KANSAS STATE UNIVERSITY: HUMAN NUTRITION

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Human Nutrition

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Detailed Licensing

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About the Author

Brian Lindshield, Ph.D. is an Associate Professor in the Department of Food, Nutrition, Dietetics and Health. He received an A.S. from Pratt Community College in '01, a B.S. in Human Nutrition from Kansas State University in '03, and Ph.D. in Nutritional Sciences from the University of Illinois at Urbana-Champaign in '08.

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About the Book

The CK-12 foundation defines a flexbook as a “free and open source textbook platform where one can build and edit collaborative textbooks1.” The FNDH 400 (formerly HN 400, department changed its name from Human Nutrition to Food, Nutrition, Dietetics and Health) Flexbook fits this definition, but I felt the name was particularly accurate due to the flexibility of Google Docs that it was built on.

The flexbook is divided into 13 chapters with sections and subsections. These are numbered in such a way that the first number represents the chapter. A period separates the chapter from the section number, and another period is followed by the subsection number. The figures are non-copyrighted figures or I have made them myself in PowerPoint. The flexbook also contains links to articles, videos, and animations in Web Link boxes. These can be clicked to open the link, and urls for these resources are also provided at the end of the section or subsection.

I am happy to share the flexbook and PowerPoint slides that I use for class with other instructors teaching similar courses. Please email me and we can get something arranged.

Here’s a citation to use for this purpose, but if this doesn’t work for your purpose, please cite the URL which is also provided below.

Citation:

Lindshield, B. L. Kansas State University Human Nutrition (FNDH 400) Flexbook (2018). NPP eBooks. 19. http://newprairiepress.org/ebooks/19

The flexbook was a finalist for the 2012 Education-Portal.com People’s Choice Award for the Most Open Resource (note Education-Portal.com is now Study.com).



About the Course

FNDH 400 is a 3-hour, intermediate-level, nutrition course at Kansas State University taught on campus every spring semester, and all 3 semesters (fall, spring, summer) via the Division of Continuing Education. Ideally on-campus students take the course during the spring semester of their sophomore year. Most on-campus students in the class are majoring in Nutritional Sciences, Nutrition and Health (previously Public Health Nutrition), Nutrition and Kinesiology, Athletic Training, or Dietetics. There is an increasing number of Biology, Life Sciences and other majors taking the course. Online, more students are nontraditional and a little more than half are distance dietetics students (K-State offers a distance dietetics degree).

Peer-reviewed flexbook/OER journal articles

- Lindshield, B.L., Adhikari, K. Campus and Online U.S. College Students’ Attitudes Toward an Open Educational Resource Course Fee. Int J High Educ. 2(4): 42-51, 2013. doi:10.5430/ijhe.v2n4p42 http://www.sciedu.ca/journal/index.php/ijhe/article/

view/3312/2003
- Lindshield, B.L., Adhikari, K. Online and Campus College Students Like Using an Open Educational Resource Instead of a Traditional Textbook. Journal of Online Learning and Teaching. 9(1): 26-38, 2013. http://jolt.merlot.org/vol9no1/lindshield_0313.htm
- Lindshield, B.L., Adhikari, K. The Kansas State University Human Nutrition (HN 400) Flexbook. Educause Quarterly. 34(4), 2011.
- http://www.educause.edu/ero/article/kansas-state-university-human-nutrition-hn-400-flexbook

Flexbook Presentations

3/5/13 Innovations in Teaching & Learning Showcase: “Open Educational Resources, Textbook Replacements?”

3/4/13 Innovations in Teaching & Learning Workshop Panel: “Take 5: Teaching Technologies that Work”

9/27/12 IDT Roundtable: “E-textbooks and Beyond”

One of 3 speakers at session.

id.ome.ksu.edu/roundtable/e-textbooks-and-beyond/

3/16/12 Teaching, Learning, and Technology Showcase 2012: “Using Flexbooks to Supplement/Replace the Traditional Textbook”

9/28/11 Axio Learning Conference 2011: Peer Showcase: “Using flexbooks to supplement/replace the traditional textbook”

7/25/11 Society for Nutrition Education and Behavior Oral Presentation: “Kansas State University Human Nutrition (HN 400) Flexbook”

9/29/10 Axio Learning Conference 2010: “Flexbooks”

1/12/10 7th annual K-State Teaching Retreat: “Flexbooks: Better than Textbooks?”

Media Stories about the Flexbook

9/26/13 K-State Today: K-State faculty receive funding to develop open alternative textbooks

http://www.k-state.edu/today/announcement.php?id=10136&category=kudos&referredBy=email

1/29/13 Kansas State Collegian: Open-sourced ‘flexbook’ earns K-State educator national acclaim

http://www.kstatecollegian.com/2013/01/29/open-sourced-flexbook-earns-k-state-educator-national-acclaim/

9/19/12 College Human Ecology Press Release: Lindshield’s flexbook nominated for national people’s choice award

http://www.he.k-state.edu/news/2012/09/19/lindshields-flexbook-nominated-for-national-peoples-choice-award/

9/12/12 Partnership for Technology Innovation: Providing an Open Resource, Lowering the Financial Burden

partnership4techinnovation.org/providing-an-open-resource-lowering-the-financial-burden/

8/24/12 Kansas City Star: K-State professor develops textbook flexibility

www.kansascity.com/2012/08/24/3777552/k-state-professor-develops-textbook.html

Other media outlets where article was published:

- Chicago Tribune: www.chicagotribune.com/business/yourmoney/sns-201208271800--tms--kidmoneyctnsr-a20120827-20120827,0,77297.story
- McClatchy Wire

- Sacramento Bee
- Sun Herald (Biloxi-Gulfport and Mississippi Gulf Coast
- Lexington Herald-Leader
- The Telegraph (Georgia)
- The South Carolina State
- The Olympian (Olympia, Washington)
- The Bradenton Herald (Florida)
- Bellingham Herald (Washington)
- News Observer (Raleigh, North Carolina)
- The Modesto Bee (Modesto, California)
- The Idaho Statesman (Boise, Idaho)
- Civic Plus (Blog)
- The Stockton Record (Stockton, California):
- The Detroit News

8/16/12 Up to Date KCUR 89.3 (Kansas City NPR station): The 'Flexbook': A Textbook Replacement: http://kcur.org/post/flexbook-textbook-replacement

8/13/12 Kansas State University Press Release: From textbook to flexbook: Professor uses new collaborative tool in the classroom

http://www.k-state.edu/media/newsreleases/aug12/flexbook81312.html

Other media outlets that published the release:

- **Campus Technology:** http://campustechnology.com/articles/2012/08/13/ksu-professor-creates-flexbook.aspx
- **Phys.org:** http://phys.org/news/2012-08-textbook-flexbook-professor-collaborative-tool.html
- **News Medical:** http://www.news-medical.net/news/20120814/Flexbook-helps-students-save-money-on-course-materials.aspx
- **Kansas City infoZine:** http://www.infozine.com/news/stories/op/storiesView/sid/52822/

8/13/12 K-State Today: Professor's collaborative flexbook nominated for national people's choice award http://www.k-state.edu/today/announcement.php?id=4284&category=kudos&referredBy=email

2/22/12 Just In Blog: Lindshield flexes his flexbook muscle and tells how you can, too

http://updatejustin.wordpress.com/2012/02/22/lindshield-flexes-his-flexbook-muscle-and-tells-how-you-can-too/

12/15/10 Issue 16 Axio Quarterly: Flexbooks: What Can They Do For You?

axiolearning.org/news/2010/dec/15/flexbooks-what-can-they-do-you/

Acknowledgement

Thanks to former Kansas State University student Russ Wolters for his input and feedback on the flexbook design and revision. Thanks to Erin Ward for her assistance in the development and implementation of the Top Hat version of the flexbook. Feedback from FNDH 400 students over the years has also been extremely important in improving the flexbook.

Reference

1. http://creativecommons.org/weblog/entry/9378

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1: NUTRITION BASICS

The field of nutrition is dynamic. This means that our understanding and practices are constantly changing and being updated. Some of nutrition's dynamic nature may be due to the fact that nutrition, as a discipline, is relatively young (many vitamins weren't isolated until the 1930s) compared to many other scientific fields. New research is always being conducted and the findings are continuously being reported to the public. With so much information, discernment must be exercised. In order to interpret these new findings, you need to understand how the research was conducted and the nutrition research hierarchy. Everyone eats, so people are going to face nutrition choices and questions on a daily basis. This section will provide you with an integrated understanding of the different forms of nutrition research and how to evaluate them relative to one another.

1.1: The Basics

1.2: Epidemiology

1.3: In Vitro and Animal Studies

1.4: Human Intervention Studies

1.5: Nutrition Research Statistics

1.6: Publishing Research

1.7: Interpreting Research

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1.1: The Basics

Nutrition can be defined as the science of the action of food, beverages, and their components in biological systems. A nutrient is a compound that provides a needed function in the body. Nutrients can be further classified based on the amount needed in the body.

- **Macronutrients**: nutrients needed in larger amounts
- **Micronutrients**: nutrients needed in smaller amounts (but still important)

The following table lists the different macronutrients and micronutrients.

Table 1.1.1*: Macronutrients and Micronutrients*

Macronutrients	Micronutrients
Carbohydrates	Vitamins
Proteins	Minerals
Lipids	
Water	

- **Carbohydrates**: The name carbohydrate means "hydrated carbon", or carbon with water. Thus, it isn't a surprise that carbohydrates are made up of carbon, hydrogen, and oxygen. Sucrose (table sugar) is an example of a commonly consumed carbohydrate. Some dietary examples of carbohydrates are whole-wheat bread, oatmeal, rice, sugary snacks/drinks, and pasta.
- **Proteins**: Proteins are also made up of carbon, hydrogen, and oxygen, but they also contain nitrogen. Several dietary sources of proteins include nuts, beans/legumes, skim milk, egg whites, and meat.
- **Lipids**: Lipids consist of fatty acids, triglycerides, phospholipids, and sterols (i.e. cholesterol). Lipids are also composed of carbon, hydrogen, and oxygen. Some dietary sources of lipids include oils, butter, and egg yolks.
- **Water**: Water is made up of hydrogen and oxygen (H_2O) and is the only macronutrient that doesn't provide energy.
- **Vitamins**: Organic compounds that are essential for normal physiologic processes in the body.
- **Minerals**: Elements (think periodic table) that are essential for normal physiological processes in the body.

Query 1.1.1

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Calories (Food Energy)

Food energy is measured in kilocalories (kcals), commonly referred to as calories by the general public. The general public “calorie” term is incorrect (most do not know or understand the difference between the kilocalorie and calorie terms), but it is important to understand what the term calorie represents when it is used in this way. A kilocalorie is the amount of energy needed to raise 1 kilogram of water 1 degree Celsius. A food’s kilocalories are determined by putting the food into a bomb calorimeter and determining the energy output (energy = heat produced). The link below is to an animation of a bomb calorimeter.

Web Links

Bomb Calorimeter

Among the nutrients, the amount of kilocalories per gram that each provide are shown below.

Table 1.1.2*: Energy providing and no energy provided nutrients*

Energy (kcal/g)	No Energy
Carbohydrates (4)	Vitamins
Proteins (4)	Minerals
Lipids (9)	Water

As can be seen, only carbohydrates, proteins, and lipids provide energy. However, there is another energy source in the diet that is not a nutrient.....alcohol. Just to re-emphasize, alcohol is NOT a nutrient! But it does provide energy.

Below is a list of energy sources in the diet from lowest calories per gram to the highest calories per gram. Knowing these numbers allows a person to calculate/estimate the amount of calories the food contains if you know the grams of the different energy sources.

- Energy Sources (kcal/g)
- Carbohydrates 4
- Protein 4
- Alcohol 7
- Lipids 9

Query 1.1.2

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Phytochemicals, Zoochemicals & Functional Foods

Beyond macronutrients and micronutrients, there is a lot of interest in non-nutritive compounds found in foods that may be either beneficial or detrimental to health.

Phytochemicals

Phytochemicals are compounds in plants (phyto) that are believed to provide health benefits beyond the traditional nutrients. One example is lycopene in tomatoes, which is thought to potentially decrease the risk of some cancers (in particular prostate cancer). Diets rich in fruits and vegetables have been associated with decreased risk of chronic diseases. Many fruits and vegetables are rich in phytochemicals, leading some to hypothesize that phytochemicals are responsible for the decreased risk of chronic diseases. The role that phytochemicals play in health is still in the early stages of research, relative to other areas of nutrition such as micronutrients. The following link contain good information on phytonutrients if you are interested in learning more about them.

Web Link

Linus Pauling Institute: Phytochemicals

Zoochemicals

Zoochemicals are the animal equivalent of phytochemicals in plants. They are compounds in animals that are believed to provide health benefits beyond the traditional nutrients that food contains. Hopefully the name is pretty easy to remember because you can find animals at a zoo. Some compounds can be both phytochemicals and zoochemicals. An example of compounds that can be classified as both are the yellow carotenoids lutein and zeaxanthin. Kale, spinach, and corn contain phytochemicals and are good sources of lutein and zeaxanthin. Whereas egg yolks contain zoochemicals and are also a good source of these carotenoids.

Functional Foods

There are a number of definitions of functional foods. Functional foods are generally understood to be a food, or a food ingredient, which may provide a health benefit beyond the traditional nutrients (macronutrients and micronutrients) it contains. Functional foods are often a rich source of a phytochemical or zoochemical, or contain more of a certain nutrient than a normal food.

Query 1.1.3

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The Scientific Method

The basis of what we know about nutrition is derived from research and the scientific method underlies how research is conducted. The following figure shows the steps in the scientific method.

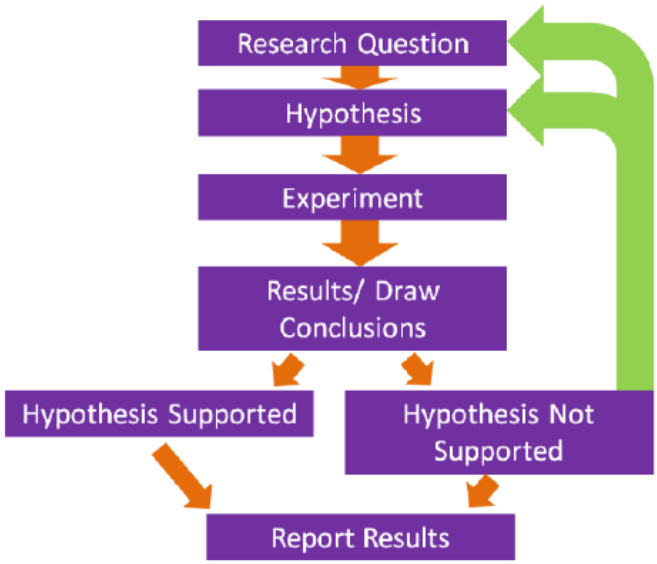


Figure 1.1.1: The scientific method

Steps in the Scientific Method

1. The first step is to come up with a scientific or research question that you are interested in investigating.
2. Based on your research question, a hypothesis or an educated guess is formulated.
3. The next step is to design and conduct the experiment. A good design should take into account what has been done previously. Thus, a thorough review of methods and results published previously should be undertaken. This will help prevent making the same mistakes and save a lot of time conducting the research.
4. Perform the experiment/research and collect results and draw conclusions.
5. If the hypothesis is not supported, then a new hypothesis/research question should be created and a new experiment be conducted.
6. Ultimately, researchers hope to publish their research in peer-reviewed journals.

Query 1.1.4

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1.2: Epidemiology

Epidemiology is defined as the study of human populations. These studies often investigate the relationship between dietary consumption and disease development. There are three main types of epidemiological studies: cross-sectional, case-control, and prospective cohort studies.

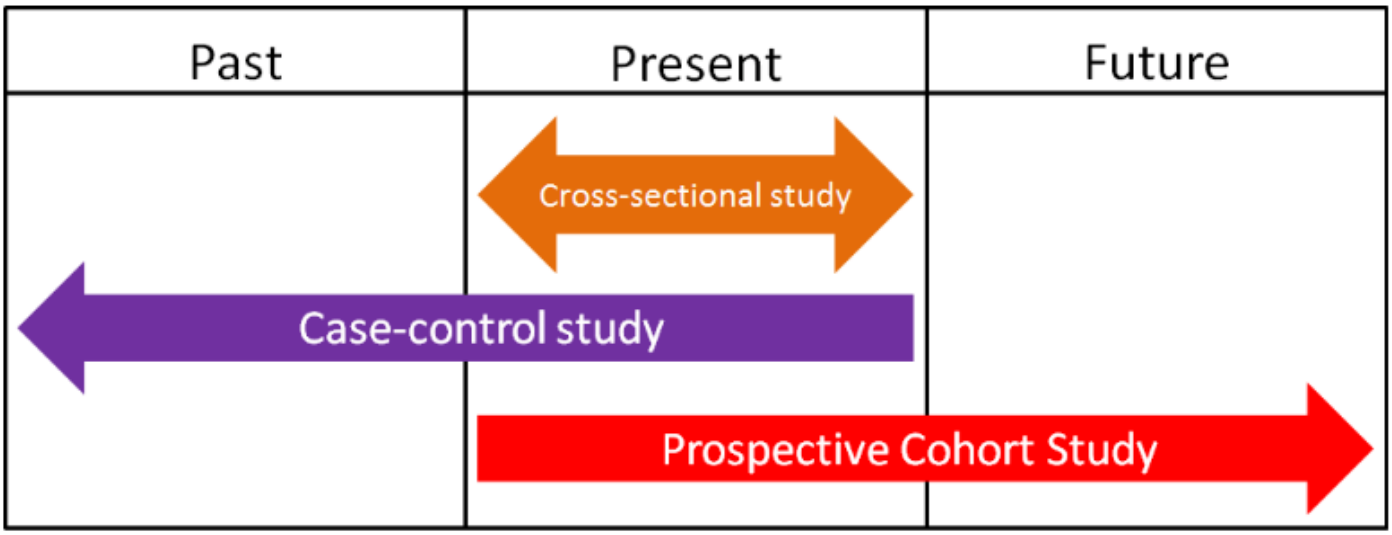


Figure 1.2.1: Types of epidemiology. Adapted from reference 1.

Cross-Sectional Studies

Cross-sectional studies compare different populations at the same point in time. It is as if you take a snapshot of the two different populations to compare them to one another. An example of a cross-sectional study led to a phenomenon known as the "French Paradox." Cholesterol and saturated fat intake were associated with increased risk of coronary heart disease across a wide variety of countries. However, within the study they noticed a surprising result. European countries with very similar cholesterol-saturated fat intakes had hugely different death rates from coronary heart disease deaths, as shown below.

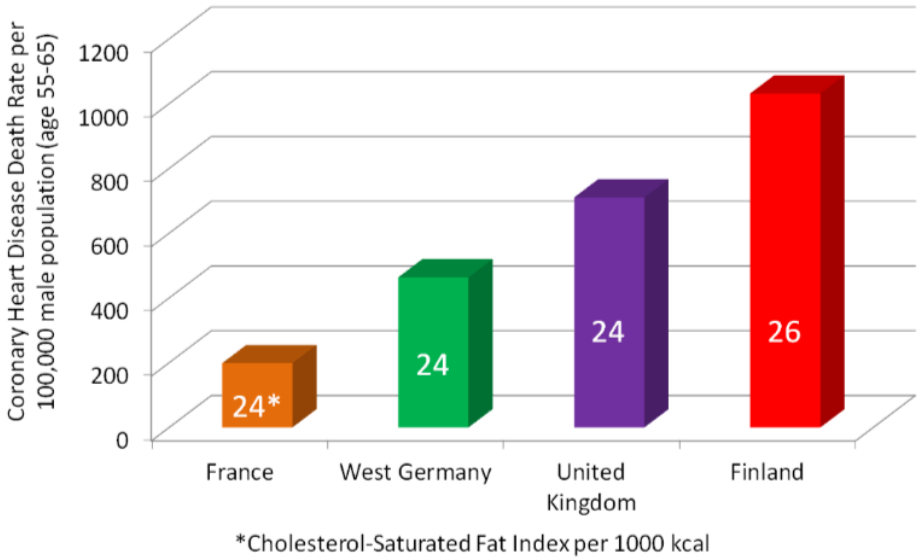


Figure 1.2.2: An example of a cross-sectional study, "The "French Paradox". The x-axis shows four different European countries with similar cholesterol-saturated fat intakes2 (the numbers shown within the bars), and the y-axis represents coronary heart disease rate.

The French had a 5-fold lower risk of dying from coronary heart disease than the Finns, despite having similar cholesterol-saturated fat intakes2. A paradox means something contradictory, which this finding seemed to be. The "French Paradox" has led to research on red wine, and one of its active components, resveratrol, because the French consume a lot of this alcoholic beverage. Cross-sectional studies are considered the weakest type of epidemiology because they are based only on group outcomes. This may lead people to believe that members of the group have characteristics, which as individuals they do not. This is known as ecologic (another name that is used to refer to this type of study) fallacy, and is a limitation of cross-sectional studies3.

Query 1.2.1

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Case-Control Studies

Case-control studies look at a group of cases (e.g. people with a disease) vs. controls (e.g. people without the disease). Most case-control studies are retrospective (looking back in time, or looking at the past). These studies try to determine if there were differences in the diets of the cases compared to controls in the past. Cases and controls are matched on characteristics such as age, sex, BMI, history of disease, and many others. This means researchers try to choose a control that has similar characteristics to the case. The researchers then compare the exposure levels between cases and controls, as shown below. In this example a greater proportion of diseased (cases) individuals than disease-free individuals (controls) were exposed to something.

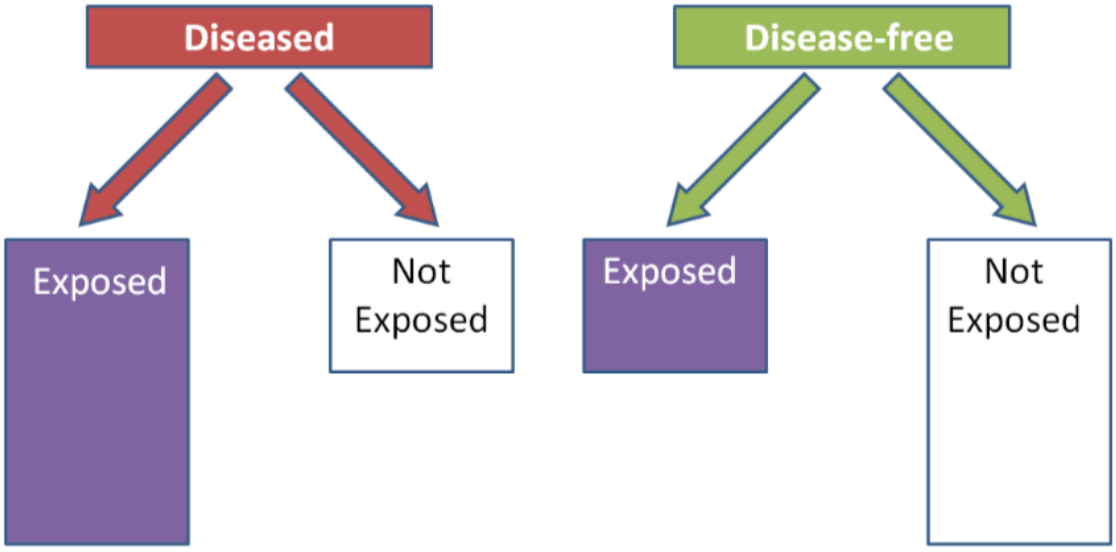


Figure 1.2.3: An example of a case-control study in which the diseased were more likely to have been exposed than those who were disease-free. Cases are represented by the red box on the left, and the controls are the green box on the right3.

Using trans-fat intake as the exposure, and cardiovascular disease as the disease, the figure would be expected to look like this:

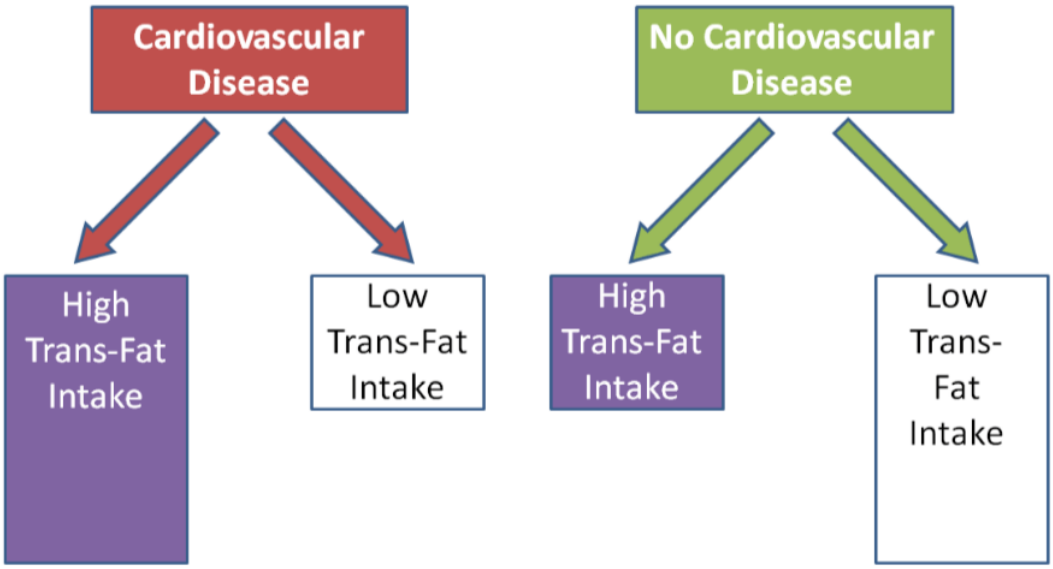


Figure 1.2.4: An example of a case-control study that indicates that more cases had high trans-fat intake compared to the controls[3]

To determine people's intakes of foods and food components, food frequency questionnaires are commonly used. As the name suggests, a food frequency questionnaire is a series of questions that determines how frequently you consume a certain food. An example of a question on a food frequency questionnaire is shown below:

"Over the past 12 months, how often did you drink milk?"

- Never
- 1 time/month less
- 2-3 times/month
- 1-2 times/week
- 3-4 times/week
- 5-6 times/week
- 1 time/day
- 2-3 times/day
- 4-5 times/day
- 6 or more times/day

An example of a food frequency questionnaire is shown in the link below.

Web Link

NHANES Food Frequency Questionnaire

Query 1.2.2

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Prospective Cohort Studies

A cohort is "a group of subjects." Most cohort studies are prospective. Initial information is collected (usually by food frequency questionnaires) on the intake of a cohort of people at baseline, or the beginning. This cohort is then followed over time (normally many years) to quantify health outcomes of the individual within it. Cohort studies are normally considered to be more robust than case-control studies, because these studies do not start with diseased people and normally do not require people to remember their dietary habits in the distant past or before they developed a disease. An example of a prospective cohort study would be if you filled out a questionnaire on your current dietary habits and are then followed into the future to see if you develop osteoporosis. As shown below, instead of separating based on disease versus disease-free, individuals are separated based on exposure. In this example, those who are exposed are more likely to be diseased than those who were not exposed.

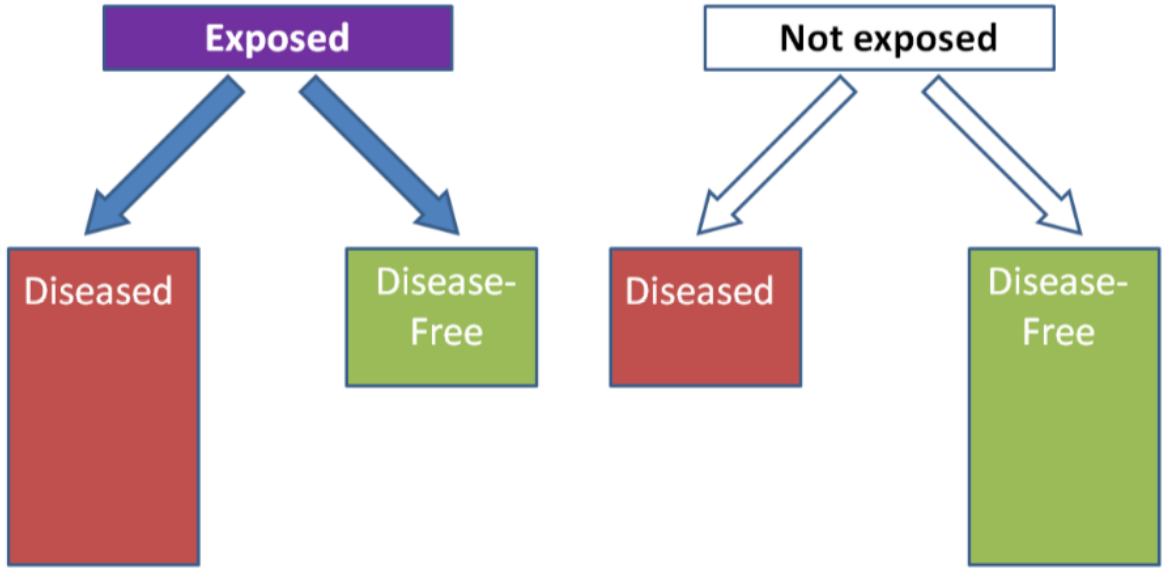


Figure 1.2.5: An example of cohort study in which those exposed are more likely to develop the disease3

Using trans-fat intake again as the exposure and cardiovascular disease as the disease, the figure would be expected to look like this:

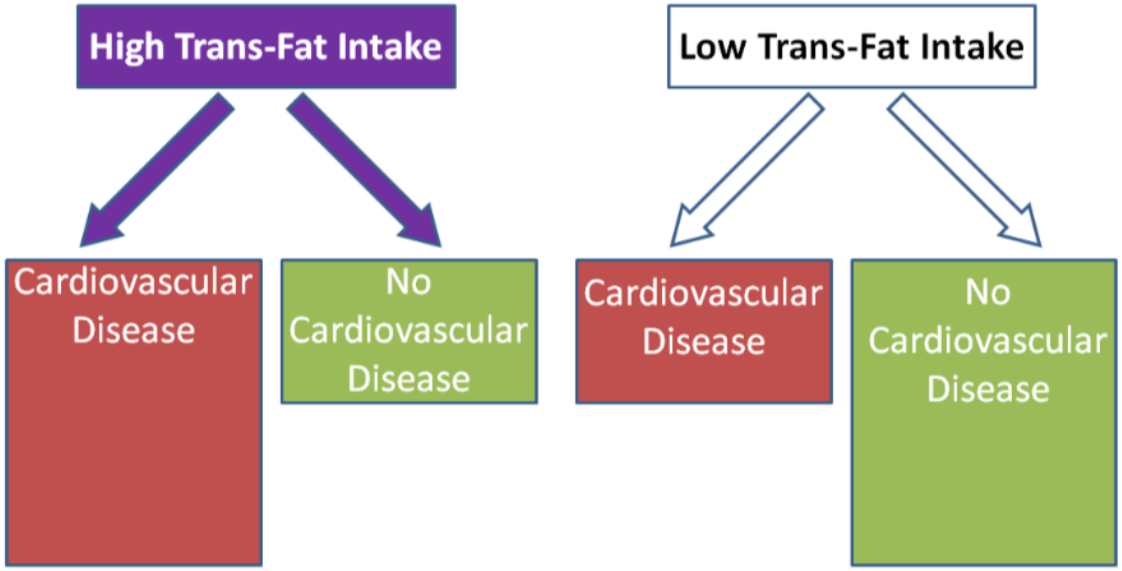


Figure 1.2.6: An example of a cohort study where higher trans-fat intake is associated with a higher incidence of cardiovascular disease3

There are several well known examples of prospective cohort' studies as listed below.

Framingham Heart Study

The Framingham Heart Study started in 1948 and has been following the residents of Framingham, Massachusetts to identify risk factors for heart disease. This cohort has been very fruitful in finding a number of important factors associated with coronary heart disease. In 2002, a third generation of participants was enrolled to be followed. The following links show more about the Framingham Heart Study

Web Links

Framingham Heart Study History

Framingham Heart Study Research Milestones

Nurses Health Study

The Nurses' Health Study started in 1976 and enrolled 122,000 female nurses. Every 4 years they received a food frequency questionnaire to assess their dietary habits.

Web Link

The Nurses' Health Study

Health Professionals Follow-Up Study

The Health Professionals Follow-Up Study started in 1986 and enrolled 51,529 male health professionals (dentists, pharmacists, optometrists, osteopathic physicians, podiatrists, and veterinarians). Every 4 years they received a food frequency questionnaire to assess their dietary habits.

Web Link

Health Professionals Follow-up Study

The Health Professionals Follow-Up Study is a good example for how cohort studies can be important in nutrition research. We will consider one example in which the researchers administered food frequency questionnaires that contained 131 food and beverage items to determine whether their intake was associated with increased or decreased risk of developing prostate cancer. Of these items, intake of four foods (tomatoes, tomato sauce, pizza, and strawberries) were associated with decreased incidence of prostate cancer, as illustrated in the figure below[4].

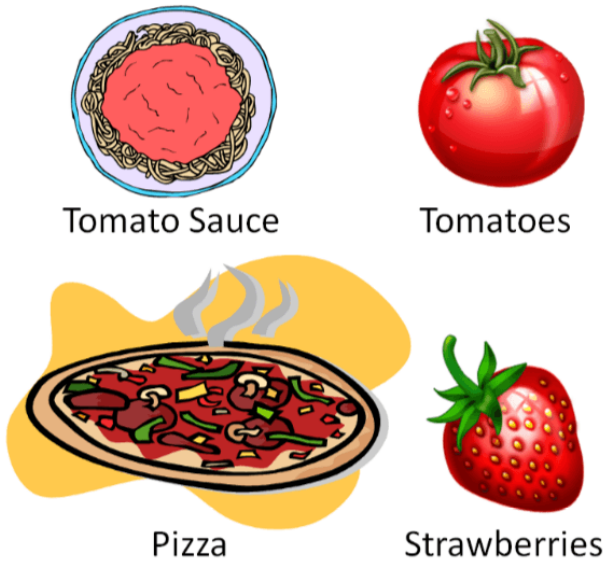


Figure 1.2.7: Four foods items associated with decreased risk of prostate cancer[4]

The three tomato-based foods are red due to the presence of the carotenoid lycopene. Strawberries don't contain lycopene (their red color is due to anthocyanins). This finding has led to interest in the potential of tomatoes/lycopene to decrease the risk of prostate cancer.

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Query 1.2.5

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1. Levin K. (2006) Study design III: Cross-sectional studies. Evidence - Based Dentistry 7(1): 24.
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3. Gordis L. (2004) Epidemiology. Philadelphia, PA: Elsevier Saunders.
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1.3: In Vitro and Animal Studies

The simplest form of nutrition research is an *in vitro* study. In vitro means "within glass", so these methods are performed within flasks, dishes, plates, and test tubes, although most of these are no longer glass (mostly plastic now). These studies are performed outside of a living organism, so the results need to be interpreted with this fact in mind.

One common form of in vitro research is cell culture. This involves growing cells in flasks and dishes. In order for cells to grow they need a nutrient source. For cell culture the nutrient source is referred to as media. Media supplies nutrients to the cells in vitro similarly to how blood performs this function within the body. Most cells adhere to the bottom of the flask and are so small that a microscope is needed to see them.

Cells are only handled inside a biosafety cabinet (aka cell culture hood). The hood is sterile and protects the cells from the outside environment. The cells need to be protected because they do not have human skin as a barrier to keep microorganisms, etc. from contaminating them.



Figure 1.3.1: Flask containing media and cells (left); biosafety cabinet (cell culture hood, right)

Cells are grown inside an incubator, which is a device that provides the optimal temperature, humidity, and carbon dioxide (CO_2) concentrations for cells and microorganisms. By imitating the body's temperature and CO_2 levels (37 degrees Celsius, 5% CO_2), the incubator allows cells to grow even though they are outside the body.

A limitation of in vitro research compared to in vivo research is that it typically does not take digestion or bioavailability into account. This means that the concentration used might not be physiologically possible (it might be much higher) and that digestion and metabolism of what is being provided to cells may not be taken into account. Cell-based in vitro research is not as complex of a biological system as animals or people that have tissues, organs, etc. working together as well.

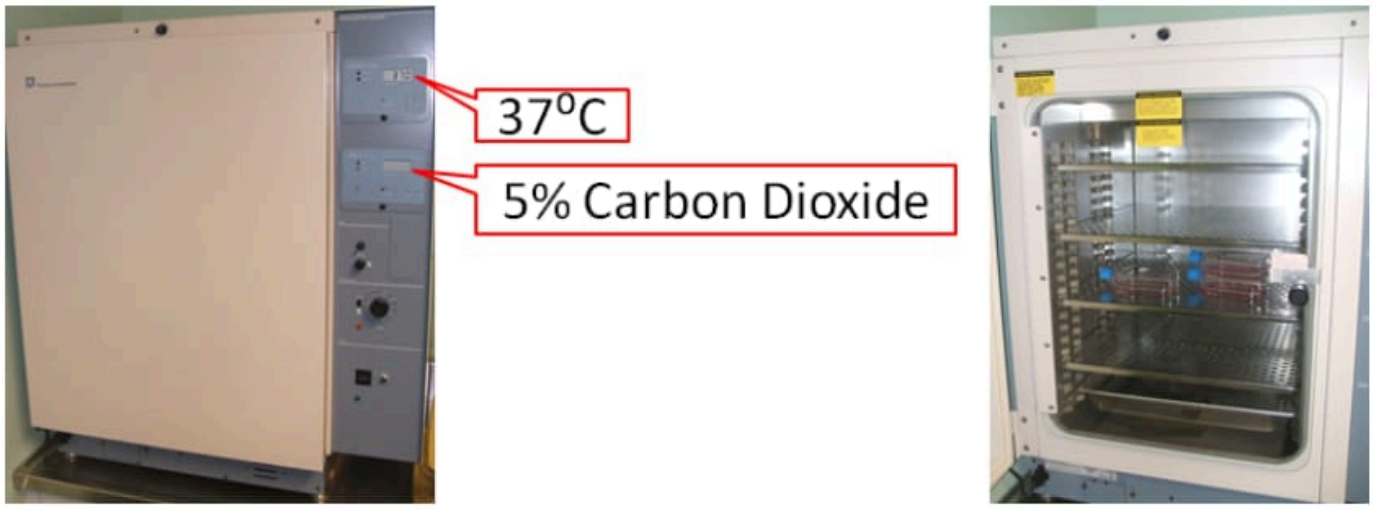


Figure 1.3.2: Outside and inside of an incubator

Animal Studies

Animal studies are one form of in vivo research, which translates to "within the living". Rats and mice are the most common animals used in nutrition research.

Why do animal research?

Animals can be used in research that would be unethical to conduct in humans. Researchers can make sure that a certain regimen is safe before it is researched in humans. One advantage of animal dietary studies is that researchers can control exactly what the animals eat. In human studies, researchers can tell subjects what to eat and provide them with the food, but that does not necessarily mean that they are going to consume exactly what they are supposed to. Also people are not great at estimating, recording, or reporting how much or what they eat/ate. Animal studies are also, normally, far less expensive than human studies.

There are some important factors to keep in mind when interpreting animal research. First, an animal's metabolism and physiology is different than humans. As a result, animals' absorption and bioavailability of compounds can differ from humans. Furthermore, animal models of disease (cancer, cardiovascular disease, etc.), although similar, are different from the human disease. So these factors have to be considered when interpreting results from this type of research. Nevertheless, animal studies have been, and continue to be, important for nutrition research.

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Query 1.3.2

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1.4: Human Intervention Studies

There are a variety of human intervention study designs in nutrition research, but the most common, especially in pharmaceutical/medical research, is the clinical trial. A clinical trial is a scientifically controlled study using consenting people to find the safety and effectiveness of different items/regimens. Clinical trials are the "gold standard" research method. Their findings carry the most weight when making decisions about a certain research area because they are the most rigorous scientific studies. Every pharmaceutical must go through a series of clinical trials (specifically randomized, double-blind, placebo-controlled trials) before being approved in the US by the Food and Drug Administration (FDA). As shown in the figure below, human intervention studies/clinical trials are normally prospective. By the end of this section you should have an understanding of what randomized, double-blind, and placebo-controlled means.

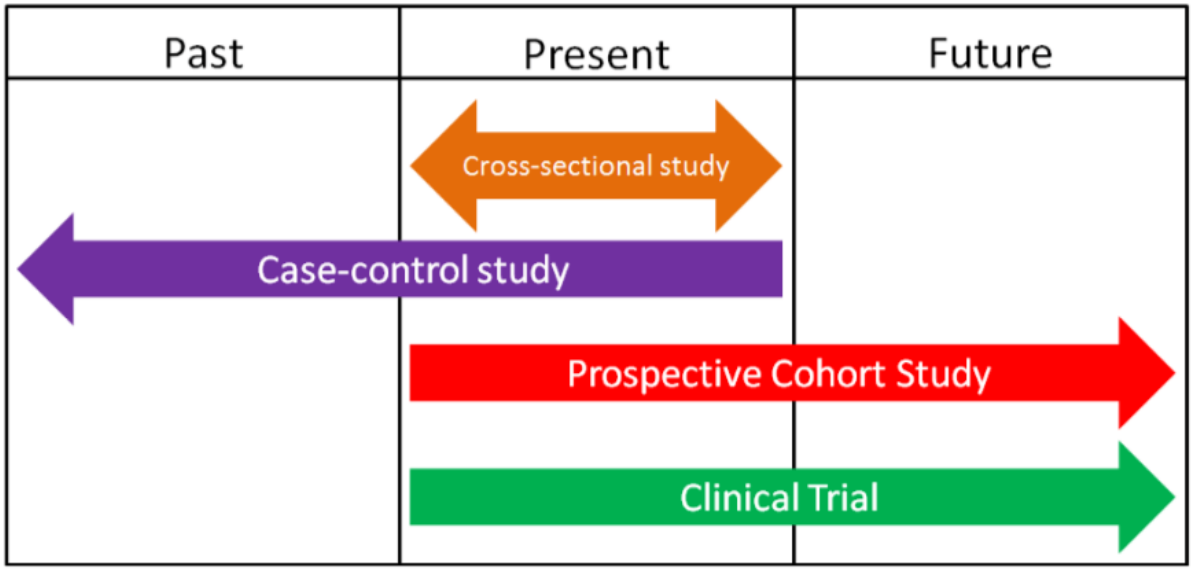


Figure 1.4.1: Clinical trials are prospective. Adapted from reference 1.

Placebo and The Placebo Effect

A placebo is a inert pill or treatment that serves as the control comparison to an active intervention. Some example placebo pills are shown below.



Figure 1.4.2: Placebo pills2

The use of a placebo is necessary in research because of a phenomenon known as the "placebo effect". The placebo effect is the postive effect that can occur from a subject's belief that the intervention that they are receiving will improve their condition, even if they are not receiving an active intervention. An example would be an athlete who consumes a sports drink and runs the 100 meter dash in 11.00 seconds. The athlete then, under the exact same conditions, drinks what he is told is "Super Duper Sports Drink" and runs the 100 meter dash in 10.50 seconds. But what the athlete didn't know was that Super Duper Sports Drink was the Sports Drink + Food Coloring. There was nothing different between the drinks, but the athlete believed that the "Super Duper Sports Drink" was going to help him run faster, so he did. This improvement is due to the placebo effect.

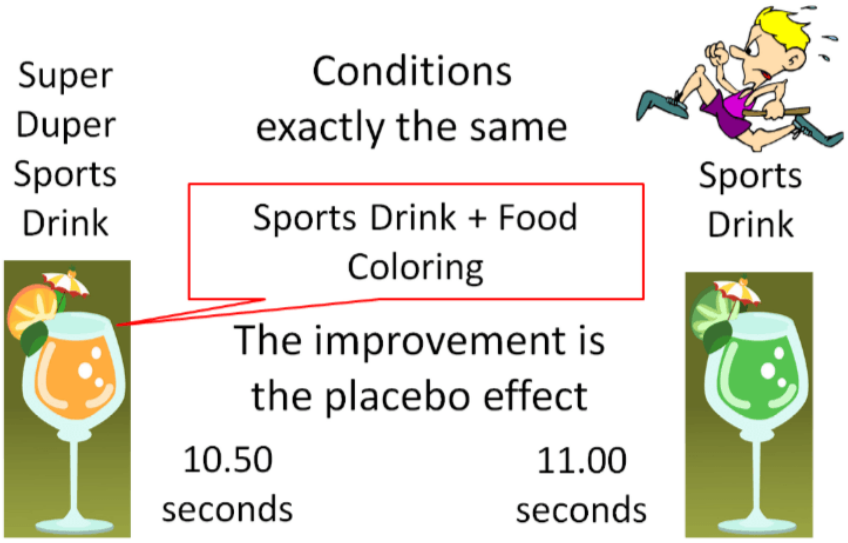


Figure 1.4.3: Placebo effect example

Ironically, a study similar to the example given above has been conducted and its results support that there is a “placebo effect.”

Web Link

A Placebo Can Make You Run Faster

Query 1.4.1

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Randomization

Randomization is the process of randomly assigning subjects to groups to decrease bias. Bias is a systematic error that may influence results. Bias can occur in assigning subjects to groups in a way that will influence the results. An example of bias in a study of an antidepressant drug is shown below. In this nonrandomized antidepressant drug example, researchers (who know what the subjects are receiving) put depressed subjects into the placebo group, while "less depressed" subjects are put into the antidepressant drug group. As a result, even if the drug isn't effective, the group assignment may make the drug appear effective, thus biasing the results as shown below.

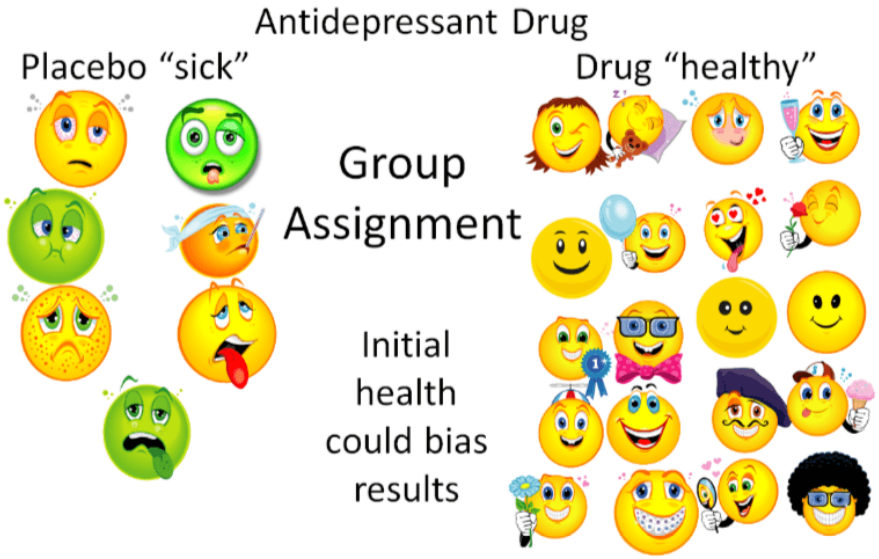


Figure 1.4.4: Non-randomized antidepressant drug example

This is a bit of an extreme example, but even if the researchers are trying to prevent bias, sometimes bias can still occur. However, if the subjects are randomized, the sick and the healthy people will ideally be equally distributed between the groups. Thus, the trial will be unbiased and a true test of whether or not the drug is effective.

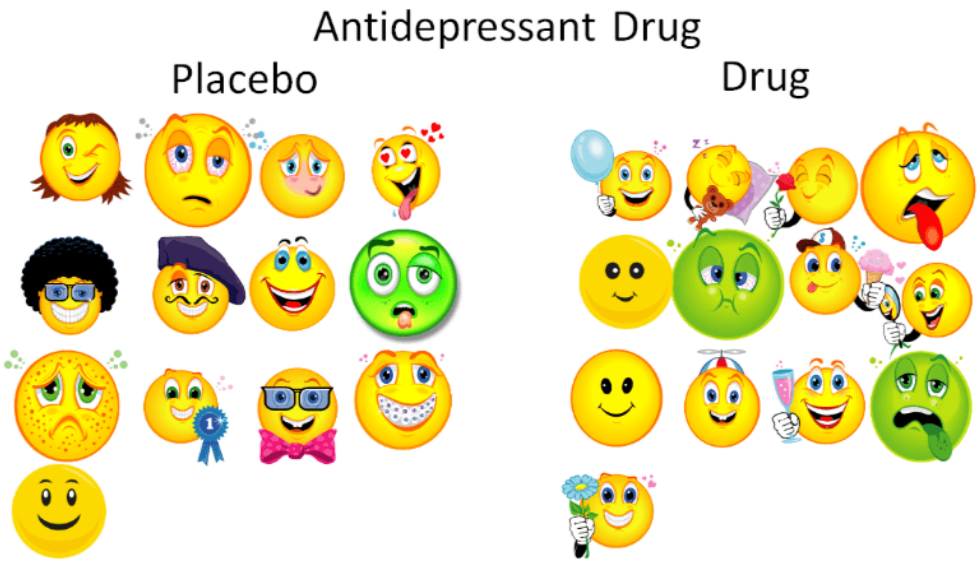


Figure 1.4.5: Randomized antidepressant drug example

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Blinding

Blinding is a technique to prevent bias in human intervention studies. A study without blinding is referred to as "open label" because both the subject and the researchers know what intervention the subject is receiving (i.e. placebo or drug). This can lead to bias, so these types of trials are used less frequently.

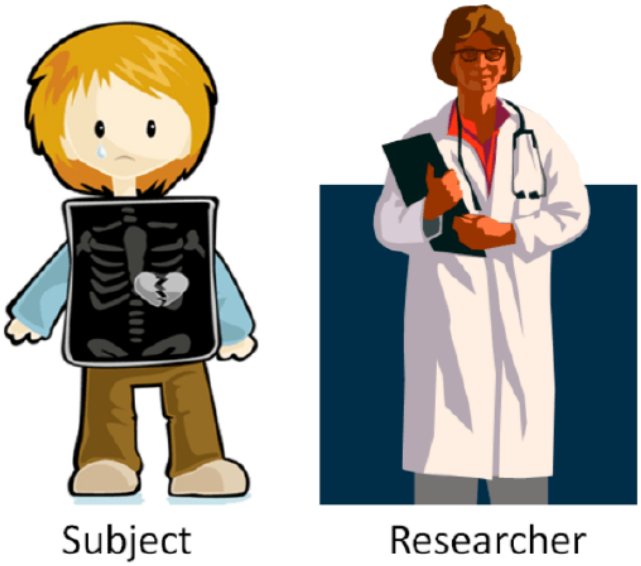


Figure 1.4.6: In an open-label study, both the subject and researcher know what treatment the subject is receiving.

In a single-blind study, the researcher knows what intervention the subject is receiving, but the subject does not. If the subjects are randomized, these types of trials should produce robust results, but it is still possible that the researcher can bias the results.

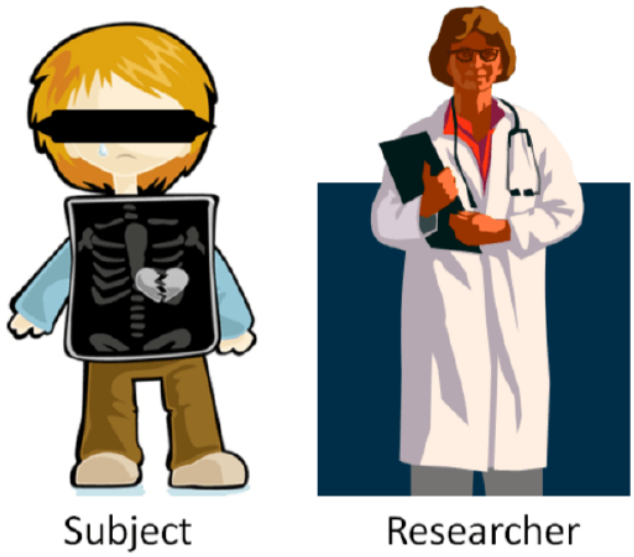


Figure 1.4.7: In a single-blind study, the researcher knows what treatment the subject is receiving, but the subject does not.

Finally there is the double-blind study, where neither the researcher nor the subject know what intervention the subject is receiving. A separate board reviews the collected results and decides the fate of the trial. This is the "gold standard" because it prevents observer bias from occurring.

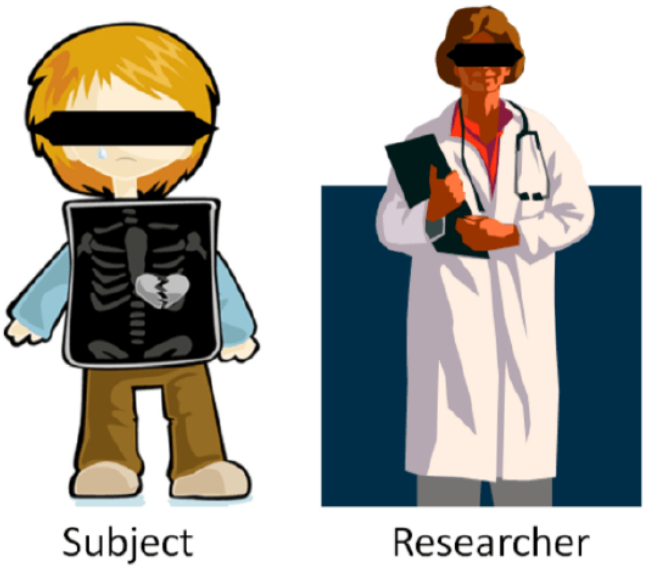


Figure 1.4.8: In a double-blind study, neither the subject nor the researcher know what treatment the subject is receiving.

The following video does a nice job explaining and illustrating how double-blind randomized trials are performed.

Web Link

Video: Double-blind clinical trial (1:40)*

*The above video does not contain captioning, and is posted in a way that we cannot add it to it. Below is the transcript for what is said in the video.

To conduct a randomized controlled trial a statistician will select a sample size large enough to produce a significant result.

Care must be taken that test subjects are properly representative of the target population and not tainted by selection biases that might skew the results.

The subjects are blinded knowing as little as possible about what is being tested.

They are randomly and blindly assigned to one of several groups.

There may be a group that will receive the treatment being studied, a group receiving an established treatment and always at least one control group receiving a control or placebo treatment.

Test administrators are also blinded.

This is called double blinding.

Such as that they don't know what group each subject is assigned to and whenever possible they don't know what the treatment is they are administering.

Everything is coded to avoid experimenter bias and to cancel out any effects like patients trying to respond the way experimenters want them to.

The trial lasts long enough to satisfy the statisticians and the scientist.

Finally, when the results are tabulated by a blinded statistician, this is called triple blinding.

We get the results.

The cloaks of anonymity are whisked aside and we finally learn with statistical certainty which treatments are effective and which are not.

When this process shows significant benefits for a new treatment and the trial can be repeated by other experimenters and yields similar results, then and only then do scientists say that this is a product that works and is supported by evidence.

Query 1.4.3

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References

1. Levin K. (2006) Study design III: Cross-sectional studies. Evidence - Based Dentistry 7(1): 24.
2. http://en.Wikipedia.org/wiki/File:Cebocap.jpg

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1.5: Nutrition Research Statistics

One important aspect in being able to interpret research is to have a basic understanding of statistical significance. Statistical significance means that there is sufficient statistical evidence to suggest that the results are most likely not due to chance.

Statistical significance is represented by p-values in most research. The p-value is an estimate of whether the difference is a statistical accident or due to random chance. A p-value of less than 0.05 (commonly written p-value <0.05 or p <0.05) is used in most cases to indicate statistical significance. This value means that 5% of the time the statistical results are accidental or not true. Researchers accept this level of uncertainty. Figure 1.5.1 demonstrates how to interpret p-values in a humorous way.

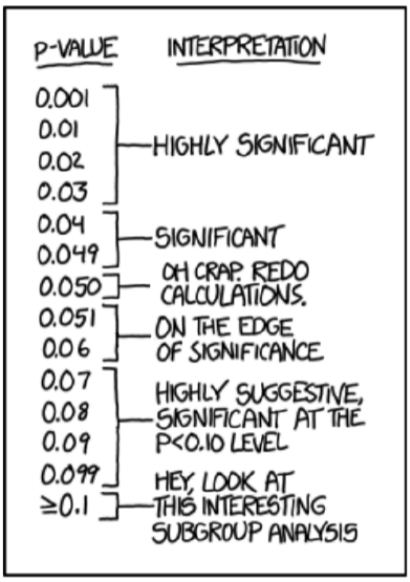


Figure 1.5.1: p-value interpretation. (CC BY-NC 2.5; xkcd)

Query 1.5.1

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Epidemiological research usually uses different statistics to analyze their results. Epidemiological results are commonly reported as odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs). These values can be interpreted similarly regardless of which is used. For example, the odds ratio represents the odds of a certain event occurring (often a disease) in response to a certain exposure (in nutrition this is often a food or dietary compound). In a paper it is common to see one of these measures in this form: OR = 2.0. What does this mean? As Figure 1.5.2 shows, an OR, RR, or HR of 1 means that exposure is associated with neither increased or decreased risk (neutral). If an OR, RR or HR is less than 1, that exposure is associated with a decreased risk. If an OR, RR, or HR is greater than 1, that exposure is associated with an increased risk. An OR,RR, or HR of 2 means there is twice the risk, while an OR, RR, or HR of 0.5 means there is half the risk of the exposure versus the comparison group.

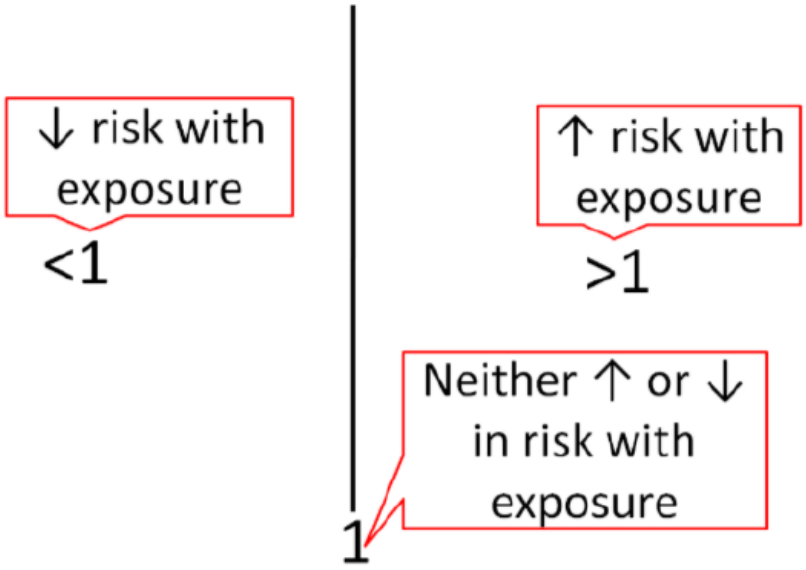


Figure 1.5.2: Risk in relation to exposure for OR, RR, or HR

To determine whether OR, RR, and HR are significantly different for a given exposure, most epidemiological research uses 95% confidence intervals. Confidence intervals indicate the estimated range that the measure is calculated to include. They go below and above the OR, RR, and HR itself. It is a calculation of how confident the researchers are that the OR, RR, and HR value is correct. Thus:

Large Confidence Intervals = Less Confidence in Value

Small Confidence Intervals = More Confidence in Value

Thus, 95% confidence intervals indicate that researchers are 95% confident that the true value is within the confidence intervals. A confidence interval is normally written in parentheses following the OR, RR, or HR or represented as bars in Figure 1.5.3.

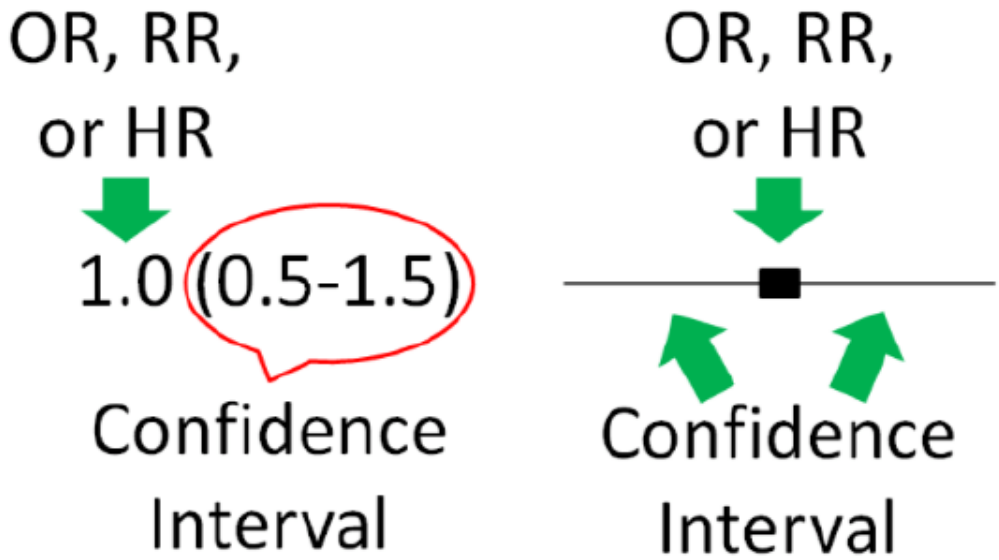


Figure 1.5.3: Confidence Intervals for OR, RR, or HRs in text form (left) and figure form (right)

Most of the time, the OR, RR, or HR will be found in the middle of the 95% confidence interval, but not necessarily all of the time. For instance, there could be much greater confidence that the value is not much lower than the OR, RR, or HR, but not much confidence that the value does not exceed the OR, RR, or HR. This could lead to confidence interval looking skewed above the OR, RR, or HR (more confidence interval above, than below, the OR, RR, or HR).

If the 95% confidence intervals of the OR, RR, or HR does not include or overlap 1, then the value is significant. If the 95% confidence intervals include or overlap 1, then the OR, RR, or HR is not significant, because it is possible the the true value is 1, which is neutral, and can not be significantly different than 1 (Figure 1.5.4).

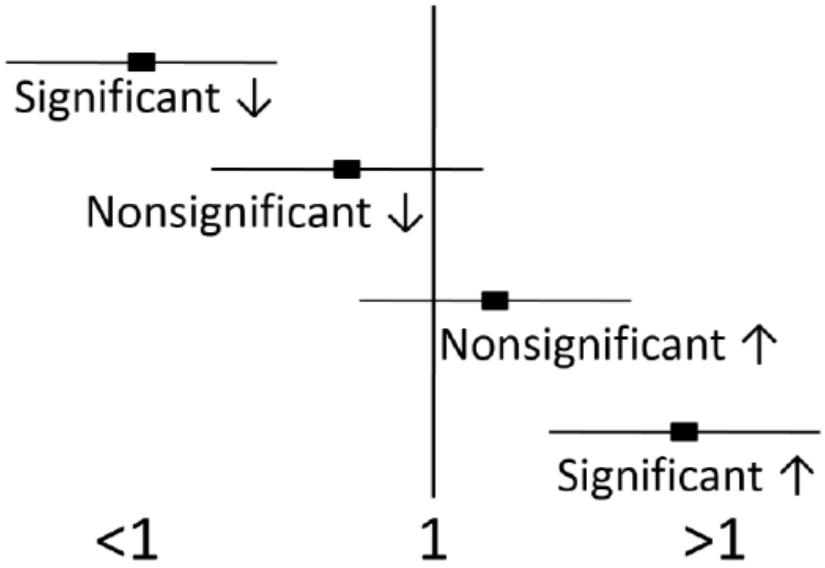


Figure 1.5.4: Confidence intervals (95%) that include 1 indicate that the value is not significantly different. Confidence intervals above or below 1 without including it indicate that the value is significantly different.

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1.6: Publishing Research

After nutrition researchers have obtained their results, they want to disseminate them, or let people know what they found. The primary way they do this is by publishing their results in journals. The researchers put together a paper explaining what they did and what they found in a journal article. An article's primary components are normally an introduction, abstract, methods, results, and discussion/conclusion. They submit the paper to a chosen journal and the journal editor then selects expert researchers who will critically review the article. These reviewers make sure that research published in journals is of good quality and of interest to readers. In more rigorous journals the article might also need to meet a certain theme of an issue that a journal wants to publish. This is a rigorous process that is humorously depicted by this cartoon.

Web Link

Peer Review Process

To give you an idea of how rigorous this process is, let's consider some major nutrition journals.

- Journal of Nutrition (JN)
- American Journal of Clinical Nutrition (AJCN)
- Journal of the Academy of Nutrition and Dietetics (formerly Journal of the American Dietetic Association)
- Nutrition Reviews
- Annual Reviews of Nutrition
- British Journal of Nutrition
- European Journal of Clinical Nutrition

There are two major nutrition societies in the US: The American Society for Nutrition (ASN) and the Academy of Nutrition and Dietetics (AND, formerly the American Dietetic Association). ASN publishes the Journal of Nutrition and the American Journal of Clinical Nutrition, while AND publishes the Journal of the Academy of Nutrition and Dietetics. If you want to see more about the major nutrition societies, use the following links.

Web Links

- American Society for Nutrition
- Academy of Nutrition and Dietetics

The following table contains 2 measures, impact factor and acceptance rate for these journals. The impact factor is a measure of the influence of the journal. This measure indicates how many people read the articles that are published in that journal. The acceptance rate is the % of articles that are submitted that are actually accepted for publication.

Table 1.6.1*: Selected nutrition journal impact factors and acceptance rates*

Journal	Impact Factor[1]	Acceptance Rate
Annual Reviews of Nutrition	6.8	
American Journal of Clinical Nutrition	6.7	25%[2]
Journal of Nutrition	3.7	25%[3]
Advances in Nutrition	5.2	
Nutrition Reviews	5.6	
Journal of the Academy of Nutrition and Dietetics	3.6	
British Journal of Nutrition	3.3	
European Journal of Clinical Nutrition	3.9	40%[4]

The acceptance rate for three of these journals ranged from 25-40%. Thus, the majority of submitted articles are rejected and sent back to the researchers. To put nutrition journals in perspective, some of the top medical and science journals with a broad following have impact factors as high as 75 and an acceptance rate of 5-10%.

Hopefully these numbers help you understand that peer review is a rigorous process where peer reviewers "tear the article to pieces."



Figure 1.6.1: Dr. L's article after peer review

They do not physically shred the article (it is all done online), but there are often extensive revisions to make (maybe even multiple times) before the paper can be published, if you're so lucky. Generally, the more difficult it is to get a paper accepted into a journal, the more solid the research must be. Most of the information on the internet has not gone through peer review and should be explored with some caution.

The following video clearly depicts the peer review process. There is also a diagram in the link below that explains how the peer review process works.

YouTube Video

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Video 1.6.1: How do articles get peer reviewed? What role does peer review play in scholarly research and publication? This video will explain. https://www.youtube.com/watch?v=rOCQZ7QnoN0

Web Link

Peer Review Process Diagram

Query 1.6.1

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1. ISI Web of Knowledge, http://admin-apps.webofknowledge.com/JCR/JCR, Nutrition and Dietetics, accessed 1/11/2017.
2. http://www.nutrition.org/publication...cal-nutrition/
3. http://www.nutrition.org/publication...-of-nutrition/
4. Seidell J, Shetty P . (2007) The baton passes on. Eur J Clin Nutr 61: 1-2.

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1.7: Interpreting Research

Now that you are familiar with the different forms of nutrition research, the next step is understanding how to interpret and synthesize the information. To synthesize information on a certain topic, the two most popular methods are meta-analyses and systematic literature reviews. While there are differences between these two methods, they are similar in that they aim to draw a conclusion from the body of research evidence rather than from one study. We will focus on systematic literature reviews because of their rising popularity in biomedical literature.

A systematic literature review does what the name implies, it systematically reviews the literature related to a certain research question. For example, the research question might be, "Does chocolate decrease blood pressure?" There is a method for performing the review established ahead of time that details answers to questions such as:

- How will journal articles be identified?
- Using what databases?
- What search terms will be used?

The end product is a conclusion based on the evidence in the identified journal articles. The figure below illustrates how a systematic literature review identifies articles to utilize.

Figure 1.7.1: An example of the process of a systematic literature review.

The video below, by the Cochrane Collaboration that performs many systematic literature reviews, describes what systematic literature are.

YouTube Video

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Video 1.7.1: This video explains why systematic reviews are important and how they are done. This includes an explanation of how the effects of interventions are compared in order to provide evidence. https://www.youtube.com/watch?v=egJlW4vkb1Y

Because they synthesize the findings from multiple trials or studies, systematic literature reviews are considered the highest level of nutrition research evidence and are therefore shown at the top of the strength of nutrition research pyramid below. In vitro studies are shown at the bottom of the triangle because they are the weakest form of evidence overall. It should be pointed out that most systematic literature reviews only consider epidemiological studies and clinical trials and do not include animal studies or in vitro evidence. While these studies are of less strength, they should still be considered.

