbonate Deficiency

Metabolic acidosis occurs when the blood is too acidic (pH below 7.35) due to too little bicarbonate, a condition called primary bicarbonate deficiency. At the normal pH of 7.40, the ratio of bicarbonate to carbonic acid buffer is 20:1. If a person's blood pH drops below 7.35, then the person is in metabolic acidosis. The most common cause of metabolic acidosis is the presence of organic acids or excessive ketone bodies in the blood. Table 6.5.1 lists some other causes of metabolic acidosis.

Table 6.5.1:Common Causes of Metabolic Acidosis and Blood Metabolites

Cause	Metabolite
Diarrhea	Bicarbonate
Uremia	Phosphoric, sulfuric, and lactic acids
Diabetic ketoacidosis	Increased ketone bodies

Cause	Metabolite
Strenuous exercise	Lactic acid
Methanol	Formic acid*
Paraldehyde	β-Hydroxybutyric acid*
Isopropanol	Propionic acid*
Ethylene glycol	Glycolic acid, and some oxalic and formic acids*
Salicylate/aspirin	Sulfasalicylic acid (SSA)*

The first three of the eight causes of metabolic acidosis listed are medical (or unusual physiological) conditions. Strenuous exercise can cause temporary metabolic acidosis due to the production of lactic acid. The last five causes result from the ingestion of specific substances. The active form of aspirin is its metabolite, sulfasalicylic acid. An overdose of aspirin causes acidosis due to the acidity of this metabolite. Metabolic acidosis can also result from uremia, which is the retention of urea and uric acid. Metabolic acidosis can also arise from diabetic ketoacidosis, wherein an excess of ketone bodies are present in the blood. Other causes of metabolic acidosis are a decrease in the excretion of hydrogen ions, which inhibits the conservation of bicarbonate ions, and excessive loss of bicarbonate ions through the gastrointestinal tract due to diarrhea.

Metabolic Alkalosis: Primary Bicarbonate Excess

Metabolic alkalosis is the opposite of metabolic acidosis. It occurs when the blood is too alkaline (pH above 7.45) due to too much bicarbonate (called primary bicarbonate excess).

A transient excess of bicarbonate in the blood can follow ingestion of excessive amounts of bicarbonate, citrate, or antacids for conditions such as stomach acid reflux—known as heartburn. Cushing's disease, which is the chronic hypersecretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland, can cause chronic metabolic alkalosis. The oversecretion of ACTH results in elevated aldosterone levels and an increased loss of potassium by urinary excretion. Other causes of metabolic alkalosis include the loss of hydrochloric acid from the stomach through vomiting, potassium depletion due to the use of diuretics for hypertension, and the excessive use of laxatives.

Respiratory Acidosis: Primary Carbonic Acid/CO_2 Excess

Respiratory acidosis occurs when the blood is overly acidic due to an excess of carbonic acid, resulting from too much CO_2 in the blood. Respiratory acidosis can result from anything that interferes with respiration, such as pneumonia, emphysema, or congestive heart failure.

Respiratory Alkalosis: Primary Carbonic Acid/CO_2 Deficiency

Respiratory alkalosis occurs when the blood is overly alkaline due to a deficiency in carbonic acid and CO_2 levels in the blood. This condition usually occurs when too much CO_2 is exhaled from the lungs, as occurs in hyperventilation, which is breathing that is deeper or more frequent than normal. An elevated respiratory rate leading to hyperventilation can be due to extreme emotional upset or fear, fever, infections, hypoxia, or abnormally high levels of catecholamines, such as epinephrine and norepinephrine. Surprisingly, aspirin overdose—salicylate toxicity—can result in respiratory alkalosis as the body tries to compensate for initial acidosis.

Compensation Mechanisms

Various compensatory mechanisms exist to maintain blood pH within a narrow range, including buffers, respiration, and renal mechanisms. Although compensatory mechanisms usually work very well, when one of these mechanisms is not working properly (like kidney failure or respiratory disease), they have their limits. If the pH and bicarbonate to carbonic acid ratio are changed too drastically, the body may not be able to compensate. Moreover, extreme changes in pH can denature proteins. Extensive damage to proteins in this way can result in disruption of normal metabolic processes, serious tissue damage, and ultimately death.

Respiratory Compensation

Respiratory compensation for metabolic acidosis increases the respiratory rate to drive off CO_2 and readjust the bicarbonate to carbonic acid ratio to the 20:1 level. This adjustment can occur within minutes. Respiratory compensation for metabolic alkalosis is not as adept as its compensation for acidosis. The normal response of the respiratory system to elevated pH is to increase the amount of CO_2 in the blood by decreasing the respiratory rate to conserve CO_2. There is a limit to the decrease in respiration, however, that the body can tolerate. Hence, the respiratory route is less efficient at compensating for metabolic alkalosis than for acidosis.

Metabolic Compensation

Metabolic and renal compensation for respiratory diseases that can create acidosis revolves around the conservation of bicarbonate ions. In cases of respiratory acidosis, the kidney increases the conservation of bicarbonate and secretion of H^+ through the exchange mechanism discussed earlier. These processes increase the concentration of bicarbonate in the blood, reestablishing the proper relative concentrations of bicarbonate and carbonic acid. In cases of respiratory alkalosis, the kidneys decrease the production of bicarbonate and reabsorb H^+ from the tubular fluid. These processes can be limited by the exchange of potassium by the renal cells, which use a K^+-H^+ exchange mechanism (antiporter).

Diagnosing Acidosis and Alkalosis

Lab tests for pH, CO_2 partial pressure (PCO_2), and HCO_3^- can identify acidosis and alkalosis, indicating whether the imbalance is respiratory or metabolic, and the extent to which compensatory mechanisms are working. The blood pH value, as shown in Table 6.5.2, indicates whether the blood is in acidosis, the normal range, or alkalosis. The PCO_2 and total HCO_3^- values aid in determining whether the condition is metabolic or respiratory, and whether the patient has been able to compensate for the problem. Table 6.5.2 lists the conditions and laboratory results that can be used to classify these conditions. Metabolic acid-base imbalances typically result from kidney disease, and the respiratory system usually responds to compensate.

Table 6.5.2: Types of Acidosis and Alkalosis

	pH	PCO_2	Total HCO_3^-
Metabolic acidosis	↓	N, then ↓	↓
Respiratory acidosis	↓	↑	N, then ↑
Metabolic alkalosis	↑	N, then↑	↑
Respiratory alkalosis	↑	↓	N, then ↓

Table 6.5.2 Reference values (arterial): pH: 7.35–7.45; pCO_2: male: 35–48 mm Hg, female: 32–45 mm Hg; total venous bicarbonate: 22–29 mM. N denotes normal; ↑ denotes a rising or increased value; and ↓ denotes a falling or decreased value.

Metabolic acidosis is problematic, as lower-than-normal amounts of bicarbonate are present in the blood. The PCO_2 would be normal at first, but if compensation has occurred, it would decrease as the body reestablishes the proper ratio of bicarbonate and carbonic acid/CO_2.

Respiratory acidosis is problematic, as excess CO_2 is present in the blood. Bicarbonate levels would be normal at first, but if compensation has occurred, they would increase in an attempt to reestablish the proper ratio of bicarbonate and carbonic acid/CO_2.

Alkalosis is characterized by a higher-than-normal pH. Metabolic alkalosis is problematic, as elevated pH and excess bicarbonate are present. The PCO_2 would again be normal at first, but if compensation has occurred, it would increase as the body attempts to reestablish the proper ratios of bicarbonate and carbonic acid/CO_2.

Respiratory alkalosis is problematic, as CO_2 deficiency is present in the bloodstream. The bicarbonate concentration would be normal at first. When renal compensation occurs, however, the bicarbonate concentration in blood decreases as the kidneys attempt to reestablish the proper ratios of bicarbonate and carbonic acid/CO_2 by eliminating more bicarbonate to bring the pH

into the physiological range.

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6.6: Terms and Definitions

Key Terms

Select to View Definition

Antidiuretic hormone (ADH)
: also known as vasopressin, a hormone that increases the volume of water reabsorbed from the collecting tubules of the kidney

Dehydration
: state of containing insufficient water in blood and other tissues

Dihydroxyvitamin D
: active form of vitamin D required by the intestinal epithelial cells for the absorption of calcium

Diuresis
: excess production of urine

Extracellular fluid (ECF)
: fluid exterior to cells; includes the interstitial fluid, blood plasma, and fluids found in other reservoirs in the body

Fluid compartment
: fluid inside all cells of the body constitutes a compartment system that is largely segregated from other systems

Hydrostatic pressure
: pressure exerted by a fluid against a wall, caused by its own weight or pumping force

Hypercalcemia
: abnormally increased blood levels of calcium

Hypercapnia
: abnormally elevated blood levels of CO_2

Hyperchloremia
: higher-than-normal blood chloride levels

Hyperkalemia
: higher-than-normal blood potassium levels

Hypernatremia
: abnormal increase in blood sodium levels

Hyperphosphatemia
: abnormally increased blood phosphate levels

Hypocalcemia
: abnormally low blood levels of calcium

Hypocapnia
: abnormally low blood levels of CO_2

Hypochloremia
: lower-than-normal blood chloride levels

Hypokalemia
: abnormally decreased blood levels of potassium

Hyponatremia
lower-than-normal levels of sodium in the blood

Hypophosphatemia
abnormally low blood phosphate levels

Interstitial fluid (IF)
fluid in the small spaces between cells not contained within blood vessels

Intracellular fluid (ICF)
fluid in the cytosol of cells

Metabolic acidosis
condition wherein a deficiency of bicarbonate causes the blood to be overly acidic

Metabolic alkalosis
condition wherein an excess of bicarbonate causes the blood to be overly alkaline

Plasma osmolality
ratio of solutes to a volume of solvent in the plasma; plasma osmolality reflects a person's state of hydration

Respiratory acidosis
condition wherein an excess of carbonic acid or CO_2 causes the blood to be overly acidic

Respiratory alkalosis
condition wherein a deficiency of carbonic acid/CO_2 levels causes the blood to be overly alkaline

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6.7: Chapter Review Questions

Multiple Choice Section

- Use the end-of-chapter multiple-choice section as a regular self-check tool, not just before exams.
- Read each item carefully, think about what is really being tested (concept, definition, application, or calculation), and choose the option (A, B, C, or D) that best reflects what you have learned in this chapter.
  - After you read through the chapter, attempt all items without looking at your notes; then return to the chapter to review any you missed or felt unsure about.
  - Afterward, explain to yourself why the correct option is right and why the others are not. Finally, repeat the multiple-choice section a few days later to see what you truly remember and understand.
- Students who consistently use these prompts in this way typically perform better across the course because they turn reading into active practice

1. A patient receiving IV fluids develops swelling of tissues as water moves out of cells into the interstitial space, following a change in solute concentration. Solutes contribute to the movement of water between cells and the surrounding medium primarily by creating:
   A. Osmotic pressure
   B. Hydrostatic pressure
   C. Brownian movement
   D. Random motion

2. A lab report shows an ion with a net positive electrical charge. This ion is referred to as a:
   A. Neutral particle
   B. Cation
   C. Alternating ion
   D. Anion

3. A researcher is sampling different body fluid compartments. Interstitial fluid (IF) is best described as:
   A. The fluid in the cytosol of the cells
   B. The fluid component of blood (plasma)
   C. The fluid that bathes all of the body's cells except for blood cells
   D. The intracellular fluids found between organelle membranes

4. A dietitian is teaching a patient about fluid balance. On an average day, the largest amount of water enters the body via:
   A. Metabolic water production
   B. Water content of solid foods
   C. Ingested liquids
   D. Humidified air

5. A person with normal kidney function records fluid intake and output over 24 hours. The largest amount of water typically leaves the body via:
   A. Feces from the GI tract
   B. The skin as sweat
   C. Water vapor in expired air
   D. Urine

6. A nurse explains to a patient that some daily water loss occurs even when they are not aware of it. Insensible water loss refers to water lost via:
   A. Skin evaporation and exhaled air from the lungs
   B. Urine
   C. Excessive sweating during exercise
   D. Vomiting or diarrhea

7. A healthy adult drinks a large glass of water. Studies on renal physiology show that the kidneys respond relatively quickly to this intake. On average, how soon after drinking will a measurable increase in urine output begin?
   A. 5 minutes
   B. 30 minutes
   C. 1 hour
   D. 3 hours

8. A patient with osteoporosis is told that bone acts as a mineral reservoir for certain ions important in nerve conduction and energy metabolism. Bone serves as a mineral reserve primarily for which two ions?
   A. Sodium and potassium
   B. Calcium and phosphate
   C. Chloride and bicarbonate
   D. Calcium and bicarbonate

9. A marathon runner is told to replace not only water but also electrolytes lost in sweat. Over the course of a typical day, most electrolytes are lost from the body through:
   A. Renal function (urine)
   B. Sweating
   C. Feces
   D. Respiration

10. A basic metabolic panel shows normal extracellular ion levels. The major cation in extracellular fluid (such as plasma and interstitial fluid) is:
    A. Sodium
    B. Potassium
    C. Chloride
    D. Bicarbonate

11. An intracellular fluid sample from skeletal muscle cells is analyzed. The major cation in intracellular fluid is:
    A. Sodium
    B. Potassium
    C. Chloride
    D. Bicarbonate

12. A physician explains to a patient that an imbalance of a major anion in the extracellular fluid can affect nerve and muscle function. The major anion in extracellular fluid is:
    A. Sodium
    B. Potassium
    C. Chloride
    D. Bicarbonate

13. A 70-year-old woman is evaluated for osteoporosis. A bone density scan shows reduced mineral content. Most of the body's calcium is found in:
    A. Teeth only
    B. Bone
    C. Plasma
    D. Extracellular fluids outside the skeleton

14. A dehydrated patient receiving hypertonic saline develops neurologic symptoms. Laboratory tests reveal abnormally high blood sodium levels. Abnormally increased blood levels of sodium are termed:
    A. Hyperkalemia
    B. Hyperchloremia
    C. Hypernatremia
    D. Hypercalcemia

15. A laboratory report compares typical plasma concentrations of major ions. Which of the following ions normally has the lowest concentration in blood plasma?
    A. Sodium
    B. Potassium

C. Chloride
D. Bicarbonate

16. A patient with adrenal gland dysfunction has abnormal levels of a hormone that alters kidney handling of certain ions. Which two ions are most directly affected by aldosterone in the kidneys?
A. Sodium and potassium
B. Chloride and bicarbonate
C. Calcium and phosphate
D. Sodium and phosphate

17. A physiologist is studying buffering systems in red blood cells (RBCs). Inside RBCs, which of the following is the most important buffer that helps maintain intracellular pH?
A. Plasma proteins
B. Hemoglobin
C. Phosphate buffers
D. Bicarbonate–carbonic acid buffer

18. A professor explains how proteins help maintain blood pH. Which explanation best describes why plasma proteins can function as buffers?
A. Plasma proteins combine with bicarbonate to form a stronger buffer
B. Plasma proteins are not affected by acids
C. Proteins have both positive and negative charges on their surfaces that can bind H
D. Proteins are strongly alkaline at all times

19. The main buffer system that is actively regulated to control the body's overall acid–base balance is the:
A. Plasma protein buffer system
B. Hemoglobin buffer system
C. Phosphate buffer system
D. Bicarbonate–carbonic acid buffer system

20. A patient with chronic lung disease has altered levels of carbon dioxide and carbonic acid. Carbonic acid (H_2CO_3) levels in the blood are primarily controlled through the:
A. Respiratory system
B. Renal system
C. Digestive system
D. Metabolic rate of cells

21. A patient with chronic kidney disease has difficulty regulating bicarbonate (HCO_3) levels in the blood. Bicarbonate ion concentrations in the blood are primarily controlled through the:
A. Respiratory system
B. Renal system
C. Digestive system
D. Metabolic rate of cells

22. Red blood cells contain the enzyme carbonic anhydrase, which helps rapidly interconvert carbon dioxide and water with carbonic acid and bicarbonate. Which reaction is catalyzed by carbonic anhydrase?
A. $CO_2 + H_2O$ H_2CO_3 H + HCO_3
B. $HCl + HCO_3$ $H_2CO_3 + Cl$
C. $NaHCO_3$ Na + HCO_3
D. H_2CO_3 $CO_2 + ½O_2$

23. A patient with severe diarrhea loses large amounts of bicarbonate-rich intestinal fluid and presents with low blood pH. Which of the following is a common cause of metabolic acidosis?
A. Excessive loss of gastric HCl from vomiting
B. Increased aldosterone
C. Diarrhea
D. Prolonged use of loop diuretics

24. A 65-year-old man with long-term emphysema has chronic CO_2 retention and low blood pH. Which of the following is a typical

cause of respiratory acidosis?
A. Emphysema with hypoventilation
B. Low blood potassium (hypokalemia)
C. Increased aldosterone secretion
D. Increased blood ketones in diabetes

25. In an arterial blood gas from a healthy adult, pH is 7.40 and the bicarbonate–carbonic acid buffer system is in its normal ratio. At a pH of 7.40, the HCO_3^- to H_2CO_3 (bicarbonate to carbonic acid) ratio is approximately:
A. 35:1
B. 4:1
C. 20:1
D. 3:1

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6.8: Applied Thinking Self - Assessment

Challenge Yourself

- Extended response questions are assessment items that require students to construct written answers of substantial length - typically several sentences to multiple paragraphs - rather than selecting from predefined options. They represent a form of constructed response assessment designed to measure complex, higher-order thinking skills.
- First, try answering without using your notes. Then review reliable resources and revise your response if needed. Make a note of any areas where you felt unsure and revisit those topics.

Writing Guidelines

- Answer each question in your own words.
- Write 4–8 clear, complete sentences per question, organized into short paragraphs (not bullet points).
- Focus on explaining your reasoning, not just stating the answer.
- Use correct scientific vocabulary, and briefly define terms when needed.
- For questions that ask you to compare, contrast, or explain why/how:
  - Clearly state similarities or differences
  - Support your ideas with a brief explanation or example

Basic Fluid & Electrolyte Concepts

1. Movement of Fluid Between Compartments
    a. Explain how fluid moves between the intracellular fluid (ICF) and extracellular fluid (ECF) compartments. In your answer, describe the roles of
        i. Osmosis
        ii. Hydrostatic pressure
        iii. Oncotic (colloid osmotic) pressure
        iv. Include at least one example of a situation that shifts fluid into or out of cells.
2. ADH and the Collecting Ducts
    a. Describe the effect of antidiuretic hormone (ADH) on the renal collecting ducts/tubules. Include:
        i. What happens to the permeability of the tubule
        ii. How this changes urine volume and concentration
        iii. The main stimulus for ADH release
3. Water Balance: Intake vs. Output
    a. Explain why, over time, water intake must equal water output.
    b. Discuss what happens - if intake is chronically greater or less than output to:
        i. Plasma osmolarity
        ii. Blood pressure
        iii. Cell volume
4. Imbalance Without Abnormal Total Amount
    a. Explain how a person can have a water or electrolyte *imbalance* even if the total amount of that substance in the body is not actually increased or decreased.
    b. Use at least one example (e.g., sodium shifting between ECF and ICF, or rapid gain of water without adequate sodium).
5. Compartment-Specific Changes
    a. Describe how a loss of *isotonic* fluid (e.g., hemorrhage or isotonic saline loss) affects: ECF volume, ICF volume and Osmolarity in each compartment.
    b. Then describe how a gain of primarily *free water* (e.g., excessive plain water intake) affects those same variables.

Acid–Base Transport and Regulation

1. CO_2 Transport as Bicarbonate

   a. Explain how CO_2 generated by cells is carried to the lungs primarily as bicarbonate (HCO_3^-) in the blood. Include:

   - The role of carbonic anhydrase
   - The reaction converting CO_2 and water to carbonic acid and then to bicarbonate and H^+
   - The chloride shift in red blood cells

2. Renal Conservation of Bicarbonate
   a. Describe how the kidneys conserve and regenerate bicarbonate (HCO_3^-). In your answer, address:
      i. Reabsorption of filtered bicarbonate in the proximal tubule
      ii. Secretion of H^+ and formation of “new” bicarbonate
      iii. The roles of phosphate and ammonia buffers in the tubular fluid
3. Respiratory Control of Carbonic Acid
   a. Describe how the respiratory system regulates levels of carbonic acid (H_2CO_3) in the blood. Include:
      i. How changes in ventilation alter CO_2 and thus pH
      ii. The role of central and peripheral chemoreceptors
      iii. An example of how the body responds to metabolic acidosis via respiration
4. Integrated Acid–Base Response
   a. Compare and contrast respiratory and renal compensation for acid–base disturbances. Address:
      - Speed of onset
      - Mechanisms involved
      - Which system compensates for primarily respiratory vs. primarily metabolic disturbances.

Case Studies – Fluid & Electrolytes

Case 1: Elderly Patient with Dehydration

A 70-year-old patient is brought to the ER after spending several hours outside on a hot day with little water. He is confused, his mucous membranes are dry, and his blood tests show increased plasma osmolality.

- ECF Volume and Composition
- Renal Response
- Compensatory Mechanisms

1. Explain what has happened to his extracellular fluid (ECF) volume and composition, particularly regarding sodium (Na^+) concentration and water content. Discuss changes in:
   a. ECF volume
   b. ECF osmolarity
   c. Water movement between ICF and ECF
   d. Predict how the kidneys will adjust water reabsorption and urine concentration in this situation. Include:
      i. Expected changes in ADH secretion
      ii. Changes in urine volume and osmolarity
2. Besides ADH, describe one additional hormonal or neural mechanism (e.g., RAAS, thirst, sympathetic activity) that will be activated and explain its effect on blood pressure and sodium handling.

Case 2: Marathon Runner with Hyponatremia

A marathon runner drinks large amounts of plain water but very little electrolyte replacement during a race. After finishing, she becomes confused and nauseated. Lab tests show low plasma Na^+ (hyponatremia) and decreased plasma osmolality.

- Fluid Compartments and Brain Swelling
- ADH Response
- Treatment Strategy

- Prevention

1. Using the concepts of ICF and ECF, explain why her brain cells may swell in this condition.
2. Discuss how her body's ADH levels are likely to respond to prolonged exercise and stress, and whether this response makes the hyponatremia and brain swelling better or worse.
3. Suggest an appropriate treatment strategy based on your understanding of fluid and electrolyte balance.
4. Explain why rapid correction can be dangerous and how it should generally be approached.
5. Propose at least two preventive strategies for endurance athletes to avoid this type of fluid and electrolyte disturbance.

Case Studies – Acid–Base Disorders

Case 3: Asthma Exacerbation

Brooks is a 64-year-old admitted to the emergency room for asthma. The laboratory results are as follows: pH 7.31, pCO_2 higher than normal, and total HCO_3 also higher than normal.

- Classification of Acid–Base Status
- Evidence of Compensation
- Mechanism Related to Asthma
- Further Evaluation

1. Classify the acid–base disturbance as acidosis or alkalosis, and as metabolic or respiratory.
2. Explain how each lab value supports your classification.
3. Is there evidence of compensation?
4. If so, identify whether it is respiratory or renal compensation and describe the mechanism.
5. Propose how the pathophysiology of asthma led to the lab results seen (consider ventilation, CO_2 retention, and subsequent renal response).
6. Identify one additional lab test or clinical datum that would help you determine whether the disturbance is acute vs. chronic and explain why.

Case 4: Metabolic Acidosis vs. Alkalosis

A patient has these arterial blood gas values: pH 7.50, pCO_2 normal, HCO_3 high.

1. Explain what these numbers tell you about the patient's acid–base status. In your answer, name the type of acid–base problem, say whether the primary change is respiratory or metabolic, and explain your reasoning in simple steps.

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6.9: Alternate Text Descriptions

Figure 6.1.1: Water Content of the Body's Organs and Tissues

This image illustrates the approximate percentage of water content in different parts of the human body using a front-view outline of a human figure. Key information is presented as labeled values associated with each body part:

- The brain contains approximately 80 to 85 percent water, indicating that it is one of the most water-rich organs.
- The kidneys also contain about 80 to 85 percent water, reflecting their role in fluid balance.
- The heart and lungs each contain approximately 75 to 80 percent water.
- The liver and muscles contain about 70 to 75 percent water.
- The skin contains approximately 70 to 75 percent water.
- Blood contains about 50 percent water, which is lower compared to most organs.
- The bones contain approximately 20 to 25 percent water, showing that they have relatively low water content.
- The teeth contain the lowest proportion, at about 8 to 10 percent water.

Figure 6.1.2: Fluid Compartments of the Human Body

This image shows a small blood vessel surrounded by several body cells. It illustrates how body fluids are divided into compartments. The fluid inside the blood vessel is extracellular fluid, or ECF. The fluid located in the spaces between the body cells is called interstitial fluid, or IF, which is also a type of extracellular fluid. The fluid inside each body cell, within the cytoplasm, is intracellular fluid, or ICF. The main idea of the figure is that extracellular fluid includes both the fluid in blood vessels and the interstitial fluid between cells, while intracellular fluid is the fluid found inside the cells.

Figure 6.1.3: Distribution of Body fluid Compartments

This image is a pie graph represents the distribution of fluids in the fluid compartments of human body. The circle is divided into several labeled sections that vary in size to indicate relative proportions.

- The largest section, occupying more than half of the circle, is labeled "Intracellular fluid." This section represents fluid located inside cells.
- The remaining portion of the circle represents extracellular fluid, shown as a combined outer grouping. Within this extracellular portion:
  - A large segment is labeled "Interstitial fluid," representing fluid located between cells.
  - A smaller segment is labeled "Plasma," representing the fluid component of blood.
  - A very small segment is labeled "Other fluid," indicating minor fluid compartments (such as transcellular fluids).
- The diagram also includes:
  - A label outside the circle reading "Extracellular fluid," indicating that interstitial fluid, plasma, and other fluid are grouped together.
  - Arrows at the boundary of the circle, suggesting movement or exchange of fluid between intracellular and extracellular compartments.

Figure 6.1.4: Relative Solute Concentrations in Body Fluid Compartments

This image is a bar graph comparing the relative concentrations of four major solutes—sodium ions (Na^+), potassium ions (K^+), chloride ions (Cl^-), and proteins—in three body fluid compartments: intracellular fluid (ICF), interstitial fluid (IF), and blood plasma.

The x-axis lists the three fluid types (ICF, IF, plasma). For each fluid, there are four vertical bars grouped together, one for each solute (sodium, potassium, chloride, proteins). The y-axis represents relative concentration; exact numerical values are not shown, but the bar heights allow visual comparison.

For interstitial fluid and plasma:

- Sodium (Na^+) and chloride (Cl^-) bars are both tall and of similar height, indicating high and comparable concentrations of these ions in both fluids.
- Potassium (K^+) bars are short in both IF and plasma, indicating low potassium concentration outside cells.
- Plasma has a clearly taller protein bar than IF, showing that plasma contains substantially more protein than interstitial fluid. IF has a small or very short protein bar, indicating low protein content.

For intracellular fluid:

- The potassium (K^+) bar is very tall, much higher than in IF or plasma, indicating that potassium is the major intracellular cation.
- The sodium (Na^+) bar is short, much lower than in IF or plasma, showing that sodium is relatively scarce inside cells.
- The chloride (Cl^-) bar is moderate in height (shorter than the extracellular chloride bars), indicating a lower chloride concentration in ICF than in IF and plasma.
- The protein bar is clearly present and of noticeable height, indicating that ICF contains significant proteins, generally more than interstitial fluid and often comparable to, or somewhat less than, plasma proteins.

Overall interpretation communicated by the figure:

- Intracellular fluid has high potassium and relatively low sodium and chloride compared with extracellular fluids.
- Interstitial fluid and plasma have similar ionic patterns—high sodium and chloride and low potassium—reflecting that they are both components of the extracellular compartment.
- Plasma is distinguished from interstitial fluid by its higher protein content.
- The data emphasizes that ion and protein concentrations are not uniform across body fluids: the composition inside cells (ICF) is markedly different from that of the fluids outside cells (IF and plasma), and plasma contains more proteins than interstitial fluid.

Figure 6.1.5: The Sodium–Potassium Pump

This image is the sodium–potassium pump (Na^+/K^+-ATPase) in a cell membrane, showing how it uses ATP to move ions in opposite directions and maintain the concentration differences between intracellular and extracellular fluid.

A horizontal phospholipid bilayer represents the cell membrane. The region above the membrane is labeled ‘extracellular fluid (ECF),’ and the region below is labeled ‘cytoplasm’ or ‘intracellular fluid (ICF).’ Embedded in the membrane is a large, rounded transport protein labeled ‘sodium–potassium pump’ or ‘Na^+/K^+ pump.’

On the cytoplasmic (inside) side of the pump, three sodium ions (Na^+) are shown bound to the protein. An ATP molecule is drawn nearby with an arrow pointing toward the pump, indicating that ATP binds and is hydrolyzed; ADP and phosphate are shown as products. An arrow from the cytoplasmic side through the pump toward the extracellular side shows the three Na^+ ions being transported out of the cell into the ECF, against their concentration gradient.

On the extracellular (outside) side of the pump, two potassium ions (K^+) are shown binding to the protein. A second arrow points from the extracellular side through the pump down into the cytoplasm, indicating that the two K^+ ions are transported into the cell, also against their concentration gradient.

Overall, the figure communicates that each pumping cycle uses one ATP molecule to move three sodium ions out of the cell and two potassium ions into the cell. This active transport maintains high sodium concentration in the extracellular fluid and high potassium concentration inside the cytoplasm, helping to preserve the distinct ionic compositions of ICF and ECF.

Figure 6.1.6: Capillary Filtration and Reabsorption Forces

This image showing how fluid moves across a single capillary from the arterial end to the venous end, based on two opposing pressures: capillary hydrostatic pressure, abbreviated CHP, which pushes fluid out of the capillary, and blood colloidal osmotic pressure, abbreviated BCOP, which pulls fluid into the capillary.

From left to right, the capillary is divided into three labeled regions: arterial end, midpoint, and venous end. Above or near the capillary, text or arrows indicate relative pressure values and the direction of fluid movement across the capillary wall.

1. Arterial end of the capillary (left side):
    - The capillary segment is labeled “Net filtration.”
    - A labeled outward arrow extends from the inside of the capillary to the surrounding interstitial space, indicating fluid moving out of the blood into the tissue.
    - Capillary hydrostatic pressure (abbreviated CHP) is shown as higher than blood colloidal osmotic pressure (abbreviated BCOP). The diagram may explicitly state that CHP > BCOP at this end.
    - This region visually emphasizes that because CHP is greater than BCOP, fluid is pushed out of the capillary (filtration).
2. Midpoint of the capillary (center):
    - The capillary segment is labeled to indicate “no net movement of fluid” or “equilibrium.”
    - If arrows are present, they are either absent or balanced in opposing directions, indicating that outward and inward forces are equal overall.
    - CHP and BCOP are shown as equal in magnitude at this point, often written as “CHP = BCOP.”
    - The meaning is that fluid movement into and out of the capillary is balanced, so there is no net gain or loss of fluid at the midpoint.
3. Venous end of the capillary (right side):
    - The capillary segment is labeled “Net reabsorption.”
    - A labeled inward arrow points from the interstitial space into the capillary, indicating fluid moving from the tissue back into the bloodstream.
    - BCOP is shown as greater than CHP at this end, often written as “BCOP > CHP.”
    - This region visually emphasizes that because the osmotic pull (BCOP) exceeds the hydrostatic push (CHP), fluid is drawn back into the capillary (reabsorption).

Overall, the image illustrates how the balance of two primary opposing pressures—capillary hydrostatic pressure (pushing fluid out) and blood colloidal osmotic pressure (pulling fluid in)—changes from the arterial end to the venous end of a capillary. It conveys that:

- Near the arterial end, higher CHP causes net filtration of fluid out of the capillary.
- Near the midpoint, equal CHP and BCOP result in no net fluid movement.
- Near the venous end, higher BCOP causes net reabsorption of fluid back into the capillary.

Figure 6.1.7: Facilitated Diffusion of Glucose Across the Cell Membrane

This image showing how glucose crosses a cell membrane with the help of a carrier protein, moving from an area of higher concentration to an area of lower concentration without using energy.

A single cell membrane is drawn as two parallel horizontal lines forming a barrier across the image. The space above the membrane represents the outside of the cell (extracellular fluid), and the space below the membrane represents the inside of the cell (intracellular fluid).

Outside the cell, above the membrane, there are many small shapes labeled “glucose,” indicating a high concentration of glucose molecules on this side. Inside the cell, below the membrane, there are fewer shapes labeled “glucose,” indicating a lower concentration of glucose on this side. This difference represents the concentration gradient: more glucose outside, less glucose inside.

Embedded in the membrane is a specific protein structure labeled “carrier protein” or “carrier protein channel.” It spans all the way from the outside of the cell to the inside of the cell, forming a passageway. Glucose molecules are shown interacting only with this protein, not passing directly through the membrane.

Arrows are drawn to show the direction of glucose movement: they begin in the region of higher glucose concentration outside the cell, pass through the carrier protein in the membrane, and end in the region of lower glucose concentration inside the cell. The arrows point only from outside to inside, illustrating movement “down” the concentration gradient, from higher to lower concentration.

The diagram may depict the carrier protein in two states: one open to the outside with a glucose molecule bound, and one open to the inside releasing the glucose. This suggests that the protein changes shape to move the glucose across. There are no symbols for ATP or energy use; the absence of any energy notation indicates that this process is passive and does not require cellular energy.

Overall, the image demonstrates that:

- Glucose cannot freely cross the lipid part of the membrane.
- Glucose moves from a region where it is more concentrated to a region where it is less concentrated.
- This movement occurs only through specific carrier protein channels embedded in the membrane.
- The process is called facilitated diffusion because the carrier protein "facilitates," or helps, diffusion down the concentration gradient without using energy.

Figure 6.1.8: Edema

This image is illustrating how an allergic reaction can cause excess fluid to leak from capillaries in the hand and accumulate in surrounding tissues, leading to swelling.

- A human hand is shown from the top, including fingers, back of the hand, and wrist.
- The hand appears enlarged or swollen, representing edema, which is abnormal buildup of fluid in the tissues.
- The skin surface is smooth and stretched, suggesting that extra fluid under the skin is causing the swelling.

Figure 6.2.1: The Thirst Response

This image is a flowchart shows how the body responds to insufficient water and triggers thirst.

- "Insufficient H_2O in the body" (top box): Starting condition—low body water. Function: initiates physiological responses to restore fluid balance.

Left pathway (blood pressure response):

- "Decreases blood volume": Less water reduces blood fluid. Function: lowers circulating volume.
- "Decreases blood pressure": Reduced volume lowers pressure in vessels. Function: signals need to restore pressure.
- "Increases angiotensin II": Hormone level rises. Function: promotes thirst and helps raise blood pressure.

Right pathway (osmotic response):

- "Increases blood osmolality": Solutes become more concentrated. Function: indicates dehydration.
- "Osmoreceptors in the hypothalamus": Specialized brain sensors. Function: detect high osmolality and signal need for water.
- "Dry mouth": Reduced saliva due to dehydration. Function: provides sensory cue to drink.

Convergence:

- "Stimulates thirst center in the hypothalamus": Integration point in brain. Function: processes signals and activates thirst.
- "Increases thirst": Conscious urge to drink. Function: drives behavior to restore water.

Outcome:

- "H_2O taken in" (drinking): Water consumption. Function: replaces lost fluids.
- "Decreases blood osmolality": Blood becomes diluted again. Function: returns body fluids to homeostasis.

Decreased blood volume resulting from water loss has two additional effects. First, baroreceptors, blood-pressure receptors in the arch of the aorta and the carotid arteries in the neck, detect a decrease in blood pressure that results from decreased blood volume. The heart is ultimately signaled to increase its rate and/or strength of contractions to compensate for the lowered blood pressure.

Second, the kidneys have a renin-angiotensin hormonal system that increases the production of the active form of the hormone angiotensin II, which helps stimulate thirst, but also stimulates the release of the hormone aldosterone from the adrenal glands. Aldosterone increases the reabsorption of sodium in the distal tubules of the nephrons in the kidneys, and water follows this reabsorbed sodium back into the blood.

Figure 6.2.2: Antidiuretic Hormone

This image shows the effects of antidiuretic hormone (ADH) on the brain, blood vessels, and kidneys.

- Brain (cerebrum): Labeled “affects some social behaviors in mammals.” Function: ADH acts in the brain to influence certain behaviors, especially social bonding in some species.
- Hypothalamus: Labeled “produced by hypothalamus.” Function: ADH is synthesized here; it is the control center that regulates its production.
- Posterior pituitary: Labeled “released by posterior pituitary.” Function: Stores and releases ADH into the bloodstream when needed.
- Arterioles (small blood vessels): Labeled “constricts arterioles.” Function: ADH causes vasoconstriction, narrowing blood vessels to help increase blood pressure.
- Kidney: Labeled “increases reabsorption of H_2O in kidneys.” Function: ADH makes kidney tubules more permeable to water, increasing water reabsorption and reducing urine output.

Figure 6.2.3: Water Reabsorption in the Collecting Duct

This image shows water reabsorption across collecting tubule cells in the kidney.

- Lumen of collecting tubule: Located on the left side and contains urine. This is the source of water that may be reabsorbed.
- H2O arrows: Blue arrows show water moving out of the urine and toward the collecting tubule cells. These arrows indicate the direction of water flow down an osmotic gradient.
- Collecting tubule cells: Positioned in the center as a layer of stacked cells forming the wall of the tubule. These cells act as a barrier and controlled pathway for water movement.
- Aquaporins: Water channels located in the cell membranes. They allow water to move rapidly through the membranes.
- Aquaporin storage vesicles: Located inside the cells. These vesicles contain aquaporins before they are inserted into the membrane. Their role is to deliver aquaporins to the membrane and increase water permeability, a process regulated by antidiuretic hormone.
- Interstitial fluid: Located to the right of the cells. This surrounding fluid receives water after it passes out of the collecting tubule cells.
- Bloodstream or plasma: Shown in a nearby vessel on the far right. This blood vessel takes up the reabsorbed water and returns it to circulation.
- Arrows across the cells: These show the complete pathway of water movement from the lumen, through the collecting tubule cells, into the interstitial fluid, and then into the blood.

A diuretic is a compound that increases urine output and therefore decreases water conservation by the body. Diuretics are used to treat hypertension, congestive heart failure, and fluid retention associated with menstruation. Alcohol acts as a diuretic by inhibiting the release of ADH. Additionally, caffeine, when consumed in high concentrations, acts as a diuretic.

Figure 6.3.1: Angiotensin–Aldosterone System

This image is a schematic feedback loop illustrating angiotensin–aldosterone system showing how the body regulates fluid volume and electrolytes.

- A stimulus such as low blood pressure, low blood volume, or low blood sodium is shown as the starting point of the loop.
- In response to this stimulus, the adrenal glands are shown releasing aldosterone into the bloodstream.
- Aldosterone is depicted acting on the kidneys, specifically on the parts of the kidney tubules that handle final adjustments of urine composition.
- At the kidney level, aldosterone increases reabsorption of sodium ions from the forming urine back into the bloodstream.
- Because water follows sodium, this increased sodium reabsorption leads to increased water reabsorption into the blood.
- The combined reabsorption of sodium and water raises blood volume and contributes to an increase in blood pressure.
- The diagram also indicates that aldosterone promotes increased excretion of potassium ions into the urine, helping regulate potassium balance.
- The rise in blood volume and blood pressure is shown feeding back to reduce the original stimulus, decreasing further aldosterone release and completing the negative feedback loop.

Figure 6.3.2: Renin–Angiotensin System

This image is a flow-style diagram illustrates the renin–angiotensin system, emphasizing how it leads to aldosterone release.

- A decrease in blood pressure, blood volume, or blood sodium, or an increase in blood potassium, is shown as the trigger for RAAS activation.
- The kidneys, specifically juxtaglomerular cells, detect these changes and release the enzyme renin into the bloodstream.
- Renin acts on angiotensinogen, a precursor protein produced by the liver and present in the blood, converting it into angiotensin I.
- As blood circulates through the lungs and other tissues, angiotensin-converting enzyme (ACE) converts angiotensin I into angiotensin II.
- Angiotensin II is depicted with two main actions:
  - It causes blood vessels to constrict, increasing resistance and raising blood pressure.
  - It stimulates the adrenal cortex to secrete the hormone aldosterone.
- Aldosterone acts on the kidneys, promoting increased reabsorption of sodium and water back into the bloodstream and increased excretion of potassium into the urine.
- The retention of sodium and water increases blood volume, which in turn raises blood pressure.
- The resulting rise in blood pressure and blood volume feeds back to the kidneys and reduces further renin release, completing a negative feedback loop that stabilizes fluid balance, electrolytes, and blood pressure.

Figure 6.4.1: The pH Scale

This image is a horizontal pH scale is shown as a numbered line ranging from 0 to 14, representing how acidic or basic a solution is.

- The center of the scale, pH 7, is labeled neutral and associated with pure water.
- Values below pH 7 indicate increasing acidity.
  - Battery acid is placed near pH 0–1.
  - Gastric (stomach) acid and lemon juice are shown around pH 1–2.
  - Vinegar and soda are depicted in the acidic range around pH 2–3.
  - Black coffee and tomato juice are shown around pH 4–5.
- Values above pH 7 indicate increasing basicity.
  - A baking soda solution is shown around pH 8–9.
  - Soapy water and household ammonia are placed in the basic range around pH 10–11.
  - Bleach and concentrated cleaning products are shown near the strongly basic end around pH 12–14.
- The overall purpose of the chart is to demonstrate where familiar substances fall on the pH scale, from strongly acidic through neutral to strongly basic.

Figure 6.4.2: The Respiratory System

This image is a simplified physiology diagram shows how the respiratory system helps regulate blood pH by removing carbon dioxide, or CO_2. One part of the image represents body tissues producing CO_2 as a waste product of metabolism. Arrows indicate that this CO2 enters the bloodstream, where it combines with water to form carbonic acid, which can release hydrogen ions and lower blood pH, making the blood more acidic.

Another part of the image shows blood flowing to the lungs. Labels explain that when a person breathes out, the lungs eliminate CO_2 from the blood into the exhaled air. Arrows from the blood to the air spaces of the lungs indicate CO_2 leaving the bloodstream, with accompanying text noting that as CO_2 is removed, less carbonic acid and fewer free hydrogen ions are present in the blood. This reduces acidity and helps raise blood pH back toward normal. The overall purpose of the diagram is to illustrate that by adjusting how much CO_2 is exhaled—such as by breathing faster or deeper—the respiratory system can help regulate and stabilize blood pH

Figure 6.4.3: Conservation of Bicarbonate in the Kidney

Cross-section of a nephron segment in the image showing, from top to bottom, the tubular lumen, a single tubular epithelial cell,

and the peritubular capillary (blood). Arrows show how filtered bicarbonate is conserved even though it cannot directly cross the tubular cell membrane.

- Lumen of proximal tubule (top):
  - Contains filtered bicarbonate (HCO_3^-) and CO_2.
  - Note that tubular cells are not permeable to bicarbonate.
  - Step 1: Secreted hydrogen ions (H^+) from the epithelial cell combine with filtered HCO_3^- to form H_2CO_3, which converts to CO_2 and H_2O.
  - CO_2 then diffuses from the lumen into the epithelial cell.
- Proximal tubule epithelial cell (middle):
  - Separates lumen from blood.
  - Step 2: CO_2 plus H_2O are converted by carbonic anhydrase to H_2CO_3, which dissociates into H^+ and HCO_3^-.
  - H^+ is secreted back into the lumen; HCO_3^- is retained in the cell and then transported to the blood side.
- Peritubular capillary / bloodstream (bottom):
  - Bicarbonate (HCO_3^-) is transported from the cell into the blood.
  - Net effect: The original filtered bicarbonate does not cross the membrane directly, but an equivalent amount of new bicarbonate is returned to the blood, conserving bicarbonate.

Figure 6.5.1: Symptoms of Acidosis and Alkalosis

This image compares the symptoms associated with acidosis and alkalosis. A human body illustration is centered between the two lists to indicate the body systems affected. Symptoms are grouped by organ system.

Symptoms of Acidosis

Central Nervous System

- Headache
- Sleepiness
- Confusion
- Loss of consciousness
- Coma

Respiratory System

- Shortness of breath
- Coughing

Heart

- Arrhythmia
- Increased heart rate

Muscular System

- Seizures
- Weakness or fatigue

Digestive System

- Nausea
- Vomiting
- Diarrhea

Symptoms of Alkalosis

Central Nervous System

- Confusion
- Light-headedness
- Stupor
- Coma

Peripheral Nervous System

- Hand tremor
- Numbness or tingling in the face, hands, or feet

Muscular System

- Muscle twitching
- Prolonged muscle spasms

Digestive System

- Nausea
- Vomiting

The figure demonstrates that disturbances in acid-base balance can affect multiple organ systems. Acidosis is associated with neurological depression, respiratory symptoms, cardiovascular effects, muscle weakness, and digestive disturbances. Alkalosis is associated with neurological symptoms, increased nerve and muscle excitability, muscle spasms, and digestive symptoms. Both conditions can become severe enough to affect consciousness and may result in coma.

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7: THE REPRODUCTIVE SYSTEM

Chapter Overview

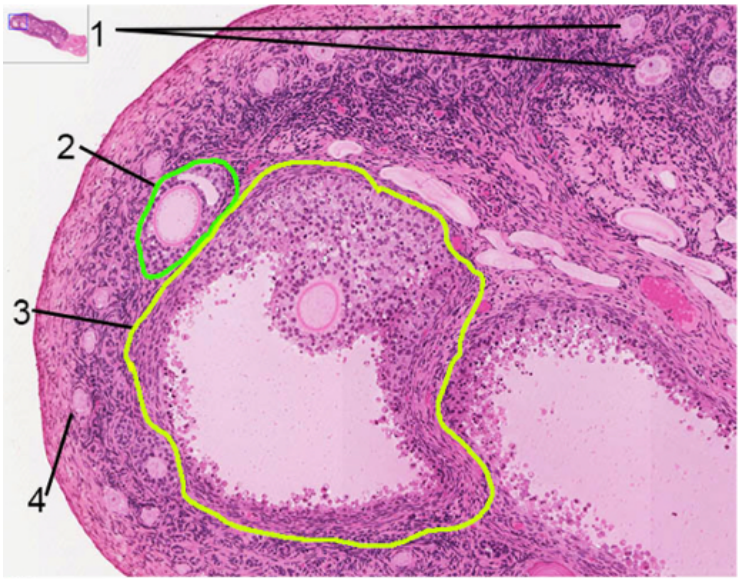


Figure 7.1: Light micrograph of ovarian tissue with a prominent antral (Graafian) follicle outlined in green. The follicle shows a fluid-filled antrum, surrounding granulosa cell layers, and adjacent theca layers; nearby smaller follicles and stromal tissue are also visible. Numbered labels indicate different structural regions. Detailed text description of the Figure 7.1.

Human reproduction relies on the coordinated structure and function of two complementary reproductive systems—typically described as male and female—that work together to make the continuation of the species possible. Each system includes specialized organs that produce gametes: sperm in the testes and oocytes in the ovaries. Both systems also have accessory structures that store, protect, nourish, and transport these cells. The female reproductive system additionally provides the environment for fertilization, supports the developing embryo and fetus, and participates in childbirth and lactation. Although external and internal anatomy differ markedly, both systems are governed by shared higher-level endocrine control centers in the brain. Appreciating this shared control system helps in understanding diverse bodies and in recognizing that reproductive health is deeply connected to overall endocrine health, nutrition, and access to care.

The Hypothalamic–Pituitary–Gonadal (HPG) Axis

At the core of reproductive physiology is the hypothalamic–pituitary–gonadal (HPG) axis, a regulatory network that links the brain and the gonads. Neurons in the hypothalamus secrete gonadotropin-releasing hormone (GnRH) in a pulsatile pattern. GnRH travels to the anterior pituitary, where it stimulates the release of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These pituitary hormones act on the gonads—testes in most males and ovaries in most females—to support gamete production and to stimulate the secretion of sex steroid hormones. In testes, LH primarily promotes testosterone production, while FSH supports sperm development in concert with local factors. In ovaries, FSH and LH coordinate follicle development, ovulation, and the production of estrogens and progesterone.

The sex steroids produced by the gonads feed back to the hypothalamus and pituitary to modulate GnRH, FSH, and LH release. This feedback loop maintains reproductive homeostasis, supports fertility, and guides the development of secondary sex characteristics and the transition from childhood to reproductive maturity during puberty. Because the HPG axis is sensitive to nutrition, stress, chronic illness, and some environmental exposures, disruptions in social and physical environments can affect timing of puberty, menstrual regularity, sperm production, and other aspects of reproductive health, often unequally across

populations.

Reproductive Anatomy and Gamete Pathways

Reproductive anatomy is tightly integrated with this hormonal regulation. In the male reproductive system, the testes contain seminiferous tubules where sperm are produced through spermatogenesis. Within these tubules, developing germ cells are supported and protected by specialized Sertoli (sustentacular) cells, while nearby Leydig cells synthesize testosterone under LH stimulation. After formation, sperm move into the epididymis, where they mature and are stored. During ejaculation, sperm travel through the vas deferens and pass through accessory glands—the seminal vesicles, prostate, and bulbourethral glands—that add fluids to form semen. These fluids provide nutrients, buffering, and other factors necessary for sperm function and transport through the male and female reproductive tracts.