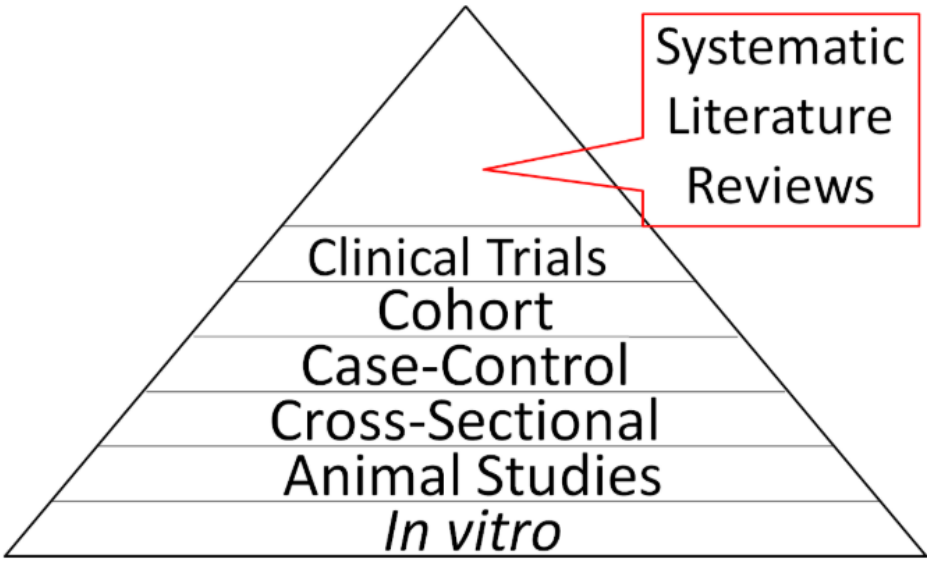


Figure 1.7.2: Strength of scientific research, a higher position on the pyramid means greater strength of that form of evidence.

There are a couple of other factors to consider relating to the different forms of research. First, epidemiological studies cannot show causality (i.e. smoking causes lung cancer), but instead identify relationships or associations (i.e. smoking is associated with lung cancer occurrence). Clinical trials/human studies are the best form of primary research because their findings should be directly translatable to patients. So why use other forms of research? The description below should help explain why the other forms of research are also important.

In general, a certain sequence of studies in nutrition research is often followed as shown in the figure below.

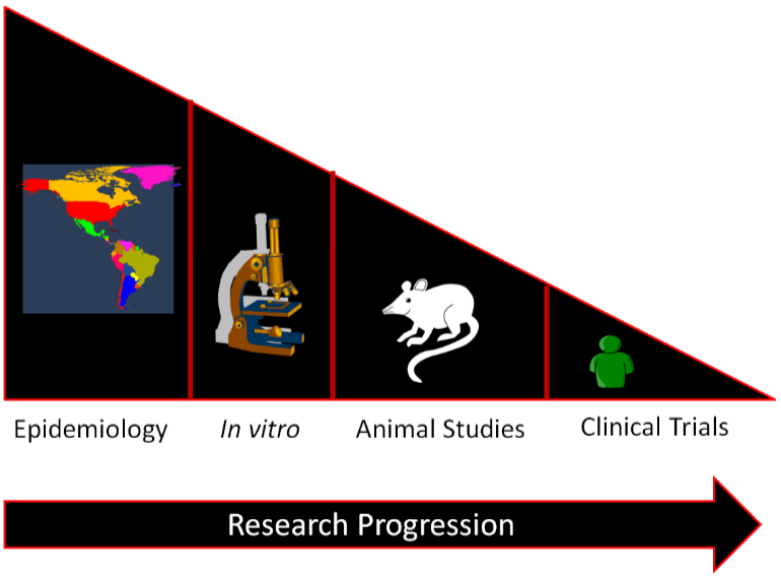


Figure 1.7.3: The progression of nutrition research. The shape indicates the selection of the most promising and safest hypotheses being moved to the next level. Thus, there is a decrease in the overall number of hypotheses represented by the height of the figure) being investigated by the next form of research.

Epidemiological studies find relationships between food/food components and a specific health outcome. This relationship is then investigated by in vitro studies and then, some of the most promising move to animal studies. Then the most promising and safe food/food components are moved into clinical trials/human studies. If it is an individual compound, there will be smaller trials designed to see if the compound is safe before it is moved into larger clinical trials to determine whether the food/food component results in beneficial health outcomes. The overall effect of this process is to select the most promising and safe food/food components for the clinical trials/human studies. This allows time and money to be used more efficiently, because while clinical trials/human studies are the best form of research, they are also normally the most expensive and time-consuming.

Researchers nevertheless have been tempted to skip directly to clinical trials in the past rather than following the research progression. To illustrate what happens in these situations, the following describes a couple of examples when "normal" research progression hasn't been followed.

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Beta-Carotene and Lung Cancer

In the early 1980s there was a lot of excitement among researchers over the epidemiological evidence showing that higher dietary consumption of the carotenoid, beta-carotene, decreased lung cancer risk[1]. By the mid 1980's, two large, randomized, double-blind placebo-controlled trials began to determine whether high-dose beta-carotene supplementation (far higher than dietary intake) could decrease lung cancer incidence in high-risk populations before in vitro or animal studies had investigated this relationship. The research community was shocked when these two studies were terminated early in the mid 1990s because of significant increases in lung cancer incidence among smokers receiving beta-carotene supplements[2,3]. In vitro and animal studies completed after the clinical trial found that as beta-carotene intake shifts from normal dietary levels to high, supplement-type levels, the effect on lung cancer development also shifts from beneficial to detrimental in combination with smoke or carcinogen exposure[4]. Thus, if the normal research progression had been followed, it is likely that a lower dose of beta-carotene would have been used or trials wouldn't have been undertaken at all.

Selenium, Vitamin E, and Prostate Cancer

Another example of when the research progression was not followed was the relationship between selenium, vitamin E, and prostate cancer. Two clinical trials had found secondary outcomes that suggested that selenium and vitamin E supplementation may decrease prostate cancer risk [5,6]. A secondary outcome is one that was not the primary outcome that the clinical trial was designed to find, thus they need to be interpreted with some caution. Rather than examining the relationship using in vitro and animal studies, a clinical trial was undertaken to determine if selenium and vitamin E supplementation alone, or in combination, could decrease the development of prostate cancer incidence[7]. This clinical trial was also terminated early because

of a nonsignificant increase in prostate cancer in those receiving vitamin E8, and a nonsignificant increase in diabetes among those receiving selenium9. In vitro studies and animal models performed since the clinical trial was undertaken and after its termination suggest that vitamin E is not effective and that another form of selenium could have possibly been more effective10.

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In addition to the lessons learned about the sequence of research in nutrition, these studies add to growing evidence that suggests that single-agent interventions, even in combination, may not be an effective strategy for improving health. The common nutrition research approach was, after epidemiology finds an association or relationship, is to use in vitro and animal studies to identify the specific compound in a certain food that is responsible. This has been termed the reductionist approach because it takes something complex (food) and reduces it down to its simpler components. However, there is growing evidence that this may be a flawed approach. Some nutrition researchers feel that more focus should be on the food itself, rather than trying to discern exactly what is responsible for the beneficial health outcomes. Because it may not be one or 2 compounds alone that are responsible for the effect, it might be difficult to determine from the multitude of nutrients in foods which are responsible for the beneficial effect. This will mean changes in the overall research approach, especially at the human intervention studies/clinical trials level, because in most cases there is not a way to give a “placebo food”11,12.

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2: MACRONUTRIENT STRUCTURES

As you have learned, there are three energy-yielding macronutrients: carbohydrates, proteins, and lipids. This chapter goes more in depth about these major dietary components.

2.1: Carbohydrates

2.2: Protein

2.3: Lipids

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2.1: Carbohydrates

Carbohydrates have become surprisingly divisive. Some people swear by them, others swear against them. But it is important to understand that carbohydrates are a diverse group of compounds that have a multitude of effects in the body. Thus, trying to make blanket statements about carbohydrates is probably not a good idea.

Carbohydrates are named because they are hydrated (as in water, H_2O) carbon. Below is the formula showing how carbon dioxide (CO_2) and water (H_2O) are used to make carbohydrates ($(CH_2O)_n$) and molecular oxygen (O_2). The "n" after the carbohydrate in the formula indicates that the chemical formula is repeated an unknown number of times, but that for every carbon and oxygen, there will always be two hydrogens.

$$n\,CO_2 + n\,H_2O \rightarrow (CH_2O)_n + n\,O_2 \tag{2.1.1}$$

Carbohydrates are produced by plants through a process known as photosynthesis. In this process, plants use the energy from photons of light to synthesize carbohydrates. The formula for this reaction looks like this:

$$6\,CO_2 + 6\,H_2O + \text{Light} \rightarrow C_6H_{12}O_6 + 6\,O_2 \tag{2.1.2}$$

There are many different types of carbohydrates as shown in the figure below. The first way that carbohydrates can be divided into simple, complex, and sugar alcohols. As the names imply, complex carbohydrates contain more sugar units, while simple carbohydrates contain either 1 or 2 sugars. In the next sections, you will learn more about the different forms of carbohydrates.

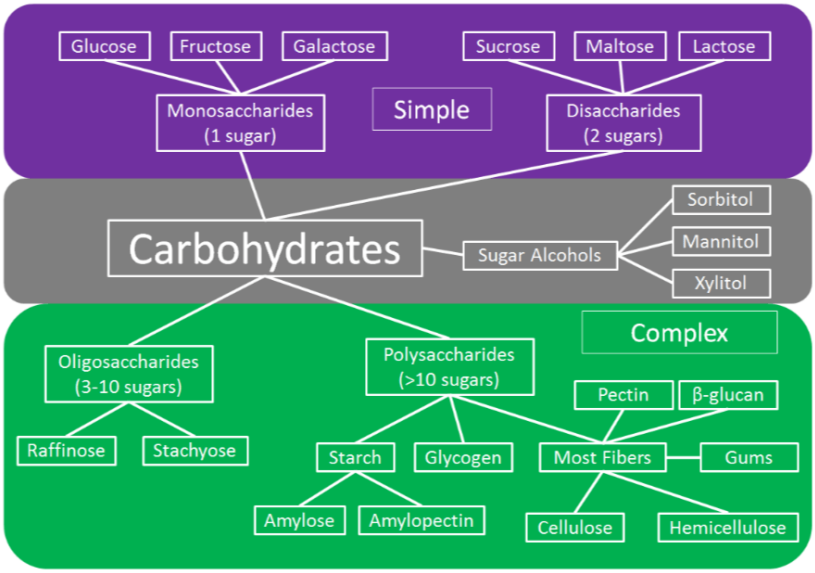


Figure 2.1.1 Different categorizations of carbohydrates

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Simple Carbohydrates

As shown in the figure below, simple carbohydrates can be further divided into monosaccharides and disaccharides. Mono- means one, thus monosaccharides contain one sugar. Di- means two, thus disaccharides contain 2 sugar units. Refer to Figure 2.1.1 for a general overview of carbohydrates.

Monosaccharides

The 3 monosaccharides are: glucose, fructose and galactose. Notice that all are 6-carbon sugars (hexoses). However, fructose has a five member ring, while glucose and galactose have 6 member rings. Also notice that the only structural difference between glucose and galactose is the position of the hydroxyl (OH) group that is shown in red.

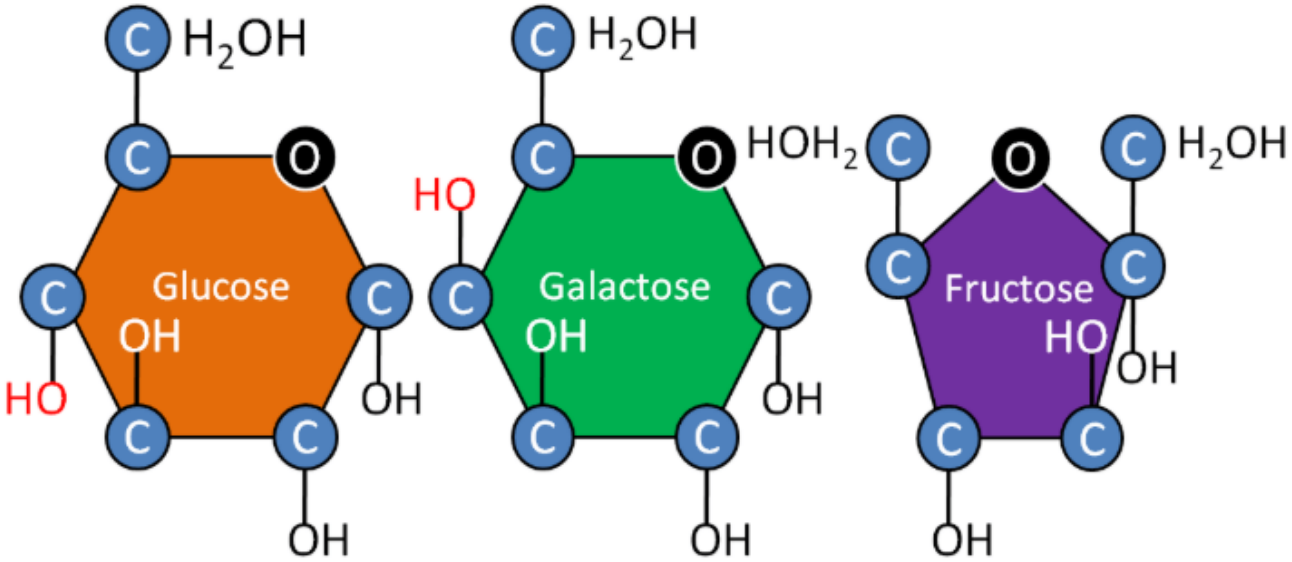


Figure 2.1.2: The 3 monosaccharides

- **Glucose** - Product of photosynthesis, major source of energy in our bodies
- **Galactose** - Not normally found in nature alone, normally found in the disaccharide lactose
- **Fructose** - Commonly found in fruits and used commercially in many beverages

Web Link

Not familiar with ring structures, see how glucose forms a ring

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Disaccharides

Disaccharides are produced from 2 monosaccharides. The commonly occurring disaccharides are:

- **Maltose** (glucose + glucose, aka malt sugar) - seldom found in foods, present in alcoholic beverages and barley
- **Sucrose** (glucose + fructose, aka table sugar) - only made by plants.
- **Lactose** (galactose + glucose, aka milk sugar) - primary milk sugar

The different disaccharides and their monosaccharides components are illustrated below.

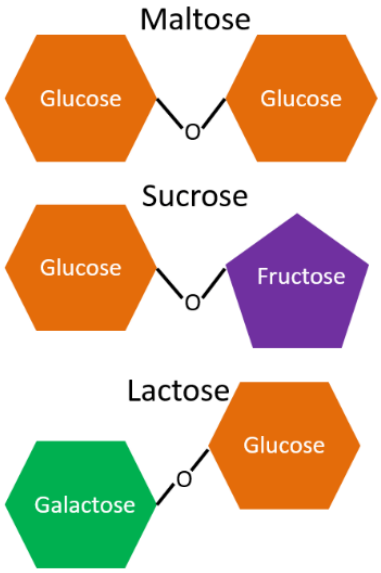


Figure 2.1.3: The 3 disaccharides

Notice the difference in the bond structures. Maltose and sucrose have alpha-bonds, which are depicted as v-shaped above. You might hear the term glycosidic used in some places to describe bonds between sugars. A glycoside is a sugar, so glycosidic is referring to a sugar bond. Lactose, on the other hand, contains a beta-bond. We need a special enzyme, lactase, to break this bond, and the absence of lactase activity leads to lactose intolerance.

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High-Fructose Corn Syrup

Food manufacturers are always searching for cheaper ways to produce their food. One method that has been popular is the use of high-fructose corn syrup as an alternative to sucrose. High-fructose corn syrup contains either 42 or 55% fructose, with the rest being up of glucose meaning it similar to sucrose in the amount of these monosaccharides it contains1. The major difference is in high-fructose corn syrup glucose and fructose are free, rather than being bonded together like in sucrose. Nevertheless, because an increase in high-fructose corn syrup consumption (see figure below) has coincided with the increase in obesity in the U.S., there is a lot of controversy surrounding its use.

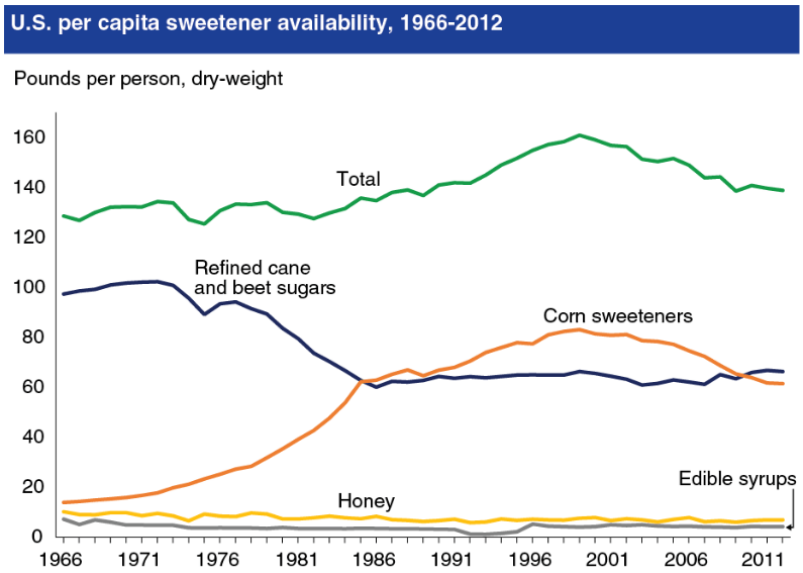


Figure 2.1.4: U.S. per capita sugar and sweetener consumption2

Opponents claim that high-fructose corn syrup is contributing to the rise in obesity rates. As a result, food products are being formulated with table sugar instead and high-fructose corn syrup and the fact that the product does not contain high-fructose corn syrup is being marketed or noted on packaging. Manufacturers tried to rebrand high-fructose corn syrup as "corn sugar" to get around the negative perception of the name. But the FDA rejected this request as described in the link below.

Web Link

FDA rejects new name for high-fructose corn syup

However, this concern with high-fructose corn syrup is not warranted given that fructose consumption is what ideally should be limited because it is metabolized differently than the other monosaccharides and may lead to the adverse effects that people are conflating with high-fructose corn syrup because of its name. High-fructose corn syrup provides about the same amount of fructose, and as you will learn later, we digest carbohydrates down to free monosaccharides before they are taken up and absorbed. Thus, what we get from consuming high-fructose corn syrup and sucrose is about the same amount of fructose. There is no reason to believe that there should be differences in outcomes given that what we get from each is so similar.

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Sugar Alcohols (Polyols, Sugar Replacers)

Sugar(s) can provide a lot of calories and contribute to tooth decay. Thus there are many other compounds that are used as alternatives to sugar that have been developed or discovered. We will first consider sugar alcohols and then the alternative sweeteners in subsequent sections.

Below you can see the structure of three common sugar alcohols: xylitol, sorbitol, and mannitol.

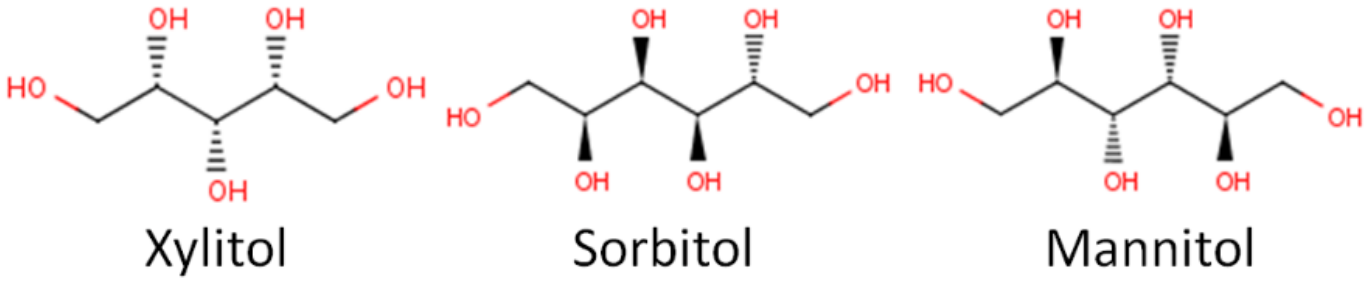


Figure 2.1.5: Structure of three commonly used sugar alcohols: xylitol, sorbitol, and mannitol3-5

Remember that hydroxyl groups are ($-\mathrm{OH}$), and you can see many of them in these structures. An alcohol is a carbon containing compound that includes at least one hydroxyl group.

Sugar alcohols are also known as "sugar replacers", because some in the public might get confused by the name sugar alcohol. Some might think a sugar alcohol is a sweet alcoholic beverage. Another name for them is nutritive sweeteners, which indicates that they do provide calories. Sugar alcohols are nearly as sweet as sucrose but only provide approximately half the calories as shown below. The name polyols also seems to be increasingly used to describe these compounds.

Table 2.1.1: Relative sweetness of monosaccharides, disaccharides, and sugar alcohols6,7

Sweetener	Relative Sweetness	Energy (kcal/g)
Lactose	0.2	4*
Maltose	0.4	4
Glucose	0.7	4
Sucrose	1.0	4
Fructose	1.2-1.8	4
Erythritol	0.7	0.4
Isomalt	0.5	2.0
Lactitol	0.4	2.0

*Differs based on a person's lactase activity

Sugars are fermented by bacteria on the surfaces of teeth. Acid is a product of this fermentation, which results in decreased pH (higher acidity) that leads to tooth decay and, potentially, cavity formation. The major advantage of sugar alcohols over sugars is that sugar alcohols are not fermented by bacteria on the tooth surface. There is a nice picture of this process in the link below as well as a video explaining the process of tooth decay.

Web Links

Sugar and Dental Caries

YouTube Video

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Tagatose

While not a sugar alcohol, tagatose is very similar to sugar alcohols. Tagatose is an isomer of fructose, that provides a small amount of energy (1.5 kcal/g). 80% of tagatose reaches the large intestine, where it is fermented by bacteria, meaning it has a prebiotic-type effect[6]. Notice the similarity in structure of tagatose to sugar alcohols, the only difference being a ketone ($=O$) instead of an alcohol ($-OH$) group.

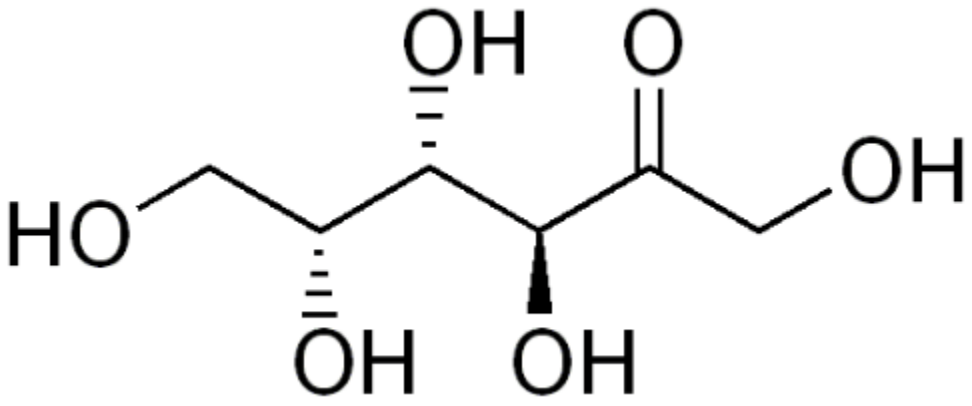


Figure 2.1.6: Structure of tagatose[8]

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Alternative Sweeteners

Alternative sweeteners are simply alternatives to sucrose and other mono- and disaccharides that provide sweetness. Many have been developed to provide zero-calorie or low calorie sweetening for foods and drinks.

Because many of these provide little to no calories, these sweeteners are also referred to as non-nutritive sweeteners (FDA is using high-intensity sweeteners to describe these products[10]). Aside from tagatose (described in the sugar alcohol section), all sweeteners on the list below meet this criteria. Aspartame does provide calories, but because it is far sweeter than sugar, the small amount used does not contribute meaningful calories to a person's diet. Until the FDA allowed the use of stevia, this collection of sweeteners were commonly referred to as artificial sweeteners because they were synthetically or artificially produced. However, with stevia, the descriptor artificial can no longer be used to describe these sweeteners. More recently, Luo Han Guo Fruit extracts have also been allowed to be used as another high-intensity sweetener that is not synthesized or artificially

produced. The table in the link below summarizes the characteristics of the FDA approved high-intensity sweeteners.

Web Link

FDA High-Intensity Sweeteners

Saccharin

Saccharin is the oldest of the artificial sweeteners. However, it should be noted that both sweet and bitter taste receptors are triggered by it, so for some people it has an aftertaste that is off-putting[11,12]. It has been found that this bitter or metallic flavor can sometimes be masked by mixing alternative sweeteners[13].

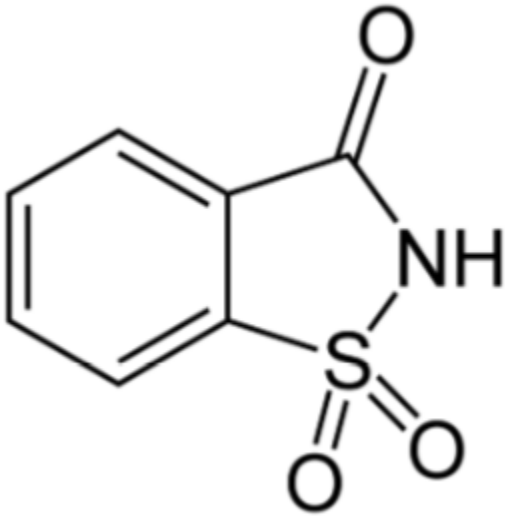


Figure 2.1.7: Structure of saccharin[14]

Aspartame

Aspartame is made up of 2 amino acids (phenylalanine and aspartate) and a methyl ($-CH_3$) group. The compound is broken down during digestion into the individual amino acids. This is why it provides 4 kcal/g, just like protein[11]. However, it is still considered noncaloric because it is so sweet that we use very small amounts that don't provide any meaningful caloric value. Because it can be broken down to phenylalanine, products that contain aspartame contain the following message: "Phenylketonurics: Contains phenylalanine." Phenylketonuria (PKU) will be covered in greater detail in the protein section. When heated, aspartame breaks down and loses its sweet flavor[7].

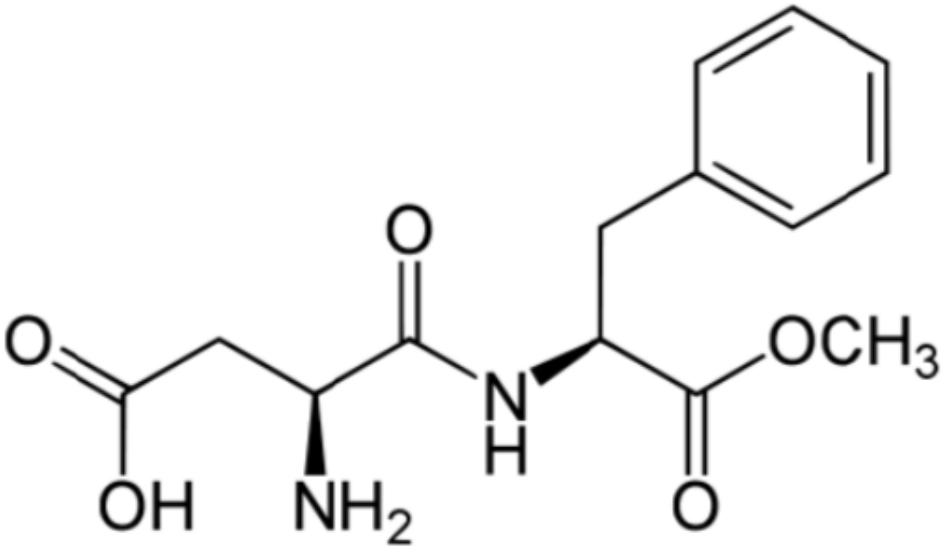


Figure 2.1.8: Structure of aspartame[15]

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Neotame

Neotame is like aspartame version 2.0. Neotame is structurally identical to aspartame except that it contains an additional side group (bottom of the figure below, which is flipped backwards to make it easier to compare their structures). While this looks like a minor difference, it has profound effects on the properties of neotame. Neotame is much sweeter than aspartame and is heat-stable. It can still be broken down to phenylalanine, but such small amounts are used that it is not a concern for those with PKU[7,11].

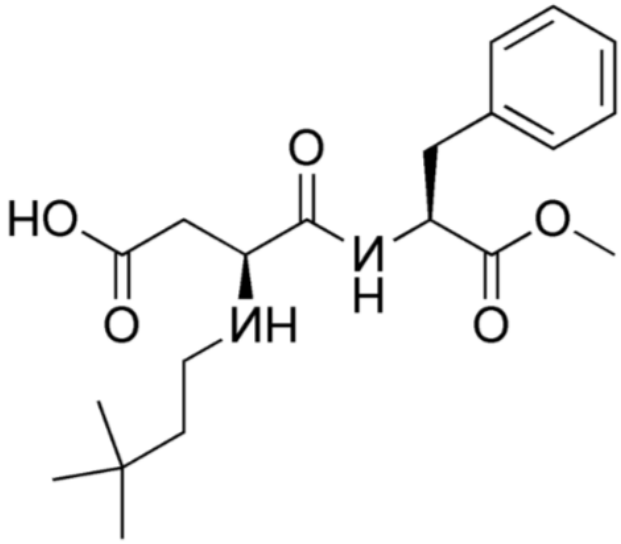


Figure 2.1.9: Structure of neotame[16]

Advantame

The newest, sweetest alternative sweetener approved by the FDA in 2014 is advantame. It is heat-stable and does not have a trade name yet[10]. Notice it also has a similar structure to aspartame and neotame. Like Neotame, it can be broken down to phenylalanine, but such small amounts are used that it is not a concern for those with PKU. However, it has a much higher acceptable daily intake than Neotame[11], meaning there is less concern about adverse effects from consuming too much.

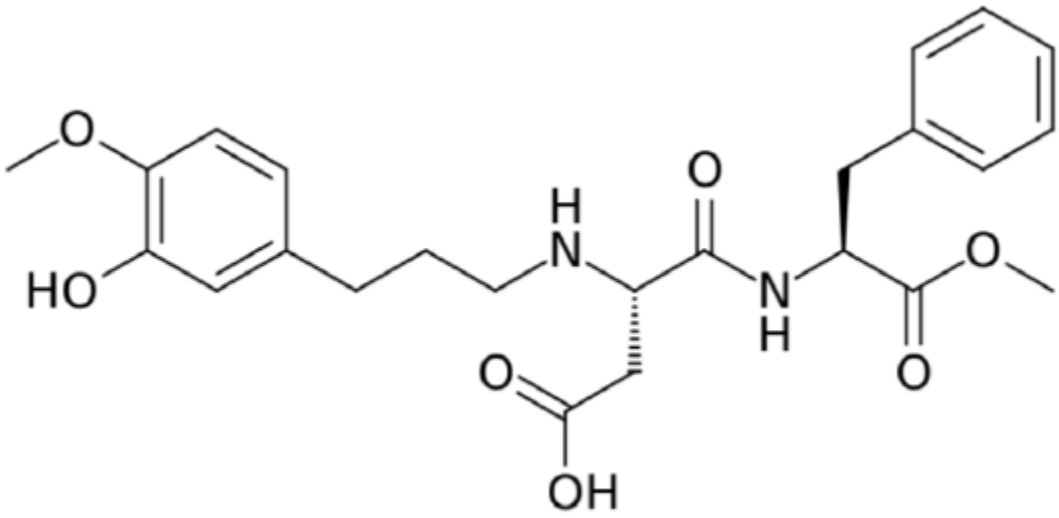


Figure 2.1.10: Structure of advantame[17]

Acesulfame-Potassium (K)

Acesulfame-potassium (K) is not digested or absorbed, therefore it provides no energy or potassium to the body[7]. It is a heat-stable alternative sweetener.

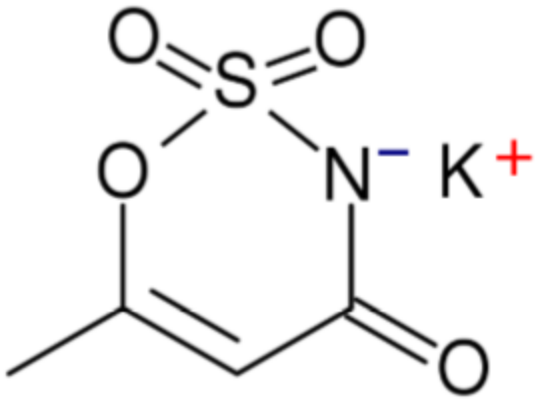


Figure 2.1.11: Structure of acesulfame-potassium (K)[18]

Sucralose

Sucralose is structurally identical to sucrose except that 3 of the hydroxyl groups (OH) are replaced by chlorine molecules (Cl). This small change causes sucralose to not be digested and as such is excreted in feces[7,11]. It is a heat-stable alternative sweetener.

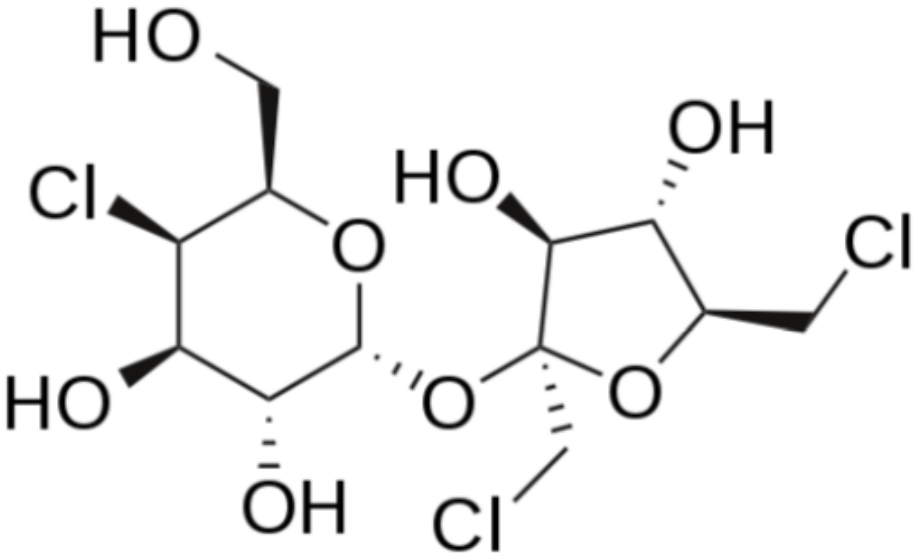


Figure 2.1.12: Structure of sucralose[19]

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Stevia

Stevia is derived from a South American shrub, with the leaves being the sweet part. The components responsible for this sweet

taste are a group of compounds known as steviol glycosides. The structure of steviol is shown below.

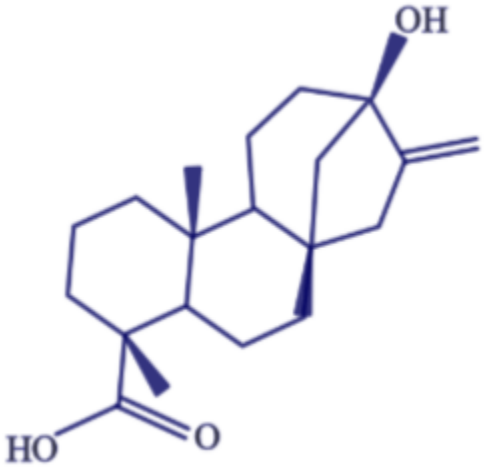


Figure 2.1.13: Structure of steviol[20]

The term glycoside means that there are sugar molecules bonded to steviol. The two predominant steviol glycosides are stevioside and rebaudioside A. The structure of these two steviol glycosides are very similar[21]. The structure of stevioside is shown below as an example.

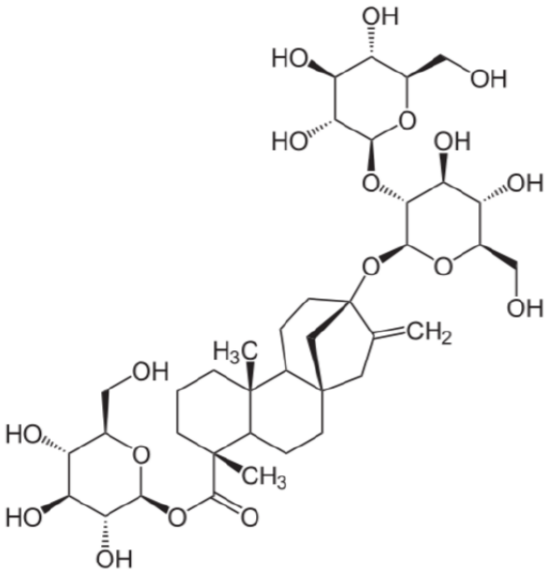


Figure 2.1.14: Structure of stevioside[22]

The common name for a sweetener containing primarily rebaudioside A is rebiana. Stevia sweeteners are heat-stable and have been marketed as a natural alternative sweeteners, something that has been challenged by lawsuits as described in the following link.

Web Link

What is natural and who decides?

Stevia is a heat-stable alternative sweetener.

Luo Han Guo Fruit Extracts

Luo Han Guo (aka Siraitia grosvenrii Swingle, monk) fruit extracts are a newer, natural heat-stable alternative sweetener option derived from a native Chinese fruit. These extracts are sweet because of the mogrosides that they contain10. The structure of a mogroside is shown below.

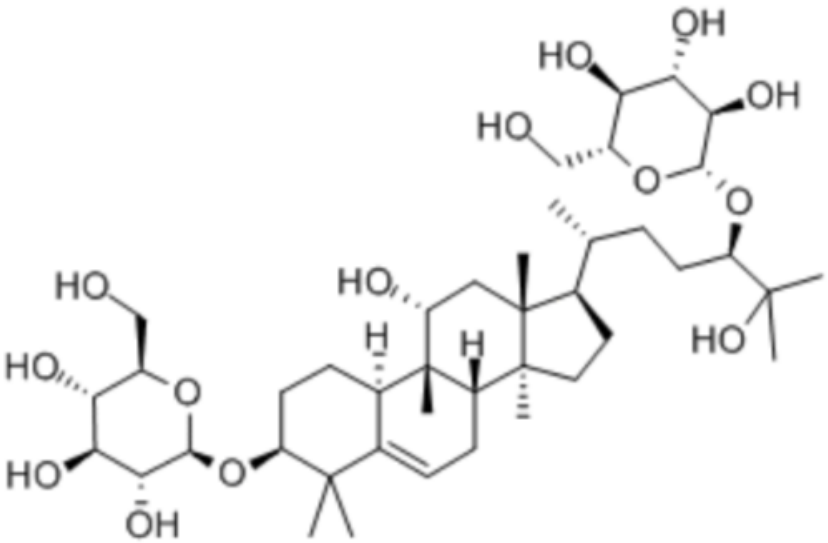


Figure 2.1.15: Structure of a mogroside23

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Oligosaccharides

Within complex carbohydrates, there are oligosaccharides and polysaccharides. Oligosaccharides (oligo means few) are composed of 3-10 monosaccharides bonded together and polysaccharides contain greater than 10 monosaccharides bonded together. Refer to Figure 2.1.1 for a general overview of carbohydrates.

Raffinose and stachyose are the most common oligosaccharides. They are found in legumes, onions, broccoli, cabbage, and whole wheat11. The link below shows the raffinose and stachyose content of some plant foods.

Web Link

Raffinose and stachyose content of selected plant foods

The structures of the two oligosaccharides are shown below.

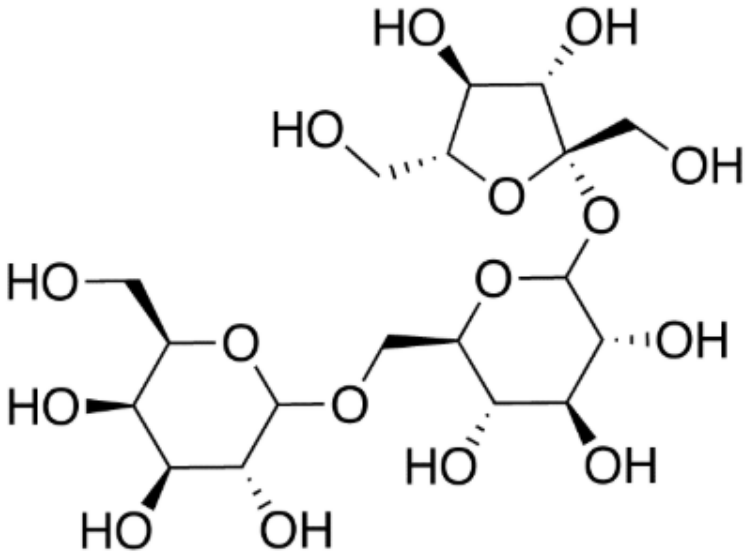


Figure 2.1.16: Structure of raffinose[24]

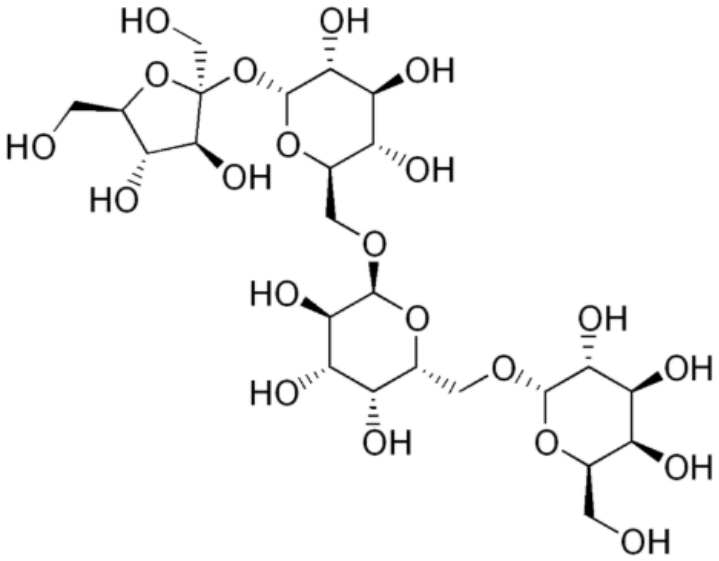


Figure 2.1.17: Structure of stachyose[25]

Our digestive system lacks the enzymes necessary to digest these alpha 1-6 glycosidic bonds found in oligosaccharides. As a result, the oligosaccharides are not digested and reach the colon where they are fermented by the bacteria there. Gas is produced as a byproduct of this bacteria fermentation that can lead to flatulence. To combat this problem, Beano® is a popular product that contains an enzyme (alpha-galactosidase) to break down oligosaccharides, thereby preventing them from reaching the colon and being fermented to produce gas.

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Polysaccharides

Poly means "many" and thus polysaccharides are made up of many monosaccharides (>10). There are 3 main classes of polysaccharides: starch, glycogen, and most fibers. The following sections will describe the structural similarities and differences between the 3 classes of polysaccharides that are divided as shown in Figure 2.1.1.

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Starch

Starch is the storage form of glucose in plants. There are two forms of starch: amylose and amylopectin. Structurally they differ in that amylose is a linear polysaccharide, whereas amylopectin is branched. The linear portion of both amylose and amylopectin contains alpha 1-4 glycosidic bonds, while the branches of amylopectin are made up of alpha 1-6 glycosidic bonds.



Figure 2.1.18: Structure of amylose



Figure 2.1.19: Structure of amylopectin

Amylopectin is more common than amylose (4:1 ratio on average) in starch11,26. Some starchy foods include grains, root crops, tubers, and legumes.

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Glycogen

Glycogen is similar to starch in that it is a storage form of glucose. Glycogen, however, is the carbohydrate storage form in animals, rather than plants. It is even more highly branched than amylopectin, as shown below.



Figure 2.1.20: Structure of glycogen

Like amylopectin, the branch points of glycogen are alpha 1-6 glycosidic bonds, while the linear bonds are alpha 1-4 bonds. The figure below shows that the difference between these bonds (1-4 vs. 1-6) are carbons in the glucose carbons involved.

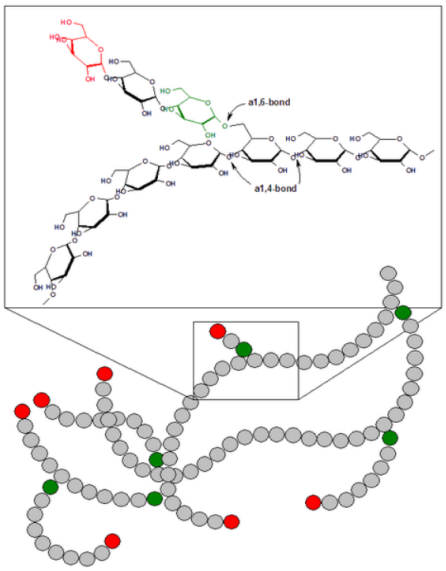


Figure 2.1.21: Structure of glycogen[27]

The advantage of glycogen's highly branched structure is that the multiple ends (shown in red above) are where enzymes start to cleave off glucose molecules. As a result, with many ends available, it can provide glucose much more quickly to the body than it could if it was a linear molecule like amylose with only two ends. We consume almost no glycogen, because it is rapidly broken down by enzymes in animals after slaughter[7].

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Fiber

The simplest definition of fiber is indigestible matter. Indigestible means that it survives digestion in the small intestine and reaches the large intestine.

There are 3 major fiber classifications[28]:

- **Dietary Fiber** - nondigestible carbohydrates and lignin that are intrinsic and intact in plants
- **Functional Fiber** - isolated, nondigestible carbohydrates that have beneficial physiological effects in humans
- **Total Fiber** - dietary fiber + functional fiber

The differences between dietary and functional fiber are compared in the table below:

Table 2.1.2: Differences between dietary fiber and functional fiber

Dietary Fiber	Functional Fiber
Intact in plants	Isolated, extracted, or synthesized
Carbohydrates + lignins	Only carbohydrates
Only from plants	From plants or animals
No proven benefit	Must prove benefit

Dietary fiber is always intact in plants, whereas functional fiber can be isolated, extracted or synthesized. Functional fiber is only carbohydrates, while dietary fiber also includes lignins. Functional fiber can be from plants or animals, while dietary fiber is only from plants. Functional fiber must be proven to have a physiological benefit, while dietary fiber does not.

Polysaccharide fiber differs from other polysaccharides in that it contains beta-glycosidic bonds (as opposed to alpha-glycosidic bonds). To illustrate these differences, consider the structural differences between amylose and cellulose (type of fiber). Both are linear chains of glucose, the only difference is that amylose has alpha-glycosidic bonds, while cellulose has beta-glycosidic bonds as shown below.

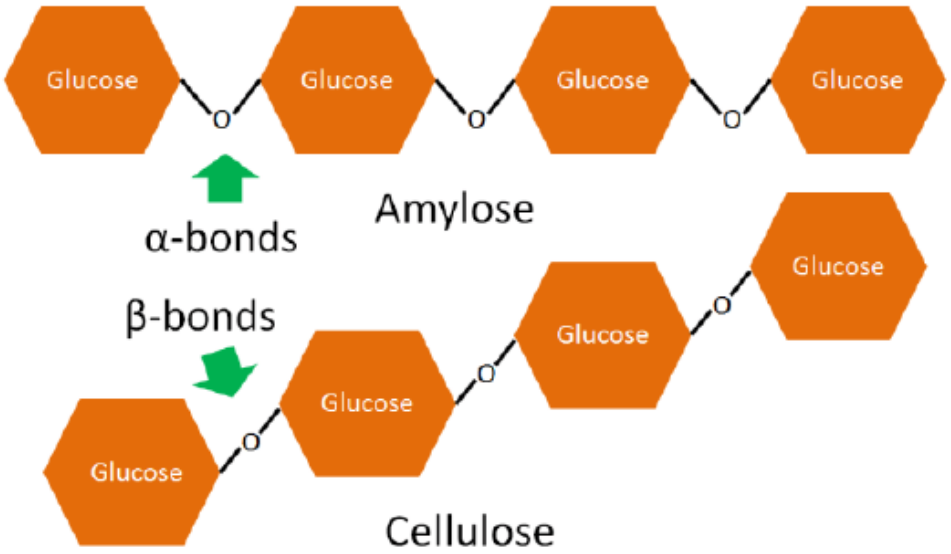


Figure 2.1.2: Structures of amylose and cellulose

The beta-bonds in fiber cannot be broken down by the digestive enzymes in the small intestine so they continue into the large intestine.

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Fiber can be classified by its physical properties. In the past, fibers were commonly referred to as soluble and insoluble. This classification distinguished whether the fiber was soluble in water. However, this classification is being phased out in the nutrition community. Instead, most fibers that would have been classified as insoluble fiber are now referred to as nonfermentable and/

or nonviscous and soluble fiber as fermentable, and/or viscous because these better describe the fiber's characteristics29. Fermentable refers to whether the bacteria in the colon can ferment or degrade the fiber into short chain fatty acids and gas. Viscous refers to the capacity of certain fibers to form a thick gel-like consistency. The following table lists some of the common types of fiber and provides a brief description about each.

Table 2.1.3: Common types of nonfermentable, nonviscous (insoluble) fiber

Fiber	Description
Cellulose	Main component of plant cell walls
Hemicellulose	Surround cellulose in plant cell walls
Lignin	Noncarbohydrate found within “woody” plant cell walls

Table 2.1.4: Common types of fermentable, viscous (soluble) fiber

Fiber	Description
Hemicellulose	Surround cellulose in plant cell walls
Pectin	Found in cell walls and intracellular tissues of fruits and berries
Beta-glucans	Found in cereal brans
Gums	Viscous, usually isolated from seeds

The following table gives the percentage of total dietary fiber in 5 foods.

Table 2.1.5: Total dietary fiber (as percent of sample weight)34

Food	Total Dietary Fiber
Cereal, all bran	30.1
Blueberries, fresh	2.7
Broccoli, fresh, cooked	3.5
Pork and beans, canned	4.4
Almonds, with skin	8.8

The table below shows the amount of nonfermentable, nonviscous fiber in these same five foods.

Table 2.1.6: Nonviscous fiber (as percent of sample weight)30

Food	Hemicellulose	Cellulose	Pectin	Lignin	Total
Cereal, all bran	15.3	7.5	0.9	4.3	28.0
Blueberries, fresh	0.7	0.4	0.4	0.9	2.4
Broccoli, fresh, cooked	0.9	1.2	0.7	0.3	3.1
Pork and beans, canned	0.9	1.6	0.3	0.2	3.0
Almonds, with skin	1.8	3.3	1.6	1.9	8.6

The table below shows the amount of fermentable, viscous fiber in these same five foods.

Table 2.1.7: Viscous Fiber (as percent of sample weight)30

Food	Hemicellulose	Pectin	Total
Cereal, all bran	2.0	0.1	2.1
Blueberries, fresh	0.1	0.2	0.3

Food	Hemicellulose	Pectin	Total
Broccoli, fresh, cooked	0.2	0.2	0.4
Pork and beans, canned	1.1	0.3	1.4
Almonds, with skin	0.2	tr	0.2

tr = trace amounts

Foods that are good sources of nonfermentable, nonviscous fiber include whole wheat, whole grain cereals, broccoli, and other vegetables. This type of fiber is believed to decrease the risk of constipation and colon cancer, because it increases stool bulk and reduces transit time11. This reduced transit time theoretically means shorter exposure to consumed carcinogens in the intestine, and thus lower cancer risk.

Fermentable, viscous fiber can be found in oats, rice, psyllium seeds, soy, and some fruits. This type of fiber is believed to decrease blood cholesterol containing lipoproteins and glucose concentrations, thus also lowering the risk of heart disease and diabetes, respectively11. Its viscous nature slows the absorption of glucose preventing blood glucose from spiking after consuming carbohydrates. It lowers blood cholesterol concentrations primarily by binding bile acids, which are made from cholesterol, and causing them to be excreted. As such, more cholesterol is used to synthesize new bile acids.

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2.2: Protein

Protein is another major macronutrient that, like carbohydrates, are made up of small repeating units. But instead of sugars, protein is made up of amino acids. In the following sections, you will learn more about how protein is synthesized and why it is important in the body.

Amino Acids

Similar to carbohydrates, proteins contain carbon (C), hydrogen (H), and oxygen (O). However, unlike carbohydrates (and lipids) proteins also contain nitrogen (N). Proteins are made up of smaller units called amino acids. This name, amino acid, signifies that each contains an amino ($\mathrm{NH_2}$) and carboxylic acid (COOH) groups. The only structural difference in the 20 amino acids is the side group represented by the R below.

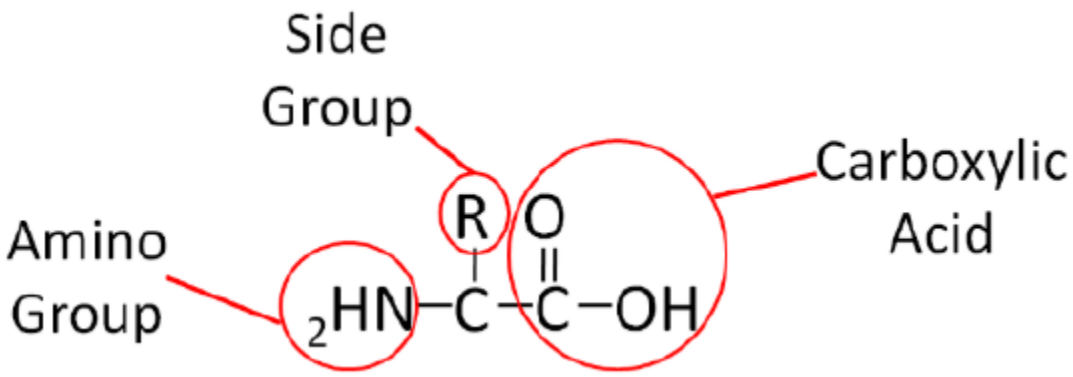


Figure 2.2.1: Structure of an amino acid

To illustrate the differences in the side group we will consider glycine and alanine, the two simplest amino acids. For glycine the R group is hydrogen (H), while in alanine the R group is a methyl ($\mathrm{CH_3}$). The structures of these two amino acids are shown below.

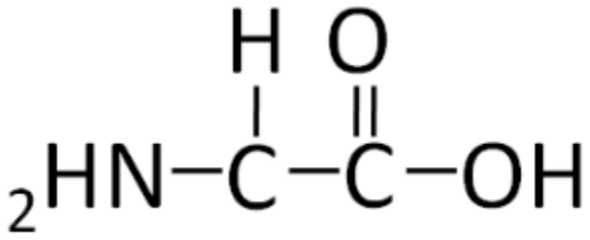


Figure 2.2.2: Structure of glycine

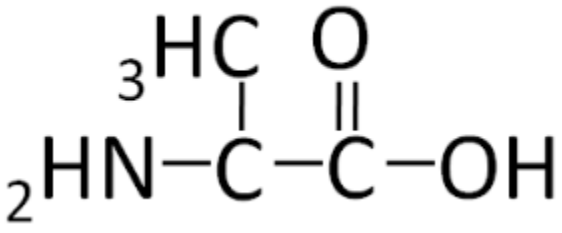


Figure 2.2.3: Structure of alanine

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Individual amino acids are joined together using a peptide bond (green) and is shown in the figure below.

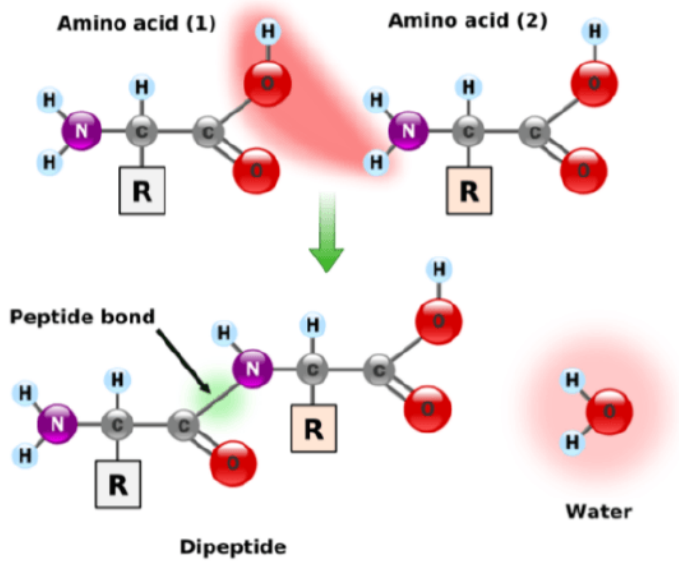


Figure 2.2.4: Peptide bond formation[1]

Amino acids can also come together to form tripeptides (three amino acids), oligopeptides (medium size peptide, there isn't a formal cutoff), and polypeptides (large size). A polypeptide is a chain of amino acids as shown below.

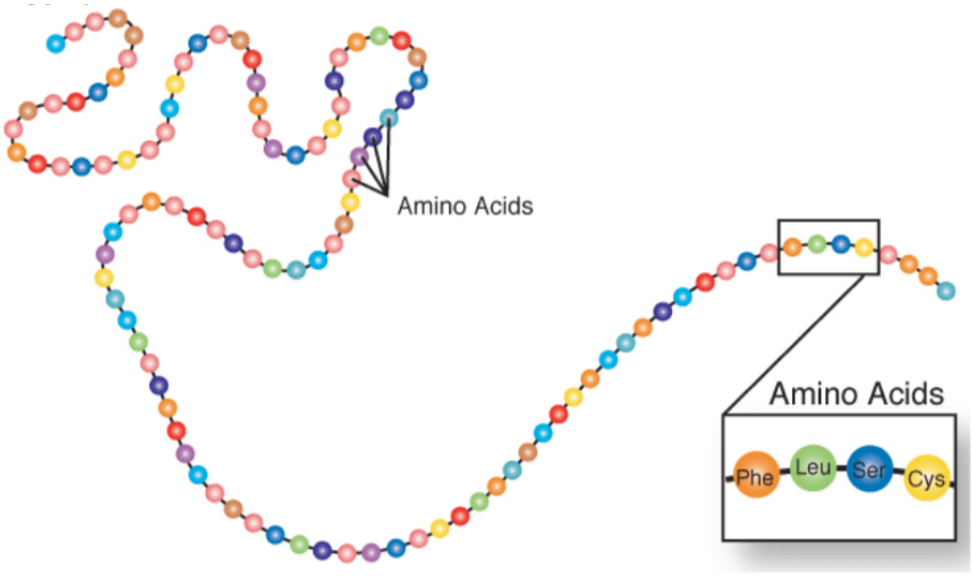


Figure 2.2.5: A polypeptide chain[2]

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Protein Synthesis

The process of protein synthesis is not as simple as stringing together amino acids to form a polypeptide. As shown below, this is a fairly involved process. DNA contains the genetic code that is used as a template to create mRNA in a process known as transcription. The mRNA then moves out of the nucleus into the cytoplasm where it serves as the template for translation, where tRNAs bring in individual amino acids that are bonded together to form a polypeptide.

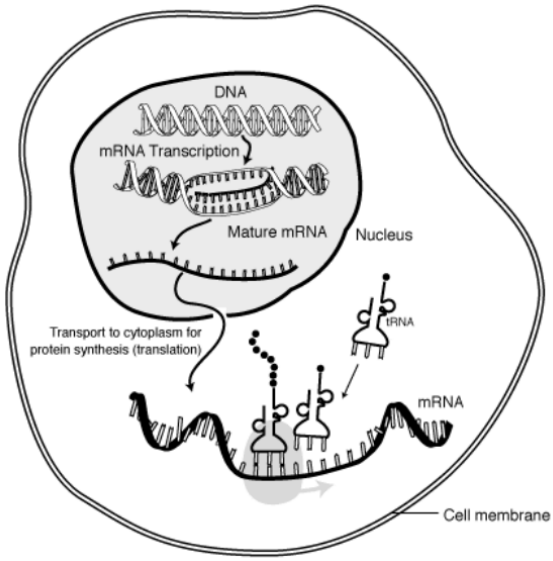


Figure 2.2.6: The process of creating a polypeptide3

Proteins, known as ribosomes, assist with translation. After translation, the polypeptide can be folded or gain structure as shown below and will be discussed in the next subsection (Protein Structure).

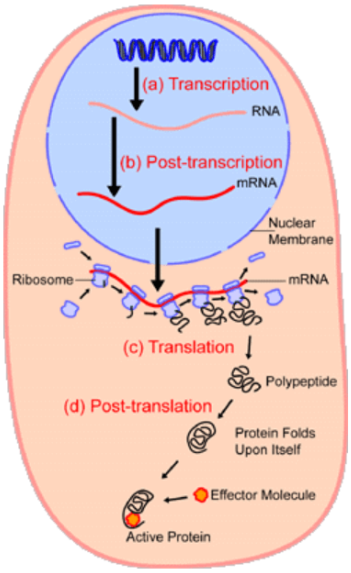


Figure 2.2.7: Protein synthesis and processing[4]

These videos do an excellent job of showing and explaining transcription and translation, respectively.

YouTube Video

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Video 2.2.1: Transcription is the process by which the information in DNA is copied into messenger RNA (mRNA) for protein production. https://www.youtube.com/watch?v=5MfSYnItYvg

YouTube Video

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Video 2.2.2: mRNA Translation. https://www.youtube.com/watch?v=8dsTvBaUMvw

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Protein Structure

Protein structure is the orientation of the amino acids within a protein. There are four levels of protein structure. Primary structure is the linear polypeptide chain. Secondary structure occurs when hydrogen bonding between amino acids in the same polypeptide chain causes the formation of structures such as beta-pleated sheets and alpha-helices. Tertiary structure occurs as a result of an attraction between different amino acids of the polypeptide chain and interactions between the different secondary structures. Finally, certain proteins contain quaternary structure where multiple polypeptide chains are bonded together to form a larger molecule. Hemoglobin is an example of a protein with quaternary structure. The figure below illustrates the different levels of protein structure.

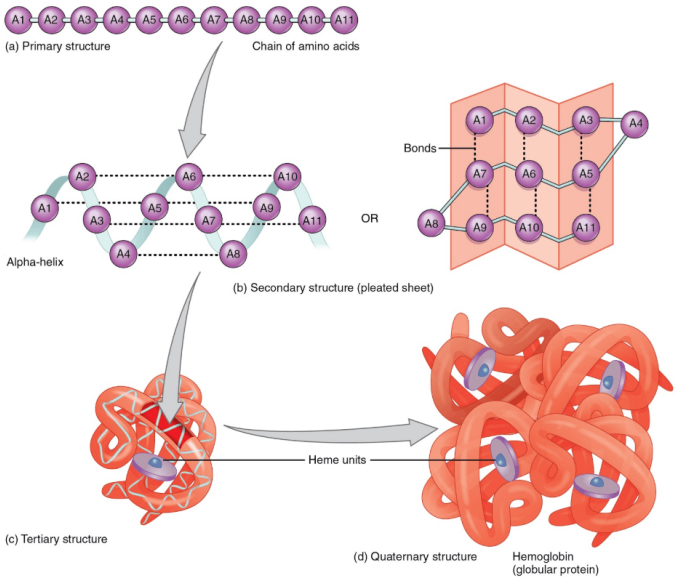


Figure 2.2.8: Different Protein Structures[5]

This video does a nice job of illustrating and explaining the different protein structures.

YouTube Video

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Video 2.2.3: A short video about protein primary, secondary, tertiary and quaternary structure. https://www.youtube.com/watch?v=lijQ3a8yUYQ

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Protein Functions

There are various functions of proteins in the body that are described below.

Structural

Proteins, such as collagen, serve as the scaffolding of the body, and thus are important for the structure of tissues.

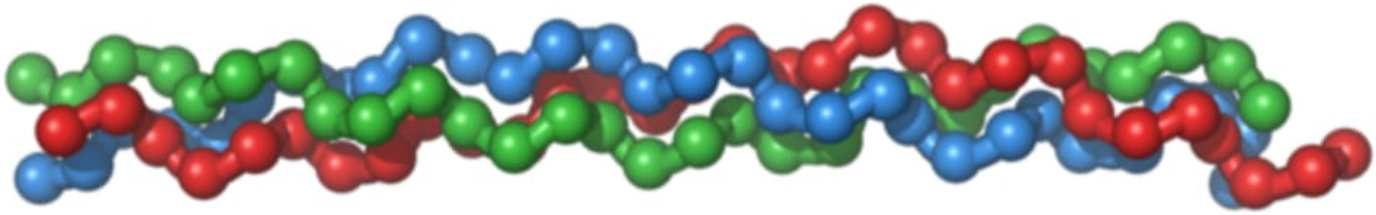


Figure 2.2.9: Triple-helix structure of collagen6

Enzymes

We will discuss a number of enzymes throughout this class, and the vast majority are proteins. An enzyme catalyzes (enhances the rate of) a chemical reaction. The key part of an enzyme is its "active site". The active site is where a compound to be acted on, known as a substrate, enters. Enzymes are specific for their substrates; they do not catalyze reactions on any random compounds floating by. You might have heard the "lock and key" analogy used for enzymes and substrates, respectively. After the substrate enters the active site and binds, the enzyme slightly changes shape (conformation). The enzyme then catalyzes a reaction that, in the example below, splits the substrate into two parts. The products of this reaction are released and the enzyme returns to its native or original shape. It is then ready to catalyze another reaction. The figure and video below nicely illustrate the function of an enzyme.

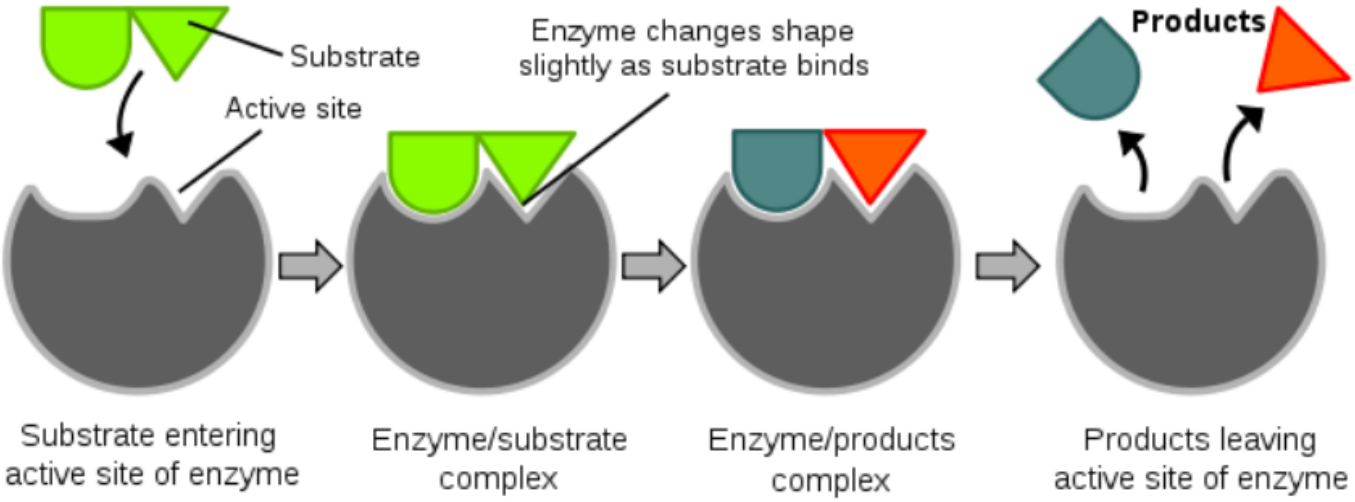


Figure 2.2.10: The function of enzymes[7]

YouTube Video

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Video 2.2.4: Enzymes allow many chemical reactions to occur within the homeostasis constraints of a living system. Enzymes function as organic catalysts. A catalyst is a chemical involved in, but not changed by, a chemical reaction. https://www.youtube.com/watch?v=cbZsXjgPDLQ

Enzymes' names commonly end in -ase, and many are named for their substrate. For example the enzyme amylase cleaves bonds found in amylose and amylopectin.

Hormones

Many hormones are proteins. A hormone is a compound that is produced in one tissue, released into circulation, then has an effect on a different organ. Most hormones are produced from several organs, collectively known as endocrine organs. Insulin is an example of a hormone that is a protein. The video below describes and illustrates the functions of hormones.

YouTube Video

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Video 2.2.5: Many of the body's most basic functions are regulated by the endocrine system—eight different glands located throughout the body. The endocrine system constantly and quietly does its work—secreting liquid chemical messengers called hormones. https://www.youtube.com/watch?v=kIPYVV4aThM

Fluid Balance

Proteins help to maintain the balance between fluids in the plasma and the interstitial fluid. Interstitial fluid is the fluid that surrounds cells. Interstitial fluid and plasma (fluid part of blood) are the two components of extracellular fluid, or the fluid outside of cells. The following figure illustrates the exchange of fluid between interstitial fluid and plasma.

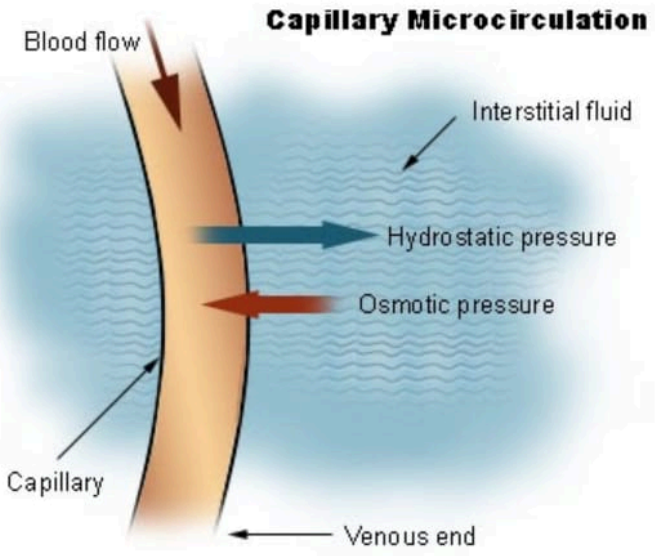


Figure 2.2.11: Interstitial Fluid and plasma[8]

Acid-Base Balance

Proteins serve as buffers, meaning that they help to prevent the pH of the body from getting too high or too low.

Transport

Transport proteins move molecules through circulation or across cell membranes. One example is hemoglobin that transports oxygen through the body. We will see a number of other examples as we move through class.

Immune Function

Antibodies are proteins that recognize antigens (foreign substances that generate antibody or inflammatory response) and bind to and inactivate them. Antibodies are important in our ability to ward off disease.