In the female reproductive system, the ovaries contain follicles, each housing an oocyte surrounded by supporting cells. Across the ovarian cycle, groups of follicles begin to grow under FSH influence, but usually only one becomes dominant, fully matures, and ovulates in response to a surge in LH. The released oocyte is captured by the fimbriae of the uterine tube (fallopian tube), where fertilization typically occurs if sperm are present. The uterine tubes provide an environment for sperm capacitation, gamete interaction, and early cleavage divisions of the conceptus. Meanwhile, the uterus undergoes cyclic changes in its lining (the endometrium), preparing either to support implantation and pregnancy or to shed during menstruation if fertilization and implantation do not occur.

Understanding how sperm are produced, mature, and move through the ducts and glands of the male system, and how an oocyte develops, is ovulated, and travels through the uterine tube, requires integrating anatomical routes with hormonal signals and cellular events. This integrated view is central for understanding fertility, contraception, pregnancy, and common reproductive disorders. It also underpins patient-centered care for people of all genders, including those using gender-affirming hormones or contraception.

Lifespan Changes: Puberty, Maturity, and Beyond

The structure and function of the reproductive systems change across the lifespan. During childhood, the HPG axis is relatively quiet, with low levels of gonadotropins and sex steroids. At puberty, increased GnRH pulsatility activates the pituitary and gonads. In most females, this leads to maturation of the ovaries, onset of ovulatory cycles and menstruation, and the appearance of secondary sex characteristics such as breast development, changes in body fat distribution, and growth of body hair. In most males, puberty involves testicular enlargement, increased testosterone production, initiation of spermatogenesis, deepening of the voice, growth of facial and body hair, and increased muscle mass and bone density.

These changes reflect the interplay between endocrine regulation, growth processes, and tissue responses to hormones, and they can be influenced by genetics, nutrition, physical activity, psychosocial stress, and chronic disease. Inequities in diet quality, environmental safety, and healthcare access can lead to earlier or later onset of puberty, differences in growth patterns, and unequal risks of reproductive disorders. Later in life, further changes occur: in many individuals with ovaries, ovarian function declines and eventually ceases at menopause, with associated changes in hormone levels and reproductive capacity; individuals with testes also experience age-related changes in hormone production and fertility, though often more gradually.

Recognizing that reproductive anatomy and physiology are dynamic and deeply influenced by environment and social context helps in understanding diverse developmental trajectories. It also emphasizes the importance of equitable access to reproductive healthcare, education, and supportive resources across all stages of life, from puberty through reproductive years and into older adulthood.

Learning Objectives

To achieve these chapter objectives, actively engage with the material. Learning tissues is not a passive process. Your understanding will grow as you interact with the content, peers, and your instructor. Regularly check your thinking against feedback. Revisit complex concepts until you can confidently explain and apply them on your own.

By the end of this chapter, you will be able to:

- Describe the anatomy of the male and female reproductive systems, including their accessory structures
- Explain the role of hypothalamic and pituitary hormones in male and female reproductive function
- Trace the path of a sperm cell from its initial production through fertilization of an oocyte
- Explain the events in the ovary prior to ovulation
- Describe the development and maturation of the sex organs and the emergence of secondary sex characteristics during puberty

7.1: Anatomy and Physiology of the Male Reproductive System

7.2: Anatomy and Physiology of the Female Reproductive System

7.3: Development of the Male and Female Reproductive Systems

7.4: Terms and Definitions

7.5: Chapter Review Questions

7.6: Applied Thinking Self - Assessment

7.7: Alternate Text Descriptions

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7.1: Anatomy and Physiology of the Male Reproductive System

How the Male Reproductive System Works

People often use the words "female" and "male" to describe two different concepts: our sense of gender identity, and our biological sex as determined by our X/Y chromosomes, hormones, sex organs, and other physical characteristics. For some people, gender identity is different from biological sex or their sex assigned at birth. In this chapter and the next chapter, "female" and "male" refer to sex only, and the typical reproductive anatomy of XX and XY individuals is discussed.

Unique for its role in reproduction, a gamete is a specialized sex cell, which in humans carries 23 chromosomes—one half the number in body cells. In almost all sexually reproducing species, these two haploid cells differ in size; the smaller gamete is called the male gamete and the larger one is called the female gamete. At fertilization, the chromosomes in one male gamete, called a sperm (or spermatozoon), combine with the chromosomes in one female gamete, called an ovum. The function of the male, or testicular, reproductive system (Figure 7.1.1) is to produce sperm and transfer them to the female reproductive tract. The paired testes are a crucial component in this process, as they produce both sperm and androgens, the hormones that support male reproductive physiology. In male humans, the most important androgen is testosterone. For people with a penis, several accessory organs and ducts aid the process of sperm maturation and transport the sperm and other seminal components to the penis, which may deliver sperm to the female reproductive tract. In this section, we examine each of these different structures, and discuss the process of sperm production and transport.

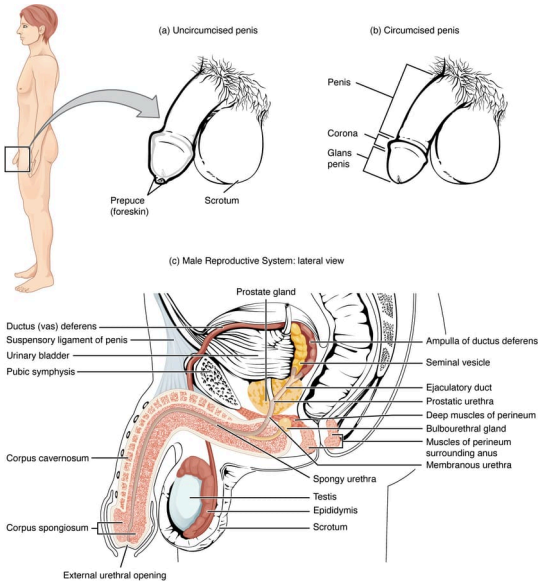


Figure 7.1.1: The structures of the testicular reproductive system include the testes, the epididymides, the penis, and the ducts and glands that produce and carry semen. Sperm exit the scrotum through the ductus deferens, which is bundled in the spermatic cord. The seminal vesicles and prostate gland add fluids to the sperm to create semen. (CC BY 4.0; via Anatomy and Physiology of Male Reproductive System). Detailed text description of the Figure 7.1.1.

Scrotum

The testes are located in a skin-covered, highly pigmented, muscular sack called the scrotum that extends from the body behind the penis (Figure 7.1.1). This location is important in sperm production, which occurs within the testes, and proceeds more efficiently when the testes are kept 2 to 4°C below core body temperature.

The dartos muscle makes up the subcutaneous muscle layer of the scrotum (Figure 7.1.2). It continues internally to make up the scrotal septum, a wall that divides the scrotum into two compartments, each housing one testis. Descending from the internal

oblique muscle of the abdominal wall are the two cremaster muscles, which cover each testis like a muscular net. By contracting simultaneously, the dartos and cremaster muscles can elevate the testes in cold weather (or water), moving the testes closer to the body and decreasing the surface area of the scrotum to retain heat. Alternatively, as the environmental temperature increases, the scrotum relaxes, moving the testes farther from the body core and increasing scrotal surface area, which promotes heat loss. Externally, the scrotum has a raised medial thickening on the surface called the raphae.

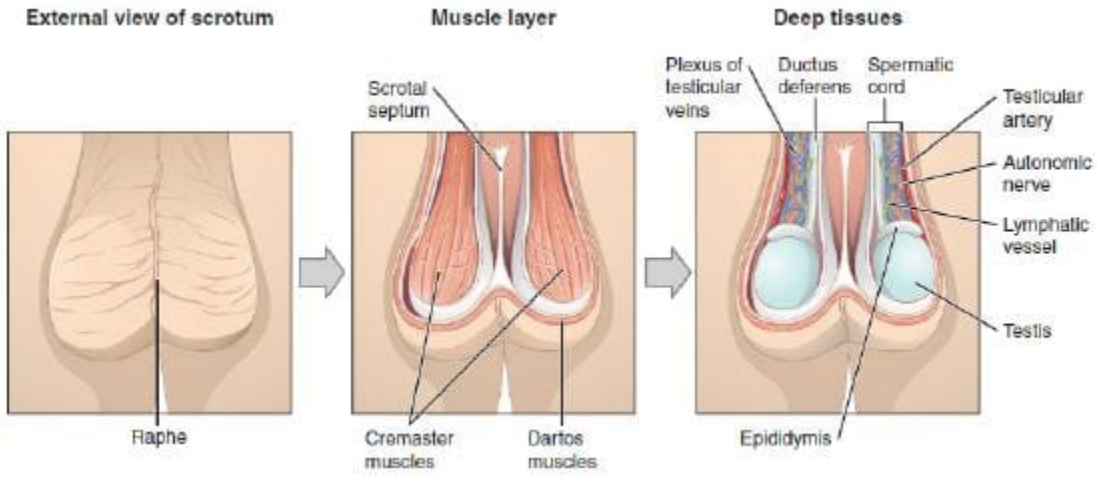


Figure 7.1.2: This anterior view shows the structures of the scrotum and testes. (CC BY 4.0; via Anatomy and Physiology of Male Reproductive System). Detailed text description of the Figure 7.1.2.

Testes

The testes (singular = testis) are the male gonads—that is, the male reproductive organs. They produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan.

Paired ovals, adult testes are each approximately 4 to 5 cm in length and are housed within the scrotum (Figure 7.1.2). They are surrounded by two distinct layers of protective connective tissue (Figure 7.1.3). The outer tunica vaginalis is a serous membrane that has both a parietal and a thin visceral layer. Beneath the tunica vaginalis is the tunica albuginea, a tough, white, dense connective tissue layer covering the testis itself. Not only does the tunica albuginea cover the outside of the testis, it also invaginates to form septa that divide the testis into 300 to 400 structures called lobules. Within the lobules, sperm develop in structures called seminiferous tubules. During the seventh month of the developmental period of a male fetus, each testis moves through the abdominal musculature to descend into the scrotal cavity. This is called the “descent of the testis.” Cryptorchidism is the clinical term used when one or both of the testes fail to descend into the scrotum prior to birth.

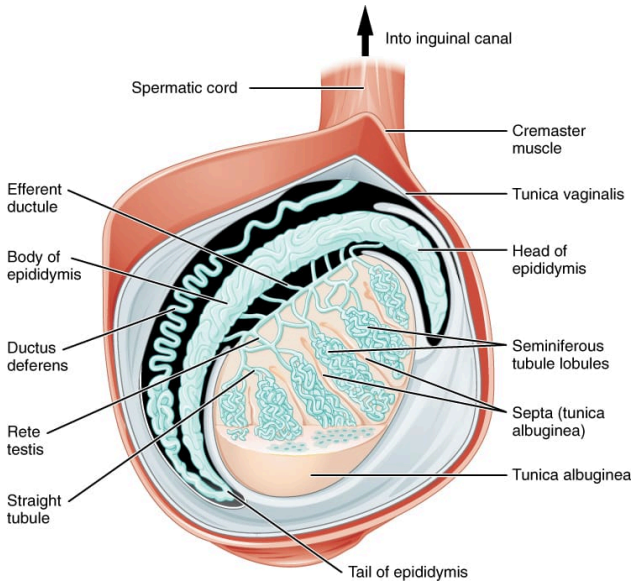


Figure 7.1.3: This sagittal view shows the seminiferous tubules, the site of sperm production. Formed sperm are transferred to the epididymis, where they mature. They leave the epididymis during an ejaculation via the ductus deferens. (CC BY 4.0; via Anatomy and Physiology of Male Reproductive System). Detailed text description of the Figure 7.1.3.

The body of the epididymis runs along the side of the testis, and the tail of the epididymis lies at the lower end. From the tail, the ductus deferens exits the scrotum and ascends toward the pelvic cavity. The figure emphasizes the internal organization of the testis and the pathway sperm follows from the seminiferous tubules into the epididymis and then into the ductus deferens.

The tightly coiled seminiferous tubules form the bulk of each testis. They are composed of developing sperm cells surrounding a lumen, the hollow center of the tubule, where formed sperm are released into the duct system of the testis. Specifically, from the lumens of the seminiferous tubules, sperm move into the straight tubules (or tubuli recti), and from there into a fine meshwork of tubules called the rete testes. Sperm leave the rete testes, and the testis itself, through the 15 to 20 efferent ductules that cross the tunica albuginea.

Inside the seminiferous tubules are six different cell types. These include supporting cells called sustentacular cells, as well as five types of developing sperm cells called germ cells. Germ cell development progresses from the basement membrane—at the perimeter of the tubule—toward the lumen. Let's look more closely at these cell types.

Sertoli Cells

Surrounding all stages of the developing sperm cells are elongate, branching Sertoli cells. Sertoli cells are a type of supporting cell called a sustentacular cell, or sustentocyte, that are typically found in epithelial tissue. Sertoli cells secrete signaling molecules that promote sperm production and can control whether germ cells live or die. They extend physically around the germ cells from the peripheral basement membrane of the seminiferous tubules to the lumen. Tight junctions between these sustentacular cells create the blood–testis barrier, which keeps bloodborne substances from reaching the germ cells and, at the same time, keeps surface antigens on developing germ cells from escaping into the bloodstream and prompting an autoimmune response.

Germ Cells

The least mature cells, the spermatogonia (singular = spermatogonium), line the basement membrane inside the tubule. Spermatogonia are the stem cells of the testis, which means that they are still able to differentiate into a variety of different cell types throughout adulthood. Spermatogonia divide to produce primary and secondary spermatocytes, then spermatids, which finally produce formed sperm. The process that begins with spermatogonia and concludes with the production of sperm is called spermatogenesis.

Spermatogenesis

As just noted, spermatogenesis occurs in the seminiferous tubules that form the bulk of each testis (see Figure 7.1.3). The process begins at puberty, after which time sperm are produced constantly throughout a male's life. One production cycle, from spermatogonia through formed sperm, takes approximately 64 days. A new cycle starts approximately every 16 days, although this timing is not synchronous across the seminiferous tubules. Sperm counts—the total number of sperm a person produces—slowly decline after age 35, and some studies suggest that smoking can lower sperm counts irrespective of age.

The process of spermatogenesis begins with mitosis of the diploid spermatogonia (Figure 7.1.4). Because these cells are diploid (2*n*), they each have a complete copy of the person's genetic material, or 46 chromosomes. However, mature gametes are haploid (1*n*), containing 23 chromosomes—meaning that daughter cells of spermatogonia must undergo a second cellular division through the process of meiosis.

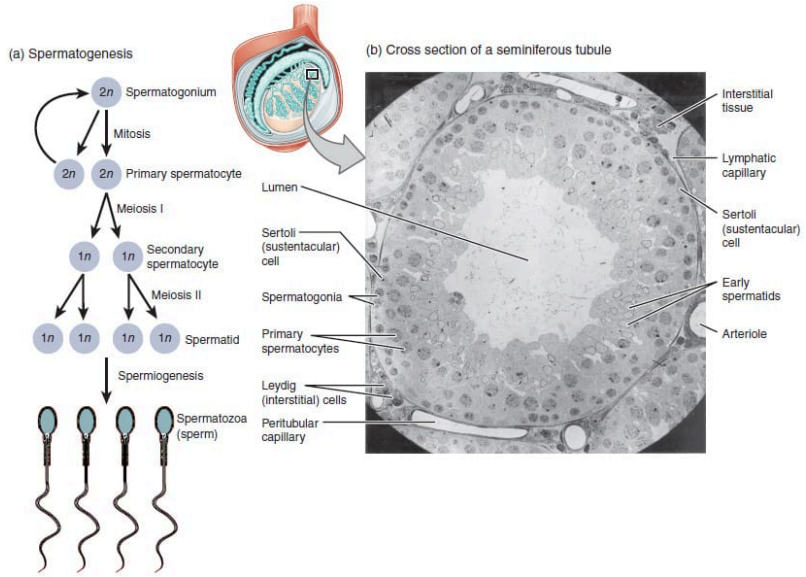


Figure 7.1.4: (a) Mitosis of a spermatogonial stem cell involves a single cell division that results in two identical, diploid daughter cells (spermatogonia to primary spermatocyte). Meiosis has two rounds of cell division: primary spermatocyte to secondary spermatocyte, and then secondary spermatocyte to spermatid. This produces four haploid daughter cells (spermatids). (b) In this electron micrograph of a cross-section of a seminiferous tubule from a rat, the lumen is the light-shaded area in the center of the image. The location of the primary spermatocytes is near the basement membrane, and the early spermatids are approaching the lumen (tissue source: rat). EM × 900. (CC BY 4.0; via Anatomy and Physiology of Male Reproductive System). Detailed text description of the Figure 7.1.4.

Two identical diploid cells result from spermatogonia mitosis. One of these cells remains a spermatogonium, and the other becomes a primary spermatocyte, the next stage in the process of spermatogenesis. As in mitosis, DNA is replicated in a primary spermatocyte, before it undergoes a cell division called meiosis I. During meiosis I each of the 23 pairs of chromosomes separates. This results in two cells, called secondary spermatocytes, each with only half the number of chromosomes. Now a second round of cell division (meiosis II) occurs in both of the secondary spermatocytes. During meiosis II each of the 23 replicated chromosomes divides, similar to what happens during mitosis. Thus, meiosis results in separating the chromosome pairs. This second meiotic division results in a total of four cells with only half of the number of chromosomes. Each of these new cells is a spermatid. Although haploid, early spermatids look very similar to cells in the earlier stages of spermatogenesis, with a round shape, central nucleus, and large amount of cytoplasm. A process called spermiogenesis transforms these early spermatids, reducing the cytoplasm, and beginning the formation of the parts of a true sperm. The fifth stage of germ cell formation—spermatozoa, or formed sperm—is the end result of this process, which occurs in the portion of the tubule nearest the lumen. Eventually, the sperm are released into the lumen and are moved along a series of ducts in the testis toward a structure called the epididymis for the next step of sperm maturation.

Structure of Formed Sperm

Sperm are smaller than most cells in the body; in fact, the volume of a sperm cell is 85,000 times less than that of the female gamete. Approximately 100 to 300 million sperm are produced each day, whereas females typically ovulate only one oocyte per

month. As is true for most cells in the body, the structure of sperm cells speaks to their function. Sperm have a distinctive head, mid-piece, and tail region (Figure 7.1.5). The head of the sperm contains the extremely compact haploid nucleus with very little cytoplasm. These qualities contribute to the overall small size of the sperm (the head is only 5 μm long). A structure called the acrosome covers most of the head of the sperm cell as a "cap" that is filled with lysosomal enzymes important for preparing sperm to participate in fertilization. Tightly packed mitochondria fill the mid-piece of the sperm. ATP produced by these mitochondria will power the flagellum, which extends from the neck and the mid-piece through the tail of the sperm, enabling it to move the entire sperm cell. The central strand of the flagellum, the axial filament, is formed from one centriole inside the maturing sperm cell during the final stages of spermatogenesis.

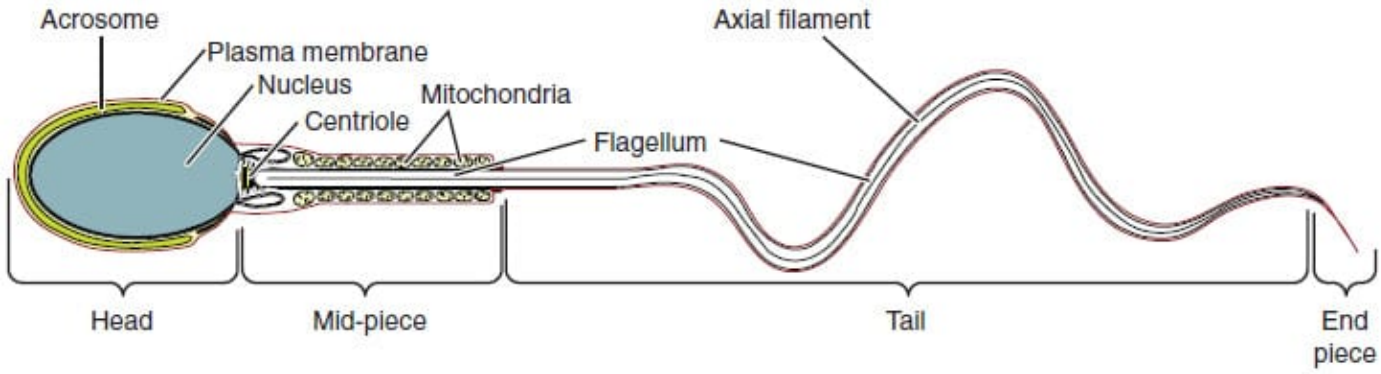


Figure 7.1.5: Sperm cells are divided into a head, containing DNA; a mid-piece, containing mitochondria; and a tail, providing motility. The acrosome is oval and somewhat flattened. (CC BY 4.0; via Anatomy and Physiology of Male Reproductive System). Detailed text description of the Figure 7.1.5.

Sperm Transport

To fertilize an egg without medical intervention, sperm must be moved from the seminiferous tubules in the testes, through the epididymis, and—later during ejaculation—along the length of the penis and out into the female reproductive tract.

Role of the Epididymis

From the lumen of the seminiferous tubules, the immotile sperm are surrounded by testicular fluid and moved to the epididymis (plural = epididymides), a coiled tube attached to the testis where newly formed sperm continue to mature (Figure 7.1.3). Though the epididymis does not take up much room in its tightly coiled state, it would be approximately 6 m (20 feet) long if straightened. It takes an average of 12 days for sperm to move through the coils of the epididymis, with the shortest recorded transit time in humans being one day. Sperm enter the head of the epididymis and are moved along predominantly by the contraction of smooth muscles lining the epididymal tubes. As they are moved along the length of the epididymis, the sperm further mature and acquire the ability to move under their own power. Once inside the female reproductive tract, they will use this ability to move independently toward the unfertilized egg. The more mature sperm are then stored in the tail of the epididymis (the final section) until ejaculation occurs.

Duct System

During ejaculation, sperm exit the tail of the epididymis and are pushed by smooth muscle contraction to the ductus deferens (also called the vas deferens). The ductus deferens is a thick, muscular tube that is bundled together inside the scrotum with connective tissue, blood vessels, and nerves into a structure called the spermatic cord (see Figure 7.1.1 and Figure 7.1.2). Because the ductus deferens is physically accessible within the scrotum, surgical sterilization to interrupt sperm delivery can be performed by cutting and sealing a small section of the ductus (vas) deferens. This procedure is called a vasectomy, and it is an effective form of birth control. Although it may be possible to reverse a vasectomy, clinicians consider the procedure permanent, and advise people to undergo it only if they are certain they no longer wish to have children.

From each epididymis, each ductus deferens extends superiorly into the abdominal cavity through the inguinal canal in the abdominal wall. From here, the ductus deferens continues posteriorly to the pelvic cavity, ending posterior to the bladder where it dilates in a region called the ampulla (meaning "flask").

Sperm make up only 5 percent of the final volume of semen, the thick, milky fluid that is ejaculated. The bulk of semen is produced by three critical accessory glands of the male reproductive system: the seminal vesicles, the prostate, and the bulbourethral glands.

Seminal Vesicles

As sperm pass through the ampulla of the ductus deferens at ejaculation, they mix with fluid from the associated seminal vesicle (see Figure 27.2). The paired seminal vesicles are glands that contribute approximately 60 percent of the semen volume. Seminal vesicle fluid contains large amounts of fructose, which is used by the sperm mitochondria to generate ATP to allow movement through the female reproductive tract.

The fluid, now containing both sperm and seminal vesicle secretions, next moves into the associated ejaculatory duct, a short structure formed from the ampulla of the ductus deferens and the duct of the seminal vesicle. The paired ejaculatory ducts transport the seminal fluid into the next structure, the prostate gland.

Prostate Gland

The centrally located prostate gland sits anterior to the rectum at the base of the bladder surrounding the prostatic urethra (the portion of the urethra that runs within the prostate). About the size of a walnut, the prostate is formed of both muscular and glandular tissues. It excretes an alkaline, milky fluid to the passing seminal fluid—now called semen—that is critical to first coagulate and then decoagulate the semen following ejaculation. The temporary thickening of semen helps retain it within the female reproductive tract, providing time for sperm to utilize the fructose provided by seminal vesicle secretions. When the semen regains its fluid state, sperm can then pass farther into the female reproductive tract.

The prostate normally doubles in size during puberty. At approximately age 25, it gradually begins to enlarge again. This enlargement does not usually cause problems; however, abnormal growth of the prostate, or benign prostatic hyperplasia (BPH), can cause constriction of the urethra as it passes through the middle of the prostate gland, leading to a number of lower urinary tract symptoms, such as a frequent and intense urge to urinate, a weak stream, and a sensation that the bladder has not emptied completely. By age 60, approximately 40 percent of males have some degree of BPH. By age 80, the number of affected individuals has jumped to as many as 80 percent. Treatments for BPH attempt to relieve the pressure on the urethra so that urine can flow more normally. Mild to moderate symptoms are treated with medication, whereas severe enlargement of the prostate is treated by surgery in which a portion of the prostate tissue is removed.

Another common disorder involving the prostate is prostate cancer. According to the Centers for Disease Control and Prevention (CDC), prostate cancer is the second most common cancer in males. However, some forms of prostate cancer grow very slowly and thus may not ever require treatment. Aggressive forms of prostate cancer, in contrast, involve metastasis to vulnerable organs like the lungs and brain. There is no link between BPH and prostate cancer, but the symptoms are similar. Prostate cancer is detected by a medical history, a blood test, and a rectal exam that allows physicians to palpate the prostate and check for unusual masses. If a mass is detected, the cancer diagnosis is confirmed by biopsy of the cells.

Bulbourethral Glands

The final addition to semen is made by two bulbourethral glands (or Cowper's glands) that release a thick, salty fluid that lubricates the end of the urethra and the vagina, and helps to clean urine residues from the penile urethra. The fluid from these accessory glands is released after the male becomes sexually aroused, and shortly before the release of the semen. It is therefore sometimes called pre-ejaculate. It is important to note that, in addition to the lubricating proteins, it is possible for bulbourethral fluid to pick up sperm already present in the urethra, and therefore it may be able to cause pregnancy.

The Penis

The penis is the male organ of copulation (sexual intercourse). It is flaccid for non-sexual actions, such as urination, and turgid and rod-like with sexual arousal. When erect, the stiffness of the organ allows it to penetrate into the vagina and deposit semen into the female reproductive tract.

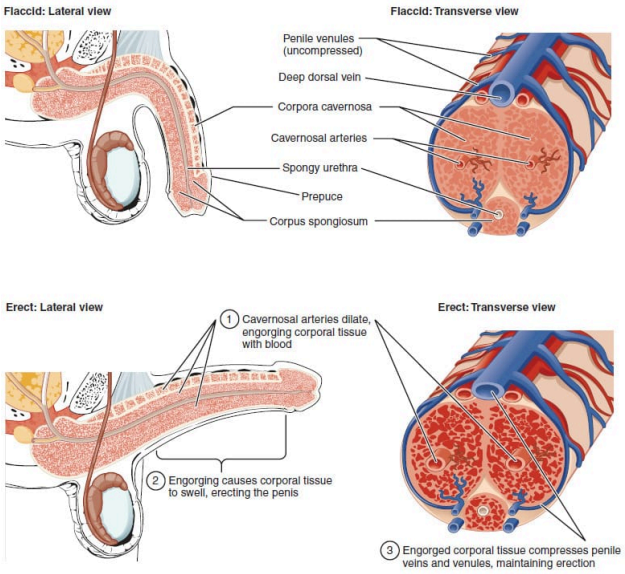


Figure 7.1.6: Three columns of erectile tissue make up most of the volume of the penis. (CC BY 4.0; via Anatomy and Physiology of Male Reproductive System). Detailed text description of the Figure 7.1.6.

The shaft of the penis surrounds the urethra (Figure 7.1.6). The shaft is composed of three column-like chambers of erectile tissue that span the length of the shaft. Each of the two larger lateral chambers is called a corpus cavernosum (plural = corpora cavernosa). Together, these make up the bulk of the penis. The corpus spongiosum, which can be felt as a raised ridge on the erect penis, is a smaller chamber that surrounds the spongy, or penile, urethra. The end of the penis, called the glans penis, has a high concentration of nerve endings, resulting in very sensitive skin that influences the likelihood of ejaculation. The skin from the shaft extends down over the glans and forms a collar called the prepuce (or foreskin). The foreskin also contains a dense concentration of nerve endings, and both lubricate and protect the sensitive skin of the glans penis. A surgical procedure called circumcision, often performed for religious or social reasons, removes the prepuce, typically within days of birth.

Both sexual arousal and REM sleep (during which dreaming occurs) can induce an erection. Penile erections are the result of vasocongestion, or engorgement of the tissues because of more arterial blood flowing into the penis than is leaving in the veins. During sexual arousal, nitric oxide (NO) is released from nerve endings near blood vessels within the corpora cavernosa and spongiosum. Release of NO activates a signaling pathway that results in relaxation of the smooth muscles that surround the penile arteries, causing them to dilate. This dilation increases the amount of blood that can enter the penis and induces the endothelial cells in the penile arterial walls to also secrete NO and perpetuate the vasodilation. The rapid increase in blood volume fills the erectile chambers, and the increased pressure of the filled chambers compresses the thin-walled penile venules, preventing venous drainage of the penis. The result of this increased blood flow to the penis and reduced blood return from the penis is erection. Depending on the flaccid dimensions of a penis, it can increase in size slightly or greatly during erection, with the average length of an erect penis measuring approximately 15 cm.

Disorders of the...

Male Reproductive System

Erectile dysfunction (ED) is a condition in which a person has difficulty either initiating or maintaining an erection. The combined prevalence of minimal, moderate, and complete ED is approximately 40 percent in males at age 40, and reaches nearly 70 percent by 70 years of age. In addition to aging, ED is associated with diabetes, vascular disease, psychiatric disorders, prostate disorders, the use of some drugs such as certain antidepressants, and problems with the testes resulting in low testosterone concentrations. These physical and emotional conditions can lead to interruptions in the vasodilation pathway and result in an inability to achieve an erection.

Recall that the release of NO induces relaxation of the smooth muscles that surround the penile arteries, leading to the vasodilation necessary to achieve an erection. To reverse the process of vasodilation, an enzyme called phosphodiesterase (PDE) degrades a key component of the NO signaling pathway called cGMP. There are several different forms of this enzyme, and PDE type 5 is the type of PDE found in the tissues of the penis. Scientists discovered that inhibiting PDE5 increases blood flow, and allows vasodilation of the penis to occur.

PDEs and the vasodilation signaling pathway are found in the vasculature in other parts of the body. In the 1990s, clinical trials of a PDE5 inhibitor called sildenafil were initiated to treat hypertension and angina pectoris (chest pain caused by poor blood flow through the heart). The trial showed that the drug was not effective at treating heart conditions, but many men experienced erection and priapism (erection lasting longer than 4 hours). Because of this, a clinical trial was started to investigate the ability of sildenafil to promote erections in men suffering from ED. In 1998, the FDA approved the drug, marketed as Viagra®. Since approval of the drug, sildenafil and similar PDE inhibitors now generate over a billion dollars a year in sales, and are reported to be effective in treating approximately 70 to 85 percent of cases of ED. Importantly, men with health problems—especially those with cardiac disease taking nitrates—should avoid Viagra or talk to their physician to find out if they are a candidate for the use of this drug, as deaths have been reported for at-risk users.

Testosterone

Testosterone, an androgen, is a steroid hormone produced by Leydig cells. The alternate term for Leydig cells, interstitial cells, reflects their location between the seminiferous tubules in the testes. In male embryos, testosterone is secreted by Leydig cells by the seventh week of development, with peak concentrations reached in the second trimester. This early release of testosterone results in the anatomical differentiation of the male sexual organs. In childhood, testosterone concentrations are low. They increase during puberty, activating characteristic physical changes and initiating spermatogenesis.

Functions of Testosterone

The continued presence of testosterone is necessary to keep the male reproductive system working properly, and Leydig cells produce approximately 6 to 7 mg of testosterone per day. Testicular steroidogenesis (the manufacture of androgens, including testosterone) results in testosterone concentrations that are 100 times higher in the testes than in the circulation. Maintaining these normal concentrations of testosterone promotes spermatogenesis, whereas low levels of testosterone can lead to infertility. In addition to intratesticular secretion, testosterone is also released into the systemic circulation and plays an important role in muscle development, bone growth, the development of secondary sex characteristics, and maintaining libido (sex drive) in both males and females. In females, the ovaries secrete small amounts of testosterone, although most is converted to estradiol. A small amount of testosterone is also secreted by the adrenal glands in both sexes.

Control of Testosterone

The regulation of testosterone concentrations throughout the body is critical for male reproductive function. The intricate interplay between the endocrine system and the reproductive system is shown in Figure 7.1.7.

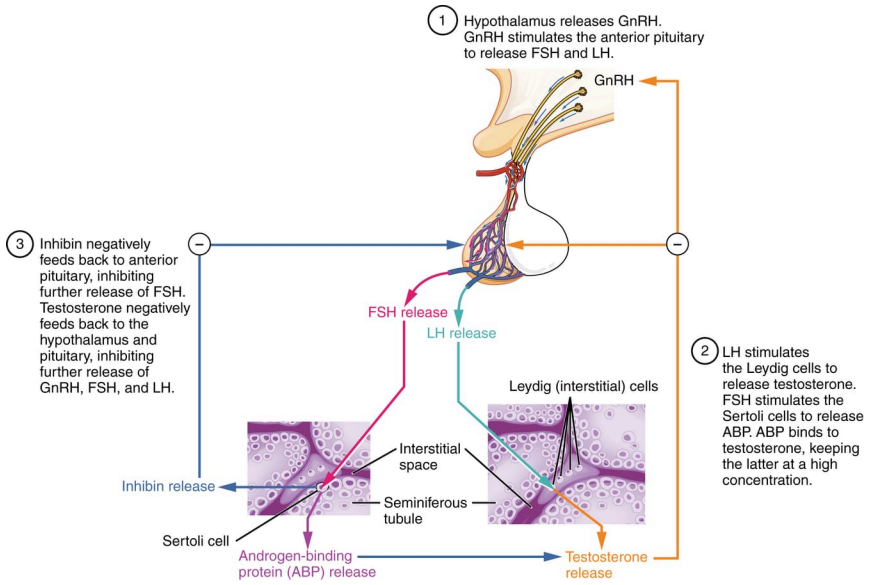


Figure 7.1.7: The hypothalamus and pituitary gland regulate the production of testosterone and the cells that assist in spermatogenesis. GnRH activates the anterior pituitary to produce LH and FSH, which in turn stimulate Leydig cells and Sertoli cells, respectively. The system is a negative feedback loop because the end products of the pathway, testosterone and inhibin, interact with the activity of GnRH to inhibit their own production. (CC BY 4.0; via Anatomy and Physiology of Male Reproductive System). Detailed text description of the Figure 7.1.7.

The regulation of Leydig cell production of testosterone begins outside of the testes. The hypothalamus and the pituitary gland in the brain integrate external and internal signals to control testosterone synthesis and secretion. The regulation begins in the hypothalamus. Pulsatile release of a hormone called gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the endocrine release of hormones from the pituitary gland. Binding of GnRH to its receptors on the anterior pituitary gland stimulates release of the two gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These two hormones are critical for reproductive function in all humans. In the testes, FSH binds predominantly to the Sertoli cells within the seminiferous tubules to promote spermatogenesis. FSH also stimulates the Sertoli cells to produce hormones called inhibins, which function to inhibit FSH release from the pituitary, thus reducing testosterone secretion. These polypeptide hormones correlate directly with Sertoli cell function and sperm number; inhibin B can be used as a marker of spermatogenic activity. LH binds to receptors on Leydig cells in the testes and upregulate the production of testosterone.

A negative feedback loop predominantly controls the synthesis and secretion of both FSH and LH. Low blood concentrations of testosterone stimulate the hypothalamic release of GnRH. GnRH then stimulates the anterior pituitary to secrete LH into the bloodstream. In the testis, LH binds to LH receptors on Leydig cells and stimulates the release of testosterone. When concentrations of testosterone in the blood reach a critical threshold, testosterone itself will bind to androgen receptors on both the hypothalamus and the anterior pituitary, inhibiting the synthesis and secretion of GnRH and LH, respectively. When the blood concentrations of testosterone once again decline, testosterone no longer interacts with the receptors to the same degree and GnRH and LH are once again secreted, stimulating more testosterone production. This same process occurs with FSH and inhibin to control spermatogenesis.

Aging and the...

Male Reproductive System

Declines in Leydig cell activity can occur in males beginning at 40 to 50 years of age. The resulting reduction in circulating testosterone concentrations can lead to symptoms of andropause, also known as male menopause. While the reduction in sex steroids is akin to female menopause, there is no clear sign—such as a lack of a menstrual period—to denote the initiation of andropause. Instead, people with this condition report feelings of fatigue, reduced muscle mass, depression, anxiety, irritability, loss of libido, and insomnia. A reduction in spermatogenesis resulting in lowered fertility is also reported, and sexual dysfunction can also be associated with andropausal symptoms.

> Whereas some researchers believe that certain aspects of andropause are difficult to tease apart from aging in general, testosterone replacement is sometimes prescribed to alleviate some symptoms. Recent studies have shown a benefit from androgen replacement therapy on the new onset of depression in elderly males; however, other studies caution against testosterone replacement for long-term treatment of andropause symptoms, showing that high doses can sharply increase the risk of both heart disease and prostate cancer.

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7.2: Anatomy and Physiology of the Female Reproductive System

How the Female Reproductive System Works

The female, or ovarian, reproductive system functions to produce gametes and reproductive hormones, just like the male reproductive system; however, it also has the additional task of supporting the developing fetus and delivering it to the outside world. Unlike its male counterpart, the female reproductive system is located primarily inside the pelvic cavity (Figure 7.2.1). Recall that the ovaries are the female gonads. The gamete they produce is called an oocyte. We'll discuss the production of oocytes in detail shortly. First, let's look at some of the structures of the female reproductive system.

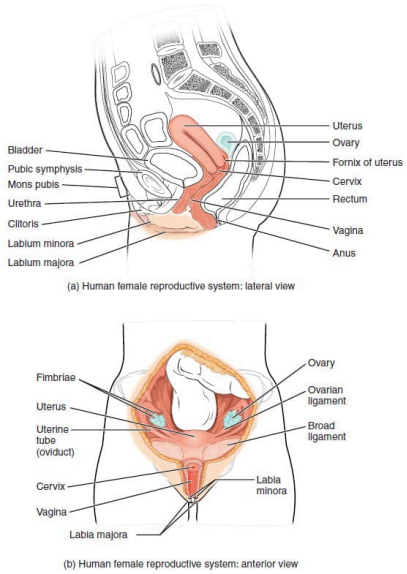


Figure 7.2.1: The major organs of the female reproductive system are located inside the pelvic cavity. (CC BY 4.0; via Anatomy and Physiology of Female Reproductive System). Detailed text description of the Figure 7.2.1.

External Female Genitals

The external female reproductive structures are referred to collectively as the vulva (Figure 7.2.2). The mons pubis is a pad of fat that is located at the anterior, over the pubic bone. After puberty, it becomes covered in pubic hair. The labia majora (labia = "lips"; majora = "larger") are folds of hair-covered skin that begin just posterior to the mons pubis. The thinner and more pigmented labia minora (labia = "lips"; minora = "smaller") extend medial to the labia majora. Although they naturally vary in shape and size from person to person, the labia minora serve to protect the urethra and the entrance to the reproductive tract.

The superior, anterior portions of the labia minora come together to encircle the clitoris (or glans clitoris), an organ that originates from the same cells as the glans penis and has abundant nerves that make it important in sexual sensation and orgasm. The hymen is a thin membrane that sometimes partially covers the entrance to the vagina. An intact hymen cannot be used as an indication of "virginity"; even at birth, this is only a partial membrane, as menstrual fluid and other secretions must be able to exit the body, regardless of penile–vaginal intercourse. The vaginal opening is located between the opening of the urethra and the anus. It is flanked by outlets to the Bartholin's glands (or greater vestibular glands).

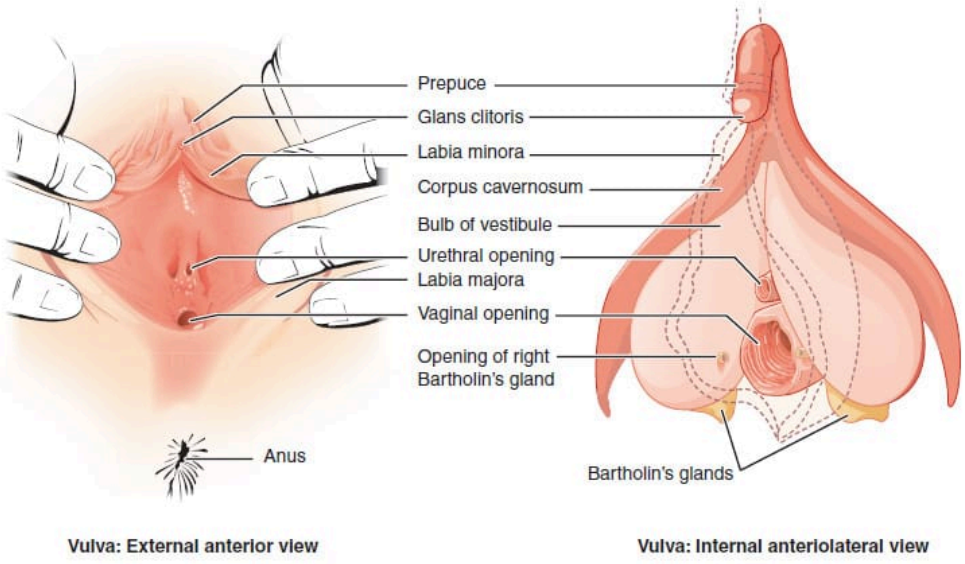


Figure 7.2.2: The external female genitalia are referred to collectively as the vulva. (CC BY 4.0; via Anatomy and Physiology of Female Reproductive System). Detailed text description of the Figure 7.2.2.

Vagina

The vagina, shown at the bottom of Figure 7.2.1 and Figure 7.2.2, is a muscular canal (approximately 10 cm long) that serves as the entrance to the reproductive tract. It also serves as the exit from the uterus during menses and childbirth. The outer walls of the anterior and posterior vagina are formed into longitudinal columns, or ridges, and the superior portion of the vagina—called the fornix—meets the protruding uterine cervix. The walls of the vagina are lined with an outer, fibrous adventitia; a middle layer of smooth muscle; and an inner mucous membrane with transverse folds called rugae. Together, the middle and inner layers allow the expansion of the vagina to accommodate intercourse and childbirth. The thin, perforated hymen can partially surround the opening to the vaginal orifice. The hymen can be ruptured with strenuous physical exercise, penile–vaginal intercourse, and childbirth. The Bartholin's glands and the lesser vestibular glands (located near the clitoris) secrete mucus, which keeps the vestibular area moist.

The vagina is home to a normal population of microorganisms that help to protect against infection by pathogenic bacteria, yeast, or other organisms that can enter the vagina. In a healthy person, the most predominant type of vaginal bacteria is from the genus *Lactobacillus*. This family of beneficial bacterial flora secretes lactic acid, and thus protects the vagina by maintaining an acidic pH (below 4.5). Potential pathogens are less likely to survive in these acidic conditions. Lactic acid, in combination with other vaginal secretions, makes the vagina a self-cleansing organ. However, douching—or washing out the vagina with fluid—can disrupt the normal balance of healthy microorganisms, and actually increase risk for infections and irritation. Indeed, the American College of Obstetricians and Gynecologists recommend that people do not douche, and that they allow the vagina to maintain its normal healthy population of protective microbial flora.

Ovaries

The ovaries are the female gonads. Paired ovals, they are each about 2 to 3 cm in length, about the size of an almond. The ovaries are located within the pelvic cavity, and are supported by the mesovarium, an extension of the peritoneum that connects the ovaries to the broad ligament. Extending from the mesovarium itself is the suspensory ligament that contains the ovarian blood and lymph vessels. Finally, the ovary itself is attached to the uterus via the ovarian ligament.

The ovary comprises an outer covering of cuboidal epithelium called the ovarian surface epithelium that is superficial to a dense connective tissue covering called the tunica albuginea. Beneath the tunica albuginea is the cortex, or outer portion, of the organ. The cortex is composed of a tissue framework called the ovarian stroma that forms the bulk of the adult ovary. Oocytes develop within the outer layer of this stroma, each surrounded by supporting cells. This grouping of an oocyte and its supporting cells is called a follicle. The growth and development of ovarian follicles will be described shortly. Beneath the cortex lies the inner ovarian medulla, the site of blood vessels, lymph vessels, and the nerves of the ovary. You will learn more about the overall anatomy of the female reproductive system at the end of this section.

The Ovarian Cycle

The ovarian cycle is a set of predictable changes in oocytes and ovarian follicles. During the reproductive years, it is a roughly 28-day cycle that can be correlated with, but is not the same as, the menstrual cycle (discussed shortly). The cycle includes two interrelated processes: oogenesis (the production of gametes) and folliculogenesis (the growth and development of ovarian follicles).

Oogenesis

Gametogenesis in females is called oogenesis. The process begins with the ovarian stem cells, or oogonia (Figure 7.2.3). Oogonia are formed during fetal development, and divide via mitosis, much like spermatogonia in the testis. Unlike spermatogonia, however, oogonia form primary oocytes in the fetal ovary prior to birth. These primary oocytes are then arrested in this stage of meiosis I, only to resume it years later, beginning at puberty and continuing until the person is near menopause (the cessation of a female's reproductive functions). The number of primary oocytes present in the ovaries declines from one to two million in an infant, to approximately 400,000 at puberty, to zero by the end of menopause.

The initiation of ovulation—the release of an oocyte from the ovary—marks the transition from puberty into reproductive maturity. From then on, throughout a the reproductive years, ovulation occurs approximately once every 28 days. Just prior to ovulation, a surge of luteinizing hormone triggers the resumption of meiosis in a primary oocyte. This initiates the transition from primary to secondary oocyte. However, as you can see in Figure 7.2.3, this cell division does not result in two identical cells. Instead, the cytoplasm is divided unequally, and one daughter cell is much larger than the other. This larger cell, the secondary oocyte, eventually leaves the ovary during ovulation. The smaller cell, called the first polar body, may or may not complete meiosis and produce second polar bodies; in either case, it eventually disintegrates. Therefore, even though oogenesis produces up to four cells, only one survives.

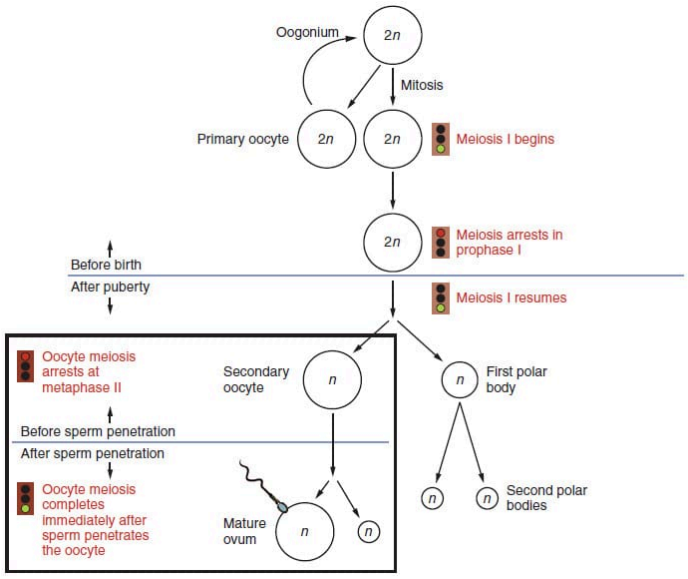


Figure 7.2.3: The unequal cell division of oogenesis produces one to three polar bodies that later degrade, as well as a single haploid ovum, which is produced only if there is penetration of the secondary oocyte by a sperm cell. (CC BY 4.0; via Anatomy and Physiology of Female Reproductive System). Detailed text description of the Figure 7.2.3.

How does the diploid secondary oocyte become an ovum—the haploid female gamete? Meiosis of a secondary oocyte is completed only if a sperm succeeds in penetrating its barriers. Meiosis II then resumes, producing one haploid ovum that, at the instant of fertilization by a (haploid) sperm, becomes the first diploid cell of the new offspring (a zygote). Thus, the ovum can be thought of as a brief, transitional, haploid stage between the diploid oocyte and diploid zygote.

The larger amount of cytoplasm contained in the female gamete is used to supply the developing zygote with nutrients during the period between fertilization and implantation into the uterus. Interestingly, sperm contribute only DNA at fertilization —not cytoplasm. Therefore, the cytoplasm and all of the cytoplasmic organelles in the developing embryo are of egg-derived origin. This includes mitochondria, which contain their own DNA. Scientific research in the 1980s determined that mitochondrial DNA

was maternally inherited, meaning that you can trace your mitochondrial DNA directly to your biological mother, her mother, and so on back through your female ancestors.

Everyday Connection

Mapping Human History with Mitochondrial DNA

When we talk about human DNA, we're usually referring to nuclear DNA; that is, the DNA coiled into chromosomal bundles in the nucleus of our cells. We inherit half of our nuclear DNA from one parent, and half from the other parent. However, mitochondrial DNA (mtDNA) comes only from the mitochondria in the cytoplasm of the fat ovum we inherit from our mother. Our mother received mtDNA from their mother, who got it from their mother, and so on. Each of our cells contains approximately 1700 mitochondria, with each mitochondrion packed with mtDNA containing approximately 37 genes.

Mutations (changes) in mtDNA occur spontaneously in a somewhat organized pattern at regular intervals in human history. By analyzing these mutational relationships, researchers have been able to determine that we can all trace our ancestry back to one female who lived in Africa about 200,000 years ago. More precisely, that human is our most recent common ancestor through matrilineal descent.

This doesn't mean that everyone's mtDNA today looks exactly like that of our common ancestor. Because of the spontaneous mutations in mtDNA that have occurred over the centuries, researchers can map different "branches" off of the "main trunk" of our mtDNA family tree. Your mtDNA might have a pattern of mutations that aligns more closely with one branch, and your neighbor's may align with another branch. Still, all branches eventually lead back to the common ancestor.

But what happened to the mtDNA of all of the other *Homo sapiens* females who were living 200,000 years ago? Researchers explain that, over the centuries, their female descendants died childless or with only male children, and thus, their maternal line—and its mtDNA—ended.

Folliculogenesis

Again, ovarian follicles are oocytes and their supporting cells. They grow and develop in a process called folliculogenesis, which typically leads to ovulation of one follicle approximately every 28 days, along with death to multiple other follicles. The death of ovarian follicles is called atresia, and can occur at any point during follicular development. Recall that, a female infant at birth will have one to two million oocytes within the ovarian follicles, and that this number declines throughout life until menopause, when no follicles remain. As you'll see next, follicles progress from primordial, to primary, to secondary and tertiary stages prior to ovulation—with the oocyte inside the follicle remaining as a primary oocyte until right before ovulation.

Folliculogenesis begins with follicles in a resting state. These small primordial follicles are present in newborn females and are the prevailing follicle type in the adult ovary (Figure 7.2.4). Primordial follicles have only a single flat layer of support cells, called granulosa cells, that surround the oocyte, and they can stay in this resting state for years—some until right before menopause.

After puberty, a few primordial follicles will respond to a recruitment signal each day, and will join a pool of immature growing follicles called primary follicles. Primary follicles start with a single layer of granulosa cells, but the granulosa cells then become active and transition from a flat or squamous shape to a rounded, cuboidal shape as they increase in size and proliferate. As the granulosa cells divide, the follicles—now called secondary follicles (Figure 7.2.4)—increase in diameter, adding a new outer layer of connective tissue, blood vessels, and theca cells—cells that work with the granulosa cells to produce estrogens.

Within the growing secondary follicle, the primary oocyte now secretes a thin acellular membrane called the zona pellucida that will play a critical role in fertilization. A thick fluid, called follicular fluid, that has formed between the granulosa cells also begins to collect into one large pool, or antrum. Follicles in which the antrum has become large and fully formed are considered tertiary follicles (or antral follicles). Several follicles reach the tertiary stage at the same time, and most of these will undergo atresia. The one that does not die will continue to grow and develop until ovulation, when it will expel its secondary oocyte surrounded by several layers of granulosa cells from the ovary. Keep in mind that most follicles don't make it to this point. In fact, roughly 99 percent of the follicles in the ovary will undergo atresia, which can occur at any stage of folliculogenesis.

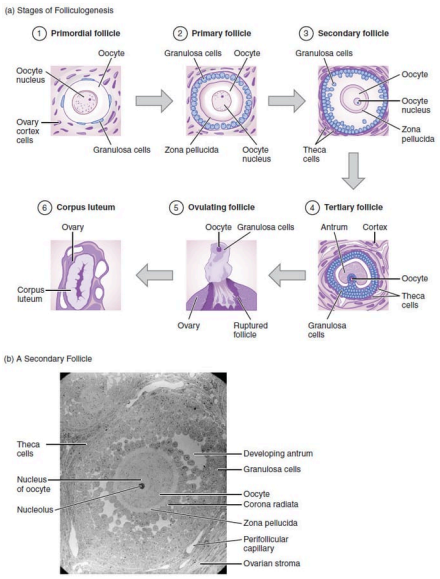


Figure 7.2.4: (a) The maturation of a follicle is shown in a clockwise direction proceeding from the primordial follicles. FSH stimulates the growth of a tertiary follicle, and LH stimulates the production of estrogen by granulosa and theca cells. Once the follicle is mature, it ruptures and releases the oocyte. Cells remaining in the follicle then develop into the corpus luteum. (b) In this electron micrograph of a secondary follicle, the oocyte, theca cells (thecae folliculi), and developing antrum are clearly visible. EM × 1100. (Micrograph provided by the Regents of University of Michigan Medical School © 2012). (CC BY 4.0; via Anatomy and Physiology of Female Reproductive System). Detailed text description of the Figure 7.2.4.

Hormonal Control of the Ovarian Cycle

The process of development that we have just described, from primordial follicle to early tertiary follicle, takes approximately two months in humans. The final stages of development of a small cohort of tertiary follicles, ending with ovulation of a secondary oocyte, occur over a course of approximately 28 days. These changes are regulated by many of the same hormones that regulate the male reproductive system, including GnRH, LH, and FSH.

As in males, the hypothalamus produces GnRH, a hormone that signals the anterior pituitary gland to produce the gonadotropins FSH and LH (Figure 7.2.5). These gonadotropins leave the pituitary and travel through the bloodstream to the ovaries, where they bind to receptors on the granulosa and theca cells of the follicles. FSH stimulates the follicles to grow (hence its name of follicle-stimulating hormone), and the five or six tertiary follicles expand in diameter. The release of LH also stimulates the granulosa and theca cells of the follicles to produce the sex steroid hormone estradiol, a type of estrogen. This phase of the ovarian cycle, when the tertiary follicles are growing and secreting estrogen, is known as the follicular phase.

The more granulosa and theca cells a follicle has (that is, the larger and more developed it is), the more estrogen it will produce in response to LH stimulation. As a result of these large follicles producing large amounts of estrogen, systemic plasma estrogen concentrations increase. Following a classic negative feedback loop, the high concentrations of estrogen will stimulate the hypothalamus and pituitary to reduce the production of GnRH, LH, and FSH. Because the large tertiary follicles require FSH to grow and survive at this point, this decline in FSH caused by negative feedback leads most of them to die (atresia). Typically only one follicle, now called the dominant follicle, will survive this reduction in FSH, and this follicle will be the one that releases an oocyte. Scientists have studied many factors that lead to a particular follicle becoming dominant: size, the number of granulosa cells, and the number of FSH receptors on those granulosa cells all contribute to a follicle becoming the one surviving dominant follicle.

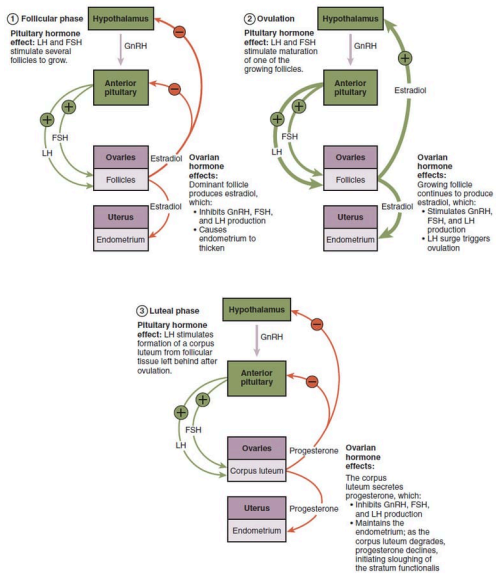


Figure 7.2.5: The hypothalamus and pituitary gland regulate the ovarian cycle and ovulation. GnRH activates the anterior pituitary to produce LH and FSH, which stimulate the production of estrogen and progesterone by the ovaries. (CC BY 4.0; via Anatomy and Physiology of Female Reproductive System). Detailed text description of the Figure 7.2.5.

When only the one dominant follicle remains in the ovary, it again begins to secrete estrogen. It produces more estrogen than all of the developing follicles did together before the negative feedback occurred. It produces so much estrogen that the normal negative feedback doesn't occur. Instead, these extremely high concentrations of systemic plasma estrogen trigger a regulatory switch in the anterior pituitary that responds by secreting large amounts of LH and FSH into the bloodstream. The positive feedback loop by which more estrogen triggers release of more LH and FSH only occurs at this point in the cycle.

It is this large burst of LH (called the LH surge) that leads to ovulation of the dominant follicle. The LH surge induces many changes in the dominant follicle, including stimulating the resumption of meiosis of the primary oocyte to a secondary oocyte. As noted earlier, the polar body that results from unequal cell division simply degrades. The LH surge also triggers proteases (enzymes that cleave proteins) to break down structural proteins in the ovary wall on the surface of the bulging dominant follicle. This degradation of the wall, combined with pressure from the large, fluid-filled antrum, results in the expulsion of the oocyte surrounded by granulosa cells into the peritoneal cavity. This release is ovulation.

In the next section, you will follow the ovulated oocyte as it travels toward the uterus, but there is one more important event that occurs in the ovarian cycle. The surge of LH also stimulates a change in the granulosa and theca cells that remain in the follicle after the oocyte has been ovulated. This change is called luteinization (recall that the full name of LH is luteinizing hormone), and it transforms the collapsed follicle into a new endocrine structure called the corpus luteum, a term meaning "yellowish body". Instead of estrogen, the luteinized granulosa and theca cells of the corpus luteum begin to produce large amounts of the sex steroid hormone progesterone, a hormone that is critical for the establishment and maintenance of pregnancy. Progesterone triggers negative feedback at the hypothalamus and pituitary, which keeps GnRH, LH, and FSH secretions low, so no new dominant follicles develop at this time.

The post-ovulatory phase of progesterone secretion is known as the luteal phase of the ovarian cycle. If pregnancy does not occur within 10 to 12 days, the corpus luteum will stop secreting progesterone and degrade into the corpus albicans, a nonfunctional "whitish body" that will disintegrate in the ovary over a period of several months. During this time of reduced progesterone secretion, FSH and LH are once again stimulated, and the follicular phase begins again with a new cohort of early tertiary follicles beginning to grow and secrete estrogen.

The Uterine Tubes

The uterine tubes (also called fallopian tubes or oviducts) serve as the conduit of the oocyte from the ovary to the uterus (Figure 7.2.6). Each of the two uterine tubes is close to, but not directly connected to, the ovary and divided into sections. The isthmus is the narrow medial end of each uterine tube that is connected to the uterus. The wide distal infundibulum flares out with slender, finger-like projections called fimbriae. The middle region of the tube, called the ampulla, is where fertilization often occurs. The

uterine tubes also have three layers: an outer serosa, a middle smooth muscle layer, and an inner mucosal layer. In addition to its mucus-secreting cells, the inner mucosa contains ciliated cells that beat in the direction of the uterus, producing a current that will be critical to move the oocyte.

Following ovulation, the secondary oocyte surrounded by a few granulosa cells is released into the peritoneal cavity. The nearby uterine tube, either left or right, receives the oocyte. Unlike sperm, oocytes lack flagella, and therefore cannot move on their own. So how do they travel into the uterine tube and toward the uterus? High concentrations of estrogen that occur around the time of ovulation induce contractions of the smooth muscle along the length of the uterine tube. These contractions occur every 4 to 8 seconds, and the result is a coordinated movement that sweeps the surface of the ovary and the pelvic cavity. Current flowing toward the uterus is generated by coordinated beating of the cilia that line the outside and lumen of the length of the uterine tube. These cilia beat more strongly in response to the high estrogen concentrations that occur around the time of ovulation. As a result of these mechanisms, the oocyte–granulosa cell complex is pulled into the interior of the tube. Once inside, the muscular contractions and beating cilia move the oocyte slowly toward the uterus. When fertilization does occur, sperm typically meet the egg while it is still moving through the ampulla.

If the oocyte is successfully fertilized, the resulting zygote will begin to divide into two cells, then four, and so on, as it makes its way through the uterine tube and into the uterus. There, it will implant and continue to grow. If the egg is not fertilized, it will simply degrade—either in the uterine tube or in the uterus, where it may be shed with the next menstrual period.

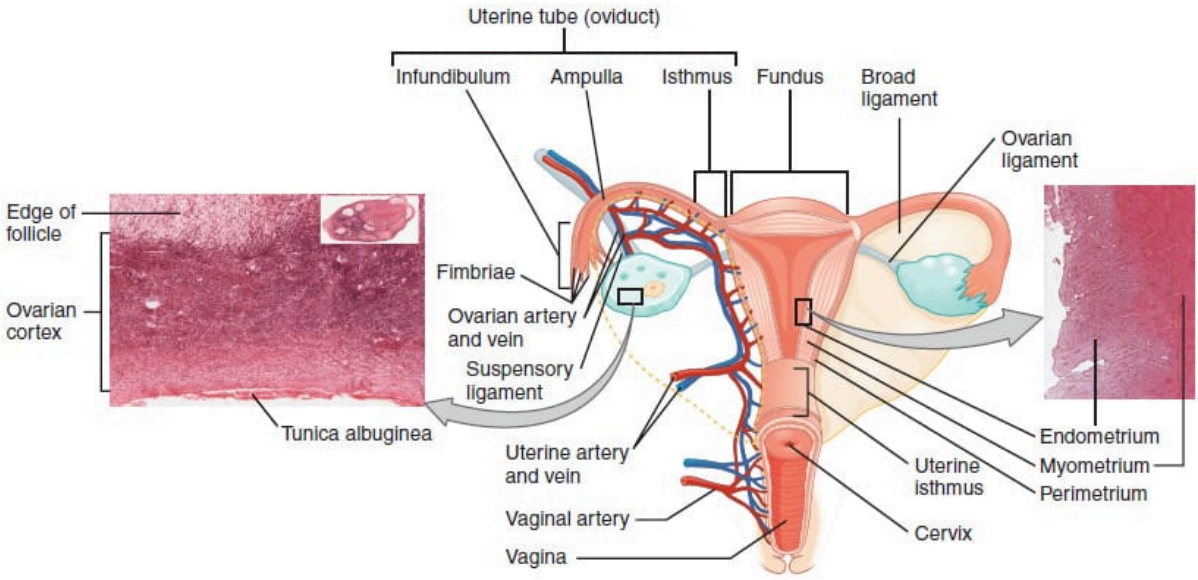


Figure 7.2.6: This anterior view shows the relationship of the ovaries, uterine tubes (oviducts), and uterus. Sperm enter through the vagina, and fertilization of an ovulated oocyte usually occurs in the distal uterine tube. From left to right, LM × 400, LM × 20. (Micrographs provided by the Regents of University of Michigan Medical School © 2012. (CC BY 4.0; via Anatomy and Physiology of Female Reproductive System). Detailed text description of the Figure 7.2.6.

The open-ended structure of the uterine tubes can have significant health consequences if bacteria or other contagions enter through the vagina and move through the uterus, into the tubes, and then into the pelvic cavity. If this is left unchecked, a bacterial infection (sepsis) could quickly become life-threatening. The spread of an infection in this manner is of special concern when unskilled practitioners perform abortions in non-sterile conditions. Sepsis is also associated with sexually transmitted bacterial infections, especially gonorrhea and chlamydia. These increase a person's risk for pelvic inflammatory disease (PID), infection of the uterine tubes or other reproductive organs. Even when resolved, PID can leave scar tissue in the tubes, leading to infertility.

The Uterus and Cervix

The uterus is the muscular organ that nourishes and supports the growing embryo (Figure 7.2.6). Its average size is approximately 5 cm wide by 7 cm long (approximately 2 in by 3 in) when a female is not pregnant. It has three sections. The portion of the uterus superior to the opening of the uterine tubes is called the fundus. The middle section of the uterus is called the body of uterus (or corpus). The cervix is the narrow inferior portion of the uterus that projects into the vagina. The cervix produces mucus secretions that become thin and stringy under the influence of high systemic plasma estrogen concentrations, and these secretions can

facilitate sperm movement through the reproductive tract.

Several ligaments maintain the position of the uterus within the abdominopelvic cavity. The broad ligament is a fold of peritoneum that serves as a primary support for the uterus, extending laterally from both sides of the uterus and attaching it to the pelvic wall. The round ligament attaches to the uterus near the uterine tubes, and extends to the labia majora. Finally, the uterosacral ligament stabilizes the uterus posteriorly by its connection from the cervix to the pelvic wall.

The wall of the uterus is made up of three layers. The most superficial layer is the serous membrane, or perimetrium, which consists of epithelial tissue that covers the exterior portion of the uterus. The middle layer, or myometrium, is a thick layer of smooth muscle responsible for uterine contractions. Most of the uterus is myometrial tissue, and the muscle fibers run horizontally, vertically, and diagonally, allowing the powerful contractions that occur during labor and the less powerful contractions (or cramps) that help to expel menstrual blood during a woman's period. Anteriorly directed myometrial contractions also occur near the time of ovulation, and are thought to possibly facilitate the transport of sperm through the female reproductive tract.

The innermost layer of the uterus is called the endometrium. The endometrium contains a connective tissue lining, the lamina propria, which is covered by epithelial tissue that lines the lumen. Structurally, the endometrium consists of two layers: the stratum basalis and the stratum functionalis (the basal and functional layers). The stratum basalis layer is part of the lamina propria and is adjacent to the myometrium; this layer does not shed during menses. In contrast, the thicker stratum functionalis layer contains the glandular portion of the lamina propria and the endothelial tissue that lines the uterine lumen. It is the stratum functionalis that grows and thickens in response to increased levels of estrogen and progesterone. In the luteal phase of the menstrual cycle, special branches off of the uterine artery called spiral arteries supply the thickened stratum functionalis. This inner functional layer provides the proper site of implantation for the fertilized egg, and—should fertilization not occur—it is only the stratum functionalis layer of the endometrium that sheds during menstruation.

Recall that during the follicular phase of the ovarian cycle, the tertiary follicles are growing and secreting estrogen. At the same time, the stratum functionalis of the endometrium is thickening to prepare for a potential implantation. The post-ovulatory increase in progesterone, which characterizes the luteal phase, is key for maintaining a thick stratum functionalis. As long as a functional corpus luteum is present in the ovary, the endometrial lining is prepared for implantation. Indeed, if an embryo implants, signals are sent to the corpus luteum to continue secreting progesterone to maintain the endometrium, and thus maintain the pregnancy. If an embryo does not implant, no signal is sent to the corpus luteum and it degrades, ceasing progesterone production and ending the luteal phase. Without progesterone, the endometrium thins and, under the influence of prostaglandins, the spiral arteries of the endometrium constrict and rupture, preventing oxygenated blood from reaching the endometrial tissue. As a result, endometrial tissue dies and blood, pieces of the endometrial tissue, and white blood cells are shed through the vagina during menstruation, or the menses. The first menses after puberty, called menarche, can occur either before or after the first ovulation.

The Menstrual Cycle

Now that we have discussed the maturation of the cohort of tertiary follicles in the ovary, the build-up and then shedding of the endometrial lining in the uterus, and the function of the uterine tubes and vagina, we can put everything together to talk about the three phases of the menstrual cycle—the series of changes in which the uterine lining is shed, rebuilds, and prepares for implantation.

The timing of the menstrual cycle starts with the first day of menses, referred to as day one of a period. Cycle length is determined by counting the days between the onset of bleeding in two subsequent cycles. Because the average length of a menstrual cycle is 28 days, this is the time period used to identify the timing of events in the cycle. However, the length of the menstrual cycle varies, and even in the same person from one cycle to the next, typically from 21 to 32 days.

Just as the hormones produced by the granulosa and theca cells of the ovary "drive" the follicular and luteal phases of the ovarian cycle, they also control the three distinct phases of the menstrual cycle. These are the menses phase, the proliferative phase, and the secretory phase.

Menses Phase

The menses phase of the menstrual cycle is the phase during which the lining is shed; that is, the days that the person menstruates. Although it averages approximately five days, the menses phase can last from 2 to 7 days, or longer. As shown in Figure 7.2.7, the menses phase occurs during the early days of the follicular phase of the ovarian cycle, when progesterone,

FSH, and LH levels are low. Recall that progesterone concentrations decline as a result of the degradation of the corpus luteum, marking the end of the luteal phase. This decline in progesterone triggers the shedding of the stratum functionalis of the endometrium.

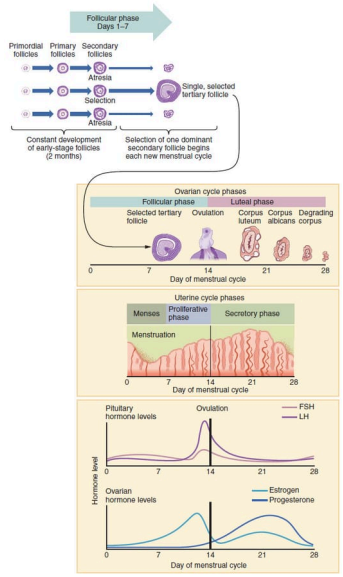


Figure 7.2.7: The correlation of the hormone levels and their effects on the female reproductive system is shown in this timeline of the ovarian and menstrual cycles. The menstrual cycle begins at day one with the start of menses. Ovulation occurs around day 14 of a 28-day cycle, triggered by the LH surge. (CC BY 4.0; via Anatomy and Physiology of Female Reproductive System). Detailed text description of the Figure 7.2.7.

Proliferative Phase

Once menstrual flow ceases, the endometrium begins to proliferate again, marking the beginning of the proliferative phase of the menstrual cycle. It occurs when the granulosa and theca cells of the tertiary follicles begin to produce increased amounts of estrogen. These rising estrogen concentrations stimulate the endometrial lining to rebuild.

Recall that the high estrogen concentrations will eventually lead to a decrease in FSH as a result of negative feedback, resulting in atresia of all but one of the developing tertiary follicles. The switch to positive feedback—which occurs with the elevated estrogen production from the dominant follicle—then stimulates the LH surge that will trigger ovulation. In a typical 28-day menstrual cycle, ovulation occurs on day 14. Ovulation marks the end of the proliferative phase as well as the end of the follicular phase.

Secretory Phase

In addition to prompting the LH surge, high estrogen levels increase the uterine tube contractions that facilitate the pick-up and transfer of the ovulated oocyte. High estrogen levels also slightly decrease the acidity of the vagina, making it more hospitable to sperm. In the ovary, the luteinization of the granulosa cells of the collapsed follicle forms the progesterone-producing corpus luteum, marking the beginning of the luteal phase of the ovarian cycle. In the uterus, progesterone from the corpus luteum begins the secretory phase of the menstrual cycle, in which the endometrial lining prepares for implantation. Over the next 10 to 12 days, the endometrial glands secrete a fluid rich in glycogen. If fertilization has occurred, this fluid will nourish the ball of cells now developing from the zygote. At the same time, the spiral arteries develop to provide blood to the thickened stratum functionalis.

If no pregnancy occurs within approximately 10 to 12 days, the corpus luteum will degrade into the corpus albicans. Levels of both estrogen and progesterone will fall, and the endometrium will grow thinner. Prostaglandins will be secreted that cause constriction of the spiral arteries, reducing oxygen supply. The endometrial tissue will die, resulting in menses—or the first day of the next cycle.

Female Reproductive System

Research over many years has confirmed that cervical cancer is most often caused by a sexually transmitted infection with human papillomavirus (HPV). There are over 100 related viruses in the HPV family, and the characteristics of each strain determine the outcome of the infection. In all cases, the virus enters body cells and uses its own genetic material to take over the host cell's metabolic machinery and produce more virus particles.

HPV infections are common in all people. Indeed, a recent study determined that 42.5 percent of females had HPV at the time of testing. These people ranged in age from 14 to 59 years and differed in race, ethnicity, and number of sexual partners. Of note, the prevalence of HPV infection was 53.8 percent among females aged 20 to 24 years, the age group with the highest infection rate.

HPV strains are classified as high or low risk according to their potential to cause cancer. Though most HPV infections do not cause disease, the disruption of normal cellular functions in the low-risk forms of HPV can cause the human host to develop genital warts. Often, the body is able to clear an HPV infection by normal immune responses within 2 years. However, the more serious, high-risk infection by certain types of HPV can result in cancer of the cervix (Figure 7.2.8). Infection with either of the cancer-causing variants HPV 16 or HPV 18 has been linked to more than 70 percent of all cervical cancer diagnoses. Although even these high-risk HPV strains can be cleared from the body over time, infections persist in some individuals. If this happens, the HPV infection can influence the cells of the cervix to develop precancerous changes.

Risk factors for cervical cancer include having unprotected sex; having multiple sexual partners; a first sexual experience at a younger age, when the cells of the cervix are not fully mature; failure to receive the HPV vaccine; a compromised immune system; and smoking. The risk of developing cervical cancer is doubled with cigarette smoking.

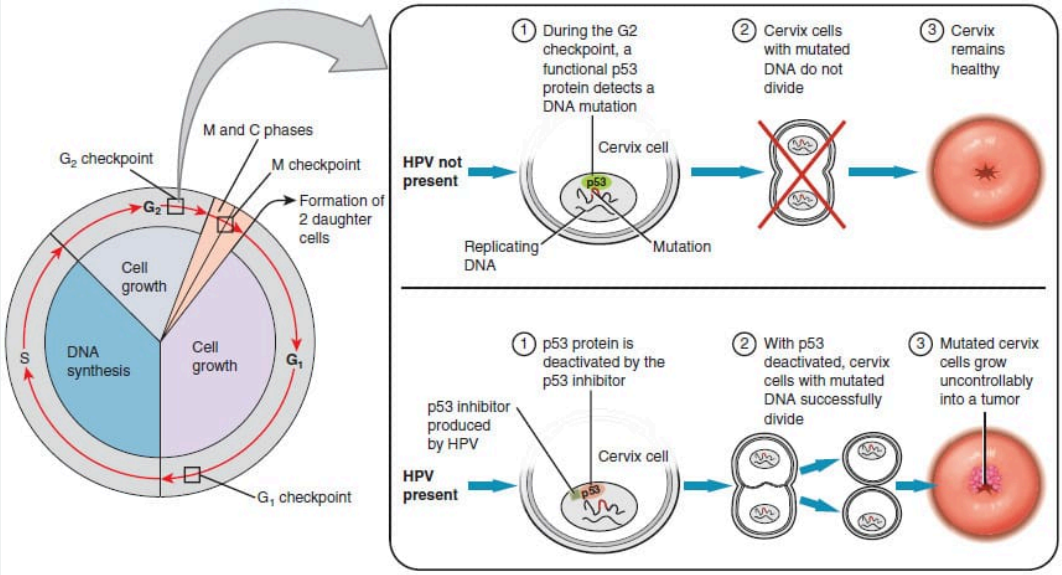


Figure 7.2.8: In most cases, cells infected with the HPV virus heal on their own. In some cases, however, the virus continues to spread and becomes an invasive cancer. (CC BY 4.0; via Anatomy and Physiology of Female Reproductive System). Detailed text description of the Figure 7.2.8.

When the high-risk types of HPV enter a cell, two viral proteins are used to neutralize proteins that the host cells use as checkpoints in the cell cycle. The best studied of these proteins is p53. In a normal cell, p53 detects DNA damage in the cell's genome and either halts the progression of the cell cycle—allowing time for DNA repair to occur—or initiates apoptosis. Both of these processes prevent the accumulation of mutations in a cell's genome. High-risk HPV can neutralize p53, keeping the cell in a state in which fast growth is possible and impairing apoptosis, allowing mutations to accumulate in the cellular DNA.

The prevalence of cervical cancer in the United States is very low because of regular screening exams called pap smears. Pap smears sample cells of the cervix, allowing the detection of abnormal cells. If pre-cancerous cells are detected, there are several highly effective techniques that are currently in use to remove them before they pose a danger. However, people in lower-income countries often do not have access to regular pap smears. As a result, these females in lower-income countries account for as many as 80 percent of the cases of cervical cancer worldwide.

In 2006, the first vaccine against the high-risk types of HPV was approved. There are now two HPV vaccines available: Gardasil® and Cervarix®. Whereas these vaccines were initially only targeted for females, because HPV is sexually transmitted, all people require vaccination for this approach to achieve its maximum efficacy. A recent study suggests that the HPV vaccine has cut the rates of HPV infection by the four targeted strains at least in half. Unfortunately, the high cost of manufacturing the vaccine is currently limiting access to many people worldwide.

The Breasts

Whereas the breasts are located far from the other female reproductive organs, they are considered accessory organs of the female reproductive system. The function of the breasts is to supply milk to an infant in a process called lactation. The external features of the breast include a nipple surrounded by a pigmented areola (Figure 7.2.9), whose coloration may deepen during pregnancy. The areola is typically circular and can vary in size from 25 to 100 mm in diameter. The areolar region is characterized by small, raised areolar glands that secrete lubricating fluid during lactation to protect the nipple from chafing. When a baby nurses, or draws milk from the breast, the entire areolar region is taken into the mouth.

Breast milk is produced by the mammary glands, which are modified sweat glands. The milk itself exits the breast through the nipple via 15 to 20 lactiferous ducts that open on the surface of the nipple. These lactiferous ducts each extend to a lactiferous sinus that connects to a glandular lobe within the breast itself that contains groups of milk-secreting cells in clusters called alveoli (see Figure 7.2.9). The clusters can change in size depending on the amount of milk in the alveolar lumen. Once milk is made in the alveoli, stimulated myoepithelial cells that surround the alveoli contract to push the milk to the lactiferous sinuses. From here, the baby can draw milk through the lactiferous ducts by suckling. The lobes themselves are surrounded by fat tissue, which determines the size of the breast; breast size differs between individuals and does not affect the amount of milk produced. Supporting the breasts are multiple bands of connective tissue called suspensory ligaments that connect the breast tissue to the dermis of the overlying skin.

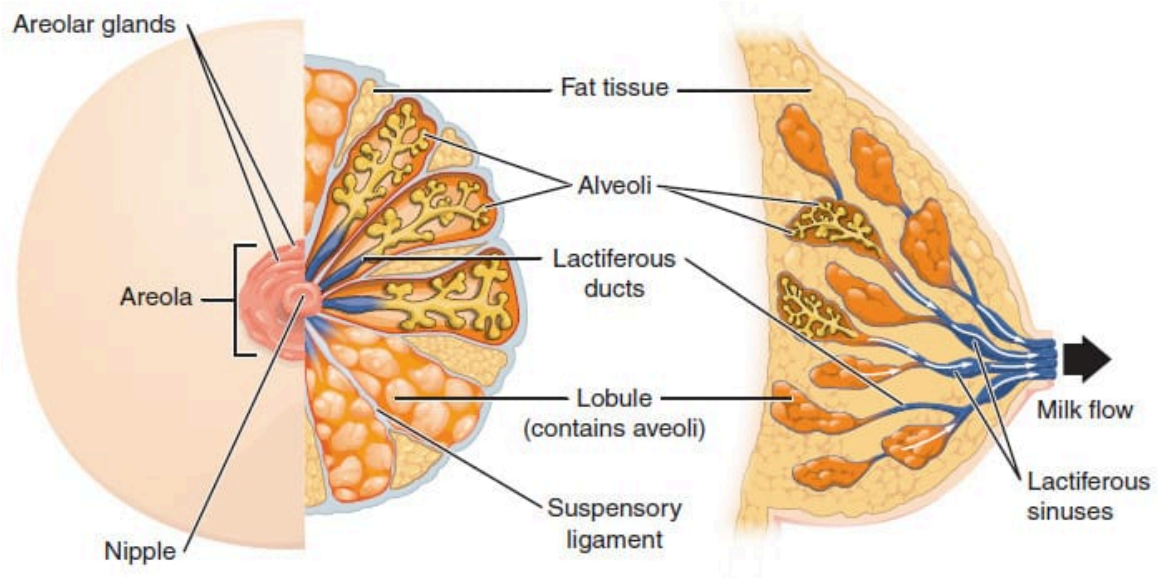


Figure 7.2.9: During lactation, milk moves from the alveoli through the lactiferous ducts to the nipple. (CC BY 4.0; via Anatomy and Physiology of Female Reproductive System). Detailed text description of the Figure 7.2.9.

During the normal hormonal fluctuations in the menstrual cycle, breast tissue responds to changing levels of estrogen and progesterone, which can lead to swelling and breast tenderness in some individuals, especially during the secretory phase. If pregnancy occurs, the increase in hormones leads to further development of the mammary tissue and enlargement of the breasts.

Hormonal Birth Control

Birth control pills take advantage of the negative feedback system that regulates the ovarian and menstrual cycles to stop ovulation and prevent pregnancy. Typically they work by providing a constant level of both estrogen and progesterone, which negatively feeds back onto the hypothalamus and pituitary, thus preventing the release of FSH and LH. Without FSH, the follicles do not mature, and without the LH surge, ovulation does not occur. Although the estrogen in birth control pills does stimulate some thickening of the endometrial wall, it is reduced compared with a normal cycle and is less likely to support implantation.

Some birth control pills contain 21 active pills containing hormones, and 7 inactive pills (placebos). The decline in hormones during the week that the person takes the placebo pills triggers menses, although it is typically lighter than a normal menstrual flow because of the reduced endometrial thickening. Newer types of birth control pills have been developed that deliver low-dose estrogens and progesterone for the entire cycle (these are meant to be taken 365 days a year), and menses never occurs. While some people prefer to have the proof of a lack of pregnancy that a monthly period provides, menstruation every 28 days is not required for health reasons, and there are no reported adverse effects of not having a menstrual period in an otherwise healthy individual.

Because birth control pills function by providing constant estrogen and progesterone levels and disrupting negative feedback, skipping even just one or two pills at certain points of the cycle (or even being several hours late taking the pill) can lead to an increase in FSH and LH and result in ovulation. It is important, therefore, to follow the directions on the birth control pill package to successfully prevent pregnancy.

Aging and the...

Female Reproductive System

Female fertility (the ability to conceive) peaks when people are in their twenties, and is slowly reduced until 35 years of age. After that time, fertility declines more rapidly, until it ends completely at the end of menopause. Menopause is the cessation of the menstrual cycle that occurs as a result of the loss of ovarian follicles and the hormones that they produce. Menopause is considered complete if an individual has not menstruated in a full year. After that point, they are considered postmenopausal. The average age for this change is consistent worldwide at between 50 and 52 years of age, but it can normally occur at any time in a person's forties or fifties. Poor health, including smoking, can lead to earlier loss of fertility and earlier menopause.

As the age of menopause approaches, depletion of the number of viable follicles in the ovaries due to atresia affects the hormonal regulation of the menstrual cycle. During the years leading up to menopause, there is a decrease in the levels of the hormone inhibin, which normally participates in a negative feedback loop to the pituitary to control the production of FSH. The menopausal decrease in inhibin leads to an increase in FSH. The presence of FSH stimulates more follicles to grow and secrete estrogen. Because small, secondary follicles also respond to increases in FSH levels, larger numbers of follicles are stimulated to grow; however, most undergo atresia and die. Eventually, this process leads to the depletion of all follicles in the ovaries, and the production of estrogen falls off dramatically. It is primarily the lack of estrogens that leads to the symptoms of menopause.

The earliest changes occur during the menopausal transition, often referred to as peri-menopause, when a menstrual cycle becomes irregular but does not stop entirely. Although the levels of estrogen are still nearly the same as before the transition, the level of progesterone produced by the corpus luteum is reduced. This decline in progesterone can lead to abnormal growth, or hyperplasia, of the endometrium. This condition is a concern because it increases the risk of developing endometrial cancer. Two harmless conditions that can develop during the transition are uterine fibroids, which are benign masses of cells, and irregular bleeding. As estrogen levels change, other symptoms that occur are hot flashes and night sweats, trouble sleeping, vaginal dryness, mood swings, difficulty focusing, and thinning of hair on the head along with the growth of more hair on the face. Depending on the individual, these symptoms can be entirely absent, moderate, or severe.

After menopause, lower amounts of estrogens can lead to other changes. Cardiovascular disease becomes as prevalent in females as in males, possibly because estrogens reduce the amount of cholesterol in the blood vessels. When estrogen is lacking, many people find that they suddenly have problems with high cholesterol and the cardiovascular issues that accompany it. Osteoporosis is another problem because bone density decreases rapidly in the first years after menopause. The reduction in bone density leads to a higher incidence of fractures.

Hormone therapy (HT), which employs medication (synthetic estrogens and progestins) to increase estrogen and progestin levels, can alleviate some of the symptoms of menopause. In 2002, the Women's Health Initiative began a study to observe for the long-term outcomes of hormone replacement therapy over 8.5 years. However, the study was prematurely terminated after 5.2 years because of evidence of a higher than normal risk of breast cancer in patients taking estrogen-only HT. The potential positive effects on cardiovascular disease were also not realized in the estrogen-only patients. The results of other hormone replacement studies over the last 50 years, including a 2012 study that followed over 1,000 menopausal women for 10 years, have shown cardiovascular benefits from estrogen and no increased risk for cancer. Some researchers believe that the age group tested in the 2002 trial may have been too old to benefit from the therapy, thus skewing the results. In the meantime, intense debate and study of the benefits and risks of replacement therapy is ongoing. Current guidelines approve HT for the reduction of hot flashes or flushes, but this treatment is generally only considered when people first start showing signs of menopausal changes, is used in the lowest dose possible for the shortest time possible (5 years or less), and it is suggested that people on HT have regular pelvic and breast exams.

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7.3: Development of the Male and Female Reproductive Systems

Development of the Sexual Organs in the Embryo and Fetus

The development of the reproductive systems begins soon after fertilization of the egg, with primordial gonads beginning to develop approximately one month after conception. Reproductive development continues in utero, but there is little change in the reproductive system between infancy and puberty.

Mammalian sex determination is generally determined by X and Y chromosomes. Individuals homozygous for X (XX) are female in sex and heterozygous individuals (XY) are male. The presence of a Y chromosome triggers the development of a certain set of male characteristics and its absence results in female characteristics. Nondisjunction during meiosis can produce other combinations such as XXY, XYY, and XO which are called chromosomal intersex.

Without much chemical prompting, all fertilized eggs would develop into females. To become a male, an individual must be exposed to the cascade of factors initiated by a single gene on the male Y chromosome. This is called the SRY (Sex-determining *R*egion of the *Y* chromosome). Because females do not have a Y chromosome, they do not have the *SRY* gene. Without a functional *SRY* gene, an individual will be female.

In both male and female embryos, the same group of cells has the potential to develop into either the male or female gonads; this tissue is considered bipotential. The *SRY* gene actively recruits other genes that begin to develop the testes, and suppresses genes that are important in female development. As part of this *SRY*-prompted cascade, germ cells in the bipotential gonads differentiate into spermatogonia. Without *SRY*, different genes are expressed, oogonia form, and primordial follicles develop in the primitive ovary.

Soon after the formation of the testis, the Leydig cells begin to secrete testosterone. Testosterone can influence tissues that are bipotential to become male reproductive structures. For example, with exposure to testosterone, cells that could become either the glans penis or the glans clitoris form the glans penis. Without testosterone, these same cells differentiate into the clitoris.

Not all tissues in the reproductive tract are bipotential. The internal reproductive structures (for example the uterus, uterine tubes, and part of the vagina in females; and the epididymis, ductus deferens, and seminal vesicles in males) form from one of two rudimentary duct systems in the embryo. For typical reproductive function in the adult, one set of these ducts must develop properly, and the other must degrade. In males, secretions from sustentacular cells trigger a degradation of the female duct, called the Müllerian duct. At the same time, testosterone secretion stimulates growth of the male tract, the Wolffian duct. Without such sustentacular cell secretion, the Müllerian duct will develop; without testosterone, the Wolffian duct will degrade. Thus, the developing offspring will be female. For more information and a figure of differentiation of the gonads, seek additional content on fetal development.

Further Sexual Development Occurs at Puberty

Puberty is the stage of development at which individuals become sexually mature. Though the outcomes of puberty for different sexes are very different, the hormonal control of the process is very similar. In addition, though the timing of these events varies between individuals, the sequence of changes that occur is predictable for male and female adolescents. As shown in Figure $7.3.1$, a concerted release of hormones from the hypothalamus (GnRH), the anterior pituitary (LH and FSH), and the gonads (either testosterone or estrogen) is responsible for the maturation of the reproductive systems and the development of secondary sex characteristics, which are physical changes that serve auxiliary roles in reproduction.

The first changes begin around the age of eight or nine when the production of LH becomes detectable. The release of LH occurs primarily at night during sleep and precedes the physical changes of puberty by several years. In pre-pubertal children, the sensitivity of the negative feedback system in the hypothalamus and pituitary is very high. This means that very low concentrations of androgens or estrogens will negatively feed back onto the hypothalamus and pituitary, keeping the production of GnRH, LH, and FSH low.

As an individual approaches puberty, two changes in sensitivity occur. The first is a decrease of sensitivity in the hypothalamus

and pituitary to negative feedback, meaning that it takes increasingly larger concentrations of sex steroid hormones to stop the production of LH and FSH. The second change in sensitivity is an increase in sensitivity of the gonads to the FSH and LH signals, meaning the gonads of adults are more responsive to gonadotropins than are the gonads of children. As a result of these two changes, the levels of LH and FSH slowly increase and lead to the enlargement and maturation of the gonads, which in turn leads to secretion of higher levels of sex hormones and the initiation of spermatogenesis and folliculogenesis.

In addition to age, multiple factors can affect the age of onset of puberty, including genetics, environment, and psychological stress. One of the more important influences may be nutrition; historical data demonstrate the effect of better and more consistent nutrition on the age of menarche in the United States, which decreased from an average age of approximately 17 years of age in 1860 to the current age of approximately 12.75 years in 1960, as it remains today. Some studies indicate a link between puberty onset and the amount of stored fat in an individual. This effect is more pronounced in females, but has been documented in both sexes. Body fat, corresponding with secretion of the hormone leptin by adipose cells, appears to have a strong role in determining menarche. This may reflect to some extent the high metabolic costs of gestation and lactation. In females who are extremely lean and highly active, such as gymnasts, there is often a delay in the onset of puberty.

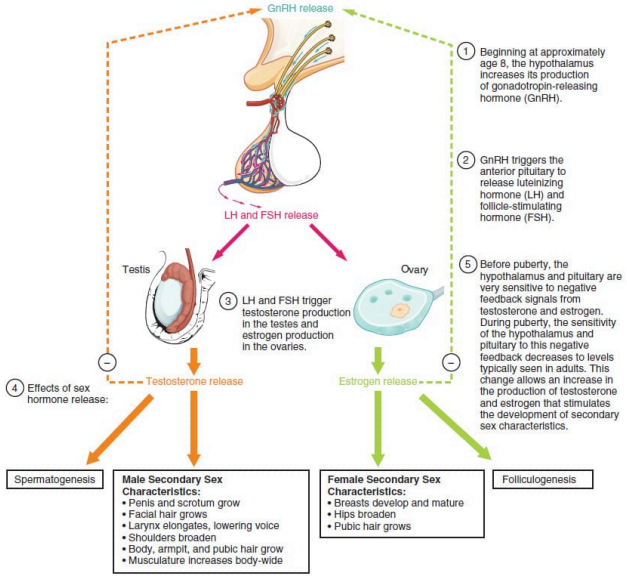


Figure 7.3.1: During puberty, the release of LH and FSH from the anterior pituitary stimulates the gonads to produce sex hormones in both male and female adolescents. (CC BY 4.0; via Development of the Male and Female Reproductive Systems). Detailed text description of the Figure 7.3.1.

Signs of Puberty

Different sex steroid hormone concentrations between the sexes also contribute to the development and function of secondary sexual characteristics. Examples of secondary sexual characteristics are listed in Table 7.3.1.

Table 7.3.1: Development of the Secondary Sexual Characteristics

Male	Female
Increased larynx size and deepening of the voice	Deposition of fat, predominantly in breasts and hips
Increased muscular development	Breast development
Growth of facial, axillary, and pubic hair, and increased growth of body hair	Broadening of the pelvis and growth of axillary and pubic hair

As a female reaches puberty, typically the first change that is visible is the development of the breast tissue. This is followed by the growth of axillary and pubic hair. A growth spurt normally starts at approximately age 9 to 11, and may last two years or more. During this time, height can increase 3 inches a year. The next step in puberty is menarche, the start of menstruation.

In males, the growth of the testes is typically the first physical sign of the beginning of puberty, which is followed by growth and

pigmentation of the scrotum and growth of the penis. The next step is the growth of hair, including armpit, pubic, chest, and facial hair. Testosterone stimulates the growth of the larynx and thickening and lengthening of the vocal folds, which causes the voice to drop in pitch. The first fertile ejaculations typically appear at approximately 15 years of age, but this age can vary widely across individuals. Unlike the early growth spurt observed in females, the male growth spurt occurs toward the end of puberty, at approximately age 11 to 13, and height can increase as much as 4 inches a year. In some males, pubertal development can continue through the early 20s.