Other Functions

Proteins can also serve as neurotransmitters and can be used for energy by forming glucose through gluconeogenesis.

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Types of Amino Acids

There are 20 amino acids our body uses to synthesize proteins. These amino acids can be classified as essential, non-essential, or conditionally essential. The table below shows how the 20 amino acids are classified.

Table 2.2.1: Essential, conditionally essential, and nonessential amino acids[9]

Essential	Conditionally Essential	Nonessential
Histidine	Arginine	Alanine
Isoleucine	Cysteine	Asparagine
Leucine	Glutamine	Aspartic Acid or Aspartate
Lysine	Glycine	Glutamic Acid or Glutamate
Methionine	Proline	Serine
Phenylalanine	Tyrosine	
Threonine		
Tryptophan		
Valine		

The body cannot synthesize nine amino acids. Thus, it is essential that these are consumed in the diet. As a result, these amino acids are known as essential, or indispensable, amino acids. As an example of how amino acids were determined to be essential, Dr. William C. Rose at the University of Illinois discovered that threonine was essential by feeding different diets to graduate students at the university as described in the following link.

Web Link

Discovery of Threonine by William C. Rose

Nonessential, or dispensable, amino acids can be made in our body, so we do not need to consume them. Conditionally essential amino acids become essential for individuals in certain situations. An example of a condition when an amino acid becomes essential is the disease phenylketonuria (PKU). Individuals with PKU have a mutation in the enzyme phenylalanine hydroxylase, which normally adds an alcohol group (OH) to the amino acid phenylalanine to form tyrosine as shown below.

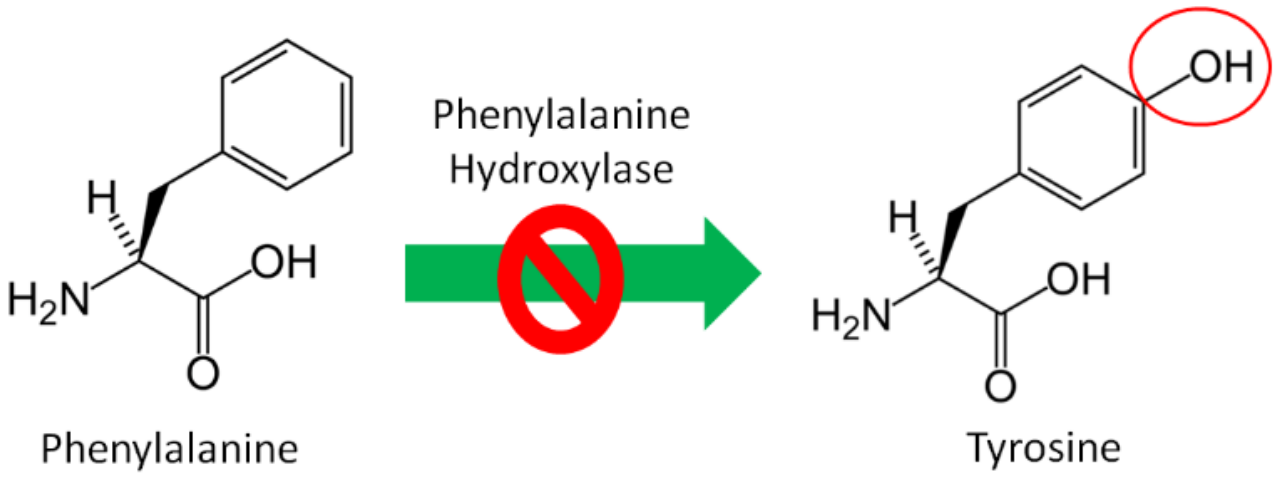


Figure 2.2.12: Phenylketonuria (PKU) results from a mutation in the enzyme phenylalanine hydroxylase[10,11]

Since tyrosine cannot be synthesized by people with PKU, it becomes essential for them. Thus, tyrosine is a conditionally essential amino acid. Individuals with PKU have to eat a very low protein diet and avoid the alternative sweetener aspartame, because it can

be broken down to phenylalanine. If individuals with PKU consume too much phenylalanine, phenylalanine and its metabolites, can build up and cause brain damage and severe mental retardation. The drug Kuvan was approved for use with PKU patients in 2007 who have low phenylalanine hydroxylase activity levels. You can learn more about this drug using the link below.

Web Link

Kuvan

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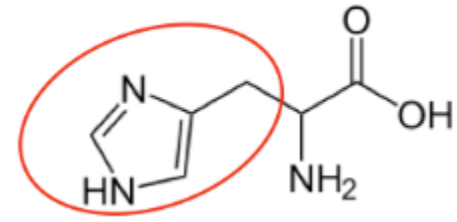
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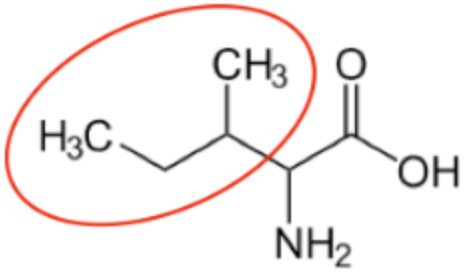
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Amino Acid Structures

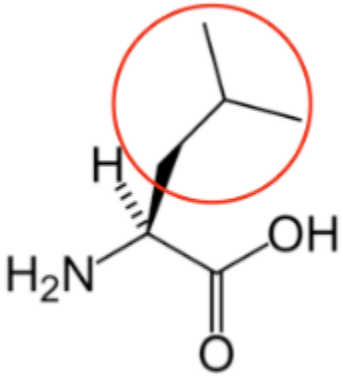
It is a good idea to have a general idea of the structure of the different amino acids and to be able to recognize them as amino acids. You are not expected to memorize these structures. Often I say the name of amino acids and not all students understand that I am talking about an amino acid. Each amino acid differs only by its side group, which is circled in red in each figure below. Also, the more familiar you become with chemical structures, the more prepared you will be for later classes.



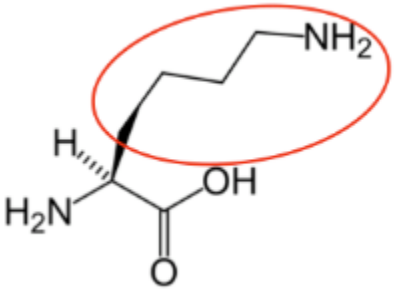
Histidine[12]



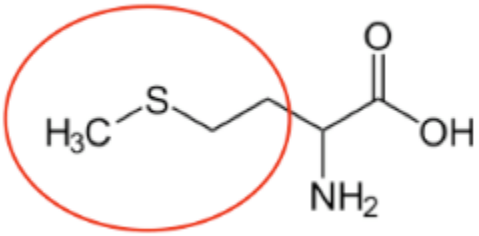
Isoleucine[13]



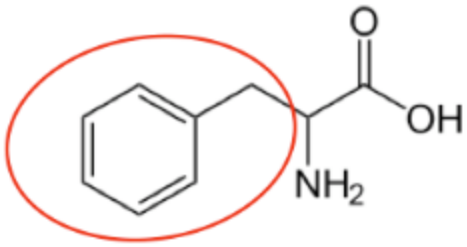
Leucine[14]



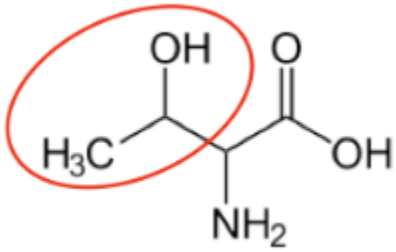
Lysine[15]



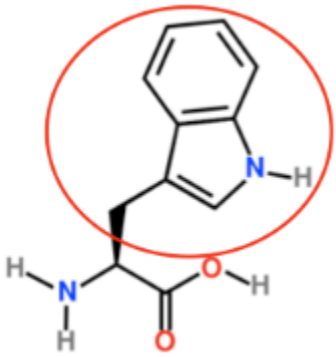
Methionine[16]



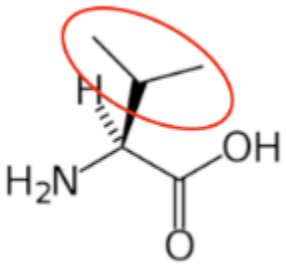
Phenylalanine[17]



Threonine[18]



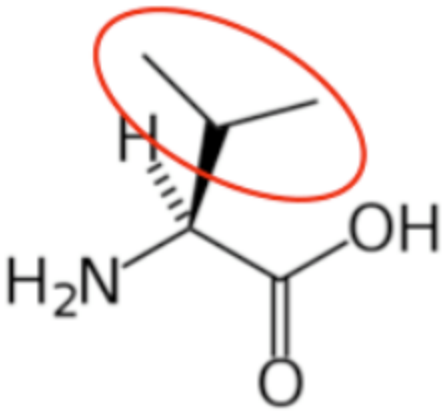
Tryptophan[19]



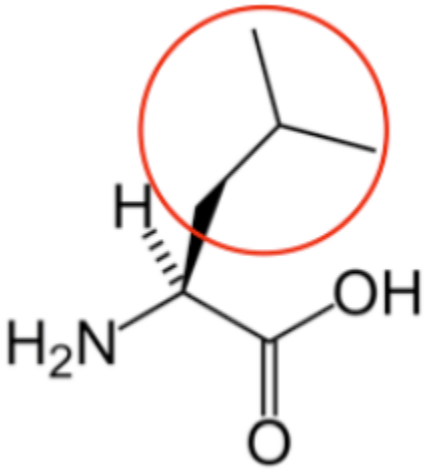
Valine [20]

Figure 2.2.13: Essential amino acids12-20

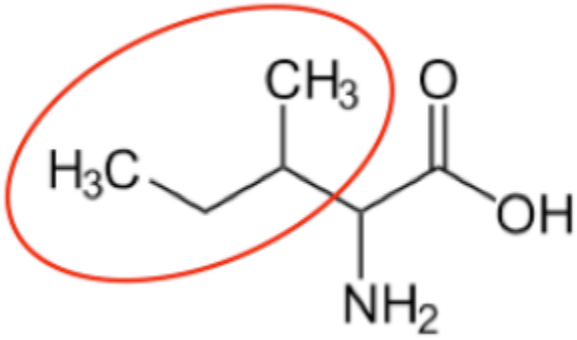
You may hear someone talk about the branch chain amino acids, which are all essential amino acids, but they are singled out in the figure below. These amino acids have branched carbons in their side chains.



Valine[20]

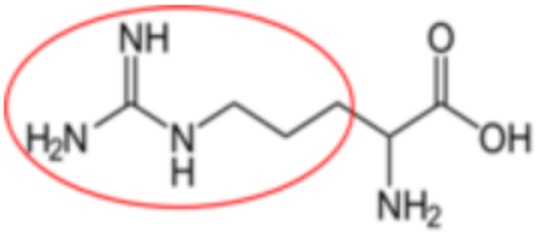


Leucine[14]

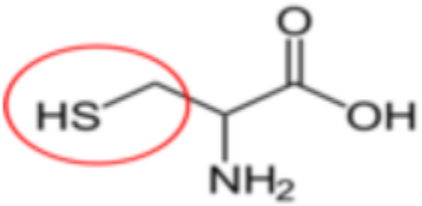


Isoleucine[13]

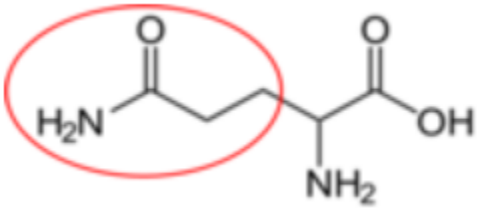
Figure 2.2.14: Branched chain amino acids[20,14,13]



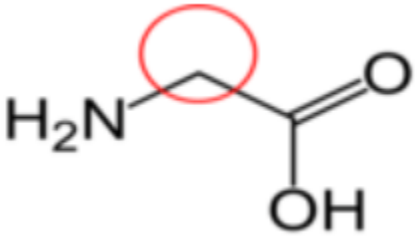
Arginine[21]



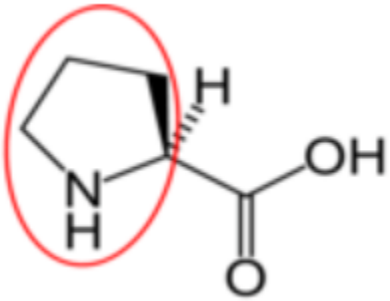
Cysteine[22]



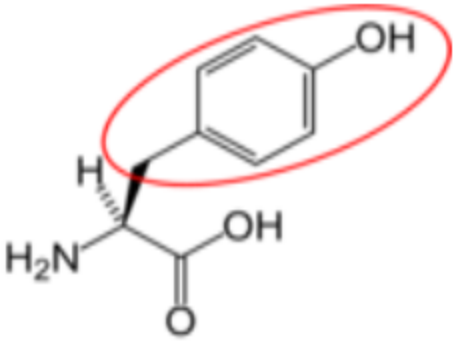
Glutamine[23]



Glycine[24]

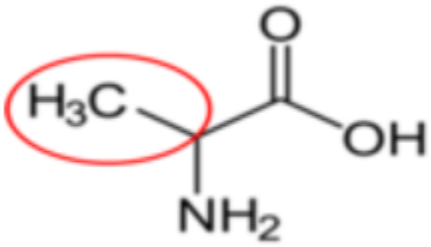


Proline[25]

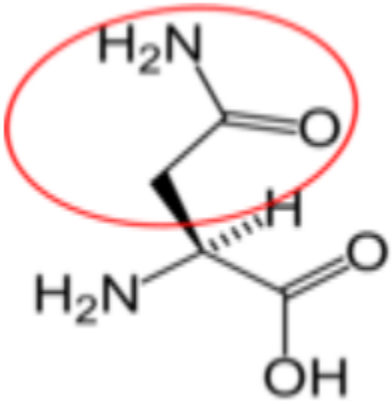


Tyrosine[26]

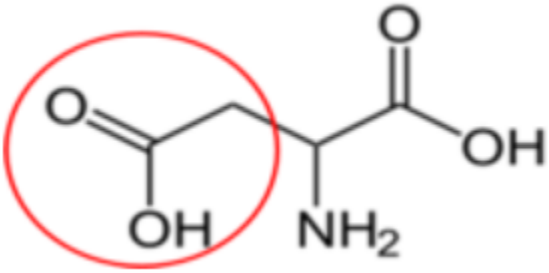
Figure 2.2.15: Conditionally essential amino acids21-26



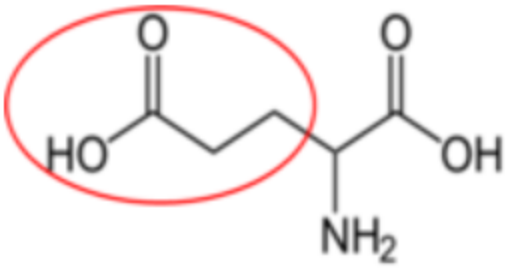
Alanine[27]



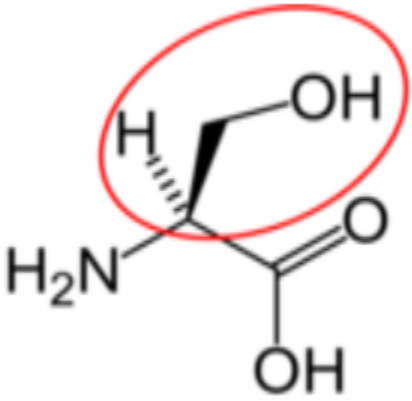
Asparagine[28]



Aspartate (aspartic acid)[29]



Glutamate (glutamic acid)[30]



Serine[31]

Figure 2.2.16: Nonessential amino acids27-31

Query 2.2.8

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Protein Quality

Proteins can be classified as either complete or incomplete. Complete proteins provide adequate amounts of all nine essential amino acids. Animal proteins such as meat, fish, milk, and eggs are good examples of complete proteins. Incomplete proteins do not contain adequate amounts of one or more of the essential amino acids. For example, if a protein doesn't provide enough of the essential amino acid leucine it would be considered incomplete. Leucine would be referred to as the limiting amino acid, because there is not enough of it for the protein to be complete. Most plant foods are incomplete proteins, with a few exceptions such as soy. The table below shows the limiting amino acids in some plant foods.

Table 2.2.2: Limiting amino acids in some common plant foods32

Food	Limiting Amino Acid(s)
Bean and Most Legumes	Methionine, Tryptophan
Tree Nuts and Seeds	Methionine, Lysine
Grains	Lysine

Food	Limiting Amino Acid(s)
Vegetables	Methionine, Lysine

Query 2.2.9

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Complementary Proteins

Even though most plant foods do not contain complete proteins, it does not mean that they should be sworn off as protein sources. It is possible to pair foods containing incomplete proteins with different limiting amino acids to provide adequate amounts of the essential amino acids. These two proteins are called complementary proteins, because they supply the amino acid(s) missing in the other protein. A simple analogy would be that of a 4 piece puzzle. If one person has 2 pieces of a puzzle, and another person has 2 remaining pieces, neither of them have a complete puzzle. But when they are combined, the two individuals create a complete puzzle.



Figure 2.2.17: Complementary proteins are kind of like puzzle pieces

Two examples of complementary proteins are shown below.

Peanut Butter and Jelly Sandwich



Red Beans and Rice



Figure 2.2.18: Two complementary protein examples[33,34]

It should be noted that complementary proteins do not need to be consumed at the same time or meal. It is currently recommended that essential amino acids be met on a daily basis, meaning that if a grain is consumed at one meal, a legume could be consumed at a later meal, and the proteins would still complement one another[35].

Query 2.2.10

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Measures of Protein Quality

How do you know the quality of the protein in the food you consume? The protein quality of most foods has been determined by one of the methods below.

- **Biological Value (BV)** - (Grams of nitrogen retained / grams of nitrogen absorbed) x 100
- **Protein Efficiency Ratio (PER)** - Grams of weight gained / grams of protein consumed. This method is commonly performed in growing rats.
- **Amino Acid Score (AAS)** - Test food limiting essential amino acid (mg/g protein) / needs of same essential amino acid (mg/g protein). An amino acid score of 100 or more indicates that the protein contains adequate amounts of all essential amino acids and thus is considered complete. An amino acid score of less than 100 indicates that at least 1 amino acid is limiting and it is incomplete.
- **Protein Digestibility Corrected Amino Acid Score (PDCAAS)** - Amino Acid Score x Digestibility

This is the most widely used method and was preferred by the Food and Agriculture Organization and World Health Organization (WHO) until recently[36,37].

The following table shows the protein quality measures for some common foods.

Table 2.2.3: Measures of protein quality[36]

Protein	PER	Digestibility	AAS (%)	PDCAAS
Egg	3.8	98	121	100*

Protein	PER	Digestibility	AAS (%)	PDCAAS
Milk	3.1	95	127	100*
Beef	2.9	98	94	92
Soy	2.1	95	96	91
Wheat	1.5	91	47	42

*PDCAAS scores are truncated (cut off) at 100. These egg and milk scores are actually 118 and 121 respectively.

The Food and Agricultural Organization (FAO) recently recommended that PDCAAS be replaced with a new measure of protein quality, the Digestible Indispensable Amino Acid Score (DIAAS). "DIAAS is defined as: DIAAS % = 100 x (mg of digestible dietary indispensable amino acid in 1g of dietary protein / mg of the same dietary indispensable amino acid in 1g of the reference protein)." Ileal digestibility should be utilized to determine the digestibility in DIAAS; ideally in humans, but if not possible in growing pigs or rats[37].

The main differences between DIAAS and PDCAAS are that DIAAS:

1. Takes into account individual amino acids' digestibility rather than protein digestibility.
2. Focuses on ileal instead of fecal (total) digestibility.
3. Has 3 different reference patterns (different age groups, 0-6 months, 6 months- 3 years, 3-10 years old) instead of a single reference pattern
4. Are not truncated[38].

Query 2.2.11

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Protein-Energy Malnutrition

Protein deficiency rarely occurs alone. Instead it is often coupled with insufficient energy intake. As a result, the condition is called protein-energy malnutrition (PEM). This condition is not common in the U.S., but is more prevalent in less developed countries. Kwashiorkor and marasmus are the two forms of protein energy malnutrition. They differ in the severity of energy deficiency as shown in the figure below.

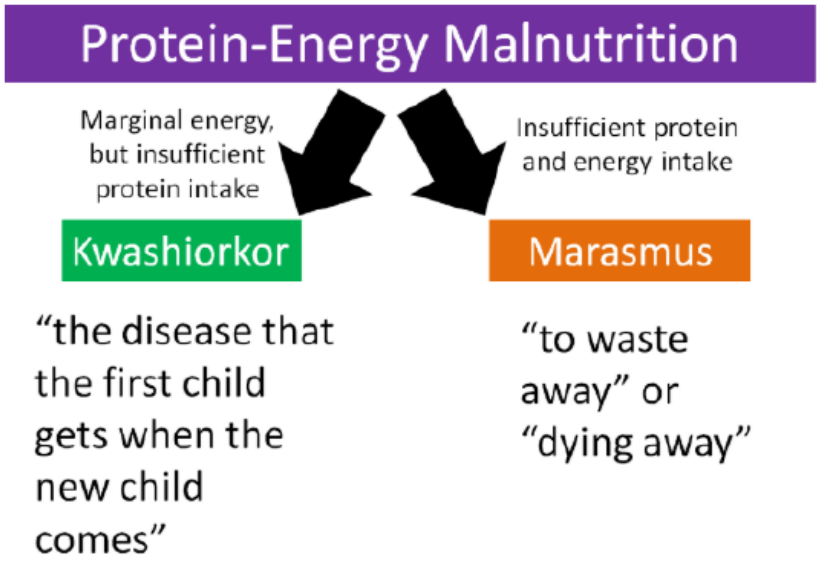


Figure 2.2.19: The 2 types of protein-energy malnutrition

Kwashiorkor is a Ghanaian word that means "the disease that the first child gets when the new child comes[39]." The characteristic symptom of kwashiorkor is a swollen abdomen. Energy intake could be adequate, but protein consumption is too low.



Figure 2.2.20: A child suffering from kwashiorkor[40]

The video below does a nice job showing the symptoms of the condition.

YouTube Video

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Video 2.2.6: Some images of the Kwashiorkor. https://www.youtube.com/watch?v=eTU3iPWAWXg

Marasmus means "to waste away" or "dying away", and thus occurs in individuals who have inadequate protein and energy intakes.



Figure 2.2.21: Two individuals suffering from marasmus41

Query 2.2.12

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Query 2.2.13

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2.3: Lipids

Lipids, commonly referred to as fats, have a poor reputation among some people, in that "fat free" is often synonymous with healthy. We do need to consume certain fats and we should try to incorporate some fats into our diets for their health benefits. However, consumption of certain fats is also associated with greater risk of developing chronic disease(s). In this section we will dive deeper into fats and why they do not need to be feared altogether.

How Does Fat Differ From Lipids?

The answer you receive from this question will depend on who you ask, so it is important to have an understanding of lipids and fats from a chemical and nutritional perspective.

To a chemist, lipids consist of:

- Triglycerides
- Fatty Acids
- Phospholipids
- Sterols

These compounds are grouped together because of their structural and physical property similarities. For instance, all lipids have hydrophobic (water-fearing) properties. Chemists further separate lipids into fats and oils based on their physical properties at room temperature:

- Fats are solid at room temperature
- Oils are liquid at room temperature

From a nutritional perspective, the definition of lipids is the same. The definition of a fat differs, however, because nutrition-oriented people define fats based on their caloric contribution rather than whether they are solid at room temperature. Thus, from a nutrition perspective:

- Fats are triglycerides, fatty acids, and phospholipids that provide 9 kcal/g.

The other difference is that from a caloric perspective, an oil is a fat. For example, let's consider olive oil. Clearly, it is an oil according to a chemist definition, but from a caloric standpoint it is a fat because it provides 9 kcal/g.

The following sections will discuss the different lipid classes introduced above in detail.

Query $2.3.1$

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Fatty Acids

Fatty acids are lipids themselves, and they are also components of triglycerides and phospholipids. Like carbohydrates, fatty acids are made up of carbon (C), hydrogen (H), and oxygen (O).

On one end of a fatty acid is a methyl group ($\mathrm{CH_3}$) that is known as the methyl or omega end. On the opposite end of a fatty acid is a carboxylic acid (COOH). This end is known as the acid or alpha end. Figure $2.3.1$ shows the structure of fatty acids.

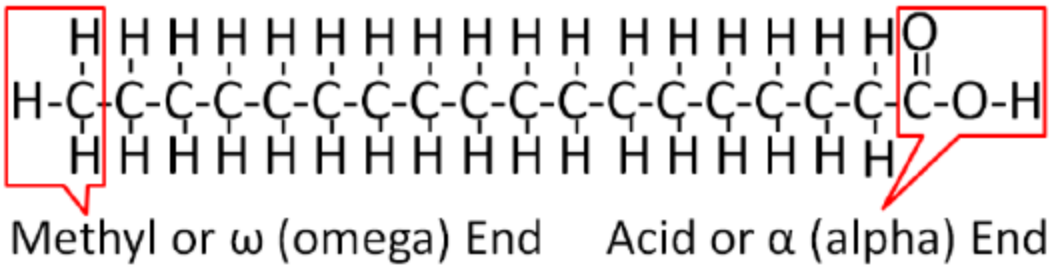


Figure 2.3.1: Structure of a saturated fatty acid

There are a number of fatty acids in nature that we consume that differ from one another in three ways:

1. Carbon chain length (i.e. 6 carbons, 18 carbons)
2. Saturation/unsaturation
3. Double bond configuration (cis, trans)

Carbon Chain Length

Fatty acids differ in their carbon chain length (number of carbons in the fatty acid). Most fatty acids contain somewhere between 4-24 carbons, with even numbers (i.e. 8, 18) of carbons occurring more frequently than odd numbers (i.e. 9, 19). Fatty acids are classified as short-chain fatty acids, medium-chain fatty acids, and long-chain fatty acids based on their carbon chain length using the criteria shown in the table below.

Table 2.3.1: Fatty acid classification

Classification	# of carbons
Short-Chain Fatty Acid	< 6
Medium-Chain Fatty Acid	6-12
Long-Chain Fatty Acid	> 12

Carbon chain length also impacts the physical properties of the fatty acid. As the number of carbons in a fatty acid chain increases, so does the melting point as illustrated in the figure below.

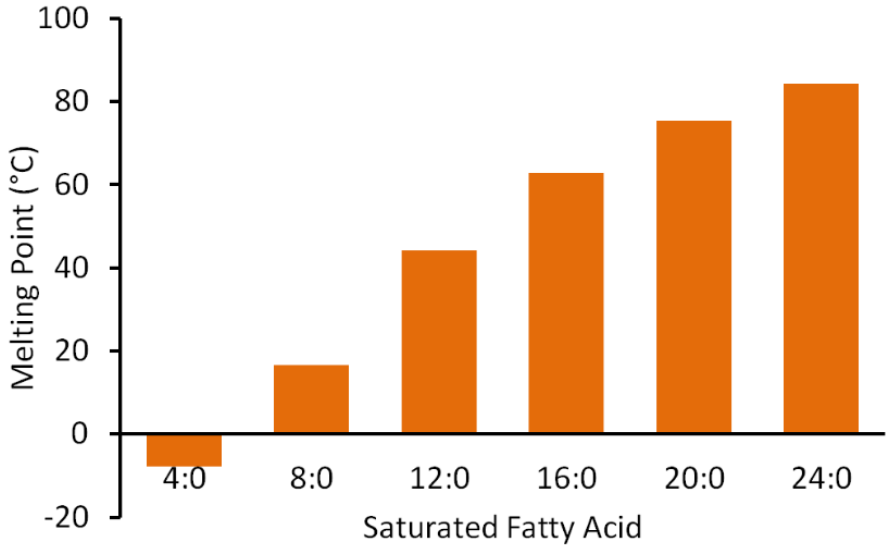


Figure 2.3.2: The melting point of saturated fatty acids of varied lengths[1]

Thus, shorter chain fatty acids are more likely to be liquid, while longer chain fatty acids are more likely to be solid at room

temperature (20-25◇C, 68-77◇F).

Query 2.3.2

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Saturation/Unsaturation

A saturated fatty acid is one that contains the maximum number of hydrogens possible, and no carbon-carbon double bonds. Carbon normally has four bonds to it. Thus, a saturated fatty acid has hydrogens at every position except carbon-carbon single bonds and carbon-oxygen bonds on the acid end. Two examples of the same 18 carbon saturated fatty acid (stearic acid/stearate) are shown in Figures 2.3.1 and 2.3.3. Figure 2.3.3 is the simplified view of this fatty acid.

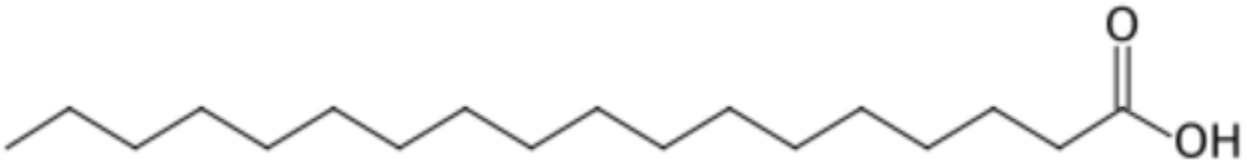


Figure 2.3.3: A simplified view of 18 carbon saturated fatty acid stearic acid2. Each inflection point the zigzag pattern represents a carbon, and the hydrogens are not shown to allow quicker recognition of the carbon chain

Unsaturation means the fatty acid doesn't contain the maximum number of hydrogens on each of its carbons. Instead, unsaturated fatty acids contain a carbon-carbon double bond and only 1 hydrogen off each carbon. The simplest example of unsaturation is a monounsaturated fatty acid. Mono means one, so these are fatty acids with one degree of unsaturation, or one double bond (shown below).

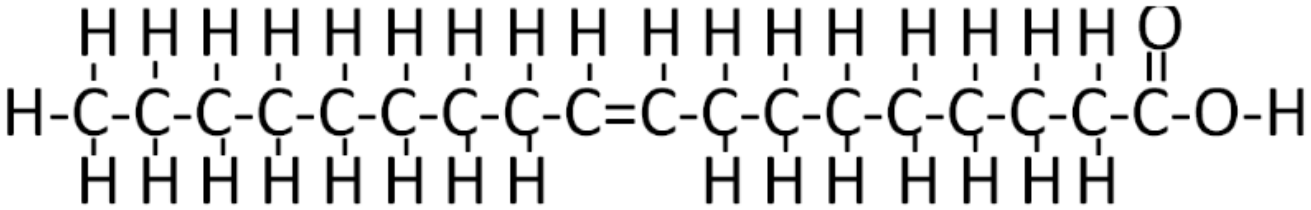


Figure 2.3.4: Structure of the monounsaturated fatty acid (oleic acid)

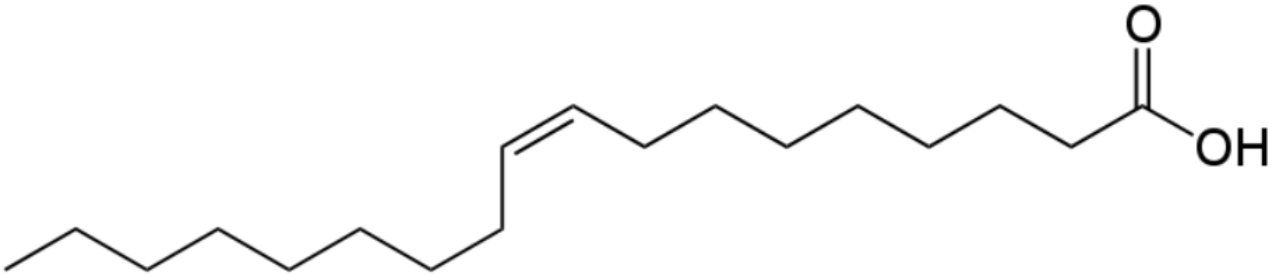


Figure 2.3.5: The simplified structure of the monounsaturated fatty acid (oleic acid)3

Any fatty acid that has two or more double bonds is considered a polyunsaturated fatty acid. As you may remember from the polysaccharide section, poly means many. A simple example of a polyunsaturated fatty acid is linoleic acid (shown below).

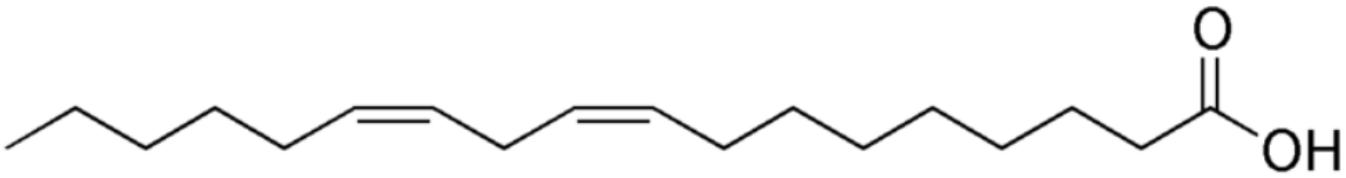


Figure 2.3.6: Structure of the polyunsaturated fatty acid linoleic acid, a polyunsaturated fatty acid with two carbon-carbon double bonds4

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Double Bond Configuration (Shape)

Double bonds in unsaturated fatty acids are in one of two structural orientations: cis or trans. In a trans orientation, the hydrogens on the carbons involved in the double bond are opposite of one another. In the cis orientation the hydrogens are on the same side of the bond. Steric hindrance in the cis orientation causes the chain to take on a more bent shape.

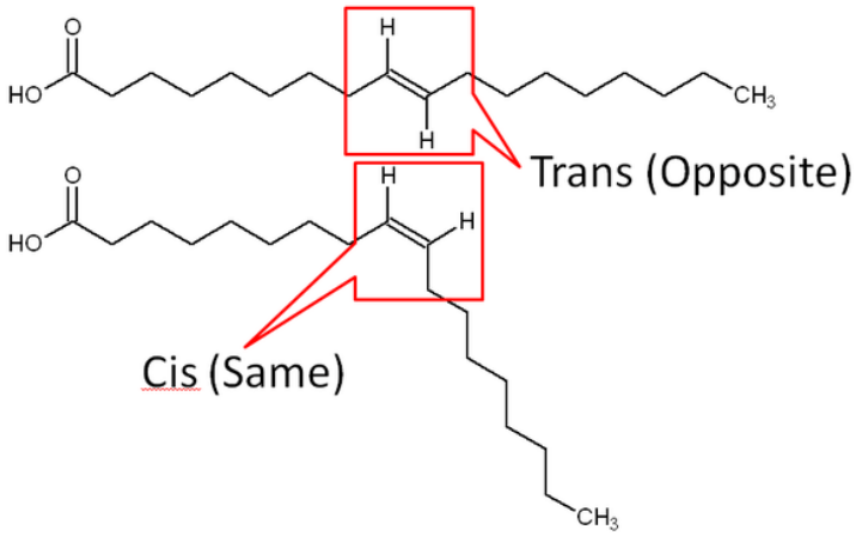


Figure 2.3.7: Cis and trans structural conformations of a monounsaturated fatty acid

Most natural unsaturated fatty acids are in the cis conformation. As can be seen in Figure 2.3.7, the cis fatty acids have a more of kinked shape, which means they do not pack together as well as the saturated or trans fatty acids. As a result, the melting point is much lower for cis fatty acids compared to trans and saturated fatty acids. To illustrate this difference, the figure below shows the difference in the melting points of saturated, trans-, and cis-monounsaturated 18 carbon fatty acids.

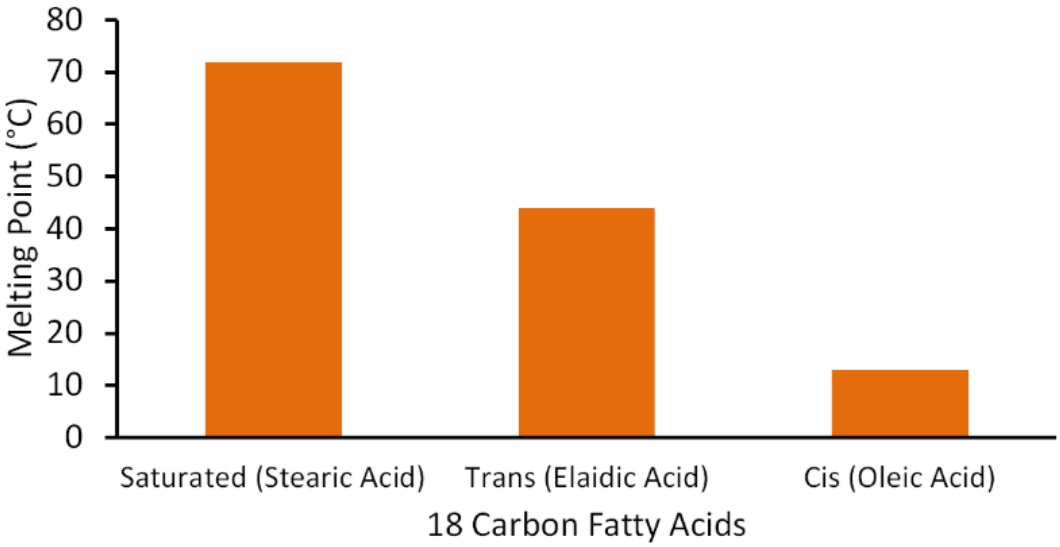


Figure 2.3.8: The melting point of saturated, trans, and cis 18 carbon monounsaturated fatty acids[1]

Query 2.3.4

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There are some naturally occurring trans fatty acids, such as conjugated linoleic acid (CLA), in dairy products. However, for the most part, trans fatty acids in our diets are not natural; instead, they have been produced synthetically. The primary source of trans fatty acids in our food supply is partially hydrogenated vegetable oil. The 'hydrogenated' means that the oil has gone through the process of hydrogenation. Hydrogenation, like the name implies, is the addition of hydrogen. If an unsaturated fatty acid is completely hydrogenated it would be converted to a saturated fatty acid as shown below.

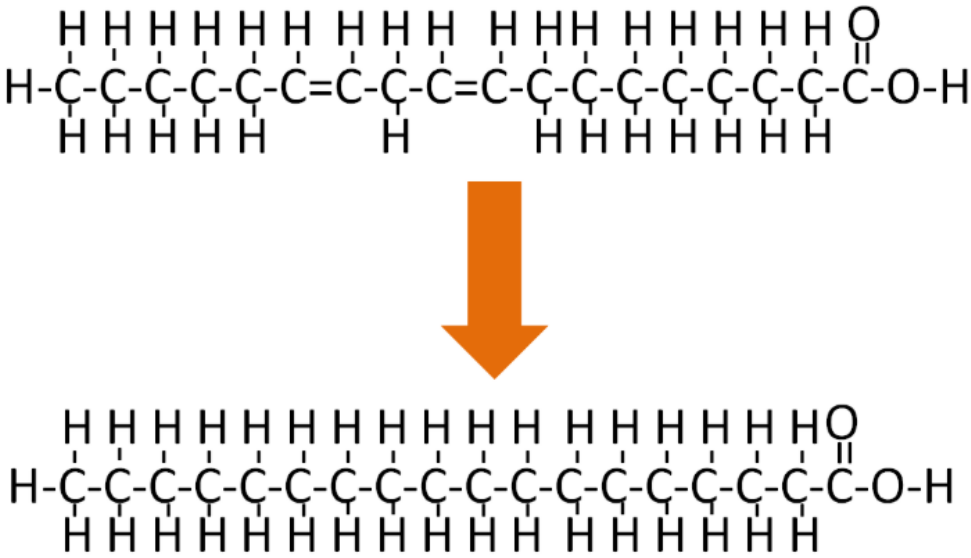


Figure 2.3.9: Fatty acid hydrogenation

However, this isn't/wasn't always desirable, thus partially hydrogenated vegetable oil became widely used. To visualize the difference in the amount of hydrogenation consider the difference between tub margarine and stick margarine.

Stick margarine is more fully hydrogenated leading it to have a much harder texture. This is one of the two reasons to hydrogenate, to get a more solid texture. The second reason is that it makes it more shelf-stable, because the double bond(s) of unsaturated fatty acids are susceptible to oxidation, which causes them to become rancid.

Partial hydrogenation causes the conversion of cis to trans fatty acids along with the formation of some saturated fatty acids. Originally, it was thought that trans fatty acids would be a better alternative to saturated fat (think margarine vs. butter). However, it turns out that trans fat is actually worse than saturated fat in altering biomarkers associated with cardiovascular disease. Trans fat increases low-density lipoprotein and decreases high-density liporotein levels, while saturated fat increases low-density lipoproteins without altering high-density lipoprotein levels. But this does not mean that butter is a better choice than margarine as described in the first link. The FDA revoked Generally Recognized as Safe (GRAS) status of partially hydrogenated vegetable oil as described in the second link, and is requiring its use to be phased out by 2018. After that point, permission will need to be requested to use them in foods.

Web Links

Butter vs. Margarine: Which is better for my heart?

FDA to Limit Trans Fats in Foods

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Query 2.3.6A

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Query 2.3.6B

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Fatty Acid Naming & Food Sources

There are three naming systems used for fatty acids:

1. Delta nomenclature
2. Omega nomenclature
3. Common names

The omega nomenclature and common names are used more in the field of nutrition than the delta nomenclature when describing specific fatty acids.

Delta Nomenclature

For delta nomenclature you need to know 3 things:

1. Number of carbons in the fatty acid
2. Number of double bonds
3. Number of carbons from the carboxylic acid (alpha) end to the first carbon in the double bond(s)

Let's consider the example in the figure below.

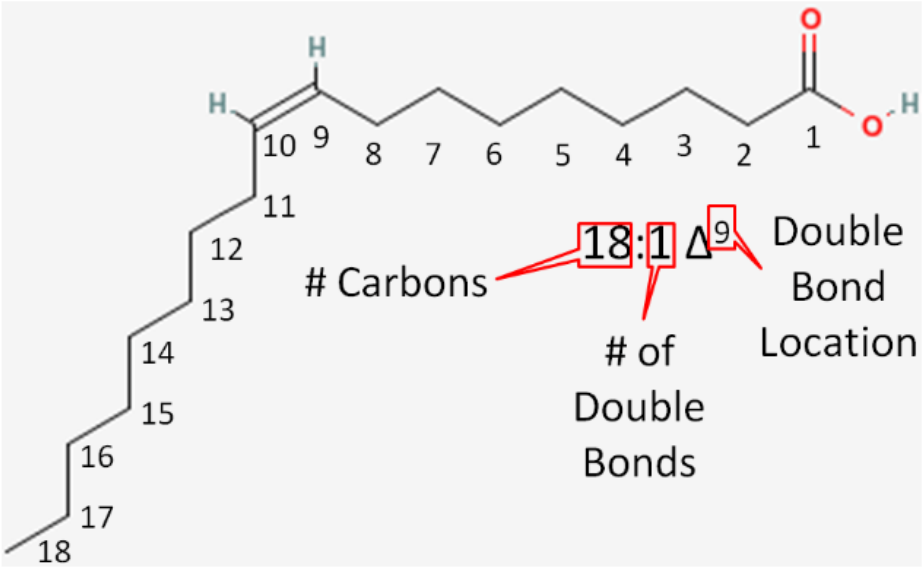


Figure 2.3.10: Delta Nomenclature

1. Number of carbons in the fatty acid = 18
2. Number of double bonds = 1
3. Number of carbons from the carboxylic acid end to the first carbon in the double bond = 9

This is then written as shown in Figure 2.3.10.

Query 2.3.7

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Omega Nomenclature

The omega nomenclature is almost exactly the same as the delta nomenclature, the only differences being:

1. Carbons are counted from the methyl (omega) end instead of the carboxylic acid end
2. The omega symbol is used instead of the delta symbol

For omega nomenclature you need to know 3 things:

1. Number of carbons in the fatty acid
2. Number of double bonds
3. Number of carbons from the methyl end (aka Omega end) to the first carbon in the double bond closest to the methyl end

We will again consider the same fatty acid.

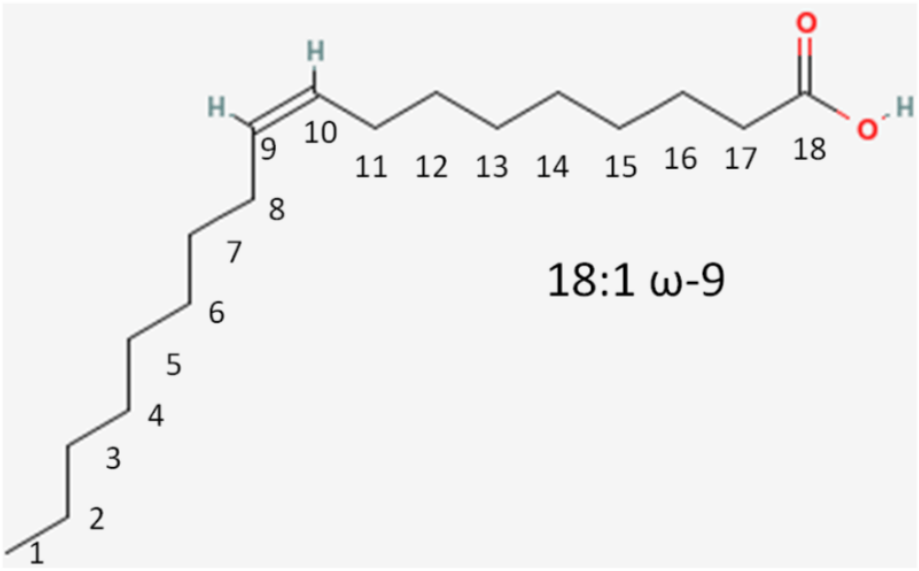


Figure 2.3.11: Omega Nomenclature

1. Number of carbons in the fatty acid = 18
2. Number of double bonds = 1
3. Number of carbons from the methyl (aka omega) end to the first carbon in the double bond closest to the methyl end = 9

If it is a saturated fatty acid, then the omega nomenclature is not added to the end of the name. If it is an 18 carbon saturated fatty acid, then it would be named 18:0.

This is written as shown in Figure 2.3.11. Instead of an omega prefix, the prefix n- (i.e. n-3) is also commonly used.

Query 2.3.8

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Common Names

The common names of fatty acids are something that, for the most part, have to be learned/memorized. The common name of the fatty acid we have been naming in this section is oleic acid.

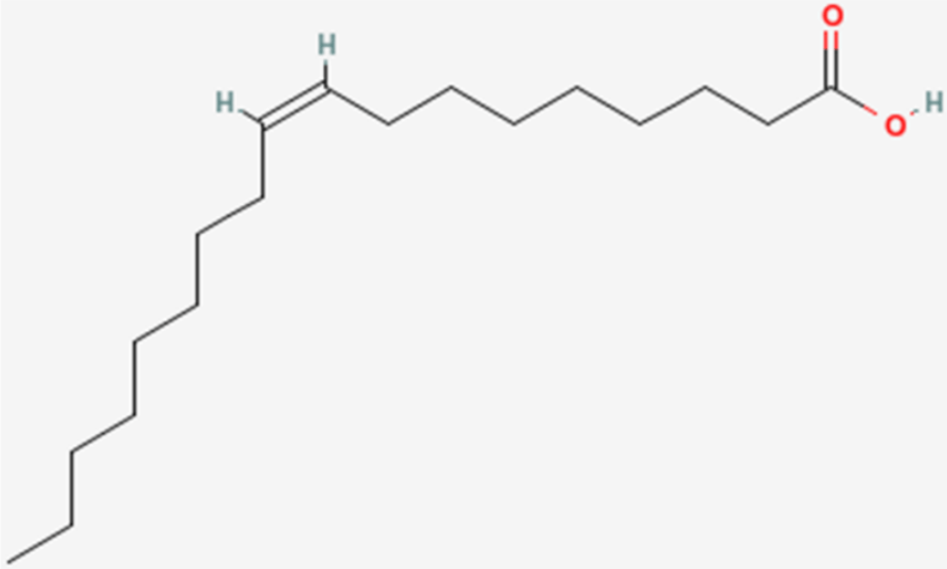


Figure 2.3.12: Oleic acid

However, it can also be called oleate. The only difference is that, instead of a carboxylic acid on the end of the fatty acid, it has been ionized to form a salt (shown below). This is what the -ate ending indicates and the two names are used interchangeably.

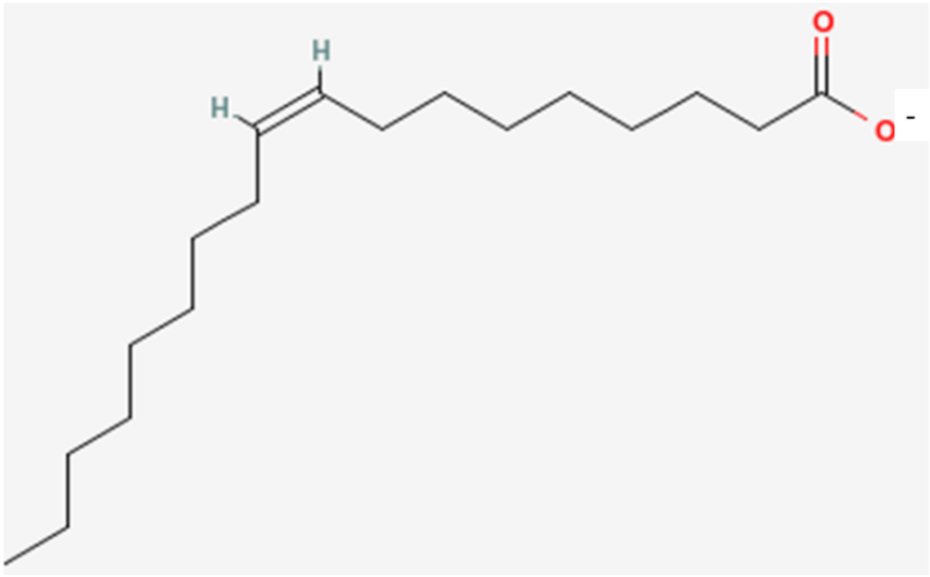


Figure 2.3.13: Oleate

The table below gives the common names and food sources of some common fatty acids.

Table 2.3.2: Common names of fatty acids5

Omega Name	Common Name
4:0	Butyric Acid
12:0	Lauric Acid
14:0	Myristic Acid
16:0	Palmitic acid
18:0	Stearic Acid
20:0	Arachidic Acid

Omega Name	Common Name
24:0	Lignoceric Acid
18:1 (n-9)	Oleic Acid
18:2 (n-6)	Linoleic Acid
18:3 (n-3)	Alpha-linolenic Acid
20:4 (n-6)	Arachidonic Acid
20:5 (n-3)	Eicosapentanoic Acid
22:6 (n-3)	Docosahexanoic Acid

The NutritionData link below can help you identify foods that are high in a specific fatty acid.

Web Link

NutritionData: Fatty Acids

Query 2.3.9

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Food Sources of Fatty Acids

After going through this wide array of fatty acids, you may be wondering where they are found in nature. The figure below shows the fatty acid composition of certain oils and oil-based foods. As you can see, most foods contain a mixture of fatty acids. Stick margarine is the only product in the figure that contains an appreciable amount of trans fatty acids. Corn, walnut, and soybean are rich sources of n-6 polyunsaturated fatty acids, while flax seed is fairly unique among plants in that it is a good source of n-3 polyunsaturated fatty acids. Canola and olive oil are rich sources of monounsaturated fatty acids. Lard, palm oil, butter and coconut oil all contain a significant amount of saturated fatty acids.

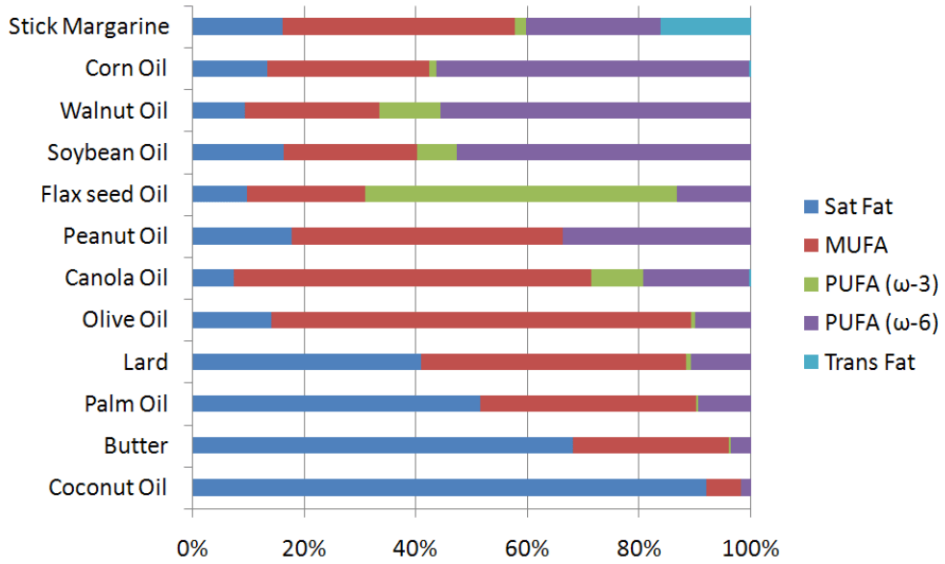


Figure 2.3.14: Fatty acid composition of foods and oils[6]

Query 2.3.10

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Essential Fatty Acids & Eicosanoids

The two essential fatty acids are:

1. linoleic acid (omega-6)
2. alpha-linolenic (omega-3)

These fatty acids are essential because we can not synthesize them. This is because we do not have an enzyme capable of adding a double bond (desaturating) at the omega-6 and 3 positions. We do have an enzyme that can add the omega-9 bond, which is why it is not essential. The structures of the two essential fatty acids are shown below.

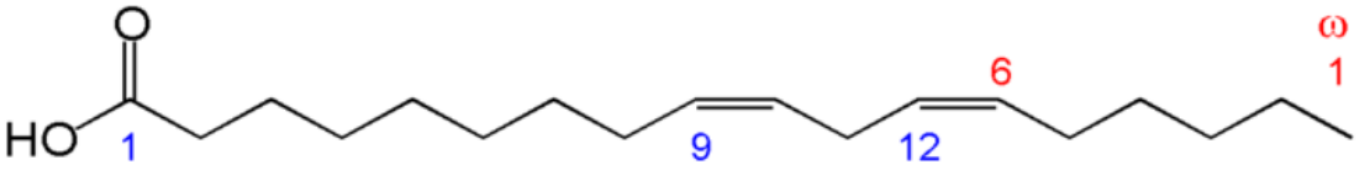


Figure 2.3.15: Linoleic acid[7]

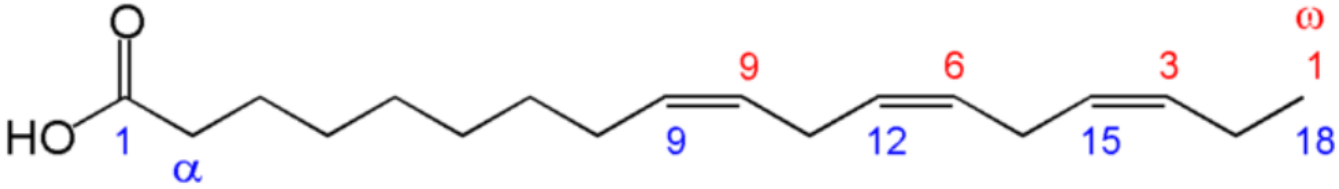


Figure 2.3.16: Alpha-linolenic acid[8]

However, we do possess enzymes that can take the essential fatty acids, elongate them (add two carbons to them), and then further desaturate them (add double bonds) to other omega-6 and omega-3 fatty acids. Thus, there are 2 families of fatty acids that the majority of polyunsaturated fatty acids fit into as shown below.

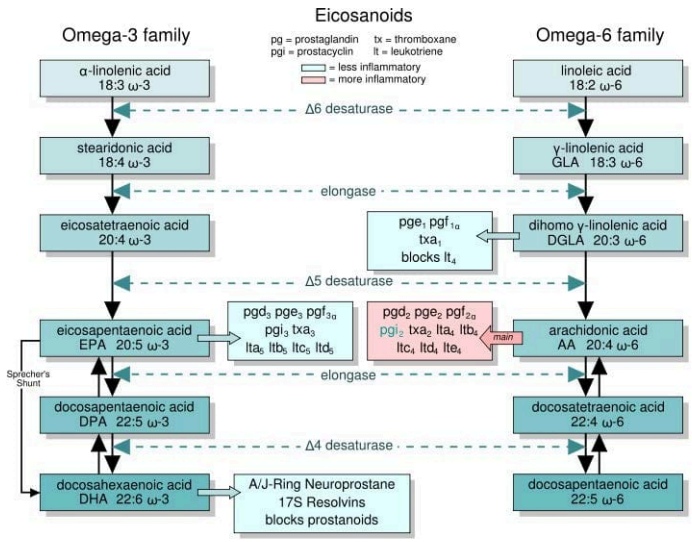


Figure 2.3.17: Omega-3 and omega-6 fatty acids and eicosanoid production[9]

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The same enzymes are used for both omega-6 and omega-3 fatty acids. However, we cannot convert omega-3 fatty acids to omega-6 fatty acids or omega-6 fatty acids to omega-3 fatty acids. Among these families, the omega-3 fatty acid, eicosapentaenoic acid, and the omega-6 fatty acids, dihomo gamma-linolenic acid and arachidonic acid, are used to form compounds known as eicosanoids. These 20 carbon fatty acid derivatives are biologically active in the body (like hormones, but they act locally in the tissue they are produced). There are four classes of eicosanoids:

- Prostaglandins (PG)
- Prostacyclins (PC)
- Thromboxanes (TX)
- Leukotrienes (LT)

Some examples of eicosanoid structures are shown in the figure below:

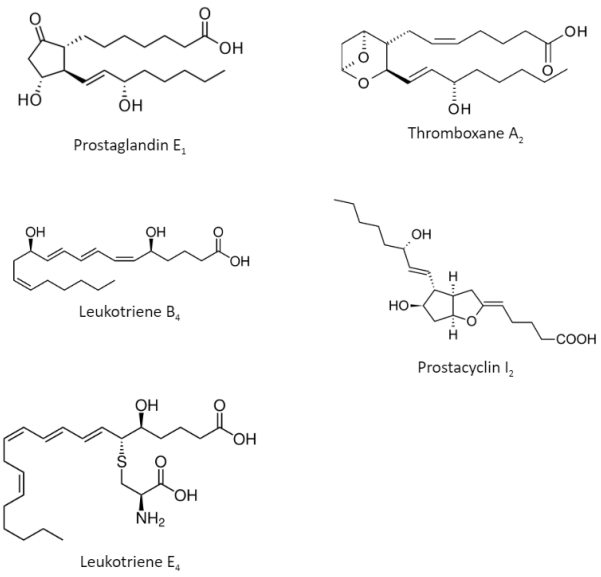


Figure 2.3.18: Eicosanoid structures10-14

Query 2.3.12

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The difference in the effects and outcomes of omega-6 and omega-3 fatty acid intake is primarily a result of the eicosanoids produced from them. Omega-6 fatty acid derived eicosanoids are more inflammatory than omega-3 fatty acid derived eicosanoids. As a result, omega-3 fatty acids are considered anti-inflammatory because replacing the more inflammatory omega-6 fatty acid derived eicosanoids with omega-3 fatty acid derived eicosanoids will decrease inflammation. As an example of the action of eicosanoids, aspirin works by inhibiting the enzymes cyclooxygenase 1 (Cox-1) and cyclooxygenase 2 (Cox-2). These enzymes convert arachidonic acid into inflammatory prostaglandins as shown below.

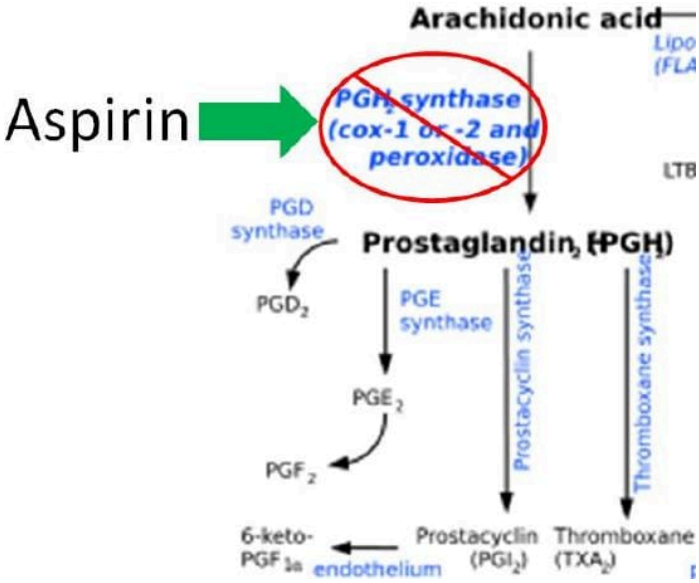


Figure 2.3.19: Aspirin inhibits Cox-1 and Cox-215

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You have probably heard that you should get more omega-3s in your diet, and in general polyunsaturated fatty acids are considered healthy. However, since omega-3 fatty acids are competing for the same enzymes as omega-6 fatty acids, and because the omega-6 fatty acids are more inflammatory, consuming too many omega-6s is probably more detrimental than helpful. As a result, there is interest in the dietary omega-3:omega-6 fatty acid ratio. For most Americans, the ratio is believed to be too high, at almost 10-20 times more omega-6 fatty acids than omega-3 fatty acids16. The table below shows good food sources of some selected omega-3 and omega-6 fatty acids.

Table 2.3.3: Good food sources of selected omega-3 and omega-6 fatty acids

Fatty Acid	Good Food Sources
Linoleic Acid (LA, n-6)	Safflower Oil, Corn Oil, Sunflower Oil
Arachidonic Acid (AA, n-6)	Eggs, Meat
Alpha-Linolenic Acid (ALA, n-3)	Walnuts, Flaxseed (linseed), Canola (rapeseed), and Soybean Oils
Eicosapentaenoic Acid (EPA, n-3)	Fatty Fish & Fish Oils
Docosahexanoic Acid (DHA, n-3)	Fatty Fish & Fish Oils

Even though Figure 2.3.17 illustrates the conversion of alpha-linolenic acid to eicosapentanoic acid and docosahexanoic acid, this conversion is actually quite limited. Only 0.2-8% and 0-4% of alpha-linolenic acid is converted to eicosapentanoic acid and docosahexanoic acid, respectively17. Thus, dietary consumption is the most effective way to get the longer chain fatty acids (eicosapentanoic acid and docosahexanoic acid) in our bodies. It is less clear whether alpha-linolenic acid consumption is as beneficial as eicosapentanoic acid and docosahexanoic acid) but a study found it to be equally effective in decreasing blood triglyceride concentrations. In that study, DHA had the added positive benefit of increasing high-density lipoprotein18. These are all positive outcomes that are expected to reduce the risk of developing cardiovascular disease. However, there is evidence accumulating that there is not much cardiovascular benefit from taking fish oil supplements as described in the article below.

Web Link

Fish Oils Claims Not Supported By Research

Essential Fatty Acid Deficiency

Essential fatty acid deficiency is rare and unlikely to occur, but the symptoms are:

- Growth inhibition
- Reproductive problems
- Skin lesions
- Neurological and visual problems

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Triglycerides

Triglycerides are the most common lipid in our bodies and in the foods we consume. Fatty acids are not typically found free in nature, instead they are found in triglycerides. Breaking down the name triglyceride tells a lot about their structure. "Tri" refers to the three fatty acids, "glyceride" refers to the glycerol backbone that the three fatty acids are bonded to. Thus, a monoglyceride contains one fatty acid, a diglyceride contains two fatty acids. Triglycerides perform the following functions in our bodies:

- Provide energy
- Primary form of energy storage in the body
- Insulate and protect
- Aid in the absorption and transport of fat-soluble vitamins.

A triglyceride is formed by three fatty acids being bonded to glycerol as shown below.

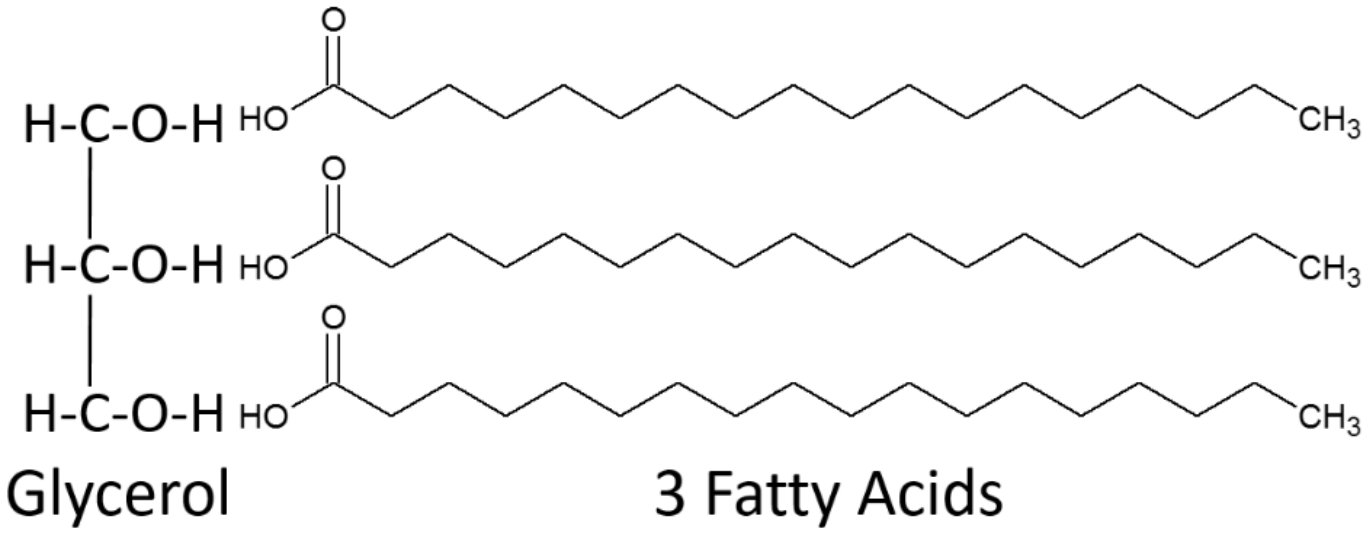


Figure 2.3.20: Triglyceride formation

When a fatty acid is added to the glycerol backbone, this process is called esterification. This process is so named because it forms an ester bond between each fatty acid and glycerol. Three molecules of water are also formed during this process as shown below.

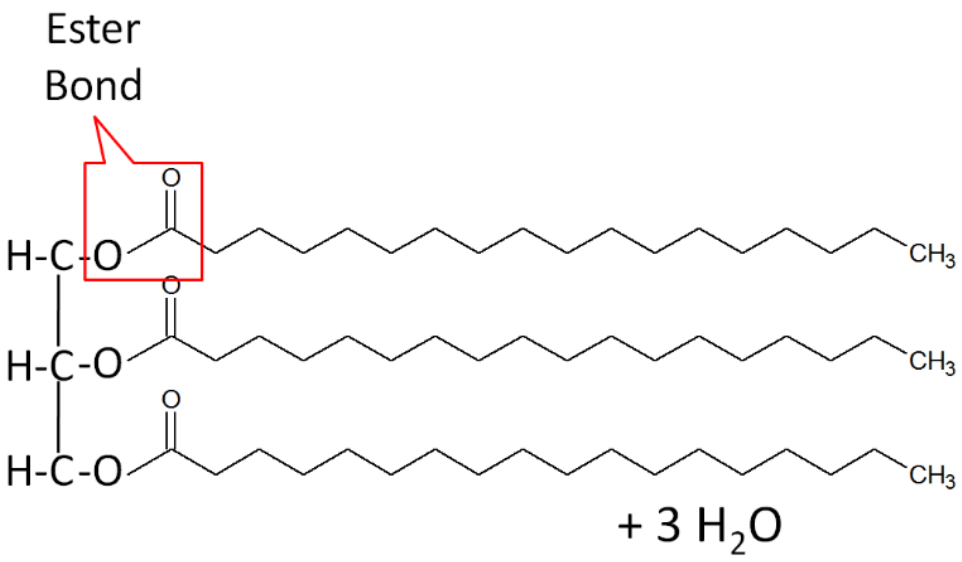


Figure 2.3.21: Esterification of three fatty acids to glycerol

A stereospecific numbering (sn) system is used to number the three fatty acids in a triglyceride sn-1, sn-2, and sn-3 respectively. A triglyceride can also be simply represented as a polar (hydrophilic) head, with 3 nonpolar (hydrophobic) tails, as shown below.

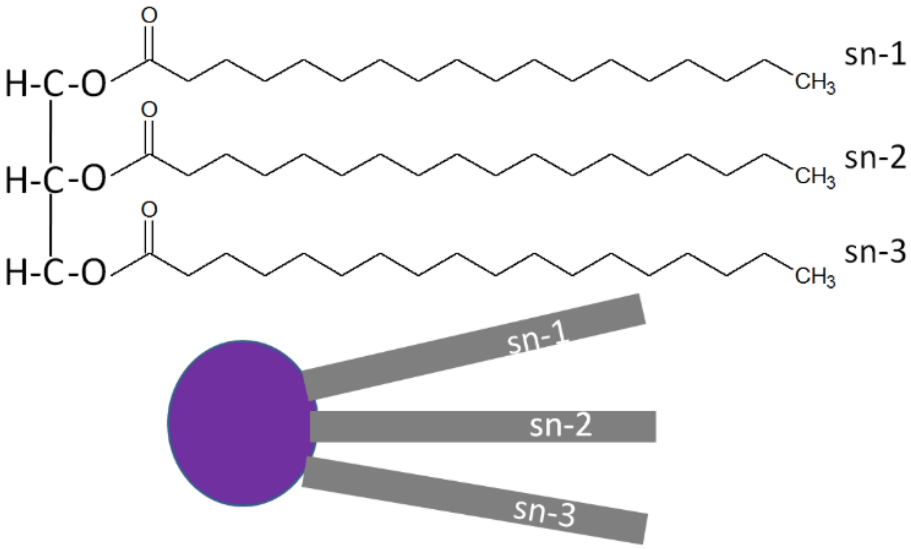


Figure 2.3.22: Stereospecific numbering (sn) of triglycerides

The three fatty acids in a triglyceride can be the same or can each be a different fatty acid. A triglyceride containing different fatty acids is known as a mixed triglyceride. An example of a mixed triglyceride is shown below.