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7.4: Terms and Definitions

Key Terms

Select to View Definition

Alveoli
(of the breast) milk-secreting cells in the mammary gland

Ampulla
(of the uterine tube) middle portion of the uterine tube in which fertilization often occurs

Antrum
fluid-filled chamber that characterizes a mature tertiary (antral) follicle

Areola
highly pigmented, circular area surrounding the raised nipple and containing areolar glands that secrete fluid important for lubrication during suckling

Bartholin's glands
(also, greater vestibular glands) glands that produce a thick mucus that maintains moisture in the vulva area; also referred to as the greater vestibular glands

Blood–testis barrier
tight junctions between Sertoli cells that prevent bloodborne pathogens from gaining access to later stages of spermatogenesis and prevent the potential for an autoimmune reaction to haploid sperm

Body of uterus
middle section of the uterus

Broad ligament
wide ligament that supports the uterus by attaching laterally to both sides of the uterus and pelvic wall

Bulbourethral glands
(also, Cowper's glands) glands that secrete a lubricating mucus that cleans and lubricates the urethra prior to and during ejaculation

Cervix
elongate inferior end of the uterus where it connects to the vagina

Clitoris
(also, glans clitoris) nerve-rich area of the vulva that contributes to sexual sensation during intercourse

Corpus albicans
nonfunctional structure remaining in the ovarian stroma following structural and functional regression of the corpus luteum

Corpus cavernosum
either of two columns of erectile tissue in the penis that fill with blood during an erection

Corpus luteum
transformed follicle after ovulation that secretes progesterone

Corpus spongiosum
(plural = corpora cavernosa) column of erectile tissue in the penis that fills with blood during an erection and surrounds the penile urethra on the ventral portion of the penis

Ductus deferens
(also, vas deferens) duct that transports sperm from the epididymis through the spermatic cord and into the ejaculatory duct; also referred as the vas deferens

Ejaculatory duct
duct that connects the ampulla of the ductus deferens with the duct of the seminal vesicle at the prostatic urethra

Endometrium
inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses

Epididymis
(plural = epididymides) coiled tubular structure in which sperm start to mature and are stored until ejaculation

Fimbriae
fingerlike projections on the distal uterine tubes

Follicle
ovarian structure of one oocyte and surrounding granulosa (and later theca) cells

Folliculogenesis
development of ovarian follicles from primordial to tertiary under the stimulation of gonadotropins

Fundus
(of the uterus) domed portion of the uterus that is superior to the uterine tubes

Gamete
haploid reproductive cell that contributes genetic material to form an offspring

Glans penis
bulbous end of the penis that contains a large number of nerve endings

Gonadotropin-releasing hormone (GnRH)
hormone released by the hypothalamus that regulates the production of follicle-stimulating hormone and luteinizing hormone from the pituitary gland

Gonads
reproductive organs (testes and ovaries) that produce gametes and reproductive hormones

Granulosa cells
supportive cells in the ovarian follicle that produce estrogen

Hymen
membrane that covers part of the opening of the vagina

Infundibulum
(of the uterine tube) wide, distal portion of the uterine tube terminating in fimbriae

Inguinal canal
opening in abdominal wall that connects the testes to the abdominal cavity

Isthmus
narrow, medial portion of the uterine tube that joins the uterus

Labia majora
hair-covered folds of skin located behind the mons pubis

Labia minora
thin, pigmented, hairless flaps of skin located medial and deep to the labia majora

Lactiferous ducts
ducts that connect the mammary glands to the nipple and allow for the transport of milk

Lactiferous sinus
area of milk collection between alveoli and lactiferous duct

Leydig cells
cells between the seminiferous tubules of the testes that produce testosterone; a type of interstitial cell

Mammary glands
glands inside the breast that secrete milk

Menarche
first menstruation in a pubertal female

Menses
shedding of the inner portion of the endometrium out though the vagina; also referred to as menstruation

Menses phase
phase of the menstrual cycle in which the endometrial lining is shed

Menstrual cycle
approximately 28-day cycle of changes in the uterus consisting of a menses phase, a proliferative phase, and a secretory phase

Mons pubis
mound of fatty tissue located at the front of the vulva

Müllerian duct
duct system present in the embryo that will eventually form the internal female reproductive structures

Myometrium
smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood

Oocyte
cell that results from the division of the oogonium and undergoes meiosis I at the LH surge and meiosis II at fertilization to become a haploid ovum

Oogenesis
process by which oogonia divide by mitosis to primary oocytes, which undergo meiosis to produce the secondary oocyte and, upon fertilization, the ovum

Oogonia
ovarian stem cells that undergo mitosis during female fetal development to form primary oocytes

Ovarian cycle
approximately 28-day cycle of changes in the ovary consisting of a follicular phase and a luteal phase

Ovaries
female gonads that produce oocytes and sex steroid hormones (notably estrogen and progesterone)

Ovulation
release of a secondary oocyte and associated granulosa cells from an ovary

Ovum
haploid female gamete resulting from completion of meiosis II at fertilization

Penis
male organ of copulation

Perimetrium
outer epithelial layer of uterine wall

Polar body
smaller cell produced during the process of meiosis in oogenesis

Prepuce
(also, foreskin) flap of skin that forms a collar around, and thus protects and lubricates, the glans penis; also referred as the foreskin

Primary follicles
ovarian follicles with a primary oocyte and one layer of cuboidal granulosa cells

Primordial follicles
least developed ovarian follicles that consist of a single oocyte and a single layer of flat (squamous) granulosa cells

Proliferative phase
phase of the menstrual cycle in which the endometrium proliferates

Prostate gland
doughnut-shaped gland at the base of the bladder surrounding the urethra and contributing fluid to semen during ejaculation

Puberty
life stage during which a male or female adolescent becomes anatomically and physiologically capable of reproduction

Rugae
(of the vagina) folds of skin in the vagina that allow it to stretch during intercourse and childbirth

Scrotum
external pouch of skin and muscle that houses the testes

Secondary follicles
ovarian follicles with a primary oocyte and multiple layers of granulosa cells

Secondary sex characteristics
physical characteristics that are influenced by sex steroid hormones and have supporting roles in reproductive function

Secretory phase
phase of the menstrual cycle in which the endometrium secretes a nutrient-rich fluid in preparation for implantation of an embryo

Semen
ejaculatory fluid composed of sperm and secretions from the seminal vesicles, prostate, and bulbourethral glands

Seminal vesicle
gland that produces seminal fluid, which contributes to semen

Seminiferous tubules
tube structures within the testes where spermatogenesis occurs

Sertoli cells
cells that support germ cells through the process of spermatogenesis; a type of sustentacular cell

Sperm
(also, spermatozoon) male gamete

Spermatic cord
bundle of nerves and blood vessels that supplies the testes; contains ductus deferens

Spermatid
immature sperm cells produced by meiosis II of secondary spermatocytes

Spermatocyte
cell that results from the division of spermatogonium and undergoes meiosis I and meiosis II to form spermatids

Spermatogenesis
formation of new sperm, occurs in the seminiferous tubules of the testes

Spermatogonia
(singular = spermatogonium) diploid precursor cells that become sperm

Spermiogenesis
transformation of spermatids to spermatozoa during spermatogenesis

Suspensory ligaments
bands of connective tissue that suspend the breast onto the chest wall by attachment to the overlying dermis

Tertiary follicles
(also, antral follicles) ovarian follicles with a primary or secondary oocyte, multiple layers of granulosa cells, and a fully formed antrum

Testes
(singular = testis) male gonads

Theca cells
estrogen-producing cells in a maturing ovarian follicle

Uterine tubes
(also, fallopian tubes or oviducts) ducts that facilitate transport of an ovulated oocyte to the uterus

Uterus
muscular hollow organ in which a fertilized egg develops into a fetus

Vagina
tunnel-like organ that provides access to the uterus for the insertion of semen and from the uterus for the birth of a baby

Vulva
external female genitalia

Wolffian duct
duct system present in the embryo that will eventually form the internal male reproductive structures

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7.5: Chapter Review Questions

Multiple-Choice Section

- Use the end-of-chapter multiple-choice section as a regular self-check tool, not just before exams.
- Read each item carefully, think about what is really being tested (concept, definition, application, or calculation), and choose the option (A, B, C, or D) that best reflects what you have learned in this chapter.
  - After you read through the chapter, attempt all items without looking at your notes; then return to the chapter to review any you missed or felt unsure about.
  - Afterward, explain to yourself why the correct option is right and why the others are not. Finally, repeat the multiple-choice section a few days later to see what you truly remember and understand.
- Students who consistently use these prompts in this way typically perform better across the course because they turn reading into active practice

1. A 17-year-old is learning about reproduction in a health education class. The teacher explains that human reproductive cells are called gametes. What are the male gametes called?
   A. Ova
   B. Sperm
   C. Testes
   D. Testosterone

2. A 25-year-old man has low blood testosterone levels on a lab test. His physician explains that certain cells in the testes normally produce most of the body's testosterone. Leydig cells:
   A. Secrete testosterone
   B. Activate the sperm flagellum
   C. Support spermatogenesis by nourishing developing sperm
   D. Secrete seminal fluid from the prostate

3. A 16-year-old with delayed puberty is evaluated by an endocrinologist, who measures a hormone made in the hypothalamus that controls pituitary release of LH and FSH. Which hypothalamic hormone primarily regulates the male reproductive system?
   A. Luteinizing hormone (LH)
   B. Gonadotropin-releasing hormone (GnRH)
   C. Follicle-stimulating hormone (FSH)
   D. Androgens

4. A 30-year-old patient asks where sperm are stored and mature after they are first formed in the testes. What is the main function of the epididymis?
   A. Sperm maturation and storage
   B. Producing the bulk of seminal fluid
   C. Providing nitric oxide needed for erections
   D. Making sperm (spermatogenesis)

5. A biopsy from a testis shows tightly coiled tubules lined with germ cells in different stages of development and sustentacular (Sertoli) cells. Spermatogenesis takes place in the:
   A. Prostate gland
   B. Glans penis
   C. Seminiferous tubules
   D. Ejaculatory duct

6. In a comparative anatomy lab, students are asked to identify the primary sex glands in females. What are the female gonads called?
   A. Oocytes
   B. Ova

C. Oviducts
D. Ovaries

7. A medical student is reviewing human development. They learn that female germ cells divide before birth and then pause. When do the oogonia (female germ cells) undergo mitosis to increase their number?
A. Before birth
B. At puberty
C. At the beginning of each menstrual cycle
D. During fertilization

8. An ultrasound report describes a structure on the ovary that forms after ovulation and secretes progesterone. From what structure does the corpus luteum originate?
A. Uterine corpus (body of the uterus)
B. Dominant (mature) ovarian follicle
C. Fallopian (uterine) tube
D. Corpus albicans

9. In a reproductive physiology class, students trace the path of an egg and sperm. In most human pregnancies, where does fertilization of the egg by the sperm typically occur?
A. Vagina
B. Uterus
C. Uterine (fallopian) tube
D. Ovary

10. A 52-year-old woman going through menopause asks why her estrogen levels have fallen, even though her pituitary hormones (FSH and LH) are high. Which of the following best explains the fall in estrogen levels after menopause?
A. The ovaries physically degrade and disappear
B. There are few or no functioning follicles left to produce estrogen
C. The pituitary secretes a menopause-specific hormone that blocks estrogen
D. The cells of the endometrium degenerate and stop making estrogen

11. During a pelvic exam, a clinician explains the structures of the external female genitalia to a patient. The vulva includes the:
A. Lactiferous duct, rugae, and hymen
B. Lactiferous duct, endometrium, and bulbourethral glands
C. Mons pubis, endometrium, and hymen
D. Mons pubis, labia majora, and Bartholin's (greater vestibular) glands

12. A couple meets with a genetic counselor who explains how sex is determined in an embryo. What primarily controls whether an embryo will develop testes or ovaries?
A. Pituitary gland hormones
B. Hypothalamic hormones
C. Y chromosome and its genes
D. Presence or absence of estrogen in the uterus

13. A genetics lecture discusses the SRY gene, which is located on the Y chromosome. Without SRY gene expression in the embryo, the reproductive system will develop into:
A. Male reproductive structures
B. Female reproductive structures
C. No reproductive structures
D. Male reproductive structures 50 percent of the time and female reproductive structures 50 percent of the time

14. Two 12-year-olds, one assigned male at birth and one assigned female at birth, begin puberty at different ages. Their pediatrician explains that the timing of puberty can vary widely. Which of the following can influence when puberty begins?
A. Genes
B. Chronic or psychosocial stress
C. Amount of body fat and overall nutritional status
D. All of the above

15. A 28-year-old man is found to have low sperm count but normal testosterone levels. His doctor suspects a problem with the

cells that physically support and nourish developing sperm. Which cells in the seminiferous tubules support spermatogenesis by forming the blood–testis barrier and secreting growth factors?
A. Leydig cells
B. Sertoli (sustentacular) cells
C. Myoid (smooth muscle–like) cells
D. Epididymal principal cells

16. A 19-year-old person taking estrogen-containing medication asks whether their brain hormones also change. In a typical male at puberty, rising GnRH from the hypothalamus stimulates the anterior pituitary to release:
A. LH and FSH, which act on the testes
B. Prolactin and oxytocin, which act on the testes
C. Testosterone and inhibin, which act on the pituitary
D. Estrogen and progesterone, which act on the ovaries

17. A 32-year-old woman is evaluated for infertility. Ultrasound shows that follicles develop but ovulation does not occur regularly. Which hormone from the anterior pituitary normally triggers ovulation of the dominant follicle?
A. Follicle-stimulating hormone (FSH)
B. Luteinizing hormone (LH)
C. Prolactin
D. Oxytocin

18. A 30-year-old woman has a normal ovulatory cycle. After ovulation, her basal body temperature rises slightly. This increase is due primarily to which hormone secreted by the corpus luteum?
A. Estrogen
B. Progesterone
C. Inhibin
D. Relaxin

19. A 26-year-old person becomes pregnant. Early in pregnancy, the corpus luteum is maintained and continues to secrete progesterone. Which hormone produced by the early embryo and placenta maintains the corpus luteum?
A. Prolactin
B. Human chorionic gonadotropin (hCG)
C. Oxytocin
D. Gonadotropin-releasing hormone (GnRH)

20. A 14-year-old assigned female at birth has not yet started menstruating. Examination reveals very low body fat and intense athletic training. Which of the following best explains how low body fat can delay the onset of menstruation?
A. Low fat directly destroys ovarian follicles
B. Low fat decreases leptin and can reduce GnRH release
C. Low fat increases testosterone production
D. Low fat blocks pituitary sensitivity to estrogen

21. A 29-year-old nonpregnant person notices cyclical changes in the uterine lining. The phase of the menstrual (uterine) cycle that is dominated by rising estrogen and regrowth of the endometrium after menstruation is the:
A. Menstrual phase
B. Proliferative phase
C. Secretory phase
D. Ovulatory phase

22. A 35-year-old person has bleeding between periods. The clinician discusses how the ovarian and uterine cycles are coordinated. In a typical 28-day cycle, ovulation most commonly occurs around:
A. Day 1
B. Day 7
C. Day 14
D. Day 28

23. A 16-year-old transmasculine patient taking testosterone notes changes in hair growth and voice deepening. These changes are examples of:
A. Primary sex characteristics

B. Secondary sex characteristics
C. Genetic sex determination
D. Gonadal differentiation

24. A 40-year-old person undergoes removal of both ovaries due to cancer. After surgery, levels of estrogen and progesterone drop sharply. Which of the following immediate hormonal changes is most likely?
A. Decreased GnRH and decreased FSH/LH
B. Increased GnRH and increased FSH/LH
C. Increased prolactin only
D. No change in pituitary hormones

25. A couple is using a fertility awareness method for contraception, tracking cervical mucus and temperature. The partner capable of pregnancy learns that the mucus becomes thinner and more stretchy around the time of ovulation. This change in cervical mucus is primarily due to rising levels of:
A. Progesterone from the corpus luteum
B. Estrogen from the dominant follicle
C. Prolactin from the anterior pituitary
D. Oxytocin from the posterior pituitary

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7.6: Applied Thinking Self - Assessment

Challenge Yourself

- Extended response questions are assessment items that require students to construct written answers of substantial length - typically several sentences to multiple paragraphs - rather than selecting from predefined options. They represent a form of constructed response assessment designed to measure complex, higher-order thinking skills.
- First, try answering without using your notes. Then review reliable resources and revise your response if needed. Make a note of any areas where you felt unsure and revisit those topics.

Writing Guidelines

- Answer each question in your own words.
- Write 4–8 clear, complete sentences per question, organized into short paragraphs (not bullet points).
- Focus on explaining your reasoning, not just stating the answer.
- Use correct scientific vocabulary, and briefly define terms when needed.
- For questions that ask you to compare, contrast, or explain why/how:
  - Clearly state similarities or differences
  - Support your ideas with a brief explanation or example

Clinical Application: Disorders of Structure and Function

Scenario 1

A patient presents with infertility, and imaging reveals that his epididymides are extremely underdeveloped while his testes and accessory glands appear normal.

Probing Prompts

- Explain how this specific anatomical defect could impair fertility even if spermatogenesis is normal.
- Predict what you would expect to see in a semen analysis (for example, sperm count, motility, morphology) and justify your reasoning.

Scenario 2

A 13-year-old girl presents with delayed puberty: she has not developed breast tissue, has no pubic hair, and has not begun menstruating. Laboratory tests show very low estrogen, but extremely high FSH and LH.

Probing Prompts

- Use your understanding of feedback regulation to explain why her gonadotropin levels are high.
- Based on these findings, hypothesize where the primary defect lies (hypothalamus, pituitary, or ovaries) and predict what her ovarian anatomy might look like.

Scenario 3

A couple has been attempting to conceive for over a year. The female partner has ultrasound evidence of multiple medium-sized ovarian follicles that fail to progress to ovulation (anovulation), and her LH levels remain chronically elevated with no clear mid-cycle surge.

Probing Prompts

- Explain how this hormonal pattern disrupts the normal sequence of ovarian events prior to ovulation.
- Discuss how this might affect the endometrium and the likelihood of successful implantation, even if occasional ovulation occurred.

Comparative and Structural Anatomy

Scenario 1

You are comparing reproductive anatomy and function in people with testes and people with ovaries to prepare patient education materials.

Probing Prompts

- Compare the functional roles of the male and female gonads and their primary accessory ducts (epididymis and uterine tube).
- How do these structures each support gamete survival, maturation, and transport?
- Discuss how their anatomical design reflects different reproductive strategies and timing in males versus females.

Scenario 2

You are following the path of a single sperm that may eventually fertilize an oocyte during natural conception.

Probing Prompts

- Trace the journey of a single sperm cell from its origin as a spermatogonium in the testis to its potential fusion with an oocyte in the female reproductive tract, naming each anatomical structure it passes through in both the male and female.
- At three key points along this journey, describe a specific cellular or biochemical change the sperm undergoes and explain why that change is essential for successful fertilization.

Scenario 3

You are reviewing the ovarian cycle of a patient with regular, ovulatory cycles to explain how hormonal contraception works.

Probing Prompts

- Consider the ovarian events during the follicular phase of the menstrual cycle. Describe the structural changes that occur in a follicle as it progresses from primordial to primary, secondary, and mature (Graafian) stages before ovulation.
- Correlate these structural changes with changing levels of FSH, LH, and estrogen, and explain how these hormones interact to produce a single dominant follicle in most cycles.

Endocrine Regulation and Feedback in Reproduction

Scenario 1

A teenage male has normal hypothalamic GnRH secretion but a mutation that prevents his anterior pituitary from producing FSH, while LH secretion is intact.

Probing Prompts

- Predict the effects on his testicular function, including testosterone production, spermatogenesis, and testis size.
- Explain the endocrine feedback pattern you would expect to observe, including testosterone and inhibin levels and pituitary hormones.

Scenario 2

A woman has a pituitary tumor that selectively destroys the cells that produce LH, but FSH production is preserved.

Probing Prompts

- Describe how this would alter follicular development, ovulation, and corpus luteum formation.
- Predict the consequences for her estrogen and progesterone levels and her menstrual cycle pattern, and explain your reasoning.

Scenario 3

A reproductive endocrinologist is treating a patient with infertility by administering exogenous FSH early in the follicular phase and then a single large dose of LH mid-cycle.

Probing Prompts

- Explain the physiological rationale behind this treatment in terms of normal ovarian events prior to ovulation.
- Predict how this regimen might change the number of oocytes released compared with a natural cycle, and discuss potential risks.

Scenario 4

You are counseling families about what to expect during puberty in adolescents of different sexes.

Probing Prompts

- During puberty, both males and females experience a “reawakening” of the hypothalamic–pituitary–gonadal axis. Describe the changes that occur in hypothalamic GnRH secretion and pituitary responsiveness leading up to puberty.
- Compare how rising gonadal steroid hormone levels drive the development of primary and secondary sex characteristics in males versus females, linking specific hormones to specific anatomical and physiological changes.

Developmental and Embryologic Perspectives

Scenario 1

You are studying prenatal development of the internal reproductive ducts in an XY fetus with a known mutation affecting anti-Müllerian hormone (AMH).

Probing Prompts

- Early in prenatal development, the internal reproductive ducts are “bipotential.” Explain how the presence or absence of testes and their hormones (testosterone and anti-Müllerian hormone) directs the development of male versus female internal duct systems.
- Predict the internal reproductive anatomy of an XY fetus that produces testosterone normally but lacks functional anti-Müllerian hormone, and justify your prediction based on embryologic principles.

Scenario 2

During assisted reproductive techniques, sperm are sometimes placed closer to the ovary rather than traversing the entire female reproductive tract.

Probing Prompts

- Sperm reaching the ampulla of the uterine tube must undergo capacitation before they can successfully fertilize an oocyte. Describe what capacitation is and where it normally occurs.
- Explain why sperm released directly into the peritoneal cavity near the ovary might have different fertilization success than sperm that have traveled through the full female reproductive tract.

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7.7: Alternate Text Descriptions

Figure 7.1: Human Ovary

This is an image of a histological section of a human ovary (Follicle Development Stages):

- Label 1: Primary follicle
  - Contains a growing oocyte
  - Surrounded by one to a few layers of cuboidal granulosa cells
- Label 2: Early secondary follicle
  - Shows multiple layers of granulosa cells
  - Small fluid-filled spaces begin forming within the follicle
- Label 3: Tertiary (Graafian) follicle
  - Characterized by a large fluid-filled antrum
  - Oocyte sits on a mound of cells called the cumulus oophorus
  - Has a well-defined thecal layer surrounding the follicle
- Label 4: Primordial follicle
  - Located in the ovarian cortex
  - Contains a small oocyte
  - Surrounded by a single layer of flattened follicular cells

Figure 7.1.1: Testicular Reproductive System

This image is a three-part illustration showing the location of the male reproductive system, the appearance of uncircumcised and circumcised penises, and a lateral view of the internal reproductive structures.

Left Panel: Body Location

A side view of the body identifies the location of the male reproductive organs within the pelvic region. A box highlights the area enlarged in the remaining panels.

Panel (a): Uncircumcised Penis

The penis projects anteriorly from the body, while the scrotum hangs inferior and posterior to it.

The prepuce (foreskin) extends over and covers the glans penis at the tip of the penis. The scrotum is shown as a sac of skin located beneath the penis that contains the testes.

Panel (b): Circumcised Penis

The penis and scrotum are shown in the same position as in panel (a). In this view, the foreskin has been removed, exposing the glans penis, which forms the enlarged tip of the penis. The corona is the raised ridge at the base of the glans where it meets the shaft of the penis.

Panel (c): Male Reproductive System, Lateral View

A sagittal section shows the internal and external reproductive organs and their relationship to the urinary system.

The urinary bladder occupies the superior portion of the pelvis. Directly inferior to the bladder is the prostate gland, which surrounds the upper portion of the urethra.

Posterior to the bladder is the seminal vesicle, which contributes fluid to semen. Adjacent to the seminal vesicle is the enlarged

ampulla of the ductus deferens, which joins the duct of the seminal vesicle to form the ejaculatory duct. The ejaculatory duct passes through the prostate gland and empties into the urethra.

The ductus (vas) deferens begins at the epididymis, ascends from the scrotum into the pelvic cavity, passes superior to the testis, curves around the posterior aspect of the bladder, and enlarges to form the ampulla before joining the ejaculatory duct.

Within the scrotum, each testis is suspended below the pelvis. The epididymis lies along the posterior and superior surface of the testis and serves as the connection between the testis and the ductus deferens. Both structures are enclosed within the scrotum.

The urethra extends from the urinary bladder to the exterior and is divided into three regions:

- Prostatic urethra: passes through the prostate gland immediately below the bladder
- Membranous urethra: passes through the deep muscles of the perineum inferior to the prostate
- Spongy urethra: extends through the length of the penis within the corpus spongiosum and terminates at the external urethral opening near the tip of the penis

The penis contains two dorsal columns of erectile tissue called the corpora cavernosa, located along the superior aspect of the shaft. Ventral to these structures is the corpus spongiosum, which surrounds the spongy urethra and expands distally to form the glans penis.

The suspensory ligament of the penis attaches the penis to the anterior pelvic wall near the pubic symphysis, the cartilaginous joint connecting the left and right pubic bones.

Inferior to the prostate and surrounding the membranous urethra are the deep muscles of the perineum. The bulbourethral glands are located within this region and empty their secretions into the urethra. Posteriorly, the muscles of the perineum surrounding the anus support the pelvic floor.

The figure illustrates the anatomical organization of the male reproductive system. Sperm are produced in the testes, mature in the epididymis, travel through the ductus deferens, and enter the ejaculatory duct after mixing with secretions from the seminal vesicles. Secretions from the prostate and bulbourethral glands are added as semen passes through the urethra. The figure also demonstrates that the male urethra serves both the urinary and reproductive systems, extending from the urinary bladder to the external urethral opening through the penis.

Figure 7.1.2: Scrotum and Testes: External, Muscular, and Deep Anatomy

This three-panel horizontal diagram illustrates the progressive anatomical layers of the human scrotum and testes, moving from the external surface on the left, through the superficial muscle layers in the middle, to the deep internal tissues and spermatic cords on the right.

Panel 1: External View of the Scrotum

An external anterior view shows the superficial surface of the scrotal sac.

- Raphe: A raised vertical seam runs down the center of the scrotum and divides the external pouch into left and right halves.

Panel 2: Muscle Layer

An anterior cross-sectional view shows the superficial muscular structures directly beneath the skin.

- Scrotal septum: A vertical internal wall extends inward from the external raphe and separates the left and right internal chambers.
- Dartos muscles: A thin layer of smooth muscle lies within the subcutaneous tissue along the outer wall of the scrotal sac.
- Cremaster muscles: Bands of skeletal muscle surround the internal contents of each side.

Panel 3: Deep Tissues

A deeper anterior dissection shows the reproductive organs, vascular supply, and supporting structures.

- Testis: An oval organ rests at the base of each scrotal chamber.
- Epididymis: A highly coiled structure lies along the superior and posterior side of each testis.
- Spermatic cord: A vertical bundle extends upward from each testis into the pelvic cavity.

A bracket identifies the structures contained within the spermatic cord:

- Plexus of testicular veins: A network of veins surrounding the central duct
- Ductus deferens (vas deferens): A thick tube that transports sperm
- Testicular artery: An artery running alongside the ductus deferens
- Autonomic nerve: A nerve fiber running parallel to the blood vessels
- Lymphatic vessel: A vessel located along the outer portion of the cord

The figure illustrates the layered organization of the scrotum and testes. The outer surface is divided by the raphe, while the internal scrotal septum separates the two chambers. The dartos and cremaster muscles contribute to support and temperature regulation. The deep dissection shows the testes, epididymides, and spermatic cords, along with the blood vessels, nerves, lymphatic vessels, and ductus deferens that support sperm transport and testicular function.

Figure 7.1.3: Anatomy of the Testis and Epididymis

This figure shows a cross-sectional view of the testis and the pathway sperm follow as they are produced, collected, matured, and transported out of the testis.

The testis occupies the center of the image and is enclosed within the scrotum, a pouch located outside the body. Surrounding the testis are two protective layers. The outer layer is the tunica vaginalis, and the deeper, thicker tunica albuginea forms a strong fibrous capsule around the testis.

Extensions of the tunica albuginea project inward as septa, dividing the testis into multiple compartments called lobules. Within each lobule are tightly coiled seminiferous tubules, where sperm are produced. Their coiled arrangement increases the surface area available for spermatogenesis.

The seminiferous tubules converge into straight tubules, which carry newly formed sperm toward the center of the testis. The straight tubules empty into the rete testis, a network of interconnected channels near the posterior region of the testis. The rete testis collects sperm from many seminiferous tubules and directs them toward the next stage of transport.

From the rete testis, sperm enter several efferent ductules, which pass out of the testis and into the head of the epididymis. The epididymis lies along the posterior and superior surface of the testis and is divided into a head, body, and tail. As sperm travel through the highly coiled duct of the epididymis, they mature and acquire the ability to move and fertilize an egg.

At the inferior end of the epididymis, the tail of the epididymis narrows and continues as the ductus (vas) deferens. The ductus deferens extends upward from the scrotum into the spermatic cord, which contains the vessels, nerves, and ducts that connect the testis to the body. The spermatic cord ascends through the inguinal canal, shown at the top of the figure.

Surrounding the spermatic cord and testis is the cremaster muscle. This muscle raises or lowers the testes to help regulate temperature. Maintaining the testes slightly cooler than core body temperature is important for normal sperm production.

The figure demonstrates the organization of the testis and the pathway of sperm transport. Sperm are produced within the seminiferous tubules, collected by the straight tubules and rete testis, carried through the efferent ductules into the epididymis for maturation, and then transported into the ductus deferens. The surrounding tunics, septa, scrotum, spermatic cord, and cremaster muscle provide protection, structural support, and temperature regulation necessary for normal reproductive function.

Figure 7.1.4: Spermatogenesis and Histology of a Seminiferous Tubule

This is a multi-panel figure that illustrates spermatogenesis and the structure of a seminiferous tubule.

a. Spermatogenesis (left panel) - This schematic shows the stages of sperm development with labeled cell types and chromosome numbers. Arrows indicate progression downward through each stage, showing reduction from diploid to haploid cells.

- At the top, a cell labeled Spermatogonium (2n) undergoes mitosis to produce more diploid cells.
- A cell differentiates into a Primary spermatocyte (2n).
- The primary spermatocyte undergoes Meiosis I to form two Secondary spermatocytes (1n).
- Each secondary spermatocyte undergoes Meiosis II, producing four Spermatids (1n).
- Spermatids then undergo Spermiogenesis, developing into mature sperm cells labeled Spermatozoa (sperm), shown with heads and long tails.

b. Cross section of a seminiferous tubule (right panel) - A microscope image shows a circular seminiferous tubule with a central open space labeled Lumen.
   - Cells within the tubule:
     - Near the outer edge are Spermatogonia
     - Moving inward are Primary spermatocytes
     - Closer to the lumen are Early spermatids
     - Supporting cells labeled Sertoli (sustentacular) cells extend across the thickness of the tubule
   - Outer and surrounding structures
     - The area outside the tubule is labeled Interstitial tissue
     - Within this region are Leydig (interstitial) cells, which produce hormones
     - Blood vessels labeled Arteriole and Peritubular capillary
     - A Lymphatic capillary is also identified

Figure 7.1.5: Structure of the Sperm Cells

This image shows the structure of a sperm cell, divided into labeled regions: head, mid-piece, and tail.

1. Head - The oval-shaped head is outlined and contains internal components:
   - The outer layer is labeled Plasma membrane
   - Beneath it is the Nucleus, which occupies most of the head and contains genetic material
   - At the front tip is the Acrosome, a cap-like structure that contains enzymes used to penetrate the oocyte during fertilization
2. Mid-piece - Just behind the head is a narrow segment labeled Mid-piece:
   - This region contains a Centriole, which helps organize microtubules
   - Surrounding the central core are many Mitochondria, arranged in a spiral pattern
   - The mitochondria provide energy required for movement
3. Tail - The long, whip-like Tail extends from the mid-piece:
   - The main structure is labeled Flagellum, which propels the sperm forward
   - Within the tail is an internal support structure labeled Axial filament
   - The tail tapers toward the end
4. End piece - The farthest portion is labeled End piece, representing the thin terminal segment of the tail

Figure 7.1.6: Cross-Sectional Anatomy of the Penis

This image compares the structure and blood flow of the penis in flaccid and erect conditions, using both lateral (side) and transverse (cross-section) views.

1. Top left: Flaccid – Lateral view. The penis is shown in a relaxed (flaccid) state. The tissue appears relatively less filled with blood, and the structure is soft and curved downward. Internal tissues are labeled:
   - Corpora cavernosa, two columns of erectile tissue
   - Corpus spongiosum, surrounding the urethra
   - Spongy urethra, running through the length of the penis
   - Prepuce (foreskin) covering the distal end
2. Top right: Flaccid – Transverse view. A cross-section of the penis shows circular arrangement of tissues. The venules are open, indicating normal blood drainage in the flaccid state.
   - Two large areas labeled Corpora cavernosa
   - A smaller area labeled Corpus spongiosum containing the Spongy urethra

3. Blood vessels include:
    - Deep dorsal vein
    - Penile venules (uncompressed)
    - Cavernosal arteries
4. Bottom left: Erect – Lateral view. The penis is shown in the erect state, with labeled steps. The corpora cavernosa are visibly expanded, producing rigidity.
    - “Cavernosal arteries dilate, engorging corporal tissue with blood.”
    - “Engorging causes corporal tissue to swell, erecting the penis.”
5. Bottom right: Erect – Transverse view. The cross-section shows tissues filled with blood:
    - “Engorged corporal tissue compresses penile veins and venules, maintaining erection.”
    - Structures include:
        - Enlarged Corpora cavernosa
        - Corpus spongiosum still surrounding the urethra
        - Cavernosal arteries delivering blood
        - Compressed Penile veins and venules, reducing blood outflow

Figure 7.1.7: Regulation of Testosterone Production

This image illustrates hormonal regulation of male reproductive function through a feedback loop involving the hypothalamus, pituitary gland, and testes. The diagram is organized into three numbered steps.

1. Step 1: Hypothalamus and pituitary signaling - At the top, the Hypothalamus releases a hormone labeled GnRH (gonadotropin-releasing hormone). A label states:“Hypothalamus releases GnRH. GnRH stimulates the anterior pituitary to release FSH and LH.” These are shown with colored arrows labeled “FSH release” and “LH release.” Arrows indicate GnRH moving from the hypothalamus to the anterior pituitary, which then releases:
    - FSH (follicle-stimulating hormone)
    - LH (luteinizing hormone)
2. Step 2: Testicular response - FSH and LH act on the testes. A label states “LH stimulates the Leydig cells to release testosterone. FSH stimulates the Sertoli cells to release ABP. ABP binds to testosterone, keeping the latter at a high concentration.”
    - LH targets Leydig (interstitial) cells, located in the interstitial space between seminiferous tubules, causing testosterone release
    - FSH targets Sertoli cells within the seminiferous tubule, leading to release of androgen-binding protein (ABP)
    - Arrows connect:
        - Leydig cells → Testosterone release
        - Sertoli cells → Androgen-binding protein (ABP) release
3. Step 3: Negative feedback - A label on the left states “Inhibin negatively feeds back to anterior pituitary, inhibiting further release of FSH. Testosterone negatively feeds back to the hypothalamus and pituitary, inhibiting further release of GnRH, FSH, and LH.” Negative feedback is indicated by arrows marked with a minus sign.
    - Inhibin, released from Sertoli cells, inhibits FSH release from the anterior pituitary
    - Testosterone feeds back to both the hypothalamus and pituitary, reducing production of:
        - GnRH
        - FSH
        - LH

Figure 7.2.1: Human Female Reproductive System: Lateral and Anterior Views

This two-panel illustration presents the human female reproductive system from two anatomical perspectives: a lateral (sagittal/profile) view in the top panel and an anterior (front) view in the bottom panel.

Panel (a): Human Female Reproductive System, Lateral View

A cross-sectional profile view of the female pelvis shows the reproductive organs positioned between the urinary bladder anteriorly and the rectum posteriorly.

- Uterus: A pear-shaped organ located centrally in the pelvic cavity and tilted forward over the bladder
- Ovary: A small oval gland located posterior and slightly inferior to the main body of the uterus
- Fornix of uterus: The recessed upper portion of the vaginal canal surrounding the cervix
- Cervix: The narrow inferior portion of the uterus projecting into the upper vagina
- Vagina: A muscular canal extending downward from the cervix to the exterior, positioned between the urethra and rectum
- Rectum: The terminal portion of the large intestine, located posterior to the uterus and vagina
- Anus: The external opening of the rectum
- Bladder: A hollow urinary organ located anterior to the uterus and vagina
- Urethra: A short channel extending from the bladder to the exterior, located anterior to the vagina
- Pubic symphysis: The midline cartilaginous joint connecting the pubic bones, located anterior to the bladder
- Mons pubis: A rounded pad of fatty tissue overlying the pubic symphysis
- Clitoris: A small erectile structure located at the anterior junction of the labia minora
- Labia minora: The smaller inner folds surrounding the external openings
- Labia majora: The larger outer folds enclosing the vulvar structures

Panel (b): Human Female Reproductive System, Anterior View

A front-facing view shows the bilateral symmetry and supporting structures of the internal and external reproductive organs.

- Uterus: The main muscular organ centered in the pelvis
- Uterine tubes (oviducts): A pair of ducts extending laterally from the upper corners of the uterus
- Fimbriae: Finger-like projections at the lateral ends of the uterine tubes near each ovary
- Ovaries: Paired oval glands located on either side of the uterus
- Ovarian ligaments: Fibrous bands anchoring each ovary to the uterus
- Broad ligament: A wide fold of peritoneal membrane extending from the uterus to the pelvic walls and supporting the uterine tubes, ovaries, and ovarian ligaments
- Cervix: The inferior portion of the uterus narrowing into the vaginal canal
- Vagina: The muscular tube extending downward from the cervix
- Labia minora: Inner folds bordering the vaginal opening
- Labia majora: Outer folds surrounding the labia minora

The figure demonstrates the organization of the female reproductive system from two anatomical perspectives. The lateral view emphasizes spatial relationships among the reproductive, urinary, and digestive organs within the pelvis. The anterior view highlights the paired ovaries, uterine tubes, and supporting ligaments, showing the bilateral arrangement of the internal reproductive organs and their continuity with the cervix, vagina, and external genital structures.

Figure 7.2.2: Vulva: External and Internal Anatomy

This two-panel figure illustrates the anatomy of the female vulva, showing an external anterior view on the left and an internal anterolateral view on the right.

Left Panel: Vulva, External Anterior View

A surface view from the front shows the external structures of the vulva. The tissue layers are parted to reveal structures within the pudendal cleft.

- Prepuce: A fold of skin forming a hood over the clitoris
- Glans clitoris: The external tip of the clitoris located beneath the prepuce
- Labia minora: Thin inner folds extending downward on either side of the midline
- Labia majora: Thicker outer folds located lateral to the labia minora
- Urethral opening: A small opening located inferior to the glans clitoris and superior to the vaginal opening

- Vaginal opening: The larger opening leading into the vaginal canal
- Anus: The external opening of the digestive tract, located inferior and separate from the vulvar structures

Right Panel: Vulva, Internal Anterolateral View

A deeper dissection shows the internal erectile tissues, glands, and ducts that support the external anatomy of the vulva.

- Glans clitoris and prepuce: Located at the superior end and connected to deeper erectile structures
- Corpus cavernosum: Paired erectile bodies extending downward and laterally from the clitoris
- Bulbs of the vestibule: Paired elongated masses of erectile tissue located on either side of the vaginal opening
- Labia minora: Shown in cross-section bordering the internal structures
- Urethral opening: The internal opening of the urinary passage, located between the vestibular bulbs
- Vaginal opening: The central opening bordered by the bulbs of the vestibule
- Opening of the right Bartholin's gland: A small duct opening on the lower right side of the vaginal opening
- Bartholin's glands (greater vestibular glands): Paired glands located posteriorly near the base of the vestibular bulbs

The figure compares the external and internal anatomy of the vulva. The external view identifies the visible structures of the vulva, including the labia, clitoral region, urethral opening, and vaginal opening. The internal view shows the deeper erectile tissues and glands that support sexual function, lubrication, and the structural organization of the external genital region.

Figure 7.2.3: Oogenesis and Oocyte Development

This image illustrates oogenesis (egg development) and highlights key stages of meiosis, including when the process pauses and resumes.

1. Top section: Early development (before birth) - At the top, a cell labeled Oogonium (2n) undergoes mitosis, producing additional diploid cells. One cell develops into a Primary oocyte (2n). A label indicates “Meiosis I begins.” Another label states: “Meiosis arrests in prophase I.” This indicates that primary oocytes begin meiosis before birth but remain paused. A horizontal line divides the diagram into two time periods:
    - Before birth (above the line)
    - After puberty (below the line)
2. Middle section: After puberty - Below the line labeled After puberty, a label indicates: “Meiosis I resumes.” The polar body may divide further into additional small cells labeled Second polar bodies (n). The primary oocyte completes Meiosis I, producing:
    - One Secondary oocyte (n)
    - One First polar body (n)
3. Inset box: Fertilization-dependent completion - A boxed section highlights key stages related to fertilization:
    - A label states: “Oocyte meiosis arrests at metaphase II.” This shows the secondary oocyte pauses again before fertilization.
    - Another label states: “Oocyte meiosis completes immediately after sperm penetrates the oocyte.”
    - After sperm entry:
        - The secondary oocyte completes Meiosis II
        - A Mature ovum (n) is formed
        - Additional polar bodies (n) are produced

Figure 7.2.4: Folliculogenesis

This image is a multi-panel figure illustrating (a) the stages of folliculogenesis in the ovary and (b) a histological image of a secondary follicle.

a. Stages of Folliculogenesis Six numbered stages are shown in sequence with arrows indicating progression.
    - Stage 1: Primordial follicle - A small structure contains an oocyte surrounded by cells labeled ovary cortex cells and granulosa cells. The oocyte nucleus is labeled within the center.
    - Stage 2: Primary follicle - The oocyte increases in size and becomes surrounded by multiple layers of granulosa cells. A new layer labeled zona pellucida appears around the oocyte. The oocyte nucleus remains visible.
    - Stage 3: Secondary follicle - The follicle grows larger. Labels include:

        - Granulosa cells surrounding the oocyte
        - Theca cells forming an outer layer
        - Zona pellucida around the oocyte
        - Oocyte and oocyte nucleus
    - Stage 4: Tertiary follicle - A fluid-filled space labeled Antrum appears within the follicle. Additional labels include:
        - Granulosa cells
        - Theca cells
        - Cortex
    - The oocyte, now positioned to one side of the follicle
    - Stage 5: Ovulating follicle - The follicle ruptures at the surface of the ovary. Labels show:
        - Oocyte leaving the follicle
        - Granulosa cells surrounding it
        - A label reading “Ruptured follicle”
    - Stage 6: Corpus luteum - After ovulation, the follicle transforms into the corpus luteum within the ovary. It appears as a folded, glandular structure and continues to function hormonally.

b. Secondary Follicle (microscopic image) - A grayscale histology image shows a cross-section of a follicle with labeled structures:
    - Oocyte at the center, with labeled Nucleus of oocyte and Nucleolus
    - Surrounding layer of Zona pellucida
    - Cells immediately around the oocyte labeled Corona radiata
    - Larger surrounding layers labeled Granulosa cells
    - Outer layer labeled Theca cells
    - A developing space labeled Developing antrum
    - Surrounding tissue labeled Ovarian stroma
    - A nearby vessel labeled Perifollicular capillary

Figure 7.2.5: Hormonal Regulation of the Ovarian Cycle

This image multi-panel diagram shows hormonal regulation of the ovarian cycle, divided into three phases: Follicular phase, Ovulation, and Luteal phase. The diagram illustrates interactions among the hypothalamus, anterior pituitary, ovaries, and uterus, along with positive and negative feedback loops.

1. Follicular Phase - At the top, the Hypothalamus releases GnRH (gonadotropin-releasing hormone), which stimulates the Anterior pituitary. The pituitary releases FSH (follicle-stimulating hormone) and LH (luteinizing hormone).
    - Arrows show FSH and LH acting on the Ovaries, specifically on Follicles.
    - A label states: “Pituitary hormone effect: LH and FSH stimulate several follicles to grow.”
    - The developing follicles produce estradiol, which has two effects:
        - Negative feedback (shown with a minus sign) on the hypothalamus and pituitary, inhibiting GnRH, FSH, and LH production
        - Stimulation of the Uterus, causing the endometrium to thicken
2. Ovulation - The second panel shows a shift to positive feedback. Estradiol levels increase and now stimulate (shown with a plus sign) the Hypothalamus and the Anterior pituitary. This leads to increased production of GnRH, FSH and LH. A label states: “LH surge triggers ovulation.” The arrows show continued signaling from pituitary to ovaries, leading to the release of an oocyte from a mature follicle.
3. Luteal Phase - After ovulation, the follicle transforms into the Corpus luteum in the Ovaries. The corpus luteum produces progesterone. A label states: “Pituitary hormone effect: LH stimulates formation of a corpus luteum from follicular tissue left behind after ovulation.” Progesterone has the following effects:
    1. Maintains the endometrium of the uterus
    2. Provides negative feedback (minus signs) to the hypothalamus and pituitary, reducing GnRH, FSH and LH
    3. Another label explains: If the corpus luteum degenerates, progesterone declines, leading to shedding of the uterine lining

Figure 7.2.6: Female Reproductive Anatomy and Histology of the Ovary and Uterus

This image is a multi-panel figure showing the anatomy of the female reproductive system together with microscopic images of ovarian and uterine tissues.

Central Panel: Female Reproductive Anatomy

The central illustration shows the uterus, uterine tubes, ovaries, supporting ligaments, and associated blood vessels.

The uterus occupies the center of the figure. The rounded superior portion is the fundus. Inferior to the fundus, the uterus narrows at the uterine isthmus, which forms the transition between the body of the uterus and the cervix. The cervix projects into the upper portion of the vagina, which extends inferiorly toward the exterior.

The wall of the uterus is shown in three layers:

- Endometrium: the inner lining of the uterus
- Myometrium: the thick smooth-muscle layer surrounding the endometrium
- Perimetrium: the outer covering of the uterus

Extending laterally from each side of the uterus is a uterine tube (oviduct). Each tube contains three labeled regions:

- Isthmus: the narrow portion nearest the uterus
- Ampulla: the wider central portion of the tube
- Infundibulum: the funnel-shaped distal end nearest the ovary

At the distal end of the infundibulum are finger-like projections called fimbriae, which extend toward the ovary.

Each ovary is positioned lateral to the uterus near the fimbriae. The ovary is attached to the uterus by the ovarian ligament. The suspensory ligament extends from the ovary toward the lateral pelvic wall and contains the ovarian artery and vein.

The broad ligament is shown as a sheet-like fold extending from the uterus toward the sides of the pelvic cavity, helping support the uterus, uterine tubes, and ovaries.

The blood supply of the reproductive tract is illustrated with the uterine artery and vein running alongside the uterus and the vaginal artery supplying the vagina.

Left Panel: Ovary Histology

The left micrograph shows a section of the ovary.

- Tunica albuginea: a connective tissue layer beneath the ovarian surface
- Ovarian cortex: the region deep to the tunica albuginea that contains developing ovarian follicles
- Edge of a follicle: a labeled portion showing the location of a follicle within the ovarian cortex

Right Panel: Uterine Histology

The right micrograph shows a section of the uterine wall.

- Endometrium: the inner mucosal lining of the uterus
- Myometrium: the thick smooth-muscle layer surrounding the endometrium
- Perimetrium: the outermost layer covering the uterus

The figure demonstrates the anatomical relationship among the ovaries, uterine tubes, uterus, cervix, and vagina. The ovaries produce oocytes and hormones. The fimbriae and uterine tubes provide a pathway for transport of the oocyte toward the uterus. The endometrium serves as the site of implantation and support for a developing embryo, while the myometrium provides the muscular contractions necessary for menstruation and childbirth. The accompanying histological images show the tissue

organization of both the ovary and the uterine wall.

Figure 7.2.7: Hormone Levels in Ovarian and Menstrual Cycles

This image is a multi panel diagram that shows the relationship between follicle development, ovarian cycle phases, uterine cycle phases, and hormone levels across a 28-day menstrual cycle.

1. Top panel: Follicle development and selection (Days 1–7) - At the top, an arrow labeled “Follicular phase Days 1–7” runs from left to right. Three sequences of follicle development are shown:
    - Primordial follicles → Primary follicles → Secondary follicles. Some follicles undergo Atresia (degeneration), while one pathway shows Selection of a dominant follicle. This leads to a single, selected tertiary follicle that will continue development. A label states:
        - “Constant development of early-stage follicles (2 months)”
        - “Selection of one dominant secondary follicle begins each new menstrual cycle”
2. Second panel: Ovarian cycle phases - A timeline labeled “Day of menstrual cycle” runs from 0 to 28 days.
    a. Phases include:
        - Follicular phase (days 0–14)
        - Ovulation (around day 14)
        - Luteal phase (days 14–28)
    b. Structures shown along the timeline:
        - Selected tertiary follicle (before ovulation)
        - Ovulation event at midcycle
        - Corpus luteum (after ovulation)
        - Corpus albicans and Degrading corpus toward the end of the cycle
3. Third panel: Uterine cycle phases
    a. A second timeline labeled “Uterine cycle phases” shows:
        - Menses (Menstruation) at the beginning (days 0–5)
        - Proliferative phase (approximately days 5–14)
        - Secretory phase (approximately days 14–28)
    b. The endometrium (uterine lining) is shown:
        - Shedding during menstruation
        - Thickening during the proliferative phase
        - Becoming more glandular and vascular during the secretory phase
4. Fourth panel: Pituitary hormone levels - Both hormones are plotted over days 0–28.
    a. A graph labeled “Pituitary hormone levels” shows:
        - FSH (follicle-stimulating hormone)
        - LH (luteinizing hormone)
    b. Key pattern:
        - LH shows a sharp surge at about day 14 (ovulation)
        - FSH shows a smaller increase at midcycle
5. Fifth panel: Ovarian hormone levels
    a. A second graph labeled “Ovarian hormone levels” shows:
        - Estrogen
        - Progesterone
    b. Patterns include:
        - Estrogen rises during the follicular phase and peaks just before ovulation
        - Progesterone rises after ovulation during the luteal phase and then declines before menstruation

Figure 7.2.8: HPV, p53, and Regulation of the Cell Cycle in Cervical Cells

compares normal cell-cycle regulation with the effects of human papillomavirus (HPV) on cervical cells. The figure includes a cell-cycle diagram on the left and two numbered pathways on the right labeled HPV not present and HPV present.

Cell Cycle Overview

The left side of the figure shows a circular cell-cycle diagram divided into four phases:

- G1 phase: cell growth
- S phase: DNA synthesis
- G2 phase: cell growth
- M and C phases: mitosis and cytokinesis

Arrows show progression through the cycle, ending with the formation of two daughter cells.

Three checkpoints are identified:

- G1 checkpoint
- G2 checkpoint
- M checkpoint

A large arrow emphasizes progression from the G2 phase into mitosis.

HPV Not Present

Step 1

During the G2 checkpoint, a functional p53 protein detects a DNA mutation.

The figure shows a cervical cell containing replicating DNA with a labeled mutation. The p53 protein is shown interacting with the mutated DNA.

Step 2

Cervical cells with mutated DNA do not divide.

The figure shows a dividing cervical cell marked with a red X, indicating that cell division is prevented.

Step 3

The cervix remains healthy.

The figure shows a normal cervix with no visible abnormal growth.

HPV Present

Step 1

The p53 protein is deactivated by an inhibitor produced by HPV.

The figure shows HPV within a cervical cell producing a substance that blocks normal p53 activity.

Step 2

With p53 deactivated, cervical cells with mutated DNA continue to divide.

The figure shows multiple daughter cells being produced from a cell containing mutated DNA.

Step 3

Mutated cervical cells grow uncontrollably into a tumor.

The figure shows a cervix with a visible tumor arising from abnormal cell growth.

The figure demonstrates the importance of p53 as a cell-cycle checkpoint protein. In the absence of HPV, p53 detects DNA damage during the G2 checkpoint and prevents mutated cervical cells from dividing, helping maintain healthy tissue. When HPV is present, viral activity disables p53, allowing cervical cells with DNA mutations to continue dividing. As mutated cells accumulate, uncontrolled growth can occur, leading to the formation of a cervical tumor.

Figure 7.2.9: Mammary Gland: Superficial and Internal Anatomy

This two-panel illustration shows the superficial and internal anatomy of the human mammary gland. The left panel presents a split anterior (front) view, and the right panel presents a sagittal lateral (side) cross-section.

Left Panel: Front View

A circular front-facing diagram is divided vertically. The left half shows the external surface of the breast, and the right half shows a deeper anterior dissection of the internal glandular structures.

- Areola: A circular area of darker pigmented skin at the center of the breast
- Nipple: A projection located at the center of the areola
- Areolar glands: Small raised glands on the surface of the areola
- Fat tissue: Adipose tissue beneath the skin and between the glandular structures
- Lobules: Multiple glandular subdivisions arranged around the center of the breast
- Alveoli: Branched milk-producing structures located within each lobule
- Lactiferous ducts: Narrow ducts extending from the lobules toward the nipple
- Suspensory ligaments: Fibrous bands that support and anchor the breast tissue

Right Panel: Side View

A sagittal cross-section shows the internal arrangement of the mammary gland and the pathway of milk flow from the glandular tissue to the nipple.