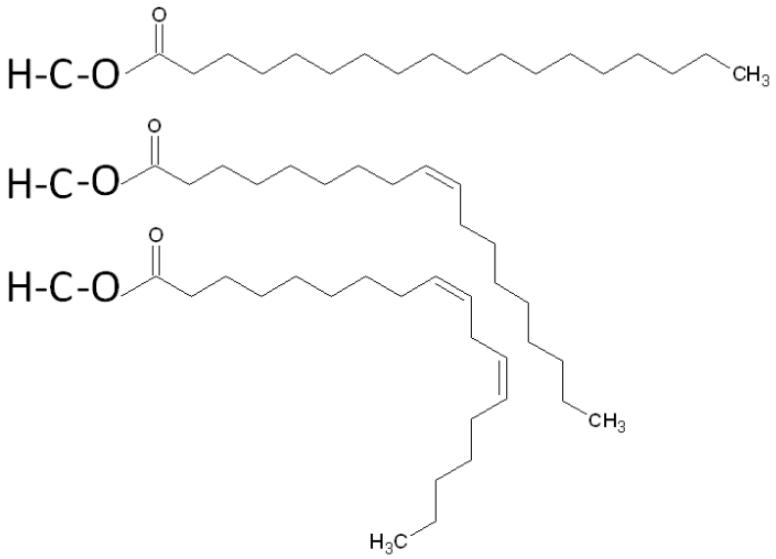


Figure 2.3.23: Structure of a mixed triglyceride

Query 2.3.15

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Phospholipids

Phospholipids are similar in structure to triglycerides, with the only difference being a phosphate group and a nitrogen-containing compound in the place of a fatty acid.

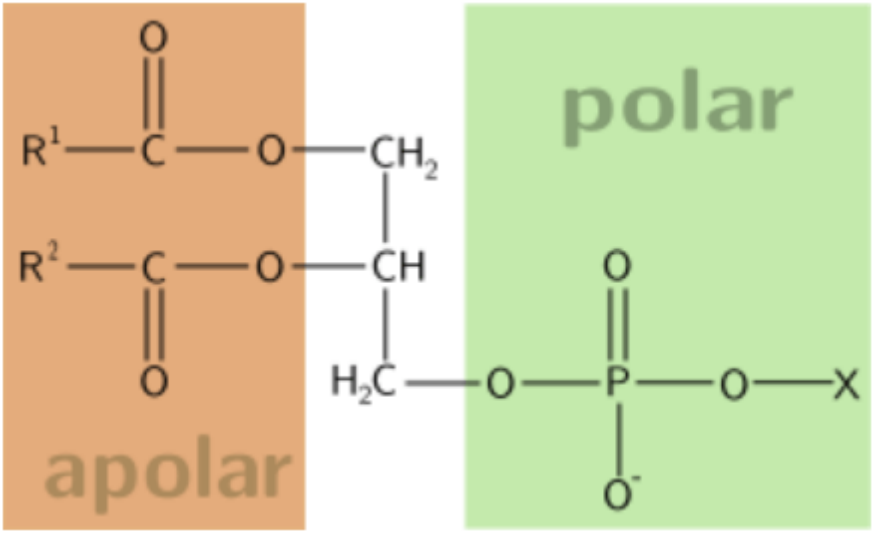


Figure 2.3.24: Structure of a phospholipid, R represents the different fatty acids, X represents the nitrogen-containing compound off of the phosphate group[19]

The best known phospholipid is phosphatidylcholine (aka lecithin). As you can see in the structure below, it contains a choline off of the phosphate group.

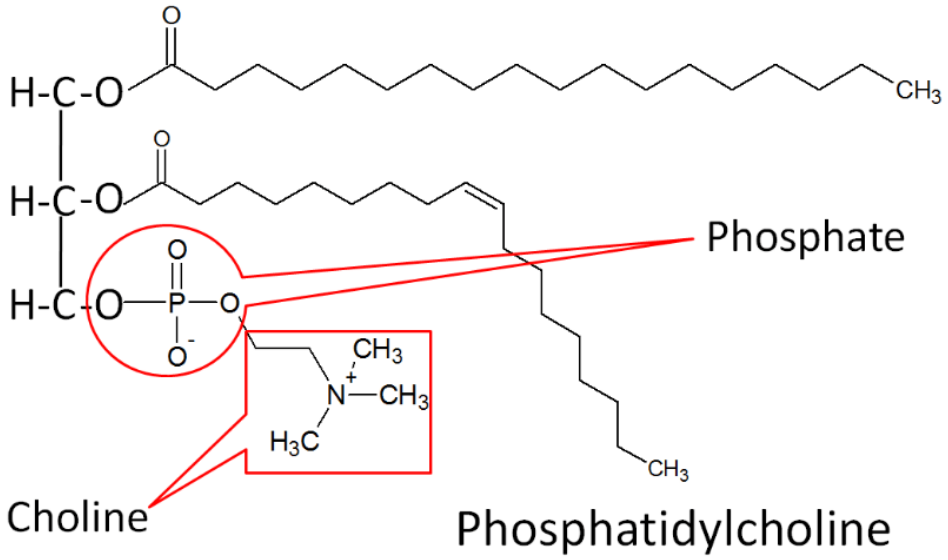


Figure 2.3.25: Structure of phosphatidylcholine (lecithin)

However, you will not normally find phospholipids arranged like a triglyceride, with the 3 tails opposite of the glycerol head. This is because the phosphate/nitrogen group of the phospholipid is polar. Thus, the structure will look like the 2 figures below.

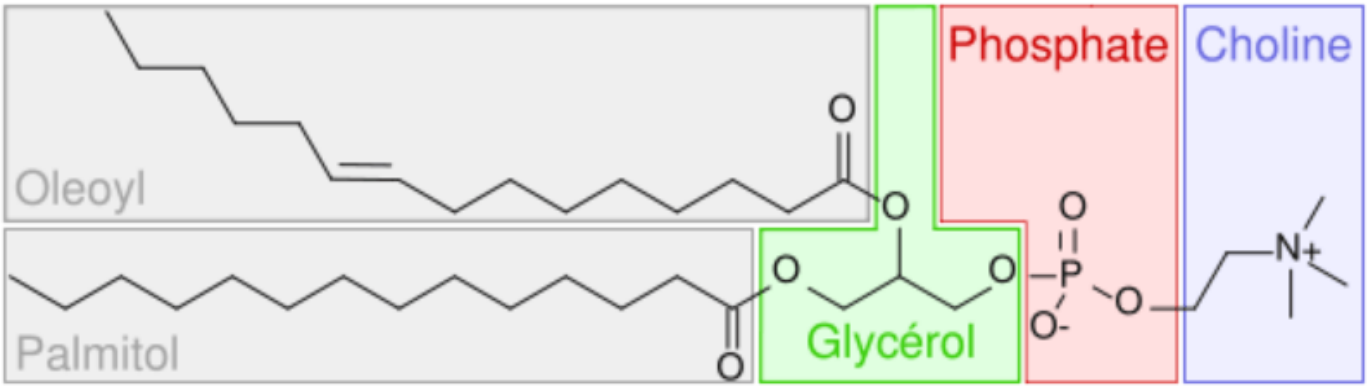


Figure 2.3.26: Structure of phosphatidylcholine (lecithin)[20]

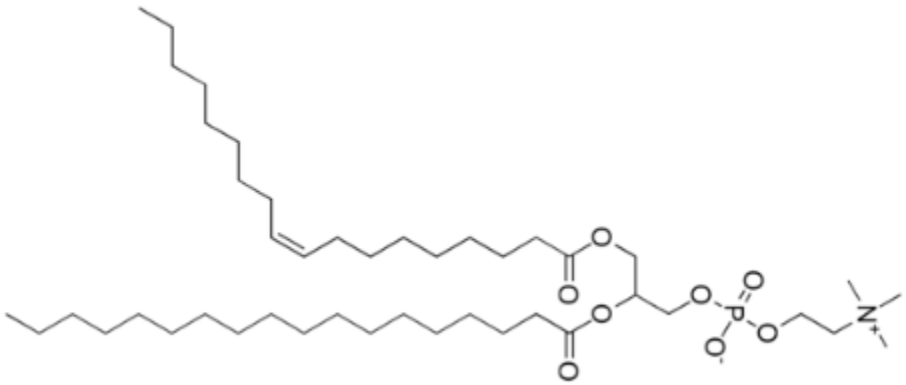


Figure 2.3.27: Structure of phosphatidylcholine (lecithin)[21]

Similar to triglycerides, phospholipids are also represented as a hydrophilic head with two hydrophobic tails as shown below.

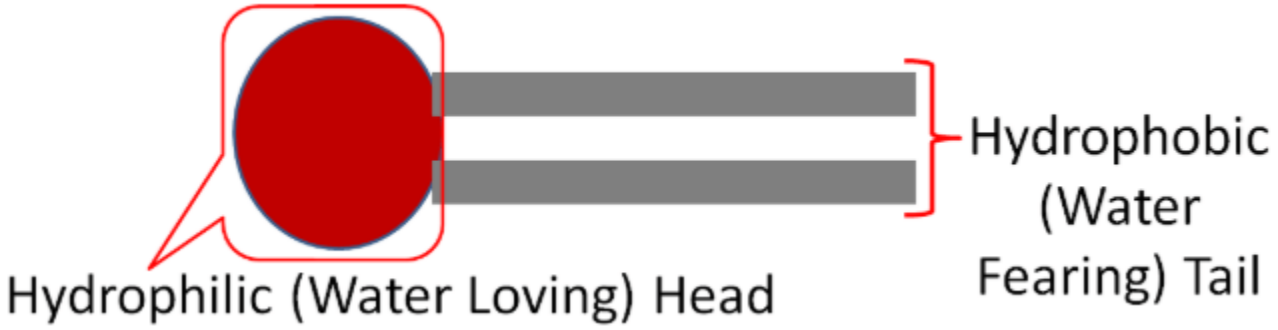


Figure 2.3.28: Schematic of a phospholipid

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Phospholipid Functions

Because its structure allows it to be at the interface of water-lipid environments, there are two main functions of phospholipids:

1. Key Component of Cells' Lipid Bilayers
2. Emulsification

Number 1 in the figure below is a cell's lipid bilayer, while 2 is a micelle that is formed by phospholipids to assist in emulsification.

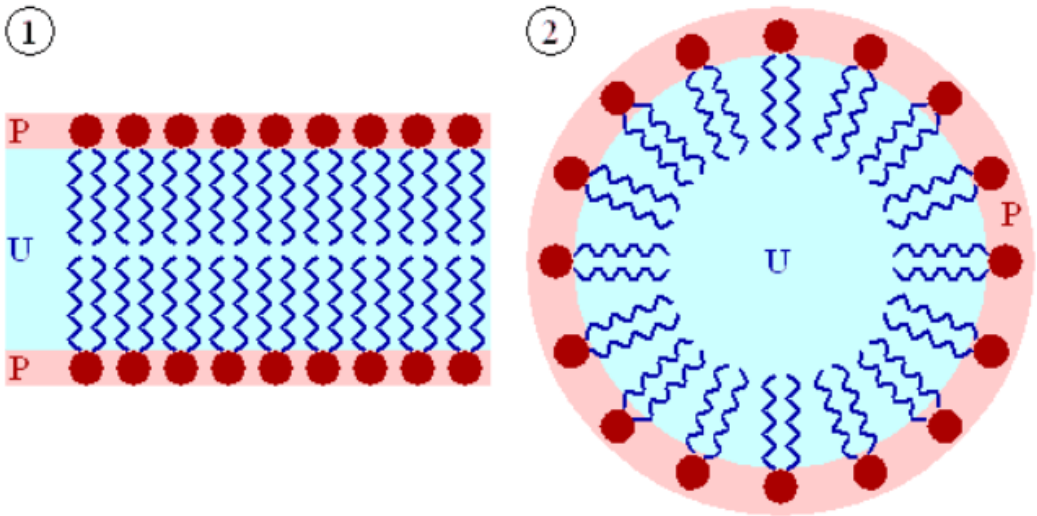


Figure 2.3.29:, 1 - lipid bilayer, 2 - micelle22

1. Key Component of Cells' Lipid Bilayers

Phospholipids are an important component of the lipid bilayers of cells. A cross section of a lipid bilayer is shown below. The hydrophilic heads are on the outside and inside of the cell; the hydrophobic tails are in the interior of the cell membrane.

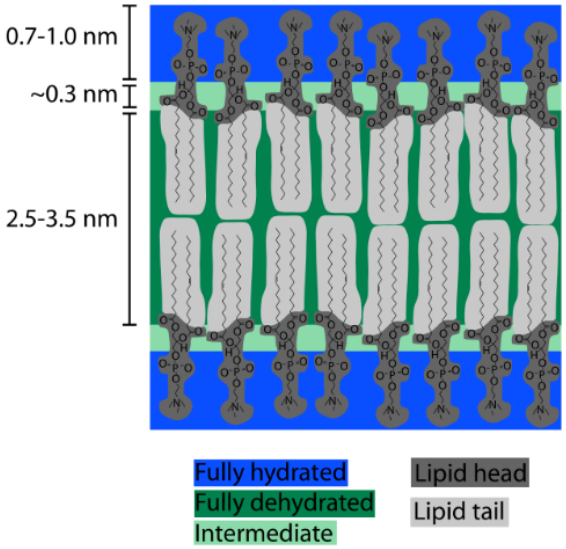


Figure 2.3.30: Phospholipids in a lipid bilayer. The blue represents the watery environment on both sides of the membrane, while the dark green represents the hydrophobic environment in between the membranes23

2. Emulsification

As emulsifiers, phospholipids help hydrophobic substances mix in a watery environment because of their amphipathic (has hydrophobic and hydrophilic) properties. It does this by forming a micelle as shown below. The hydrophobic (water fearing) substance is trapped on the interior of the micelle away from the aqueous environment.

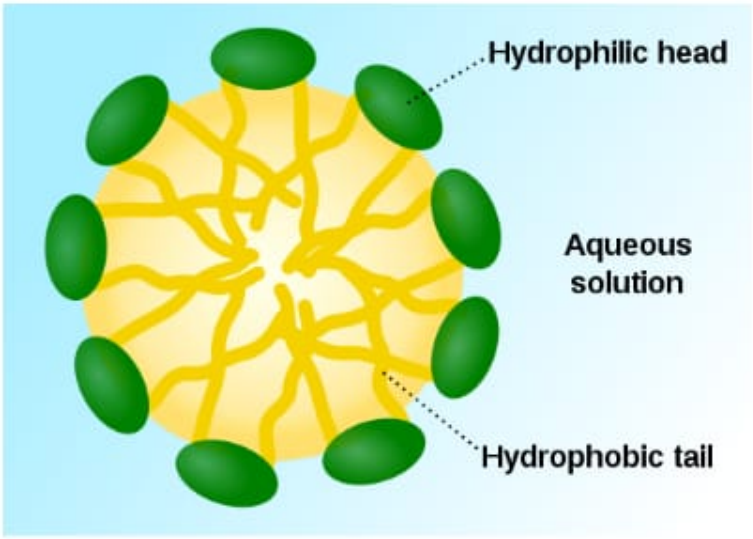


Figure 2.3.31: Structure of a micelle24

As a result, it can take a hydrophobic liquid (oil) and allow it to mix with hydrophilic (water loving) liquid (water).

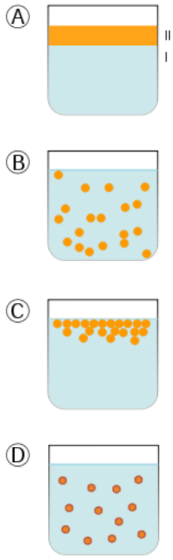


Figure 2.3.32: How an emulsion can allow the dispersion of a hydrophobic substance (II) into a hydrophilic environment (I) as shown in D25

Foods rich in phosphatidylcholine include: egg yolks, liver, soybeans, wheat germ, and peanuts8. Egg yolks serve as an emulsifier in a variety of recipes. Your body makes all the phospholipids that it needs, so they do not need to be consumed (not essential).

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Sterols

The last category of lipids are the sterols. Their structure is quite different from the other lipids because sterols are made up of a number of carbon rings. The generic structure of a sterol is shown below.

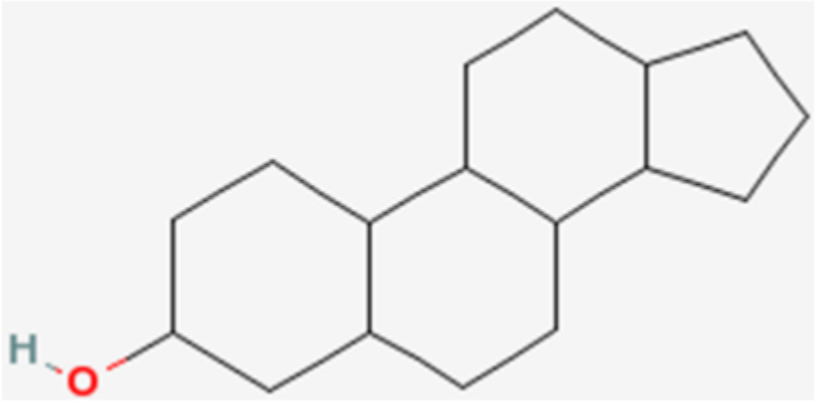


Figure 2.3.33: Generic structure of a sterol

The primary sterol that we consume is cholesterol. The structure of cholesterol is shown below.

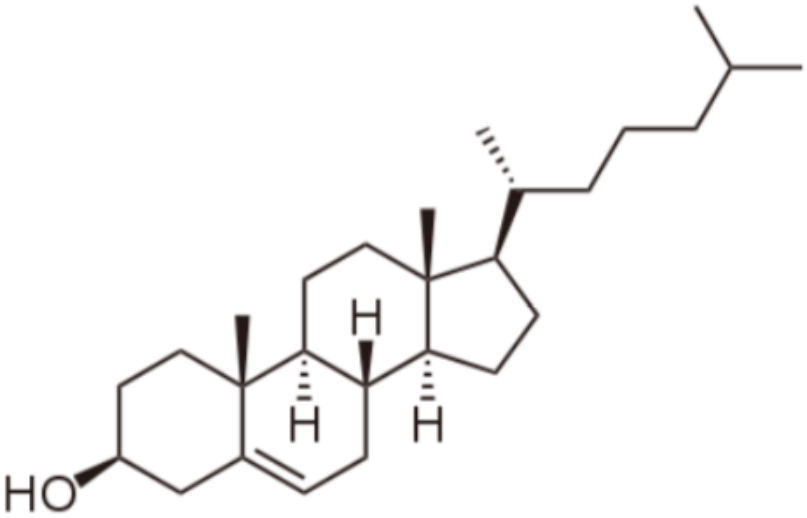


Figure 2.3.34: The carbon ring structure of cholesterol27

Cholesterol is frequently found in foods as a cholesterol ester, meaning that there is a fatty acid attached to it. The structure of a cholesterol ester is shown below.

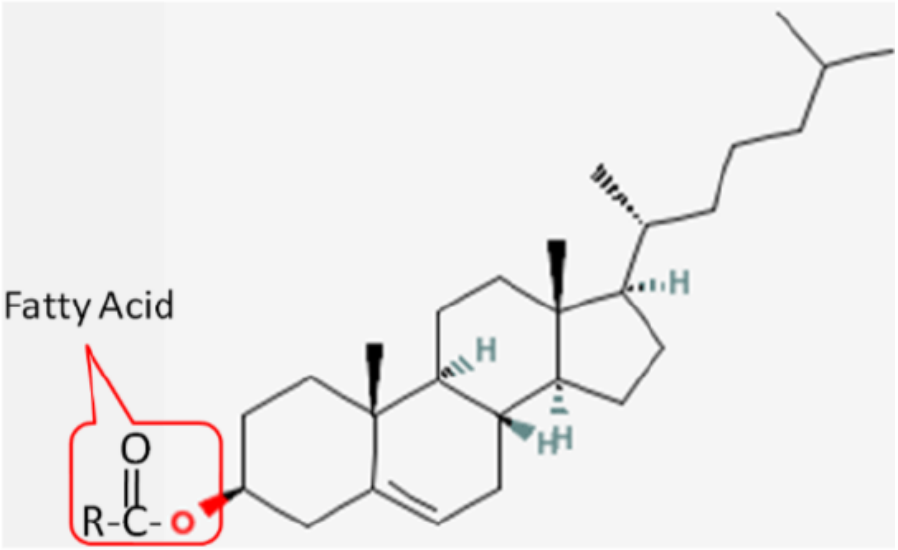


Figure 2.3.35: Structure of a cholesterol ester

All sterols have a similar structure to cholesterol. Cholesterol is only found in foods of animal origin. If consumers were more knowledgeable, intentionally misleading practices, such as labeling a banana “cholesterol free”, would not be as widespread as they currently are today.

Function

Although cholesterol has acquired the status of a nutrition "villain", it is a vital component of cell membranes and is used to produce vitamin D, hormones, and bile acids. You can see the similarity between the structures of vitamin D and estradiol, one of the forms of estrogen shown below.



Figure 2.3.36: Structures of vitamin D3 and estradiol (a form of estrogen)[28,29]

We do not need to consume any cholesterol from our diets (not essential) because our bodies have the ability to synthesize the required amounts. The figure below gives you an idea of the cholesterol content of a variety of foods.

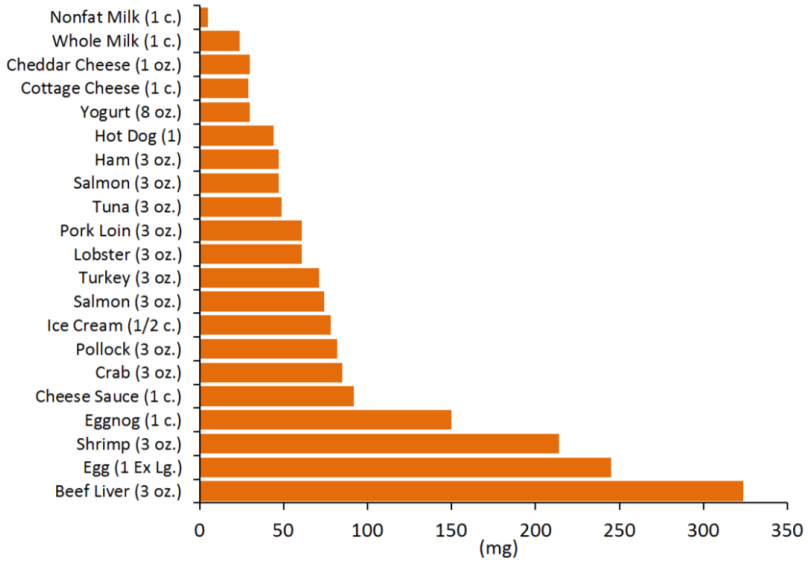


Figure 2.3.37: The cholesterol content (mg) of foods[30]

There is neither bad nor good cholesterol, despite these descriptions being commonly used for low-density lipoprotein and high-density lipoprotein, respectively. Cholesterol is cholesterol. High-density lipoprotein and low-density lipoprotein contain cholesterol but are actually lipoproteins that are described in chapter 4.

Query 2.3.18

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3: MACRONUTRIENT DIGESTION

You probably do not think too much about what actually happens to the food you eat. This section will describe in depth how what you eat is digested. The desired end result for the learner will be an integrated understanding of the process. This will require higher levels of thinking, but will prove to be well worth it in the end.

3.1: Digestion at a Glance

3.2: Mouth to the Stomach

3.3: Stomach

3.4: Small Intestine

3.5: Macronutrient Digestion Review

3.6: Large Intestine

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3.1: Digestion at a Glance

Digestion is the process of breaking down food to be absorbed or excreted. The gastrointestinal (GI, digestive) tract, the passage through which our food travels, is a "tube within a tube." The trunk of our body is the outer tube and the GI tract is the interior tube (Figure 3.1.1) Thus, even though the GI tract is within the body, the actual interior of the tract is technically outside of the body. This is because the contents have to be absorbed into the body. If it's not absorbed, it will be excreted and never enter the body itself.

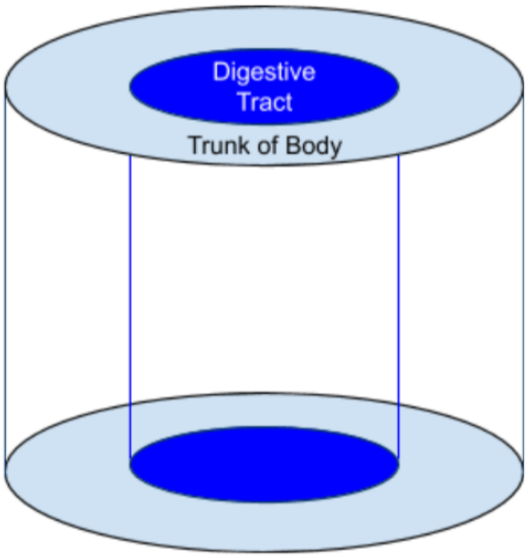


Figure 3.1.1: The digestive tract, also known as the gastrointestinal tract, is a "tube within a tube"

A number of organs are involved in digestion, which collectively are referred to as the digestive system (Figure 3.1.2).

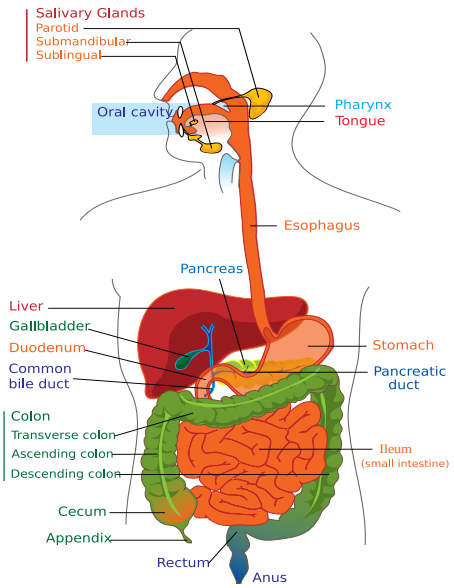


Figure 3.1.2: The digestive system. (Public Domain; via WPClipart)

The organs that form the gastrointestinal tract (mouth, pharynx, esophagus, stomach, small intestine, large intestine (aka colon), rectum, and anus) come into direct contact with the food or digestive content (Figure 3.1.3).

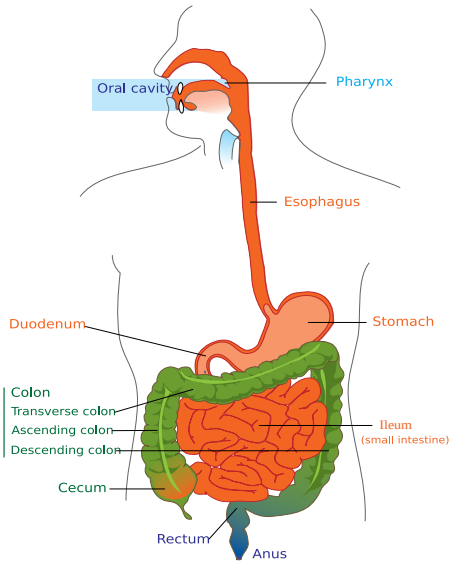


Figure 3.1.3: The gastrointestinal or digestive tract. (Public Domain; via WPClipart)

The journey through the gastrointestinal tract starts in the mouth and ends in the anus as shown below:

Mouth → Pharynx → Esophagus → Stomach → Small Intestine → Large Intestine → Rectum → Anus

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In addition to the GI tract, there are digestion accessory organs (salivary glands, pancreas, gallbladder, and liver) that play an integral role in digestion (Figure 3.1.3). The accessory organs do not come directly in contact with food or digestive content.

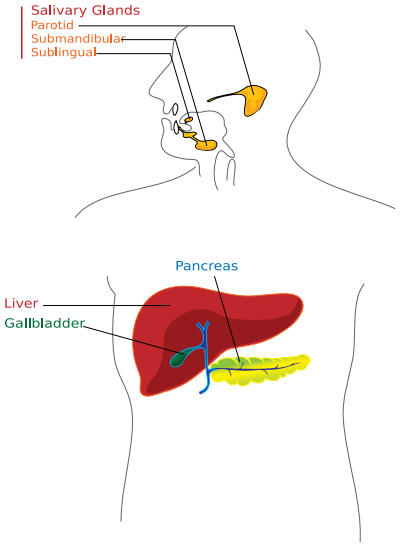


Figure 3.1.4: Digestion accessory organs. (Public Domain; via WPClipart)

There are a number of enzymes that are involved in digestion. We will go through each one in detail, but this table should help give an overview of which enzymes are active at each location of the GI tract.

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Table 3.1.1: Digestive enzymes

Location	Enzyme/Coenzyme
Mouth	Salivary amylase Lingual lipase
Stomach	Pepsin Gastric lipase

Location	Enzyme/Coenzyme
Small Intestine	Pancreatic alpha-amylase Brush border disaccharidases Pancreatic lipase Colipase Phospholipase-A2 Cholesterol esterase Proteases Brush border peptidases

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3.2: Mouth to the Stomach

Digestion begins in the mouth, both mechanically and chemically. Mechanical digestion is called mastication, which is the chewing and grinding of food into smaller pieces. The salivary glands release saliva, mucus, and the enzymes, salivary amylase, lingual lipase and lysozyme.

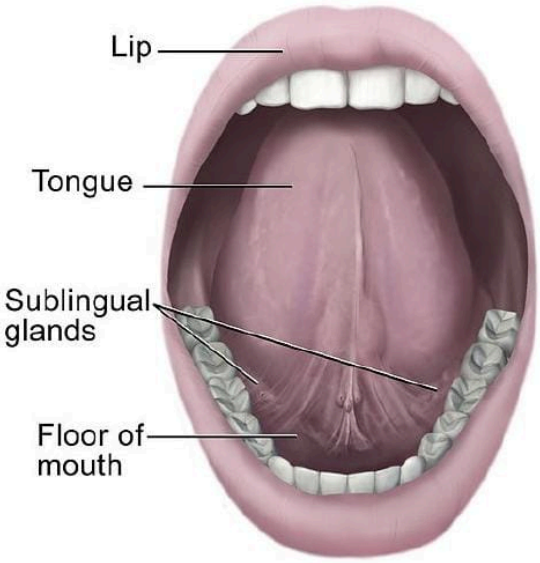


Figure 3.2.1: The mouth (public Domain; Alan Hoofring (NIH) via Wikipedia)

Salivary amylase cleaves the alpha 1-4 glycosidic bonds in the carbohydrate (typically starch) molecules, amylose and amylopectin. However, salivary amylase cannot cleave the branch points in amylopectin where there are alpha 1-6 glycosidic bonds, as shown in the figure below. Overall this enzyme accounts for a minor amount of carbohydrate digestion.

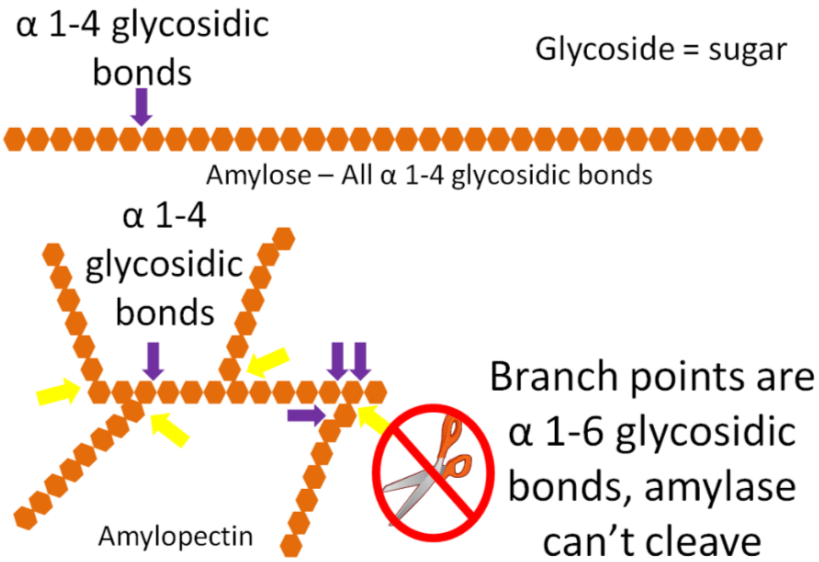


Figure 3.2.2: Enzymatic action of salivary amylase. Purple arrows point to alpha 1-4 glycosidic bonds that can be cleaved. The yellow arrows point to the alpha 1-6 glycosidic bonds that cannot be cleaved

Another enzyme, lingual lipase, is also released in the mouth. Although it is released in the mouth, it is most active in the stomach where it preferentially cleaves short-chain fatty acids in the sn-3 position of triglycerides. Lingual lipase has a small role in digestion in adults, but may be important for infants to help break down triglycerides in breast milk2. Lysozyme is a non-digestive

enzyme that breaks down bacteria cell walls to prevent a possible infection.

Query 3.2.1

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Swallowing

Now that the food has been thoroughly chewed and formed into a bolus (a ball of masticated food and saliva), it can proceed down the pharynx where it reaches a "fork in the road" with the larynx as one road and the esophagus as the other. The esophagus road leads to the stomach; this is the direction that food should go. The other road, through the larynx, leads to the trachea and ultimately the lungs. This is definitely not where you want your food or drink going, as this is the pathway for the air you breathe.

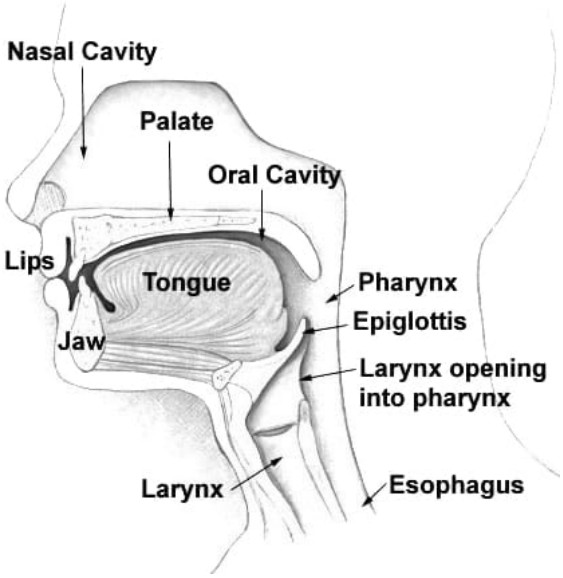


Figure 3.2.3: Cross section of face. The epiglottis covers the larynx to prevent food and drink from entering the lungs[3]

Fortunately, our body was designed in such a way that a small tissue, called the epiglottis, covers the opening to the trachea. It directs the food down the correct road as shown below.

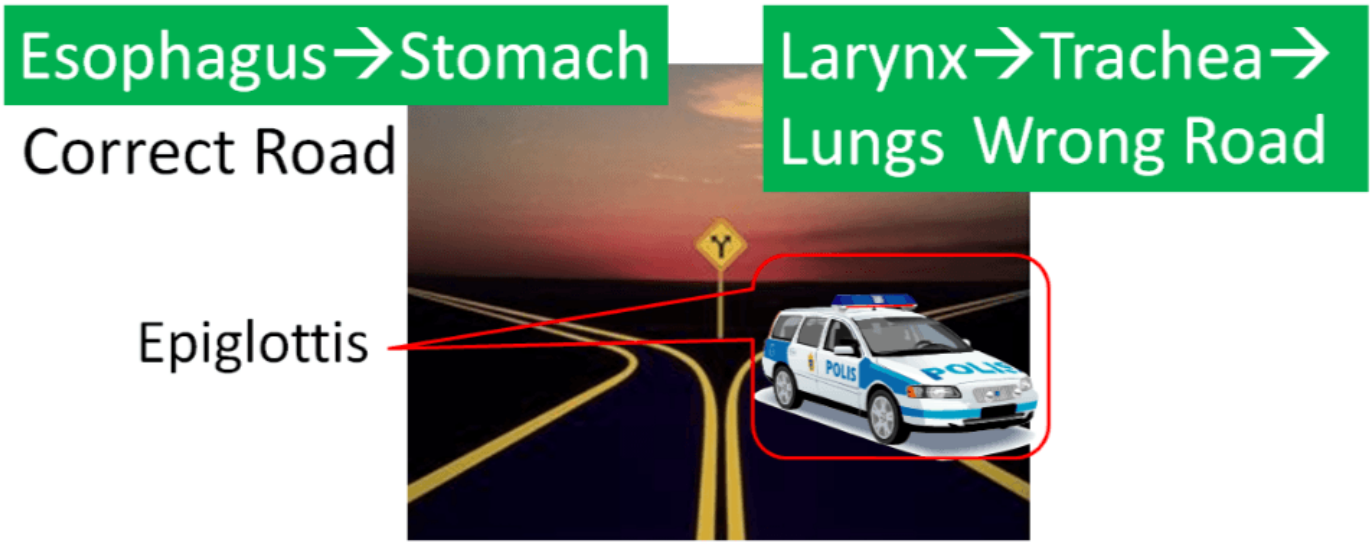


Figure 3.2.4: Epiglottis is like a traffic cop guiding food down the correct digestion road.

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Esophagus

Before being correctly guided into the esophagus, the bolus of food will travel through the upper esophageal sphincter. Sphincters are circular muscles that are found throughout the gastrointestinal tract that essentially serve as gates between the different sections. Once in the esophagus, wavelike muscular movements, known as peristalsis, occur, as shown in the following video and the animation in the link below.

YouTube Video

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Video 3.2.1: This endoscopy videoclip shows the peristalsis in the lower part of the stomach, the antrum. Peristalis is a wavelike, constant, rhytmic movement caused by muscular contraction carrying food from the stomach through the pylorus into the duodenum, which is the first part of the small bowel. https://www.youtube.com/watch?v=o18UycWRsaA

Web Link

Peristalsis Animation

Query 3.2.3

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At the end of the esophagus the bolus will encounter the lower esophageal sphincter. This sphincter keeps the harmful acids of the stomach out of the esophagus. However, in many people this sphincter is leaky, which allows stomach acid to reflux, or creep up, the esophagus. Stomach acid is very acidic (has a low pH). The ruler below will give you an idea of just how acidic the stomach is. Notice that the pH of gastric (term used to describe the stomach) fluid is lower (more acidic) than any of the listed items besides battery acid.

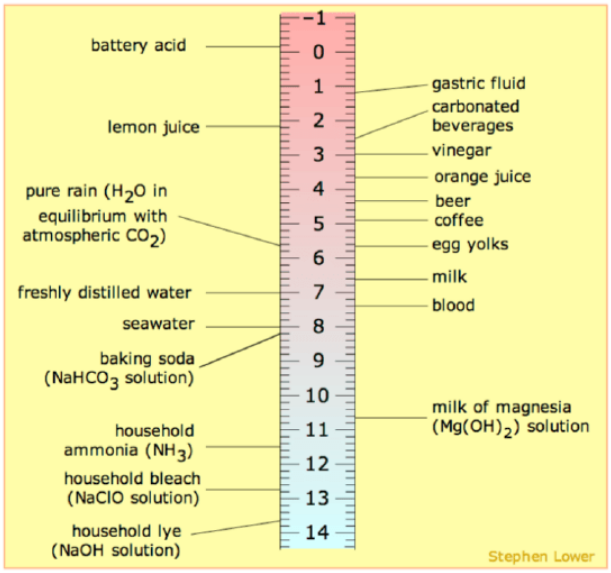


Figure 3.2.5: pH of some common items[4]

The leaking of the very acidic gastric contents results in a burning sensation, commonly referred to as "heartburn." If this occurs more than twice per week and is severe, the person may have gastroesophageal reflux disease (GERD). The following videos explain more about these conditions.

YouTube Video

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Video 3.2.2: Gastro Esophageal Reflux Disease (GERD) or Acid Reflux is an abnormal reflux (Backflow) of gastric contents into the esophagus, creating a mucosal damage. https://www.youtube.com/watch?v=SW-QfyDSY5I

YouTube Video

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Video 3.2.3: What on earth is GERD and what does it have to do with you? https://www.youtube.com/watch?v=FqdOvZkrSYk&feature=rec-lis-watch-cur_emp-farside_rn

Table 3.2.1: Review of Chemical Digestion in the Mouth

Macronutrient	Action
Carbohydrates	Salivary amylase cleaves 1,4-glycosidic bonds
Lipids	Release of lingual lipase
Protein	None

Query 3.2.4

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4. upload.wikimedia.org/wikipedi...6/PH_scale.png

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3.3: Stomach

After going through the lower esophageal sphincter, food enters the stomach. Our stomach is involved in both chemical and mechanical digestion. Mechanical digestion occurs as the stomach churns and grinds food into a semifluid substance called chyme (partially digested food).

The lining of the stomach is made up of different layers of tissue. The mucosa is the layer closest to stomach cavity as shown in the figure below.

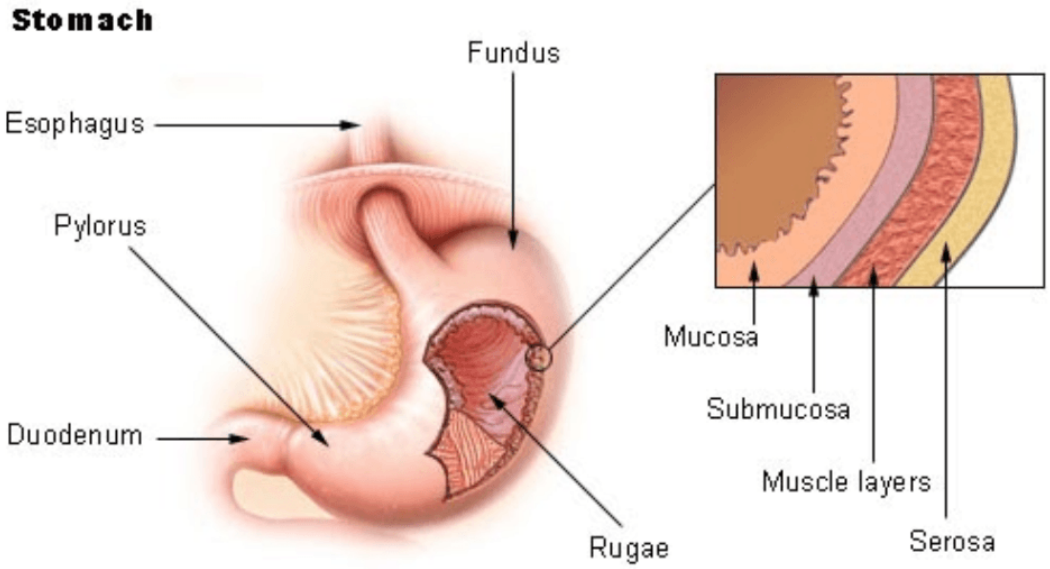


Figure 3.3.1: The anatomy of the stomach[1]

Query 3.3.1

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The mucosa is not a flat surface. Instead, its surface is lined by gastric pits, as shown in the figure below.

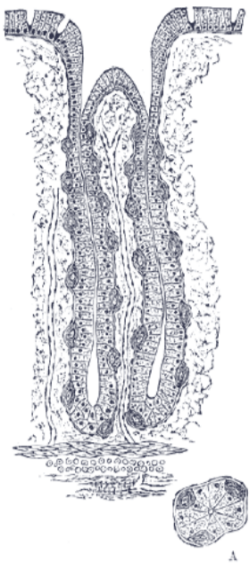


Figure 3.3.2: Gastric pits2

Gastric pits are indentations in the stomach's surface that are lined by four different types of cells.

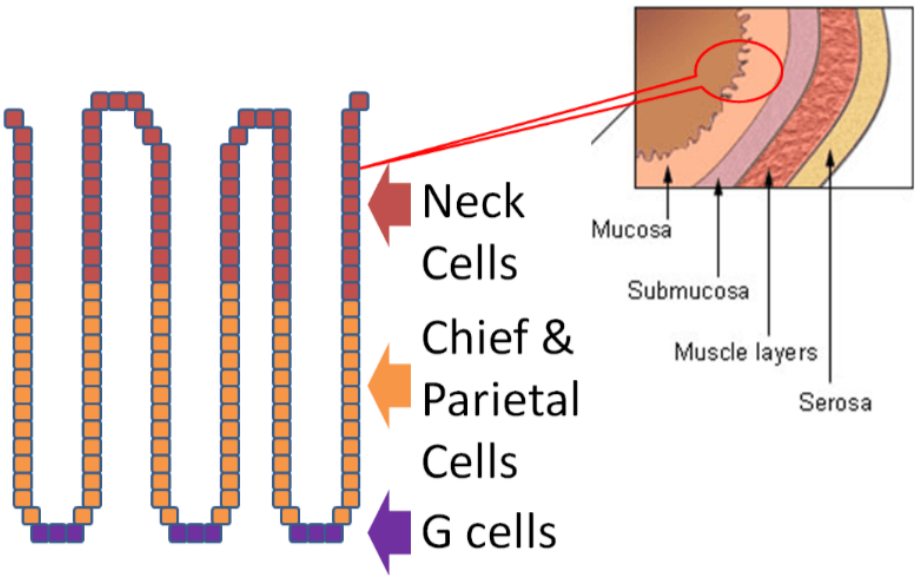


Figure 3.3.3: Blowup of mucosa to show the structure of gastric pits1

The following video is a nice introduction to gastric pits and talks about chief and parietal cells that are described in more detail below.

YouTube Video

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Video 3.3.1: Cells in the gastric pits of the stomach. https://www.youtube.com/watch?v=6hquzCXYlNg

At the bottom of the gastric pit are the G cells that secrete the hormone gastrin. Gastrin stimulates the parietal and chief cells that are found above the G cells. The chief cells secrete the zymogen pepsinogen and the enzyme gastric lipase. A zymogen is an inactive protein that must be cleaved or altered to form the active protein. The parietal cells secrete hydrochloric acid (HCl), which lowers the pH of the gastric juice (water + enzymes + acid). Hydrochloric acid inactivates salivary amylase and catalyzes the conversion of pepsinogen to pepsin. Finally, the top of the pits are the neck cells that secrete mucus to prevent the gastric juice from digesting or damaging the stomach mucosa3. The table below summarizes the actions of the different cells in the gastric pits.

Table 3.3.1: Cells involved in the digestive processes in the stomach

Type of Cell	Secrete
Neck	Mucus
Chief	Pepsinogen and gastric lipase
Parietal	Hydrochloric acid
G	Gastrin

The figure below shows the action of all these different secretions in the stomach.

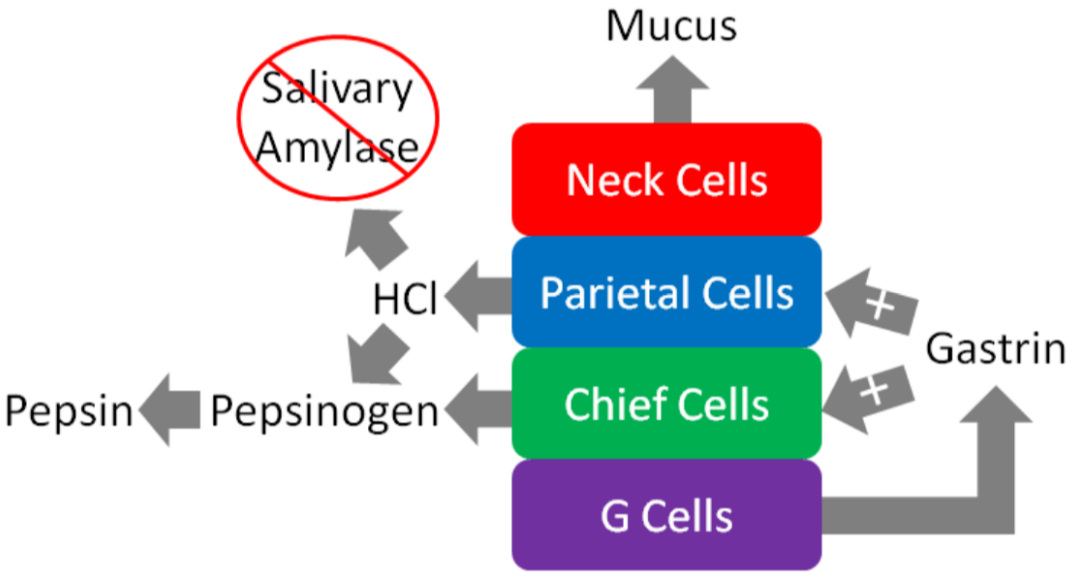


Figure 3.3.4: The action of gastric secretions in the stomach

To reiterate, the figure above illustrates that the neck cells of the gastric pits secrete mucus to protect the mucosa of the stomach from essentially digesting itself. Gastrin from G cells stimulates the parietal and chief cells to secrete hydrochloric acid and enzymes, respectively.

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Hydrochloric acid in the stomach denatures salivary amylase and other proteins by breaking down the structure and, thus, the function of it. Hydrochloric acid also converts pepsinogen to the active enzyme pepsin. Pepsin is a protease, meaning that it cleaves bonds in proteins. It breaks down the proteins in food into individual peptides (shorter segments of amino acids). The other enzyme that is active in the stomach is gastric lipase. This enzyme preferentially cleaves the sn-3 position of triglycerides to produce 1,2-diglyceride and a free fatty acid, as shown below[4]. It is responsible for up to 20% of triglyceride digestion[3].

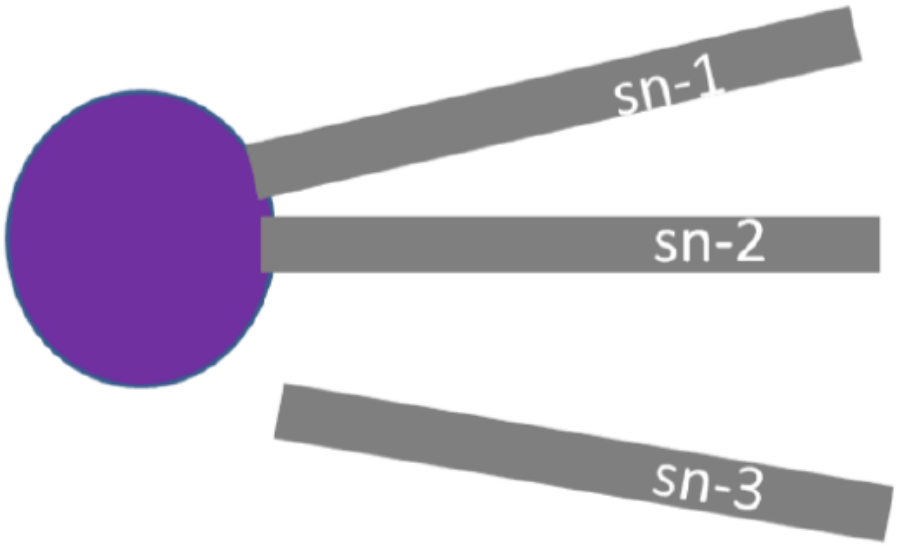


Figure 3.3.5: Gastric Lipase action results in production of 1,2-diglyceride and a free fatty acid

The chyme will then leave the stomach and enter the small intestine via the pyloric sphincter (shown below).

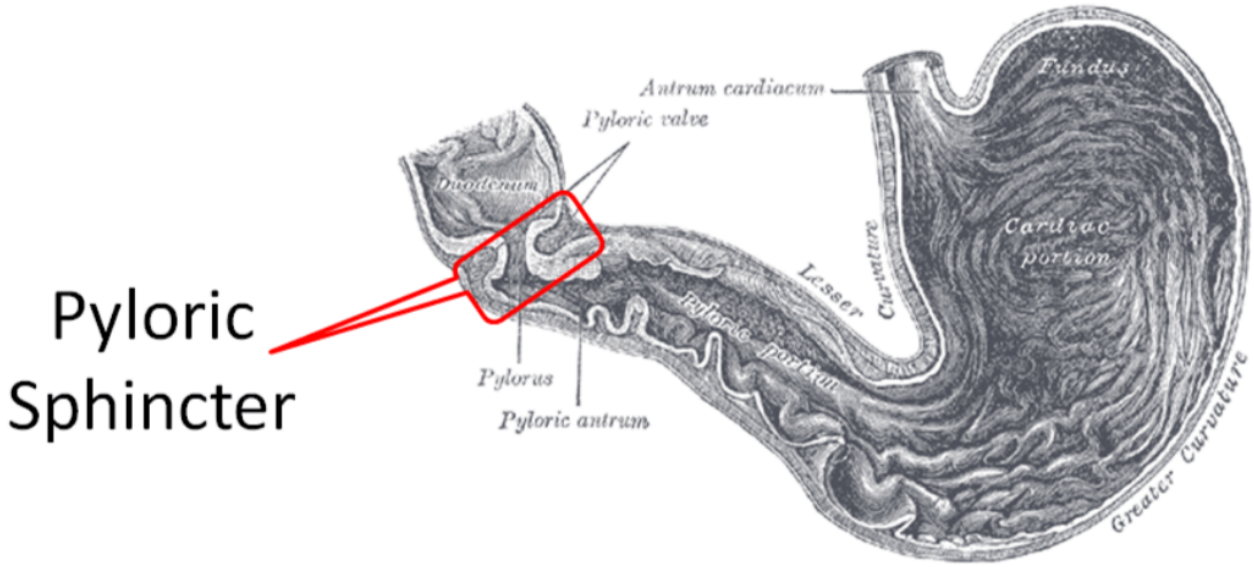


Figure 3.3.6: Cross section of the stomach showing the pyloric sphincter[5]

Table 3.3.2: Summary of chemical digestion in the stomach

Chemical or Enzyme	Action
Gastrin	Stimulates chief cells to release pepsinogen Stimulates parietal cells to release HCl

Chemical or Enzyme	Action
HCl	Denatures salivary amylase Denatures proteins Activates pepsinogen to pepsin
Pepsin	Cleaves proteins to peptides
Gastric lipase	Cleaves sn-3 FA of triglycerides

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References

1. https://en.Wikipedia.org/wiki/Stomac...u_stomach2.jpg
2. http://en.Wikipedia.org/wiki/File:Gray1055.png
3. Gropper SS, Smith JL, Groff JL. (2008) Advanced nutrition and human metabolism. Belmont, CA: Wadsworth Publishing.
4. Stipanuk MH. (2006) Biochemical, physiological, & molecular aspects of human nutrition. St. Louis, MO: Saunders Elsevier.
5. https://en.Wikipedia.org/wiki/Pyloru...e:Gray1050.png

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3.4: Small Intestine

The small intestine is the primary site of digestion. It is divided into three sections: the duodenum, jejunum, and ileum (shown below). After leaving the stomach, the first part of the small intestine that chyme will encounter is the duodenum.

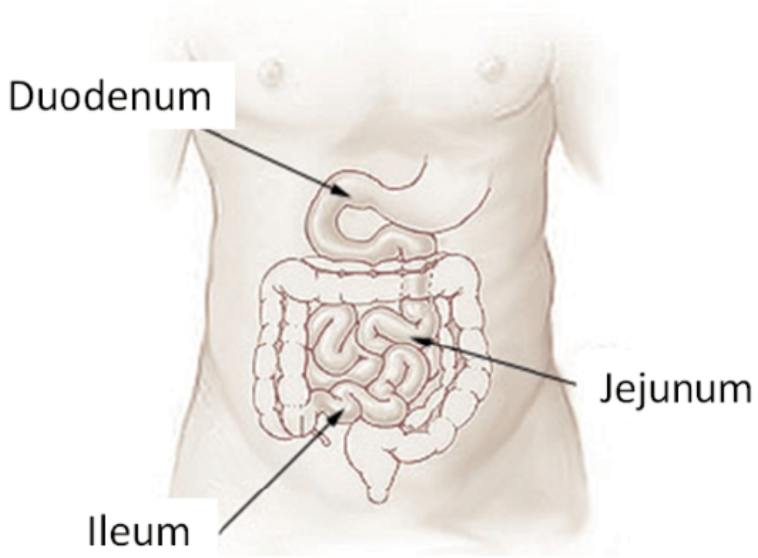


Figure 3.4.1: Three sections of the small intestine[1]

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The small intestine consists of many layers, which can be seen in the cross section below.

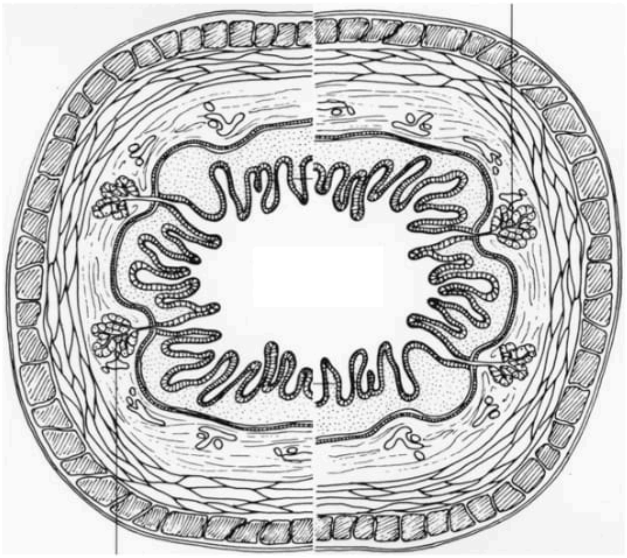


Figure 3.4.2: Cross section of the small intestine2

Examining these layers closer, we are going to focus on the epithelium, which comes into contact with the chyme and is responsible for absorption. The lumen is the name of the cavity that is considered “outside the body” that chyme moves through.

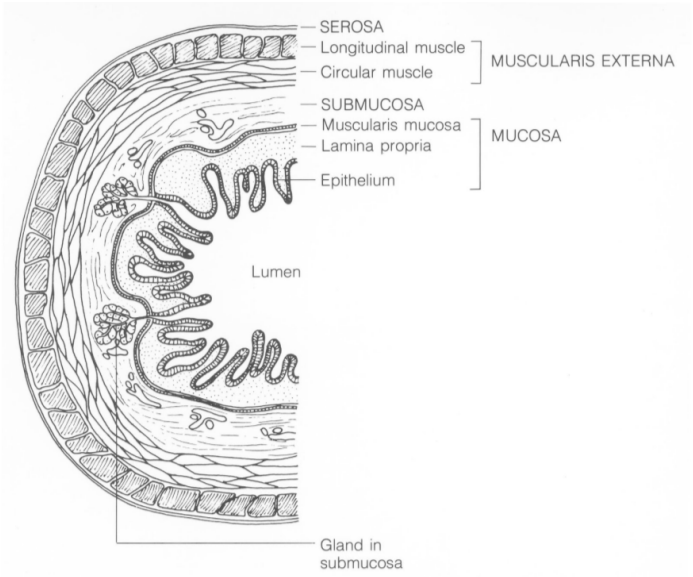


Figure 3.4.3: Cross section of small intestine with the structures labeled2

The organization of the small intestine is in such a way that it contains circular folds and finger-like projections known as villi. The folds and villi are shown in the next few figures.

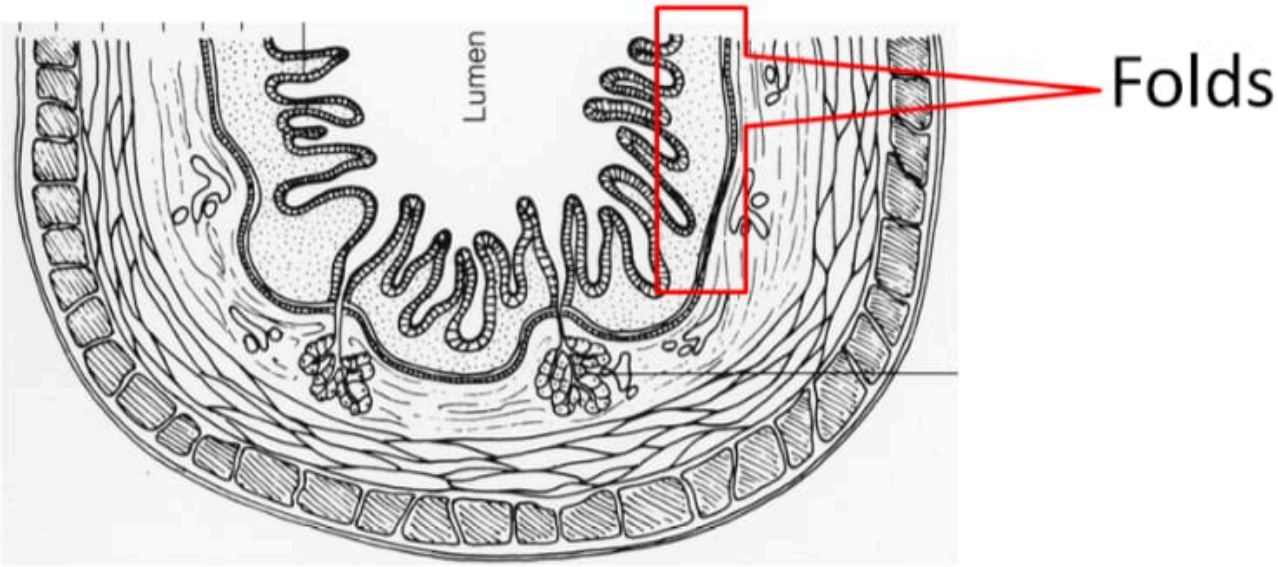


Figure 3.4.4: Folds in the small intestine2

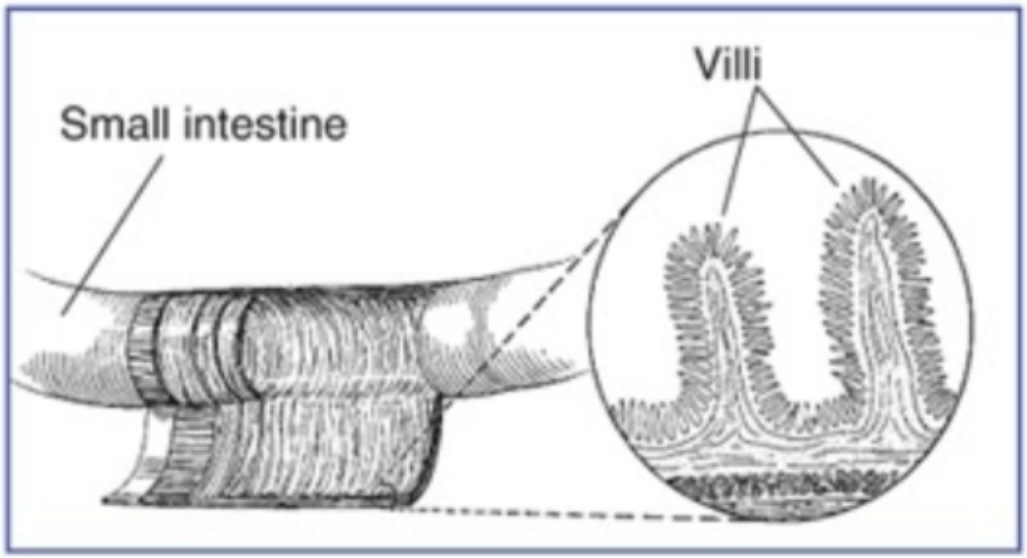


Figure 3.4.5: Villi in the small intestine3

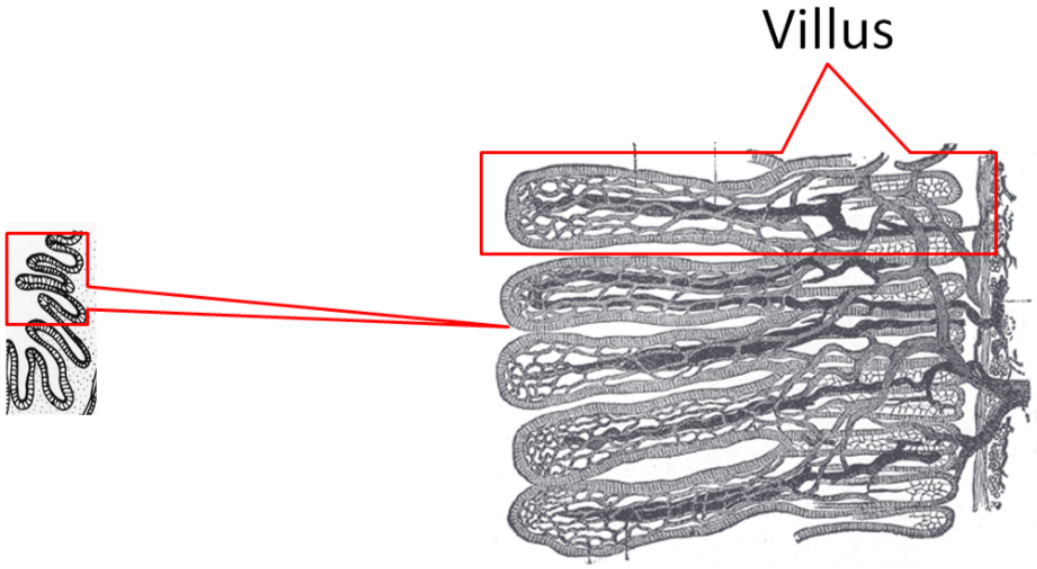


Figure 3.4.6: Villi line the surface of the small intestine2,4

If we were to zoom in even closer, we would be able to see that enterocytes (small intestine absorptive cells) line villi as shown below.

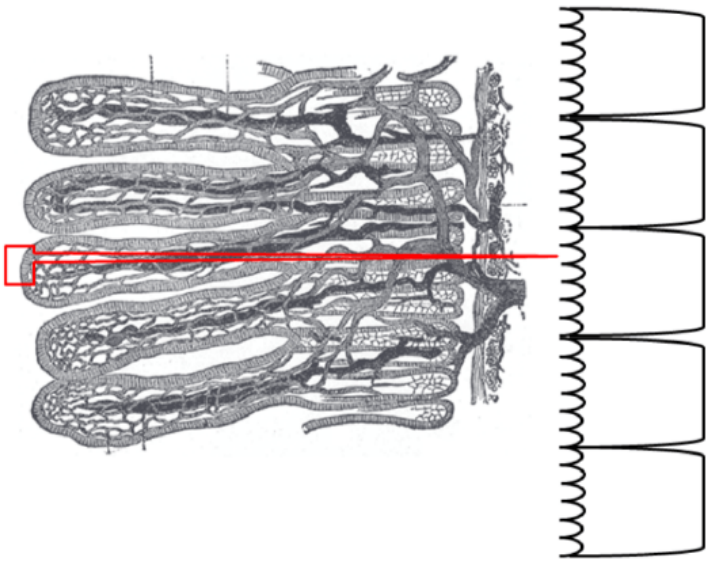


Figure 3.4.7: Enterocytes line villi4

The side, or membrane, of the enterocyte that faces the lumen is not smooth either. It is lined with microvilli, and is known as the brush border (aka apical) membrane, as shown below.

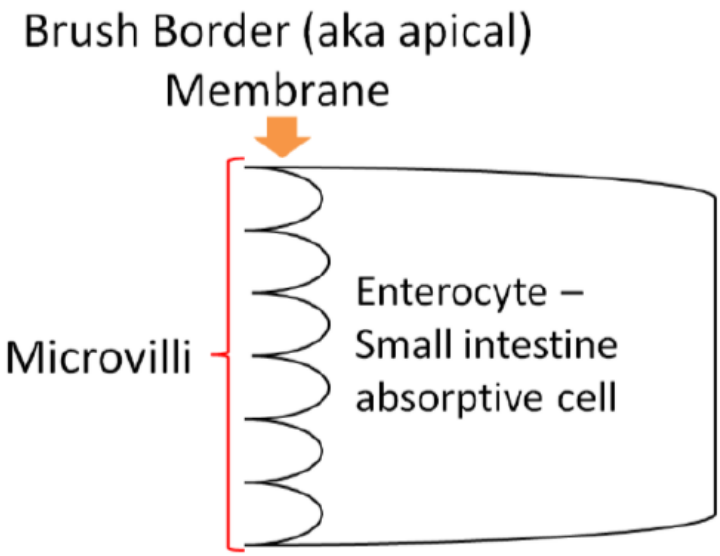


Figure 3.4.8: Enterocyte, or small intestinal absorptive cell is lined with microvilli. This lined surface is referred to as the brush border membrane.

Together these features (folds + villi + microvilli) increase the surface area ~600 times versus if it was a smooth tube5. More surface area leads to more contact with the enterocytes and thus, increased absorption.

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Going even closer, we discover that the surface of the microvilli is covered by the hair-like glycocalyx, which is made up of glycoproteins (proteins with carbohydrates attached to them) and carbohydrates as shown below.

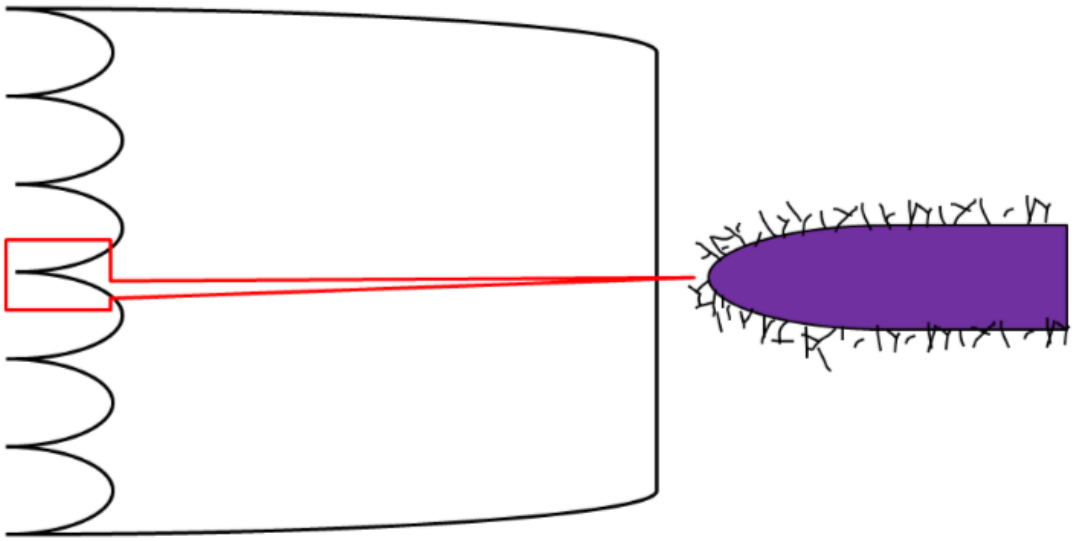


Figure 3.4.9: Glycocalyx lines the microvilli

Now that you have learned about the anatomy of the small intestine, the following subsections go through the different digestive processes that occur there.

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Digestive Hormones, Accessory Organs & Secretions

Before we go into the digestive details of the small intestine, it is important that you have a basic understanding of the anatomy and physiology of the following digestion accessory organs: pancreas, liver, and gallbladder. Digestion accessory organs assist in digestion, but are not part of the gastrointestinal tract. How are these organs involved?

Upon entering the duodenum, chyme causes the release of two hormones from the small intestine: secretin and cholecystokinin (CCK, previously known as pancreozymin) in response to acid and fat, respectively. These hormones have multiple effects on different tissues. In the pancreas, secretin stimulates the secretion of bicarbonate (HCO_3), while CCK stimulates the secretion of digestive enzymes. The bicarbonate and digestive enzymes released together are collectively known as pancreatic juice, which travels to the small intestine, as shown below.

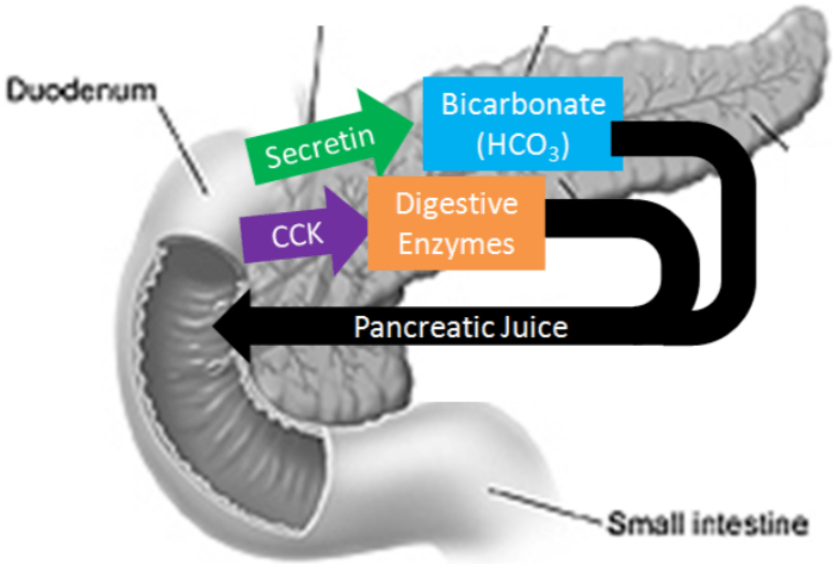


Figure 3.4.10: The hormones secretin and CCK stimulate the pancreas to secrete pancreatic juice6

In addition, CCK also stimulates the contraction of the gallbladder causing the secretion of bile into the duodenum.

Pancreas

The pancreas is found behind the stomach and has two different portions. It has an endocrine (hormone-producing) portion that contains alpha and beta cells that secrete the hormones glucagon and insulin, respectively. However, the vast majority of the pancreas is made up of acini that are responsible for producing pancreatic juice. The following video does a nice job of showing and explaining the function of the different pancreatic cells.

YouTube Video

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Video 3.4.1: The pancreas is shown here with the foreground highly magnified to reveal its inner anatomy. Ninety-nine percent of pancreatic tissue is composed of acinar glands, which secrete an alkaline digestive juice into the duodenum via the pancreatic duct to help digest food. The endocrine areas of the pancreas, known as the islets of Langerhans, are composed of two major types of cell. The alpha cells secrete the hormone glucagon, and the beta cells secrete insulin, into the bloodstream. https://www.youtube.com/watch?v=j5WF8wUFNkI

Video: How the Body Works - The Pancreas.

Bicarbonate is a base (high pH) meaning that it can help neutralize acid. You can find sodium bicarbonate ($NaHCO_3$, baking soda) on the ruler below to get an idea of its pH.

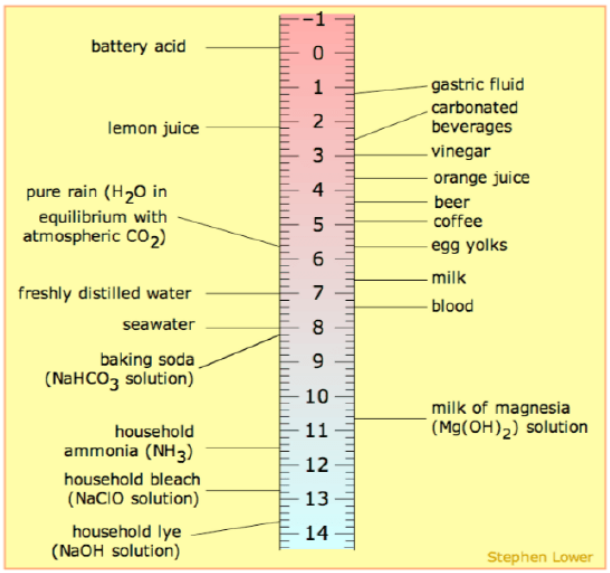


Figure 3.4.11: pH of some common items[7]

The main digestive enzymes in pancreatic juice are listed in the table below. Their function will be discussed further in later subsections.

Table 3.4.1: Enzymes in pancreatic juice

Enzyme
Pancreatic alpha-amylase
Proteases
Pancreatic Lipase & Procolipase*
Phospholipase A2
Cholesterol Esterase

*Not an enzyme

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Liver

The liver is the largest internal and most metabolically active organ in the body. The figure below shows the liver and the accessory organs position relative to the stomach.

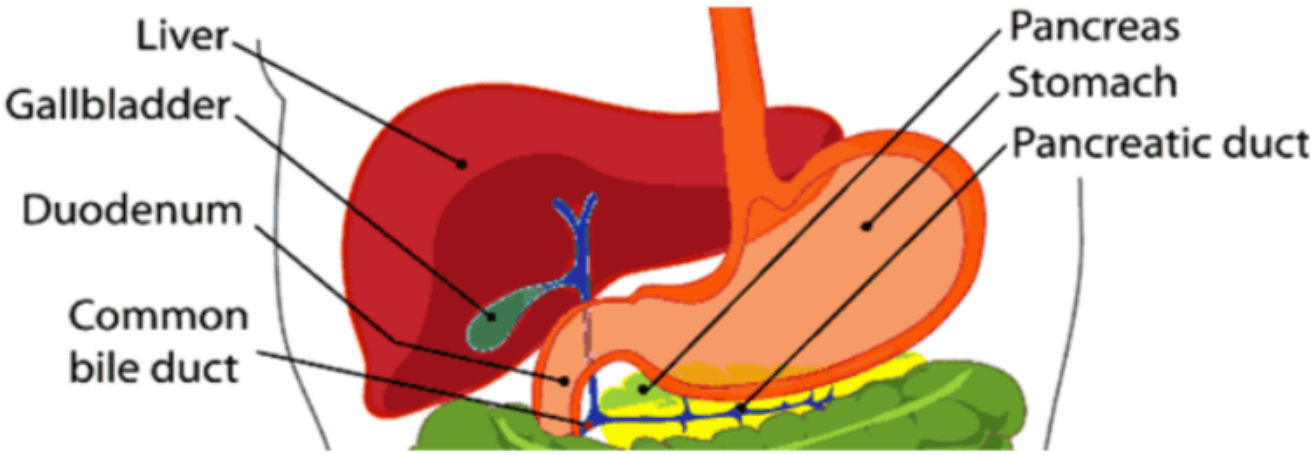


Figure 3.4.12: Location of digestion accessory organs relative to the stomach[8]

The liver is made up of two major types of cells. The primary liver cells are hepatocytes, which carry out most of the liver's functions. Hepatic is another term for liver. For example, if you are going to refer to liver concentrations of a certain nutrient, these are often reported as hepatic concentrations. The other major cell type are hepatic stellate (also known as Ito) cells. These are lipid storing cells in the liver. These two cell types are depicted below.

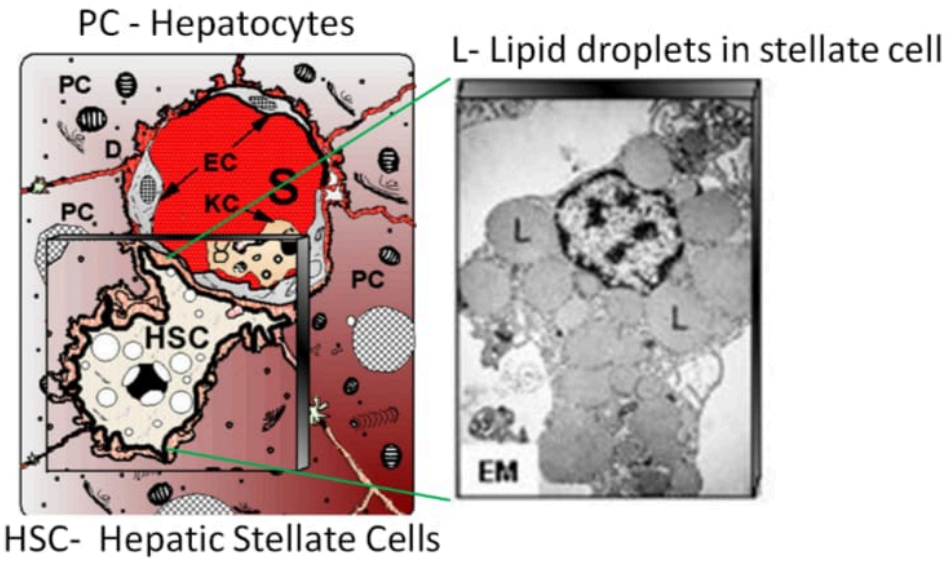


Figure 3.4.13: Hepatocytes (PC) and hepatic stellate cells (HSC) along with an electron microscope image showing the lipid droplets within a stellate cell[9]

The liver's major role in digestion is to produce bile. This is a greenish-yellow fluid that is composed primarily of bile acids, but also contains cholesterol, phospholipids, and the pigments bilirubin and biliverdin. Bile acids are synthesized from cholesterol. The two primary bile acids are chenodeoxycholic acid and cholic acid. In the same way that fatty acids are found in the form of salts, these bile acids can also be found as salts. These salts have an (-ate) ending, as shown below.

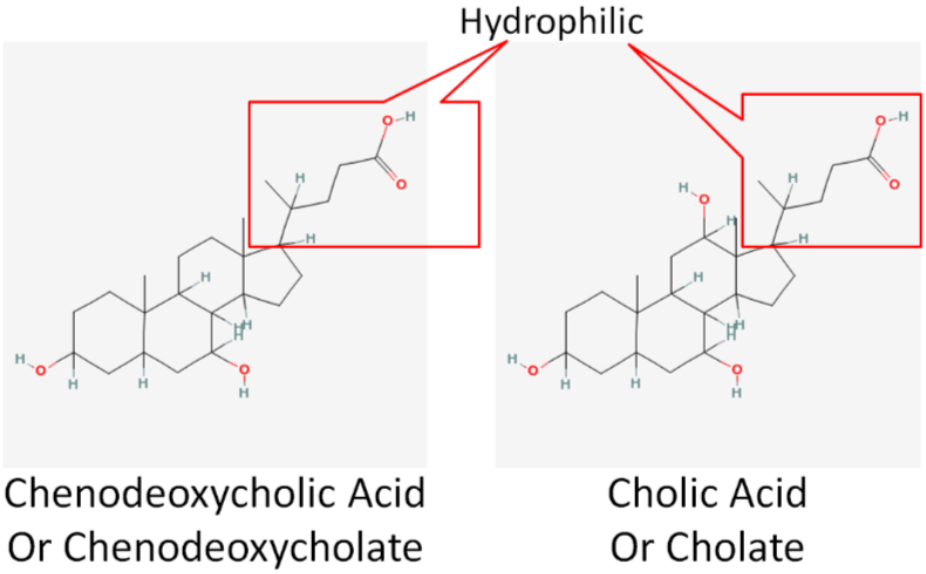


Figure 3.4.14: Structures of the 2 primary bile acids

Bile acids, much like phospholipids, have a hydrophobic and hydrophilic end. This makes them excellent emulsifiers that are instrumental in fat digestion. Bile is then transported to the gallbladder.

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Gallbladder

The gallbladder is a small sac-like organ found just off the liver (see figures above). Its primary function is to store and concentrate bile made by the liver. The bile is then transported to the duodenum through the common bile duct.

Why do we need bile?

Bile is important because fat is hydrophobic and the environment in the lumen of the small intestine is watery. In addition, there is an unstirred water layer that fat must cross to reach the enterocytes in order to be absorbed.



Figure 3.4.15: Fat is not happy alone in the watery environment of the small intestine.

Here triglycerides form large triglyceride droplets to keep the interaction with the watery environment to a minimum. This is inefficient for digestion, because enzymes cannot access the interior of the droplet. Bile acts as an emulsifier. It, along with phospholipids, form smaller triglyceride droplets that increase the surface area that is accessible for triglyceride digestion enzymes, as shown below.

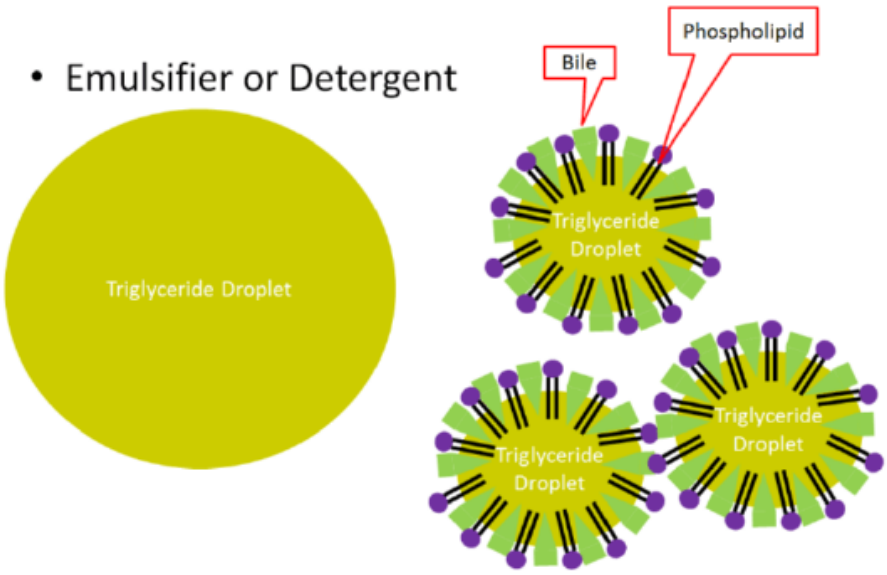


Figure 3.4.16: Bile acids and phospholipids facilitate the production of smaller triglyceride droplets.

The following video does a nice job of showing and explaining what bile does.

YouTube Video

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Video 3.4.2: In this video I discuss what bile is, and its main functions in fat digestion, red blood cell recycling, and cholesterol removal. https://www.youtube.com/watch?v=XvqsUZXtwE8&feature=youtu.be

Secretin and CCK also control the production and secretion of bile. Secretin stimulates the flow of bile from the liver to the gallbladder. CCK stimulates the gallbladder to contract, causing bile to be secreted into the duodenum, as shown below.

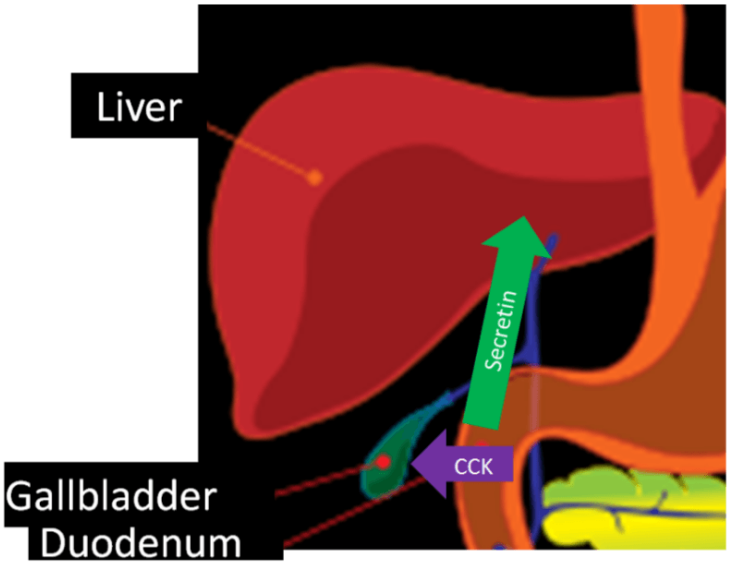


Figure 3.4.17: Secretion stimulates bile flow from the liver; CCK stimulates the gallbladder to contract[8]

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Carbohydrate Digestion in the Small Intestine

The small intestine is the primary site of carbohydrate digestion. Pancreatic alpha-amylase is the primary carbohydrate digesting enzyme. Pancreatic alpha-amylase, like salivary amylase, cleaves the alpha 1-4 glycosidic bonds of carbohydrates, reducing them to simpler carbohydrates, such as glucose, maltose, maltotriose, and dextrins (oligosaccharides containing 1 or more alpha 1-6 glycosidic bonds). Pancreatic alpha-amylase is also unable to cleave the branch point alpha 1-6 bonds[10].

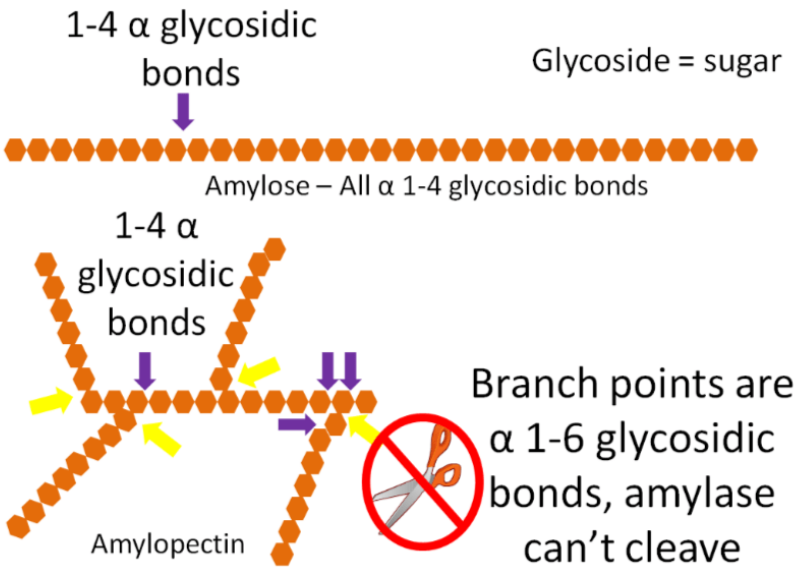


Figure 3.4.18: The function of pancreatic alpha-amylase



Figure 3.4.19: Products of pancreatic alpha-amylase

The pancreatic alpha-amylase products, along with the disaccharides sucrose and lactose, then move to the surface of the enterocyte. Here, there are disaccharidase enzymes (lactase, sucrase, maltase) on the outside of the enterocyte. Enzymes, like these, that are on the outside of cell walls are referred to as ectoenzymes. Individual monosaccharides are formed when lactase cleaves lactose, sucrase cleaves sucrose, and maltase cleaves maltose. There is also another brush border enzyme, alpha-dextrinase. This enzyme cleaves alpha 1-6 glycosidic bonds in dextrins, primarily the branch point bonds in amylopectin. The products from these brush border enzymes are the single monosaccharides glucose, fructose, and galactose that are ready for absorption into the enterocyte10.

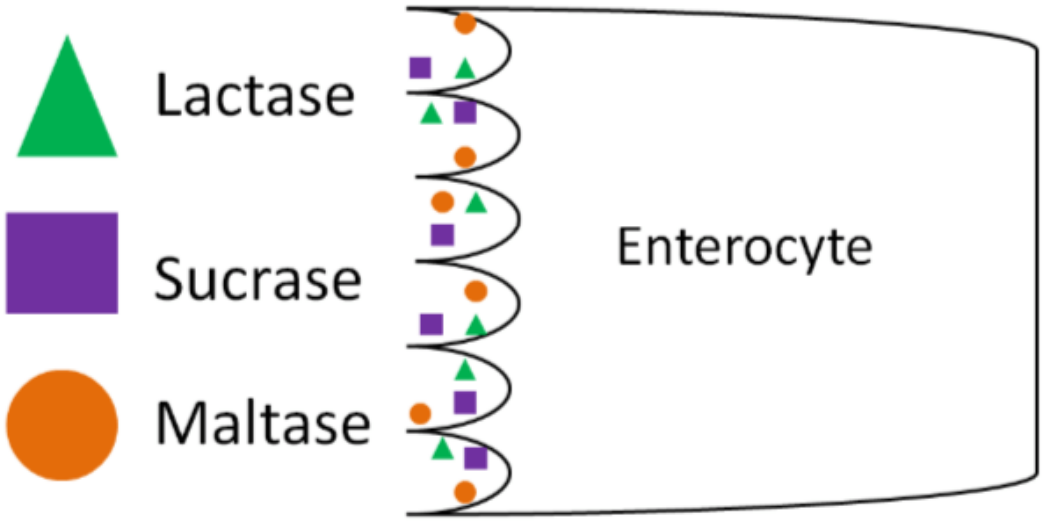


Figure 3.4.20: Disaccharidases on the outside of the enterocyte.

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Protein Digestion in the Small Intestine

The small intestine is the major site of protein digestion by proteases (enzymes that cleave proteins). The pancreas secretes a number of proteases as zymogens into the duodenum where they must be activated before they can cleave peptide bonds[10]. This activation occurs through an activation cascade. A cascade is a series of reactions in which one step activates the next in a sequence that results in an amplification of the response. An example of a cascade is shown below.

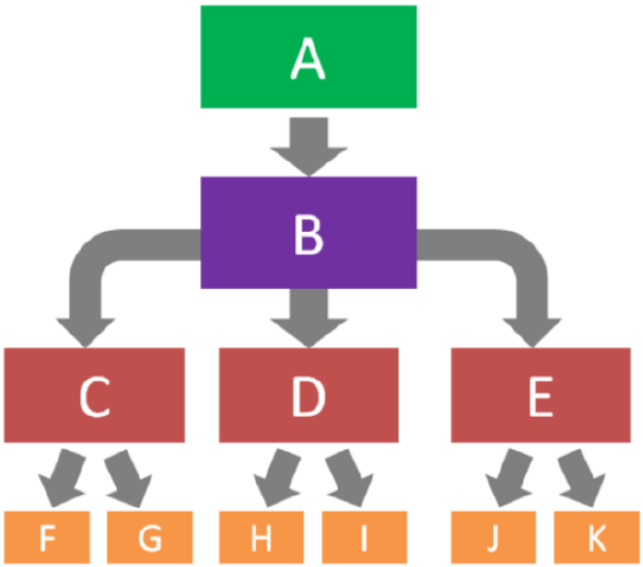


Figure 3.4.21: An example of a cascade, with one event leading to many more events

In this example, A activates B, B activates C, D, and E, C activates F and G, D activates H and I, and E activates K and L. Cascades also help to serve as control points for certain process. In the protease cascade, the activation of B is really important because it starts the cascade.

The protease/colipase activation scheme starts with the enzyme enteropeptidase (secreted from the intestinal brush border) that converts trypsinogen to trypsin. Trypsin can activate all the proteases (including itself) and colipase (involved in fat digestion)1 as shown in the 2 figures below.

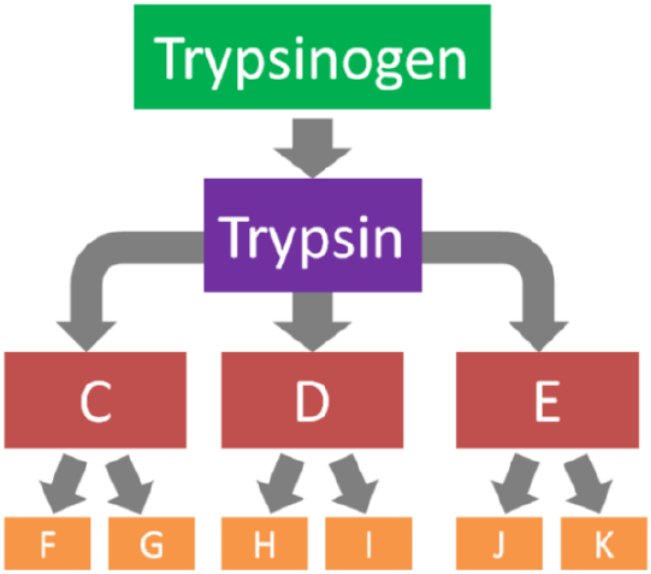


Figure 3.4.22: Protease/colipase activation cascade

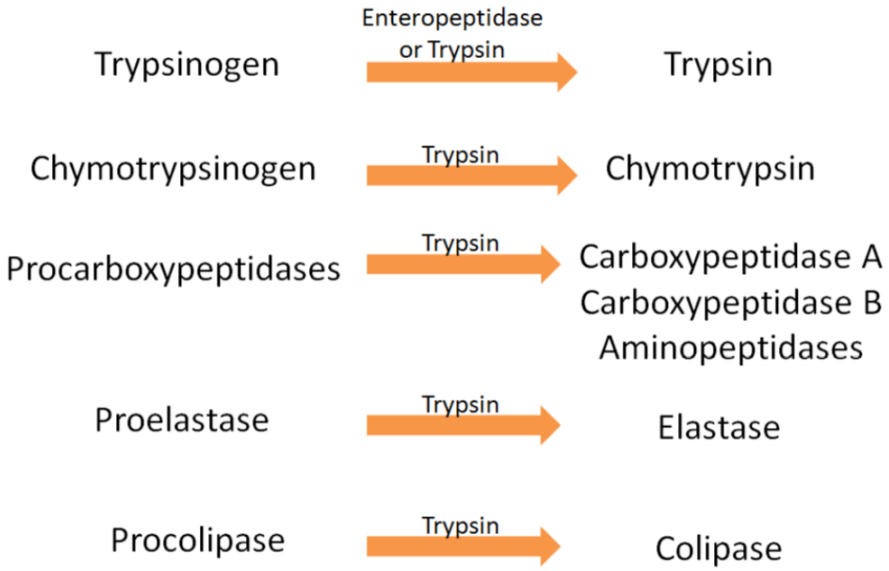


Figure 3.4.23: The protease/colipase activation cascade

The products of the action of proteases on proteins are dipeptides, tripeptides, and individual amino acids, as shown below.

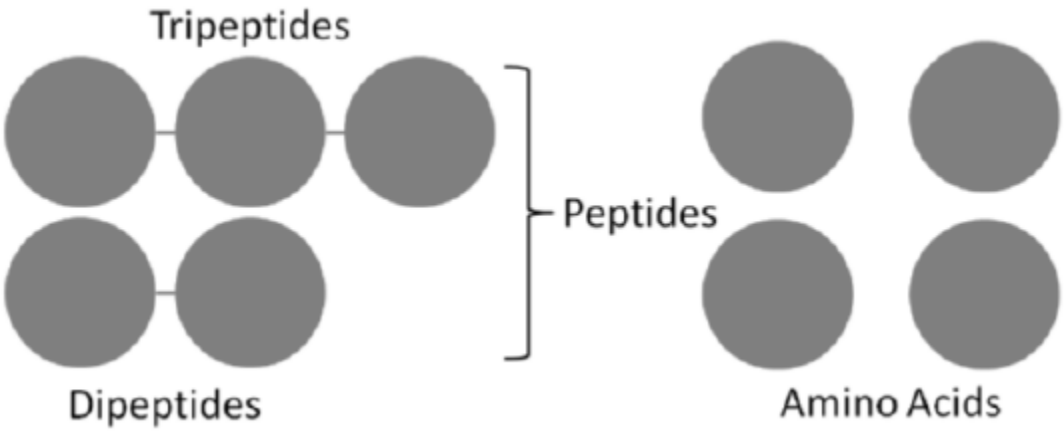


Figure 3.4.24: Products of pancreatic proteases

At the brush border, much like disaccharidases, there are peptidases that cleave some peptides down to amino acids. Not all peptides are cleaved to individual amino acid, because small peptides can be taken up into the enterocyte, thus, the peptides do not need to be completely broken down to individual amino acids. Thus the end products of protein digestion are primarily dipeptides and tripeptides, along with individual amino acids[10].

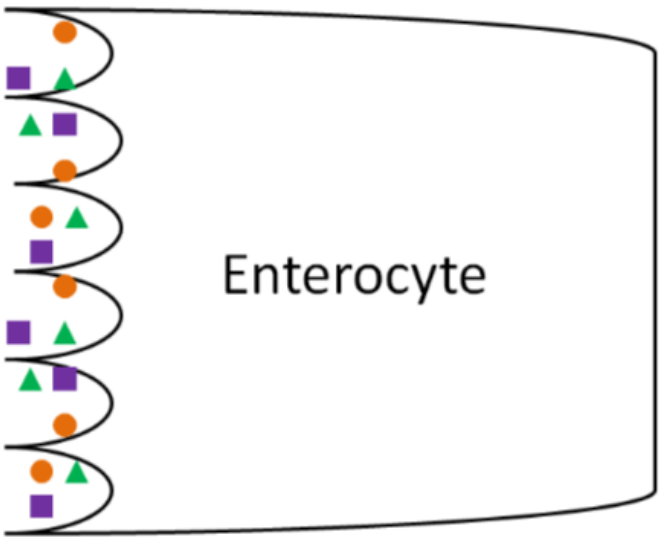


Figure 3.4.25: Peptidases are produced by the brush border to cleave some peptides into amino acids

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Lipid Digestion in the Small Intestine

The small intestine is the major site for lipid digestion. There are specific enzymes for the digestion of triglycerides, phospholipids, and cleavage of esters from cholesterol. We will look at each in this section.

Triglycerides

The pancreas secretes pancreatic lipase into the duodenum as part of pancreatic juice. This major triglyceride digestion enzyme preferentially cleaves the sn-1 and sn-3 fatty acids from triglycerides. This cleavage results in the formation of a 2-monoglyceride and two free fatty acids as shown below.

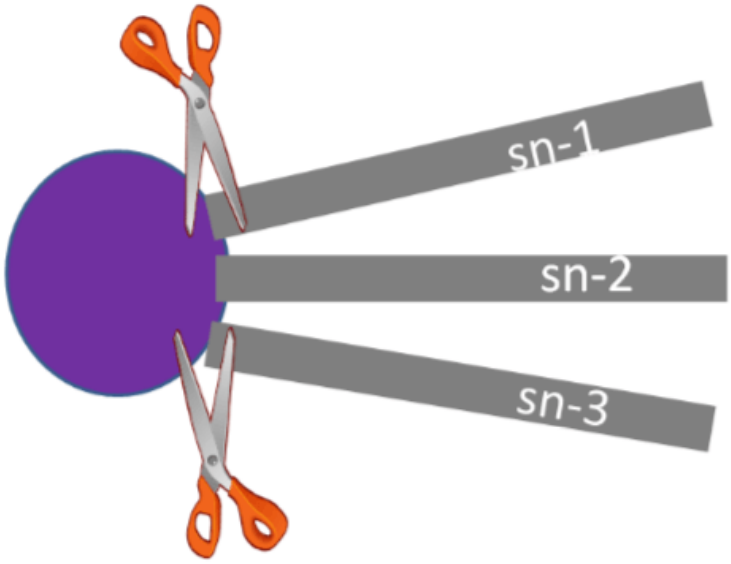


Figure 3.4.26: Pancreatic lipase cleaves the sn-1 and sn-3 fatty acids of triglycerides

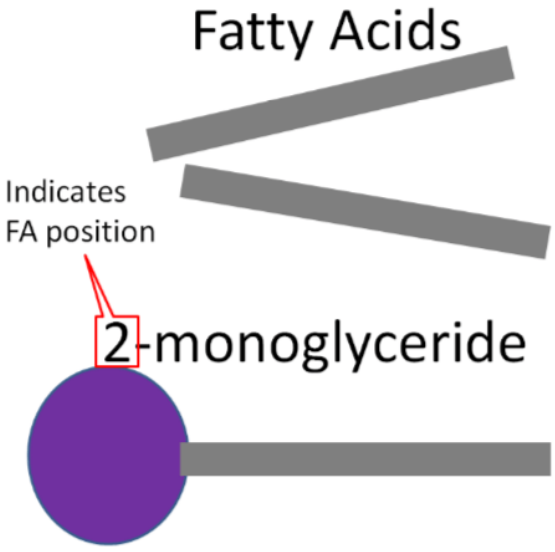


Figure 3.4.27: The products of pancreatic lipase are a 2-monoglyceride and two free fatty acids

To assist lipase, colipase serves as an anchor point to help pancreatic lipase attach to the triglyceride droplet.

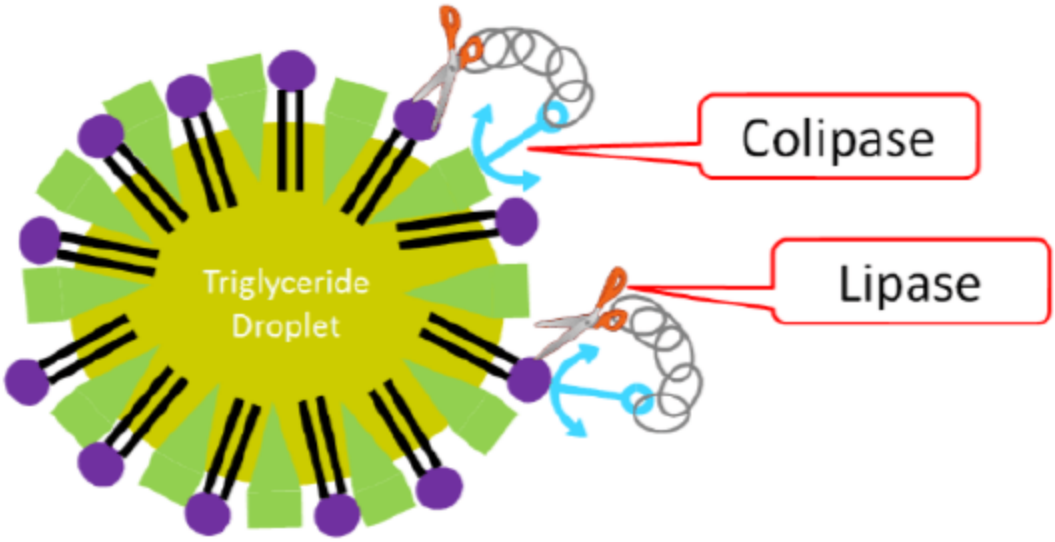


Figure 3.4.28: Colipase helps anchor lipase to the triglyceride droplet

Phospholipids

The enzyme phospholipase A_2 cleaves the C-2 fatty acid of lecithin, producing lysolecithin and a free fatty acid.



Figure 3.4.29: Phospholipase A_2 cleaves the C-2 fatty acid of lecithin

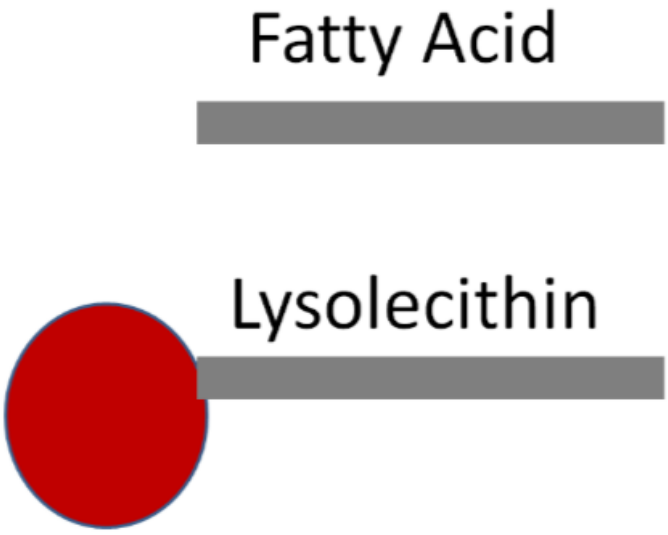


Figure 3.4.30: Products of phospholipase A_2 cleavage

Cholesterol Esters

The fatty acid in cholesterol esters is cleaved by the enzyme, cholesterol esterase, producing cholesterol and a fatty acid.

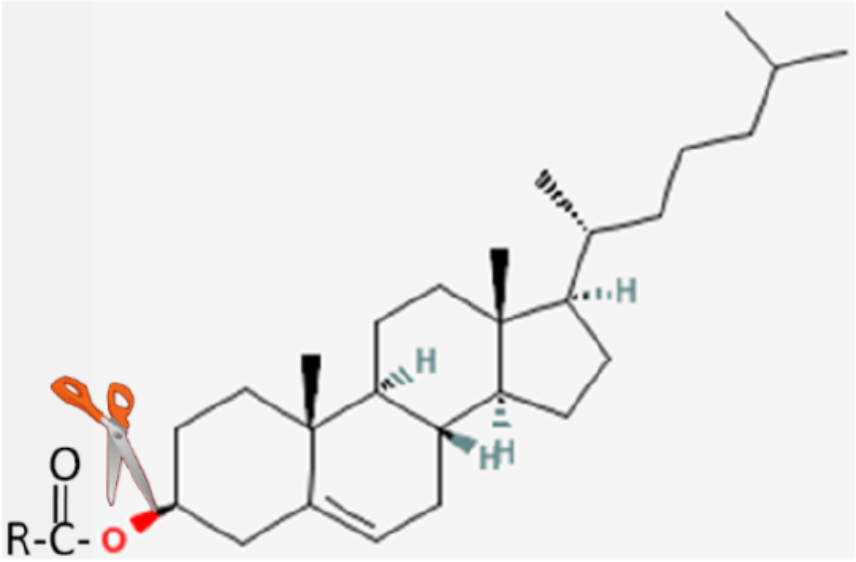


Figure 3.4.31: Cholesterol esterase cleaves fatty acids off of cholesterol

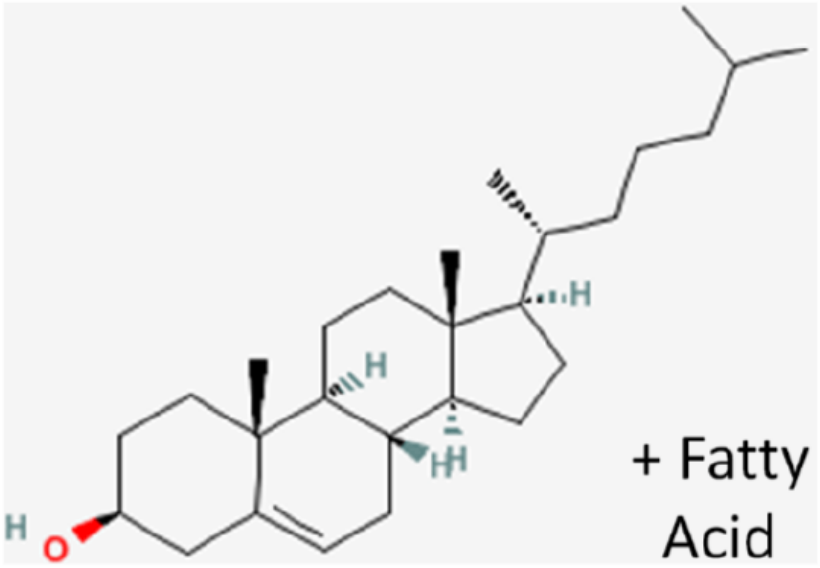


Figure 3.4.32: Products of cholesterol esterase

Formation of Mixed Micelles

If nothing else happened at this point, the 2-monoglycerides and fatty acids produced by pancreatic lipase would form micelles. The hydrophilic heads would be outward and the fatty acids would be buried on the interior. These micelles are not sufficiently water-soluble to cross the unstirred water layer to get to the brush border of enterocytes. Thus, mixed micelles are formed containing cholesterol, bile acids, and lysolecithin in addition to the 2-monoglycerides and fatty acids, as illustrated below[10].

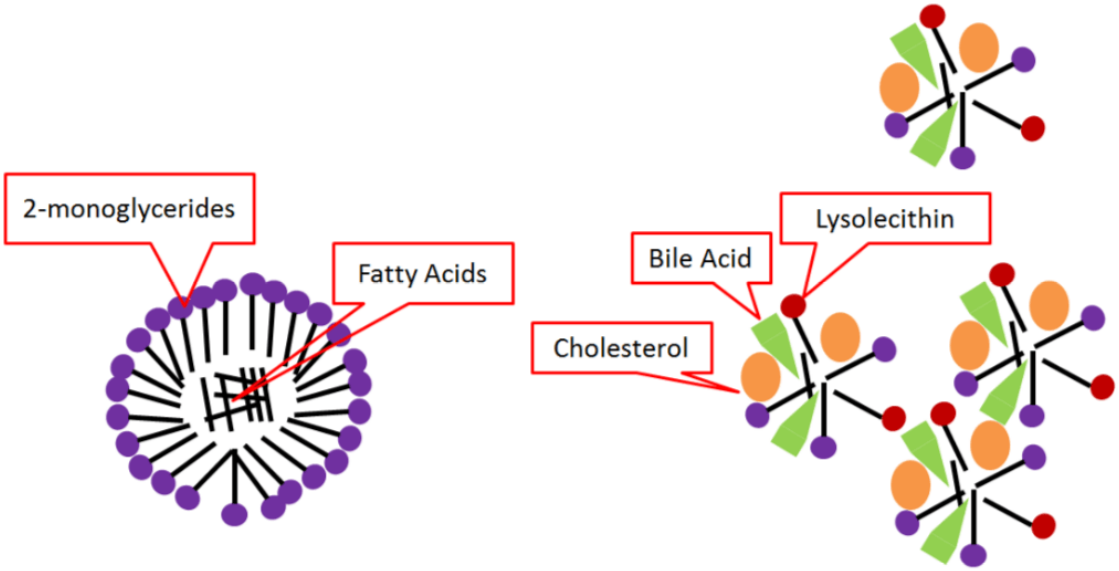


Figure 3.4.33: Normal (left) and mixed (right) micelles

Mixed micelles are more water-soluble, allowing them to cross the unstirred water layer to the brush border of enterocytes for absorption.

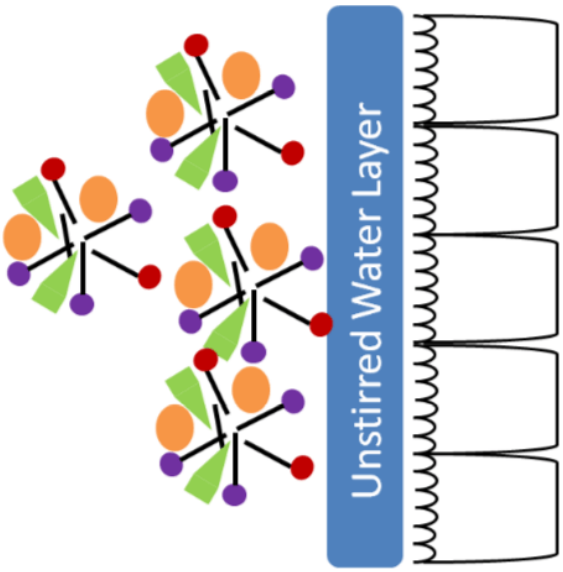


Figure 3.4.34: Mixed micelles can cross the unstirred water layer for absorption into the enterocytes

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3.5: Macronutrient Digestion Review

The following figures review the digestion of the different macronutrients.

Carbohydrate Digestion

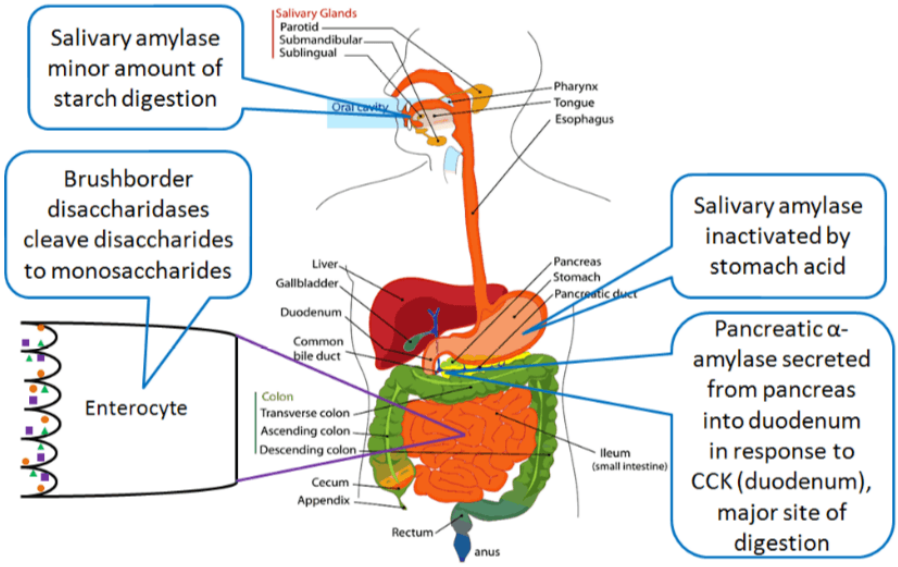


Figure 3.5.1: Review of carbohydrate digestion[1]

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Protein Digestion

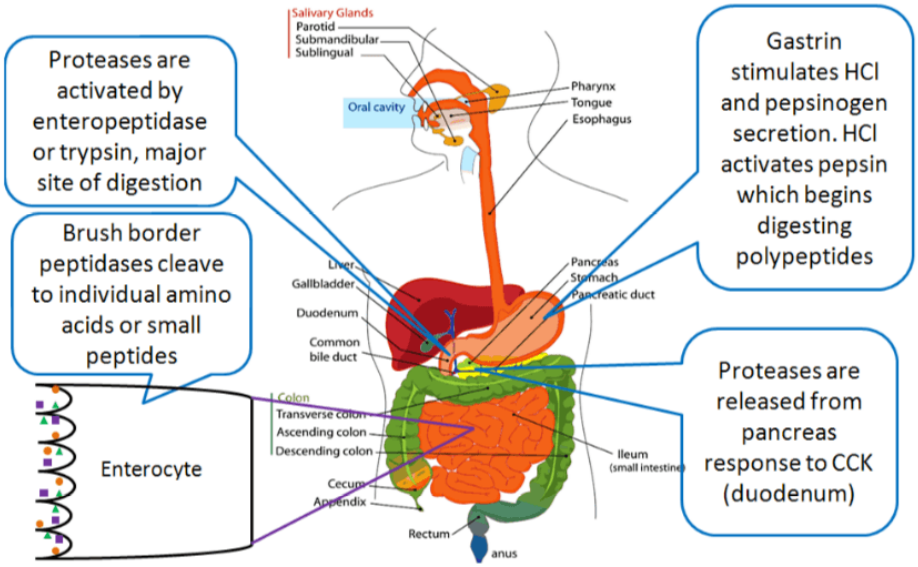


Figure 3.5.2: Review of protein digestion[1]

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Triglyceride Digestion

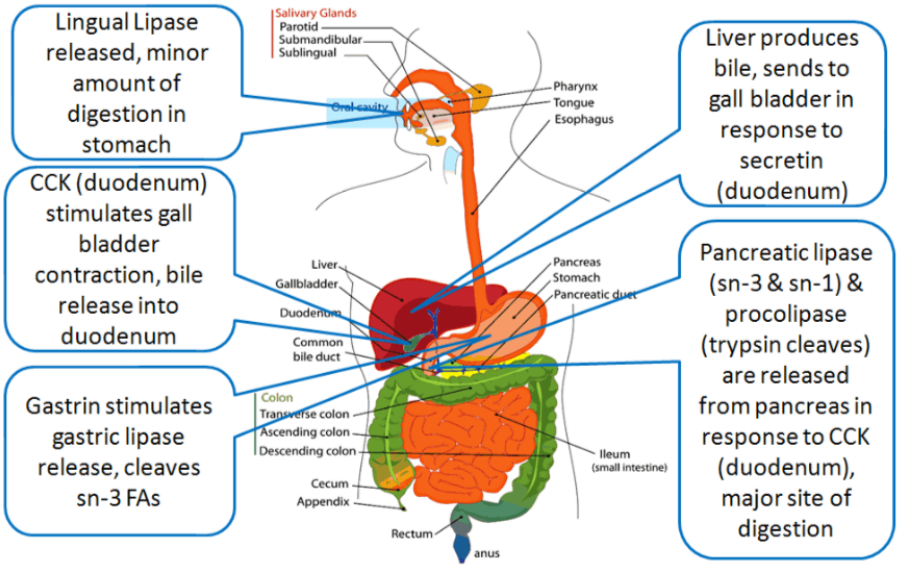


Figure 3.5.3: Review of triglyceride digestion[1]

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Cholesterol Ester and Phospholipid Digestion

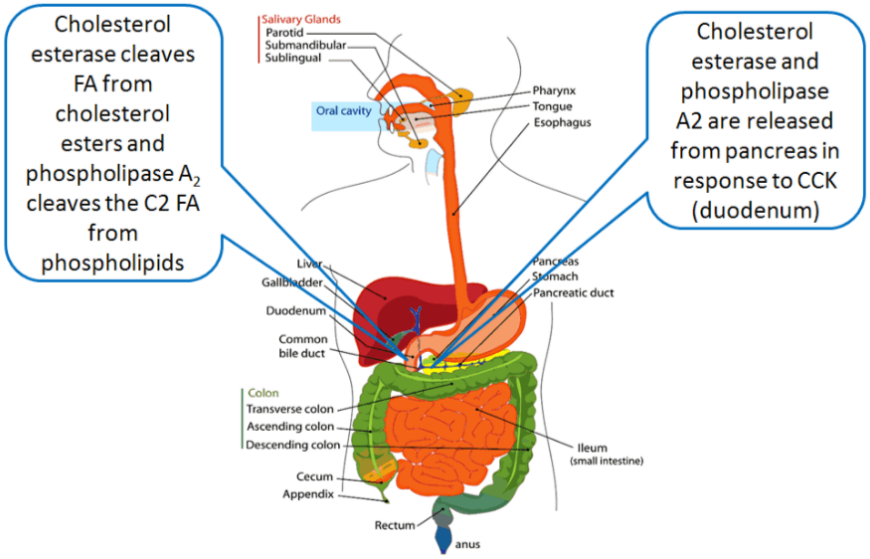


Figure 3.5.4: Review of cholesterol ester and phospholipid digestion[1]

After digestion, the products below are ready for uptake into the enterocyte.

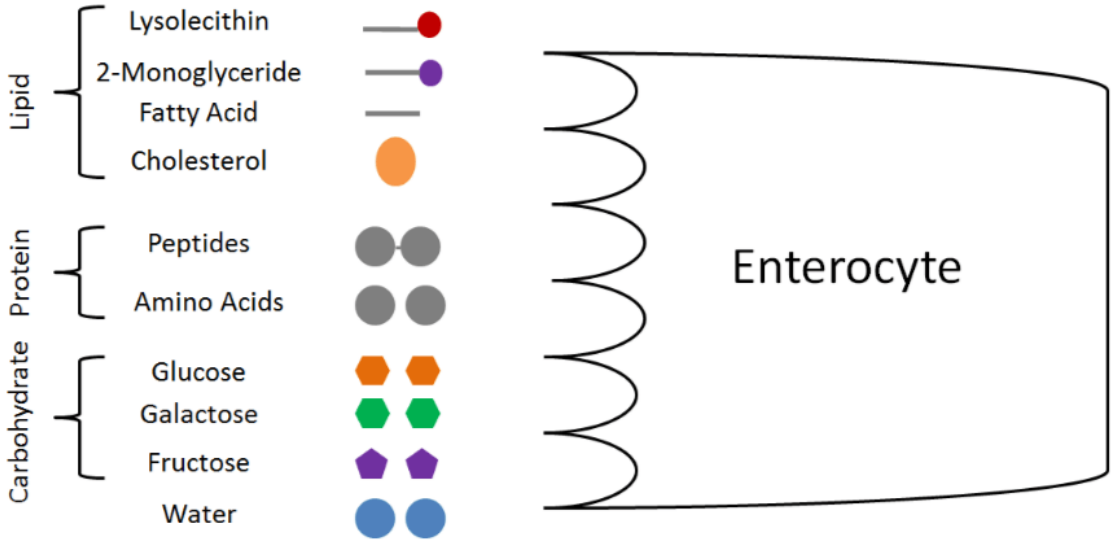


Figure 3.5.5: Macronutrient digestion products ready for uptake into the enterocyte

References

1. http://www.wpclipart.com/medical/ana..._page.png.html

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3.6: Large Intestine

We have reached a fork in the road. We could follow the uptake of the digested compounds into the enterocyte or we could finish following what has escaped digestion and is going to continue into the large intestine. Obviously from the title of this section we are going to do the latter. As we learned previously, fiber is a crude term for physical material (since there is some water as well) has survived digestion and reached the large intestine.

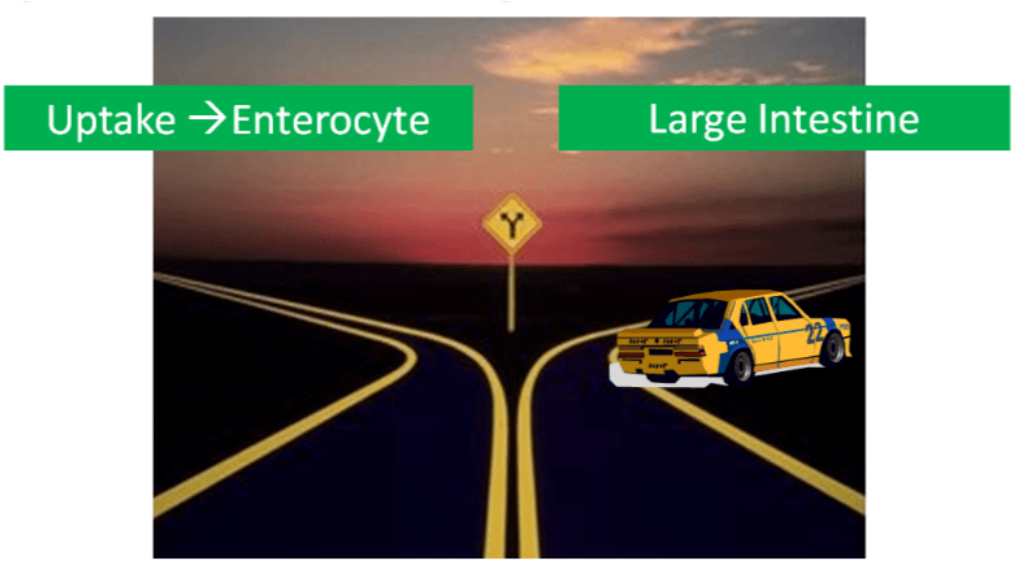


Figure 3.6.1: The fork in the road between finishing digestion in the colon and absorption into the enterocyte

The ileocecal valve is the sphincter between the ileum and the large intestine. This name should make more sense as we go through the anatomy of the large intestine.

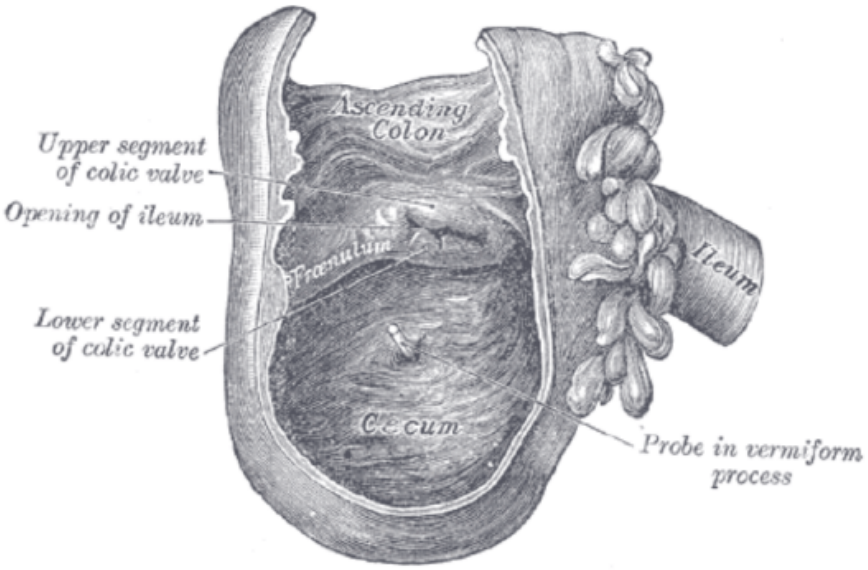


Figure 3.6.2: The ileocecal valve[1]

The large intestine consists of the colon, the rectum, and the anus. The colon can be further divided into the cecum (hence the -cecal in ileocecal valve, ileo- refers to ileum), ascending colon, transverse colon, descending colon, and sigmoid colon as shown below.

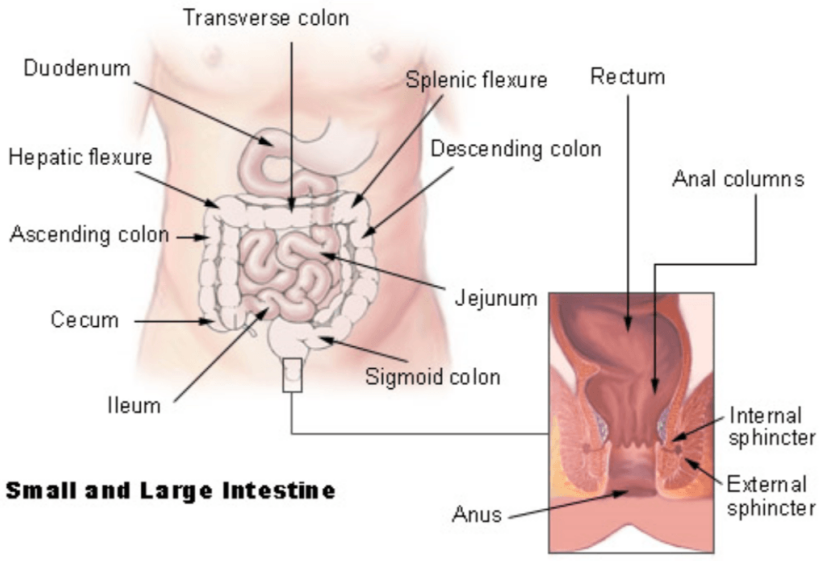


Figure 3.6.3: Anatomy of the large intestine and rectum2

The large intestine is responsible for absorbing the remaining water and electrolytes (sodium, potassium, and chloride). It also forms and excretes feces. The large intestine contains large amounts of microorganisms like those shown in the figure below.

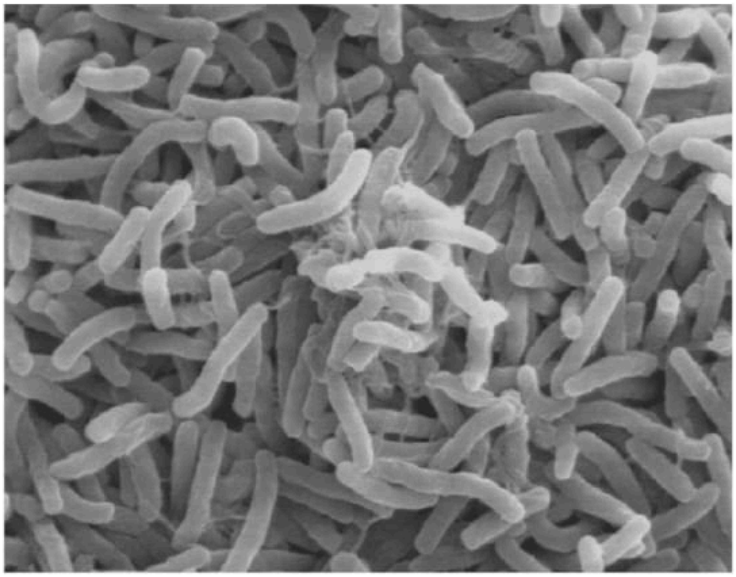


Figure 3.6.4: Magnified image of bacteria3

The large intestine can also be referred to as the gut. There are a large number of microorganisms found throughout the gastrointestinal tract that collectively are referred to as the flora, microflora, or microbiota. Technically, microbiota is the preferred term because flora means "pertaining to plants". There are 10 times more microorganisms in the gastrointestinal tract than cells in the whole human body4. As can be seen in the figure below, the density of microorganisms increases as you move down the digestive tract.

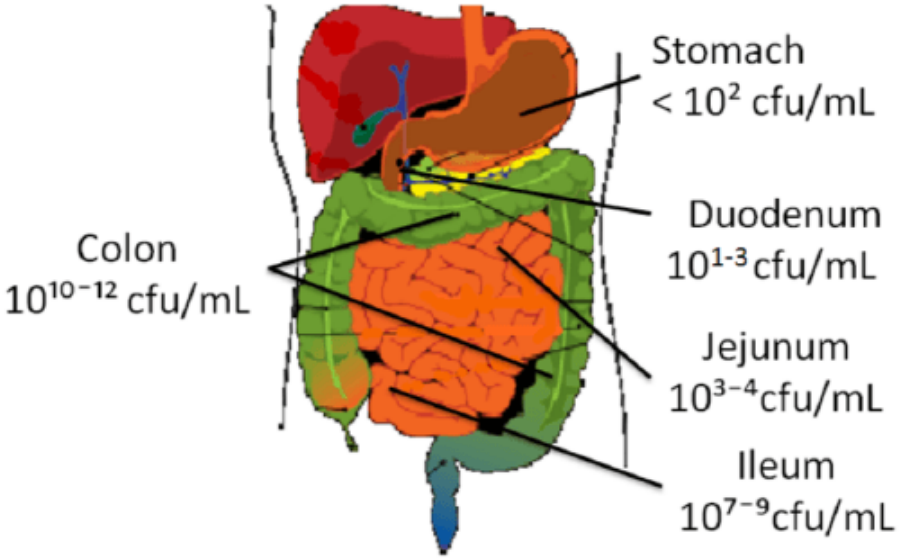


Figure 3.6.5: Relative amount of bacteria in selected locations of the gastrointestinal tract. cfu/ml = colony forming unit, a measure of the number of live microorganisms in 1 mL of digestive sample[5,6]

As described in the fiber sections, there are two different fates for fiber once it reaches the large intestine. The fermentable, viscous fiber is fermented by bacteria. An example of fermentation is the utilization of the oligosaccharides raffinose and stachyose by microorganisms that results in the production of gas, which can lead to flatulence. Also, some bile acids are fermented by microorganisms to form secondary bile acids that can be reabsorbed. These secondary bile acids represent approximately 20% of the total bile acids in our body. Fermentable fibers can be used to form short-chain fatty acids that can then be absorbed and used by the body. The nonfermentable, nonviscous fiber is not really altered and will be a component of feces, that is then excreted through the rectum and anus. This process involves both an internal and external sphincter that are shown in Figure 3.6.3 above.

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Microbiota

There is increased attention given to the potential of a person's microbiota to impact health. This is because there are beneficial and nonbeneficial bacteria inhabiting our gastrointestinal tracts. Thus, theoretically, if you can increase the beneficial or decrease the non- beneficial bacteria, there may be improved health outcomes. In response to this, probiotics and prebiotics have been identified/developed. A probiotic is a live microorganism that is consumed, and colonizes in the body as shown in the figures

below.

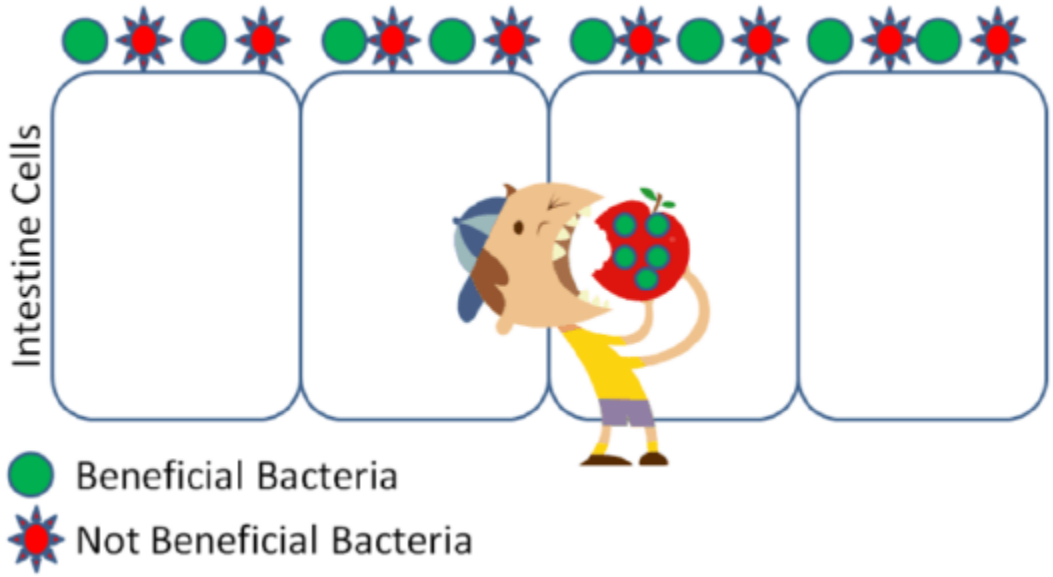


Figure 3.6.6: Probiotics the consumption of the bacteria itself

A prebiotic is a nondigestible food component that selectively stimulates the growth of beneficial intestinal bacteria. Typically the food component is fermented by the bacteria. An example of a prebiotic is inulin, which is shown in the figure below.

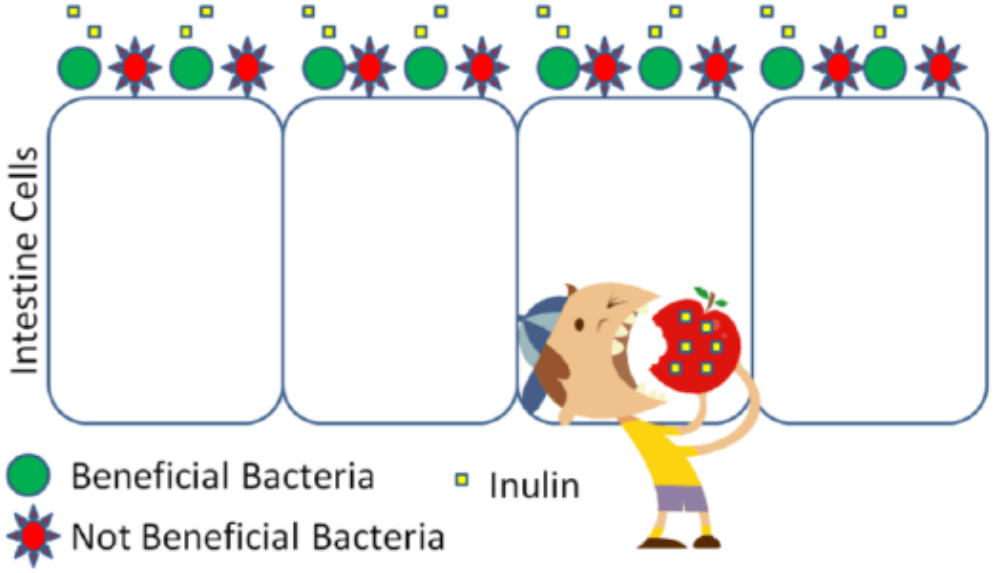


Figure 3.6.7: Inulin, an indigestible food component that is a commonly used prebiotic

The net result is the same for both prebiotics and probiotics, an increase in the beneficial/non beneficial microorganism ratio.

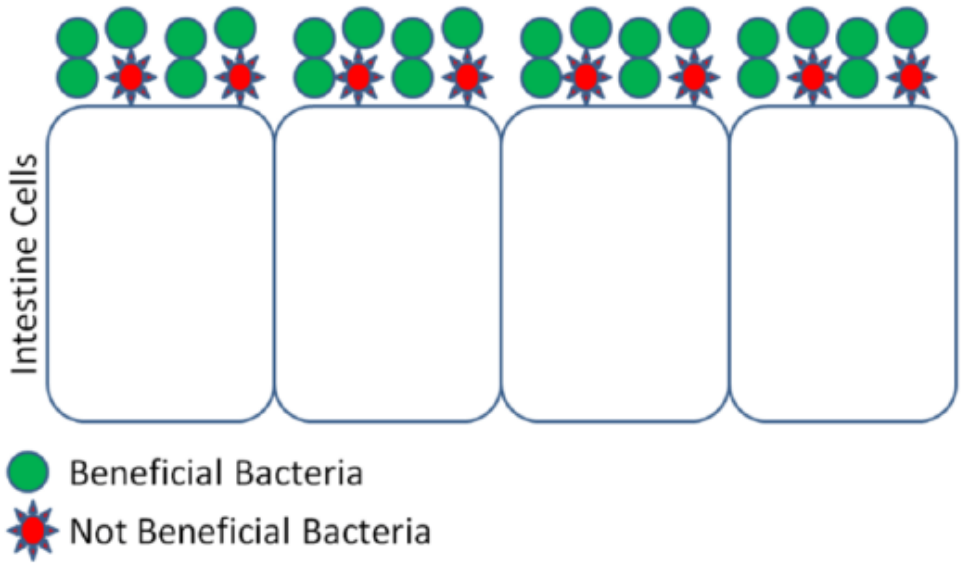


Figure 3.6.8: An effective prebiotic or probiotic should result in an increase in the beneficial bacteria

The following video does a nice job of explaining and illustrating how probiotics work.