- Fat tissue: Adipose tissue along the outer borders of the breast
- Alveoli: Clusters of milk-secreting glands within the deeper breast tissue
- Lobule: A structural unit containing the alveoli
- Lactiferous ducts: Ducts that collect milk from the alveoli and carry it toward the nipple
- Lactiferous sinuses: Expanded portions of the ducts near the base of the nipple
- Milk flow: An arrow indicates milk moving outward through the nipple during lactation

The figure demonstrates the structural organization of the mammary gland. Lobules contain alveoli, which produce milk. Milk travels from the alveoli into the lactiferous ducts, collects in the lactiferous sinuses near the nipple, and then exits through the nipple during lactation. Fat tissue and suspensory ligaments provide shape, cushioning, and structural support for the breast.

Figure 7.3.1: Hormonal Regulation of Puberty

This image illustrates the hormonal regulation of puberty through the hypothalamus–pituitary–gonadal axis and its effects on male and female reproductive systems.

1. Top section: Hormone initiation - At the top center, the Hypothalamus is shown releasing GnRH (gonadotropin-releasing hormone). A labeled step states: 1. “Beginning at approximately age 8, the hypothalamus increases its production of gonadotropin-releasing hormone (GnRH).” Arrows show GnRH moving downward toward the anterior pituitary.

2. Middle section: Pituitary response - A second labeled step states: 2. “GnRH triggers the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH).” Arrows labeled “LH and FSH release” show these hormones traveling from the pituitary to two target organs:
    - Testis (left)
    - Ovary (right)
3. Step 3: Gonadal hormone production - A third labeled step states: 3. “LH and FSH trigger testosterone production in the testes and estrogen production in the ovaries.” Arrows labeled “Testosterone release” and “Estrogen release” extend downward.
    - On the left, the testis releases Testosterone
    - On the right, the ovary releases Estrogen
4. Step 4: Effects of sex hormones - A labeled step states: 4. “Effects of sex hormone release:”
    a. Male outcomes
        - Spermatogenesis begins
        - Male secondary sex characteristics develop, including:
            - Penis and scrotum growth
            - Facial hair growth
            - Larynx elongation (voice lowers)
            - Shoulders broaden
            - Body, armpit, and pubic hair grow
            - Muscle mass increases
    b. Female outcomes
        - Folliculogenesis begins
        - Female secondary sex characteristics develop, including:
            - Breast development and maturation
            - Hip widening
            - Pubic hair growth
5. Step 5: Feedback regulation - A labeled step states: 5. “Before puberty, the hypothalamus and pituitary are very sensitive to negative feedback signals from testosterone and estrogen. During puberty, this sensitivity decreases.” This decreased sensitivity allows increased hormone production, promoting puberty and secondary sex characteristic development. Arrows marked with a minus sign indicate negative feedback from:
    - Testosterone (left pathway)
    - Estrogen (right pathway)

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8: DEVELOPMENT AND INHERITANCE

Chapter Overview



Figure 8.1: Infant lying on a soft surface with arms extended, illustrating typical newborn posture. (CC BY 4.0; via Introduction).

In approximately nine months, a single fertilized egg develops into a fully formed infant composed of trillions of specialized cells. This remarkable transformation depends on tightly coordinated stages: fertilization, embryonic development, fetal development, birth, and the early neonatal period. At every step, normal development relies on the appropriate synthesis of structural and functional proteins, guided by the genetic material inherited from the egg and sperm and shaped by environmental influences such as nutrition, toxins, and access to prenatal care. Understanding these processes is essential not only for appreciating human biology but also for recognizing how social and environmental inequities can affect pregnancy outcomes and infant health.

Continuum of Human Development and Inheritance

Human development and inheritance link the continuity of life across generations, beginning with the union of two gametes and extending through the growth of a new individual and the transmission of genetic information to the next generation. This chapter follows that continuum from the moment a sperm cell encounters an oocyte to the complex physiological changes of pregnancy, birth, and the early neonatal period, and into the genetic principles that underlie inherited traits. Development is not an isolated biological event; it is influenced by the parent's health, environment, and supports, which are themselves shaped by broader social conditions.

Fertilization and Pre-Embryonic Development

Fertilization marks the starting point of a new individual's life. Within the female reproductive tract, sperm undergo capacitation, a functional maturation that enables them to recognize and penetrate the protective layers surrounding the oocyte. The fertilization process includes passage through the outer cell layer around the oocyte, binding and digestion of the glycoprotein coat, fusion of sperm and oocyte plasma membranes, completion of the oocyte's second meiotic division, and union of the male and female pronuclei to form a diploid zygote. These events restore the full chromosome number and establish the unique genetic identity of the new individual.

In the days immediately after fertilization, the zygote undergoes cleavage, a series of rapid mitotic divisions that increase cell number without increasing overall size. This produces smaller daughter cells that organize into a hollow structure called a blastocyst, which contains an inner cell mass that will form the embryo and a surrounding trophoblast that will contribute to support structures. Around the end of the first week, the blastocyst implants into the uterine lining, a critical step that depends on

a receptive endometrium and adequate hormonal support. Barriers to early prenatal care, differences in environmental exposures, and unequal access to safe nutrition and housing can influence the success of these earliest stages.

Embryonic Development and Early Organ Formation

Embryonic development spans roughly weeks 3 through 8 of gestation and is characterized by rapid cell differentiation and the establishment of the basic body plan. Gastrulation reorganizes the inner cell mass into three primary germ layers. The ectoderm gives rise to the nervous system and skin. The mesoderm forms muscles, bones, the circulatory system, kidneys, and much of the reproductive system. The endoderm forms the lining of the digestive and respiratory tracts and associated organs such as the liver and pancreas.

Organogenesis, the process of organ formation, begins during this embryonic period. The neural tube forms and begins the development of the central nervous system; the heart starts to beat and set up early circulatory patterns; and key support structures, including the placenta, amnion, chorion, and umbilical cord, develop. The placenta establishes an interface between maternal and fetal circulations, allowing the exchange of oxygen, nutrients, and wastes and the transfer of some antibodies. It also produces hormones that support pregnancy. Environmental factors such as maternal nutrition, teratogenic exposures (for example, certain drugs, alcohol, or infections), and occupational or environmental toxins are especially impactful during this time, when organs are forming and particularly vulnerable.

Fetal Development: Growth and Maturation

Once the major body structures and organ systems are established, development enters the fetal period, from about week 9 until birth. During this phase, development focuses less on forming new structures and more on growth, refinement, and functional maturation. Organ systems such as the lungs, brain, liver, kidneys, and immune system increase in size and complexity, preparing the fetus for life outside the uterus. The lungs develop alveoli and produce surfactant to reduce surface tension; the brain undergoes rapid growth and connection of neural circuits; and the liver and kidneys expand their metabolic and excretory capacities.

The placenta and maternal circulation remain central to fetal well-being. They provide oxygen and nutrients, remove carbon dioxide and metabolic wastes, and secrete hormones that help regulate maternal physiology. Pregnancy is traditionally divided into three trimesters, each with characteristic developmental milestones. Inequities in prenatal care, differences in diet quality, and exposure to chronic stress can influence fetal growth, contributing to outcomes such as low birth weight, preterm birth, and differences in long-term health.

Maternal Adaptations During Pregnancy and Birth

Pregnancy requires widespread adaptations by nearly all maternal organ systems. Cardiovascular output and blood volume increase significantly to supply the growing uterus and placenta, while vascular resistance changes to accommodate this increased flow. The respiratory system adjusts to meet higher oxygen demands and to facilitate increased carbon dioxide removal, often leading to changes in breathing patterns. The kidneys adapt by altering filtration and reabsorption to handle changes in fluid and electrolyte balance, and the gastrointestinal system modifies motility and absorption, sometimes contributing to symptoms such as nausea or constipation.

Musculoskeletal changes support uterine expansion and shifting center of gravity, and the endocrine system coordinates hormonal signals that support fetal growth, prepare the breasts for lactation, and time the onset of labor. Hormones including estrogen, progesterone, human chorionic gonadotropin, prolactin, relaxin, and oxytocin all play roles in these processes. Understanding these adaptations offers insight into both the normal physiology of pregnancy and common discomforts or complications, such as gestational hypertension, gestational diabetes, or musculoskeletal pain. Unequal access to prenatal care, safe workplaces, and supportive social structures can significantly affect how safely and comfortably these adaptations proceed.

Labor, or parturition, is the culmination of pregnancy. Rising estrogen relative to progesterone, along with increased uterine sensitivity to oxytocin and prostaglandins, promotes coordinated uterine contractions. These contractions, along with cervical ripening and dilation, lead to the delivery of the fetus and then the placenta. Experiences of labor and birth are influenced not only by physiology but also by access to skilled birth attendants, cultural practices, systemic bias, and the availability of pain management and emergency care.

Newborn Adaptations to Extrauterine Life

Birth abruptly changes the newborn's environment from the protected, liquid-filled uterus to the air-filled, more variable external world. In the first minutes and hours after delivery, the neonate must make rapid physiological adjustments. The lungs must inflate and begin gas exchange as the newborn initiates independent breathing. Fetal circulatory shunts, such as the foramen ovale and ductus arteriosus, functionally close, redirecting blood flow through the lungs and altering pressures in the heart and great vessels. The newborn must regulate body temperature in a cooler, less stable environment, relying on mechanisms such as brown fat metabolism, shivering, and behavioral responses.

The neonate must also begin effective feeding, whether by breastfeeding or formula feeding, and maintain adequate glucose and electrolyte balance as the constant placental supply ceases. The liver and kidneys increase their functional contributions to metabolism and excretion. These transitions require coordinated efforts of the cardiovascular, respiratory, nervous, and endocrine systems. Access to immediate newborn care, including support for thermal regulation, feeding assistance, and screening for congenital conditions, strongly influences outcomes in this vulnerable period and is not equally available in all communities.

Lactation and Early Infant Nutrition

Lactation represents a key link between maternal physiology and infant nutrition and immunity. Under the influence of prolactin, the mammary glands synthesize milk, while oxytocin causes milk ejection in response to suckling. These processes operate through neuroendocrine reflexes: sensory stimulation from the infant's suckling is transmitted to the hypothalamus and pituitary, which adjust hormone release accordingly. Early milk, known as colostrum, is rich in antibodies, growth factors, and immune cells that help protect the newborn against infection and support maturation of the gut. Mature breast milk provides an appropriate balance of nutrients, including fats, carbohydrates, and proteins, tailored to human infants.

At the same time, feeding decisions are influenced by cultural norms, workplace policies, family support, and economic conditions. Some parents may face challenges in breastfeeding due to medical issues, unstable housing, lack of paid leave, or limited access to lactation support. Understanding the physiology of lactation and recognizing these social factors is important for promoting equitable support for all feeding choices and ensuring that every infant has access to safe, adequate nutrition.

Genetic Principles and Inheritance of Traits

Underlying all stages of development is the genetic blueprint inherited from the parents. The human genome consists of genes arranged on chromosomes, and each gene may exist in different versions called alleles. The combination of alleles (genotype) influences observable characteristics (phenotype), though environment and random developmental events also play important roles.

Patterns of inheritance include autosomal dominant and recessive traits, in which a single copy or two copies of an allele, respectively, are needed for expression; X-linked traits, where alleles on the X chromosome may affect individuals differently based on their chromosomal sex; codominance, where two alleles are both expressed; incomplete dominance, where heterozygous individuals show intermediate traits; and polygenic inheritance, where multiple genes contribute to a single characteristic such as height, skin tone, or blood pressure. Many traits relevant to health and disease are polygenic and strongly influenced by environment, which helps explain why social determinants such as nutrition, stress, and exposure to pollutants interact with genetic risk.

Understanding these principles allows clinicians and learners to predict inheritance risks using tools like Punnett squares, explain patterns of genetic variation, and interpret congenital and inherited conditions in the context of development. Equally important, it highlights the limitations of genetic determinism and underscores that health outcomes arise from complex interactions among genes, environments, and social conditions.

Learning Objectives

To achieve these chapter objectives, actively engage with the material. Learning tissues is not a passive process. Your understanding will grow as you interact with the content, peers, and your instructor. Regularly check your thinking against feedback. Revisit complex concepts until you can confidently explain and apply them on your own.

By the end of this chapter, you will be able to:

- List and explain the steps involved in fertilization
- Describe the major events in embryonic development
- Describe the major events in fetal development
- Discuss the adaptations of the body to pregnancy
- Describe the physiologic adjustments that the newborn must make in the first hours of extrauterine life
- Summarize the physiology of lactation
- Classify and describe the different patterns of inheritance

8.1: Fertilization
8.2: Embryonic Development
8.3: Fetal Development
8.4: Changes During Pregnancy, Labor, and Birth
8.5: Adjustments of the Infant at Birth and Postnatal Stages
8.6: Lactation
8.7: Patterns of Inheritance
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8.1: Fertilization

Transit of Sperm

Fertilization occurs when a sperm and an oocyte (egg) combine and their nuclei fuse. Because each of these reproductive cells is a haploid cell containing half of the genetic material needed to form a human being, their combination forms a diploid cell. This new single cell, called a zygote, contains all of the genetic material needed to form a human—half from each biological parent.

Fertilization is a numbers game. During ejaculation, hundreds of millions of sperm (spermatozoa) are released into the vagina. Almost immediately, millions of these sperm are overcome by the acidity of the vagina (approximately pH 3.8), and millions more may be blocked from entering the uterus by thick cervical mucus. Of those that do enter, thousands are destroyed by phagocytic uterine leukocytes. Thus, the race into the uterine tubes, which is the most typical site for sperm to encounter the oocyte, is reduced to a few thousand contenders. Their journey—thought to be facilitated by uterine contractions—usually takes from 30 minutes to 2 hours. If the sperm do not encounter an oocyte immediately, they can survive in the uterine tubes for another 3–5 days. Thus, fertilization can still occur if intercourse takes place a few days before ovulation. In comparison, an oocyte can survive independently for only approximately 24 hours following ovulation. Intercourse more than a day after ovulation will therefore usually not result in fertilization.

During the journey, fluids in the female reproductive tract prepare the sperm for fertilization through a process called capacitation, or priming. The fluids improve the motility of the spermatozoa. They also deplete cholesterol molecules embedded in the membrane of the head of the sperm, thinning the membrane in such a way that will help facilitate the release of the lysosomal (digestive) enzymes needed for the sperm to penetrate the oocyte's exterior once contact is made. Sperm must undergo the process of capacitation in order to have the "capacity" to fertilize an oocyte. If they reach the oocyte before capacitation is complete, they will be unable to penetrate the oocyte's thick outer layer of cells.

Contact Between Sperm and Oocyte

Upon ovulation, the oocyte released by the ovary is swept into—and along—the uterine tube. Fertilization must occur in the distal uterine tube because an unfertilized oocyte cannot survive the 72-hour journey to the uterus. As you will recall from your study of the oogenesis, this oocyte (specifically a secondary oocyte) is surrounded by two protective layers. The corona radiata is an outer layer of follicular (granulosa) cells that form around a developing oocyte in the ovary and remain with it upon ovulation. The underlying zona pellucida (pellucid = "transparent") is a transparent, but thick, glycoprotein membrane that surrounds the cell's plasma membrane.

As it is swept along the distal uterine tube, the oocyte encounters the surviving capacitated sperm, which stream toward it in response to chemical attractants released by the cells of the corona radiata. To reach the oocyte itself, the sperm must penetrate the two protective layers. The sperm first burrow through the cells of the corona radiata. Then, upon contact with the zona pellucida, the sperm bind to receptors in the zona pellucida. This initiates a process called the acrosomal reaction in which the enzyme-filled "cap" of the sperm, called the acrosome, releases its stored digestive enzymes. These enzymes clear a path through the zona pellucida that allows sperm to reach the oocyte. Finally, a single sperm makes contact with sperm-binding receptors on the oocyte's plasma membrane (Figure 8.1.1). The plasma membrane of that sperm then fuses with the oocyte's plasma membrane, and the head and mid-piece of the "winning" sperm enter the oocyte interior.

How do sperm penetrate the corona radiata? Some sperm undergo a spontaneous acrosomal reaction, which is an acrosomal reaction not triggered by contact with the zona pellucida. The digestive enzymes released by this reaction digest the extracellular matrix of the corona radiata. As you can see, the first sperm to reach the oocyte is never the one to fertilize it. Rather, hundreds of sperm cells must undergo the acrosomal reaction, each helping to degrade the corona radiata and zona pellucida until a path is created to allow one sperm to contact and fuse with the plasma membrane of the oocyte. If you consider the loss of millions of sperm between entry into the vagina and degradation of the zona pellucida, you can understand why a low sperm count can cause male infertility.

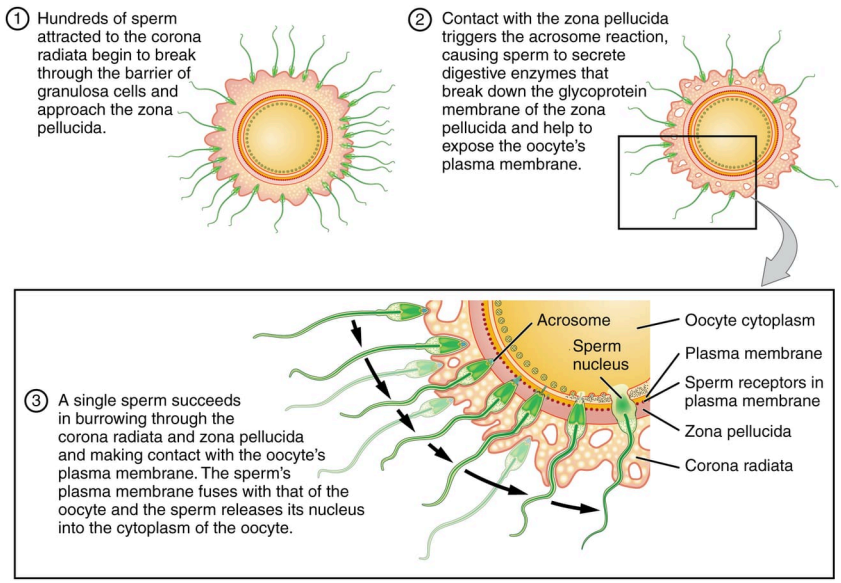


Figure 8.1.1: Fertilization showing sperm penetrating outer layers, triggering acrosome reaction, and one sperm fusing with the oocyte membrane. (CC BY 4.0; via Fertilization). Detailed text description of the Figure 8.1.1.

When the first sperm fuses with the oocyte, the oocyte deploys two mechanisms to prevent polyspermy, which is penetration by more than one sperm. This is critical because if more than one sperm were to fertilize the oocyte, the resulting zygote would be a triploid organism with three sets of chromosomes. This is incompatible with life.

The first mechanism is the fast block, which involves a near instantaneous change in sodium ion permeability upon binding of the first sperm, depolarizing the oocyte plasma membrane and preventing the fusion of additional sperm cells. The fast block sets in almost immediately and lasts for about a minute, during which time an influx of calcium ions following sperm penetration triggers the second mechanism, the slow block. In this process, referred to as the cortical reaction, cortical granules sitting immediately below the oocyte plasma membrane fuse with the membrane and release zonal inhibiting proteins and mucopolysaccharides into the space between the plasma membrane and the zona pellucida. Zonal inhibiting proteins cause the release of any other attached sperm and destroy the oocyte's sperm receptors, thus preventing any more sperm from binding. The mucopolysaccharides then coat the nascent zygote in an impenetrable barrier that, together with hardened zona pellucida, is called a fertilization membrane.

The Zygote

Recall that at the point of fertilization, the oocyte has not yet completed meiosis; all secondary oocytes remain arrested in metaphase of meiosis II until fertilization. Only upon fertilization does the oocyte complete meiosis. The unneeded complement of genetic material that results is stored in a second polar body that is eventually ejected. At this moment, the oocyte has become an ovum, the female haploid gamete. The two haploid nuclei derived from the sperm and oocyte and contained within the egg are referred to as pronuclei. They decondense, expand, and replicate their DNA in preparation for mitosis. The pronuclei then migrate toward each other, their nuclear envelopes disintegrate, and the male- and female-derived genetic material intermingles. This step completes the process of fertilization and results in a single-celled diploid zygote with all the genetic instructions it needs to develop into a human.

Most of the time, a person releases a single egg during an ovulation cycle. However, in approximately 1 percent of ovulation cycles, two eggs are released and both are fertilized. Two zygotes form, implant, and develop, resulting in the birth of dizygotic (or fraternal) twins. Because dizygotic twins develop from two eggs fertilized by two sperm, they are no more identical than siblings born at different times.

Much less commonly, a zygote can divide into two separate offspring during early development. This results in the birth of monozygotic (or identical) twins. Although the zygote can split as early as the two-cell stage, splitting occurs most commonly during the early blastocyst stage, with roughly 70–100 cells present. These two scenarios are distinct from each other, in that the twin embryos that separated at the two-cell stage will have individual placentas, whereas twin embryos that form from separation at the blastocyst stage will share a placenta and a chorionic cavity.

Everyday Connection

In Vitro Fertilization

IVF, which stands for in vitro fertilization, is an assisted reproductive technology. In vitro, which in Latin translates to “in glass,” refers to a procedure that takes place outside of the body. There are many different indications for IVF. The procedure is used frequently in supporting LGBTQ people, people using surrogates/gestational carriers, and also people who have difficulties reproducing. For example, a person may produce healthy eggs, but the eggs cannot reach the uterus because the uterine tubes are blocked or otherwise compromised. A person may have a low sperm count, low sperm motility, sperm with an unusually high percentage of morphological abnormalities, or sperm that are incapable of penetrating the zona pellucida of an egg.

A typical IVF procedure begins with egg collection. A normal ovulation cycle produces only one oocyte, but the number can be boosted significantly (to 10–20 oocytes) by administering a short course of gonadotropins. The course begins with follicle-stimulating hormone (FSH) analogs, which support the development of multiple follicles, and ends with a luteinizing hormone (LH) analog that triggers ovulation. Right before the ova would be released from the ovary, they are harvested using ultrasound-guided oocyte retrieval. In this procedure, ultrasound allows a physician to visualize mature follicles. The ova are aspirated (sucked out) using a syringe.

In parallel, sperm are obtained from the male partner or from a sperm bank. The sperm are prepared by washing to remove seminal fluid because seminal fluid contains a peptide, FPP (or, fertilization promoting peptide), that—in high concentrations—prevents capacitation of the sperm. The sperm sample is also concentrated, to increase the sperm count per milliliter.

Next, the eggs and sperm are mixed in a petri dish. The ideal ratio is 75,000 sperm to one egg. If there are severe problems with the sperm—for example, the count is exceedingly low, or the sperm are completely nonmotile, or incapable of binding to or penetrating the zona pellucida—a sperm can be injected into an egg. This is called intracytoplasmic sperm injection (ICSI).

The embryos are then incubated until they either reach the eight-cell stage or the blastocyst stage. In the United States, fertilized eggs are typically cultured to the blastocyst stage because this results in a higher pregnancy rate. Finally, the embryos are transferred to a woman’s uterus using a plastic catheter (tube). Figure 8.1.2 illustrates the steps involved in IVF.

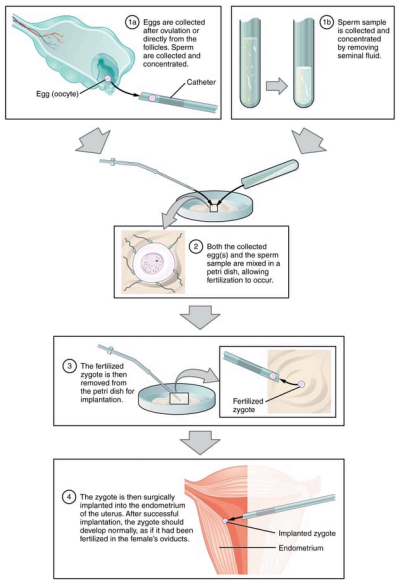


Figure 8.1.2: In vitro fertilization involves egg collection from the ovaries, fertilization in a petri dish, and the transfer of embryos into the uterus. (CC BY 4.0; via Fertilization). Detailed text description of the Figure 8.1.2.

IVF is a relatively new and still evolving technology, and until recently it was necessary to transfer multiple embryos to achieve a good chance of a pregnancy. Today, however, transferred embryos are much more likely to implant successfully, so countries that regulate the IVF industry cap the number of embryos that can be transferred per cycle at two. This reduces the risk of multiple-birth pregnancies.

The rate of success for IVF is correlated with the age of the gestational carrier (which may be the child's mother or a surrogate). More than 40 percent of females under 35 succeed in giving birth following IVF, but the rate drops to a little over 10 percent in females over 40.

Learn More: Fertilization

For a detailed, step-by-step explanation of fertilization processes and related embryological concepts, visit the UNSW Embryology resource on Fertilization, which includes materials covering various aspects of fertilization, including movies and animations demonstrating sperm structure and motility, ovulation, and fertilization.

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8.2: Embryonic Development

Pre-implantation Embryonic Development

Throughout this chapter, we will express embryonic and fetal ages in terms of weeks from fertilization, commonly called conception. The period of time required for full development of a fetus in utero is referred to as gestation (gestare = “to carry” or “to bear”). It can be subdivided into distinct gestational periods. The first 2 weeks of prenatal development are referred to as the pre-embryonic stage. A developing human is referred to as an embryo during weeks 3–8, and a fetus from the ninth week of gestation until birth. In this section, we’ll cover the pre-embryonic and embryonic stages of development, which are characterized by cell division, migration, and differentiation. By the end of the embryonic period, all of the organ systems are structured in rudimentary form, although the organs themselves are either nonfunctional or only semi-functional.

Following fertilization, the zygote and its associated membranes, together referred to as the conceptus, continue to be projected toward the uterus by peristalsis and beating cilia of the epithelial cells of the Fallopian tube. During its journey to the uterus, the zygote undergoes five or six rapid mitotic cell divisions. Although each cleavage results in more cells, it does not increase the total volume of the conceptus (Figure 8.2.1). Each daughter cell produced by cleavage is called a blastomere (blastos = “germ,” in the sense of a seed or sprout).

Approximately 3 days after fertilization, a 16-cell conceptus reaches the uterus. The cells that had been loosely grouped are now compacted and look more like a solid mass. The name given to this structure is the morula (morula = “little mulberry”). Once inside the uterus, the conceptus floats freely for several more days. It continues to divide, creating a ball of approximately 100 cells, and consuming nutritive endometrial secretions called uterine milk while the uterine lining thickens. The ball of now tightly bound cells starts to secrete fluid and organize themselves around a fluid-filled cavity, the blastocoel. At this developmental stage, the conceptus is referred to as a blastocyst. Within this structure, a group of cells forms into an inner cell mass, which is fated to become the embryo. The cells that form the outer shell are called trophoblasts (trophe = “to feed” or “to nourish”). These cells will develop into the chorionic sac and the fetal portion of the placenta (the organ of nutrient, waste, and gas exchange between a pregnant person and the developing offspring).

The inner mass of embryonic cells is totipotent during this stage, meaning that each cell has the potential to differentiate into any cell type in the human body. Totipotency lasts for only a few days before the cells’ fates are set as being the precursors to a specific lineage of cells.

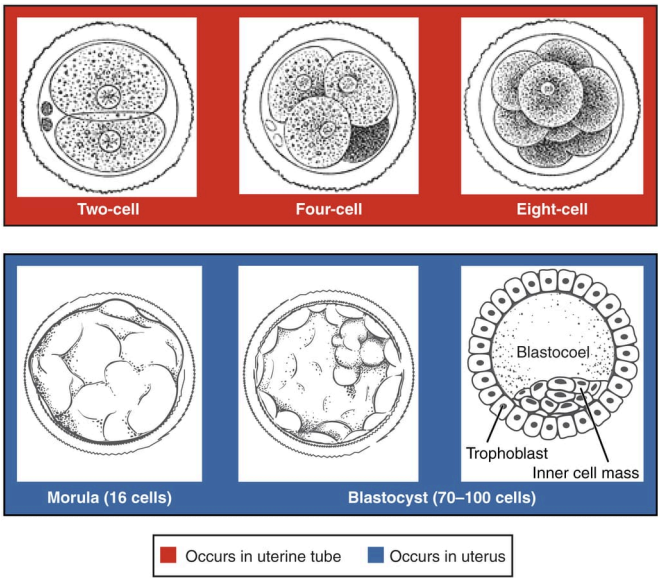


Figure 8.2.1: Pre-embryonic cleavages make use of the abundant cytoplasm of the conceptus as the cells rapidly divide without changing the total volume. (CC BY 4.0; via Embryonic Development). (CC BY 4.0; via Fertilization). Detailed text description of the Figure 8.2.1.

Observing Blastocyst Development (Days 3–6)

Video Activity: Early Embryo Development

Overview

This silent time-lapse video shows the development of a human conceptus from approximately days 3 to 6 after fertilization. The video visually demonstrates the developmental sequence described in Figure 8.2.1 and the accompanying discussion, including continued cell division, formation of the blastocoel, and development of the blastocyst.

Accessibility Note

This video is video-only and does not include spoken audio. Because important information is conveyed visually over time, students should be provided with a text alternative for time-based media that explains the sequence shown in the video. This supports accessibility for learners who cannot see the video or who benefit from a written description of the developmental process.

Alternative for time-based media
The video begins with an early-stage conceptus undergoing cleavage divisions. As development continues, the cells become more numerous and compact, forming a morula. A fluid-filled cavity then begins to appear inside the conceptus, marking formation of the blastocoel. As the cavity enlarges, the structure becomes a blastocyst, with a more defined outer cell layer and an inner group of cells. Near the end of the video, the blastocyst begins to hatch from the zona pellucida, an important step that allows implantation into the uterine lining.

Implantation

At the end of the first week, the blastocyst comes in contact with the uterine wall and adheres to it, embedding itself in the uterine lining via the trophoblast cells. Thus begins the process of implantation, which signals the end of the pre-embryonic stage of development (Figure 8.2.2). Implantation can be accompanied by minor bleeding. The blastocyst typically implants in the fundus of the uterus or on the posterior wall. However, if the endometrium is not fully developed and ready to receive the blastocyst, the blastocyst will detach and find a better spot. A significant percentage (50–75 percent) of blastocysts fail to implant; when this occurs, the blastocyst is shed with the endometrium during menses. The high rate of implantation failure is one reason why pregnancy typically requires several ovulation cycles to achieve.

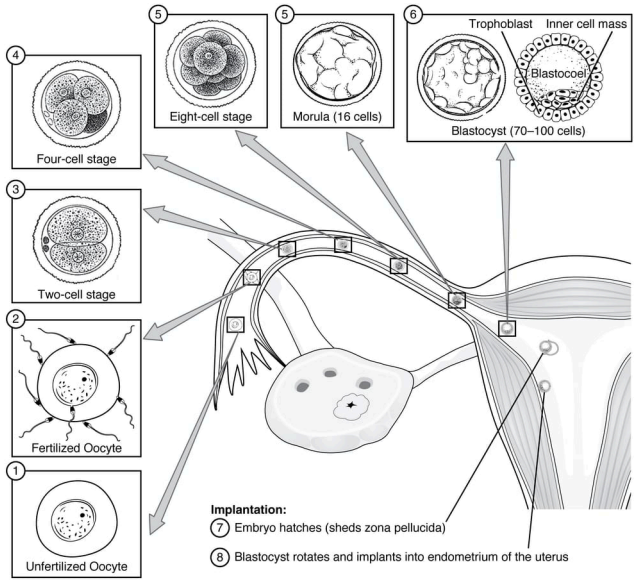


Figure 8.2.2: Ovulation, fertilization, pre-embryonic development, and implantation occur at specific locations within the female reproductive system in a time span of approximately 1 week. (CC BY 4.0; via Embryonic Development). Detailed text description of the Figure 8.2.2.

When implantation succeeds and the blastocyst adheres to the endometrium, the superficial cells of the trophoblast fuse with each other, forming the syncytiotrophoblast, a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall. In response, the uterine mucosa rebuilds itself and envelops the blastocyst (Figure 8.2.3). The trophoblast secretes human chorionic gonadotropin (hCG), a hormone that directs the corpus luteum to survive, enlarge, and continue producing progesterone and estrogen to suppress menses. These functions of hCG are necessary for creating an environment suitable for the developing embryo. As a result of this increased production, hCG accumulates in the maternal bloodstream and is excreted in the urine. Implantation is complete by the middle of the second week. Just a few days after implantation, the trophoblast has secreted enough hCG for an at-home urine pregnancy test to give a positive result.

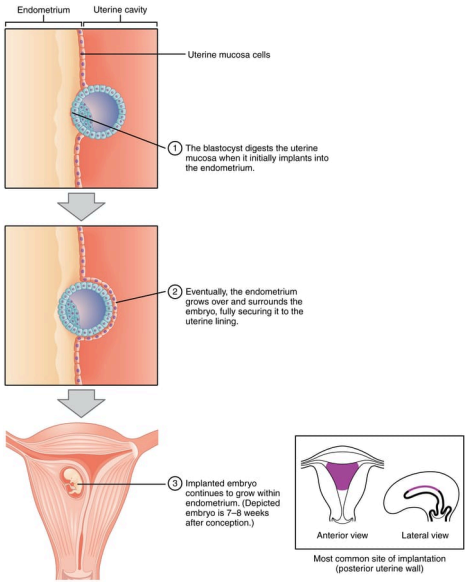


Figure 8.2.3: During implantation, the trophoblast cells of the blastocyst adhere to the endometrium and digest endometrial cells until it is attached securely. (CC BY 4.0; via Embryonic Development). Detailed text description of the Figure 8.2.3.

Most of the time an embryo implants within the body of the uterus in a location that can support growth and development. However, in one to two percent of cases, the embryo implants either outside the uterus (an ectopic pregnancy) or in a region of uterus that can create complications for the pregnancy. If the embryo implants in the inferior portion of the uterus, the placenta can potentially grow over the opening of the cervix, a condition call placenta previa.

Disorders of the...

Development of the Embryo

In the vast majority of ectopic pregnancies, the embryo does not complete its journey to the uterus and implants in the uterine tube, referred to as a tubal pregnancy. However, there are also ovarian ectopic pregnancies (in which the egg never left the ovary) and abdominal ectopic pregnancies (in which an egg was “lost” to the abdominal cavity during the transfer from ovary to uterine tube, or in which an embryo from a tubal pregnancy re-implanted in the abdomen). Once in the abdominal cavity, an embryo can implant into any well-vascularized structure—the rectouterine cavity (Douglas’ pouch), the mesentery of the intestines, and the greater omentum are some common sites.

Tubal pregnancies can be caused by scar tissue within the tube following a sexually transmitted bacterial infection. The scar tissue impedes the progress of the embryo into the uterus—in some cases “snagging” the embryo and, in other cases, blocking the tube completely. Approximately one half of tubal pregnancies resolve spontaneously. Implantation in a uterine tube causes bleeding, which appears to stimulate smooth muscle contractions and expulsion of the embryo. In the remaining cases, medical or surgical intervention is necessary. If an ectopic pregnancy is detected early, the embryo’s development can be arrested by the administration of the cytotoxic drug methotrexate, which inhibits the metabolism of folic acid. If diagnosis is late and the uterine tube is already ruptured, surgical repair is essential.

Even if the embryo has successfully found its way to the uterus, it does not always implant in an optimal location (the fundus or the posterior wall of the uterus). Placenta previa can result if an embryo implants close to the internal os of the uterus (the internal opening of the cervix). As the fetus grows, the placenta can partially or completely cover the opening of the cervix (Figure 8.2.4). Although it occurs in only 0.5 percent of pregnancies, placenta previa is the leading cause of antepartum hemorrhage (profuse vaginal bleeding after week 24 of pregnancy but prior to childbirth).

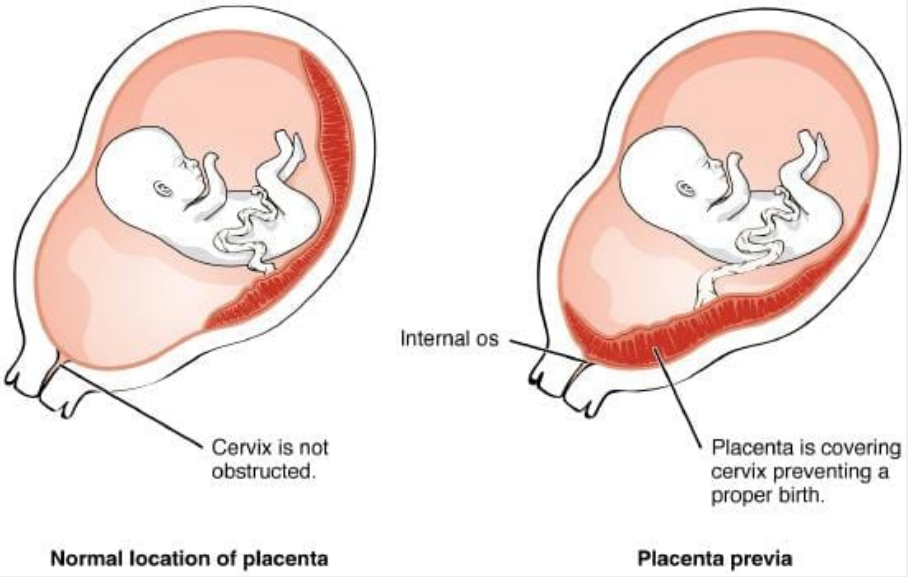


Figure 8.2.4: An embryo that implants too close to the opening of the cervix can lead to placenta previa, a condition in which the placenta partially or completely covers the cervix. (CC BY 4.0; via Embryonic Development). Detailed text description of the Figure $PageIndex4$.

Embryonic Membranes

During the second week of development, with the embryo implanted in the uterus, cells within the blastocyst start to organize into layers. Some grow to form the extra-embryonic membranes needed to support and protect the growing embryo: the amnion, the yolk sac, the allantois, and the chorion.

At the beginning of the second week, the cells of the inner cell mass form into a two-layered disc of embryonic cells, and a space—the amniotic cavity—opens up between it and the trophoblast (Figure 8.2.5). Cells from the upper layer of the disc (the epiblast) extend around the amniotic cavity, creating a membranous sac that forms into the amnion by the end of the second week. The amnion fills with amniotic fluid and eventually grows to surround the embryo. Early in development, amniotic fluid consists almost entirely of a filtrate of maternal plasma, but as the kidneys of the fetus begin to function at approximately the eighth week, they add urine to the volume of amniotic fluid. Floating within the amniotic fluid, the embryo—and later, the fetus—is protected from trauma and rapid temperature changes. It can move freely within the fluid and can prepare for swallowing and breathing out of the uterus.

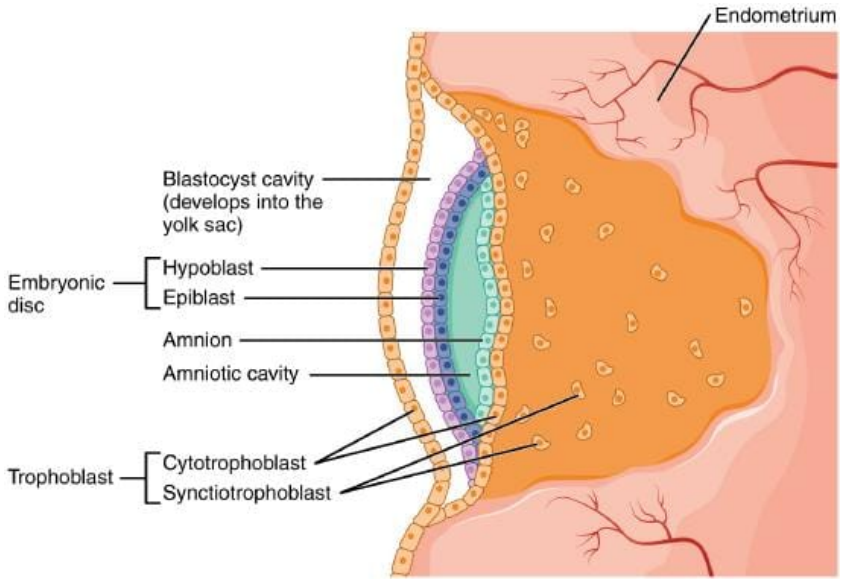


Figure 8.2.5: Formation of the embryonic disc creates two fluid-filled spaces that develop into the amniotic cavity and the yolk sac. (CC BY 4.0; via Embryonic Development). Detailed text description of the Figure 8.2.5.

On the ventral side of the embryonic disc, opposite the amnion, cells in the lower layer of the embryonic disk (the hypoblast) extend into the blastocyst cavity and form a yolk sac. The yolk sac supplies some nutrients absorbed from the trophoblast and also provides primitive blood circulation to the developing embryo for the second and third week of development. When the placenta takes over nourishing the embryo at approximately week 4, the yolk sac has been greatly reduced in size and its main function is to serve as the source of blood cells and germ cells (cells that will give rise to gametes). During week 3, a finger-like outpocketing of the yolk sac develops into the allantois, a primitive excretory duct of the embryo that will become part of the urinary bladder. Together, the stalks of the yolk sac and allantois establish the outer structure of the umbilical cord.

The last of the extra-embryonic membranes is the chorion, which is the one membrane that surrounds all others. The development of the chorion will be discussed in more detail shortly, as it relates to the growth and development of the placenta.

Embryogenesis

As the third week of development begins, the two-layered disc of cells becomes a three-layered disc through the process of gastrulation, during which the cells transition from totipotency to multipotency. The embryo, which takes the shape of an oval-shaped disc, forms an indentation called the primitive streak along the dorsal surface of the epiblast. A node at the caudal or “tail” end of the primitive streak emits growth factors that direct cells to multiply and migrate. Cells migrate toward and through the primitive streak and then move laterally to create two new layers of cells. The first layer is the endoderm, a sheet of cells that displaces the hypoblast and lies adjacent to the yolk sac. The second layer of cells fills in as the middle layer, or mesoderm. The cells of the epiblast that remain (not having migrated through the primitive streak) become the ectoderm (Figure 8.2.6).

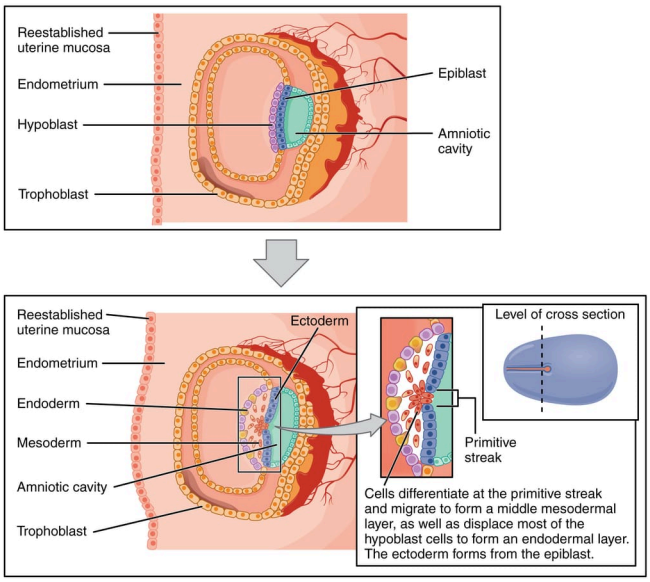


Figure 8.2.6: Germ layer formation during early embryonic development. The three primary germ layers ectoderm, mesoderm, and endoderm. These form during week 3 (gastrulation). The embryo at this stage measures only a few millimeters in length. (CC BY 4.0; via Embryonic Development). Detailed text description of the Figure 8.2.6.

Each of these germ layers will develop into specific structures in the embryo. Whereas the ectoderm and endoderm form tightly connected epithelial sheets, the mesodermal cells are less organized and exist as a loosely connected cell community. The ectoderm gives rise to cell lineages that differentiate to become the central and peripheral nervous systems, sensory organs, epidermis, hair, and nails. Mesodermal cells ultimately become the skeleton, muscles, connective tissue, heart, blood vessels, and kidneys. The endoderm goes on to form the epithelial lining of the gastrointestinal tract, liver, and pancreas, as well as the lungs (Figure 8.2.7).

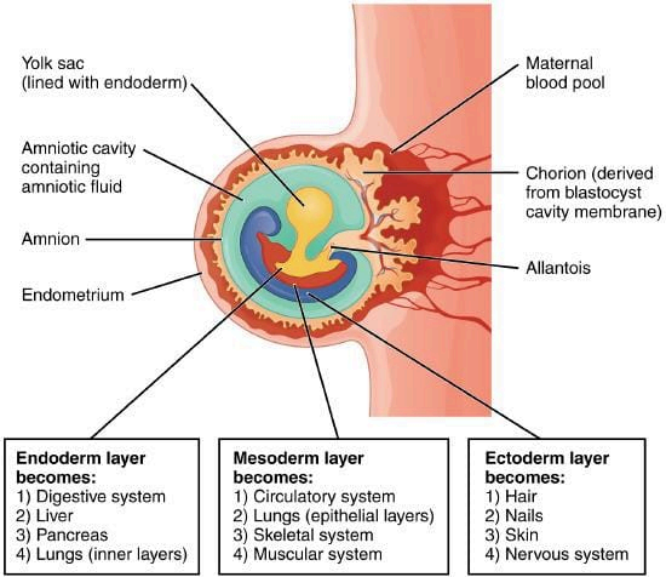


Figure 8.2.7: Following gastrulation of the embryo in the third week, embryonic cells of the ectoderm, mesoderm, and endoderm begin to migrate and differentiate into the cell lineages that will give rise to mature organs and organ systems in the infant. (CC BY 4.0; via Embryonic Development). Detailed text description of the Figure 8.2.7.

Development of the Placenta

During the first several weeks of development, the cells of the endometrium—referred to as decidual cells—nourish the nascent embryo. During prenatal weeks 4–12, the developing placenta gradually takes over the role of feeding the embryo, and the decidual

cells are no longer needed. The mature placenta is composed of tissues derived from the embryo, as well as maternal tissues of the endometrium. The placenta connects to the conceptus via the umbilical cord, which carries deoxygenated blood and wastes from the fetus through two umbilical arteries; nutrients and oxygen are carried from the pregnant person to the fetus through the single umbilical vein. The umbilical cord is surrounded by the amnion, and the spaces within the cord around the blood vessels are filled with Wharton's jelly, a mucous connective tissue.

The maternal portion of the placenta develops from the deepest layer of the endometrium, the decidua basalis. To form the embryonic portion of the placenta, the syncytiotrophoblast and the underlying cells of the trophoblast (cytotrophoblast cells) begin to proliferate along with a layer of extraembryonic mesoderm cells. These form the chorionic membrane, which envelops the entire conceptus as the chorion. The chorionic membrane forms finger-like structures called chorionic villi that burrow into the endometrium like tree roots, making up the fetal portion of the placenta. The cytotrophoblast cells perforate the chorionic villi, burrow farther into the endometrium, and remodel maternal blood vessels to augment maternal blood flow surrounding the villi. Meanwhile, fetal mesenchymal cells derived from the mesoderm fill the villi and differentiate into blood vessels, including the three umbilical blood vessels that connect the embryo to the developing placenta (Figure 8.2.8).

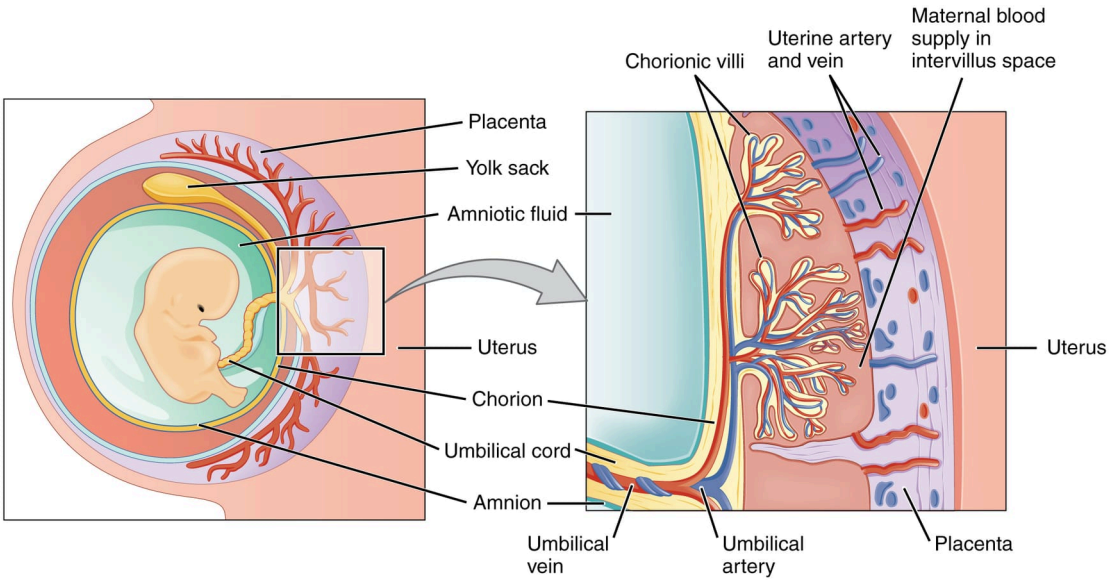


Figure 8.2.8: In the placenta, maternal and fetal blood components are conducted through the surface of the chorionic villi, but maternal and fetal bloodstreams never mix directly. (CC BY 4.0; via Embryonic Development). Detailed text description of the Figure 8.2.8.