YouTube Video

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Video 3.6.1: An example of how probiotics work. https://www.youtube.com/watch?v=2k8Puxz54FQ&NR=1

The NCCAM website is a good source of information if you have further questions on the topic.

Web Links

NCCAM: Probiotics

Some common examples of probiotics are DanActive® and Activia®.

Web Links

DanActive®

Activia®

The claims that companies made about their produce probiotic products have come under scrutiny. Dannon settled with the US Federal Trade Commission to drop claims that its probiotic products will help prevent colds or alleviate digestive problems, as seen in the top link below. General Mills also settled a lawsuit that accused them of falsely advertising the digestive benefits of Yo-Plus a product it no longer sells, as seen in the second link.

Web Links

Dannon Agrees to Drop Exaggerated Health Claims for Activia Yogurt and DanActive Dairy Drink General Mills Settles Yo-Plus Lawsuit

Some examples of prebiotics include inulin, other fructose-containing oligosaccharides and polysaccharides, and resistant starch. Inulin is an oligosaccharide that contains mainly fructoses that are joined by beta-bonds, which allows them to survive digestion. The structure of inulin is shown below.

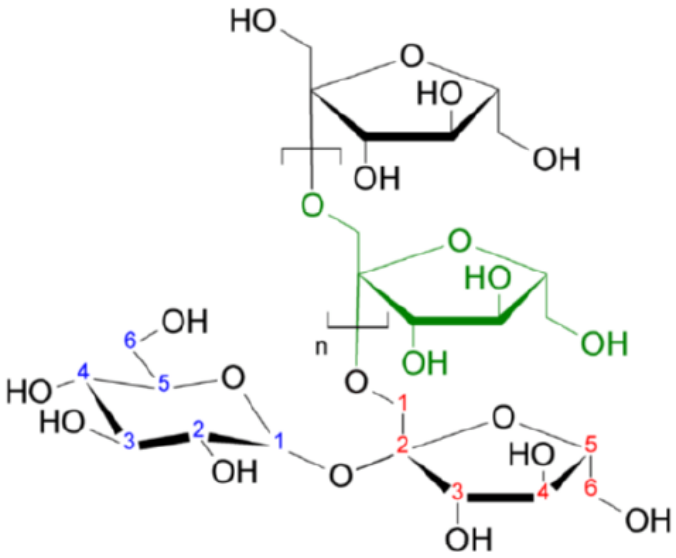


Figure 3.6.9: Structure of inulin[7]

Resistant starch is so named because it is a starch that is resistant to digestion. As a result, it arrives in the colon to be fermented.

A couple of newer terms related to the microbiota that are increasingly being used are:

- A synbiotic is a product that contains both probiotics and prebiotics. The syn-part of the term is meant to indicate that there may be synergy by the combination of the two.
- Postbiotics are metabolites secreted by the microbiota. There is increased interest in the impact of these metabolites rather than just focusing on the population of the microbiota.

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4: MACRONUTRIENT UPTAKE, ABSORPTION, AND TRANSPORT

The term absorption can have a number of different meanings. Not everything that is taken up into the enterocyte from the lumen will be absorbed, so the term uptake refers to compounds being transported into the enterocyte. Absorption means that a compound is transported from the enterocyte into circulation. Under most circumstances, compounds that are taken up will then be absorbed. After this chapter, hopefully this distinction between these terms will be clear. After later micronutrient chapters, hopefully you will understand the reason for emphasizing this distinction.

4.1: Crypts of Lieberkuhn and Enterocyte Maturation

4.2: Uptake Lineup and Cell Membranes

4.3: Types of Cell Uptake and Transport

4.4: Carbohydrate Uptake, Absorption, Transport and Liver Uptake

4.5: Glycemic Response, Insulin, and Glucagon

4.6: Protein Uptake, Absorption, Transport and Liver Uptake

4.7: Lipid Uptake, Absorption and Transport

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4.1: Crypts of Lieberkuhn and Enterocyte Maturation

There are some additional anatomical and physiological features of the small intestine that are important to understand before defining uptake and absorption. Crypts of Lieberkuhn are pits between villi as pointed out by the green arrow in Figure 4.1.1.

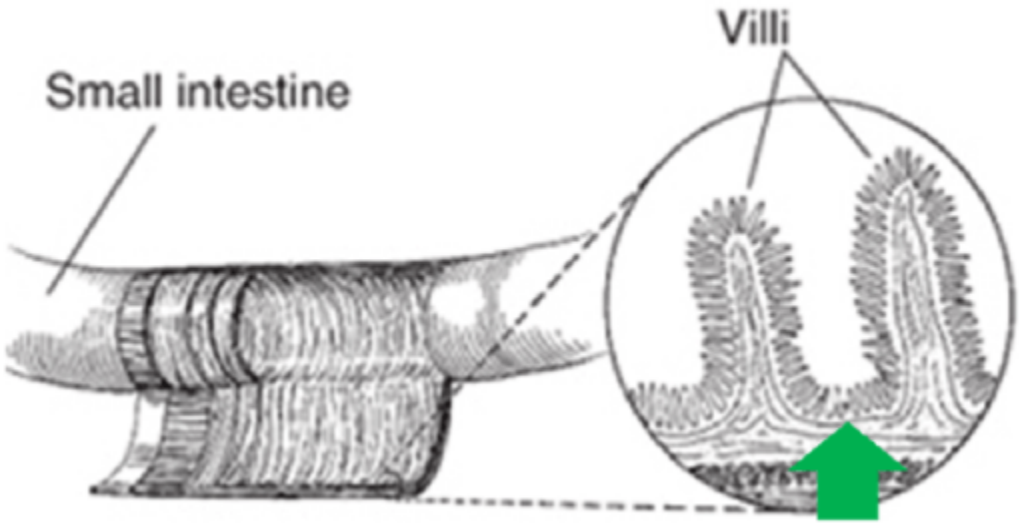


Figure 4.1.1: A crypt of Lieberkuhn is the pit between the villi in the small intestine as pointed out by the green arrow[1]

The crypts of Lieberkuhn (often referred to simply as crypts) are similar to the gastric pits in the stomach. The crypts contain stem cells that can differentiate to produce a number of different cell types, including enterocytes[2]. From these stem cells in the crypt, immature enterocyte cells are formed that mature as they rise, or migrate, up the villi. Thus, the tips at the top of the villi are where the mature, fully functioning enterocytes are located, as represented by the purple cells in Figure 4.1.2[3].

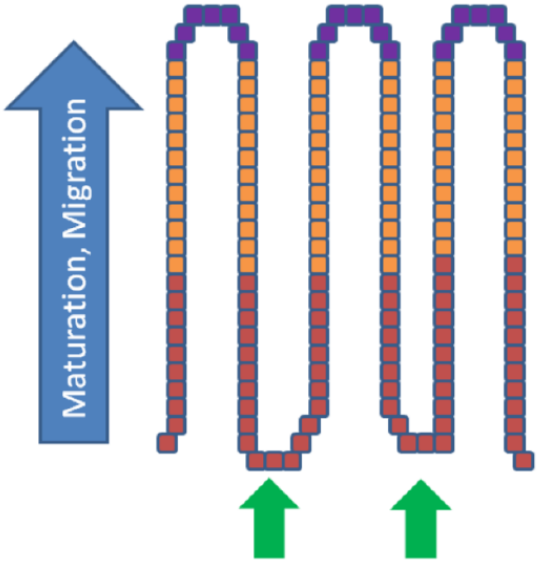


Figure 4.1.2: Crypts are represented by green arrows, fully mature enterocytes are represented by the purple cells at the top of the villi

This maturation and migration is a continuous process. The life cycle of an enterocyte is 72 hours once it enters the villus from the crypt[2]. Once enterocytes have reached the top of the villus, they are sloughed off and are either digested (lipid and protein contents taken up by other enterocytes), or excreted in feces as depicted in Figure 4.1.3.

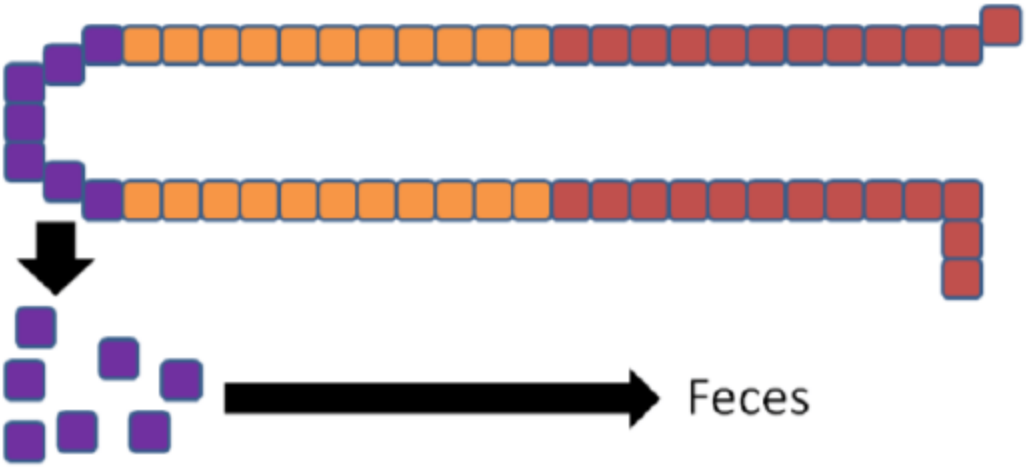


Figure 4.1.3: Enterocytes sloughed off the villus. Unless these cells are digested and their components are taken up by other enterocytes on the villus, they will be excreted in feces

Thus, we define absorption as reaching body circulation, because compounds taken up into enterocytes might not make it into body circulation, and thus are not necessarily absorbed.

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4.2: Uptake Lineup and Cell Membranes

Having completed digestion in the small intestine, a number of compounds are ready for uptake into the enterocyte. The figure below shows the macronutrient uptake lineup, or what is ready to be taken up into the enterocyte.

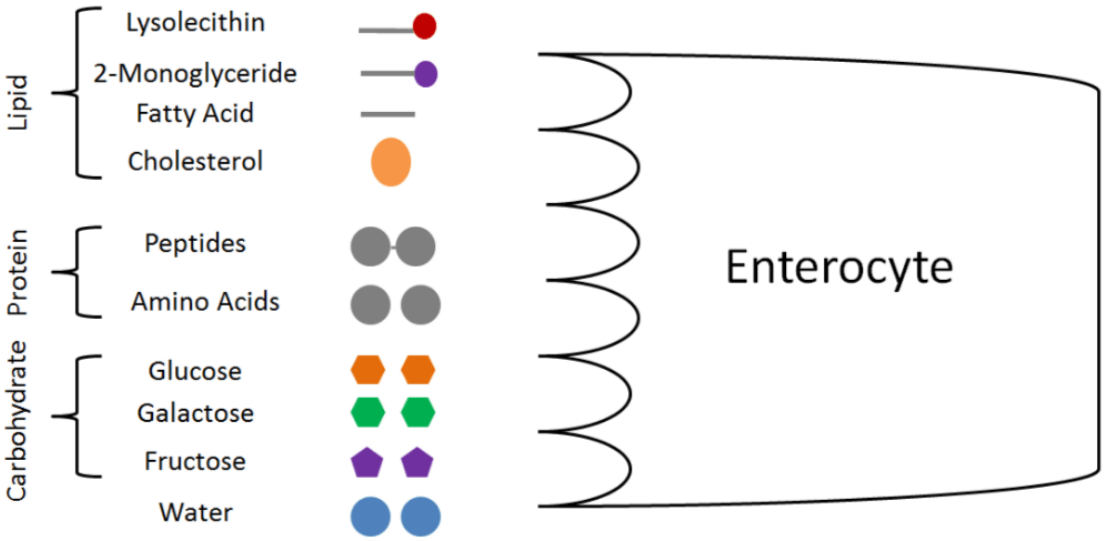


Figure 4.2.1: The macronutrient uptake lineup

From lipids, we have the lysolecithin (from phospholipid), 2-monoglyceride (from triglycerides), fatty acids, and cholesterol. From protein, there are small peptides (di- and tripeptides) and amino acids. From carbohydrates, only the monosaccharides glucose, galactose, and fructose will be taken up. The other macronutrient, water, has not been discussed so far because it does not undergo digestion.

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However, these compounds must now cross the plasma (cell) membrane, which is a phospholipid bilayer. In the cell membrane, the hydrophilic heads of the phospholipids point into the lumen as well as towards the interior of the cell, while the tails are on the interior of the plasma membrane as shown below.

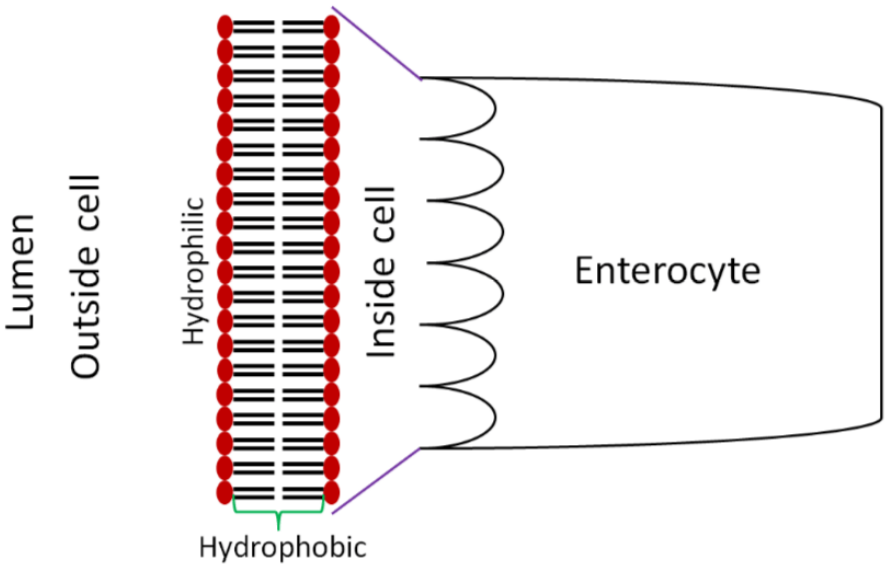


Figure 4.2.2: Plasma membrane of a cell

The plasma membrane contains proteins, cholesterol, and carbohydrates in addition to the phospholipids. Membrane proteins, such as channel proteins are important for moving some compounds through the cell membrane. The figure and two videos below do a nice job of illustrating the components of the cell membrane.

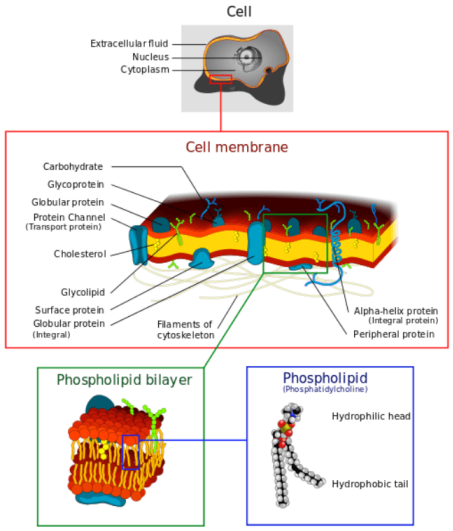


Figure 4.2.3: Cell membrane1

YouTube Video

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Video 4.2.1: The movement of molecules across the cell membrane requiring energy. https://www.youtube.com/watch?v=owEgqrq51zY

YouTube Video

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Video 4.2.2: A video showing inside a cell. https://www.youtube.com/watch?v=GW0lqf4Fqpg

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References

1. en.Wikipedia.org/wiki/File:Ce..._diagram_4.svg

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4.3: Types of Cell Uptake and Transport

There are a number of different forms of uptake/transport utilized by your body. These can be classified as passive or active. The difference between the two is whether energy is required and whether (from a solute perspective) they move with or against a concentration gradient. Passive transport does not require energy to move with a concentration gradient. Active transport requires energy to move against the concentration gradient.

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The energy for active uptake/transport is provided by adenosine triphosphate (ATP), which is the energy currency in the body. The structures of adenosine and phosphate are shown below.



Figure 4.3.1: Structures of adenosine (left) and phosphate (right)

Tri- means three, thus ATP is adenosine with three phosphate groups bonded to it, as shown below.

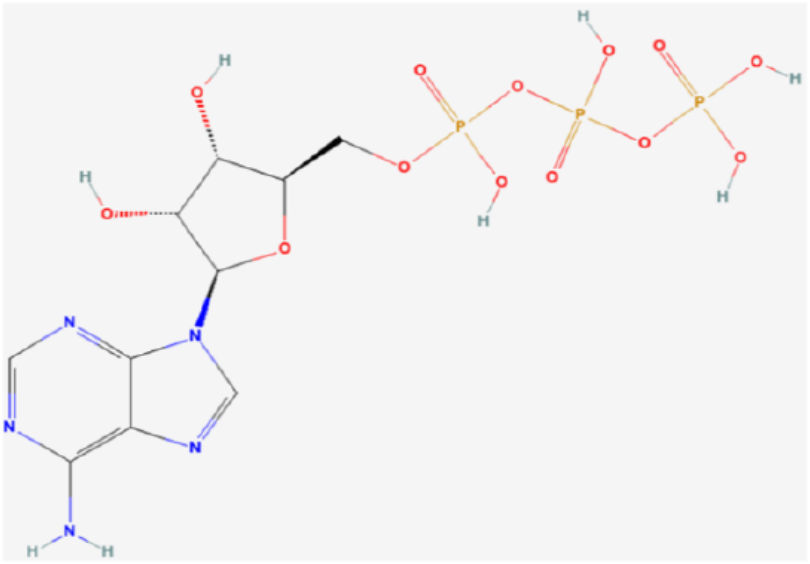


Figure 4.3.2: Structure of adenosine triphosphate (ATP)

Phosphorylation is the addition of a phosphate group. Dephosphorylation is removal of a phosphate group. Overall phosphorylation is a process that requires energy. The net effect of dephosphorylation is the release of energy. Thus, energy is required to add phosphates to ATP, energy is released through removing phosphates from ATP.

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The concentration gradient is a way to describe the difference between the concentration of the solute outside of a cell versus the concentration inside of a cell. A solute is dissolved in a solvent in a solution; the more solute the higher the concentration. Moving with the gradient is typically moving of solute from a region of higher concentration to an area of lower concentration (in order to reach equal solute concentrations on both sides of the membrane). The exception is osmosis, which moves solvent instead of solute to have the same effect of equalizing concentrations on both sides of the membrane. Moving against the gradient is moving solute from an area of lower concentration to an area of higher concentration.

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Passive Uptake/Transport

There are three forms of passive uptake/transport:

1. Simple Diffusion
2. Osmosis
3. Facilitated Diffusion

Below is more information of each type of uptake/transport.

Simple Diffusion

Simple diffusion is the movement of solutes from an area of higher concentration (with the concentration gradient) to an area of lower concentration without the help of a protein, as shown below.

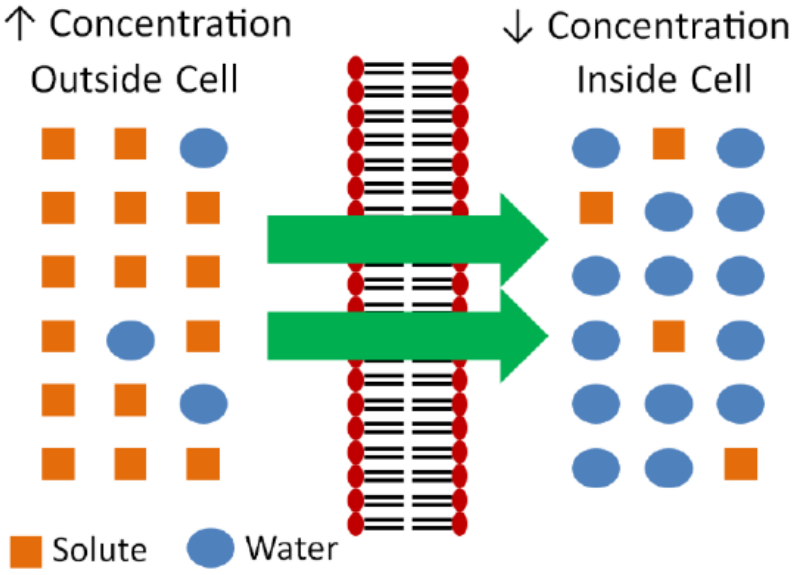


Figure 4.3.3: Simple diffusion

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Osmosis

Osmosis is similar to simple diffusion, but water moves instead of solutes. In osmosis water molecules move from an area of lower solute concentration to an area of higher solute concentration of solute as shown below. The effect of this movement is to dilute the area of higher solute concentration to equalize the solute concentrations on both sides of the membrane.

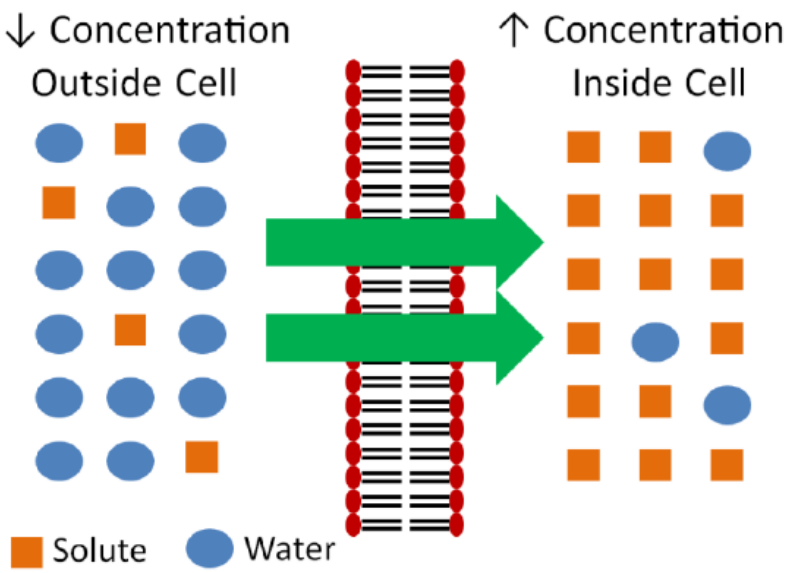


Figure 4.3.4: Osmosis

The following videos do a nice job of illustrating osmosis.

YouTube Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

Video 4.3.1: Osmosis is the diffusion of water down its concentration gradient. Normally one thinks of water as the solvent, and focuses on the concentration of the solutes, but water itself has a concentration in any solution. https://www.youtube.com/watch?v=sdiJtDRJQEc

YouTube Video

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Video 4.3.2: Dried and wrinkled salad/lettuce can be "refreshed" by immersing it in cold water. This is due to osmosis. The process is shown in a time lapse video where things are speeded up 720x. https://www.youtube.com/watch?v=H6N1IiJTmnc&NR=1&feature=fvwp

Another example illustrating osmosis is the red blood cells in different solutions shown below.

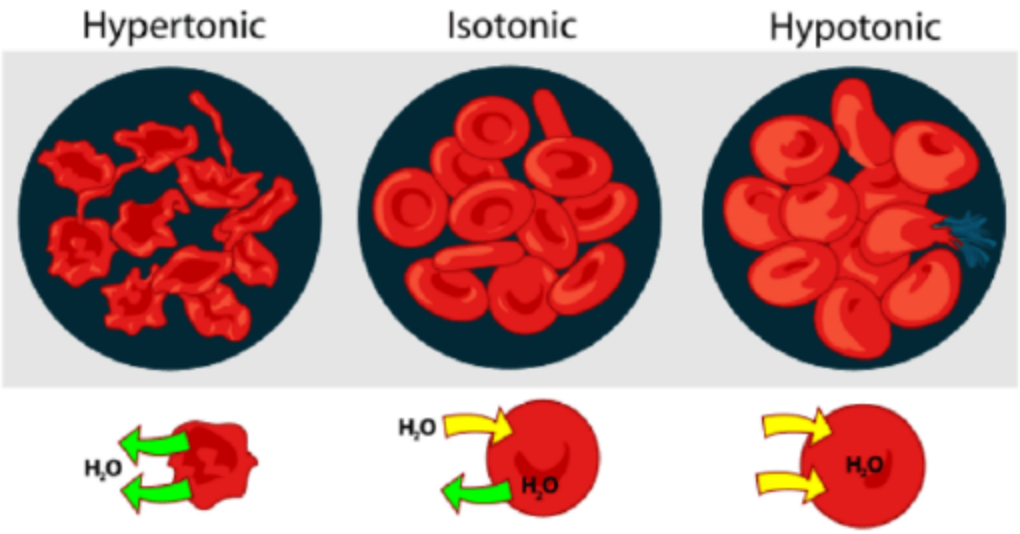


Figure 4.3.5: Effect of salt solution concentration on red blood cells[1]

We will consider the simple example of salt as the solute. If the solution is hypertonic, there is a greater concentration of salt outside (extracellular) the red blood cells than within them (intracellular). Water will then move out of the red blood cells to the area of higher salt concentration, resulting in the shriveled red blood cells depicted. Isotonic means that there is no difference between concentrations. There is an equal exchange of water between intracellular and extracellular fluids. Thus, the cells are normal, functioning red blood cells. A hypotonic solution contains a lower extracellular concentration of salt than the red blood cell intracellular fluid. As a result, water enters the red blood cells, possibly causing them to burst.

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Facilitated Diffusion

The last form of passive absorption is similar to simple diffusion in that it follows the concentration gradient (higher concentration to lower concentration). However, it requires a protein to transport (channel or carrier protein) the solute across the membrane. The following figure and video do a nice job of illustrating facilitated diffusion.

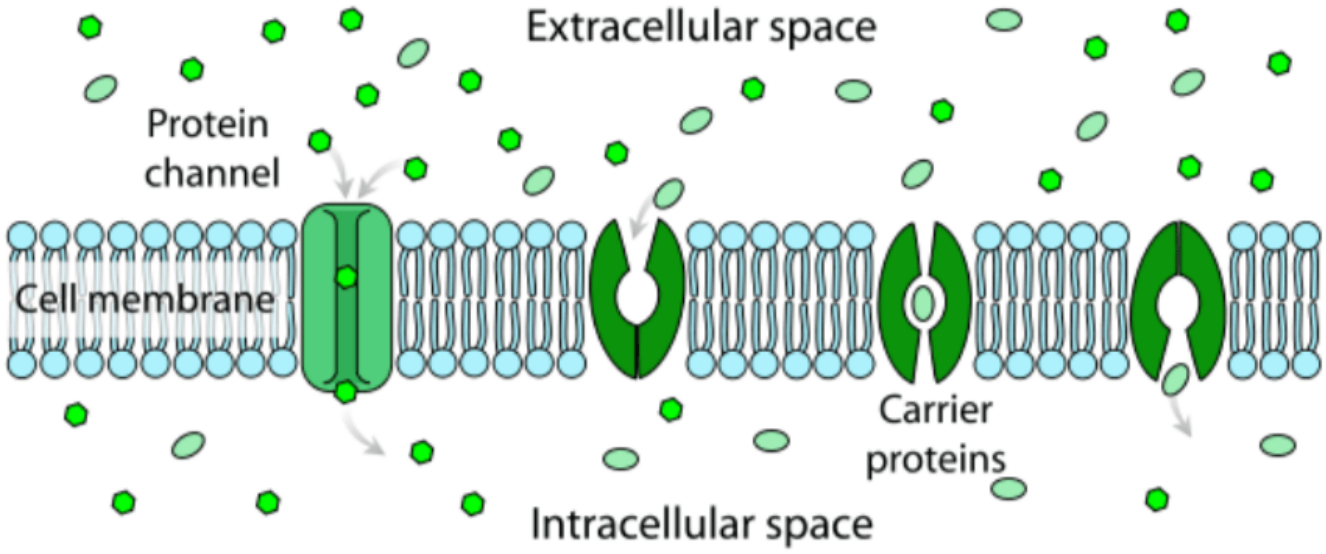


Figure 4.3.6: Facilitated diffusion examples2

YouTube Video

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Video 4.3.3: Passive transport. https://www.youtube.com/watch?v=s0p1ztrbXPY

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Active Uptake/Transport

There are two forms of active uptake/transport:

1. Active Carrier Transport
2. Endocytosis

Active Carrier Transport

Active carrier transport is similar to facilitated diffusion in that it utilizes a protein (carrier or transport). However, energy is also used to move compounds against their concentration gradient. The following figure and video do a nice job of illustrating active carrier transport.

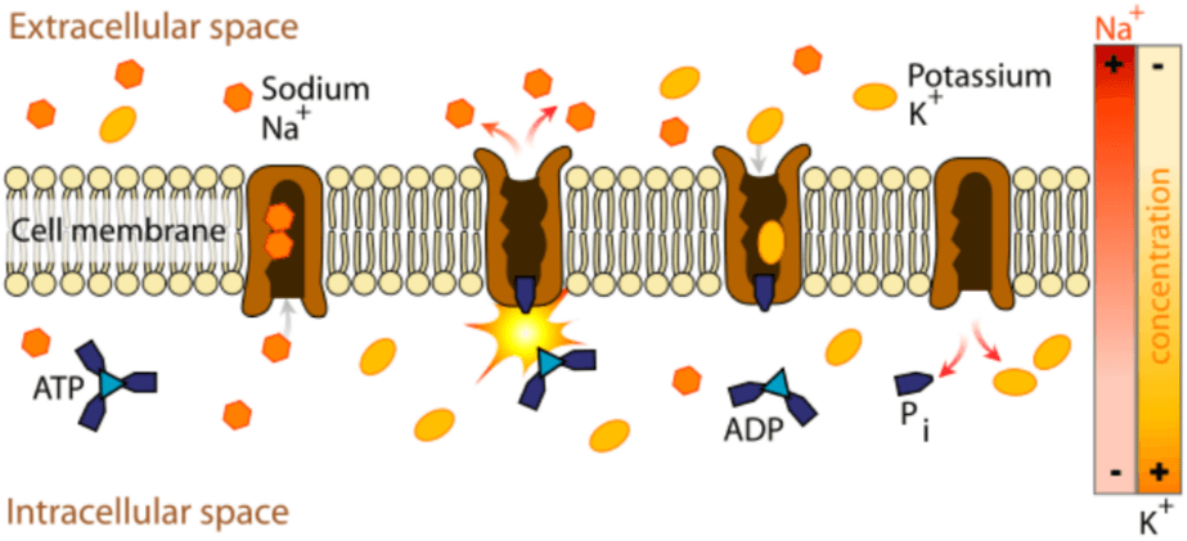


Figure 4.3.7: Sodium-potassium ATPase (aka sodium-potassium pump) an example of active carrier transport[3]

YouTube Video

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Video 4.3.4: Active transport. https://www.youtube.com/watch?v=STzOiRqzzL4

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Endocytosis

Endocytosis is the engulfing of particles, or fluids, to be taken up into the cell in vesicles formed from the cell membrane. If a particle is endocytosed, this process is referred to as phagocytosis. If a fluid is endocytosed, this process is referred to as pinocytosis as shown below.

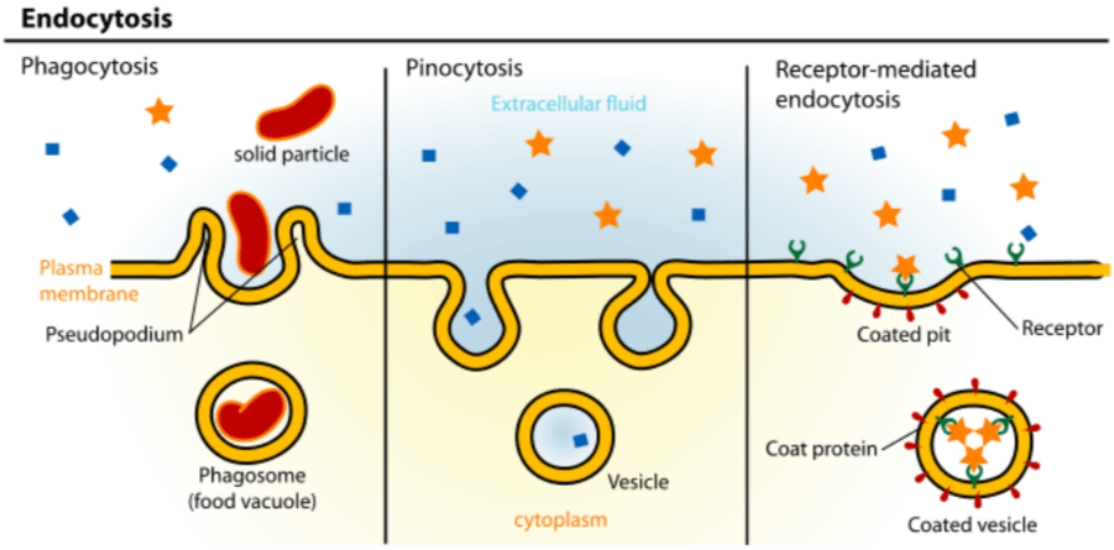


Figure 4.3.8: Different types of endocytosis[4]

The following video does a really nice job of showing how endocytosis occurs.

YouTube Video

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Video 4.3.5: Endocytosis. https://www.youtube.com/watch?v=4gLtk8Yc1Zc

Query 4.3.8

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1. en.Wikipedia.org/wiki/File:Os...ls_diagram.svg
2. en.Wikipedia.org/wiki/Facili...embrane-en.svg
3. en.Wikipedia.org/wiki/File:S...um_pump-en.svg
4. commons.wikimedia.org/wiki/Fi...osis_types.svg

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4.4: Carbohydrate Uptake, Absorption, Transport and Liver Uptake

Monosaccharides are taken up into the enterocyte. Glucose and galactose are taken up by the sodium-glucose cotransporter 1 (SGLT1, active carrier transport). The cotransporter part of the name of this transporter means that it also transports sodium along with glucose or galactose. Fructose is taken up by facilitated diffusion through glucose transporter (GLUT) 5. There are 12 glucose transporters that are named GLUT 1-12, and all use facilitated diffusion to transport monosaccharides. The different GLUTs have different functions and are expressed at high levels in different tissues. Thus, the intestine might be high in GLUT5, but not in GLUT12. Moving back to monosaccharides, inside the enterocyte, all three are then transported out of the enterocyte into the capillary (absorbed) through GLUT2 as shown below1.

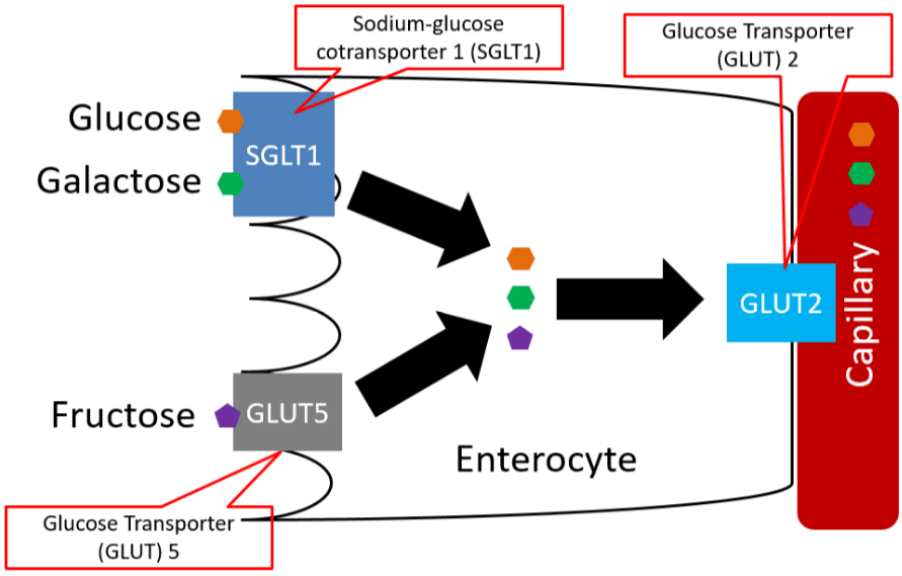


Figure 4.4.1: Carbohydrate uptake and absorption

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Inside of each villus there are capillaries and lacteals as shown below. Capillaries are the smallest blood vessels in the body, lacteals are also small vessels but are part of the lymphatic system, as will be described further in a later subsection.

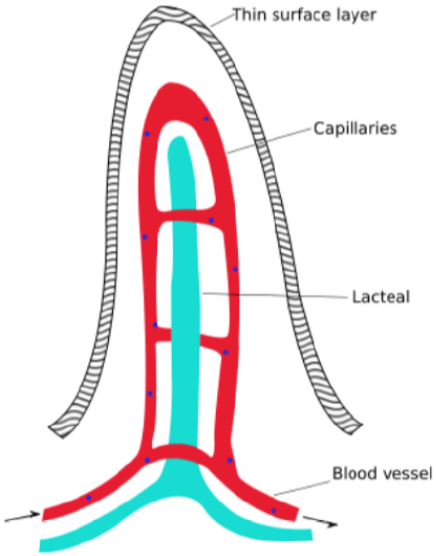


Figure 4.4.2: Anatomy of a villus2

The following video does a nice job of illustrating capillaries and lacteal and provides some basic details on uptake and absorption.

YouTube Video

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Video 4.4.1: Absorption in the small intestine. https://www.youtube.com/watch?v=P1sDOJM65Bc

The capillaries in the small intestine join to the portal vein, which transports monosaccharides directly to the liver. The figure below shows the portal vein and all the smaller vessels from the stomach, small intestine, and large intestine that feed into it.

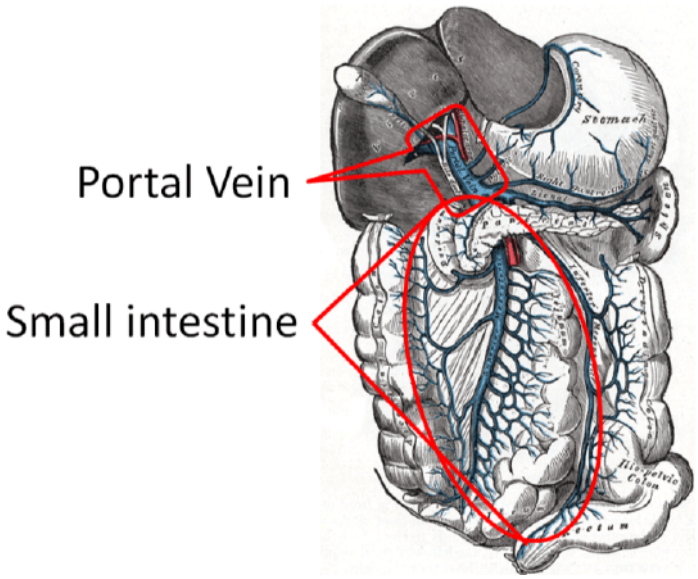


Figure 4.4.3: The portal vein transports monosaccharides and amino acids to the liver[3]

The video below shows how hepatic portal circulation flows.

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At the liver, galactose and fructose are completely taken up through GLUT 2 and GLUT5, respectively, while only 30-40% of glucose is taken up through GLUT2. After the monosaccharides are taken up, they are phosphorylated by their respective kinase enzymes forming galactose-1-phosphate, fructose-1-phosphate, and glucose-6-phosphate as shown below.

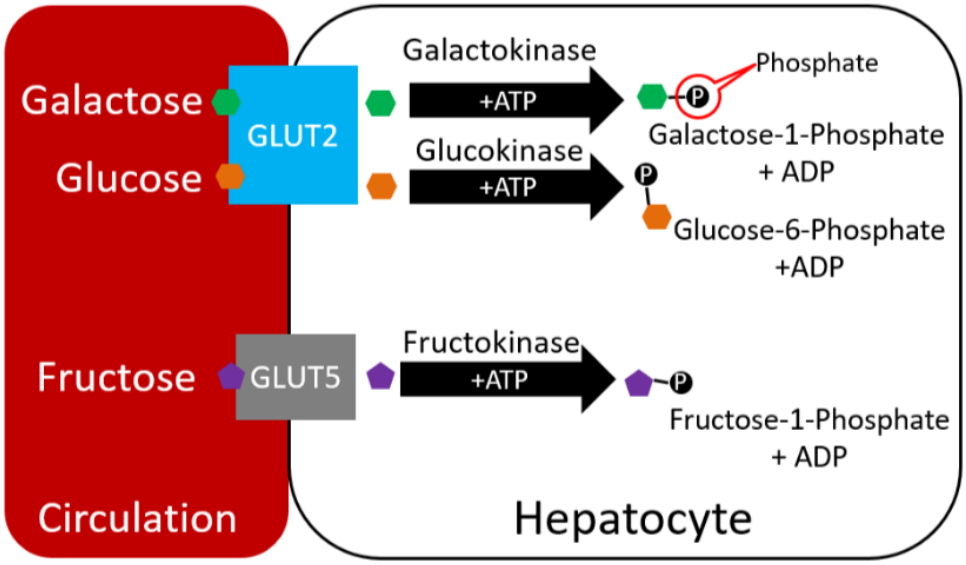


Figure 4.4.4: Hepatic monosaccharide uptake

Kinase enzymes normally phosphorylate substrates. Phosphorylation of the monosaccharides is important for maintaining the concentration gradient (by keeping nonphosphorylated monosaccharide levels within hepatocytes low) needed for facilitated diffusion through the GLUT transporters and for keeping monosaccharides in cells (so they do not move back out if the concentration gradient changes)3. In order, for the monosaccharide to leave the phosphate will need to be cleaved or removed.

Query 4.4.3

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References

1. Stipanuk MH. (2006) Biochemical, physiological, & molecular aspects of human nutrition. St. Louis, MO: Saunders Elsevier.
2. en.Wikipedia.org/wiki/File:In...simplified.svg
3. commons.wikimedia.org/wiki/File:Gray591.png

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4.5: Glycemic Response, Insulin, and Glucagon

If only 30-40% of glucose is being taken up by the liver, then what happens to the rest? How the body handles the rise in blood glucose after dietary intake is referred to as the glycemic response. The pancreas senses the blood glucose levels and responds appropriately. After dietary intake, the pancreatic beta-cells sense that glucose concentrations are high and secrete the hormone insulin, as shown below1.

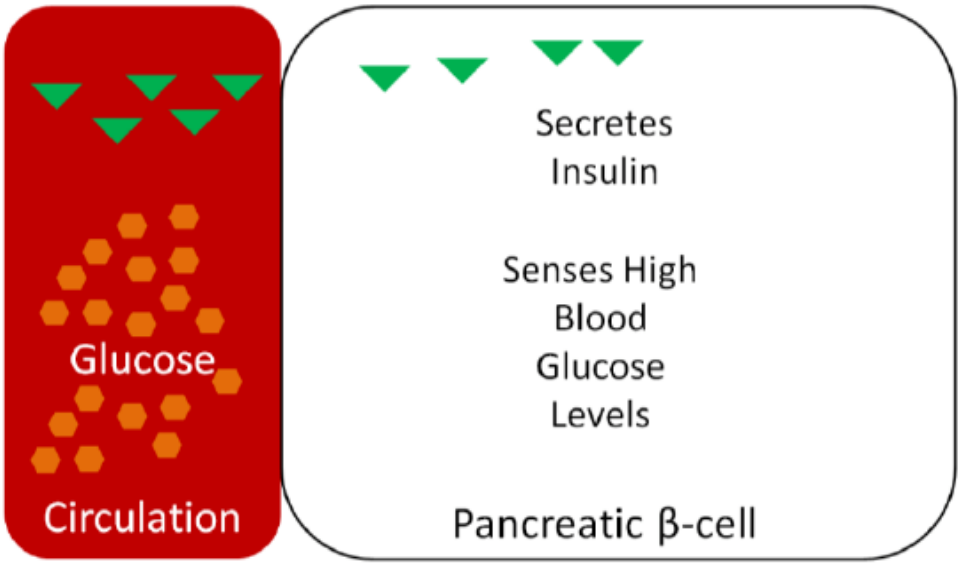


Figure 4.5.1: Pancreatic beta-cells sense high blood glucose and secrete insulin

Thus, as can be seen in the following figure, blood insulin concentrations peak and drop with blood glucose concentrations over the course of a day.

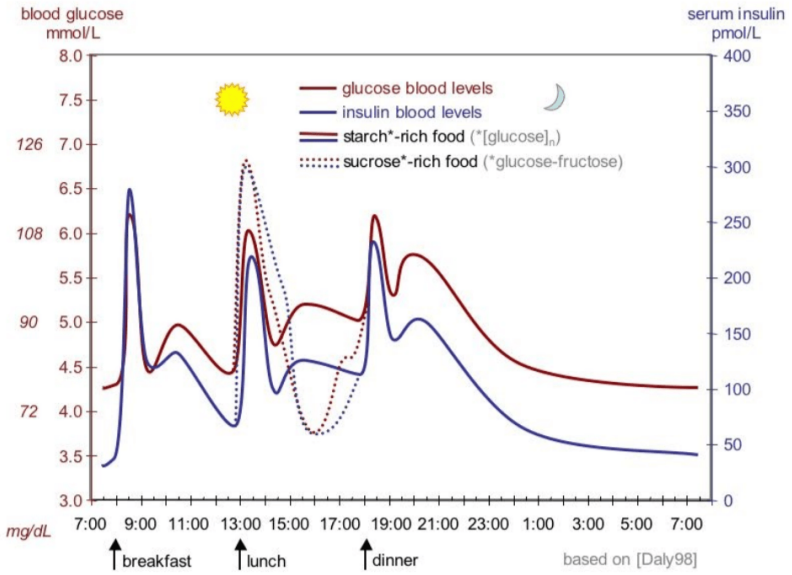


Figure 4.5.2: Representative figure of blood glucose and insulin levels during a 24-hour period2

Blood glucose and insulin concentrations rise following carbohydrate intake, and they drop after tissues have taken up the glucose from the blood (described below). Higher than normal blood sugar concentrations are referred to as hyperglycemia, while lower than normal blood sugar concentrations are known as hypoglycemia.

Insulin travels through the bloodstream to the muscle and adipose cells. There, insulin binds to the insulin receptor. This causes GLUT4 transporters that are in vesicles inside the cell to move to the cell surface as shown below.

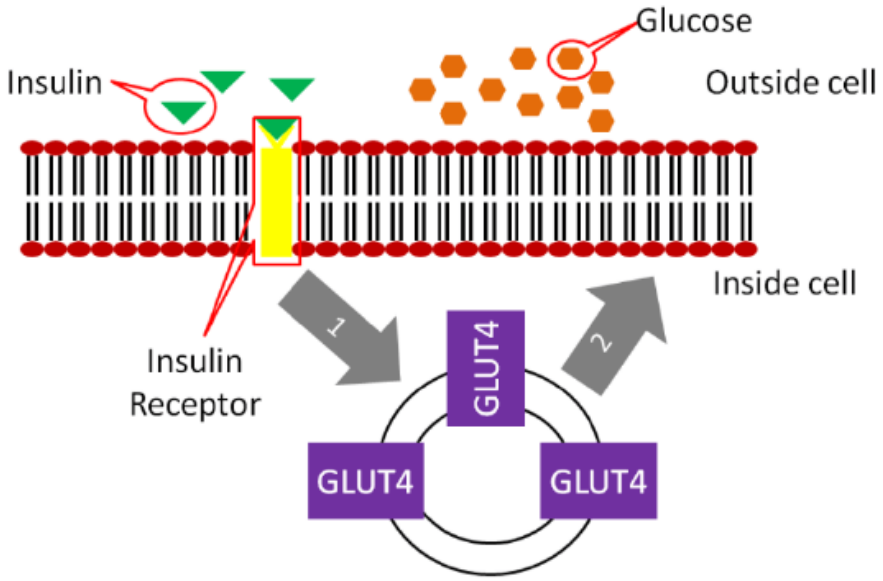


Figure 4.5.3: Response of muscle and adipose cells to insulin; 1) binding of insulin to its receptor, 2) movement of GLUT4 vesicles to the cell surface.

The movement of GLUT4 to the cell surface allows glucose to enter the muscle and adipose cells. The glucose is phosphorylated to glucose-6-phosphate by hexokinase (different enzyme but same function as glucokinase in liver) to maintain the concentration gradient.

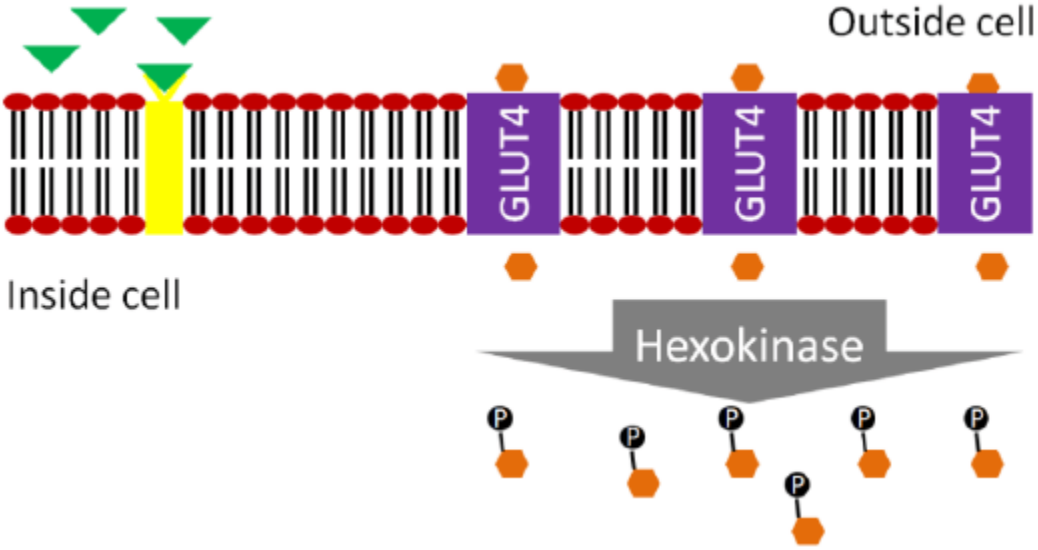


Figure 4.5.4: Response of muscle and adipose cells to insulin part 2; hexokinase phosphorylates glucose to glucose-6-phosphate

Glucagon is a hormone that has the opposite action of insulin. Glucagon is secreted from the alpha-cells of the pancreas when they sense that blood glucose levels are low, as shown below.

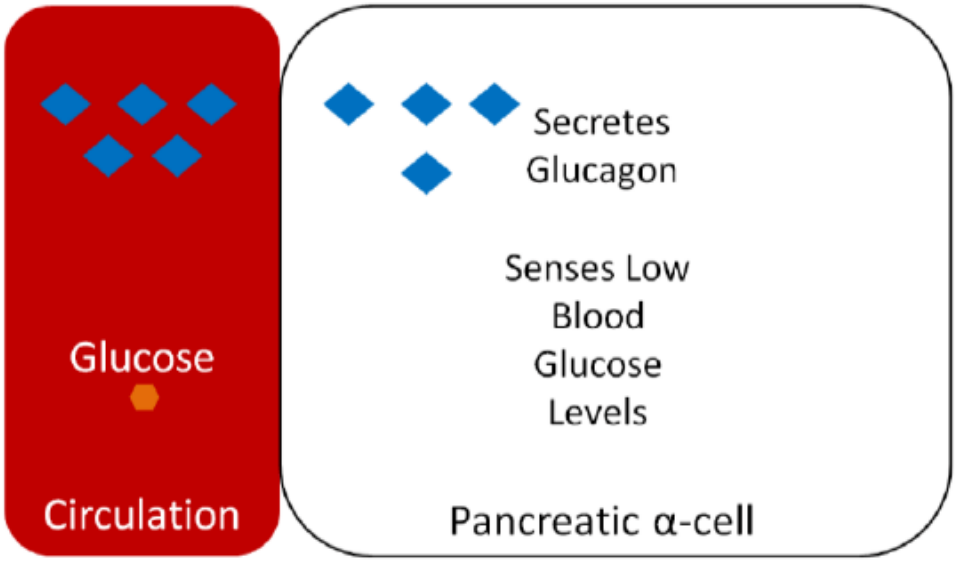


Figure 4.5.5: Glucagon secretion from pancreatic alpha-cells in response to low blood glucose levels.

Glucagon binds to the glucagon receptor in the liver, which causes the breakdown of glycogen to glucose-1-phosphate (which is then converted to glucose-6-phosphate) as illustrated below.

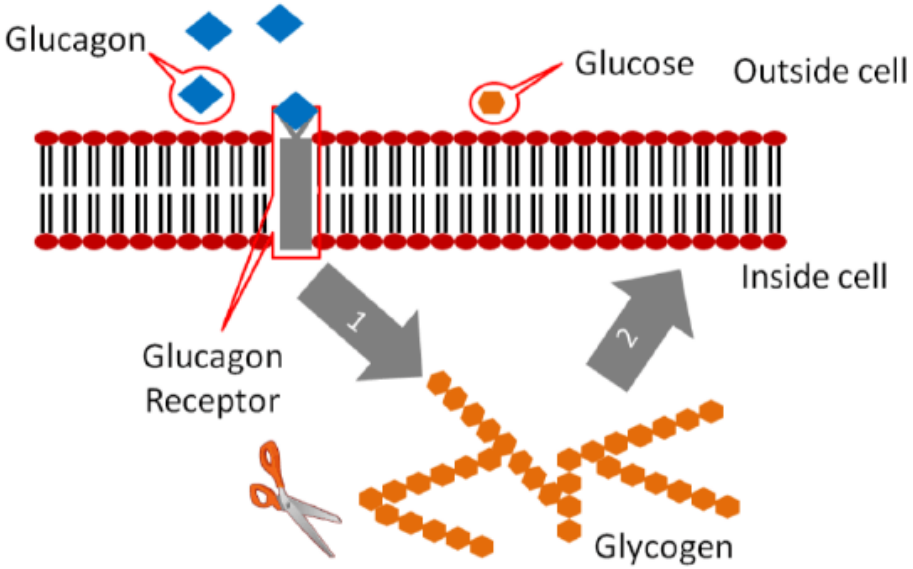


Figure 4.5.6: Glucagon binding to its receptor leads to the breakdown of glycogen to glucose.

The glucose-6-phosphate has a phosphate removed and glucose is then released into circulation to raise blood glucose concentrations as shown below. You'll learn more about these pathways in chapter 6.

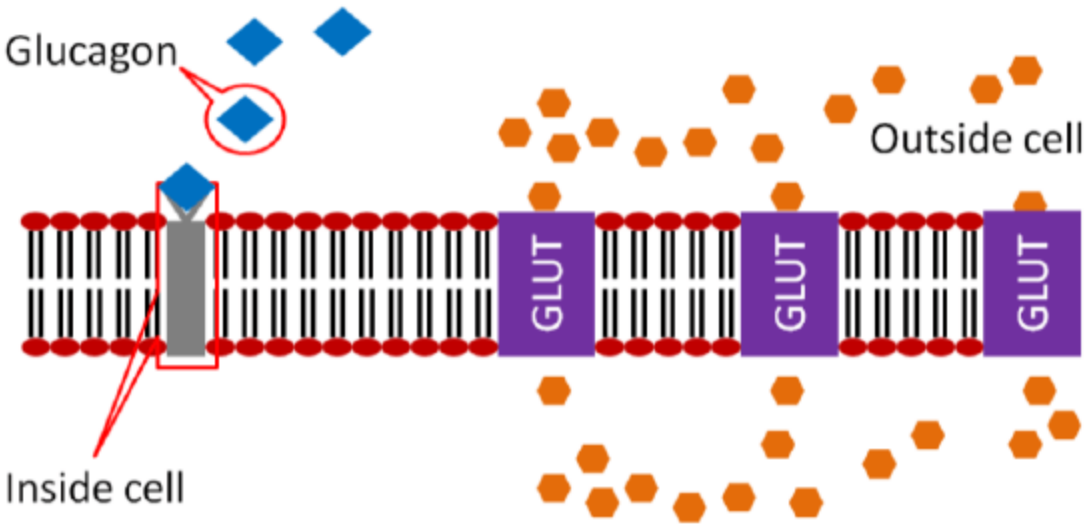


Figure 4.5.7: Glucagon leads to the release of glucose from the liver.

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Diabetes

Diabetes mellitus is a condition of chronically high blood sugar levels. The prevalence of diabetes in the US has been rapidly increasing; the link below provides some statistics about prevalence.

Web Link

Diabetes Statistics

There are 2 forms of diabetes, type 1 and type 2.

In type 1 diabetes, not enough insulin is produced and not enough binds to the insulin receptor as shown in the figure below.

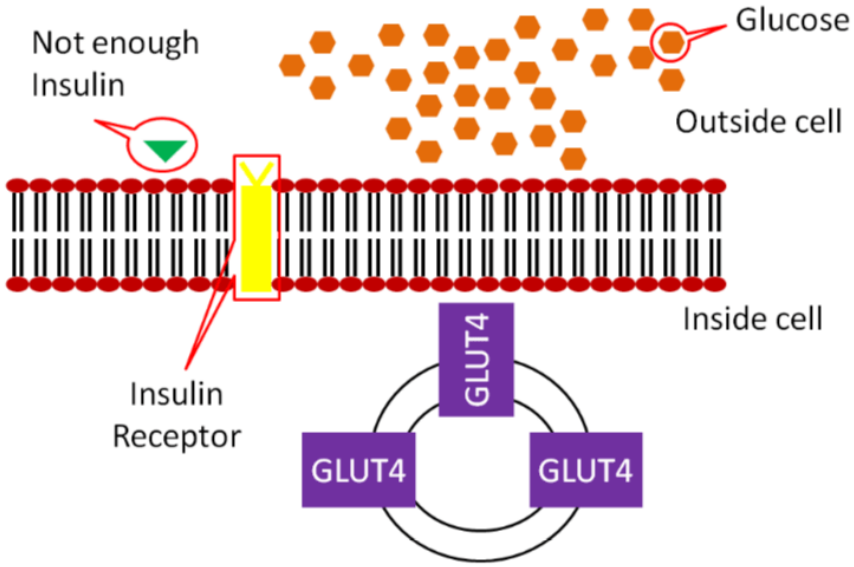


Figure 4.5.8: Type 1 diabetes

As a result, not enough GLUT4 makes it to the surface of muscle and adipose cells, meaning not enough glucose is taken up into these cells.

Type 1 diabetes was previously known as juvenile-onset, or insulin-dependent diabetes and is estimated to account for 5-10% of diabetes cases3. Type 1 diabetics receive insulin through injections or pumps to manage their blood sugar.

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In Type 2 diabetes, the body produces enough insulin, but the person's body is resistant to it. In Type 2 diabetics the binding of insulin to its receptor does not cause enough GLUT4 to move to the surface of the muscle and adipose cells, thus not enough glucose is taken up.

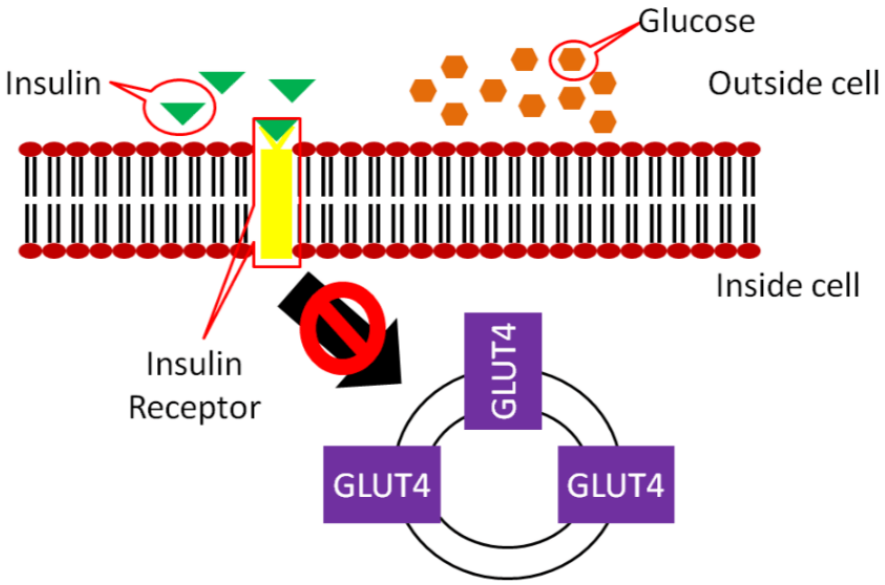


Figure 4.5.9: Type 2 diabetes

Type 2 diabetes accounts for 90-95% of diabetes cases and was once known as non-insulin-dependent diabetes or adult-onset diabetes3. However, with the increasing rates of obesity, many younger people are being diagnosed with Type 2, making the latter definition no longer appropriate. Some people with Type 2 diabetes can control their condition with a diet and exercise regimen. This regimen improves their insulin sensitivity, or their response to the body's own insulin. Others with Type 2 diabetes must receive insulin. These individuals may be producing enough insulin, but are so resistant to it that more is needed for glucose to be taken up by their muscle and adipose cells.

The video below illustrates Type 2 diabetes. However, I do not agree, nor do I teach, that type 2 diabetics have decreased insulin levels as described in the video.

YouTube Video

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Video 4.5.1: Type 2 diabetes. I do not agree, nor do I teach, that type 2 diabetics have decreased insulin levels as described. https://www.youtube.com/watch?v=VLiTbb6MaEU

Query 4.5.4

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Glycemic Index

Research has indicated that hyperglycemia is associated with chronic diseases and obesity. As a result, measures of the glycemic response to food consumption have been developed so that people can choose foods with a smaller glycemic response. The first measure developed for this purpose was the glycemic index. The glycemic index is the relative change in blood glucose after consumption of 50 g of carbohydrate in a test food compared to 50 g of carbohydrates of a reference food (white bread or glucose). Thus, a high glycemic index food will produce a greater rise in blood glucose concentrations compared to a low glycemic index food, as shown below.

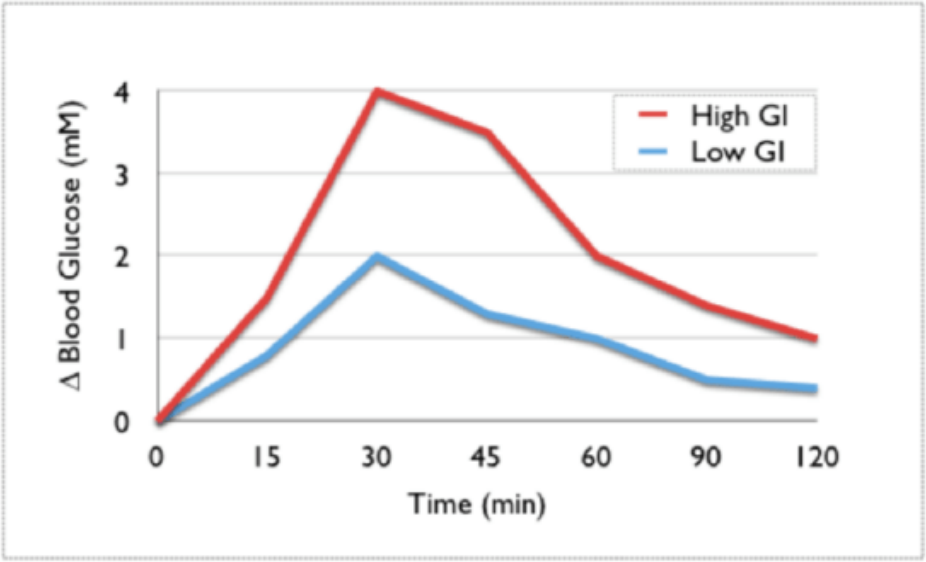


Figure 4.5.10: Blood glucose response to a high glycemic index (GI) food compared to a low glycemic index food4

As a general guideline, a glycemic index that is 70 or greater is high, 56-69 is medium, and 55 and below is low. A stop light graphical presentation has been designed to emphasize the consumption of low glycemic index foods while cautioning against the consumption of too many high glycemic index foods5.

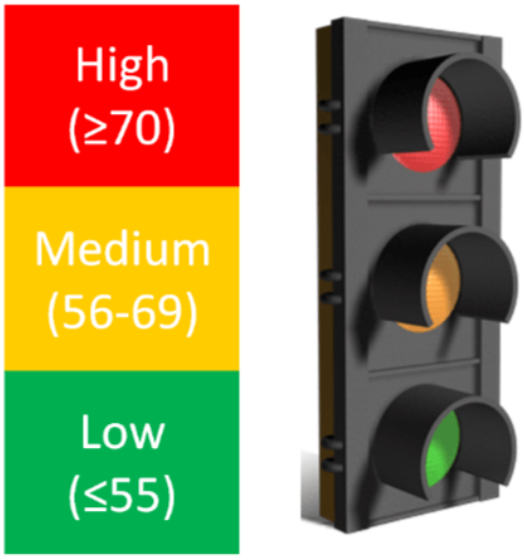


Figure 4.5.11: Food glycemic index classifications5

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The main problem with the glycemic index is that it does not take into account serving size. Let's take popcorn (glycemic index 89-127) as an example. A serving size of popcorn is 20 g, 11 g of which is carbohydrate6. This is equal to approximately 2.5 cups of popcorn7. Thus, a person would have to consume over 11 cups of popcorn to consume 50 g of carbohydrate needed for the glycemic index measurement. Another example is watermelon, which has a glycemic index of 103, with a 120 g serving containing only 6 g of carbohydrates3. To consume 50 g of carbohydrates needed for glycemic index measurement, a person would need to consume over 1000 g (1 kg) of watermelon. Assuming this is all watermelon flesh (no rind), this would be over 6.5 cups of watermelon7.

The website glycemicindex.com (link provided below) contains a database where you can search to see the food's glycemic index and glycemic load (covered in the next section). The database contains details on how the measurement was done and more information on the product itself. The top link below will take you to this website. The second link is to another database that contains the same information that might be easier for some people to use. However, please note that in the second link the glycemic loads are calculated using 100 g serving sizes for all foods. This might not be the actual serving size for all foods, which is what is typically used, so it is important to keep this in mind.

Web Links

- glycemicindex.com
- Glycemic Index & Glycemic Load of Foods

Query 4.5.6

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Glycemic Load

To incorporate serving size into the calculation, another measure known as the glycemic load has been developed. It is calculated as shown below:

$$\text{Glycemic Load } = (\text{Glycemic Index } \times X\text{gCarbs/serving})/100$$

Thus, in most instances, the glycemic load is a more meaningful measure of the glycemic response of different foods. Considering the two examples from the glycemic index section, their glycemic loads would be:

Popcorn: $(89-127 \times 11\text{g Carbs/Serving })/100 = 10-14$

Watermelon: $(103 \times 6\text{g Carbs/Serving })/100 = 6.18$

As a general guideline for glycemic loads of foods : 20 or above is high, 11-19 is medium, and 10 or below is low8,9.

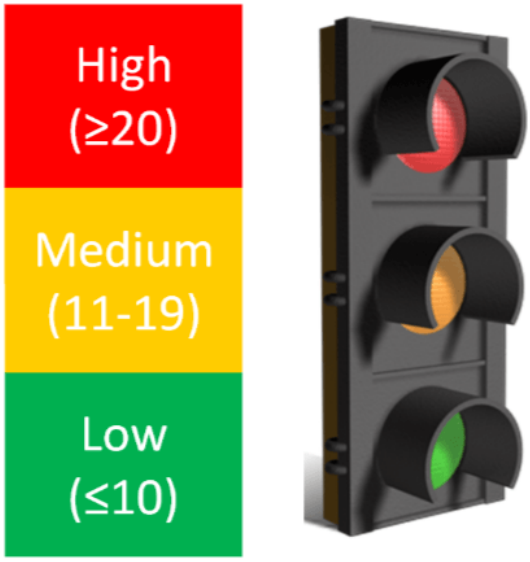


Figure 4.531 Food glycemic load classifications[8,9]

Putting it all together, popcorn and watermelon have high glycemic indexes, but medium and low glycemic loads, respectively.

You can also use the top two links below to find the glycemic load of foods. However, please note that in the second link the glycemic loads are calculated using 100g serving sizes for all foods. This might not be the actual serving size for all foods, which is what is typically used, so it is important to keep this in mind. The third link is to the NutritionData estimated glycemic load tool that is pretty good at estimating the glycemic loads of foods, even if actual glycemic indexes have not been measured.

Web Links

- glycemicindex.com
- Glycemic Index & Glycemic Load of Foods
- Estimated Glycemic Load

Query 4.5.7

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3. diabetes.niddk.nih.gov/dm/pub...atistics/#what
4. upload.wikimedia.org/wikipedi...c/Glycemic.png
5. www.glycemicindex.com
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7. USDA National Nutrient Database - http://www.nal.usda.gov/fnic/foodcomp/search/
8. http://www.mendosa.com/gilists.htm

9. http://www.nutritiondata.com/help/es...-glycemic-load

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4.6: Protein Uptake, Absorption, Transport and Liver Uptake

There are a number of similarities between carbohydrate and protein uptake, absorption, transport, and uptake by the liver. Hopefully after this section you will understand these similarities.

Over 60% of all amino acids are taken up into the enterocyte as di- and tripeptides through the PepT1 transporter. Individual amino acids are taken up through a variety of amino acid transporters. Once inside the enterocyte, peptidases cleave the peptides to individual amino acids. These cleaved amino acids, along with those that were taken up as individual amino acids, are moved into the capillary by another variety of amino acid transporters (some are the same as on the brush border, some are different).

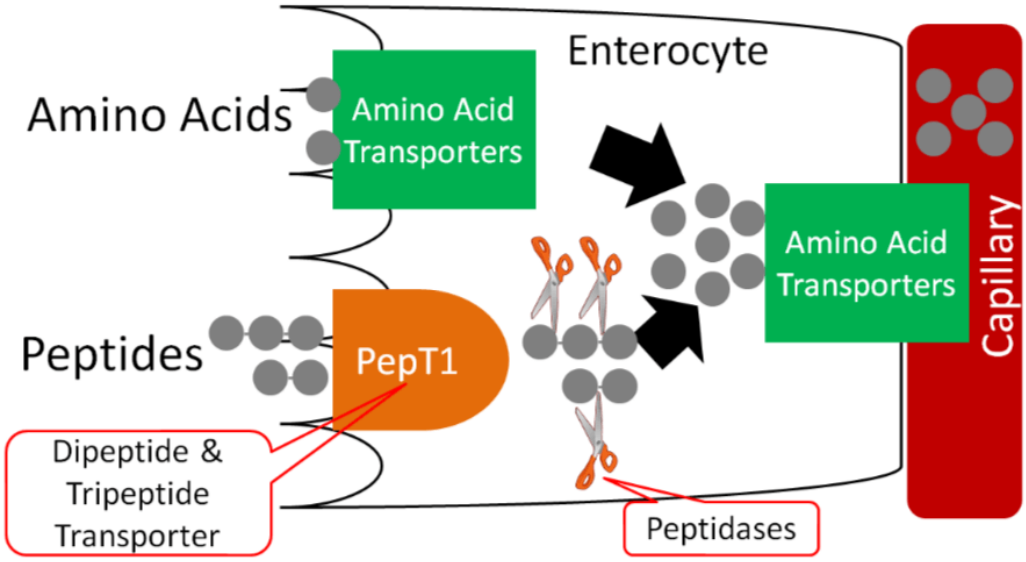


Figure 4.6.1: Protein uptake and absorption

The capillary inside a villus is shown below.

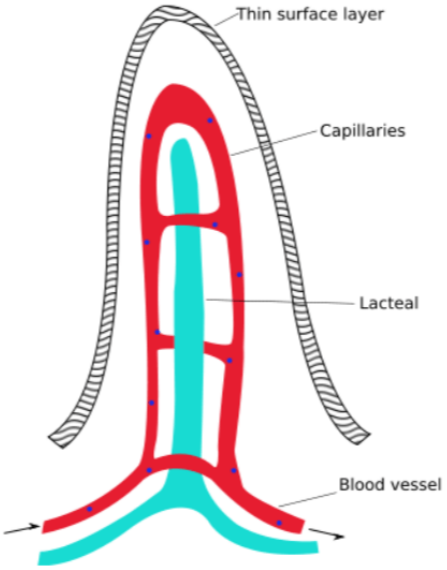


Figure 4.6.2: Anatomy of a villus1

Like monosaccharides, amino acids are transported directly to the liver through the portal vein.

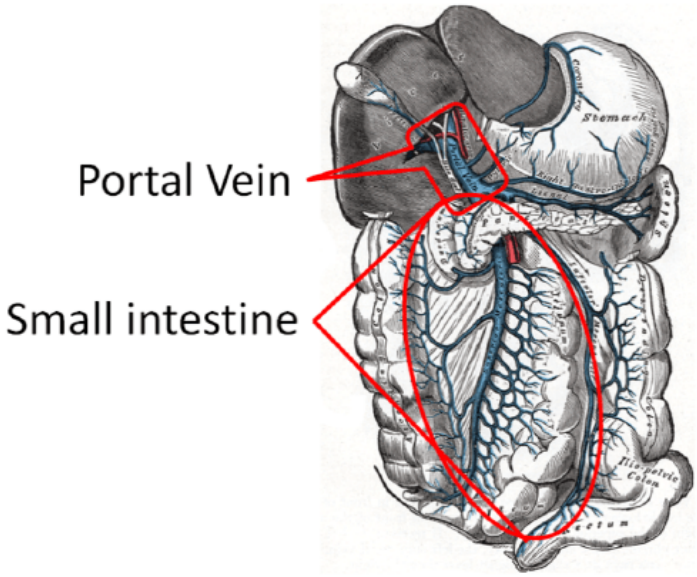


Figure 4.6.3: The portal vein transports monosaccharides and amino acids to the liver2

Amino acids are taken up into the hepatocyte through a variety of amino acid transporters. The amino acids can then be used to either make proteins or are broken down to produce glucose, as will be described in chapter 6.

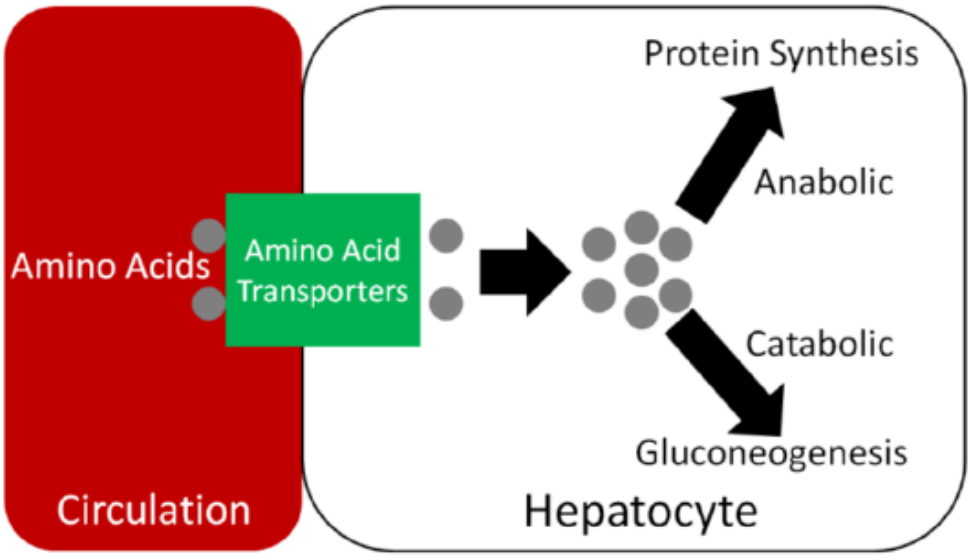


Figure 4.6.4: Hepatic amino acid uptake

Query 4.6.1

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References

1. en.Wikipedia.org/wiki/File:In...simplified.svg
2. commons.wikimedia.org/wiki/File:Gray591.png

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4.7: Lipid Uptake, Absorption and Transport

Once mixed micelles reach the brush border of the enterocyte, two different lipid uptake mechanisms are believed to occur, but lipid uptake is not completely understood. One mechanism is that individual components of micelles may diffuse across the enterocyte. Otherwise, it is believed that some components may be taken up through unresolved transporters. For example, cholesterol transporters have been identified, but their overall mechanism of absorption is not well understood. The individual compounds are taken up as shown below.

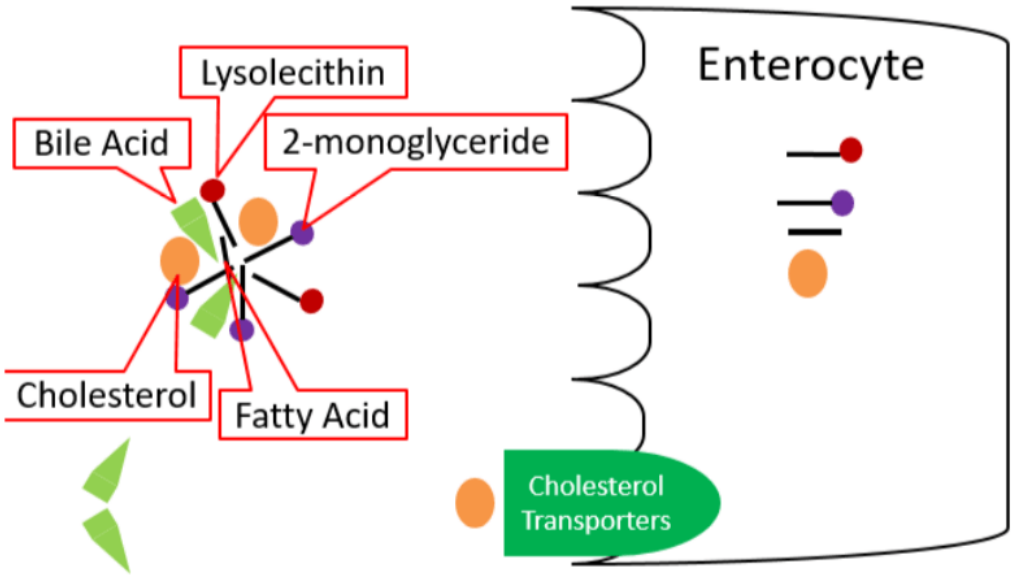


Figure 4.7.1: Uptake of mixed micelle components into the enterocyte

Once inside the enterocyte, there are different fates for fatty acids, depending on their length. Short- and medium-chain fatty acids move through the enterocyte and enter circulation through the capillaries; they are transported by the protein albumin. They will be carried to the liver by the portal vein, like monosaccharides and amino acids. Long-chain fatty acids, 2-monoglyceride, lysolecithin, and cholesterol will be re-esterified forming triglycerides, phosphatidylcholine, and cholesterol esters, respectively. These re-esterified lipids are then packaged into chylomicrons, which are lipoproteins, that are described in further detail in the next section. These chylomicrons are too large to fit through the pores in the capillaries, but they can fit through the larger fenestrations (openings) in the lacteal.

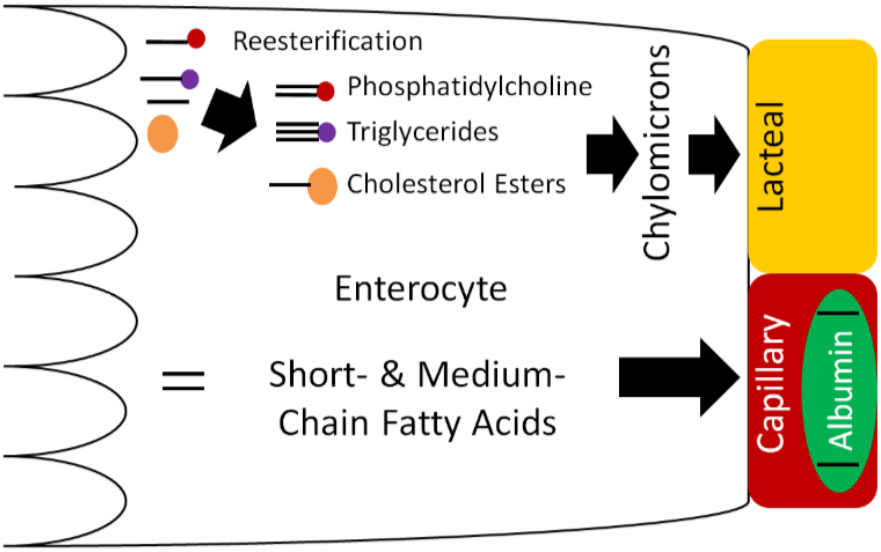


Figure 4.7.2: Fates of lipids in the enterocyte

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Lacteals (shown below) are small vessels that feed into the lymphatic system. Thus, the chylomicrons enter the lacteals and enter into lymphatic circulation.

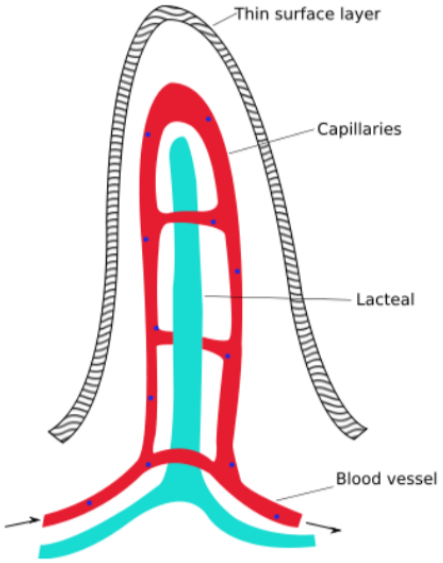


Figure 4.7.3: Anatomy of a villus, with the lacteal shown in blue[1]

The lymphatic system is a system similar to the circulatory system in that it contains vessels that transport fluid. However, instead of blood, the lymphatic system contains a clear fluid known as lymph. There are a number of lymph nodes (small glands) within the lymphatic system that play a key role in the body's immune system. The figure below shows the lymphatic system.

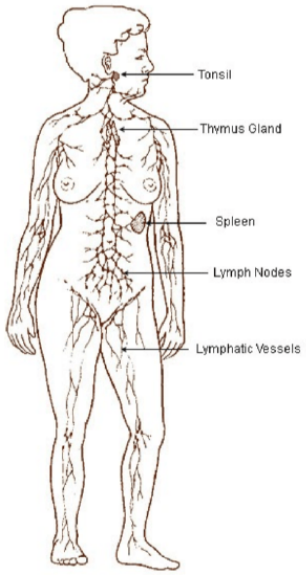


Figure 4.7.4: The lymphatic system2

The following videos describe and illustrate how the lymphatic system and lymph functions.

YouTube Video

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Video 4.7.1: The lymphatic system. https://www.youtube.com/watch?v=qTXTDqvPnRk

YouTube Video

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View this YouTube Video online

Video 4.7.2: Lymph movement. https://www.youtube.com/watch?v=UpiJMzfHgYM

The lymphatic system enters general circulation through the thoracic duct that enters the left subclavian vein as shown below. General in this case means that it is not directed to the liver like other components that have been absorbed.

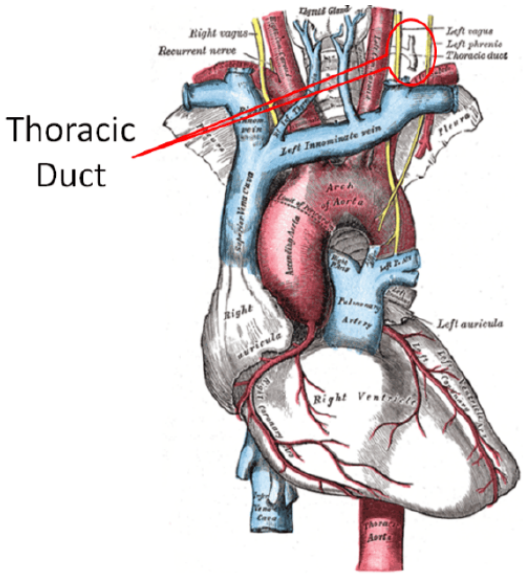


Figure 4.7.5: The thoracic duct is where the lymphatic system enters circulation[3]

The animation below is an overview of lipid digestion, uptake, and initial transport.

Web Links

Animation: Lipid Digestion, Uptake, and Transport

Query 4.7.2

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Lipoproteins

Lipoproteins, as the name suggests, are complexes of lipids and protein. The proteins within a lipoprotein are called apolipoproteins (aka apoproteins). There are a number of different apolipoproteins that are abbreviated apo-, then an identifying letter (i.e. Apo A) as shown in the chylomicron below.

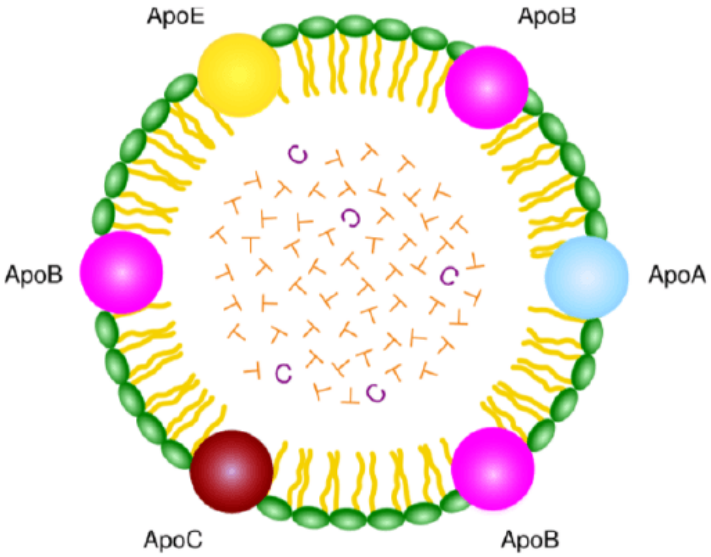


Figure 4.7.6: Chylomicron structure[4]

The following video does a nice job of illustrating the different lipoprotein components.

YouTube Video

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Video 4.7.3: Animation describing the structure and components of a lipoprotein. https://www.youtube.com/watch?v=x-4ZQaiZry8

There are a number of lipoproteins in the body. They differ by the apolipoproteins they contain, size (diameter), density, and composition. The table below shows the difference in density and diameter of different lipoproteins. Notice that as diameter decreases, density increases.

Table 4.7.1: The density and diameter of different lipoproteins[5]

Lipoprotein	Density (g/dL)	Diameter (nm)
Chylomicrons	0.95	75-1200
VLDL (very low-density lipoproteins)	0.95-1.006	30-80
IDL (intermediate-density lipoproteins)	1.006-1.019	25-35
LDL (low-density lipoproteins)	1.019-1.063	18-25
HDL (high-density lipoproteins)	1.063-1.21	5-12

This inverse relationship is a result of the larger lipoproteins being composed of a higher percentage of triglyceride and a lower percentage of protein as shown below.

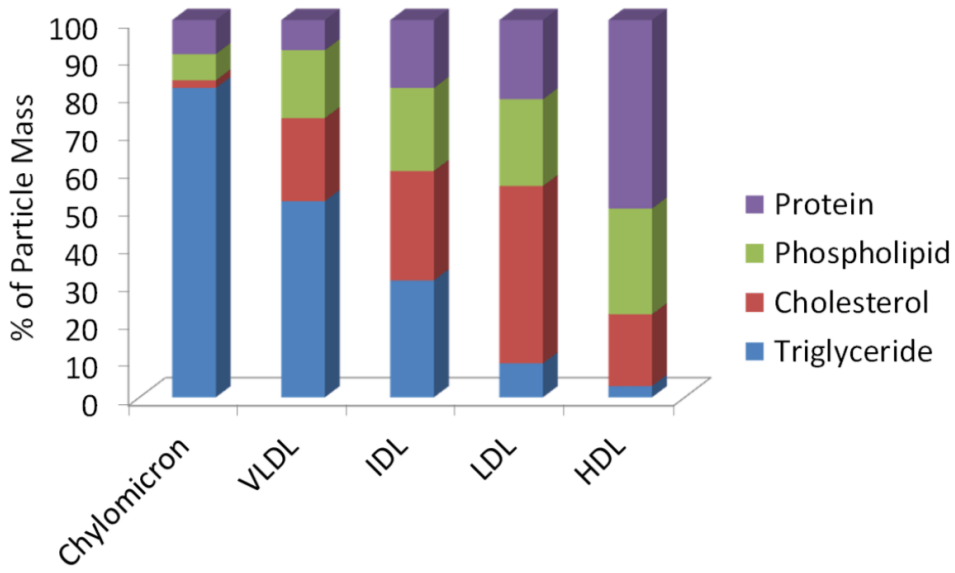


Figure 4.7.7: Composition of lipoproteins6

Protein is more dense than triglyceride (why muscle weighs more than fat), thus the higher protein/lower triglyceride composition, the higher the density of the lipoprotein. Many of the lipoproteins are named based on their densities (i.e. very low-density lipoproteins).

As described in the last subsection, the lipoproteins released from the small intestine are chylomicrons. The video below does a nice job of showing, describing, and illustrating how chylomicrons are constructed and function.

YouTube Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

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Video 4.7.4: How chylomicrons are constructed and function. https://www.youtube.com/watch?v=hRx_i9npTDU

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Query 4.7.4

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The endothelial cells that line blood vessels, especially in the muscle and adipose tissue, contain the enzyme lipoprotein lipase (LPL). LPL cleaves the fatty acids from lipoprotein triglycerides so that the fatty acids can be taken up into tissues. The figure below illustrates how endothelial cells are in contact with the blood that flows through the lumen of blood vessels.

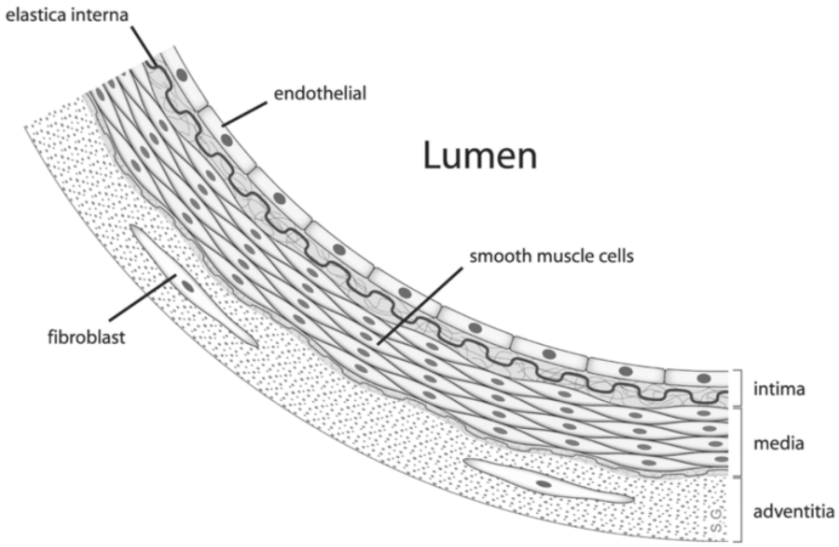


Figure 4.7.8: Lining of a blood vessel. The lumen is where the blood would be flowing, thus endothelial cells are those that are in contact with blood[7]

LPL cleaves fatty acids from the triglycerides in the chylomicron, decreasing the amount of triglyceride in the lipoprotein. This lipoprotein with less triglycerides becomes what is known as a chylomicron remnant, as shown below.

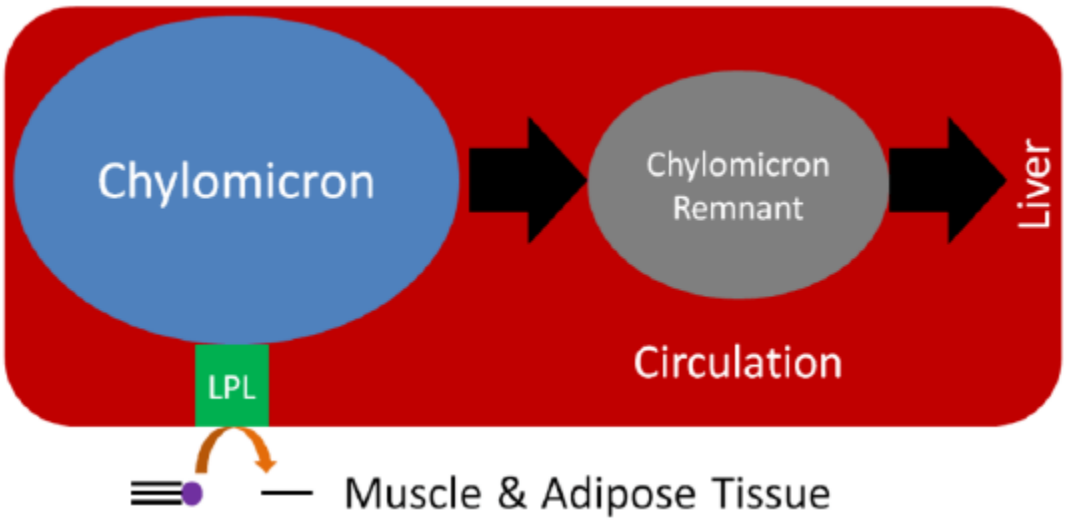


Figure 4.7.9: The cleavage of triglycerides by LPL from a chylomicron leads to the formation of a chylomicron remnant.

Now in the form of a chylomicron remnant, the digested lipid components originally packaged into the chylomicron are directed to the liver where the chylomicron remnant is endocytosed. This process of clearing chylomicrons from the blood takes 2-10 hours after a meal5. This is why people must fast 12 hours before having their blood lipids (triglycerides, HDL, LDL etc.) measured. This fast allows all the chylomicrons and chylomicron remnants to be cleared before blood is taken. However, whether patients should be asked to fast has been questioned as described in the link below.

Web Link

Should you fast before a cholesterol test?

After the chylomicron remnant is endocytosed, it is broken down to its individual components (triglycerides, cholesterol, protein etc.). In the liver, VLDL are produced, similar to how chylomicrons are produced in the small intestine. The individual components are packaged into VLDL and secreted into circulation as shown below.

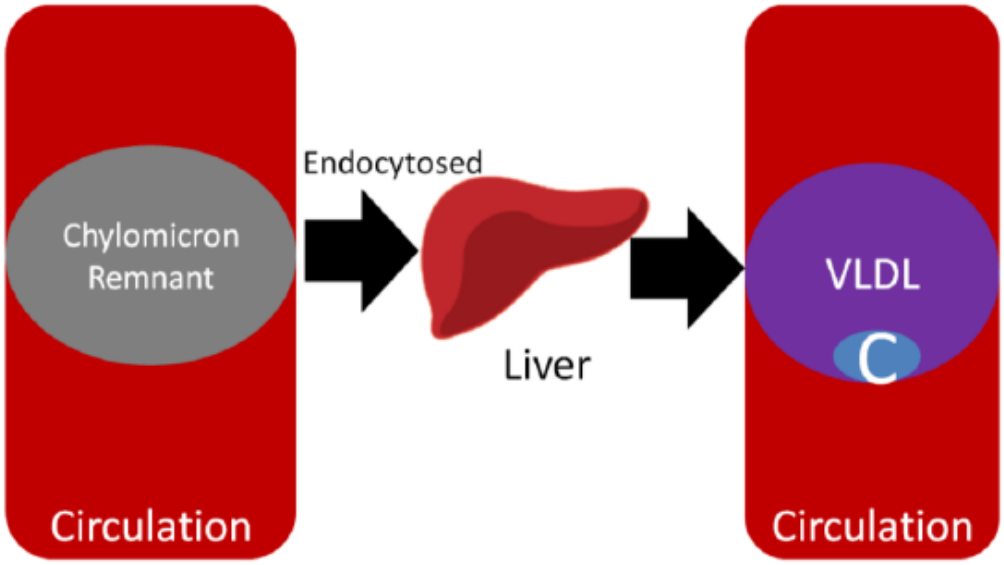


Figure 4.7.10: Chylomicron remnants are taken up by the liver. The liver secretes VLDL that contain cholesterol (C)

Like it does to chylomicrons, LPL cleaves fatty acids from triglycerides in VLDL, forming the smaller IDL (aka VLDL remnant). Further action of LPL on IDL results in the formation of LDL. The C in Figures 4.715 and 4.716 represents cholesterol, which is not increasing; rather, since triglyceride is being removed, it constitutes a greater percentage of particle mass of lipoproteins. As a result, LDL is composed mostly of cholesterol, as depicted in the figure below.

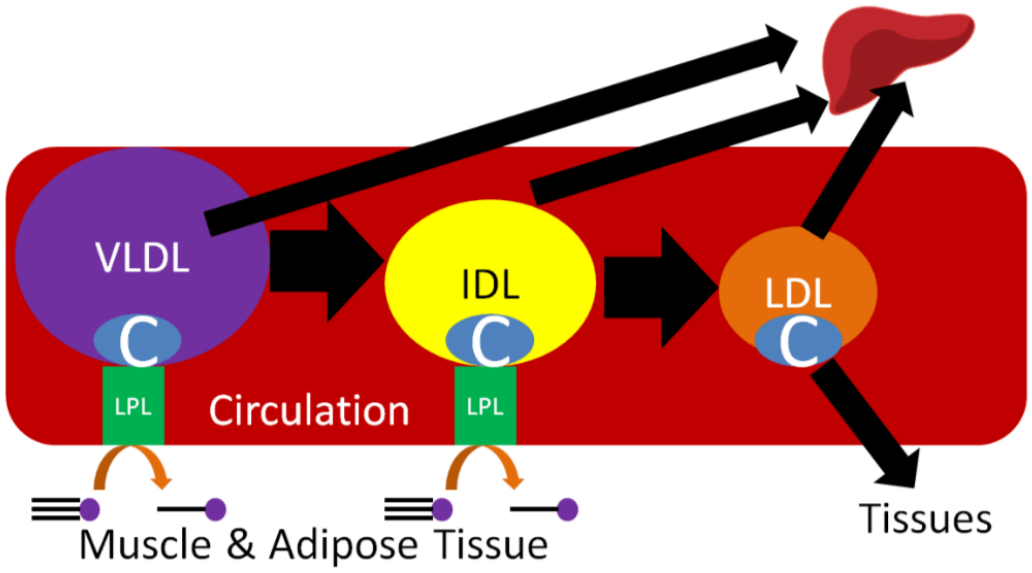


Figure 4.7.11: Formation of IDL and LDL from VLDL

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LDL contains a specific apolipoprotein (Apo B100) that binds to LDL receptors on the surface of target tissues. The LDL are then endocytosed into the target tissue and broken down to cholesterol and amino acids.

HDL are made up of mostly protein and are derived from the liver and intestine. HDL participates in reverse cholesterol transport, which is the transport of cholesterol back to the liver. HDL picks up cholesterol from tissues/blood vessels and returns it to the liver itself or transfers it to other lipoproteins returning to the liver.

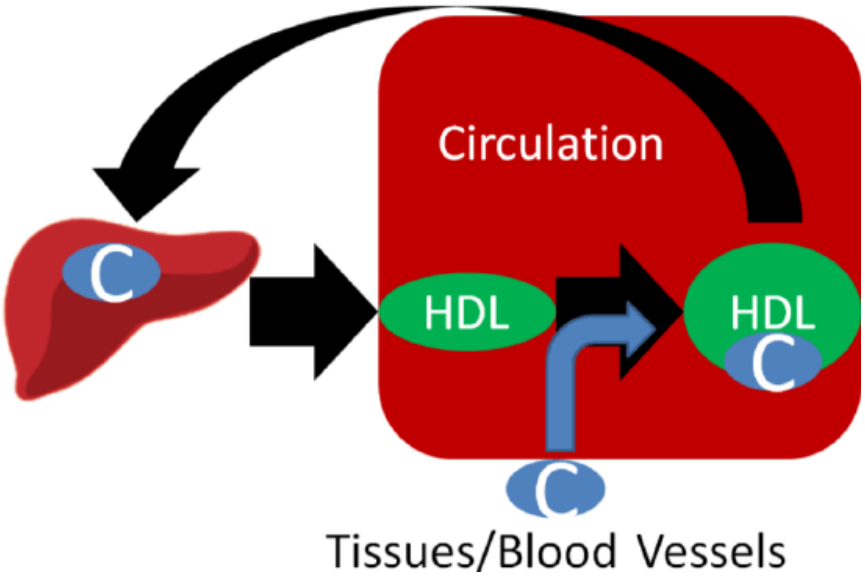


Figure 4.7.12: HDL is involved in reverse cholesterol transport

The animation under the transport button in the following link does a really nice job of going through the process of lipoprotein transport.

Web Link

- Lipoprotein Animation

Query 4.7.6

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You are probably familiar with HDL and LDL being referred to as "good cholesterol" and "bad cholesterol," respectively. This is an oversimplification to help the public interpret their blood lipid values, because cholesterol is cholesterol; it's not good or bad. LDL and HDL are lipoproteins, and as a result you can't consume good or bad cholesterol, you consume cholesterol. A more appropriate descriptor for these lipoproteins would be HDL "good cholesterol transporter" and LDL "bad cholesterol transporter."

What's so bad about LDL? LDL enters the endothelium where it is oxidized. This LDL and/or oxidized LDL is engulfed by white blood cells (macrophages), leading to the formation of what are known as foam cells. The foam cells eventually accumulate so much LDL that they die and accumulate, forming a fatty streak. From there the fatty streak, which is the beginning stages of a lesion, can continue to grow until it blocks the artery. This can result in a myocardial infarction (heart attack) or a stroke. HDL is good in that it scavenges cholesterol from other lipoproteins or cells and returns it to the liver. The figure below shows the formation of the fatty streak and how this can progress to a point where it greatly alters blood flow.

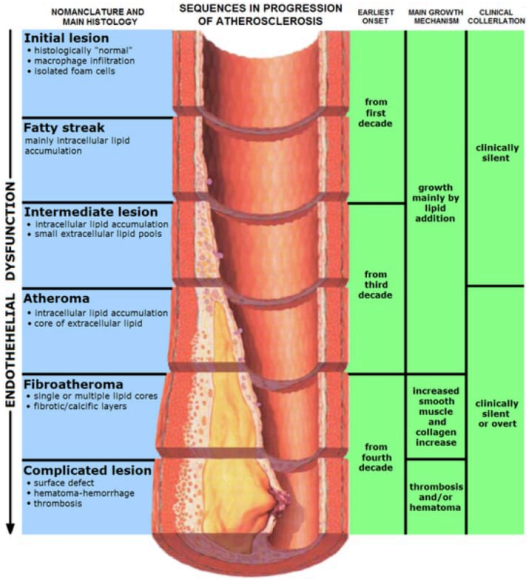


Figure 4.7.13: The formation of a lesion in an artery[9]

The video below does an excellent job of illustrating this process. However there are two caveats to point out. First, it incorrectly refers to cholesterol (LDL-C etc.), and second, it is clearly made by a drug company, so keep these factors in mind. The link below is the American Heart Association's simple animation of how atherosclerosis develops.

YouTube Video

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Video 4.7.5: Atherosclerosis and its complex biological process. First, it incorrectly refers to cholesterol (LDL-C etc.), and second, it is clearly made by a drug company, so keep these factors in mind. https://www.youtube.com/watch?v=fLonh7ZesKs&feature=rec-HM-r2

Web Link

Cholesterol and CAD

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Query 4.7.8

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Despite what you learned above about HDL, a recent study questions its importance in preventing cardiovascular disease. It found that people who have genetic variations that lead to higher HDL levels were not at decreased risk of developing cardiovascular disease. You can read more about this interesting finding in the first link below. In addition, another recent study is questioning whether saturated fat is associated with an increased risk of cardiovascular disease.

Web Link

Doubt Cast on the 'Good' in 'Good Cholesterol'

Study Questions Fat and Heart Disease Link

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Query 4.7.10

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References

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5: COMMON DIGESTIVE PROBLEMS

Before moving to metabolism, in this chapter you will learn about some common digestive problems.

5.1: Peptic Ulcers

5.2: Gallstones

5.3: Irritable Bowel Syndrome

5.4: Inflammatory Bowel Disease

5.5: Celiac Disease and Gluten

5.6: Diverticulosis and Diverticulitis

5.7: Hemorrhoids

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5.1: Peptic Ulcers

When the mucus layer of the stomach or duodenum becomes too thin, acid can erode the cells lining these tissues. This results in a lesion known as a peptic ulcer, as shown below.

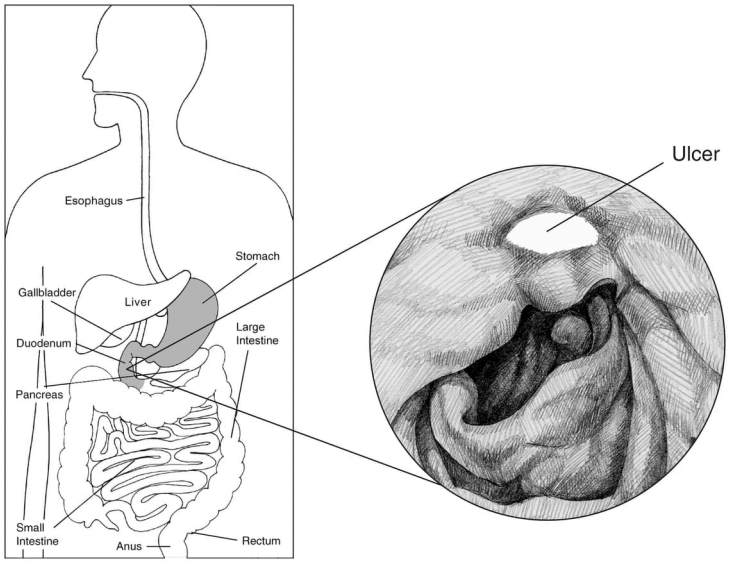


Figure 5.1.1: A peptic ulcer in the duodenum[1]

10% of Americans will develop an ulcer in their lifetime. Despite common beliefs, these ulcers are not caused by stress or spicy foods. Most ulcers are believed to be caused by the acid-resistant bacteria, Helicobacter pylori. 30-40% of Americans are infected with this bacteria. Helicobacter pylori causes a thinning of the mucus that protects the stomach and duodenum from gastric acid. It is not clear how Helicobacter pylori is transmitted, though it may be through contaminated food or water. It might also be spread through contact with vomit, feces, or saliva of an infected person[1].

Prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, or naproxen (Aleve) are also frequent causes of peptic ulcers. NSAIDs inhibit the production of a protective eicosanoid[1]. The first video describes and illustrates this effect. It describes how goblet cells secrete mucus in the stomach. This is not correct, they secrete mucus in the intestine. It should be neck cells in the stomach.

The second video shows what two gastric (stomach) ulcers look like.

YouTube Video

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Video 5.1.1: How aspirin, ibuprofen cause peptic ulcers. It describes how goblet cells secrete mucus in the stomach. This is not correct, they secrete mucus in the intestine. It should be neck cells in the stomach. https://www.youtube.com/watch?v=98JaiKH2q3E

YouTube Video

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Video 5.1.2: Endoscopy of two giant gastric (stomach) ulcers. https://www.youtube.com/watch?v=ncHcpzCnjGQ&feature=related

Query 5.1.1

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References

1. https://www.niddk.nih.gov/health-inf...finition-facts

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5.2: Gallstones

It is estimated that up to 1 million Americans are hospitalized annually as a result of gallstones, making it the most common of all digestive diseases[1]. Gallstones are formed when bile hardens in the gallbladder. 80% of gallstones are a result of cholesterol precipitation, while 20% are a result of bile pigment precipitation[2]. The cause of gallstones is unknown[2]. The way in which gallstones are formed is shown in the following video.

YouTube Video

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View this YouTube Video online

Video 5.2.1: How gallstones are formed. https://www.youtube.com/watch?v=1q3NxfwSENM&feature=rec-HM-fresh+div

The following figure shows a severe case of gallstones.



Figure 5.2.1: Gallstones within a dissected gallbladder[3]

Many people do not experience symptoms from gallstones. They are usually discovered during examination for another health condition. However, some people experience an "attack" or pain that results from blockage of the bile ducts. The gallbladder is not essential, so the primary treatment is cholecystectomy, the removal of the gallbladder. Bile then flows directly from the liver into the small intestine.

Query 5.2.1

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References

1. Bar-Meir S. (2001) Gallstones: Prevalence, diagnosis and treatment. The Israel Medical Association Journal 3(2): 111.
2. www.niddk.nih.gov/health-info...ges/facts.aspx
3. en.Wikipedia.org/wiki/File:Gallstones.jpg

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5.3: Irritable Bowel Syndrome

Up to 20% of Americans may have irritable bowel syndrome (IBS). A syndrome is a group of symptoms, not a disease. In IBS, the colon does not function correctly. The symptoms of IBS are cramping, bloating, gas, diarrhea, and/or constipation. The cause of IBS is unknown. Diet changes, stress reduction, and medicine may help manage the condition[1]. To learn more about IBS, see the reference below.

Reference

1. www.niddk.nih.gov/health-info...ion-facts.aspx

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5.4: Inflammatory Bowel Disease

Inflammatory bowel disease refers to a number of inflammatory conditions in the intestine. The two most common are Crohn's Disease and ulcerative colitis. These two conditions differ mainly in the areas of the intestine that are affected. Crohn's disease can occur anywhere throughout the GI tract, but most commonly occurs in the last part of the ileum. Crohn's disease may also involve all layers of the intestine1. Ulcerative colitis are ulcers in the lining of the colon and/or rectum2. It is estimated that up to 1 million people have IBD in the United States. Half of these individuals have Crohn's disease, and the other half have ulcerative colitis3.

The figure in the link below illustrates the differences between these two conditions.

Web Links

Ulcerative Colitis vs. Crohn's Disease

The exact causes of these two diseases is not known. One hypothesized cause is an overactive immune system (autoimmune response, the immune system attacks tissues/cells rather than pathogens) that results in the chronic inflammation and collateral damage to the cells of the intestine, resulting in formation of lesions.

Crohn's disease and ulcerative colitis present symptoms similar to other gastrointestinal diseases, such as irritable bowel syndrome and GERD.

Query 5.4.1

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References

1. http://www.niddk.nih.gov/health-info...ges/facts.aspx
2. www.niddk.nih.gov/health-info...ges/facts.aspx
3. http://www.ccfa.org/info/about/crohns

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5.5: Celiac Disease and Gluten

1 out of every 133 people in the United States has celiac disease[1]. People with celiac disease cannot consume the protein gluten because it causes their body to generate an autoimmune response (immune cells attack the body's own cells) that causes damage to the villi in the intestine, as shown below.

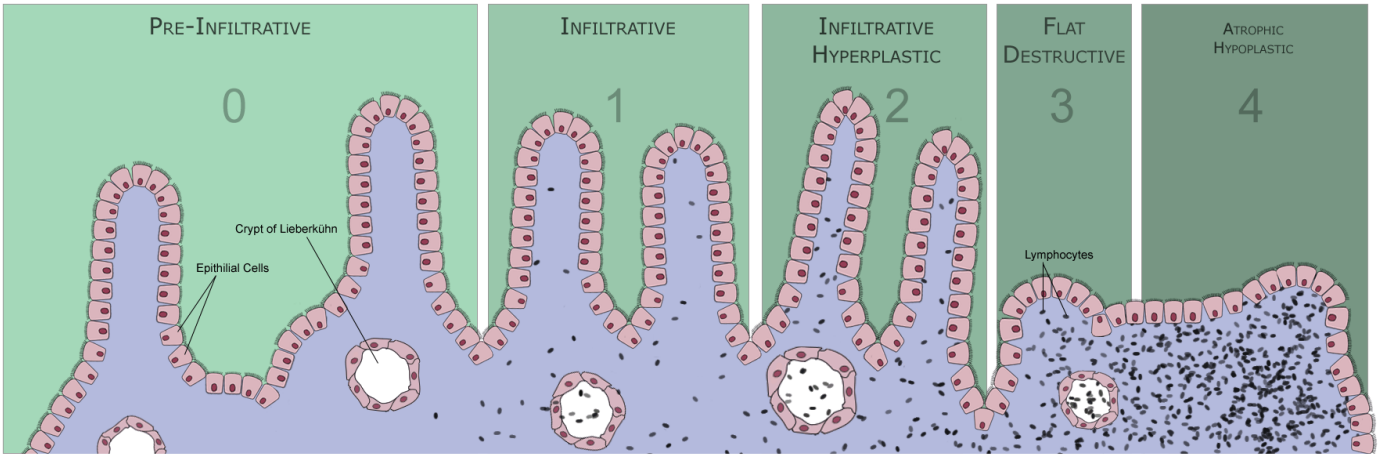


Figure 5.5.1: Different stages of celiac disease[2]

This damage to the villi impairs the absorption of macronutrients and micronutrients from food. There are a variety of symptoms for celiac disease that vary depending on age and from person to person.

Query 5.5.1

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What is gluten?

Gluten is a protein that is bound to starch in the endosperm of grains such as:

- Wheat
- Barley
- Rye
- Triticale

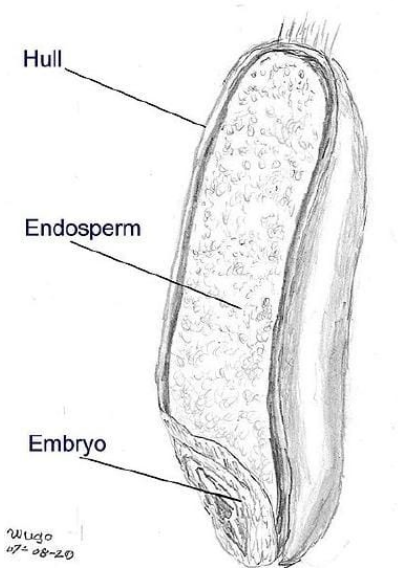


Figure 5.5.2: Parts of a wheat granule[3]

Gluten-free diets have been increasing in popularity even for people who don't have celiac disease. The thinking among those consuming these diets is that they might be non-celiac, gluten-sensitive, meaning that they experience adverse effects from consuming it. However, as the study describes, it seems more likely that it is fructan, a fructooligosaccharide, that causes these issues as found in the research described in the abstract below. These are apart of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs). Low FODMAP diets are increasing in use for similar reasons as gluten-free diets were used, but there is better evidence justification for their use.

Web Link

Fructan, Rather Than Gluten, Induces Symptoms in Patients With Self-Reported Non-Celiac Gluten Sensitivity

Query 5.5.2

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References

1. http://www.celiac.org/
2. en.Wikipedia.org/wiki/File:Coeliac_Disease.png
3. en.Wikipedia.org/wiki/File:Wheat_seed.jpg

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5.6: Diverticulosis and Diverticulitis

Approximately 10% of people under 40, and 50% of people over 60 years old have a condition known as diverticulosis[1]. In this condition, diverticula (plural, diverticulum singular), or outpouches, are formed at weak points in the large intestine, primarily in the lowest section of the sigmoid colon, as nicely shown in the figure and video below.

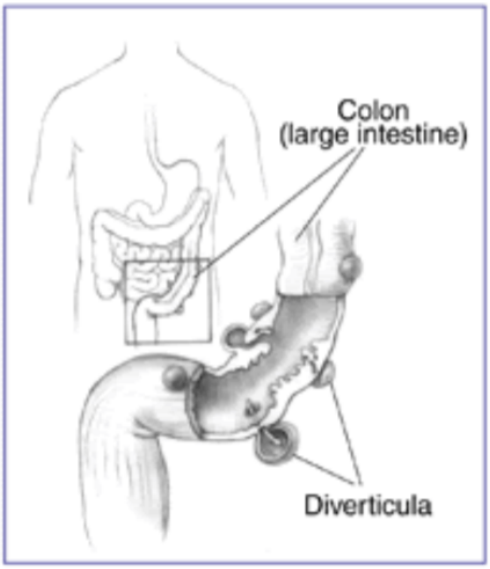


Figure 5.6.1: Diverticula on the large intestine[1]

YouTube Video

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Video 5.6.1: Diverticulosis. https://www.youtube.com/watch?v=ThuBZxbLo9g

It is believed that diverticula are formed as a result of a low-fiber diet because people may strain more during bowel movements. Most people with diverticulosis do not know that they have the condition. However, if the pouches become inflamed, then the condition is known as diverticulitis. The most common symptom of this condition is abdominal pain. A liquid diet may be needed until the inflammation is decreased, then fiber is gradually increased[1].

Query 5.6.1

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References

1. http://www.niddk.nih.gov/health-info...s/facts.aspx#1

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5.7: Hemorrhoids

Hemorrhoids are swollen or inflamed veins of the anus or lower rectum. An internal hemorrhoid occurs within the anus, while an external hemorrhoid occurs in the skin surrounding the anus. Symptoms of hemorrhoids include bleeding, pain during bowel movements, and/or itching1. It is estimated that “about 75% of people will have hemorrhoids at some point in their lives”2.

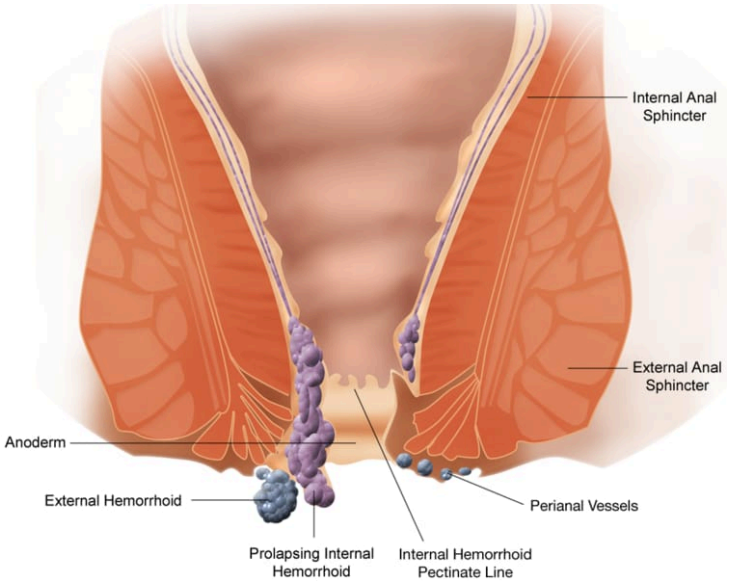


Figure 5.7.1: Hemorrhoids. (CC BY-SA 3.0 Unported; WikipedianProlific via Wikipedia)

The first 55 seconds of the following video does a nice job of illustrating what hemorrhoids are and how they develop.

YouTube Video

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Video 5.7.1: What are hemorrhoids? https://www.youtube.com/watch?v=C8vZoIhQCwU

The anus and lower rectum experience high pressure during bowel movements. Thus, hemorrhoids are believed to be caused by straining during bowel movements. To prevent this condition from occurring, it is recommended that people consume a high-fiber diet, drink plenty of water, and exercise to produce regular, large, soft stools. In addition, people should "go" at first urge and not wait until it is more than an urge2.

Query 5.7.1

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References

1. http://www.webmd.com/a-to-z-guides/h...topic-overview
2. www.niddk.nih.gov/health-info...ges/facts.aspx
3. en.Wikipedia.org/wiki/File:Hemorrhoid.png

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6: MACRONUTRIENT AND ALCOHOL METABOLISM

Now that we have digested, taken up, absorbed, and transported the macronutrients, the next step is to learn how these macronutrients are metabolized. Alcohol is also included at the end of this chapter, even though it is not a macronutrient.

6.1: Metabolism Basics

6.2: Carbohydrate Metabolism

6.3: Lipid Metabolism Pathways

6.4: Protein Metabolism

6.5: Alcohol Metabolism

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6.1: Metabolism Basics

Metabolism consists of all the chemical processes that occur in living cells. These processes/reactions can generally be classified as either anabolic or catabolic. Anabolic means to build, catabolic means to breakdown. If you have trouble remembering the difference between the two, remember that anabolic steroids are what are used to build enormous muscle mass.



Figure 6.1.1: One of these two is taking anabolic steroids, which one would be your guess?

An anabolic reaction/pathway requires energy to build something. A catabolic reaction/pathway generates energy by breaking down something. This is shown in the example below of glucose and glycogen. The same is true for other macronutrients.

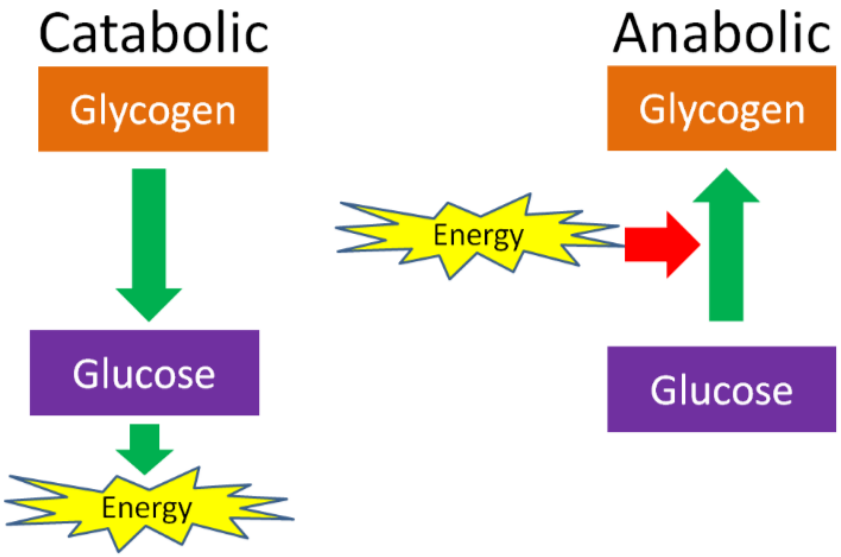


Figure 6.1.2: The breakdown of glycogen to glucose is catabolic. The glucose can then be used to produce energy. The synthesis of glycogen from glucose is anabolic and requires energy.

Anabolic and catabolic can also be used to describe conditions in the body. For instance, after a meal there is often a positive energy balance, or there is more energy and macronutrients than the body needs at that time. Thus, some energy needs to be stored and the macronutrients will be used for synthesis, such as amino acids being used for protein synthesis. However, after a fast, or a prolonged period without energy intake, the body is in negative energy balance and is considered catabolic. In this

condition, macronutrients will be mobilized from their stores to be used to generate energy. For example, if prolonged enough, protein can be broken down, then the released amino acids can be broken down to be used as an energy source.

Query 6.1.1

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A number of the metabolic reactions oxidize or reduce compounds. A compound that is oxidized loses at least one electron, while a compound that is reduced gains at least 1 electron. To remember the difference, a mnemonic device such as OIL (oxidation is lost), RIG (reduction is gained) is helpful. Oxidation-reduction reactions are illustrated in the figure below.

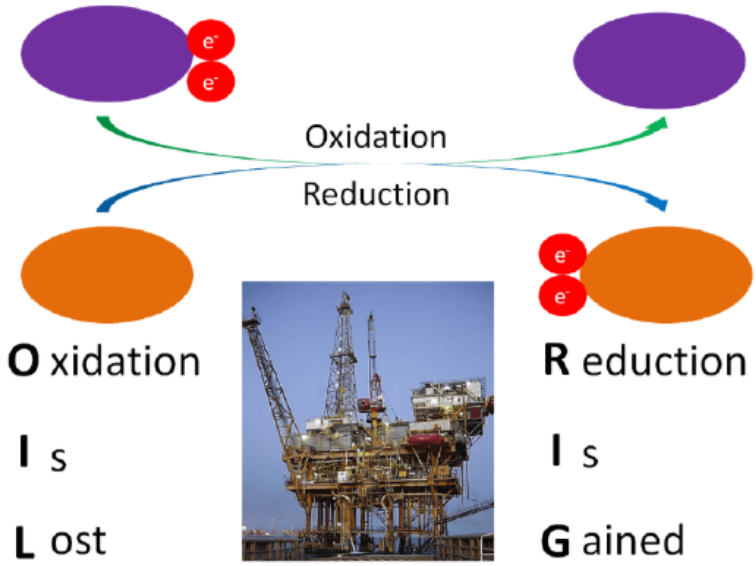


Figure 6.1.3: The purple compound is being oxidized, the orange compound is being reduced[1]

Another way to remember oxidation versus reduction is **LEO goes GER** (like a lion)

Lose **E**lectrons = **O**xidize

Gain **E**lectrons = **R**educe

Iron is a good example we can use to illustrate oxidation-reduction reactions. Iron commonly exists in two oxidation states (Fe^{3+} or Fe^{2+}). It is constantly oxidized/reduced back and forth between the two states. The oxidation/reduction of iron is shown below.

$$Fe^{3+} + e^- \longrightarrow Fe^{2+} \text{ Reduced}$$

$$Fe^{2+} \longrightarrow Fe^{3+} + e^- \text{ Oxidized}$$

However, some oxidation reduction reactions are not as easy to recognize. There are some simple rules to help you recognize less obvious oxidation/reduction reactions that are based upon the gain or loss of oxygen or hydrogen. These are as follows:

- Oxidation: gains oxygen or loses hydrogen
- Reduction: loses oxygen or gains hydrogen

Query 6.1.2

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Cofactors

A number of enzymes require cofactors to function. Some also require what other textbooks and resources refer to as coenzymes. But to keep things simple, we are going to include these coenzymes in our definition of cofactors. Thus, cofactors can be either organic or inorganic molecules that are required by enzymes to function. Many organic cofactors are vitamins or molecules derived from vitamins. Most inorganic cofactors are minerals. The reason why some vitamins and minerals are essential nutrients is because of their required role as cofactors for some enzymes. Cofactors can be oxidized or reduced for the enzymes to catalyze the reactions.

Two common cofactors that are derived from the B vitamins, niacin and riboflavin, are nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD), respectively. The structure of NAD and FAD are shown below.

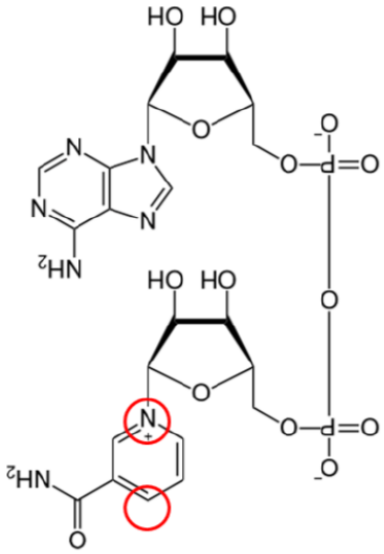


Figure 6.1.6

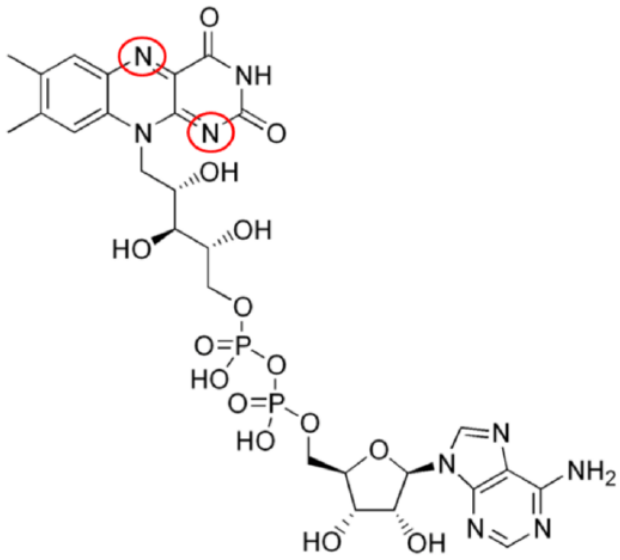


Figure 6.1.7

Both of these cofactors can be reduced (or oxidized as well); NAD is reduced to form NADH, while FAD is reduced to form $FADH_2$ as shown in the 2 figures below.

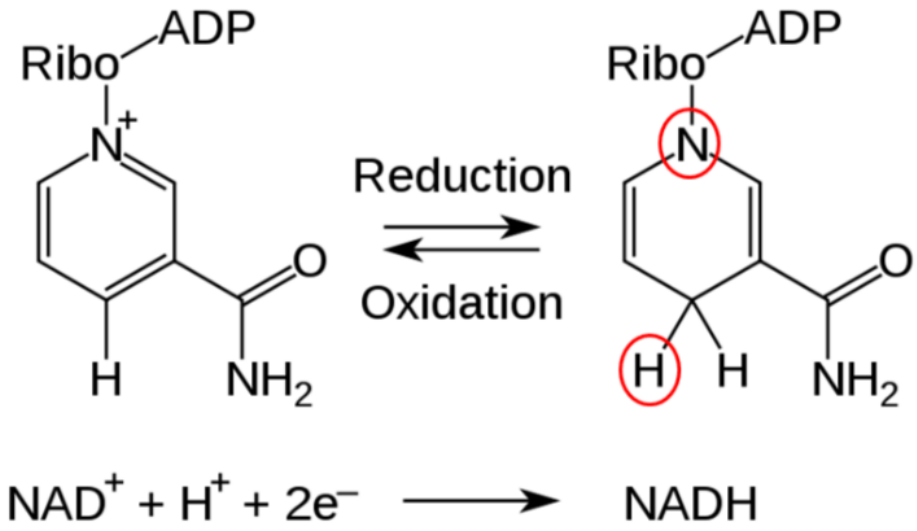


Figure 6.1.6: The reduction of NAD to form NADH4

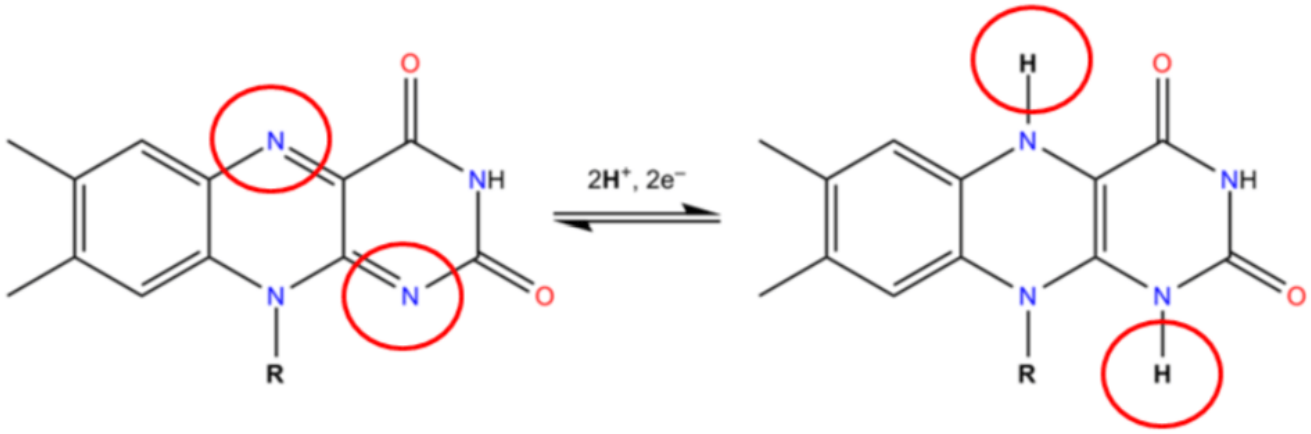


Figure 6.1.7: The reduction of FAD5 to $\mathrm{FADH_2}$

An example of a mineral that serves as a cofactor is $\mathrm{Fe^{2+}}$ for proline and lysyl hydroxylases. We will discuss later in detail why vitamin C (ascorbic acid) is needed to reduce iron to $\mathrm{Fe^{2+}}$ so that it can serve as a cofactor for proline and lysyl hydroxylases.

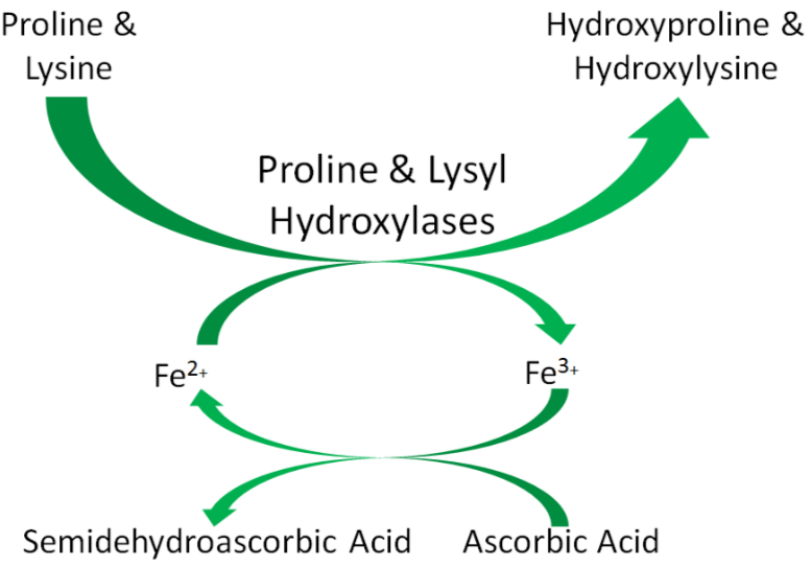


Figure 6.1.8: Iron ($\mathrm{Fe^{2+}}$) is a cofactor for proline and lysyl hydroxylases

Query 6.1.3

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References

1. en.Wikipedia.org/wiki/Image:G...e_Platform.jpg
2. en.Wikipedia.org/wiki/File:NAD%2B_phys.svg
3. en.Wikipedia.org/wiki/File:Fl...nucleotide.png
4. en.Wikipedia.org/wiki/File:NA..._reduction.svg

5. en.Wikipedia.org/wiki/File:FA...equlibrium.png

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6.2: Carbohydrate Metabolism

There are many metabolic pathways/cycles/processes/reactions that are involved in the synthesis or degradation of carbohydrates and compounds formed from them. Please note that most of these pathways are not specific to carbohydrates only. Gluconeogenesis will be learned about in the protein section, because amino acids are a common substrate used for synthesizing glucose.

Carbohydrate Pathways/Cycles/Processes/Reactions

- **Glycogenesis:** glycogen synthesis
- **Glycogenolysis:** glycogen breakdown
- **Gluconeogenesis:** synthesis of glucose from a non-carbohydrate source
- **Glycolysis:** breakdown of glucose to pyruvate
- **Transition Reaction:** conversion of pyruvate to acetyl-CoA
- **Citric Acid (Tricarboxylic acid (TCA), Kreb's) Cycle:** acetyl-CoA combines with oxaloacetate to form citrate; ATP, NADH, and $\mathrm{FADH_2}$ are produced in the cycle
- **Electron Transport Chain:** oxidative phosphorylation, producing ATP from NADH and $\mathrm{FADH_2}$

Query 6.2.1

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Monosaccharide Metabolism

Galactose and fructose metabolism is a logical place to begin looking at carbohydrate metabolism, before shifting focus to the preferred monosaccharide glucose. The figure below reminds you that in the liver, galactose and fructose have been phosphorylated.

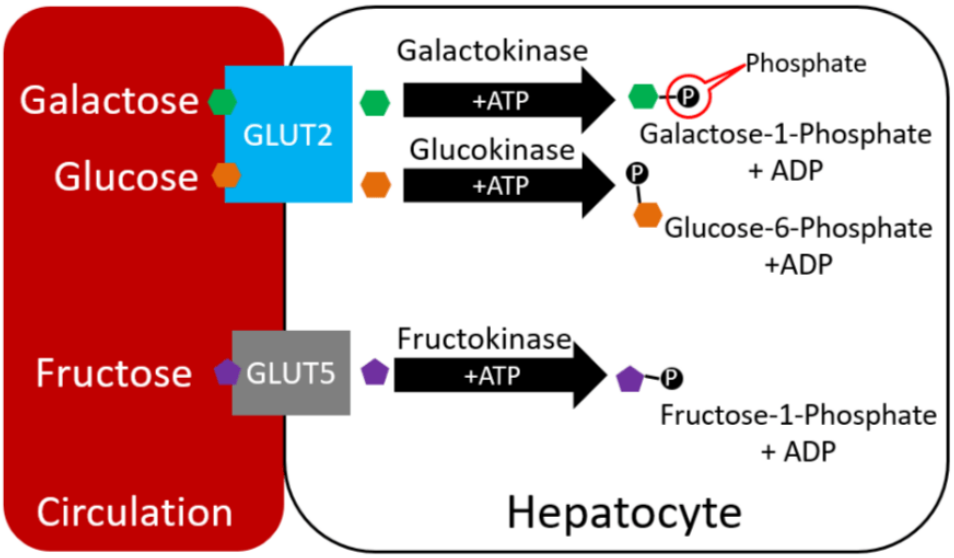


Figure 6.2.1: Uptake of monosaccharides into the hepatocyte

Galactose

In the liver, galactose-1-phosphate is converted to glucose-1-phosphate, before finally being converted to glucose-6-phosphate1. As shown below, glucose 6-phosphate can then be used in either glycolysis or glycogenesis, depending on the person's current energy state.

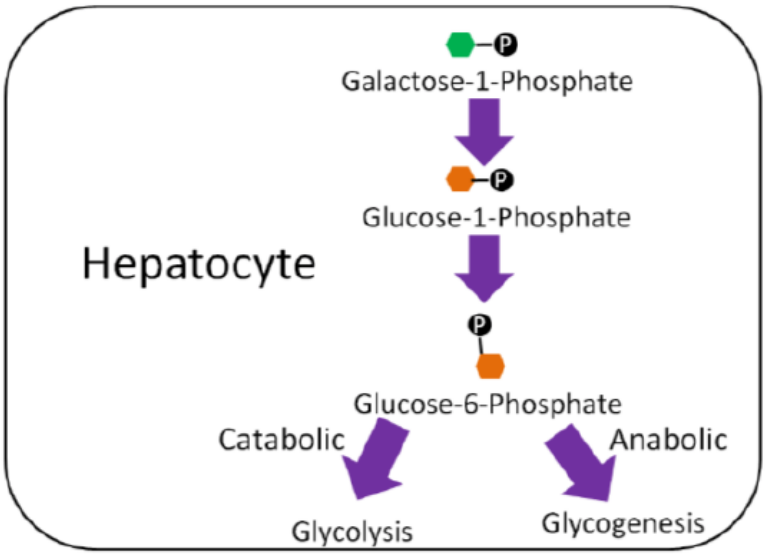


Figure 6.2.2: Conversion of galactose-1-phosphate to glucose-6-phosphate

Fructose

Unlike galactose, fructose cannot be used to form phosphorylated glucose. Instead, fructose-1-phosphate is cleaved in the liver to form glyceraldehyde 3-phosphate (glycolysis intermediate, you will learn more about below). This occurs through multiple steps, as depicted below.