The placenta develops throughout the embryonic period and during the first several weeks of the fetal period; placentation is complete by weeks 14–16. As a fully developed organ, the placenta provides nutrition and excretion, respiration, and endocrine function (Table 8.2.1 and Figure 8.2.9). It receives blood from the fetus through the umbilical arteries. Capillaries in the chorionic villi filter fetal wastes out of the blood and return clean, oxygenated blood to the fetus through the umbilical vein. Nutrients and oxygen are transferred from maternal blood surrounding the villi through the capillaries and into the fetal bloodstream. Some substances move across the placenta by simple diffusion. Oxygen, carbon dioxide, and any other lipid-soluble substances take this route. Other substances move across by facilitated diffusion. This includes water-soluble glucose. The fetus has a high demand for amino acids and iron, and those substances are moved across the placenta by active transport.

Maternal and fetal blood does not commingle because blood cells cannot move across the placenta. This separation prevents the pregnant person's cytotoxic T cells from reaching and subsequently destroying the fetus, which bears "non-self" antigens. Further, it ensures the fetal red blood cells do not enter the pregnant person's circulation and trigger antibody development (if they carry "non-self" antigens)—at least until the final stages of pregnancy or birth. This is the reason that, even in the absence of preventive treatment, an Rh^- person doesn't develop antibodies that could cause hemolytic disease in their first Rh^+ fetus.

Although blood cells are not exchanged, the chorionic villi provide ample surface area for the two-way exchange of substances between maternal and fetal blood. The rate of exchange increases throughout gestation as the villi become thinner and increasingly branched. The placenta is permeable to lipid-soluble fetotoxic substances: alcohol, nicotine, barbiturates, antibiotics, certain pathogens, and many other substances that can be dangerous or fatal to the developing embryo or fetus. For these reasons, pregnant people should avoid fetotoxic substances. Alcohol consumption by pregnant people, for example, can result in a range of abnormalities referred to as fetal alcohol spectrum disorders (FASD). These include organ and facial malformations, as

well as cognitive and behavioral disorders.

Table 8.2.1: Functions of the Placenta

Nutrition and digestion	Respiration	Endocrine function
• Mediates diffusion of maternal glucose, amino acids, fatty acids, vitamins, and minerals • Stores nutrients during early pregnancy to accommodate increased fetal demand later in pregnancy • Excretes and filters fetal nitrogenous wastes into maternal blood	• Mediates maternal-to-fetal oxygen transport and fetal-to-maternal carbon dioxide transport	• Secretes several hormones, including hCG, estrogens, and progesterone, to maintain the pregnancy and stimulate maternal and fetal development • Mediates the transmission of maternal hormones into fetal blood and vice versa

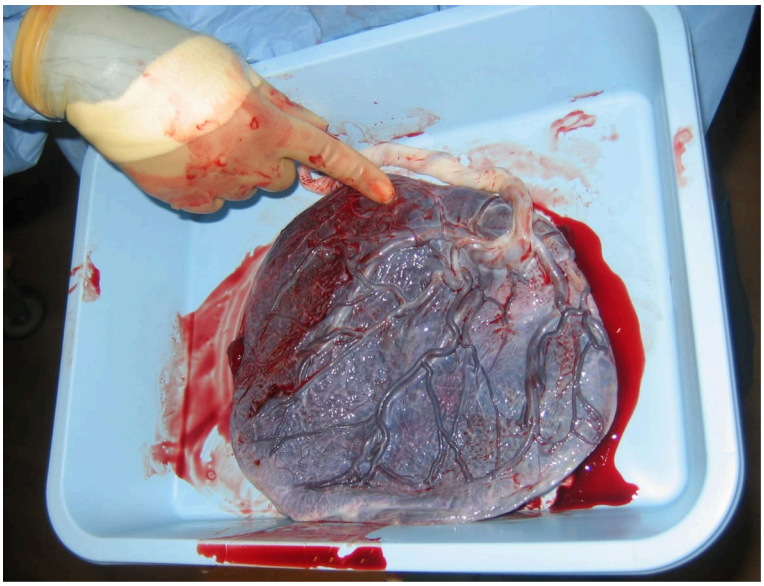


Figure 8.2.9: This post-expulsion placenta and umbilical cord (white) are viewed from the fetal side. (CC BY 4.0; via Embryonic Development). Detailed text description of the Figure 8.2.9.

Organogenesis

Following gastrulation, rudiments of the central nervous system develop from the ectoderm in the process of neurulation (Figure 8.2.10). Specialized neuroectodermal tissues along the length of the embryo thicken into the neural plate. During the fourth week, tissues on either side of the plate fold upward into a neural fold. The two folds converge to form the neural tube. The tube lies atop a rod-shaped, mesoderm-derived notochord, which eventually becomes the nucleus pulposus of intervertebral discs. Block-like structures called somites form on either side of the tube, eventually differentiating into the axial skeleton, skeletal muscle, and dermis. During the fourth and fifth weeks, the anterior neural tube dilates and subdivides to form vesicles that will become the brain structures.

Folate, one of the B vitamins, is important to the healthy development of the neural tube. A deficiency of maternal folate in the first weeks of pregnancy can result in neural tube defects, including spina bifida—a birth defect in which spinal tissue protrudes through the newborn's vertebral column, which has failed to completely close. A more severe neural tube defect is anencephaly, a partial or complete absence of brain tissue.

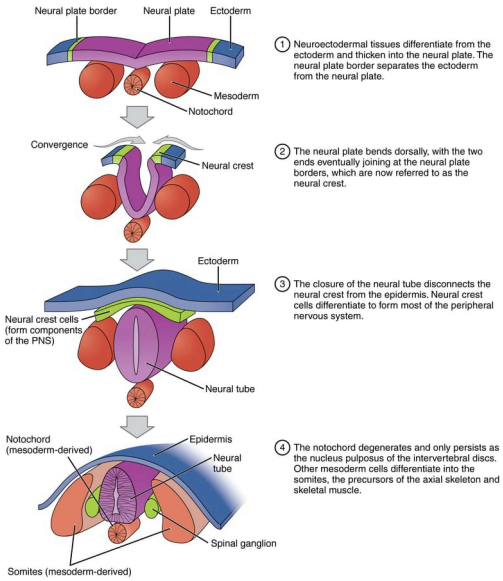


Figure 8.2.10: The embryonic process of neurulation establishes the rudiments of the future central nervous system and skeleton. (CC BY 4.0; via Embryonic Development). Detailed text description of the Figure 8.2.10.

The embryo, which begins as a flat sheet of cells, begins to acquire a cylindrical shape through the process of embryonic folding (Figure 8.2.11). The embryo folds laterally and again at either end, forming a C-shape with distinct head and tail ends. The embryo envelops a portion of the yolk sac, which protrudes with the umbilical cord from what will become the abdomen. The folding essentially creates a tube, called the primitive gut, that is lined by the endoderm. The amniotic sac, which was sitting on top of the flat embryo, envelops the embryo as it folds.

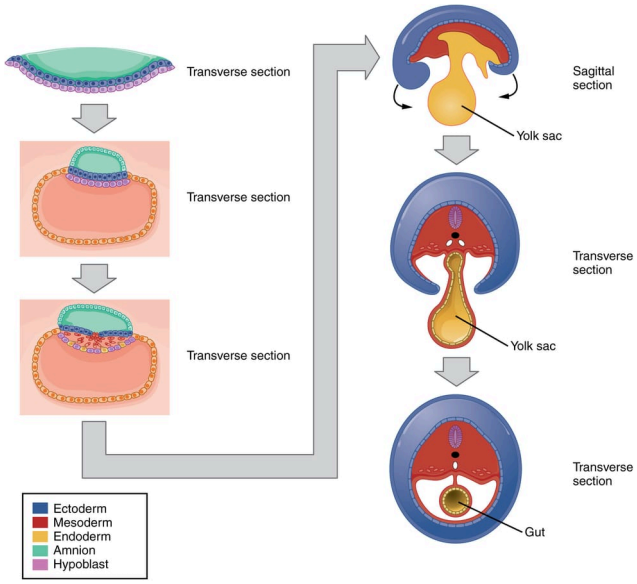


Figure 8.2.11: Embryonic folding converts a flat sheet of cells into a hollow, tube-like structure. (CC BY 4.0; via Embryonic Development). Detailed text description of the Figure 8.2.11.

Within the first 8 weeks of gestation, a developing embryo establishes the rudimentary structures of all of its organs and tissues from the ectoderm, mesoderm, and endoderm. This process is called organogenesis.

Like the central nervous system, the heart also begins its development in the embryo as a tube-like structure, connected via capillaries to the chorionic villi. Cells of the primitive tube-shaped heart are capable of electrical conduction and contraction. The heart begins beating in the beginning of the fourth week, although it does not actually pump embryonic blood until a week later, when the oversized liver has begun producing red blood cells. (This is a temporary responsibility of the embryonic liver that the

bone marrow will assume during fetal development.) During weeks 4–5, the eye pits form, limb buds become apparent, and the rudiments of the pulmonary system are formed.

During the sixth week, uncontrolled fetal limb movements begin to occur. The gastrointestinal system develops too rapidly for the embryonic abdomen to accommodate it, and the intestines temporarily loop into the umbilical cord. Paddle-shaped hands and feet develop fingers and toes by the process of apoptosis (programmed cell death), which causes the tissues between the fingers to disintegrate. By week 7, the facial structure is more complex and includes nostrils, outer ears, and lenses (Figure 8.2.12). By the eighth week, the head is nearly as large as the rest of the embryo's body, and all major brain structures are in place. The external genitalia are apparent, but at this point, male and female embryos are indistinguishable. Bone begins to replace cartilage in the embryonic skeleton through the process of ossification. By the end of the embryonic period, the embryo is approximately 3 cm (1.2 in) from crown to rump and weighs approximately 8 g (0.25 oz).



Figure 8.2.12: An embryo at the end of 7 weeks of development is only 10 mm in length, but its developing eyes, limb buds, and tail are already visible. (This embryo was derived from an ectopic pregnancy). (CC BY 4.0; via Embryonic Development). Detailed text description of the Figure 8.2.12.

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8.3: Fetal Development

Sexual Differentiation

As you will recall, a developing human is called a fetus from the ninth week of gestation until birth. This 30-week period of development is marked by continued cell growth and differentiation, which fully develop the structures and functions of the immature organ systems formed during the embryonic period. The completion of fetal development results in a newborn who, although still immature in many ways, is capable of survival outside the womb.

Sexual differentiation does not begin until the fetal period, during weeks 9–12. Embryonic males and females, though genetically distinguishable, are morphologically identical (Figure 8.3.1). Bipotential gonads, or gonads that can develop into male or female sexual organs, are connected to a central cavity called the cloaca via Müllerian ducts and Wolffian ducts. (The cloaca is an extension of the primitive gut.) Several events lead to sexual differentiation during this period.

During male fetal development, the bipotential gonads become the testes and associated epididymis. The Müllerian ducts degenerate. The Wolffian ducts become the vas deferens, and the cloaca becomes the urethra and rectum.

During female fetal development, the bipotential gonads develop into ovaries. The Wolffian ducts degenerate. The Müllerian ducts become the uterine tubes and uterus, and the cloaca divides and develops into a vagina, a urethra, and a rectum.

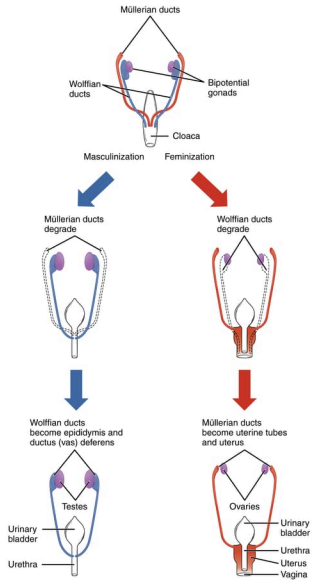


Figure 8.3.1: Differentiation of the male and female reproductive systems does not occur until the fetal period of development. (CC BY 4.0 ; via Fetal Development). Detailed text description of the Figure 8.3.1.

The Fetal Circulatory System

During prenatal development, the fetal circulatory system is integrated with the placenta via the umbilical cord so that the fetus receives both oxygen and nutrients from the placenta. However, after childbirth, the umbilical cord is severed, and the newborn's circulatory system must be reconfigured. When the heart first forms in the embryo, it exists as two parallel tubes derived from mesoderm and lined with endothelium, which then fuse together. As the embryo develops into a fetus, the tube-shaped heart folds and further differentiates into the four chambers present in a mature heart. Unlike a mature cardiovascular system, however, the fetal cardiovascular system also includes circulatory shortcuts, or shunts. A shunt is an anatomical (or sometimes surgical) diversion that allows blood flow to bypass immature organs such as the lungs and liver until childbirth.

The placenta provides the fetus with necessary oxygen and nutrients via the umbilical vein. (Remember that veins carry blood toward the heart. In this case, the blood flowing to the fetal heart is oxygenated because it comes from the placenta. The

respiratory system is immature and cannot yet oxygenate blood on its own.) From the umbilical vein, the oxygenated blood flows toward the inferior vena cava, all but bypassing the immature liver, via the ductus venosus shunt (Figure 8.3.2). The liver receives just a trickle of blood, which is all that it needs in its immature, semi functional state. Blood flows from the inferior vena cava to the right atrium, mixing with fetal venous blood along the way.

Although the fetal liver is semi functional, the fetal lungs are nonfunctional. The fetal circulation therefore bypasses the lungs by shifting some of the blood through the foramen ovale, a shunt that directly connects the right and left atria and avoids the pulmonary trunk altogether. Most of the rest of the blood is pumped to the right ventricle, and from there, into the pulmonary trunk, which splits into pulmonary arteries. However, a shunt within the pulmonary artery, the ductus arteriosus, diverts a portion of this blood into the aorta. This ensures that only a small volume of oxygenated blood passes through the immature pulmonary circuit, which has only minor metabolic requirements. Blood vessels of uninflated lungs have high resistance to flow, a condition that encourages blood to flow to the aorta, which presents much lower resistance. The oxygenated blood moves through the foramen ovale into the left atrium, where it mixes with the now deoxygenated blood returning from the pulmonary circuit. This blood then moves into the left ventricle, where it is pumped into the aorta. Some of this blood moves through the coronary arteries into the myocardium, and some moves through the carotid arteries to the brain.

The descending aorta carries partially oxygenated and partially deoxygenated blood into the lower regions of the body. It eventually passes into the umbilical arteries through branches of the internal iliac arteries. The deoxygenated blood collects waste as it circulates through the fetal body and returns to the umbilical cord. Thus, the two umbilical arteries carry blood low in oxygen and high in carbon dioxide and fetal wastes. This blood is filtered through the placenta, where wastes diffuse into the maternal circulation. Oxygen and nutrients from the pregnant person diffuse into the placenta and from there into the fetal blood, and the process repeats.

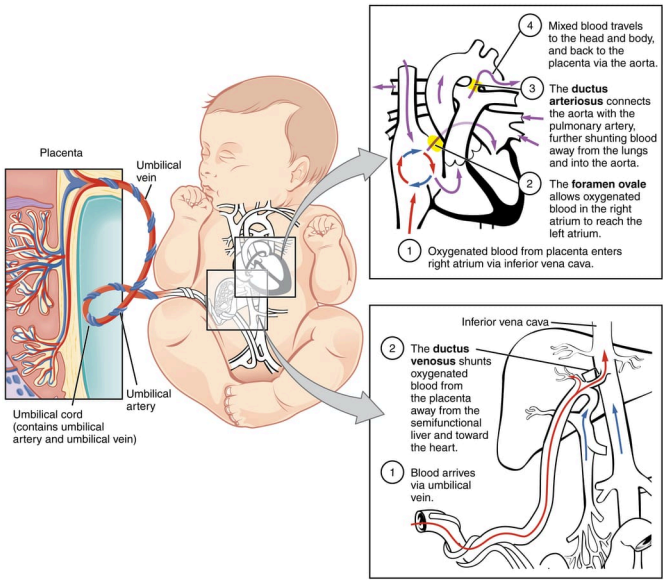


Figure 8.3.2: The fetal circulatory system includes three shunts to divert blood from undeveloped and partially functioning organs, as well as blood supply to and from the placenta. (CC BY 4.0 ; via Fetal Development). Detailed text description of the Figure 8.3.2.

Other Organ Systems

During weeks 9–12 of fetal development, the brain continues to expand, the body elongates, and ossification continues. Fetal movements are frequent during this period, but are jerky and not well-controlled. The bone marrow begins to take over the process of erythrocyte production—a task that the liver performed during the embryonic period. The liver now secretes bile. The fetus circulates amniotic fluid by swallowing it and producing urine. The eyes are well-developed by this stage, but the eyelids are fused shut. The fingers and toes begin to develop nails. By the end of week 12, the fetus measures approximately 9 cm (3.5 in) from crown to rump.

Weeks 13–16 are marked by sensory organ development. The eyes move closer together; blinking motions begin, although the eyes remain sealed shut. The lips exhibit sucking motions. The ears move upward and lie flatter against the head. The scalp begins to grow hair. The excretory system is also developing: the kidneys are well-formed, and meconium, or fetal feces, begins

to accumulate in the intestines. Meconium consists of ingested amniotic fluid, cellular debris, mucus, and bile.

During approximately weeks 16–20, as the fetus grows and limb movements become more powerful, the pregnant person may begin to feel quickening, or fetal movements. However, space restrictions limit these movements and typically force the growing fetus into the "fetal position," with the arms crossed and the legs bent at the knees. Sebaceous glands coat the skin with a waxy, protective substance called vernix caseosa that protects and moisturizes the skin and may provide lubrication during childbirth. A silky hair called lanugo also covers the skin during weeks 17–20, but it is shed as the fetus continues to grow. Extremely premature infants sometimes exhibit residual lanugo.

Developmental weeks 21–30 are characterized by rapid weight gain, which is important for maintaining a stable body temperature after birth. The bone marrow completely takes over erythrocyte synthesis, and the axons of the spinal cord begin to be myelinated, or coated in the electrically insulating glial cell sheaths that are necessary for efficient nervous system functioning. (The process of myelination is not completed until adolescence.) During this period, the fetus grows eyelashes. The eyelids are no longer fused and can be opened and closed. The lungs begin producing surfactant, a substance that reduces surface tension in the lungs and assists proper lung expansion after birth. Inadequate surfactant production in premature newborns may result in respiratory distress syndrome, and as a result, the newborn may require surfactant replacement therapy, supplemental oxygen, or maintenance in a continuous positive airway pressure (CPAP) chamber during their first days or weeks of life. In male fetuses, the testes descend into the scrotum near the end of this period. The fetus at 30 weeks measures 28 cm (11 in) from crown to rump and exhibits the approximate body proportions of a full-term newborn, but still is much leaner.

The fetus continues to lay down subcutaneous fat from week 31 until birth. The added fat fills out the hypodermis, and the skin transitions from red and wrinkled to soft and pink. Lanugo is shed, and the nails grow to the tips of the fingers and toes. Immediately before birth, the average crown-to-rump length is 35.5–40.5 cm (14–16 in), and the fetus weighs approximately 2.5–4 kg (5.5–8.8 lbs). Once born, the newborn is no longer confined to the fetal position, so subsequent measurements are made from head-to-toe instead of from crown-to-rump. At birth, the average length is approximately 51 cm (20 in).

Disorders of the...

Developing Fetus

Throughout the second half of gestation, the fetal intestines accumulate a tarry, greenish black meconium. The newborn's first stools consist almost entirely of meconium; they later transition to seedy yellow stools or slightly formed tan stools as meconium is cleared and replaced with digested breast milk or formula, respectively. Unlike these later stools, meconium is sterile; it is devoid of bacteria because the fetus is in a sterile environment and has not consumed any breast milk or formula. Typically, an infant does not pass meconium until after birth. However, in 5–20 percent of births, the fetus has a bowel movement in utero, which can cause major complications in the newborn.

The passage of meconium in the uterus signals fetal distress, particularly fetal hypoxia (i.e., oxygen deprivation). This may be caused by maternal drug abuse (especially tobacco or cocaine), maternal hypertension, depletion of amniotic fluid, long labor or difficult birth, or a defect in the placenta that prevents it from delivering adequate oxygen to the fetus. Meconium passage is typically a complication of full-term or post-term newborns because it is rarely passed before 34 weeks of gestation, when the gastrointestinal system has matured and is appropriately controlled by nervous system stimuli. Fetal distress can stimulate the vagus nerve to trigger gastrointestinal peristalsis and relaxation of the anal sphincter. Notably, fetal hypoxic stress also induces a gasping reflex, increasing the likelihood that meconium will be inhaled into the fetal lungs.

Although meconium is a sterile substance, it interferes with the antibiotic properties of the amniotic fluid and makes the newborn and pregnant person more vulnerable to bacterial infections at birth and during the perinatal period. Specifically, inflammation of the fetal membranes, inflammation of the uterine lining, or neonatal sepsis (infection in the newborn) may occur. Meconium also irritates delicate fetal skin and can cause a rash.

The first sign that a fetus has passed meconium usually does not come until childbirth, when the amniotic sac ruptures. Normal amniotic fluid is clear and watery, but amniotic fluid in which meconium has been passed is stained greenish or yellowish.

Aspiration of meconium with the first breath can result in labored breathing, a barrel-shaped chest, or a low Apgar score. An obstetrician can identify meconium aspiration by listening to the lungs with a stethoscope for a coarse rattling sound. Blood gas tests and chest X-rays of the infant can confirm meconium aspiration. Inhaled meconium after birth could

obstruct a newborn's airways leading to alveolar collapse, interfere with surfactant function by stripping it from the lungs, or cause pulmonary inflammation or hypertension. Any of these complications will make the newborn much more vulnerable to pulmonary infection, including pneumonia.

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8.4: Changes During Pregnancy, Labor, and Birth

Physiology of Pregnancy and the Process of Childbirth

A full-term pregnancy lasts approximately 270 days (approximately 38.5 weeks) from conception to birth. Because it is easier to remember the first day of the last menstrual period (LMP) than to estimate the date of conception, obstetricians set the due date as 284 days (approximately 40.5 weeks) from the LMP. This assumes that conception occurred on day 14 of the menstrual cycle, which is usually a good approximation. The 40 weeks of an average pregnancy are usually discussed in terms of three trimesters, each approximately 13 weeks. During the second and third trimesters, the pre-pregnancy uterus—about the size of a fist—grows dramatically to contain the fetus, causing a number of anatomical changes in the pregnant person (Figure 8.4.1).

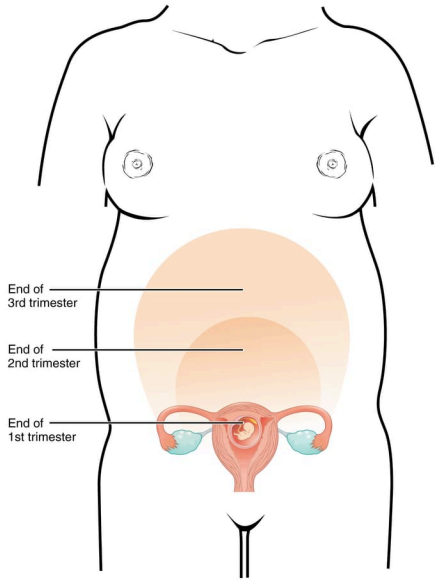


Figure 8.4.1: The uterus grows throughout pregnancy to accommodate the fetus. (CC BY 4.0 ; via Changes During Pregnancy, Labor and Birth).
Detailed text description of the Figure 8.4.1.

Effects of Hormones

Virtually all of the effects of pregnancy can be attributed in some way to the influence of hormones—particularly estrogens, progesterone, and hCG. During weeks 7–12 from the LMP, the pregnancy hormones are primarily generated by the corpus luteum. Progesterone secreted by the corpus luteum stimulates the production of decidual cells of the endometrium that nourish the blastocyst before placentation. As the placenta develops and the corpus luteum degenerates during weeks 12–17, the placenta gradually takes over as the endocrine organ of pregnancy.

The placenta converts weak androgens secreted by the maternal and fetal adrenal glands to estrogens, which are necessary for pregnancy to progress. Estrogen levels climb throughout the pregnancy, increasing 30-fold by childbirth. Estrogens have the following actions:

- They suppress FSH and LH production, effectively preventing ovulation. (This function is the biological basis of hormonal birth control pills.)
- They induce the growth of fetal tissues and are necessary for the maturation of the fetal lungs and liver.
- They promote fetal viability by regulating progesterone production and triggering fetal synthesis of cortisol, which helps with the maturation of the lungs, liver, and endocrine organs such as the thyroid gland and adrenal gland.
- They stimulate maternal tissue growth, leading to uterine enlargement and mammary duct expansion and branching.

Relaxin, another hormone secreted by the corpus luteum and then by the placenta, helps prepare the body for childbirth. It increases the elasticity of the symphysis pubis joint and pelvic ligaments, making room for the growing fetus and allowing

expansion of the pelvic outlet for childbirth. Relaxin also helps dilate the cervix during labor.

The placenta takes over the synthesis and secretion of progesterone throughout pregnancy as the corpus luteum degenerates. Like estrogen, progesterone suppresses FSH and LH. It also inhibits uterine contractions, protecting the fetus from preterm birth. This hormone decreases in late gestation, allowing uterine contractions to intensify and eventually progress to true labor. The placenta also produces hCG. In addition to promoting survival of the corpus luteum, hCG stimulates the male fetal gonads to secrete testosterone, which is essential for the development of the male reproductive system.

The anterior pituitary enlarges and ramps up its hormone production during pregnancy, raising the levels of thyrotropin, prolactin, and adrenocorticotropic hormone (ACTH). Thyrotropin, in conjunction with placental hormones, increases the production of thyroid hormone, which raises the maternal metabolic rate. This can markedly augment a pregnant person's appetite and cause hot flashes. Prolactin stimulates enlargement of the mammary glands in preparation for milk production. ACTH stimulates maternal cortisol secretion, which contributes to fetal protein synthesis. In addition to the pituitary hormones, increased parathyroid levels mobilize calcium from maternal bones for fetal use.

Weight Gain

The second and third trimesters of pregnancy are associated with dramatic changes in maternal anatomy and physiology. The most obvious anatomical sign of pregnancy is the dramatic enlargement of the abdominal region, coupled with weight gain. This weight results from the growing fetus as well as the enlarged uterus, amniotic fluid, and placenta. Additional breast tissue and dramatically increased blood volume also contribute to weight gain (Table 8.4.1). Surprisingly, fat storage accounts for only approximately 2.3 kg (5 lbs) in a normal pregnancy and serves as a reserve for the increased metabolic demand of breastfeeding.

During the first trimester, a pregnant person does not need to consume additional calories to maintain a healthy pregnancy. However, a weight gain of approximately 0.45 kg (1 lb) per month is common. During the second and third trimesters, the appetite increases, but it is only necessary to consume an additional 300 calories per day to support the growing fetus. Most pregnant people gain approximately 0.45 kg (1 lb) per week.

Table 8.4.1: Contributors to Weight Gain During Pregnancy

Component	Weight (kg)	Weight (lb)
Fetus	3.2–3.6	7–8
Placenta and fetal membranes	0.9–1.8	2–4
Amniotic fluid	0.9–1.4	2–3
Breast tissue	0.9–1.4	2–3
Blood	1.4	4
Fat	0.9–4.1	3–9
Uterus	0.9–2.3	2–5
Total	10–16.3	22–36

Changes in Organ Systems During Pregnancy

As the body adapts to pregnancy, characteristic physiologic changes occur. These changes can sometimes prompt symptoms often referred to collectively as the common discomforts of pregnancy.

Digestive and Urinary System Changes

Nausea and vomiting, sometimes triggered by an increased sensitivity to odors, are common during the first few weeks to months of pregnancy. This phenomenon is often referred to as “morning sickness,” although the nausea may persist all day. The source of pregnancy nausea is thought to be the increased circulation of pregnancy-related hormones, specifically circulating estrogen, progesterone, and hCG. Decreased intestinal peristalsis may also contribute to nausea. By about week 12 of pregnancy, nausea typically subsides.

A common gastrointestinal complaint during the later stages of pregnancy is gastric reflux, or heartburn, which results from the upward, constrictive pressure of the growing uterus on the stomach. The same decreased peristalsis that may contribute to nausea in early pregnancy is also thought to be responsible for pregnancy-related constipation as pregnancy progresses.

The downward pressure of the uterus also compresses the urinary bladder, leading to frequent urination. The problem is exacerbated by increased urine production. In addition, the maternal urinary system processes both maternal and fetal wastes, further increasing the total volume of urine.

Circulatory System Changes

Blood volume increases substantially during pregnancy, so that by childbirth, it exceeds its preconception volume by 30 percent, or approximately 1–2 liters. The greater blood volume helps to manage the demands of fetal nourishment and fetal waste removal. In conjunction with increased blood volume, the pulse and blood pressure also rise moderately during pregnancy. As the fetus grows, the uterus compresses underlying pelvic blood vessels, hampering venous return from the legs and pelvic region. As a result, many pregnant people develop varicose veins or hemorrhoids.

Respiratory System Changes

During the second half of pregnancy, the respiratory minute volume (volume of gas inhaled or exhaled by the lungs per minute) increases by 50 percent to compensate for the oxygen demands of the fetus and the increased maternal metabolic rate. The growing uterus exerts upward pressure on the diaphragm, decreasing the volume of each inspiration and potentially causing shortness of breath, or dyspnea. During the last several weeks of pregnancy, the pelvis becomes more elastic, and the fetus descends lower in a process called lightening. This typically ameliorates dyspnea.

The respiratory mucosa swell in response to increased blood flow during pregnancy, leading to nasal congestion and nose bleeds, particularly when the weather is cold and dry. Humidifier use and increased fluid intake are often recommended to counteract congestion.

Integumentary System Changes

The dermis stretches extensively to accommodate the growing uterus, breast tissue, and fat deposits on the thighs and hips. Torn connective tissue beneath the dermis can cause striae (stretch marks) on the abdomen, which appear as red or purple marks during pregnancy that fade to a silvery white color in the months after childbirth.

An increase in melanocyte-stimulating hormone, in conjunction with estrogens, darkens the areolae and creates a line of pigment from the umbilicus to the pubis called the linea nigra (Figure 8.4.2). Melanin production during pregnancy may also darken or discolor skin on the face to create a chloasma, or “mask of pregnancy.”



Figure 8.4.2: The linea nigra, a dark medial line running from the umbilicus to the pubis, forms during pregnancy and persists for a few weeks following childbirth. The linea nigra shown here corresponds to a pregnancy that is 22 weeks along. (CC BY 4.0 ; via Changes During Pregnancy, Labor and Birth).

Physiology of Labor

Childbirth, or parturition, typically occurs within a week of the due date, unless the pregnancy involves more than one fetus, which usually causes labor to begin early. As a pregnancy progresses into its final weeks, several physiological changes occur in response to hormones that trigger labor.

First, recall that progesterone inhibits uterine contractions throughout the first several months of pregnancy. As the pregnancy enters its seventh month, progesterone levels plateau and then drop. Estrogen levels, however, continue to rise in the maternal circulation (Figure 8.4.3). The increasing ratio of estrogen to progesterone makes the myometrium (the uterine smooth muscle) more sensitive to stimuli that promote contractions (because progesterone no longer inhibits them). Moreover, in the eighth month of pregnancy, fetal cortisol rises, which boosts estrogen secretion by the placenta and further overpowers the uterine-calming effects of progesterone. Some people may feel the result of the decreasing levels of progesterone in late pregnancy as weak and irregular peristaltic Braxton Hicks contractions, also called false labor. These contractions can often be relieved with rest or hydration.

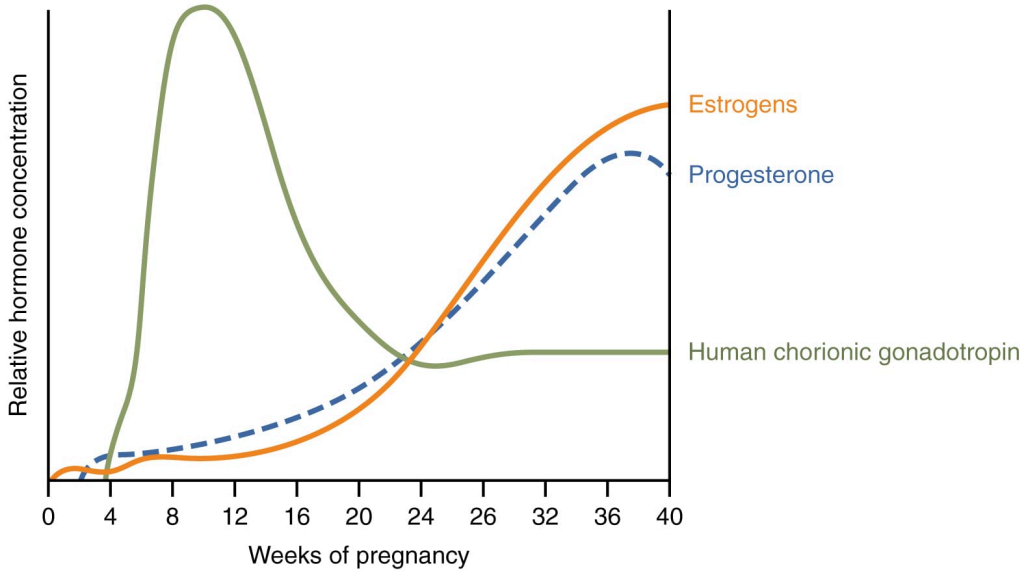


Figure 8.4.3: A positive feedback loop of hormones works to initiate labor. (CC BY 4.0 ; via Changes During Pregnancy, Labor and Birth). Detailed text description of the Figure 8.4.3.

A common sign that labor will be short is the so-called "bloody show." During pregnancy, a plug of mucus accumulates in the cervical canal, blocking the entrance to the uterus. Approximately 1–2 days prior to the onset of true labor, this plug loosens and is expelled, along with a small amount of blood.

Meanwhile, the posterior pituitary has been boosting its secretion of oxytocin, a hormone that stimulates the contractions of labor. At the same time, the myometrium increases its sensitivity to oxytocin by expressing more receptors for this hormone. As labor nears, oxytocin begins to stimulate stronger, more painful uterine contractions, which—in a positive feedback loop—stimulate the secretion of prostaglandins from fetal membranes. Like oxytocin, prostaglandins also enhance uterine contractile strength. The fetal pituitary also secretes oxytocin, which increases prostaglandins even further. Given the importance of oxytocin and prostaglandins to the initiation and maintenance of labor, it is not surprising that, when a pregnancy is not progressing to labor and needs to be induced, a pharmaceutical version of these compounds (called pitocin) is administered by intravenous drip.

Finally, stretching of the myometrium and cervix by a full-term fetus in the vertex (head-down) position is regarded as a stimulant to uterine contractions. The sum of these changes initiates the regular contractions known as true labor, which become more powerful and more frequent with time. The pain of labor is attributed to myometrial hypoxia during uterine contractions.

Stages of Childbirth

The process of childbirth can be divided into three stages: cervical dilation, expulsion of the newborn, and afterbirth (Figure 8.4.4).

Cervical Dilation

For vaginal birth to occur, the cervix must dilate fully to 10 cm in diameter—wide enough to deliver the newborn's head. The dilation stage is the longest stage of labor and typically takes 6–12 hours. However, it varies widely and may take minutes, hours, or days, depending in part on whether the person has given birth before; in each subsequent labor, this stage tends to be shorter.

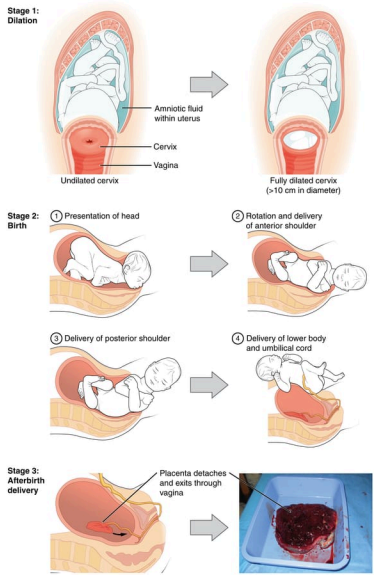


Figure 8.4.4: The stages of childbirth include Stage 1, early cervical dilation; Stage 2, full dilation and expulsion of the newborn; and Stage 3, delivery of the placenta and associated fetal membranes. (The position of the newborn's shoulder is described relative to the person giving birth). (CC BY 4.0 ; via Changes During Pregnancy, Labor and Birth). Detailed text description of the Figure 8.4.4.

True labor progresses in a positive feedback loop in which uterine contractions stretch the cervix, causing it to dilate and efface, or become thinner. Cervical stretching induces reflexive uterine contractions that dilate and efface the cervix further. In addition, cervical dilation boosts oxytocin secretion from the pituitary, which in turn triggers more powerful uterine contractions. When labor begins, uterine contractions may occur only every 3–30 minutes and last only 20–40 seconds; however, by the end of this stage, contractions may occur as frequently as every 1.5–2 minutes and last for a full minute.

Each contraction sharply reduces oxygenated blood flow to the fetus. For this reason, it is critical that a period of relaxation occur after each contraction. Fetal distress, measured as a sustained decrease or increase in the fetal heart rate, can result from severe contractions that are too powerful or lengthy for oxygenated blood to be restored to the fetus. Such a situation can be cause for an emergency birth with vacuum, forceps, or surgically by Caesarian section.

The amniotic membranes rupture before the onset of labor in about 12 percent of people; they typically rupture at the end of the dilation stage in response to excessive pressure from the fetal head entering the birth canal.

Expulsion Stage

The expulsion stage begins when the fetal head enters the birth canal and ends with birth of the newborn. It typically takes up to 2 hours, but it can last longer or be completed in minutes, depending in part on the orientation of the fetus. The vertex presentation known as the occiput anterior vertex is the most common presentation and is associated with the greatest ease of vaginal birth. The fetus faces the maternal spinal cord and the smallest part of the head (the posterior aspect called the occiput) exits the birth canal first.

In fewer than 5 percent of births, the infant is oriented in the breech presentation, or buttocks down. In a complete breech, both legs are crossed and oriented downward. In a frank breech presentation, the legs are oriented upward. Before the 1960s, it was common for breech presentations to be delivered vaginally. Today, most breech births are accomplished by Caesarian section.

Vaginal birth is associated with significant stretching of the vaginal canal, the cervix, and the perineum. Until recent decades, it was routine procedure for an obstetrician to numb the perineum and perform an episiotomy, an incision in the posterior vaginal wall and perineum. The perineum is now more commonly allowed to tear on its own during birth. Both an episiotomy and a perineal tear need to be sutured shortly after birth to ensure optimal healing. Although suturing the jagged edges of a perineal tear may be more difficult than suturing an episiotomy, tears heal more quickly, are less painful, and are associated with less damage to the muscles around the vagina and rectum.

Upon birth of the newborn's head, an obstetrician will aspirate mucus from the mouth and nose before the newborn's first breath. Once the head is birthed, the rest of the body usually follows quickly. The umbilical cord is then double-clamped, and a cut is

made between the clamps. This completes the second stage of childbirth.

Afterbirth

The delivery of the placenta and associated membranes, commonly referred to as the afterbirth, marks the final stage of childbirth. After expulsion of the newborn, the myometrium continues to contract. This movement shears the placenta from the back of the uterine wall. It is then easily delivered through the vagina. Continued uterine contractions then reduce blood loss from the site of the placenta. Delivery of the placenta marks the beginning of the postpartum period—the period of approximately 6 weeks immediately following childbirth during which the body gradually returns to a non-pregnant state. If the placenta does not birth spontaneously within approximately 30 minutes, it is considered retained, and the obstetrician may attempt manual removal. If this is not successful, surgery may be required.

It is important that the obstetrician examines the expelled placenta and fetal membranes to ensure that they are intact. If fragments of the placenta remain in the uterus, they can cause postpartum hemorrhage. Uterine contractions continue for several hours after birth to return the uterus to its pre-pregnancy size in a process called involution, which also allows the abdominal organs to return to their pre-pregnancy locations. Breastfeeding facilitates this process.

Although postpartum uterine contractions limit blood loss from the detachment of the placenta, the person who has recently given birth does experience a postpartum vaginal discharge called lochia. This is made up of uterine lining cells, erythrocytes, leukocytes, and other debris. Thick, dark, lochia rubra (red lochia) typically continues for 2–3 days, and is replaced by lochia serosa, a thinner, pinkish form that continues until about the tenth postpartum day. After this period, a scant, creamy, or watery discharge called lochia alba (white lochia) may continue for another 1–2 weeks.

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8.5: Adjustments of the Infant at Birth and Postnatal Stages

Fetal to Neonatal Transition

From a fetal perspective, the process of birth is a crisis. In the womb, the fetus was snuggled in a soft, warm, dark, and quiet world. The placenta provided nutrition and oxygen continuously. Suddenly, the contractions of labor and vaginal childbirth forcibly squeeze the fetus through the birth canal, limiting oxygenated blood flow during contractions and shifting the skull bones to accommodate the small space. After birth, the newborn's system must make drastic adjustments to a world that is colder, brighter, and louder, and where they will experience hunger and thirst. The neonatal period (neo- = "new"; -natal = "birth") spans the first to the thirtieth day of life outside of the uterus.

Respiratory Adjustments

Although the fetus "practices" breathing by inhaling amniotic fluid in utero, there is no air in the uterus and thus no true opportunity to breathe. (There is also no need to breathe because the placenta supplies the fetus with all the oxygenated blood it needs.) During gestation, the partially collapsed lungs are filled with amniotic fluid and exhibit very little metabolic activity. Several factors stimulate newborns to take their first breath at birth. First, labor contractions temporarily constrict umbilical blood vessels, reducing oxygenated blood flow to the fetus and elevating carbon dioxide levels in the blood. High carbon dioxide levels cause acidosis and stimulate the respiratory center in the brain, triggering the newborn to take a breath.

The first breath typically is taken within 10 seconds of birth, after mucus is aspirated from the infant's mouth and nose. The first breaths inflate the lungs to nearly full capacity and dramatically decrease lung pressure and resistance to blood flow, causing a major circulatory reconfiguration. Pulmonary alveoli open, and alveolar capillaries fill with blood. Amniotic fluid in the lungs drains or is absorbed, and the lungs immediately take over the task of the placenta, exchanging carbon dioxide for oxygen by the process of respiration.

Circulatory Adjustments

The process of clamping and cutting the umbilical cord collapses the umbilical blood vessels. In the absence of medical assistance, this occlusion would occur naturally within 20 minutes of birth because the Wharton's jelly within the umbilical cord would swell in response to the lower temperature outside of the mother's body, and the blood vessels would constrict. Natural occlusion has occurred when the umbilical cord is no longer pulsating. For the most part, the collapsed vessels atrophy and become fibrotic remnants, existing in the mature circulatory system as ligaments of the abdominal wall and liver. The ductus venosus degenerates to become the ligamentum venosum beneath the liver. Only the proximal sections of the two umbilical arteries remain functional, taking on the role of supplying blood to the upper part of the bladder (Figure 8.5.1).

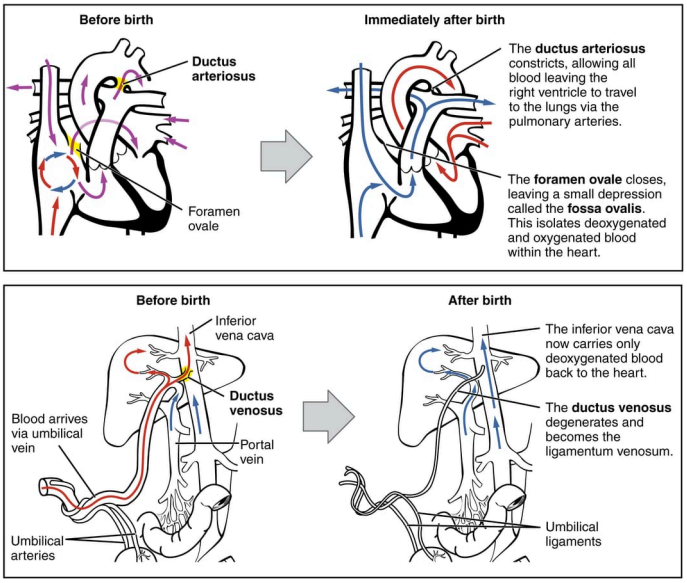


Figure 8.5.1: A newborn's circulatory system reconfigures immediately after birth. The three fetal shunts have been closed permanently, facilitating blood flow to the liver and lungs. (CC BY 4.0; via Anatomy and Physiology). Detailed text description of the Figure 8.5.1.

The newborn's first breath is vital to initiate the transition from the fetal to the neonatal circulatory pattern. Inflation of the lungs decreases blood pressure throughout the pulmonary system, as well as in the right atrium and ventricle. In response to this pressure change, the flow of blood temporarily reverses direction through the foramen ovale, moving from the left to the right atrium, and blocking the shunt with two flaps of tissue. Within 1 year, the tissue flaps usually fuse over the shunt, turning the foramen ovale into the fossa ovalis. The ductus arteriosus constricts as a result of increased oxygen concentration, and becomes the ligamentum arteriosum. Closing of the ductus arteriosus ensures that all blood pumped to the pulmonary circuit will be oxygenated by the newly functional neonatal lungs.

Thermoregulatory Adjustments

The fetus floats in warm amniotic fluid that is maintained at a temperature of approximately 98.6°F with very little fluctuation. Birth exposes newborns to a cooler environment in which they have to regulate their own body temperature. Newborns have a higher ratio of surface area to volume than adults. This means that their body has less volume throughout which to produce heat, and more surface area from which to lose heat. As a result, newborns produce heat more slowly and lose it more quickly. Newborns also have immature musculature that limits their ability to generate heat by shivering. Moreover, their nervous systems are underdeveloped, so they cannot quickly constrict superficial blood vessels in response to cold. They also have little subcutaneous fat for insulation. All these factors make it harder for newborns to maintain their body temperature.

Newborns, however, do have a special method for generating heat: nonshivering thermogenesis, which involves the breakdown of brown adipose tissue, or brown fat, which is distributed over the back, chest, and shoulders. Brown fat differs from the more familiar white fat in two ways:

- It is highly vascularized. This allows for faster delivery of oxygen, which leads to faster cellular respiration.
- It is packed with a special type of mitochondria that are able to engage in cellular respiration reactions that produce less ATP and more heat than standard cellular respiration reactions.

The breakdown of brown fat occurs automatically upon exposure to cold, so it is an important heat regulator in newborns. During fetal development, the placenta secretes inhibitors that prevent metabolism of brown adipose fat and promote its accumulation in preparation for birth.

Gastrointestinal and Urinary Adjustments

In adults, the gastrointestinal tract harbors bacterial flora—trillions of bacteria that aid in digestion, produce vitamins, and protect from the invasion or replication of pathogens. In stark contrast, the fetal intestine is sterile. The first consumption of breast milk or formula floods the neonatal gastrointestinal tract with beneficial bacteria that begin to establish the bacterial flora.

The fetal kidneys filter blood and produce urine, but the neonatal kidneys are still immature and inefficient at concentrating urine. Therefore, newborns produce very dilute urine, making it particularly important for infants to obtain sufficient fluids from breast milk or formula.

Homeostatic Imbalances

Homeostasis in the Newborn: Apgar Score

In the minutes following birth, a newborn must undergo dramatic systemic changes to be able to survive outside the womb. An obstetrician, midwife, or nurse can estimate how well a newborn is doing by obtaining an Apgar score. The Apgar score was introduced in 1952 by the anesthesiologist Dr. Virginia Apgar as a method to assess the effects on the newborn of anesthesia given to the person giving birth. Healthcare providers now use it to assess the general wellbeing of the newborn, whether or not analgesics or anesthetics were used.

Five criteria—skin color, heart rate, reflex, muscle tone, and respiration—are assessed, and each criterion is assigned a score of 0, 1, or 2. Scores are taken at 1 minute after birth and again at 5 minutes after birth. Each time that scores are taken, the five scores are added together. High scores (out of a possible 10) indicate the baby has made the transition from the womb well, whereas lower scores indicate that the baby may be in distress.

The technique for determining an Apgar score is quick and easy, painless for the newborn, and does not require any instruments except for a stethoscope. A convenient way to remember the five scoring criteria is to apply the mnemonic APGAR, for “appearance” (skin color), “pulse” (heart rate), “grimace” (reflex), “activity” (muscle tone), and “respiration.”

Of the five Apgar criteria, heart rate and respiration are the most critical. Poor scores for either of these measurements may indicate the need for immediate medical attention to resuscitate or stabilize the newborn. In general, any score lower than 7 at the 5-minute mark indicates that medical assistance may be needed. A total score below 5 indicates an emergency situation. Normally, a newborn will get an intermediate score of 1 for some of the Apgar criteria and will progress to a 2 by the 5-minute assessment. Scores of 8 or above are normal.

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8.6: Lactation

Structure of the Lactating Breast

Lactation is the process by which milk is synthesized and secreted from the mammary glands of the postpartum female breast in response to an infant sucking at the nipple. Breast milk provides ideal nutrition and passive immunity for the infant, encourages mild uterine contractions to return the uterus to its pre-pregnancy size (i.e., involution), and induces a substantial metabolic increase in the postpartum person, consuming the fat reserves stored during pregnancy.

Mammary glands are modified sweat glands. The non-pregnant and non-lactating female breast is composed primarily of adipose and collagenous tissue, with mammary glands making up a very minor proportion of breast volume. The mammary gland is composed of milk-transporting lactiferous ducts, which expand and branch extensively during pregnancy in response to estrogen, growth hormone, cortisol, and prolactin. Moreover, in response to progesterone, clusters of breast alveoli bud from the ducts and expand outward toward the chest wall. Breast alveoli are balloon-like structures lined with milk-secreting cuboidal cells, or lactocytes, that are surrounded by a net of contractile myoepithelial cells. Milk is secreted from the lactocytes, fills the alveoli, and is squeezed into the ducts. Clusters of alveoli that drain to a common duct are called lobules; the lactating female has 12–20 lobules organized radially around the nipple. Milk drains from lactiferous ducts into lactiferous sinuses that meet at 4 to 18 perforations in the nipple, called nipple pores. The small bumps of the areola (the darkened skin around the nipple) are called Montgomery glands. They secrete oil to cleanse the nipple opening and prevent chapping and cracking of the nipple during breastfeeding.

The Process of Lactation

The pituitary hormone prolactin is instrumental in the establishment and maintenance of breast milk supply. It also is important for the mobilization of maternal micronutrients for breast milk.

Near the fifth week of pregnancy, the level of circulating prolactin begins to increase, eventually rising to approximately 10–20 times the pre-pregnancy concentration. We noted earlier that, during pregnancy, prolactin and other hormones prepare the breasts anatomically for the secretion of milk. The level of prolactin plateaus in late pregnancy, at a level high enough to initiate milk production. However, estrogen, progesterone, and other placental hormones inhibit prolactin-mediated milk synthesis during pregnancy. It is not until the placenta is expelled that this inhibition is lifted and milk production commences.

After childbirth, the baseline prolactin level drops sharply, but it is restored for a 1-hour spike during each feeding to stimulate the production of milk for the next feeding. With each prolactin spike, estrogen and progesterone also increase slightly.

When the infant suckles, sensory nerve fibers in the areola trigger a neuroendocrine reflex that results in milk secretion from lactocytes into the alveoli. The posterior pituitary releases oxytocin, which stimulates myoepithelial cells to squeeze milk from the alveoli so it can drain into the lactiferous ducts, collect in the lactiferous sinuses, and discharge through the nipple pores. It takes less than 1 minute from the time when an infant begins suckling (the latent period) until milk is secreted (the let-down). Figure 8.6.1 summarizes the positive feedback loop of the let-down reflex.

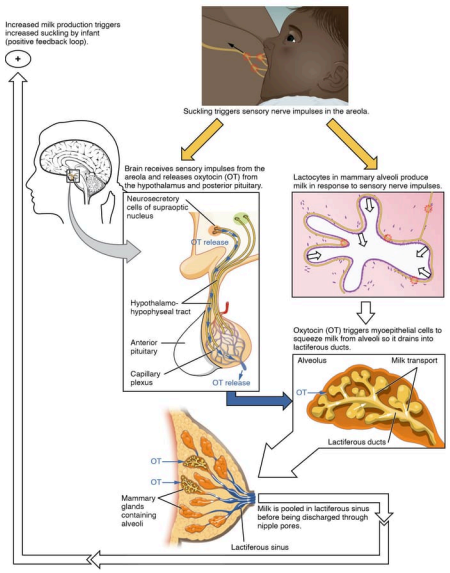


Figure 8.6.1: A positive feedback loop ensures continued milk production as long as the infant continues to breastfeed. (CC BY 4.0 ; via Lactation). Detailed text description of the Figure 8.6.1.

The prolactin-mediated synthesis of milk changes with time. Frequent milk removal by breastfeeding (or pumping) will maintain high circulating prolactin levels for several months. However, even with continued breastfeeding, baseline prolactin will decrease over time to its pre-pregnancy level. In addition to prolactin and oxytocin, growth hormone, cortisol, parathyroid hormone, and insulin contribute to lactation, in part by facilitating the transport of maternal amino acids, fatty acids, glucose, and calcium to breast milk.

Changes in the Composition of Breast Milk

In the final weeks of pregnancy, the alveoli swell with colostrum, a thick, yellowish substance that is high in protein but contains less fat and glucose than mature breast milk (Table 8.6.1). Before childbirth, some people experience leakage of colostrum from the nipples. In contrast, mature breast milk does not leak during pregnancy and is not secreted until several days after childbirth.

Table 8.6.1: Compositions of Human Colostrum, Mature Breast Milk, and Cow's Milk (g/L)

	Human colostrum	Human breast milk	Cow's milk*
Total protein	23	11	31
Immunoglobulins	19	0.1	1
Fat	30	45	38
Lactose	57	71	47
Calcium	0.5	0.3	1.4
Phosphorus	0.16	0.14	0.90
Sodium	0.50	0.15	0.41

*Cow's milk should never be given to an infant. Its composition is not suitable and its proteins are difficult for the infant to digest.

Colostrum is secreted during the first 48–72 hours postpartum. Only a small volume of colostrum is produced—approximately 3 ounces in a 24-hour period—but it is sufficient for the newborn in the first few days of life. Colostrum is rich with immunoglobulins, which confer gastrointestinal, and also likely systemic, immunity as the newborn adjusts to a nonsterile environment.

After about the third postpartum day, the breast secretes transitional milk that represents an intermediate between mature milk and colostrum. This is followed by mature milk from approximately postpartum day 10 (see Table 28.3). As you can see in the accompanying table, cow's milk is not a substitute for breast milk. It contains less lactose, less fat, and more protein and minerals.

Moreover, the proteins in cow's milk are difficult for an infant's immature digestive system to metabolize and absorb.

The first few weeks of breastfeeding may involve leakage, soreness, and periods of milk engorgement as the relationship between milk supply and infant demand becomes established. Once this period is complete, the lactating person will produce approximately 1.5 liters of milk per day for a single infant, and more if the person has twins or triplets. As the infant goes through growth spurts, the milk supply constantly adjusts to accommodate changes in demand. A person can continue to lactate for years, but once breastfeeding is stopped for approximately 1 week, any remaining milk will be reabsorbed; in most cases, no more will be produced, even if suckling or pumping is resumed.

Mature milk changes from the beginning to the end of a feeding. The early milk, called foremilk, is watery, translucent, and rich in lactose and protein. Its purpose is to quench the infant's thirst. Hindmilk is delivered toward the end of a feeding. It is opaque, creamy, and rich in fat, and serves to satisfy the infant's appetite.

During the first days of a newborn's life, it is important for meconium to be cleared from the intestines and for bilirubin to be kept low in the circulation. Recall that bilirubin, a product of erythrocyte breakdown, is processed by the liver and secreted in bile. It enters the gastrointestinal tract and exits the body in the stool. Breast milk has laxative properties that help expel meconium from the intestines and clear bilirubin through the excretion of bile. A high concentration of bilirubin in the blood causes jaundice. Some degree of jaundice is normal in newborns, but a high level of bilirubin—which is neurotoxic—can cause brain damage. Newborns, who do not yet have a fully functional blood–brain barrier, are highly vulnerable to the bilirubin circulating in the blood. Indeed, hyperbilirubinemia, a high level of circulating bilirubin, is the most common condition requiring medical attention in newborns. Newborns with hyperbilirubinemia are treated with phototherapy because UV light helps to break down the bilirubin quickly.

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8.7: Patterns of Inheritance

From Genotype to Phenotype

We have discussed the events that lead to the development of a newborn. But what makes each newborn unique? The answer lies, of course, in the DNA in the sperm and oocyte that combined to produce that first diploid cell, the human zygote.

Each human body cell has a full complement of DNA stored in 23 pairs of chromosomes. Figure 28.24 shows the pairs in a systematic arrangement called a karyotype. Among these is one pair of chromosomes, called the sex chromosomes, that determines the sex of the individual (XX in females, XY in males). The remaining 22 chromosome pairs are called autosomal chromosomes. Each of these chromosomes carries hundreds or even thousands of genes, each of which codes for the assembly of a particular protein—that is, genes are “expressed” as proteins. An individual’s complete genetic makeup is referred to as their genotype. The characteristics that the genes express, whether they are physical, behavioral, or biochemical, are a person’s phenotype.

In genetics and reproduction, "parent" is often used to describe the individual organisms that contribute genetic material to offspring, usually in the form of gamete cells and their chromosomes. The concept of a genetic parent is distinct from social and legal concepts of parenthood, and may differ from those whom people consider their parents.

You inherit one chromosome in each pair—a full complement of 23—from each parent. This occurs when the sperm and oocyte combine at the moment of your conception. Homologous chromosomes—those that make up a complementary pair—have genes for the same characteristics in the same location on the chromosome. Because one copy of a gene, an allele, is inherited from each parent, the alleles in these complementary pairs may vary. Take for example an allele that encodes for dimples. A child may inherit the allele encoding for dimples on the chromosome from the one parent and the allele that encodes for smooth skin (no dimples) on the chromosome from the other parent.

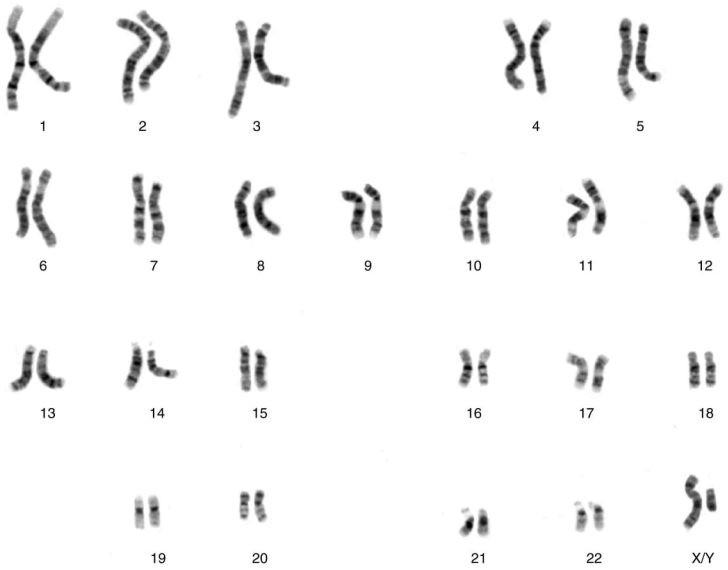


Figure 8.7.1: Each pair of chromosomes contains hundreds to thousands of genes. The banding patterns are nearly identical for the two chromosomes within each pair, indicating the same organization of genes. As is visible in this karyotype, the only exception to this is the XY sex chromosome pair in males. (CC BY 4.0; via Patterns of Inheritance). Detailed text description of the Figure 8.7.1.

Although a person can have two identical alleles for a single gene (a homozygous state), it is also possible for a person to have two different alleles (a heterozygous state). The two alleles can interact in several different ways. The expression of an allele can be dominant, for which the activity of this gene will mask the expression of a nondominant, or recessive, allele. Sometimes dominance is complete; at other times, it is incomplete. In some cases, both alleles are expressed at the same time in a form of expression known as codominance.

In the simplest scenario, a single pair of genes will determine a single heritable characteristic. However, it is quite common for multiple genes to interact to confer a feature. For instance, eight or more genes—each with their own alleles—determine eye color in humans. Moreover, although any one person can only have two alleles corresponding to a given gene, more than two alleles commonly exist in a population. This phenomenon is called multiple alleles. For example, there are three different alleles that encode ABO blood type; these are designated I^A, I^B, and i.

Over 100 years of theoretical and experimental genetics studies, and the more recent sequencing and annotation of the human genome, have helped scientists to develop a better understanding of how an individual's genotype is expressed as their phenotype. This body of knowledge can help scientists and medical professionals to predict, or at least estimate, some of the features that an offspring will inherit by examining the genotypes or phenotypes of the parents. One important application of this knowledge is to identify an individual's risk for certain heritable genetic disorders. However, most diseases have a multigenic pattern of inheritance and can also be affected by the environment, so examining the genotypes or phenotypes of a person's parents will provide only limited information about the risk of inheriting a disease. Only for a handful of single-gene disorders can genetic testing allow clinicians to calculate the probability with which a child born to the two parents tested may inherit a specific disease.

Mendel's Theory of Inheritance

Our contemporary understanding of genetics rests on the work of a nineteenth-century monk. Working in the mid-1800s, long before anyone knew about genes or chromosomes, Gregor Mendel discovered that garden peas transmit their physical characteristics to subsequent generations in a discrete and predictable fashion. When he mated, or crossed, two pure-breeding pea plants that differed by a certain characteristic, the first-generation offspring all looked like one of the parents. For instance, when he crossed tall and dwarf pure-breeding pea plants, all of the offspring were tall. Mendel called tallness dominant because it was expressed in offspring when it was present in a purebred parent. He called dwarfism recessive because it was masked in the offspring if one of the purebred parents possessed the dominant characteristic. Note that tallness and dwarfism are variations on the characteristic of height. Mendel called such a variation a trait. We now know that these traits are the expression of different alleles of the gene encoding height.

Mendel performed thousands of crosses in pea plants with differing traits for a variety of characteristics. And he repeatedly came up with the same results—among the traits he studied, one was always dominant, and the other was always recessive. (Remember, however, that this dominant–recessive relationship between alleles is not always the case; some alleles are codominant, and sometimes dominance is incomplete.)

Using his understanding of dominant and recessive traits, Mendel tested whether a recessive trait could be lost altogether in a pea lineage or whether it would resurface in a later generation. By crossing the second-generation offspring of purebred parents with each other, he showed that the latter was true: recessive traits reappeared in third-generation plants in a ratio of 3:1 (three offspring having the dominant trait and one having the recessive trait). Mendel then proposed that characteristics such as height were determined by heritable "factors" that were transmitted, one from each parent, and inherited in pairs by offspring.

In the language of genetics, Mendel's theory applied to humans says that if an individual receives two dominant alleles, one from each parent, the individual's phenotype will express the dominant trait. If an individual receives two recessive alleles, then the recessive trait will be expressed in the phenotype. Individuals who have two identical alleles for a given gene, whether dominant or recessive, are said to be homozygous for that gene (homo- = "same"). Conversely, an individual who has one dominant allele and one recessive allele is said to be heterozygous for that gene (hetero- = "different" or "other"). In this case, the dominant trait will be expressed, and the individual will be phenotypically identical to an individual who possesses two dominant alleles for the trait.

It is common practice in genetics to use capital and lowercase letters to represent dominant and recessive alleles. Using Mendel's pea plants as an example, if a tall pea plant is homozygous, it will possess two tall alleles (*TT*). A dwarf pea plant must be homozygous because its dwarfism can only be expressed when two recessive alleles are present (*tt*). A heterozygous pea plant (*Tt*) would be tall and phenotypically indistinguishable from a tall homozygous pea plant because of the dominant tall allele. Mendel deduced that a 3:1 ratio of dominant to recessive would be produced by the random segregation of heritable factors (genes) when crossing two heterozygous pea plants. In other words, for any given gene, parents are equally likely to pass down either one of their alleles to their offspring in a haploid gamete, and the result will be expressed in a dominant–recessive pattern if both parents are heterozygous for the trait.

Because of the random segregation of gametes, the laws of chance and probability come into play when predicting the likelihood of a given phenotype. Consider a cross between an individual with two dominant alleles for a trait (*AA*) and an individual with

two recessive alleles for the same trait (*aa*). All of the parental gametes from the dominant individual would be *A*, and all of the parental gametes from the recessive individual would be *a*. All of the offspring of that second generation, inheriting one allele from each parent, would have the genotype *Aa*, and the probability of expressing the phenotype of the dominant allele would be 4 out of 4, or 100 percent.

This seems simple enough, but the inheritance pattern gets interesting when the second-generation *Aa* individuals are crossed. In this generation, 50 percent of each parent's gametes are *A* and the other 50 percent are *a*. By Mendel's principle of random segregation, the possible combinations of gametes that the offspring can receive are *AA*, *Aa*, *aA* (which is the same as *Aa*), and *aa*. Because segregation and fertilization are random, each offspring has a 25 percent chance of receiving any of these combinations. Therefore, if an *Aa* × *Aa* cross were performed 1000 times, approximately 250 (25 percent) of the offspring would be *AA*; 500 (50 percent) would be *Aa* (that is, *Aa* plus *aA*); and 250 (25 percent) would be *aa*. The genotypic ratio for this inheritance pattern is 1:2:1. However, we have already established that *AA* and *Aa* (and *aA*) individuals all express the dominant trait (i.e., share the same phenotype), and can therefore be combined into one group. The result is Mendel's third-generation phenotype ratio of 3:1.

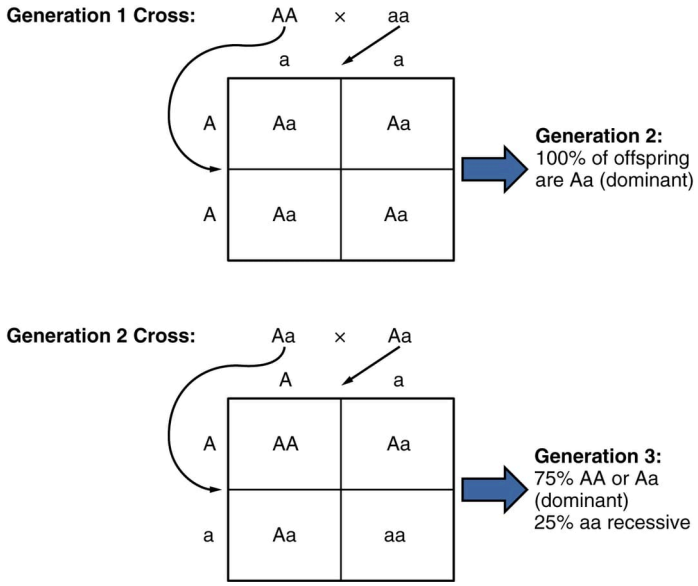


Figure 8.7.2: In the formation of gametes, it is equally likely that either one of a pair alleles from one parent will be passed on to the offspring. This figure follows the possible combinations of alleles through two generations following a first-generation cross of homozygous dominant and homozygous recessive parents. The recessive phenotype, which is masked in the second generation, has a 1 in 4, or 25 percent, chance of reappearing in the third generation. (CC BY 4.0; via Patterns of Inheritance). Detailed text description of the Figure 8.7.2.

Mendel's observation of pea plants also included many crosses that involved multiple traits, which prompted him to formulate the principle of independent assortment. The law states that the members of one pair of genes (alleles) from a parent will sort independently from other pairs of genes during the formation of gametes. Applied to pea plants, that means that the alleles associated with the different traits of the plant, such as color, height, or seed type, will sort independently of one another. This holds true except when two alleles happen to be located close to one other on the same chromosome. Independent assortment provides for a great degree of diversity in offspring.

Mendelian genetics represent the fundamentals of inheritance, but there are two important qualifiers to consider when applying Mendel's findings to inheritance studies in humans. First, as we've already noted, not all genes are inherited in a dominant–recessive pattern. Although all diploid individuals have two alleles for every gene, allele pairs may interact to create several types of inheritance patterns, including incomplete dominance and codominance.

Secondly, Mendel performed his studies using thousands of pea plants. He was able to identify a 3:1 phenotypic ratio in second-generation offspring because his large sample size overcame the influence of variability resulting from chance. In contrast, no human couple has ever had thousands of children. If we know that parents are both heterozygous for a recessive genetic disorder, we would predict that one in every four of their children would be affected by the disease. In real life, however, the influence of chance could change that ratio significantly. For example, if parents are both heterozygous for cystic fibrosis, a recessive genetic disorder that is expressed only when the individual has two defective alleles, we would expect one in four of their children to have cystic fibrosis. However, it is entirely possible for them to have seven children, none of whom is affected, or for them to have two

children, both of whom are affected. For each individual child, the presence or absence of a single gene disorder depends on which alleles that child inherits from their parents.

Autosomal Dominant Inheritance

In the case of cystic fibrosis, the disorder is recessive to the normal phenotype. However, a genetic abnormality may be dominant to the normal phenotype. When the dominant allele is located on one of the 22 pairs of autosomes (non-sex chromosomes), we refer to its inheritance pattern as autosomal dominant. An example of an autosomal dominant disorder is neurofibromatosis type I, a disease that induces tumor formation within the nervous system that leads to skin and skeletal deformities. Consider a couple in which one parent is heterozygous for this disorder (and who therefore has neurofibromatosis), *Nn*, and one parent is homozygous for the normal gene, *nn*. The heterozygous parent would have a 50 percent chance of passing the dominant allele for this disorder to their offspring, and the homozygous parent would always pass the normal allele. Therefore, four possible offspring genotypes are equally likely to occur: *Nn*, *Nn*, *nn*, and *nn*. That is, every child of this couple would have a 50 percent chance of inheriting neurofibromatosis. This inheritance pattern is shown in Figure 8.7.3, in a form called a Punnett square, named after its creator, the British geneticist Reginald Punnett.

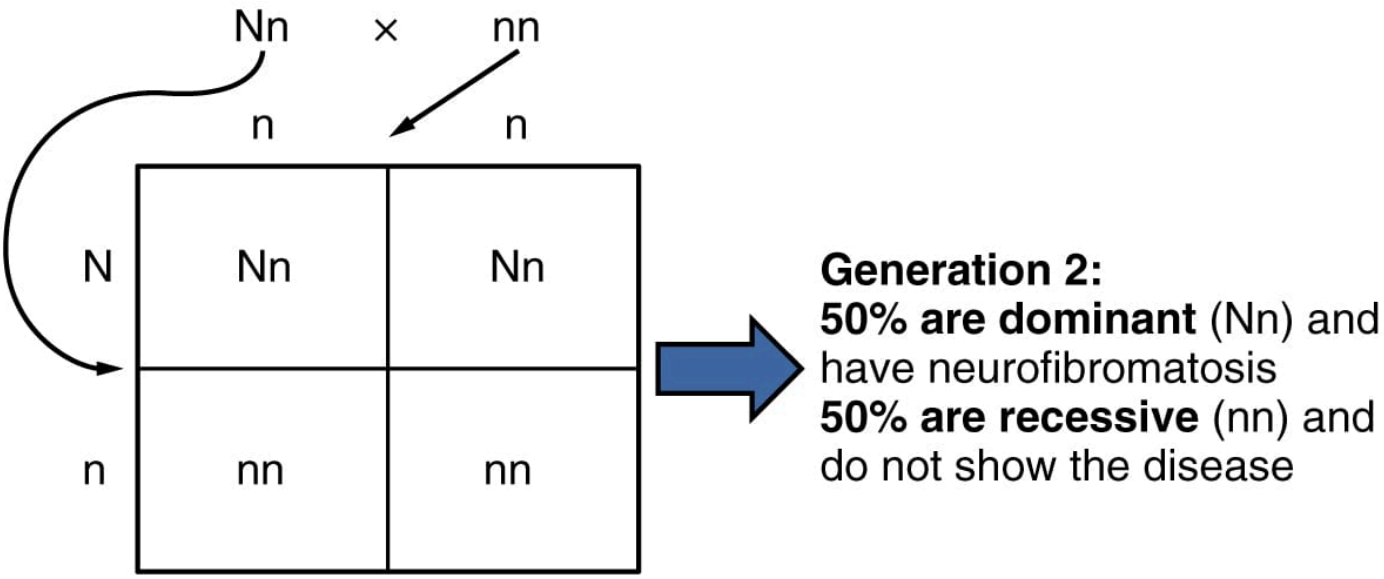


Figure 8.7.3: Inheritance pattern of an autosomal dominant disorder, such as neurofibromatosis, is shown in a Punnett square. (CC BY 4.0; via Patterns of Inheritance). Detailed text description of the Figure 8.7.3.

Other genetic diseases that are inherited in this pattern are achondroplastic dwarfism, Marfan syndrome, and Huntington's disease. Because autosomal dominant disorders are expressed by the presence of just one gene, an individual with the disorder will know that they have at least one faulty gene. The expression of the disease may manifest later in life, after the childbearing years, which is the case in Huntington's disease (discussed in more detail later in this section).

Autosomal Recessive Inheritance

When a genetic disorder is inherited in an autosomal recessive pattern, the disorder corresponds to the recessive phenotype. Heterozygous individuals will not display symptoms of this disorder, because their unaffected gene will compensate. Such an individual is called a carrier. Carriers for an autosomal recessive disorder may never know their genotype unless they have a child with the disorder.

An example of an autosomal recessive disorder is cystic fibrosis (CF), which we introduced earlier. CF is characterized by the chronic accumulation of a thick, tenacious mucus in the lungs and digestive tract. Decades ago, children with CF rarely lived to adulthood. With advances in medical technology, the average lifespan in developed countries has increased into middle adulthood. CF is a relatively common disorder that occurs in approximately 30,000 people in the United States. A child born to two CF carriers would have a 25 percent chance of inheriting the disease. This is the same 3:1 dominant:recessive ratio that Mendel observed in his pea plants would apply here. The pattern is shown in Figure 8.7.4, using a diagram that tracks the likely incidence of an autosomal recessive disorder on the basis of parental genotypes.

On the other hand, a child born to a CF carrier and someone with two unaffected alleles would have a 0 percent probability of inheriting CF, but would have a 50 percent chance of being a carrier. Other examples of autosome recessive genetic illnesses include the blood disorder sickle-cell anemia, the fatal neurological disorder Tay–Sachs disease, and the metabolic disorder phenylketonuria.

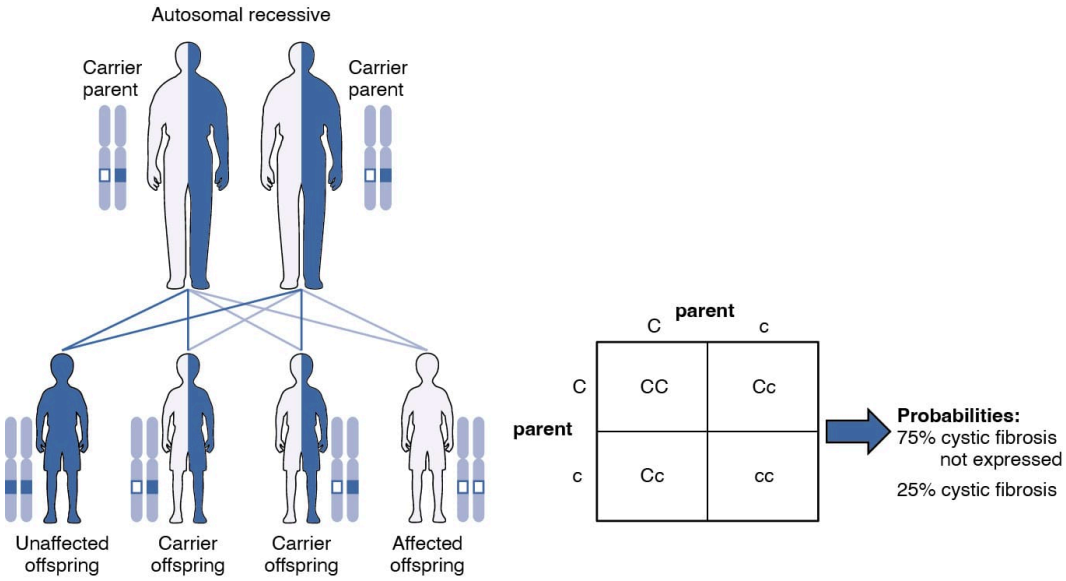


Figure 8.7.4: The inheritance pattern of an autosomal recessive disorder with two carrier parents reflects a 3:1 probability of expression among offspring. (CC BY 4.0; via Patterns of Inheritance). Detailed text description of the Figure 8.7.4.

X-linked Dominant or Recessive Inheritance

An X-linked transmission pattern involves genes located on the X chromosome of the 23rd pair. Recall that a male has one X and one Y chromosome. When a male transmits a Y chromosome, the child is male, and when a male parent transmits an X chromosome, the child is female. A female can transmit only an X chromosome, as both her sex chromosomes are X chromosomes.

When an abnormal allele for a gene that occurs on the X chromosome is dominant over the normal allele, the pattern is described as X-linked dominant. This is the case with vitamin D–resistant rickets: an affected male would pass the disease gene to all of the female offspring, but none of the male offspring, because the male transmits only the Y chromosome to male offspring (Figure 8.7.5a). If it is the female parent who is affected, all of the offspring—male or female—would have a 50 percent chance of inheriting the disorder because the female parent can only pass an X chromosome on to children (Figure 8.7.5b). For an affected female, the inheritance pattern would be identical to that of an autosomal dominant inheritance pattern in which one parent is heterozygous and the other is homozygous for the normal gene.

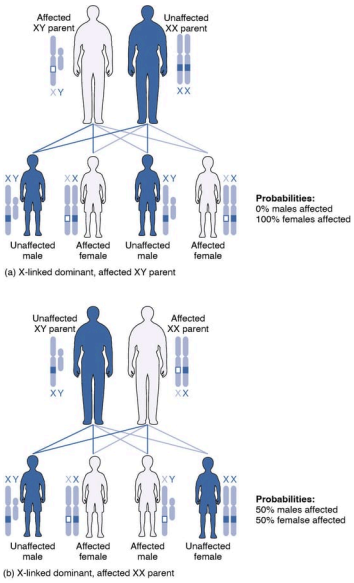


Figure 8.7.5: A chart of X-linked dominant inheritance patterns differs depending on which parent is affected with the disease. (CC BY 4.0; via Patterns of Inheritance). Detailed text description of the Figure 8.7.5.

X-linked recessive inheritance is much more common because females can be carriers of the disease yet still have a normal phenotype. Diseases transmitted by X-linked recessive inheritance include color blindness, the blood-clotting disorder hemophilia, and some forms of muscular dystrophy. For an example of X-linked recessive inheritance, consider parents in which the female is an unaffected carrier and the male is normal. None of the female offspring would have the disease because they receive a normal gene from their male parent. However, they have a 50 percent chance of receiving the disease gene from their female parent and becoming a carrier. In contrast, 50 percent of the male offspring would be affected (Figure 8.7.6).

With X-linked recessive diseases, males either have the disease or are genotypically normal—they cannot be carriers. Females, however, can be genotypically normal, a carrier who is phenotypically normal, or affected with the disease. A female can inherit the gene for an X-linked recessive illness when the female parent is a carrier or affected, or the male parent is affected. Female offspring will be affected by the disease only if they inherit an X-linked recessive gene from both parents. As you can imagine, X-linked recessive disorders affect many more males than females. For example, color blindness affects at least 1 in 20 males, but only about 1 in 400 females.

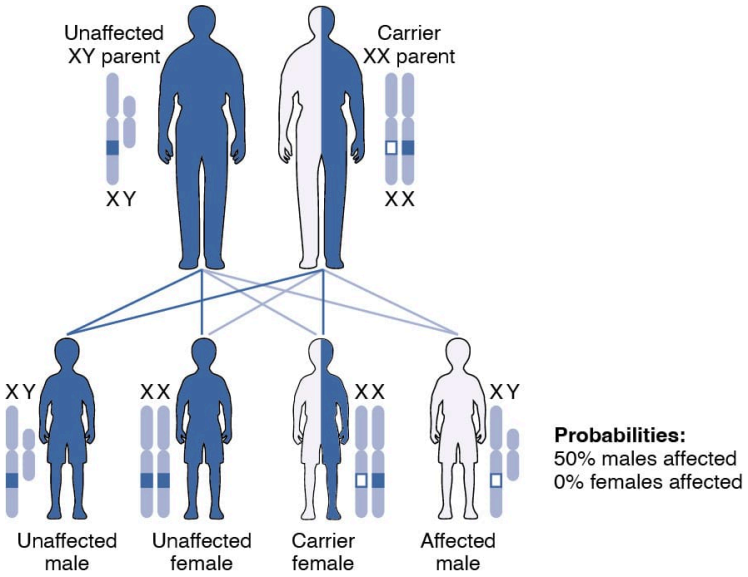


Figure 8.7.6: Given two parents in which the male is normal and the female is a carrier of an X-linked recessive disorder, a male offspring would have a 50 percent probability of being affected with the disorder, whereas female offspring would either be carriers or entirely unaffected. (CC BY 4.0; via Patterns of Inheritance). Detailed text description of the Figure 8.7.6.

Other Inheritance Patterns: Incomplete Dominance, Codominance, and Lethal Alleles

Not all genetic disorders are inherited in a dominant–recessive pattern. In incomplete dominance, the offspring express a heterozygous phenotype that is intermediate between one parent's homozygous dominant trait and the other parent's homozygous recessive trait. An example of this can be seen in snapdragons when red-flowered plants and white-flowered plants are crossed to produce pink-flowered plants. In humans, incomplete dominance occurs with one of the genes for hair texture. When one parent passes a curly hair allele (the incompletely dominant allele) and the other parent passes a straight-hair allele, the effect on the offspring will be intermediate, resulting in hair that is wavy.

Codominance is characterized by the equal, distinct, and simultaneous expression of both parents' different alleles. This pattern differs from the intermediate, blended features seen in incomplete dominance. A classic example of codominance in humans is ABO blood type. People are blood type A if they have an allele for an enzyme that facilitates the production of surface antigen A on their erythrocytes. This allele is designated I^A. In the same manner, people are blood type B if they express an enzyme for the production of surface antigen B. People who have alleles for both enzymes (I^A and I^B) produce both surface antigens A and B. As a result, they are blood type AB. Because the effect of both alleles (or enzymes) is observed, we say that the I^A and I^B alleles are codominant. There is also a third allele that determines blood type. This allele (i) produces a nonfunctional enzyme. People who have two i alleles do not produce either A or B surface antigens: they have type O blood. If a person has I^A and i alleles, the person will have blood type A. Notice that it does not make any difference whether a person has two I^A alleles or one I^A and one i allele. In both cases, the person is blood type A. Because I^A masks i, we say that I^A is dominant to i. Table 8.7.1 summarizes the expression of blood type.

Table 8.7.1: Expression of Blood Types

Blood type	Genotype	Pattern of inheritance
A	I^AI^A or I^Ai	I^A is dominant to i
B	I^BI^B or I^Bi	I^B is dominant to i
AB	I^AI^B	I^A is co-dominant to I^B
O	ii	Two recessive alleles

Certain combinations of alleles can be lethal, meaning they prevent the individual from developing in utero, or cause a shortened life span. In recessive lethal inheritance patterns, a child who is born to two heterozygous (carrier) parents and who inherited the faulty allele from both would not survive. An example of this is Tay–Sachs, a fatal disorder of the nervous system. In this disorder, parents with one copy of the allele for the disorder are carriers. If they both transmit their abnormal allele, their offspring will develop the disease and will die in childhood, usually before age 5.

Dominant lethal inheritance patterns are much more rare because neither heterozygotes nor homozygotes survive. Of course, dominant lethal alleles that arise naturally through mutation and cause miscarriages or stillbirths are never transmitted to subsequent generations. However, some dominant lethal alleles, such as the allele for Huntington's disease, cause a shortened life span but may not be identified until after the person reaches reproductive age and has children. Huntington's disease causes irreversible nerve cell degeneration and death in 100 percent of affected individuals, but it may not be expressed until the individual reaches middle age. In this way, dominant lethal alleles can be maintained in the human population. Individuals with a family history of Huntington's disease are typically offered genetic counseling, which can help them decide whether or not they wish to be tested for the faulty gene.

Mutations

A mutation is a change in the sequence of DNA nucleotides that may or may not affect a person's phenotype. Mutations can arise spontaneously from errors during DNA replication, or they can result from environmental insults such as radiation, certain viruses, or exposure to tobacco smoke or other toxic chemicals. Because genes encode for the assembly of proteins, a mutation in the nucleotide sequence of a gene can change amino acid sequence and, consequently, a protein's structure and function. Spontaneous mutations occurring during meiosis are thought to account for many spontaneous abortions (miscarriages).

Chromosomal Disorders

Sometimes a genetic disease is not caused by a mutation in a gene, but by the presence of an incorrect number of chromosomes. For example, Down syndrome is caused by having three copies of chromosome 21. This is known as trisomy 21. The most common cause of trisomy 21 is chromosomal nondisjunction during meiosis. The frequency of nondisjunction events appears to increase with age, so the frequency of bearing a child with Down syndrome increases in females over 36. The age of the male parent matters less because nondisjunction is much less likely to occur in a sperm than in an egg.

Whereas Down syndrome is caused by having three copies of a chromosome, Turner syndrome is caused by having just one copy of the X chromosome. This is known as monosomy. The affected child is always female. Women with Turner syndrome are sterile because their sexual organs do not mature.

Career Connection

Genetic Counselor

Given the intricate orchestration of gene expression, cell migration, and cell differentiation during prenatal development, it is amazing that the vast majority of newborns are healthy and free of major birth defects. When a person over 35 is pregnant or intends to become pregnant, or their partner is over 55, or if there is a family history of a genetic disorder, they may want to speak to a genetic counselor to discuss the likelihood that their child may be affected by a genetic or chromosomal disorder. A genetic counselor can interpret a couple's family history and estimate the risks to their future offspring.

For many genetic diseases, a DNA test can determine whether a person is a carrier. For instance, carrier status for Fragile X, an X-linked disorder associated with intellectual disabilites, or for cystic fibrosis can be determined with a simple blood draw to obtain DNA for testing. A genetic counselor can educate a couple about the implications of such a test and help them decide whether to undergo testing. For chromosomal disorders, the available testing options include a blood test, amniocentesis (in which amniotic fluid is tested), and chorionic villus sampling (in which tissue from the placenta is tested). Each of these has advantages and drawbacks. A genetic counselor can also help a couple cope with the news that either one or both partners is a carrier of a genetic illness, or that their unborn child has been diagnosed with a chromosomal disorder or other birth defect.

To become a genetic counselor, one needs to complete a 4-year undergraduate program and then obtain a Master of Science in Genetic Counseling from an accredited university. Board certification is attained after passing examinations by the American Board of Genetic Counseling. Genetic counselors are essential professionals in many branches of medicine, but there is a particular demand for preconception and prenatal genetic counselors.

Professional Resources in Genetic Counseling

- For information on genetic counseling, professional standards, and resources for individuals and families managing genetic conditions, visit the National Society of Genetic Counselors (NSGC) website.
- For information about certification standards, professional qualifications, and credentialing in genetic counseling, visit the American Board of Genetic Counseling (ABGC) website.

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8.8: Terms and Definitions

Key Terms

Select to View Definition

Acrosomal reaction
release of digestive enzymes by sperm that enables them to burrow through the corona radiata and penetrate the zona pellucida of an oocyte prior to fertilization

Acrosome
cap-like vesicle located at the anterior-most region of a sperm that is rich with lysosomal enzymes capable of digesting the protective layers surrounding the oocyte

Afterbirth
third stage of childbirth in which the placenta and associated fetal membranes are expelled

Allantois
finger-like outpocketing of yolk sac forms the primitive excretory duct of the embryo; precursor to the urinary bladder

Allele
alternative forms of a gene that occupy a specific locus on a specific gene

Amnion
transparent membranous sac that encloses the developing fetus and fills with amniotic fluid

Amniotic cavity
cavity that opens up between the inner cell mass and the trophoblast; develops into amnion

Autosomal chromosome
in humans, the 22 pairs of chromosomes that are not the sex chromosomes (XX or XY)

Autosomal dominant
pattern of dominant inheritance that corresponds to a gene on one of the 22 autosomal chromosomes

Autosomal recessive
pattern of recessive inheritance that corresponds to a gene on one of the 22 autosomal chromosomes

Blastocoel
fluid-filled cavity of the blastocyst

Blastocyst
term for the conceptus at the developmental stage that consists of about 100 cells shaped into an inner cell mass that is fated to become the embryo and an outer trophoblast that is fated to become the associated fetal membranes and placenta

Blastomere
daughter cell of a cleavage

Braxton Hicks contractions
weak and irregular peristaltic contractions that can occur in the second and third trimesters; they do not indicate that childbirth is imminent

Brown adipose tissue
highly vascularized fat tissue that is packed with mitochondria; these properties confer the ability to oxidize fatty

acids to generate heat

Capacitation
process that occurs in the female reproductive tract in which sperm are prepared for fertilization; leads to increased motility and changes in their outer membrane that improve their ability to release enzymes capable of digesting an oocyte's outer layers

Carrier
heterozygous individual who does not display symptoms of a recessive genetic disorder but can transmit the disorder to their offspring

Chorion
membrane that develops from the syncytiotrophoblast, cytotrophoblast, and mesoderm; surrounds the embryo and forms the fetal portion of the placenta through the chorionic villi

Chorionic membrane
precursor to the chorion; forms from extra-embryonic mesoderm cells

Chorionic villi
projections of the chorionic membrane that burrow into the endometrium and develop into the placenta

Cleavage
form of mitotic cell division in which the cell divides but the total volume remains unchanged; this process serves to produce smaller and smaller cells

Codominance
pattern of inheritance that corresponds to the equal, distinct, and simultaneous expression of two different alleles

Colostrum
thick, yellowish substance secreted from a mother's breasts in the first postpartum days; rich in immunoglobulins

Conceptus
pre-implantation stage of a fertilized egg and its associated membranes

Corona radiata
in an oocyte, a layer of granulosa cells that surrounds the oocyte and that must be penetrated by sperm before fertilization can occur

Cortical reaction
following fertilization, the release of cortical granules from the oocyte's plasma membrane into the zona pellucida creating a fertilization membrane that prevents any further attachment or penetration of sperm; part of the slow block to polyspermy

Dilation
first stage of childbirth, involving an increase in cervical diameter

Dominant
describes a trait that is expressed both in homozygous and heterozygous form

Dominant lethal
inheritance pattern in which individuals with one or two copies of a lethal allele do not survive in utero or have a shortened life span

Ductus arteriosus
shunt in the pulmonary trunk that diverts oxygenated blood back to the aorta

Ductus venosus
shunt that causes oxygenated blood to bypass the fetal liver on its way to the inferior vena cava

Ectoderm
primary germ layer that develops into the central and peripheral nervous systems, sensory organs, epidermis, hair,

and nails

Ectopic pregnancy
implantation of an embryo outside of the uterus

Embryo
developing human during weeks 3–8

Embryonic folding
process by which an embryo develops from a flat disc of cells to a three-dimensional shape resembling a cylinder

Endoderm
primary germ layer that goes on to form the gastrointestinal tract, liver, pancreas, and lungs

Epiblast
upper layer of cells of the embryonic disc that forms from the inner cell mass; gives rise to all three germ layers

Episiotomy
incision made in the posterior vaginal wall and perineum that facilitates vaginal birth

Expulsion
second stage of childbirth, during which the mother bears down with contractions; this stage ends in birth

Fertilization
unification of genetic material from male and female haploid gametes

Fertilization membrane
impenetrable barrier that coats a nascent zygote; part of the slow block to polyspermy

Fetus
developing human during the time from the end of the embryonic period (week 9) to birth

Foramen ovale
shunt that directly connects the right and left atria and helps divert oxygenated blood from the fetal pulmonary circuit

Foremilk
watery, translucent breast milk that is secreted first during a feeding and is rich in lactose and protein; quenches the infant's thirst

Gastrulation
process of cell migration and differentiation into three primary germ layers following cleavage and implantation

Genotype
complete genetic makeup of an individual

Gestation
in human development, the period required for embryonic and fetal development in utero; pregnancy

Heterozygous
having two different alleles for a given gene

Hindmilk
opaque, creamy breast milk delivered toward the end of a feeding; rich in fat; satisfies the infant's appetite

Homozygous
having two identical alleles for a given gene

Human chorionic gonadotropin (hCG)
hormone that directs the corpus luteum to survive, enlarge, and continue producing progesterone and estrogen to suppress menses and secure an environment suitable for the developing embryo

Hypoblast
lower layer of cells of the embryonic disc that extend into the blastocoel to form the yolk sac

Implantation
process by which a blastocyst embeds itself in the uterine endometrium

Incomplete dominance
pattern of inheritance in which a heterozygous genotype expresses a phenotype intermediate between dominant and recessive phenotypes

Inner cell mass
cluster of cells within the blastocyst that is fated to become the embryo

Involution
postpartum shrinkage of the uterus back to its pre-pregnancy volume

Karyotype
systematic arrangement of images of chromosomes into homologous pairs

Lactation
process by which milk is synthesized and secreted from the mammary glands of the postpartum female breast in response to sucking at the nipple

Lanugo
silk-like hairs that coat the fetus; shed later in fetal development

Let-down reflex
release of milk from the alveoli triggered by infant suckling

Lightening
descent of the fetus lower into the pelvis in late pregnancy; also called “dropping”

Lochia
postpartum vaginal discharge that begins as blood and ends as a whitish discharge; the end of lochia signals that the site of placental attachment has healed

Meconium
fetal wastes consisting of ingested amniotic fluid, cellular debris, mucus, and bile

Mesoderm
primary germ layer that becomes the skeleton, muscles, connective tissue, heart, blood vessels, and kidneys

Morula
tightly packed sphere of blastomeres that has reached the uterus but has not yet implanted itself

Mutation
change in the nucleotide sequence of DNA

Neural fold
elevated edge of the neural groove

Neural plate
thickened layer of neuroepithelium that runs longitudinally along the dorsal surface of an embryo and gives rise to nervous system tissue

Neural tube
precursor to structures of the central nervous system, formed by the invagination and separation of neuroepithelium

Neurulation
embryonic process that establishes the central nervous system

Nonshivering thermogenesis
process of breaking down brown adipose tissue to produce heat in the absence of a shivering response

Notochord
rod-shaped, mesoderm-derived structure that provides support for growing fetus

Organogenesis
development of the rudimentary structures of all of an embryo's organs from the germ layers

Parturition
childbirth

Phenotype
physical or biochemical manifestation of the genotype; expression of the alleles

Placenta
organ that forms during pregnancy to nourish the developing fetus; also regulates waste and gas exchange between mother and fetus

Placenta previa
low placement of fetus within uterus causes placenta to partially or completely cover the opening of the cervix as it grows

Placentation
formation of the placenta; complete by weeks 14–16 of pregnancy

Polyspermy
penetration of an oocyte by more than one sperm

Primitive streak
indentation along the dorsal surface of the epiblast through which cells migrate to form the endoderm and mesoderm during gastrulation

Prolactin
pituitary hormone that establishes and maintains the supply of breast milk; also important for the mobilization of maternal micronutrients for breast milk

Punnett square
grid used to display all possible combinations of alleles transmitted by parents to offspring and predict the mathematical probability of offspring inheriting a given genotype

Quickening
fetal movements that are strong enough to be felt by the mother

Recessive
describes a trait that is only expressed in homozygous form and is masked in heterozygous form

Recessive lethal
inheritance pattern in which individuals with two copies of a lethal allele do not survive in utero or have a shortened life span

Sex chromosomes
pair of chromosomes involved in sex determination; in males, the XY chromosomes; in females, the XX chromosomes

Shunt
circulatory shortcut that diverts the flow of blood from one region to another

Somite
one of the paired, repeating blocks of tissue located on either side of the notochord in the early embryo

Syncytiotrophoblast
: superficial cells of the trophoblast that fuse to form a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall

Trait
: variation of an expressed characteristic

Trimester
: division of the duration of a pregnancy into three 3-month terms

Trophoblast
: fluid-filled shell of squamous cells destined to become the chorionic villi, placenta, and associated fetal membranes

True labor
: regular contractions that immediately precede childbirth; they do not abate with hydration or rest, and they become more frequent and powerful with time

Umbilical cord
: connection between the developing conceptus and the placenta; carries deoxygenated blood and wastes from the fetus and returns nutrients and oxygen from the mother

Vernix caseosa
: waxy, cheese-like substance that protects the delicate fetal skin until birth

X-linked
: pattern of inheritance in which an allele is carried on the X chromosome of the 23rd pair

X-linked dominant
: pattern of dominant inheritance that corresponds to a gene on the X chromosome of the 23rd pair

X-linked recessive
: pattern of recessive inheritance that corresponds to a gene on the X chromosome of the 23rd pair

Yolk sac
: membrane associated with primitive circulation to the developing embryo; source of the first blood cells and germ cells and contributes to the umbilical cord structure

Zona pellucida
: thick, gel-like glycoprotein membrane that coats the oocyte and must be penetrated by sperm before fertilization can occur

Zygote
: fertilized egg; a diploid cell resulting from the fertilization of haploid gametes from the male and female lines

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8.9: Chapter Review Questions

Multiple Choice Section

- Use the end-of-chapter multiple-choice section as a regular self-check tool, not just before exams.
- Read each item carefully, think about what is really being tested (concept, definition, application, or calculation), and choose the option (A, B, C, or D) that best reflects what you have learned in this chapter.
  - After you read through the chapter, attempt all items without looking at your notes; then return to the chapter to review any you missed or felt unsure about.
  - Afterward, explain to yourself why the correct option is right and why the others are not. Finally, repeat the multiple-choice section a few days later to see what you truly remember and understand.
- Students who consistently use these prompts in this way typically perform better across the course because they turn reading into active practice

1. A couple is undergoing fertility counseling. Semen analysis shows a normal count of hundreds of millions of sperm per ejaculate. The clinician explains that only a small fraction of sperm will ever reach the egg. Although the male ejaculate contains hundreds of millions of sperm:
   A. Most do not reach the oocyte
   B. Most are destroyed by the alkaline environment of the uterus
   C. It takes millions to penetrate the outer layers of the oocyte at once
   D. Most are destroyed by capacitation

2. A diagram in embryology lab shows a sperm approaching the egg. As sperm first reach a recently ovulated oocyte in the uterine tube, they will initially contact which outermost cell layer surrounding the egg?
   A. Acrosome
   B. Corona radiata
   C. Sperm-binding receptors
   D. Zona pellucida

3. After a sperm successfully penetrates the egg, the two haploid nuclei approach each other and merge to form a single diploid nucleus. This fusion of the male and female pronuclei occurs during:
   A. Spermatogenesis
   B. Ovulation
   C. Fertilization
   D. Capacitation

4. Before sperm can successfully undergo the acrosomal reaction and fertilize an oocyte, they must be exposed to conditions in the female reproductive tract that remove certain proteins and lipids from their membranes. Sperm must first complete:
   A. Capacitation
   B. The acrosomal reaction
   C. The cortical reaction
   D. The fast block to polyspermy

5. Early in development, the fertilized egg undergoes rapid mitotic divisions without growth. This cleavage process produces many small daughter cells. These daughter cells are called:
   A. Trophoblasts
   B. Blastocysts
   C. Morulae
   D. Blastomeres

6. A fertilized egg (zygote) undergoes cleavage as it travels down the uterine tube. By the time the conceptus reaches the uterus, it is typically at the blastocyst stage. Upon entering the uterus, the blastocyst first:
   A. Implants immediately into the uterine wall
   B. Continues to divide and float freely for a short time

C. Disintegrates
D. Hatches from the endometrium

7. A blastocyst consists of an outer trophoblast and an inner cell mass. The inner cell mass of the blastocyst is destined to become the:
A. Embryo proper
B. Trophoblast
C. Chorionic villi only
D. Entire placenta

8. During early development, three primary germ layers form. The cells that eventually become the brain and spinal cord are derived from which primary germ layer?
A. Endoderm
B. Ectoderm
C. Acrosome
D. Mesoderm

9. A clinician explains early pregnancy to a patient. After implantation, the trophoblast normally secretes human chorionic gonadotropin (hCG) to maintain the corpus luteum. What would most likely happen if the trophoblast did NOT secrete hCG upon implantation of the blastocyst?
A. The embryonic cells would not continue to divide
B. The corpus luteum would continue to produce progesterone and estrogen anyway
C. Menstruation would occur and flush the blastocyst out of the uterus
D. The uterine mucosa would not physically envelop the blastocyst

10. As the flat embryonic disc grows, it folds to form a three-dimensional body with a gut and body cavities. During which process does the amnion come to envelop and surround the embryo?
A. Embryonic folding
B. Gastrulation
C. Implantation
D. Organogenesis

11. A pregnant patient asks how the placenta forms. The clinician explains that it arises from tissues from both the pregnant person and the embryo. The placenta is formed from:
A. The embryo's mesenchymal cells only
B. The pregnant person's endometrium only
C. The pregnant person's endometrium and the embryo's chorionic membrane
D. The pregnant person's endometrium and the embryo's umbilical cord

12. In the fetal circulation, a small opening between the right and left atria allows blood to bypass the nonfunctional fetal lungs. The foramen ovale causes the fetal circulatory system to bypass the:
A. Liver
B. Lungs
C. Kidneys
D. Gonads

13. During a prenatal lecture, learners are told that the fetal kidneys begin to produce urine in utero. What happens to the urine excreted by the fetus once the kidneys start functioning?
A. The umbilical cord carries it directly to the placenta for removal
B. The endometrium absorbs it into the maternal circulation
C. It is released into and adds to the amniotic fluid
D. It is converted into meconium in the intestines

14. A mid-pregnancy ultrasound evaluates fetal development between weeks 9 and 12. Which of the following events typically occurs during weeks 9–12 of fetal development?
A. Bone marrow begins to assume erythrocyte (red blood cell) production
B. Meconium begins to accumulate in the intestines
C. Surfactant production begins in the fetal lungs
D. The spinal cord begins to be myelinated

15. During pregnancy, progesterone produced by the placenta helps maintain the uterine lining and also prevents new follicles from maturing in the ovaries. Progesterone secreted by the placenta suppresses which pituitary hormones to prevent maturation of ovarian follicles?
    A. LH and estrogen
    B. hCG and FSH
    C. FSH and LH
    D. Estrogen and hCG

16. A pregnant person in the first trimester experiences nausea and vomiting described as “morning sickness.” Which of the following is a commonly proposed biological contributor to morning sickness?
    A. Increased minute ventilation (respiration)
    B. Decreased intestinal peristalsis
    C. Decreased aldosterone secretion
    D. Increased levels of pregnancy-related hormones and blood volume

17. In the last weeks of pregnancy, progesterone levels fall relative to estrogen levels, helping the uterus become more responsive to contraction signals. How does the decrease in progesterone at the end of pregnancy help to bring on labor?
    A. By stimulating FSH production
    B. By decreasing levels of estrogens
    C. By directly dilating the cervix
    D. By decreasing the inhibition of uterine contractility

18. An obstetric team evaluates fetal position before delivery. Which of these fetal presentations is typically the easiest and safest for vaginal birth?
    A. Complete breech (buttocks and feet first)
    B. Vertex occiput anterior (head down, back of head toward front of pelvis)
    C. Frank breech (buttocks first, legs extended)
    D. Vertex occiput posterior (head down, back of head toward back of pelvis)

19. During fetal life, several vascular shunts help divert blood flow. Which of these shunts exists between the right and left atria?
    A. Foramen ovale
    B. Ductus venosus
    C. Ductus arteriosus
    D. Foramen venosus

20. A neonatologist explains to caregivers why newborns have more brown fat than adults. Why is brown fat important in newborns?
    A. It is the primary source of insulation against cold
    B. It can be broken down to generate heat for thermoregulation
    C. It is used as the main energy source between feedings
    D. It can be easily converted to white fat

21. During labor and immediately after birth, the umbilical blood vessels constrict and the placenta is no longer part of the baby’s circulation. This briefly reduces oxygen delivery, leading to a rise in fetal CO_2. Constriction of umbilical blood vessels during birth primarily:
    A. Causes respiratory alkalosis
    B. Inhibits the respiratory center in the brain
    C. Elevates carbon dioxide levels in the blood, stimulating breathing
    D. Both A and B

22. A genetic counselor meets with a family in which one parent has Marfan syndrome, an autosomal dominant connective tissue disorder, and the other parent does not carry the condition. Which statement best describes the risk to each child they conceive?

    A. Female children are more likely than male children to be affected
    B. Male children are more likely than female children to be affected
    C. Each child, regardless of sex, has a 50% chance of inheriting Marfan syndrome
    D. Only children who inherit two altered copies of the gene (one from each parent) will be affected

23. A parent chooses to breastfeed their newborn and asks why early milk (colostrum) is important, even though the volume is small. How is colostrum most important to a newborn in the first days of life?
A. It helps boost the newborn's immune system with antibodies
B. It provides a large amount of fat for energy
C. It mainly satisfies the newborn's thirst
D. It fully satisfies the infant's appetite and caloric needs

24. A dietitian compares human breast milk and cow's milk for a family considering formula feeding. Mature human breast milk, compared with cow's milk, generally:
A. Has more sodium
B. Has more calcium
C. Has more protein
D. Has more fat and appropriate nutrients tailored to human infants

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8.10: Applied Thinking Self - Assessment

Challenge Yourself

- Extended response questions are assessment items that require students to construct written answers of substantial length - typically several sentences to multiple paragraphs - rather than selecting from predefined options. They represent a form of constructed response assessment designed to measure complex, higher-order thinking skills.
- First, try answering without using your notes. Then review reliable resources and revise your response if needed. Make a note of any areas where you felt unsure and revisit those topics.

Writing Guidelines

- Answer each question in your own words.
- Write 4–8 clear, complete sentences per question, organized into short paragraphs (not bullet points).
- Focus on explaining your reasoning, not just stating the answer.
- Use correct scientific vocabulary, and briefly define terms when needed.
- For questions that ask you to compare, contrast, or explain why/how:
  - Clearly state similarities or differences
  - Support your ideas with a brief explanation or example

Conceptual Foundations: Fertilization and Early Development

Scenario 1

Darcy and Raul have been trying to conceive. Darcy ovulates regularly every 28 days, and testing shows that Raul's sperm count is within the normal range. However, when a sample of Raul's semen is examined about one hour after ejaculation, most sperm are moving slowly. Later, when his sperm reach Darcy's oocyte, they do not seem able to carry out a strong acrosomal reaction.

Probing Prompts

- Explain which process in the sperm's journey or maturation is most likely not working properly (for example, capacitation or acrosome function).
- Describe how this process normally helps sperm reach and penetrate the oocyte, and why problems here can cause infertility even when sperm numbers are normal.

Scenario 2

On Saturday night, a young woman has unprotected penile–vaginal sex. On Tuesday morning, she feels the brief mid-cycle pain she usually associates with ovulation and becomes very anxious that she might already be pregnant.

Probing Prompts

- Using your understanding of the timing of ovulation, sperm survival in the reproductive tract, and fertilization, explain whether her concern about pregnancy from Saturday's encounter is biologically likely.
- Clearly describe the time window during which unprotected sex is most likely to result in pregnancy, and why.

Scenario 3

Approximately three weeks after her last menstrual period, a sexually active woman notices a short episode of mild

lower-abdominal cramping and light spotting. She is not sure whether this is a period.

Probing Prompts

- Propose at least one possible explanation related to early pregnancy for this cramping and spotting.
- Explain the underlying developmental event (for example, implantation) and why it might cause these symptoms.
- Also describe at least one non-pregnancy-related explanation, and explain why follow-up care and testing are important for all patients, regardless of income or insurance status.

Scenario 4

Public health agencies recommend that all people who might become pregnant consume at least 400 micrograms of folate per day from supplements or fortified foods, starting before conception.

Probing Prompts

- Explain the role of folate in early embryonic development, especially in relation to cell division and formation of the neural tube.
- Describe why folate must be present before many people even know they are pregnant, and how fortified foods and low-cost supplements can help reduce health inequities in birth outcomes.

Fetal Circulation, Birth, and Newborn Adaptations

Scenario 1

You are explaining fetal circulation to a patient who is curious about how their baby's heart and blood flow differ from an adult's.

Probing Prompts

Describe the major fetal circulatory shunts (for example, foramen ovale and ductus arteriosus) and explain the physiological benefit of having these shunts before birth. How do they help the fetus make the best use of the placenta and non-functioning fetal lungs?

Scenario 2

A newborn is born prematurely at 30 weeks of gestation. Soon after birth, they show signs of breathing difficulty, and the neonatal team provides supplemental oxygen.

Probing Prompts

Explain why a premature infant is more likely to need extra oxygen than a full-term infant. In your answer, discuss lung development, surfactant production, and how these affect gas exchange. Consider how limited access to prenatal care can increase the risk of preterm birth in some communities.

Scenario 3

Devin is 35 weeks pregnant with their first child. They come to the hospital reporting mild, irregular contractions for several hours. On exam, the mucus plug is still in place, the cervix has not begun to dilate, and the amniotic sac is intact. Devin is reassured and sent home.

Probing Prompts

- Explain why Devin's healthcare team did not diagnose active labor. Differentiate between false labor contractions and true labor in terms of contraction pattern, cervical changes, and membrane status.
- Discuss why careful assessment and clear communication are important for all pregnant patients, especially those who may have limited prior experience with childbirth.

Scenario 4

Janine is 41 weeks pregnant with her first child. She reports feeling like she has been in labor "for days," but contractions are infrequent and mild. On exam, she has occasional short contractions, cervical dilation is only 2 cm, and the membranes are intact. Janine is admitted, and an IV infusion of pitocin (synthetic oxytocin) is started.

Probing Prompts

- Explain why the care team chose to use pitocin in this situation. Describe how oxytocin normally affects uterine contractions and the progression of labor.
- Discuss why prolonged pregnancy and ineffective contractions can be risky, and how induction of labor can help reduce those risks when used appropriately.

Scenario 5

A healthy full-term baby takes their first breath shortly after birth.

Probing Prompts

- Describe how the newborn's first breaths change blood flow through the heart and lungs.
- Explain what happens to the fetal circulatory shunts (such as the foramen ovale and ductus arteriosus) and how these changes help the baby adapt to life outside the uterus.

Scenario 6

You are teaching a parenting class about newborn care. Many participants are surprised to hear that newborns are at higher risk for dehydration than adults.

Probing Prompts

- Explain at least two reasons why newborns become dehydrated more easily than adults (for example, body water percentage, kidney function, fluid intake).
- Describe how caregivers and healthcare teams can help prevent and recognize dehydration, especially in settings where families may have limited access to medical care or safe water.

Lactation and Early Infant Nutrition

Scenario 1

You are counseling a new parent who is curious about how milk made in the breast actually reaches the baby's mouth during feeding.

Probing Prompts

- Describe the path of breast milk from the lactocytes (milk-producing cells) to the nipple pores.
- Name the main structures along the way (for example, alveoli, small ducts, lactiferous ducts, lactiferous sinuses, nipple pores) and explain how they work together during milk ejection.

Genetics, Inheritance, and Population Health

Scenario 1

A 28-year-old woman, Amina, is referred for genetic counseling. Her younger brother has cystic fibrosis (CF), an autosomal recessive disease caused by mutations in a gene called CFTR. Neither parent has CF, and Amina herself is healthy. She is planning a pregnancy with her partner, Luis, who has no known family history of CF. Genetic testing shows that Amina carries one changed (mutated) CFTR gene, and Luis also carries one changed CFTR gene. They are worried about the chances that their future children could have CF and what that would mean for the child's health.

Probing Prompts

1. Cystic fibrosis is an autosomal recessive condition. For each pregnancy, what is the chance that a child of Amina and Luis will:
   a. have cystic fibrosis
   b. be a carrier of CF (have one normal CFTR gene and one changed CFTR gene)
   c. have two normal CFTR genes (not have CF and not be a carrier)

2. In your own words, explain why Amina and Luis do not have cystic fibrosis even though each of them carries one changed CFTR gene.

3. Choose one body system (for example, the lungs or the digestive system) and briefly describe how cystic fibrosis can affect its function. Then explain why finding and treating CF early in life can help improve the person's long-term health.

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8.11: Alternate Text Descriptions

Figure 8.1.1: Steps of Fertilization

This image illustrates fertilization in three labeled steps, showing how sperm cells reach and penetrate the oocyte and how one sperm ultimately fuses with the oocyte.

Step 1

Hundreds of sperm attracted to the corona radiata begin to break through the barrier of granulosa cells and approach the zona pellucida.

Multiple sperm surround the oocyte and move through the corona radiata, the outer layer of granulosa cells surrounding the egg. The sperm are shown approaching the zona pellucida, a protective glycoprotein layer surrounding the oocyte.

Step 2

Contact with the zona pellucida triggers the acrosome reaction, causing sperm to secrete digestive enzymes that break down the glycoprotein membrane of the zona pellucida and help expose the oocyte's plasma membrane.

As sperm contact the zona pellucida, enzymes are released from the acrosome at the tip of the sperm head. These enzymes digest portions of the zona pellucida, creating pathways that allow sperm to move closer to the oocyte's plasma membrane.

Step 3

A single sperm succeeds in burrowing through the corona radiata and zona pellucida and making contact with the oocyte's plasma membrane. The sperm's plasma membrane fuses with that of the oocyte, and the sperm releases its nucleus into the cytoplasm of the oocyte.

An enlarged view shows several sperm approaching the oocyte through the corona radiata and across the zona pellucida. Each sperm contains an acrosome at the tip of its head and a sperm nucleus within the head region. The plasma membrane surrounds the oocyte, and sperm receptors in the plasma membrane are shown at the site where sperm binding occurs. One sperm successfully penetrates the corona radiata and zona pellucida and reaches the plasma membrane. Fusion of the sperm and oocyte plasma membranes allows the sperm nucleus to enter the oocyte cytoplasm. Additional sperm remain outside the zona pellucida and do not enter the oocyte.

The figure demonstrates the sequence of events during fertilization. Sperm first move through the corona radiata, then undergo the acrosome reaction to penetrate the zona pellucida. After one sperm binds to and fuses with the oocyte plasma membrane, its nucleus enters the oocyte cytoplasm, initiating the process that leads to formation of a zygote. The corona radiata, zona pellucida, plasma membrane, and sperm receptors function together to regulate sperm access and help ensure that only one sperm fertilizes the oocyte.

Figure 8.1.2: In Vitro Fertilization (IVF)

This image illustrates in vitro fertilization (IVF) labeled steps 1a, 1b, 2, 3, and 4.

Step 1a: “Eggs are collected after ovulation or directly from the follicles. Sperm are collected and concentrated.” The image shows an Egg (oocyte) being removed using a Catheter.

Step 1b: “Sperm sample is collected and concentrated by removing seminal fluid.” Two test tubes are shown, with an arrow indicating concentration of the sperm sample.

Step 2: “Both the collected egg(s) and the sperm sample are mixed in a petri dish, allowing fertilization to occur.” A petri dish

shows sperm surrounding an oocyte.

Step 3: “The fertilized zygote is then removed from the petri dish for implantation.” A catheter removes the Fertilized zygote from the dish.

Step 4: “The zygote is then surgically implanted into the endometrium of the uterus. After successful implantation, the zygote should develop normally, as if it had been fertilized in the female’s oviducts.” The image labels Implanted zygote and Endometrium inside the uterus.

Arrows indicate progression between steps from collection to implantation

Figure 8.2.1: Stages of Early Embryonic Development

This image shows stages of early embryonic development and where they occur.

The top row, labeled as occurring in the uterine tube (red background), shows three stages: Two-cell, Four-cell, and Eight-cell, each illustrating increasing numbers of cells within the same overall size.

The bottom row, labeled as occurring in the uterus (blue background), shows later stages: Morula (16 cells), appearing as a solid ball of cells, and Blastocyst (70–100 cells), which contains a fluid-filled cavity labeled Blastocoel. The blastocyst also includes an outer layer labeled Trophoblast and a cluster of cells labeled Inner cell mass.

A legend indicates red corresponds to “Occurs in uterine tube” and blue corresponds to “Occurs in uterus.”

As the blastocyst forms, the trophoblast excretes enzymes that begin to degrade the zona pellucida. In a process called “hatching,” the conceptus breaks free of the zona pellucida in preparation for implantation.

Figure 8.2.2: The Sequence of Early Human Development

This image shows the sequence of early human development from ovulation through implantation, with numbered stages 1 through 8 arranged along the uterine tube and into the uterus.

- Stage 1: “Unfertilized Oocyte” shows an oocyte before fertilization.
- Stage 2: “Fertilized Oocyte” shows sperm surrounding and penetrating the oocyte.
- Stage 3: “Two-cell stage” shows the zygote divided into two blastomeres.
- Stage 4: “Four-cell stage” shows four cells within the same outer boundary.
- Stage 5: Two panels show progression to the Eight-cell stage and then Morula (16 cells), a solid ball of cells.
- Stage 6: “Blastocyst (70–100 cells)” shows a structure with a fluid-filled cavity labeled Blastocoel, an outer layer labeled Trophoblast, and a cluster labeled Inner cell mass. Arrows trace movement along the uterine tube toward the uterus, indicating progression of development during transport.
- Stage 7: “Embryo hatches (sheds zona pellucida)” shows the blastocyst emerging from its outer covering.
- Stage 8: “Blastocyst rotates and implants into endometrium of the uterus” shows attachment to the uterine lining.

Figure 8.2.3: Steps of Blastocyst Implantation

This image illustrates the process of implantation of the blastocyst into the uterine lining in three labeled steps.

At the top, the uterine wall is labeled with Endometrium and Uterine cavity, and individual cells are labeled Uterine mucosa cells.

- Step 1: “The blastocyst digests the uterine mucosa when it initially implants into the endometrium.” The blastocyst is shown attaching to and beginning to embed into the uterine lining. An arrow indicates progression downward.
- Step 2: “Eventually, the endometrium grows over and surrounds the embryo, fully securing it to the uterine lining.” The blastocyst is shown more deeply embedded, with surrounding endometrial tissue enclosing it. Another arrow indicates further progression.
- Step 3: “Implanted embryo continues to grow within endometrium (depicted embryo is 7–8 weeks after conception).” A cross-section of the uterus shows the developing embryo within the uterine wall.

To the right, additional diagrams labeled Anterior view and Lateral view indicate the most common site of implantation (posterior uterine wall). The figure emphasizes the sequence of implantation and the typical location within the uterus.

Figure 8.2.4: Normal Placental Position and Placenta Previa

This image is a side-by-side diagram that compares the normal location of the placenta with a condition called placenta previa.

On the left, labeled “Normal location of placenta,” a cross-section of the uterus shows the fetus positioned inside the uterine cavity. The placenta is attached to the upper uterine wall, away from the cervix. A label indicates that the cervix is not obstructed, allowing a clear passage for birth.

On the right, labeled “Placenta previa,” a similar cross-section shows the placenta attached lower in the uterus. A label identifies the internal os, the opening of the cervix. The placenta is covering the cervix, which obstructs the passage and would prevent normal vaginal delivery.

The diagram emphasizes the difference between a normal placental position and one that blocks the cervical opening.

Figure 8.2.5: Implanted Blastocyst and Early Embryonic Layers

This image shows the structure of an implanted blastocyst within the uterine lining and the formation of early embryonic layers.

On the right side, the uterine wall is labeled Endometrium, shown as a layered tissue with blood vessels. The implanted structure is embedded within this lining. Within the implanted blastocyst, a central space is labeled Blastocyst cavity (develops into the yolk sac). Adjacent to this cavity is the embryonic disc, which consists of two labeled layers:

- Hypoblast (lower layer)
- Epiblast (upper layer)

Above the embryonic disc is a small space labeled Amniotic cavity, enclosed by a membrane labeled Amnion. Surrounding the blastocyst is the trophoblast, which is divided into two labeled layers:

- Cytotrophoblast, the inner cellular layer
- Syncytiotrophoblast, the outer invasive layer that extends into the endometrium

The diagram emphasizes the organization of embryonic tissues and supporting membranes after implantation and their relationship to the uterine lining.

Figure 8.2.6: Early Post-Implantation Development and Germ Layer Formation

This image illustrates early post-implantation development and the formation of the three primary embryonic germ layers.

Early Post-Implantation Embryo

The upper panel shows an implanted blastocyst embedded within the uterine lining. The uterine lining has reestablished itself over the implantation site, enclosing the developing embryo within the endometrium. The outer layer of the implanted conceptus is the trophoblast, which contributes to the formation of extraembryonic structures and supports implantation.

Inside the conceptus is a two-layered embryonic disc known as the bilaminar embryonic disc. The upper layer is the epiblast, and the lower layer is the hypoblast. A fluid-filled space above the epiblast forms the amniotic cavity, which will eventually surround and protect the developing embryo.

An arrow between the panels indicates progression to a later stage of development.

Formation of the Germ Layers

The lower panel shows a later stage in which the embryonic disc has been reorganized into three primary germ layers:

- Ectoderm, the outer layer
- Mesoderm, the middle layer
- Endoderm, the inner layer

The amniotic cavity remains above the embryo, while the trophoblast and surrounding endometrium continue to enclose the developing conceptus.

A magnified view focuses on the primitive streak, a temporary structure that appears along the surface of the epiblast. Cells migrate inward through the primitive streak during a process called gastrulation. Some migrating cells replace most of the hypoblast cells and form the endoderm. Other migrating cells spread between the developing ectoderm and endoderm to form the mesoderm. Cells that remain in the epiblast become the ectoderm.

A second inset identifies the level of the cross section used to illustrate these developmental changes.

The figure demonstrates the transition from a bilaminar embryonic disc to a trilaminar embryonic disc during gastrulation. Initially, the embryo consists of the epiblast and hypoblast. As cells migrate through the primitive streak, three germ layers are established: ectoderm, mesoderm, and endoderm. These germ layers provide the foundation for all tissues and organs of the developing body. The ectoderm gives rise primarily to the nervous system and skin, the mesoderm forms muscles, connective tissues, and the cardiovascular system, and the endoderm forms the lining of many internal organs and glands.

Figure 8.2.7: Early Embryo, Extraembryonic Membranes, and Germ Layer Derivatives

This image illustrates an early embryo within the uterus and shows how the three primary germ layers and extraembryonic membranes contribute to embryonic development.

The embryo is surrounded by several protective and supportive structures. The outermost membrane is the chorion, which lies within the endometrium, the lining of the uterus. Spaces within the surrounding tissue contain maternal blood pools, which bring nutrients and oxygen close to the developing embryo.

Within the chorion is the amniotic cavity, a fluid-filled space surrounding the embryo. The cavity is enclosed by the amnion, a membrane that protects the embryo and provides a stable environment for growth. Inferior to the embryo is the yolk sac, which is lined with endoderm and contributes to early nutrient transfer and blood cell formation. Extending from the embryo is the allantois, an embryonic structure involved in the development of the umbilical cord and early circulatory connections.

The embryo itself contains three primary germ layers formed during gastrulation:

- Ectoderm, the outer layer
- Mesoderm, the middle layer
- Endoderm, the inner layer

The figure emphasizes that these germ layers give rise to different tissues and organ systems.

- Endoderm develops into much of the digestive tract and associated organs, including the liver and pancreas, as well as the inner lining of the lungs.
- Mesoderm forms structures involved in support, movement, and transport, including the circulatory system, skeletal system, muscular system, and portions of the lungs.
- Ectoderm develops into external coverings and the nervous system, producing structures such as the skin, hair, nails, and the nervous system.

The figure demonstrates how the early embryo is supported by extraembryonic membranes while simultaneously undergoing differentiation into three germ layers. These germ layers serve as the foundation for all tissues and organs of the body. The chorion, amnion, yolk sac, and allantois support growth and survival of the embryo, while the ectoderm, mesoderm, and endoderm establish the developmental pathways that lead to the formation of the body's organ systems.

Figure 8.2.8: Placenta and Maternal-Fetal Exchange

This image illustrates the relationship between the developing fetus, the placenta, and the maternal blood supply. It shows how nutrients, gases, and wastes are exchanged between the fetus and the mother during pregnancy.

Fetus and Extraembryonic Membranes

The left panel shows a fetus developing within the uterus. The fetus is suspended in amniotic fluid contained within the amniotic cavity, which is enclosed by the amnion. The amniotic fluid cushions and protects the fetus while allowing movement during development.

Surrounding the amnion is the chorion, the outer fetal membrane. The chorion contributes to the formation of the placenta and serves as the fetal component of the maternal-fetal interface. A small yolk sac is present near the fetus and represents an early extraembryonic structure involved in nutrient transfer and blood cell formation during early development.

The fetus is connected to the placenta by the umbilical cord, which contains blood vessels that carry blood between the fetus and the placenta.

The placenta is attached to the wall of the uterus and serves as the primary site of exchange between the maternal and fetal circulatory systems.

Placental Exchange

The right panel enlarges the region where the placenta attaches to the uterine wall.

The fetal portion of the placenta contains branching structures called chorionic villi, which extend outward from the chorion into spaces filled with maternal blood. Within the chorionic villi are fetal blood vessels connected to the umbilical arteries and umbilical vein of the umbilical cord.

The maternal portion of the placenta is supplied by the uterine artery and uterine vein. Blood from the mother enters the intervillous space, where it surrounds the chorionic villi. Although maternal blood closely bathes the villi, it remains separated from fetal blood by placental tissues.

The umbilical arteries carry fetal blood from the fetus to the placental villi, where exchange occurs. Oxygen and nutrients move from the maternal blood in the intervillous spaces into the fetal circulation, while carbon dioxide and metabolic wastes move from fetal blood into the maternal circulation. The umbilical vein then carries oxygenated, nutrient-rich blood back to the fetus.

The figure demonstrates how the placenta functions as the interface between the maternal and fetal circulatory systems. The fetus develops within the protective environment of the amnion and amniotic fluid and remains connected to the placenta through the umbilical cord. The chorionic villi greatly increase the surface area available for exchange by extending into maternal blood-filled intervillous spaces. This arrangement allows efficient transfer of oxygen, nutrients, and waste products while keeping maternal and fetal blood supplies physically separate. The placenta therefore serves as the primary organ of exchange that supports fetal growth and development throughout pregnancy.

Figure 8.2.9: Human Placenta

This image shows a post-expulsion human placenta placed in a shallow medical tray. The tray is light blue with visible fluid and blood staining around the placenta.

The placenta appears as a round, flattened organ with a smooth, slightly shiny surface. Numerous branching blood vessels are visible across its surface, radiating outward from a central point.

An umbilical cord is attached near the top of the placenta. The cord is thick, pale, and slightly twisted, extending outward from the placental surface.

A gloved hand is visible at the top left of the image, with one finger pointing toward the placental surface and the attachment site

of the umbilical cord.

The image emphasizes the physical structure of the placenta, including its vascular network and umbilical cord connection.

Figure 8.2.10: Neurulation: Formation of the Neural Tube and Neural Crest

This figure illustrates neurulation, the process by which the neural tube forms from the embryonic ectoderm. The figure is presented as a sequence of four developmental stages shown in cross section.

Step 1: Neuroectodermal tissues differentiate from the ectoderm and thicken into the neural plate. The neural plate border separates the ectoderm from the neural plate.

The diagram labels:

- Neural plate border
- Neural plate
- Ectoderm
- Mesoderm
- Notochord

Step 2: The neural plate bends dorsally, with the two ends eventually joining at the neural plate borders, which are now referred to as the neural crest.

The diagram labels:

- Convergence
- Neural crest

Step 3: The closure of the neural tube disconnects the neural crest from the epidermis. Neural crest cells differentiate to form most of the peripheral nervous system.

The diagram labels:

- Ectoderm
- Neural crest cells (form components of the PNS)
- Neural tube

Step 4: The notochord degenerates and only persists as the nucleus pulposus of the intervertebral discs. Other mesoderm cells differentiate into the somites, the precursors of the axial skeleton and skeletal muscle.

The diagram labels:

- Epidermis
- Neural tube
- Spinal ganglion
- Somites (mesoderm-derived)
- Notochord (mesoderm-derived)

The figure shows the progression from neural plate formation through neural tube closure and subsequent differentiation of surrounding embryonic tissues. The neural tube becomes positioned beneath the epidermis, neural crest cells give rise to components of the peripheral nervous system, and mesoderm-derived tissues form the somites and notochord-derived structures.

This revision includes all numbered instructional steps and image labels while avoiding information that does not appear in the figure.

Figure 8.2.11: Embryonic Folding

This image is a multi-panel diagram illustrates embryonic folding and the formation of the primitive gut from different germ layers. A color legend identifies Ectoderm (blue), Mesoderm (red), Endoderm (yellow), Amnion (green), and Hypoblast (purple).

Left column (transverse sections): The top image shows a flat embryonic disc with layers arranged from top to bottom: amnion, ectoderm, and hypoblast.

In the next transverse section, the embryo begins to fold inward. The outer layer labeled Ectoderm curves around the forming body, while Mesoderm lies beneath it, and Endoderm lines the inner surface. The Amnion surrounds the upper portion.

In the third transverse section, folding progresses further. The lateral edges move toward the midline, enclosing internal structures. The Endoderm begins forming a tube-like structure.

Arrows indicate the continuation of folding into the panels on the right.

Right column: sagittal and transverse views:

The top right image, labeled Sagittal section, shows longitudinal folding. The embryo curves, bringing the yolk sac closer to the body as folding occurs.

The next image, labeled Transverse section, shows the yolk sac narrowing and being incorporated into the embryo.

In the final transverse section, a structure labeled Gut is formed from the endoderm and enclosed within the body. The surrounding layers include Mesoderm, which forms the middle tissues, and Ectoderm, which forms the outer surface.

Figure 8.2.12: Embryo at 7 Weeks

This figure shows an early human embryo within surrounding embryonic membranes.

The embryo appears highly curved in a C-shape, with a prominent head region and a tapering tail-like structure. Small limb buds are visible, indicating early development of arms and legs. A circular structure near the head represents the developing eye.

The embryo lies within a semi-transparent environment of surrounding tissues and fluids. Thin, translucent membranes and vascular structures are visible around it, suggesting the embryonic support structures.

The overall coloration ranges from pale beige for the embryo to reddish and translucent tones in the surrounding tissues. The image emphasizes early organ formation and the curved body shape typical of early embryonic development.

Figure 8.3.1: Differentiation of the Embryonic Reproductive Ducts

This image illustrates the differentiation of the reproductive ducts from a common embryonic stage into male and female systems.

Top panel: An early embryo is shown with paired structures labeled Müllerian ducts (upper, red) and Wolffian ducts (lower, blue). On each side are Bipotential gonads, indicating that the gonads can develop into either testes or ovaries. At the bottom, a common outlet is labeled Cloaca.

Two labeled pathways extend downward: Masculinization on the left and Feminization on the right.

Left pathway (Masculinization): The label states Müllerian ducts degrade, shown as dashed outlines fading. The Wolffian ducts remain and develop further.

In the final male stage, the diagram shows Wolffian ducts become epididymis and ductus (vas) deferens, with structures labeled Testes, Urinary bladder, and Urethra.

Right pathway (Feminization): The label shows Wolffian ducts degrade, indicated by dashed outlines. The Müllerian ducts remain and develop into female reproductive structures.

In the final female stage, the diagram shows Müllerian ducts become uterine tubes and uterus, with structures labeled Ovaries, Urinary bladder, Urethra, Uterus, and Vagina.

Figure 8.3.2: Fetal Circulation and Major Fetal Shunts

This image is a multi-panel diagram illustrates fetal circulation, showing blood flow between the placenta, umbilical cord, and fetal heart.

Left panel: The Placenta is shown with branching blood vessels. A structure labeled Umbilical cord (contains umbilical artery and umbilical vein) connects the placenta to the fetus. Within the cord, the Umbilical vein carries oxygenated blood toward the fetus, while the Umbilical artery carries deoxygenated blood back to the placenta.

Bottom right panel (liver region): Blood labeled “1 Blood arrives via umbilical vein” enters the fetus. The label “2 The ductus venosus shunts oxygenated blood from the placenta away from the semi functional liver and toward the heart” shows blood bypassing much of the liver through the ductus venosus and entering the inferior vena cava.

Top right panel (heart): The fetal heart diagram includes numbered steps:

1. “Oxygenated blood from placenta enters right atrium via inferior vena cava.”
2. “The foramen ovale allows oxygenated blood in the right atrium to reach the left atrium.”
3. “The ductus arteriosus connects the aorta with the pulmonary artery, further shunting blood away from the lungs and into the aorta.”
4. “Mixed blood travels to the head and body, and back to the placenta via the aorta.”

Arrows (red, blue, and purple) show directions of blood flow and mixing. The diagram emphasizes three key fetal shunts:

- Ductus venosus (liver bypass)
- Foramen ovale (right atrium to left atrium)
- Ductus arteriosus (pulmonary artery to aorta)

Figure 8.4.1: Fetal Growth Across the Three Trimesters

This image shows the relative size and position of the fetus within the uterus across the three trimesters of pregnancy, overlaid on an outline of the human torso.

In the center, a simplified cross-section of the lower abdomen shows the uterus with a fetus inside, connected to the fallopian tubes and ovaries on either side.

Three horizontal labels appear on the left side:

- “End of 1st trimester” points to the lower pelvis region. At this stage, the fetus is small and located within the pelvis, with minimal upward expansion of the uterus.
- “End of 2nd trimester” points to the middle abdomen. The uterus has expanded upward, occupying more space in the abdominal cavity as the fetus grows larger.
- “End of 3rd trimester” points to the upper abdomen near the ribcage. The uterus is greatly enlarged, extending high into the abdomen and approaching the chest area.

Behind the labels, shaded overlapping regions illustrate increasing uterine size, progressing from small (first trimester) to very large (third trimester). The diagram emphasizes how the uterus and fetus grow upward and expand significantly in size throughout pregnancy.

Figure 8.4.3: Hormones Initiating Labor

This image shows changes in relative hormone concentration over the course of pregnancy, measured from 0 to 40 weeks on the horizontal axis. Three hormones are represented:

- Human chorionic gonadotropin (hCG) is shown as a solid green line. It rises rapidly during early pregnancy, reaching a peak around weeks 8 to 10. After this peak, hCG levels decline sharply and then level off at a lower, steady concentration for the remainder of pregnancy.
- Progesterone is shown as a dashed blue line. Progesterone levels increase gradually throughout pregnancy, with a more pronounced rise after approximately week 20. The levels peak near the end of pregnancy and then slightly decrease.
- Estrogens are shown as a solid orange line. Estrogen levels begin low, increase slowly in early pregnancy, then rise steeply after about week 20. Estrogen concentrations continue increasing and reach their highest levels near week 40.

Overall, the graph demonstrates that:

- hCG dominates early pregnancy and then declines
- Progesterone and estrogen increase steadily and become the dominant hormones in later pregnancy

Figure 8.4.4: Stages of Childbirth

This image is a multi-panel diagram illustrates the three stages of labor and delivery: dilation, birth, and afterbirth.

Stage 1: Dilation - Two side-by-side illustrations show the uterus and fetus. An arrow indicates progression from an undilated to a fully dilated cervix.

- On the left, the cervix is labeled “Undilated cervix.” The opening is small and closed at the top of the vagina. Labels identify Amniotic fluid within uterus, Cervix, and Vagina.
- On the right, the cervix is labeled “Fully dilated cervix (greater than 10 cm in diameter).” The opening is wide, allowing passage of the fetus.

Stage 2: Birth - Four sequential panels show the delivery of the baby. Arrows between panels show the sequence of movement through the birth canal.

1. “Presentation of head” – The fetus is positioned head-down, with the head entering the birth canal.
2. “Rotation and delivery of anterior shoulder” – The head rotates as the front shoulder emerges.
3. “Delivery of posterior shoulder” – The second shoulder passes through the birth canal.
4. “Delivery of lower body and umbilical cord” – The rest of the body is delivered, followed by the umbilical cord.

Stage 3: Afterbirth delivery - Two images show the placenta after the baby is delivered:

- The diagram on the left shows the placenta detaching from the uterine wall and moving toward the cervix. A label reads: “Placenta detaches and exits through vagina.”
- The image on the right is a photograph of an expelled placenta placed in a medical tray, showing its tissue structure and attached umbilical cord.

Figure 8.5.1: Neonatal Circulatory System

This image compares fetal circulation before birth with the circulation pattern immediately after birth. The top panel focuses on changes within the heart, while the bottom panel shows changes in blood flow between the placenta, liver, and circulatory system.

Before birth, fetal blood bypasses the lungs because oxygen is obtained from the placenta. In the heart, blood can flow directly from the right atrium to the left atrium through the foramen ovale, and blood leaving the right ventricle can bypass the lungs through the ductus arteriosus, a vessel connecting the pulmonary trunk to the aorta. Colored arrows illustrate these fetal shunts and the movement of blood through the fetal cardiovascular system.

Immediately after birth, when the newborn begins breathing, these bypass pathways close. The ductus arteriosus constricts, directing blood from the right ventricle to the lungs through the pulmonary arteries for oxygenation. The foramen ovale closes, leaving a depression called the fossa ovalis, which separates oxygen-poor and oxygen-rich blood within the heart.

The lower panel illustrates changes in circulation associated with the placenta. Before birth, oxygenated blood enters the fetus through the umbilical vein and travels partly through the ductus venosus, which allows blood to bypass most of the liver and enter the inferior vena cava. After birth, placental circulation ends when the umbilical cord is no longer used. The ductus venosus closes and becomes the ligamentum venosum, the umbilical vessels are converted into ligaments, and the inferior vena cava carries only deoxygenated blood returning to the heart.

This figure demonstrates how the circulatory system transitions from fetal circulation, which relies on the placenta and several temporary vascular shunts, to newborn circulation, which depends on the lungs for oxygen exchange and uses the normal postnatal pathway of blood flow through the heart, lungs, and body.

Figure 8.6.1: Let-Down Reflex

This image illustrates the positive feedback loop that regulates lactation, showing how infant suckling stimulates both milk production and milk ejection.

At the top of the figure, an infant suckles at the breast. Sensory receptors in the areola detect suckling and send nerve impulses to the brain. These signals travel to the hypothalamus and posterior pituitary gland, which respond by releasing oxytocin into the bloodstream. An inset diagram shows oxytocin-producing neurosecretory cells in the hypothalamus connected to the posterior pituitary through the hypothalamo-hypophyseal tract, where oxytocin enters nearby capillaries and is carried throughout the body.

At the same time, sensory stimulation from suckling promotes milk production within the mammary glands. In the right panel, mammary alveoli are shown producing milk. The alveoli are lined with lactocytes, specialized cells that synthesize and secrete milk into the hollow interior of each alveolus. Arrows indicate milk accumulating within these structures.

As circulating oxytocin reaches the breast, it stimulates myoepithelial cells surrounding the alveoli to contract. This contraction squeezes milk from the alveoli into the lactiferous ducts. A diagram of breast tissue shows milk moving through branching ducts toward the nipple. Milk collects temporarily in the lactiferous sinus before leaving the breast through openings in the nipple, where it becomes available to the nursing infant.

The left side of the figure shows a large arrow forming a loop labeled as a positive feedback cycle. As milk is produced and released, the infant continues to suckle. Continued suckling generates additional sensory stimulation, which promotes further oxytocin release and ongoing milk production and ejection. The result is a self-reinforcing cycle in which suckling increases milk availability, and increased milk availability encourages continued suckling.

This figure demonstrates how lactation is regulated through a positive feedback mechanism: infant suckling stimulates neural and hormonal responses that increase milk production and milk letdown, which in turn encourages further suckling and sustains the cycle.

Figure 8.7.1: A Human Karyotype

This image shows a human karyotype, which is an organized display of chromosomes arranged in numbered pairs. The chromosomes are shown as small, rod-shaped structures with banding patterns, grouped into pairs and labeled below each pair with numbers. Across the image, there are 22 numbered pairs of autosomes, labeled sequentially from 1 through 22. Each numbered group contains two chromosomes of similar size and shape, indicating homologous pairs.

- Chromosomes 1 through 3 appear largest and are shown at the top left.
- Chromosomes gradually decrease in size from left to right and top to bottom.
- Chromosomes 13 through 15 and 21 through 22 appear smaller and more compact.

At the bottom right, a final pair is labeled “X/Y”, representing the sex chromosomes. One chromosome is larger (X), and the other is smaller (Y), indicating a typical male karyotype. Each chromosome pair shows characteristic dark and light banding patterns, which reflect regions of differing DNA composition.

Figure 8.7.2: Random Segregation

This image illustrates inheritance of a trait controlled by one dominant allele and one recessive allele across two generations using Punnett squares.

In the first generation, a parent with two dominant alleles is crossed with a parent that has two recessive alleles. The Punnett square shows that every possible offspring receives one dominant allele from one parent and one recessive allele from the other parent. As a result, all offspring are heterozygous and express the dominant trait. The figure indicates that 100 percent of the second-generation offspring display the dominant phenotype.

In the second generation, two heterozygous individuals are crossed. Each parent can contribute either a dominant allele or a recessive allele. The Punnett square shows four possible offspring combinations. One offspring inherits two dominant alleles, two offspring inherit one dominant and one recessive allele, and one offspring inherits two recessive alleles. This produces a genotypic ratio of 1 homozygous dominant, 2 heterozygous, and 1 homozygous recessive.

Because both homozygous dominant and heterozygous individuals express the dominant trait, three of the four possible offspring display the dominant phenotype. Only the offspring with two recessive alleles expresses the recessive phenotype. The figure summarizes this outcome as 75 percent dominant phenotype and 25 percent recessive phenotype.

This figure demonstrates Mendel's principle of inheritance for a single gene, showing that crossing two true-breeding parents produces a generation of heterozygous offspring and that crossing those heterozygous offspring results in a 3:1 dominant-to-recessive phenotype ratio and a 1:2:1 genotype ratio in the next generation.

Figure 8.7.3: Autosomal Dominant Inheritance

This image illustrates inheritance of neurofibromatosis using a Punnett square. The disorder is associated with a dominant allele, meaning that a person needs only one copy of the disease-associated allele to express the condition.

The cross shown involves a parent who carries one disease-associated dominant allele and one normal recessive allele and a second parent who carries two recessive alleles and does not have the condition. The parent with the dominant allele can pass either the disease-associated allele or the recessive allele to offspring, whereas the unaffected parent can pass only recessive alleles.

The Punnett square shows four possible offspring outcomes. Two of the four offspring inherit the disease-associated dominant allele from the heterozygous parent and a recessive allele from the unaffected parent. These offspring have neurofibromatosis because the dominant allele is expressed. The other two offspring inherit recessive alleles from both parents and therefore do not have the condition.

The figure summarizes the results as a 50 percent probability that offspring will inherit neurofibromatosis and a 50 percent probability that offspring will not inherit the disorder.

This figure demonstrates the inheritance pattern of an autosomal dominant disorder. When an affected heterozygous parent and an unaffected parent have children, each child has a one-in-two chance of inheriting the dominant disease-associated allele and expressing the condition, and a one-in-two chance of inheriting only recessive alleles and remaining unaffected.

Figure 8.7.4: Autosomal Recessive Inheritance of Cystic Fibrosis

illustrates autosomal recessive inheritance using cystic fibrosis as an example. Two carrier parents are shown at the top of the figure. Each parent carries one normal allele and one recessive disease-associated allele but does not have cystic fibrosis because the normal allele masks the effect of the recessive allele.

Lines connect the parents to four possible offspring outcomes. One offspring inherits a normal allele from each parent and is unaffected and does not carry the disease-associated allele. Two offspring inherit one normal allele and one recessive disease-associated allele. Like the parents, these offspring are carriers who do not show symptoms but can pass the allele to future generations. One offspring inherits two recessive disease-associated alleles and is affected with cystic fibrosis.

A Punnett square on the right summarizes these possible genetic combinations. The results show one offspring with two normal

alleles, two carrier offspring with one normal and one recessive allele, and one affected offspring with two recessive alleles. This produces a genotypic ratio of 1 unaffected non-carrier : 2 carriers : 1 affected individual.

The figure also summarizes the phenotypic outcomes. Three of the four possible offspring do not express cystic fibrosis because they inherit at least one normal allele. One of the four offspring inherits two recessive disease-associated alleles and expresses cystic fibrosis. This corresponds to a 75 percent probability that cystic fibrosis is not expressed and a 25 percent probability that the disorder is expressed.

This figure demonstrates the inheritance pattern of an autosomal recessive disorder. When two carrier parents have children, each child has a 25 percent chance of being unaffected and not a carrier, a 50 percent chance of being an unaffected carrier, and a 25 percent chance of inheriting two recessive alleles and developing the disorder.

Figure 8.7.5: X-Linked Dominant Inheritance Patterns

This image illustrates two inheritance patterns for an X-linked dominant trait, comparing the outcomes when either the father or the mother carries the affected allele.

Panel (a): Affected father and unaffected mother

The first example shows a father who has an X-linked dominant trait and a mother who does not have the trait. Because fathers pass their X chromosome only to their daughters and their Y chromosome only to their sons, all daughters inherit the affected X chromosome and express the trait. None of the sons inherit the affected X chromosome because they receive the Y chromosome from the father. As a result, all daughters are affected and all sons are unaffected.

The figure summarizes these outcomes as 100 percent of females affected and 0 percent of males affected.

Panel (b): Unaffected father and affected mother

The second example shows a father without the trait and a mother who carries one affected X chromosome and one unaffected X chromosome. Each child has a 50 percent chance of inheriting the affected X chromosome from the mother. Sons who inherit the affected X chromosome express the trait because they have only one X chromosome. Daughters who inherit the affected X chromosome also express the trait because the allele is dominant. The remaining sons and daughters inherit the unaffected X chromosome and do not express the trait.

The figure summarizes these outcomes as 50 percent of males affected and 50 percent of females affected.

This figure demonstrates the characteristic inheritance pattern of X-linked dominant traits. An affected father passes the trait to all daughters and none of his sons, whereas an affected heterozygous mother can pass the trait to approximately half of both sons and daughters.

Figure 8.7.6: X-Linked Recessive Inheritance with a Carrier Mother

This image illustrates the inheritance pattern of an X-linked recessive trait when an unaffected father and a carrier mother have children.

The father does not carry the recessive disease-associated allele. The mother carries one normal X chromosome and one X chromosome with the recessive allele, making her a carrier who does not express the condition.

The figure shows four possible offspring outcomes. One son inherits the mother's normal X chromosome and is unaffected. A second son inherits the mother's X chromosome carrying the recessive allele and is affected because males have only one X chromosome and therefore cannot mask the recessive allele. One daughter inherits normal X chromosomes from both parents and is unaffected. Another daughter inherits the recessive allele from the mother and a normal X chromosome from the father, making her a carrier who does not express the condition.

The figure demonstrates that daughters are not affected because they inherit a normal X chromosome from the unaffected father. However, some daughters may become carriers if they inherit the recessive allele from the mother. Sons inherit their single X chromosome from the mother, so a son who receives the recessive allele expresses the trait.

The probability summary indicates that 50 percent of sons are affected and 50 percent of sons are unaffected, while 0 percent of daughters are affected, although 50 percent of daughters are carriers.

This figure demonstrates the characteristic inheritance pattern of an X-linked recessive trait when the mother is a carrier and the father is unaffected. Sons have a 50 percent chance of inheriting and expressing the trait, whereas daughters are not affected but may inherit the recessive allele and become carriers.

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