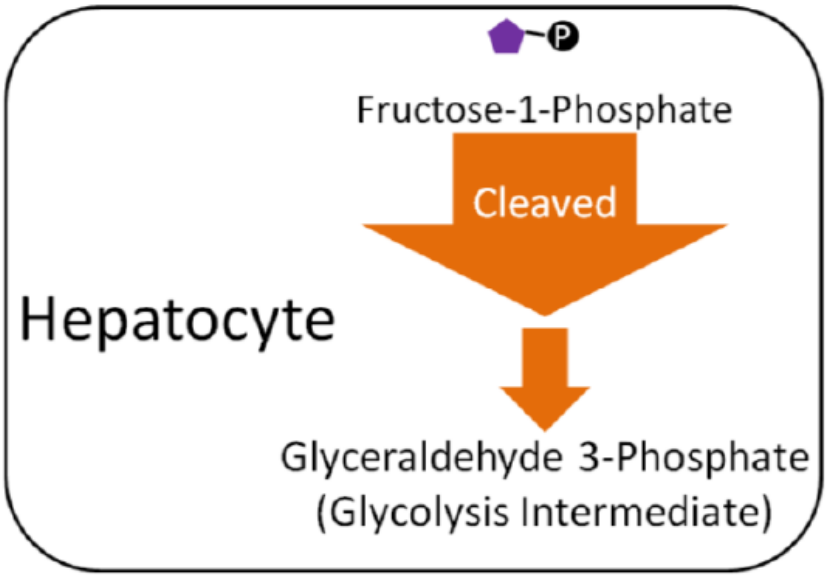


Figure 6.2.3: Conversion of fructose-1-phosphate to glyceraldehyde 3-phosphate

Glucose-6-Phosphate

Within hepatocytes or myocytes (muscle cells), glucose-6-phosphate can be used either for glycogenesis (glycogen synthesis) or

glycolysis (breakdown of glucose for energy production). If the person is in an anabolic state, they will use glucose-6-phosphate for storage. If they are in a catabolic state, they will use it for energy production. In an anabolic state, glucose-6-phosphate will be used for glycogen synthesis for storage. In catabolic state, it will be used for energy production.

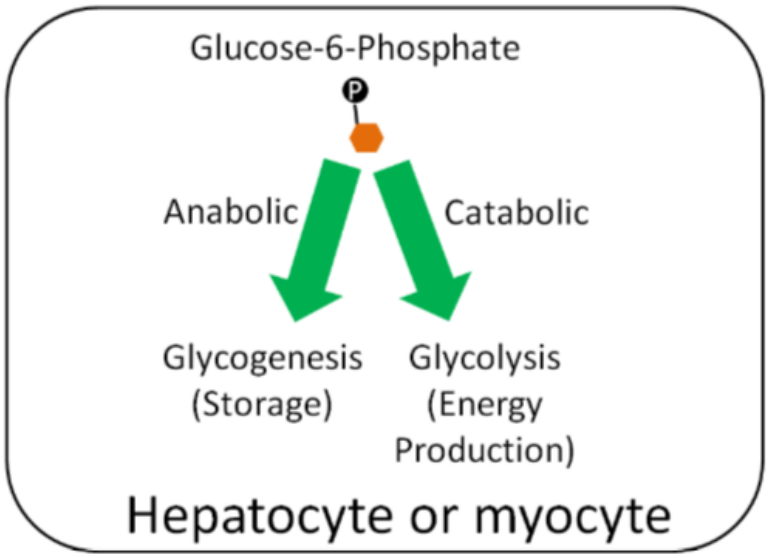


Figure 6.2.4: The "fork in the road" for glucose-6-phosphate

Query 6.2.2

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Glycogenesis & Glycogenolysis

As discussed earlier, glycogen is the animal storage form of glucose. If a person is in an anabolic state, such as after consuming a meal, most glucose-6-phosphate within the myocytes (muscle cells) or hepatocytes (liver cells) is going to be stored as glycogen. The structure is shown below as a reminder.

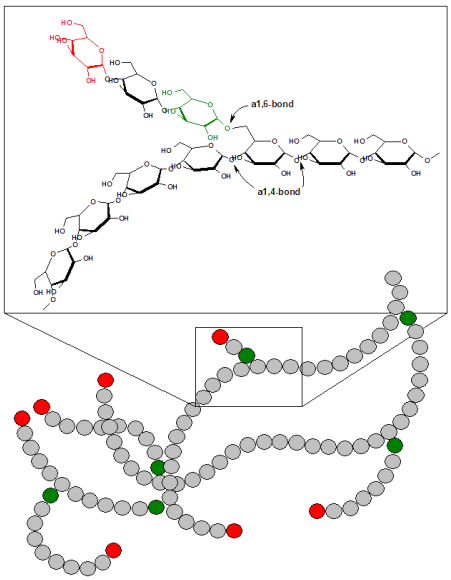


Figure 6.2.5: Structure of glycogen2

Glycogen is mainly stored in the liver and the muscle. It makes up ~6% of the wet weight of the liver and only 1% of muscle wet weight. However, since we have far more muscle mass in our body, there is 3-4 times more glycogen stored in muscle than in the liver3. We have limited glycogen storage capacity. Thus, after a high-carbohydrate meal, our glycogen stores will reach capacity. After glycogen stores are filled, glucose will have to be metabolized in different ways for it to be stored in a different form.

Query 6.2.3

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Glycogenesis

The synthesis of glycogen from glucose is a process known as glycogenesis. Glucose-6-phosphate is not inserted directly into glycogen in this process. There are a couple of steps before it is incorporated. First, glucose-6-phosphate is converted to glucose-1-phosphate and then converted to uridine diphosphate (UDP)-glucose. UDP-glucose is inserted into glycogen by either the enzyme, glycogen synthase (alpha-1,4 bonds), or the branching enzyme (alpha-1,6 bonds) at the branch points1.

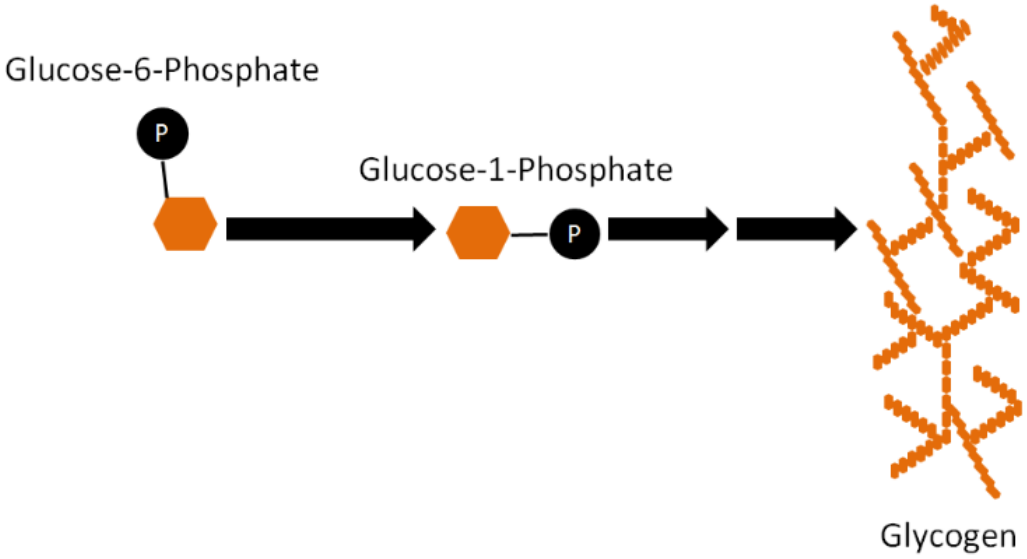


Figure 6.2.6: Glycogenesis

Glycogenolysis

The process of liberating glucose from glycogen is known as glycogenolysis. This process is essentially the opposite of glycogenesis with two exceptions:

1. There is no UDP-glucose step, and
2. A different enzyme, glycogen phosphorylase, is involved.

Glucose-1-phosphate is cleaved from glycogen by the enzyme, glycogen phosphorylase, which then can be converted to glucose-6-phosphate as shown below1.

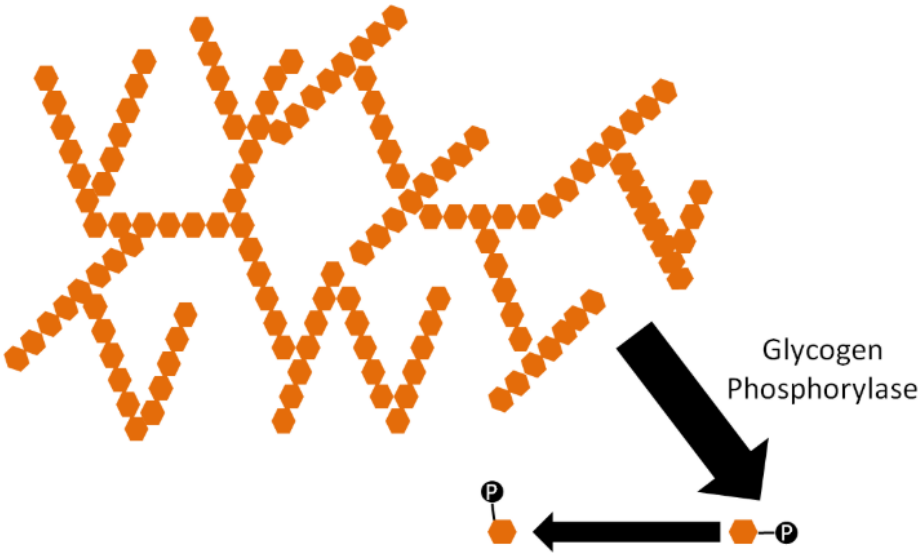


Figure 6.2.7: Glycogenolysis

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Glycolysis

If a person is in a catabolic state or in need of energy, such as during fasting, most glucose-6-phosphate will be used for glycolysis.

Glycolysis is the breaking down of one glucose molecule (6 carbons) into two pyruvate molecules (3 carbons). During the process, a net of two ATPs and two NADHs are also produced.

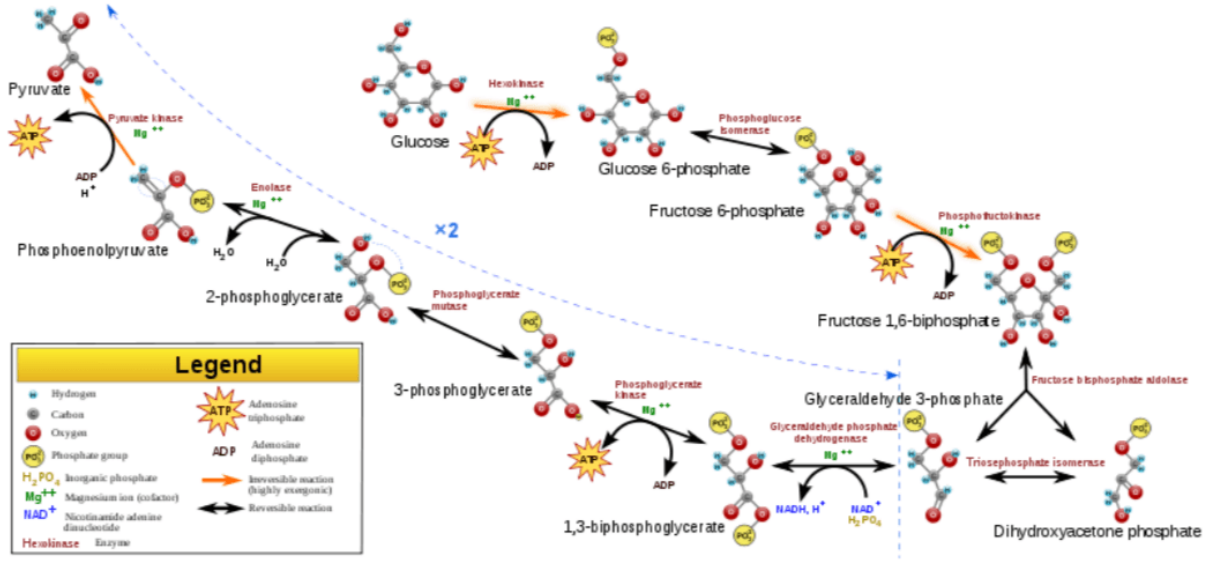


Figure 6.2.8: Glycolysis[4]

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3 steps of Glycolysis

1. **Energy investment step** - 2 ATP are added to the 6 carbon molecule.

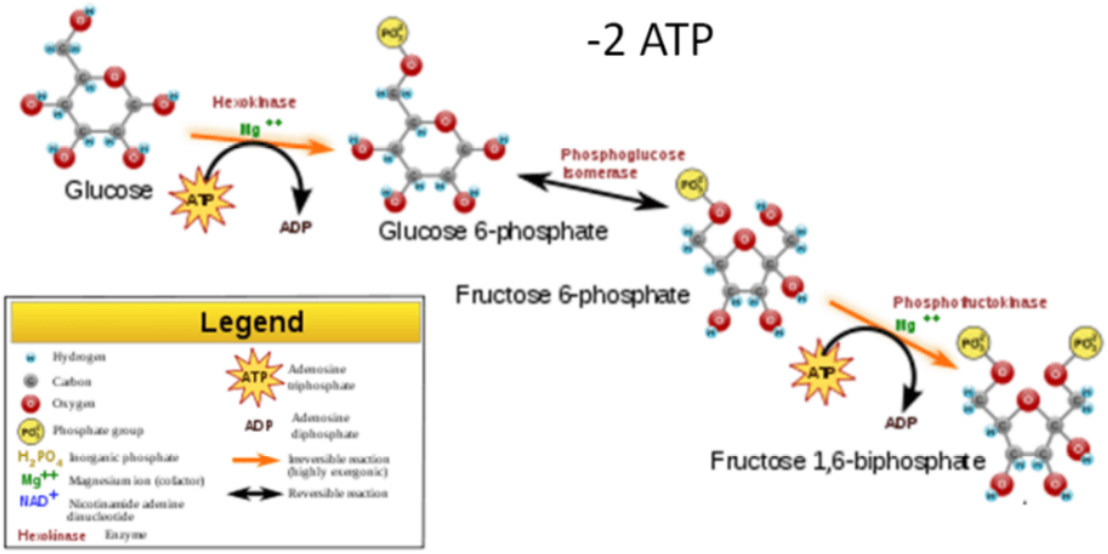


Figure 6.2.9: Glycolysis step 1, energy investment[4]

2. **Split Glucose** - The 6 carbon molecule is split into two 3 carbon molecules.

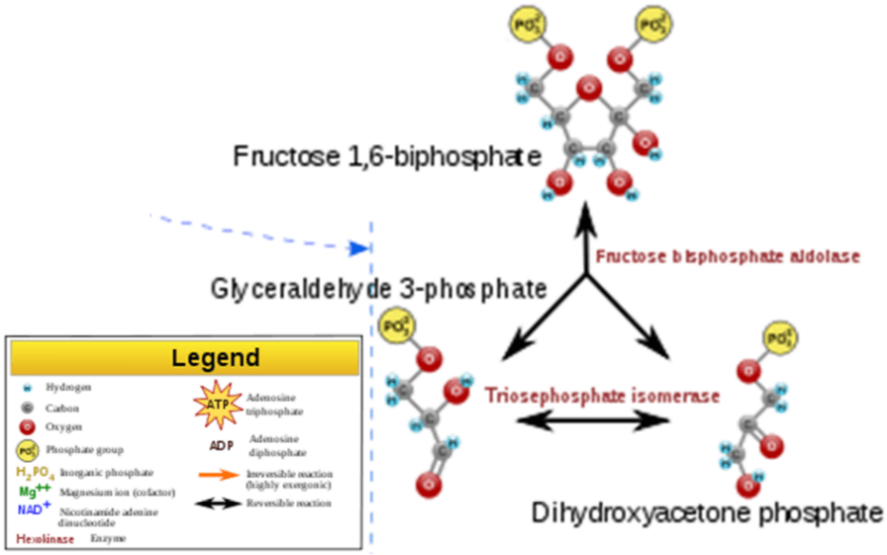


Figure 6.2.10: Glycolysis step 2, glucose split[4]

3. **Energy harvesting step** - 1 NADH and 2 ATPs are produced from each 3 carbon molecule (there are two 3 carbon molecules formed from each glucose). One is glyceraldehyde 3-phosphate, which is the intermediate that fructose is metabolized to. So this is where fructose metabolism merges with how glucose and galactose have been metabolized. There are some metabolic regulatory steps that it skips, which is part of the reason for the concern with fructose intake.

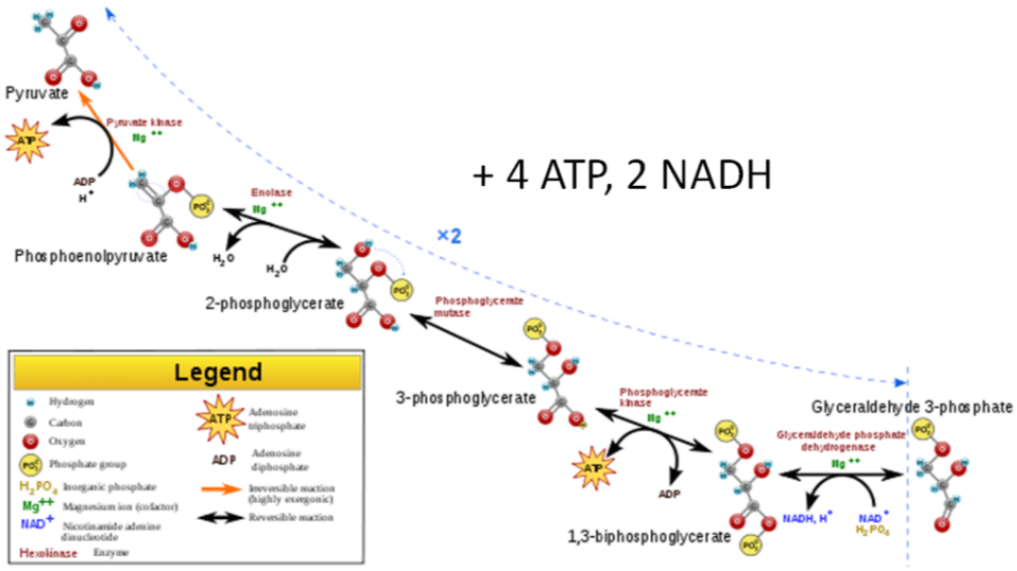


Figure 6.2.11: Glycolysis step 3, energy harvesting[4]

Thus, from a molecule of glucose, the harvesting step produces a total of four ATPs and two NADHs. Subtracting the harvesting from the investment step, the net output from one molecule of glucose is two ATPs and two NADHs.

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Video 6.2.1: Glycolysis rap. https://www.youtube.com/watch?v=EfGlznwfu9U

The figure below shows the stages of glycolysis, as well as the transition reaction, citric acid cycle, and electron transport chain that are utilized by cells to produce energy. They are also the focus of the next 3 sections.

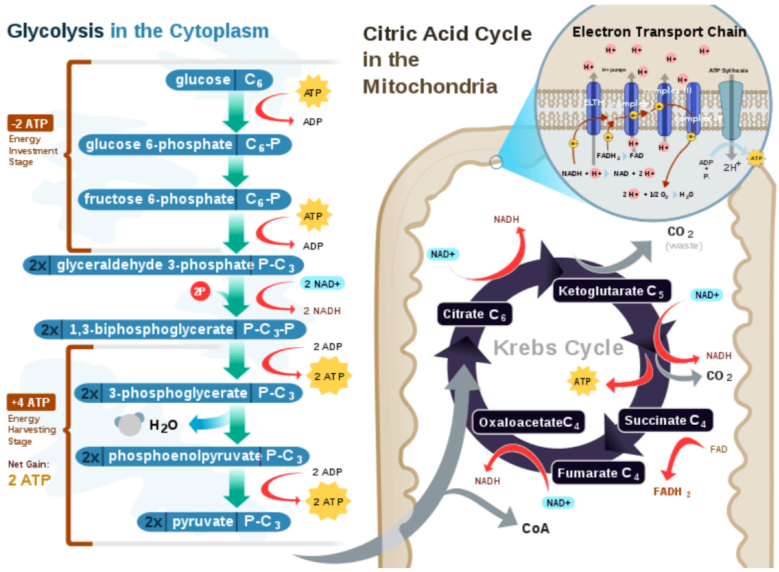


Figure 6.2.12: Glycolysis, transition reaction, citric acid cycle, and the electron transport chain[5]

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Transition Reaction

If a person is in a catabolic state, or needs energy, how pyruvate will be used depends on whether adequate oxygen levels are present. If there are adequate oxygen levels (aerobic conditions), pyruvate moves from the cytoplasm, into the mitochondria, and then undergoes the transition reaction. If there are not adequate oxygen levels (anaerobic conditions), pyruvate will instead be used to produce lactate in the cytoplasm. We are going to focus on the aerobic pathway to begin with, then we will address what happens under anaerobic conditions in the anaerobic respiration section.

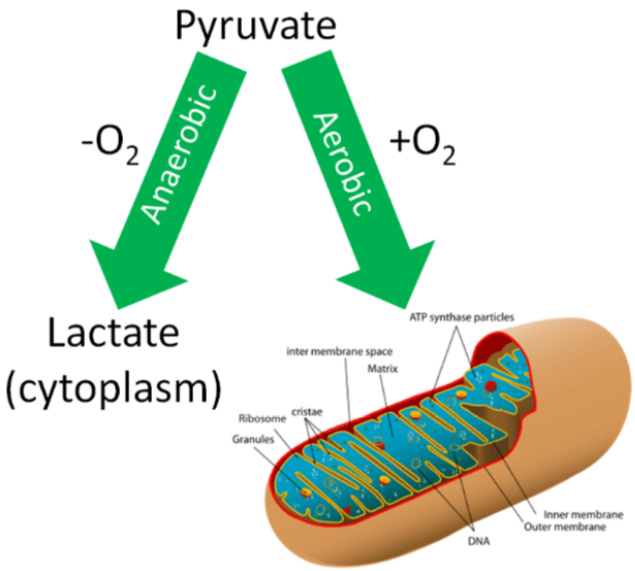


Figure 6.2.13: Pyruvate fork in the road. What happens depends on whether it is aerobic or anaerobic respiration[6]

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The transition reaction is the transition between glycolysis and the citric acid cycle. The transition reaction converts pyruvate (3 carbons) to acetyl CoA (2 carbons), producing carbon dioxide (CO_2) and an NADH as shown below. The figure below shows the transition reaction with CoA and NAD entering, and acetyl-CoA, CO_2, and NADH being produced.

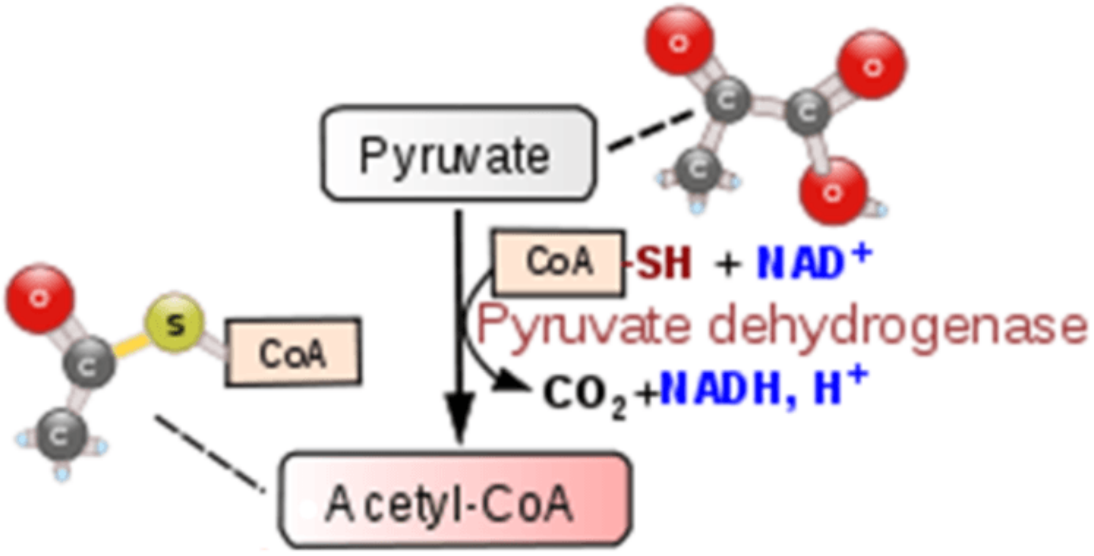


Figure 6.2.14: Transition reaction[7]

The acetyl is combined with coenzyme A (CoA) to form acetyl-CoA. The structure of CoA is shown below.

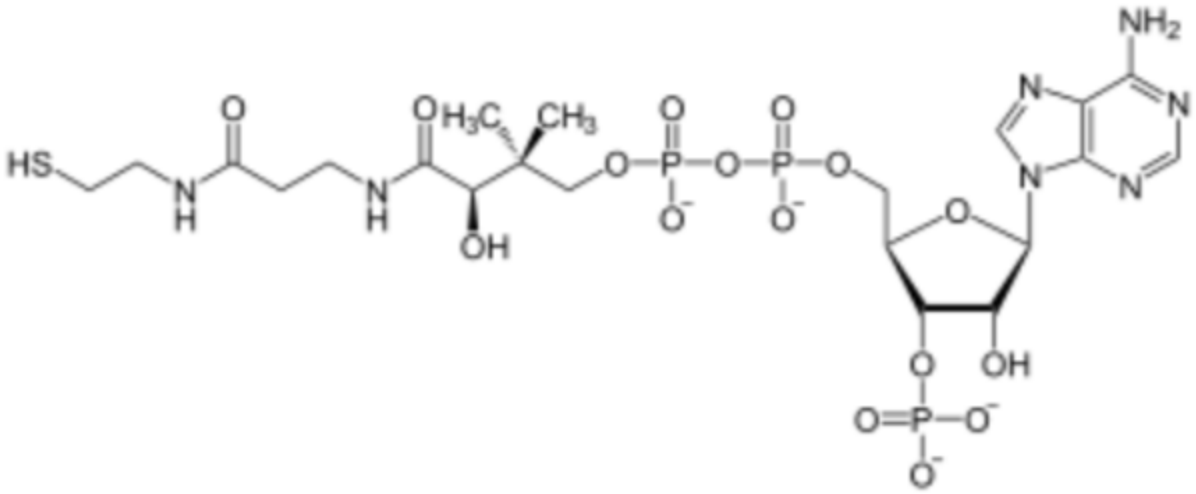


Figure 6.2.15: Structure of coenzyme A[8]

Thus, for one molecule of glucose, the transition reaction produces 2 acetyl-CoAs, 2 molecules of CO_2, and 2 NADHs.

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The Citric Acid Cycle

Acetyl-CoA is a central point in metabolism, meaning there are a number of ways that it can be used. We are going to continue to consider its use in an aerobic, catabolic state (need energy). Under these conditions, acetyl-CoA will enter the citric acid cycle (aka Krebs Cycle, TCA Cycle). The following figure shows the citric acid cycle.

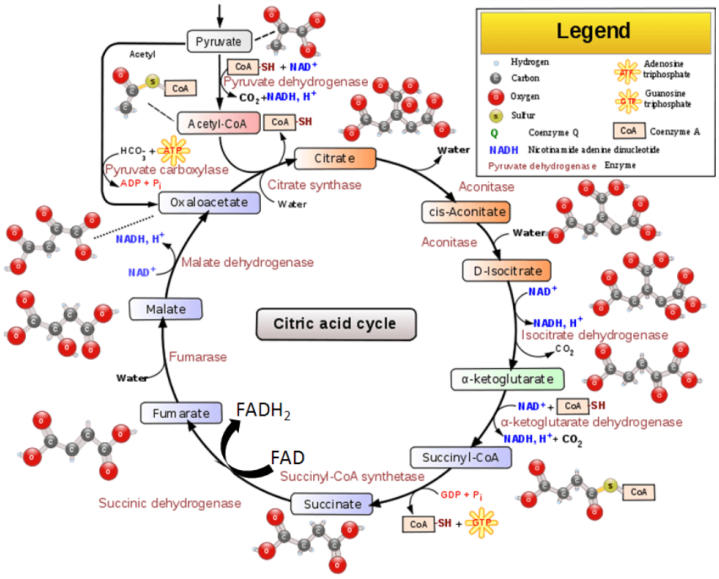


Figure 6.2.16: The citric acid cycle[9]

The citric acid cycle begins by acetyl-CoA (2 carbons) combining with oxaloacetate (4 carbons) to form citrate (aka citric acid, 6 carbons). A series of transformations occur before a carbon is given off as carbon dioxide and NADH is produced. This leaves alpha-ketoglutarate (5 carbons). Another carbon is given off as $\mathrm{CO_2}$ to form succinyl CoA (4 carbons) and produce another NADH. In the next step, one guanosine triphosphate (GTP) is produced as succinyl-CoA is converted to succinate. GTP is readily converted to ATP, thus this step is essentially the generation of 1 ATP. In the next step, an $\mathrm{FADH_2}$ is produced along with fumarate. Then, after more steps, another NADH is produced as oxaloacetate is regenerated.

Thus, the net output from one cycle is:

2 $\mathrm{CO_2}$

3 NADH

1 $\mathrm{FADH_2}$

1 GTP (converted to ATP)

The two carbons that are given off as $\mathrm{CO_2}$ originally came from acetyl-CoA.

The first video does a good job of explaining and illustrating how the cycle works. The second video is an entertaining rap about the cycle.

YouTube Video

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Video 6.2.2: Citric acid cycle. https://www.youtube.com/watch?v=hw5nWB0xN0Y

YouTube Video

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Video 6.2.3: Citric cycle acid rap. https://www.youtube.com/watch?v=aMBIs_Iw0kE

There are two acetyl-CoAs produced from one glucose, so the net from one glucose is the amount generated from two cycles:

4 $\mathrm{CO_2}$

6 NADH

2 $\mathrm{FADH_2}$

2 GTP (converted to ATP)

Through glycolysis, the transition reaction, and the citric acid cycle, multiple NADH and $\mathrm{FADH_2}$ molecules are produced. Under

aerobic conditions, these molecules will enter the electron transport chain to be used to generate energy through oxidative phosphorylation as described in the next section.

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Electron Transport Chain

The electron transport chain is located on the inner membrane of mitochondria. The electron transport chain contains a number of electron carriers. These carriers take the electrons from NADH and $\mathrm{FADH_2}$, pass them down the chain of complexes and electron carriers, and ultimately produce ATP. More specifically, the electron transport chain takes the energy from the electrons on NADH and $\mathrm{FADH_2}$ to pump protons ($\mathrm{H^+}$) into the intermembrane space. This creates a proton gradient between the intermembrane space (high) and the matrix (low) of the mitochondria. ATP synthase uses the energy from this gradient to synthesize ATP. Oxygen is required for this process because it serves as the final electron acceptor, forming water. Collectively this process is known as oxidative phosphorylation. The following figure does a nice job of illustrating how the electron transport chain functions.

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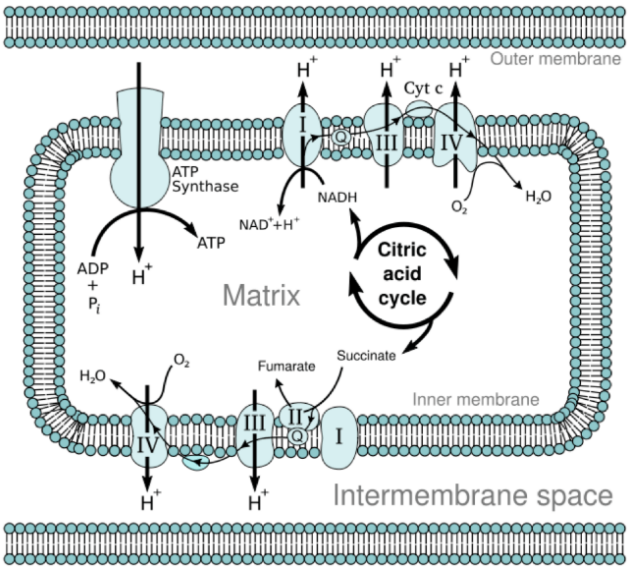


Figure 6.2.17: Location of the electron transport chain in the mitochondria[10]

2.5 ATP/NADH and 1.5 ATP/$\mathrm{FADH_2}$ are produced in the electron transport chain. Some resources will say 3 ATP/NADH and 2 ATP/$\mathrm{FADH_2}$, but these values are generally less accepted now.

For one molecule of glucose, the preceding pathways produce:

$$\begin{array}{ll} \text{Glycolysis:} & 2\text{NADH} \\ \text{Transition Reaction:} & 2\text{NADH} \\ \text{Citric Acid Cycle:} & 6\text{NADH}, 2\text{FADH}_2 \\ \text{Total:} & 10\text{NADH}, 2\text{FADH}_2 \end{array}$$

Multiply that by the amount of ATP per NADH or FADH_2 to yield:

$$\begin{aligned} \frac{10\text{NADH} \times 2.5\text{ATP}}{\text{NADH}} &= 25\text{ATP} \\ \frac{2\text{FADH}_2 \times 1.5\text{ATP}}{\text{FADH}_2} &= 3\text{ATP} \\ \text{Total} &= 28\text{ATP} \end{aligned}$$

The first video does a nice job of illustrating and reviewing the electron transport chain. Note that it uses 3 ATP/NADH and 2 ATP/FADH_2 so the totals from each cycle are different from those listed above. The second video is a great rap video explaining the steps of glucose oxidation.

YouTube Video

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Video 6.2.4: Electron transport chain. https://www.youtube.com/watch?v=1engJR_XWVU&feature=related

YouTube Video

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Video 6.2.5: Oxidate it or love it/electron to the next one. https://www.youtube.com/watch?v=VCpNk92uswY&feature=response_watch

Query 6.2.11

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Aerobic Glucose Metabolism Totals

The table below shows the ATP generated from one molecule of glucose in the different metabolic pathways.

Table 6.2.1: ATP generated from one molecule of glucose.

Metabolic Pathway	ATP Generated
Glycolysis	2
Citric Acid Cycle	2
Electron Transport Chain	28
Total	32

Notice that the vast majority of ATP is generated by the electron transport chain. If we do the math, 28/32 X 100 = 87.5% of the ATP from a molecule of glucose is generated by the electron transport chain. Remember that this is aerobic and requires oxygen to be the final electron acceptor. If 3 ATP/$NADH$ and 2 ATP/$FADH_2$ are used instead of 2.5 ATP/$NADH$ and 1.5 ATP/$FADH_2$ that were used above, total ATP and percentage of ATP produced by the electron transport chain would be different. But the takeaway message remains the same. The electron transport chain by far produces the most ATP from one molecule of glucose.

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Anaerobic Respiration

Conditions without oxygen are referred to as anaerobic. In this case, the pyruvate will be converted to lactate in the cytoplasm of the cell as shown below.

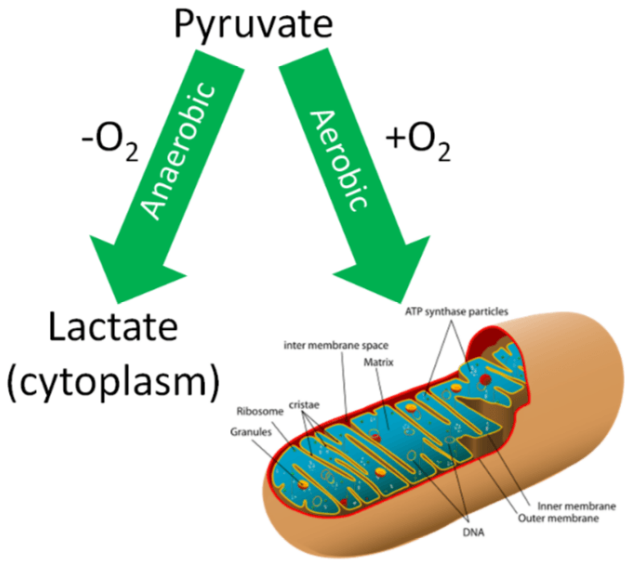


Figure 6.2.18: Pyruvate fork in the road, what happens depends on whether it is aerobic or anaerobic respiration[6]

What happens if oxygen isn't available to serve as the final electron acceptor? As shown in the following video, the ETC becomes

backed up with electrons and cannot accept them from NADH and $\mathrm{FADH_2}$.

YouTube Video

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Video 6.2.6: What happens in the electron transport chain when you run out of oxygen. https://www.youtube.com/watch?v=StXlo1W3Gvg

Query 6.2.13

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This leads to a problem in glycolysis because NAD is needed to accept electrons, as shown below. Without the electron transport chain functioning, all NADhas been reduced to NADH and glycolysis cannot continue to produce ATP from glucose.

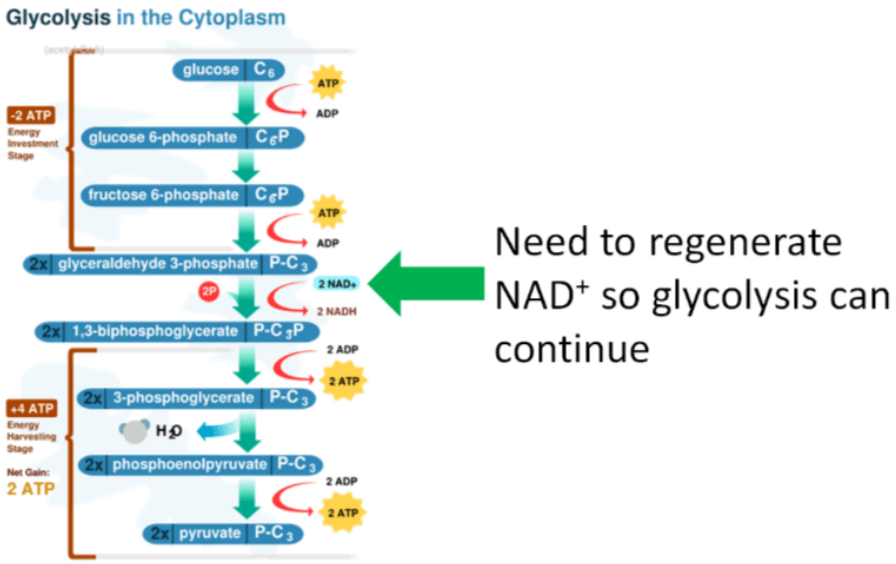


Figure 6.2.19: Why NAD needs to be regenerated under anaerobic conditions[5]

Thus, there is a workaround to regenerate NAD by converting pyruvate (pyruvic acid) to lactate (lactic acid) as shown below.

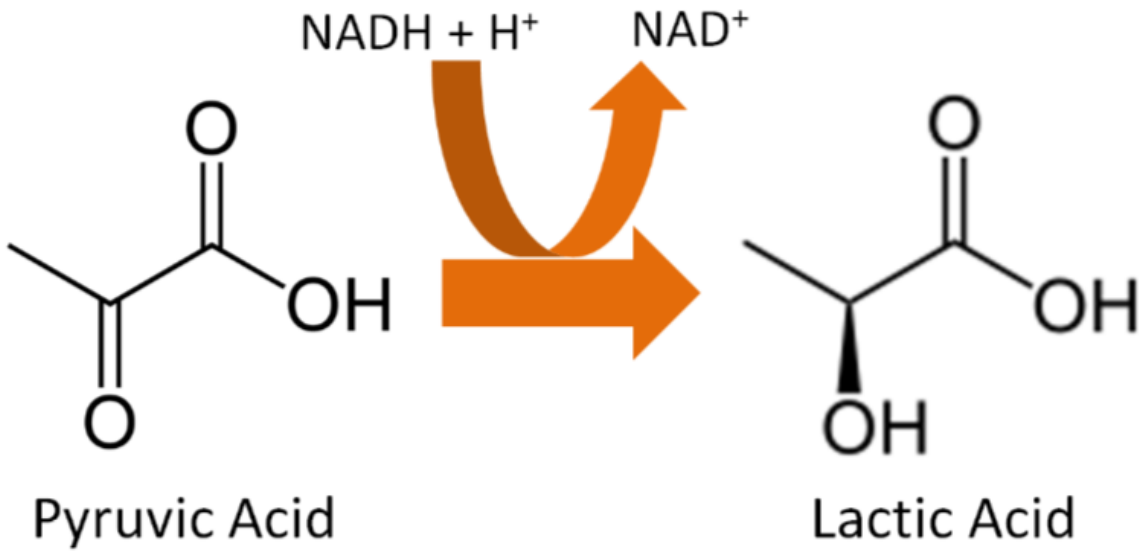


Figure 6.2.20: The conversion of pyruvic acid to lactic acid regenerates NAD[12,13]

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However, anaerobic respiration only produces 2 ATP per molecule of glucose, compared to 32 ATP for aerobic respiration. The biggest producer of lactate is the muscle. Through what is known as the Cori cycle, lactate produced in the muscle can be sent to the liver. In the liver, through a process known as gluconeogenesis, glucose can be regenerated and sent back to the muscle to be used again for anaerobic respiration forming a cycle as shown below.

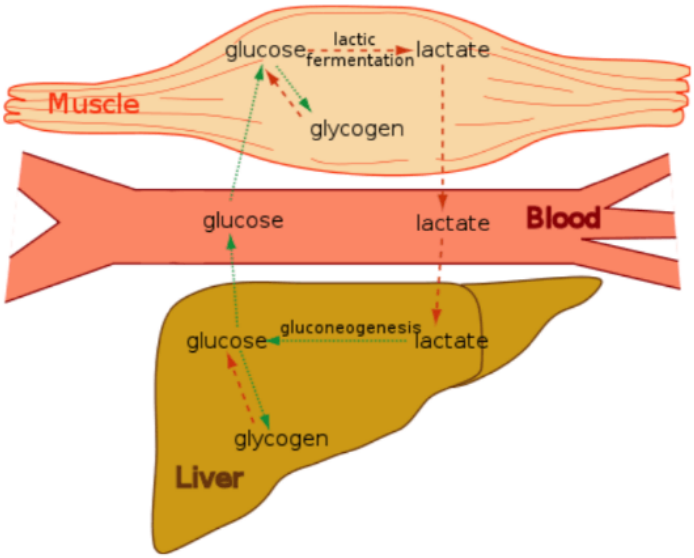


Figure 6.2.21: The Cori cycle[14]

It is worth noting that the Cori cycle also functions during times of limited glucose (like fasting) to spare glucose by not completely

oxidizing it.

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9. en.Wikipedia.org/wiki/Image:Coenzym_A.svg
10. en.Wikipedia.org/wiki/File:Mi...%80%94Etc4.svg
11. en.Wikipedia.org/wiki/File:CellRespiration.svg
12. en.Wikipedia.org/wiki/Pyruvi...D-skeletal.png
13. en.Wikipedia.org/wiki/Lactic...d-skeletal.svg
14. commons.wikimedia.org/wiki/F...iCycle-eng.svg

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6.3: Lipid Metabolism Pathways

Five lipid metabolic pathways/processes will be covered in the following subsections.

Lipolysis (Triglyceride Breakdown)

Lipolysis is the cleavage of triglycerides to glycerol and fatty acids, as shown below.

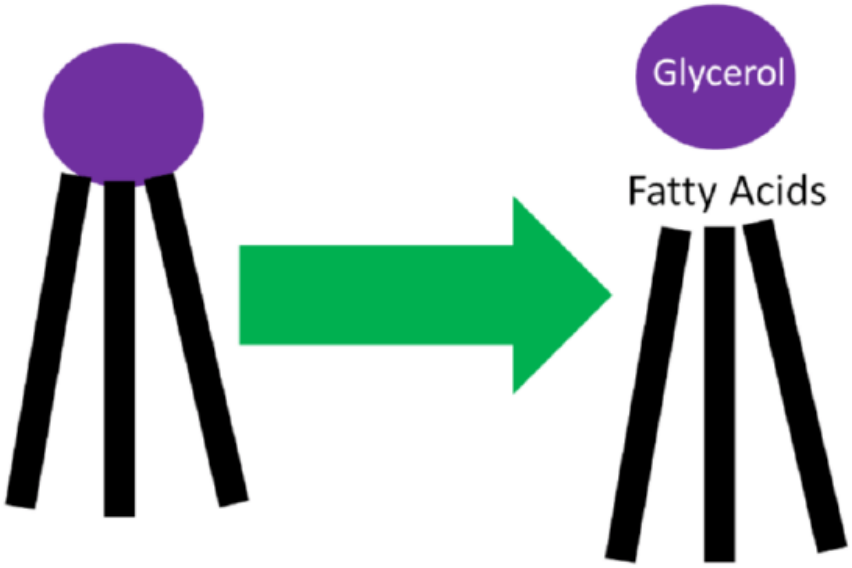


Figure 6.3.1: Lipolysis

There are two primary lipolysis enzymes:

1. Lipoprotein lipase (LPL)
2. Hormone-sensitive lipase (HSL)

Despite performing the same function, at the adipose level, the enzymes are primarily active for seemingly opposite reasons. In the fed state, LPL on the endothelium of blood vessels cleaves lipoprotein triglycerides into fatty acids so that they can be taken up into adipocytes, for storage as triglycerides, or myocytes where they are primarily used for energy production. This action of LPL on lipoproteins is shown in the two figures below.

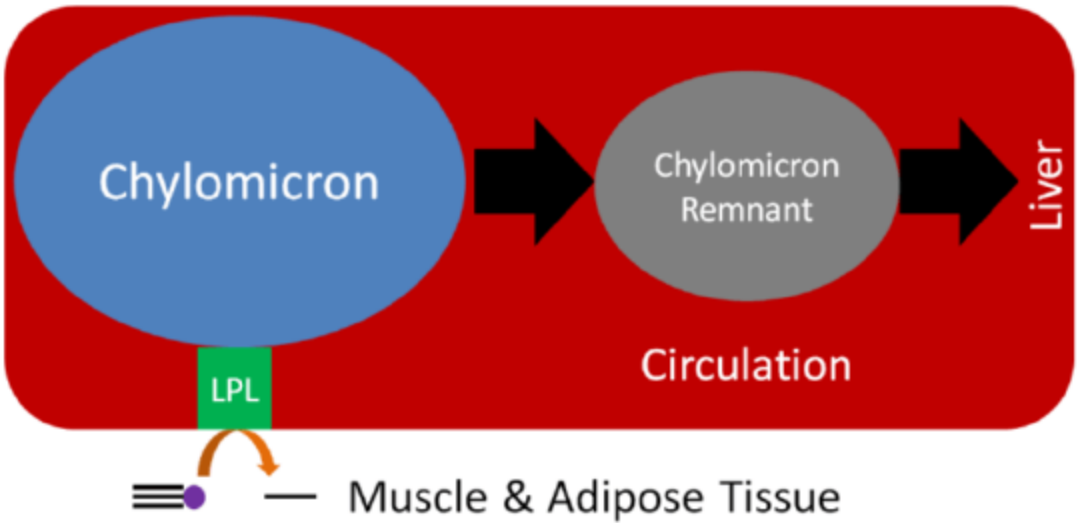


Figure 6.3.2: Lipoprotein lipase cleaves fatty acids from the chylomicron, forming a chylomicron remnant.

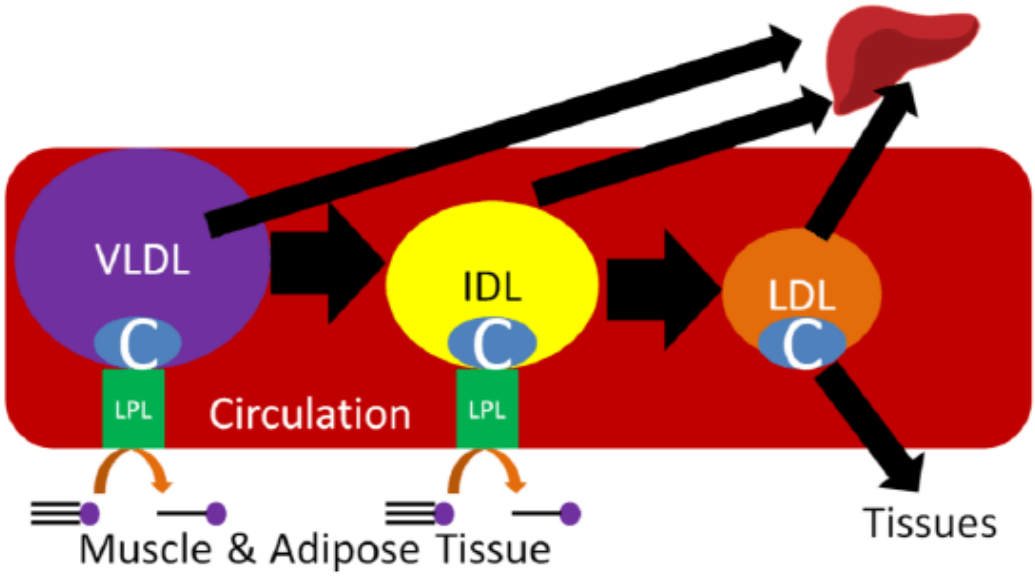


Figure 6.3.3: Lipoprotein lipase cleaves triglycerides from VLDL and IDL, forming subsequent lipoproteins (IDL and LDL) that contain less triglyceride

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HSL is an important enzyme in adipose tissue, which is a major storage site of triglycerides in the body. HSL activity is increased by glucagon and epinephrine ("fight or flight" hormone), and decreased by insulin. Thus, in hypoglycemia (such as during a fast) or a "fight or flight" response, triglycerides in the adipose are cleaved, releasing fatty acids into circulation that then bind with the transport protein albumin. Thus, HSL is important for mobilizing fatty acids so they can be used to produce energy. The figure below shows how fatty acids can be taken up and used by tissues such as the muscle for energy production1.

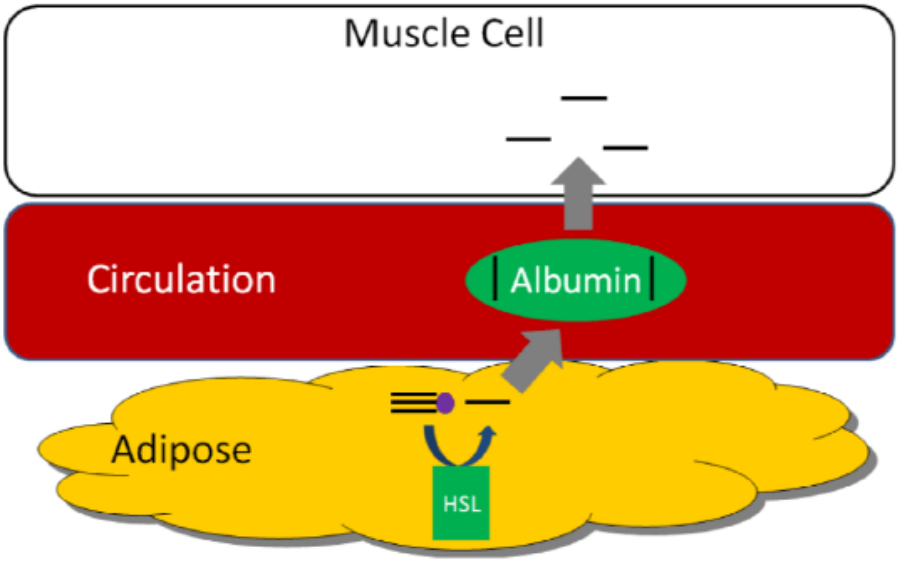


Figure 6.3.4: Hormone-sensitive lipase

We are not going to focus on glycerol, but it does have two metabolic fates.

1. It can be broken down in glycolysis
2. It can be used to synthesize glucose (gluconeogenesis)

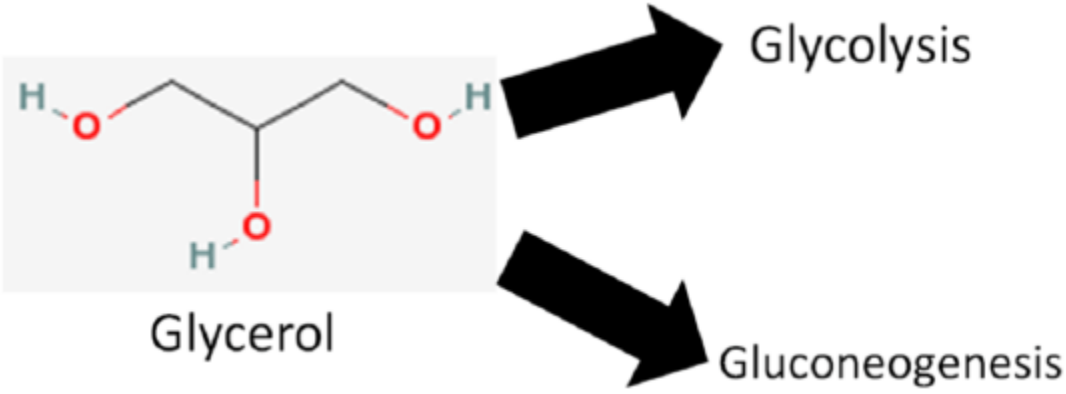


Figure 6.3.5: Metabolic fates of glycerol

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Fatty Acid Oxidation (Beta-oxidation)

To generate energy from fatty acids, they must be oxidized. This process occurs in the mitochondria, but long chain fatty acids cannot diffuse across the mitochondrial membrane (similar to absorption into the enterocyte). Carnitine, an amino acid-derived compound, helps shuttle long-chain fatty acids into the mitochondria. The structure of carnitine is shown below.

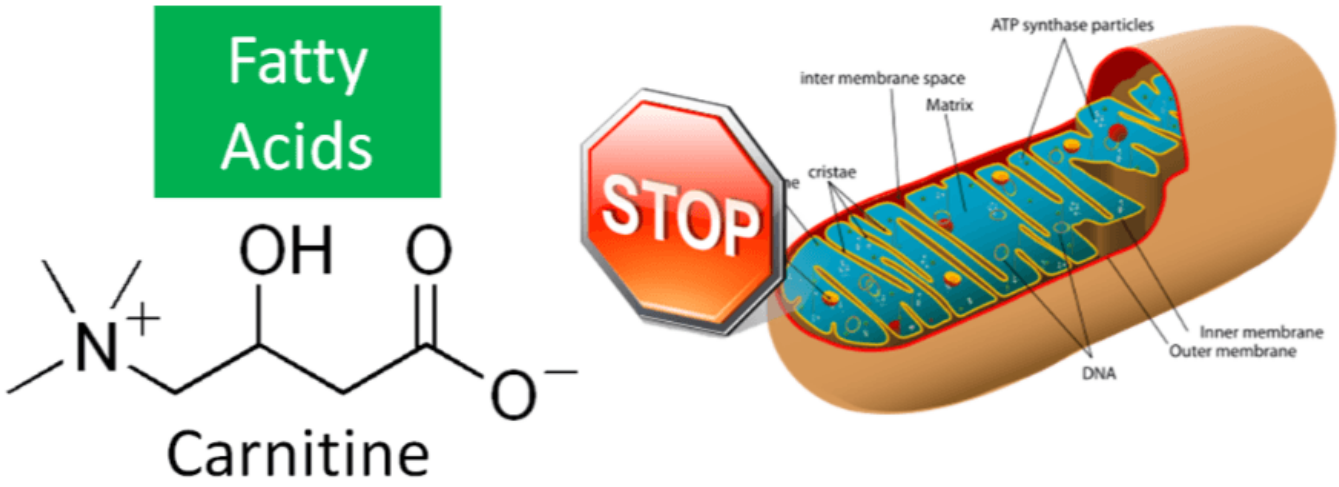


Figure 6.3.6: Carnitine shuttles fatty acids into the mitochondria2,3

Fatty Acid Shuttling

As shown below, there are two enzymes involved in this process: carnitine palmitoyltransferase I (CPTI) and carnitine palmitoyltransferase II (CPTII). CPTI is located on the outer mitochondrial membrane, CPTII is located on the inner mitochondrial membrane. The fatty acid is first activated by adding CoA (forming acyl-CoA), then CPTI adds carnitine. Acyl-Carnitine is then transported into the mitochondrial matrix with the assistance of the enzyme translocase. In the matrix, CPTII removes carnitine from the activated fatty acid (acyl-CoA). Carnitine is recycled back into the cytosol to be used again, as shown in the figure below. Even though carnitine is important for this action, taking supplemental carnitine will not increase fatty acid oxidation. This is due to the fact that the amount of carnitine available is not limiting fatty acid oxidation.

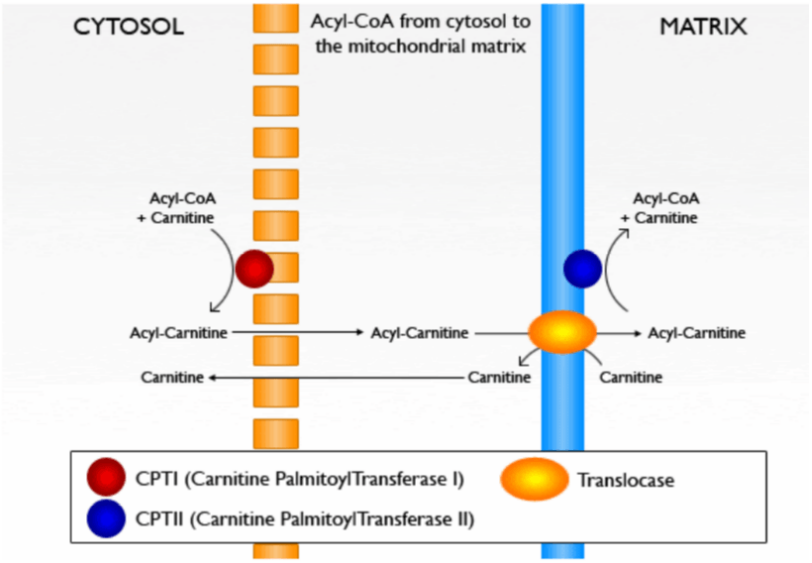


Figure 6.3.7: Transfer of fatty acids into the mitochondria4

Web Link

Fatty acid transfer from cytoplasm to mitochondria

Query 6.3.3

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Fatty Acid Activation

As shown below, the first step of fatty acid oxidation is activation. A CoA molecule is added to the fatty acid to produce acyl-CoA, converting ATP to AMP (adenosine monophosphate). Thus, activation uses the equivalent of 2 ATP molecules (since it typically cleaved to ADP)5.

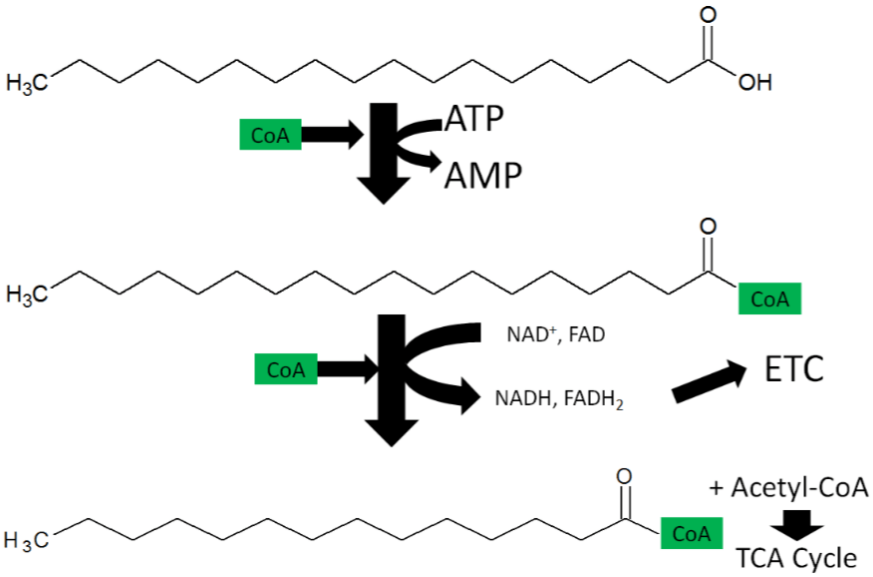


Figure 6.3.8: Fatty Acid Oxidation

Fatty Acid Oxidation

Fatty acid oxidation is also referred to as beta-oxidation because 2 carbon units are cleaved off at the beta-carbon position (2nd carbon from the acid end) of an activated fatty acid. The cleaved 2 carbon unit forms acetyl-CoA and produces an activated fatty acid (acyl-CoA) with 2 fewer carbons, acetyl-CoA, NADH, and $FADH_2$.

To completely oxidize the 18-carbon fatty acid above, 8 cycles of beta-oxidation have to occur. This might seem like one too few cycles (18 divided by 2 is nine), but the last cycle will split the 4 carbon fatty acid into 2 acetyl-CoAs, meaning that it only takes 8 cycles to completely cleave the fatty acid. Overall beta oxidation of an 18 carbon fatty acids will produce:

9 acetyl-CoAs

8 NADH

8 $FADH_2$

Those 9 acetyl-CoAs can continue into the citric acid cycle, where they can produce:

9 GTP

9 $FADH_2$

27 NADH

The products of the complete oxidation of a fatty acid are shown below.

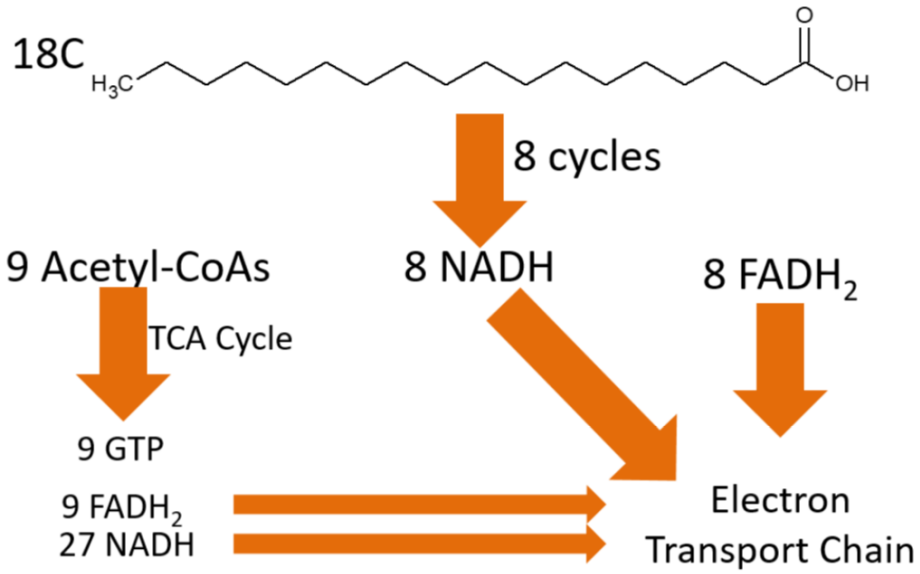


Figure 6.3.9: Complete oxidation of an 18 carbon (C) fatty acid

Adding up the NADH and FADH2, the electron transport chain ATP production from beta-oxidation and the citric acid cycle looks like this:

NADH

8 (beta-oxidation) + 27 (TCA) = 35 NADH X 2.5 ATP/NADH = 87.5 ATP

$FADH_2$

8 (beta-oxidation) + 9 (TCA) = 17 $FADH_2$ X 1.5 ATP/$FADH_2$ = 25.5 ATP

GTP

9 GTP = 9 ATP

Total ATP from complete oxidation of an 18 carbon fatty acid:

87.5 + 25.5 + 9 = 122 ATP

Subtract 2 ATP (ATP-->AMP) required for activation of the fatty acid:

122-2 = 120 Net ATP

Compared to glucose (32 ATP) you can see that there is far more energy stored in a fatty acid. This is because fatty acids are in a more reduced form and thus, they yield 9 kcal/g instead of 4 kcal/g like carbohydrates5.

The following animation reviews lipolysis and beta-oxidation.

Web Link

Fatty Acid Metabolism

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De novo Lipogenesis (Fatty Acid Synthesis)

De novo in Latin means "from the beginning." Thus, de novo lipogenesis is the synthesis of fatty acids, beginning with acetyl-CoA. Acetyl-CoA has to first move out of the mitochondria, where it is then converted to malonyl-CoA (3 carbons). Malonyl-CoA then is combined with another acetyl-CoA to form a 4 carbon fatty acid (1 carbon is given off as CO_2). The addition of 2 carbons is repeated through a similar process 7 times to produce a 16 carbon fatty acid6.

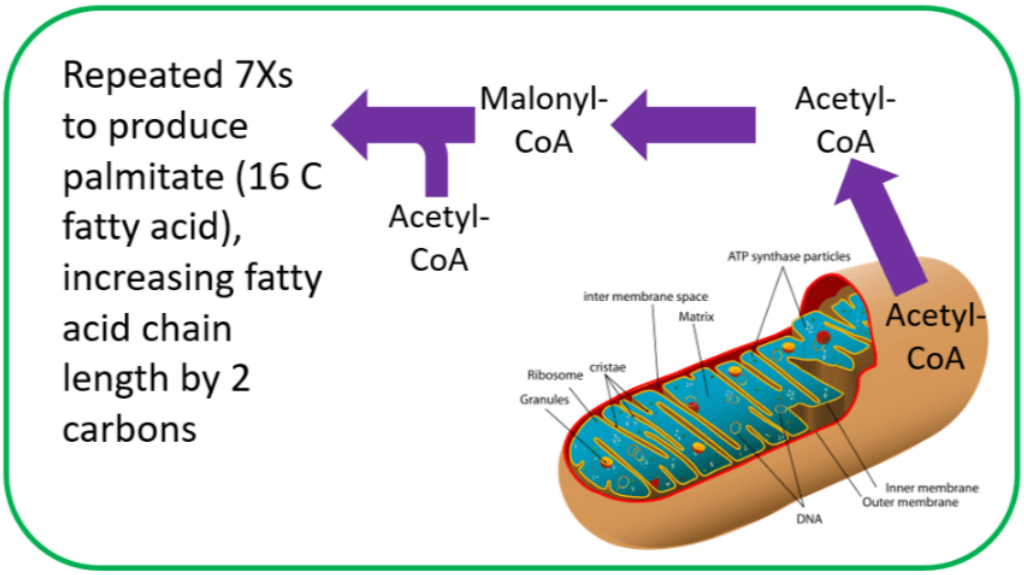


Figure 6.3.10: Fatty acid synthesis7

Most fatty acids synthesized will be esterified into triglycerides for storage.

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Ketone Body Synthesis

In cases where there is not enough glucose available for the brain (very low carbohydrate diets, starvation), the liver can use acetyl-CoA, primarily from fatty acids (but also certain amino acids), to synthesize ketone bodies (ketogenesis). The structures of the three ketone bodies; acetone, acetoacetic acid, and beta-hydroxybutyric acid, are shown below.

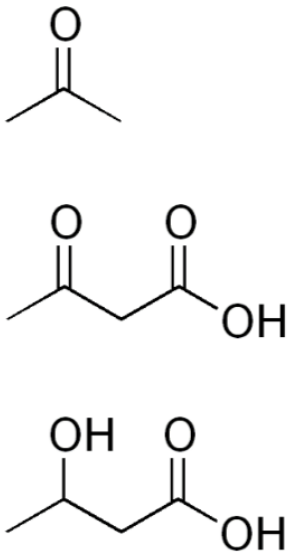


Figure 6.3.11: The three ketone bodies from top to bottom (acetone, acetoacetic acid, and beta-hydroxybutyric acid[8])

After they are synthesized in the liver, ketone bodies are released into circulation where they can travel to the brain. The brain converts the ketone bodies to acetyl-CoA that can then enter the citric acid cycle for ATP production, as shown below.

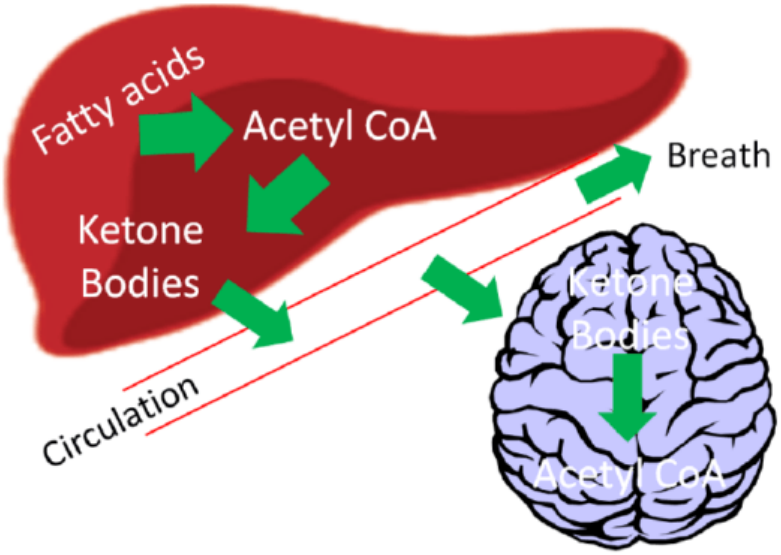


Figure 6.3.12: The production, release, use, or exhalation of ketone bodies[9]

If there are high levels of ketones secreted, it results in a condition known as ketosis or ketoacidosis. The high level of ketones in the blood decreases the blood's pH, meaning it becomes more acidic. It is debatable whether mild ketoacidosis is harmful, but severe ketoacidosis can be lethal. One symptom of this condition is fruity or sweet smelling breath, which is due to increased acetone exhalation.

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Cholesterol Synthesis

Acetyl-CoA is also used to synthesize cholesterol. As shown below, there are a large number of reactions and enzymes involved in cholesterol synthesis.

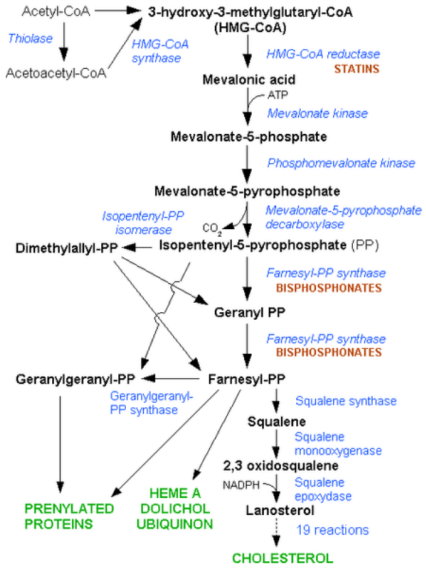


Figure 6.3.13: Cholesterol synthesis pathway[10]

Simplifying this, acetyl-CoA is converted to acetoacetyl-CoA (4 carbons) before forming 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). HMG-CoA is converted to mevalonate by the enzyme HMG-CoA reductase. This enzyme is important because it is the rate-limiting enzyme in cholesterol synthesis.

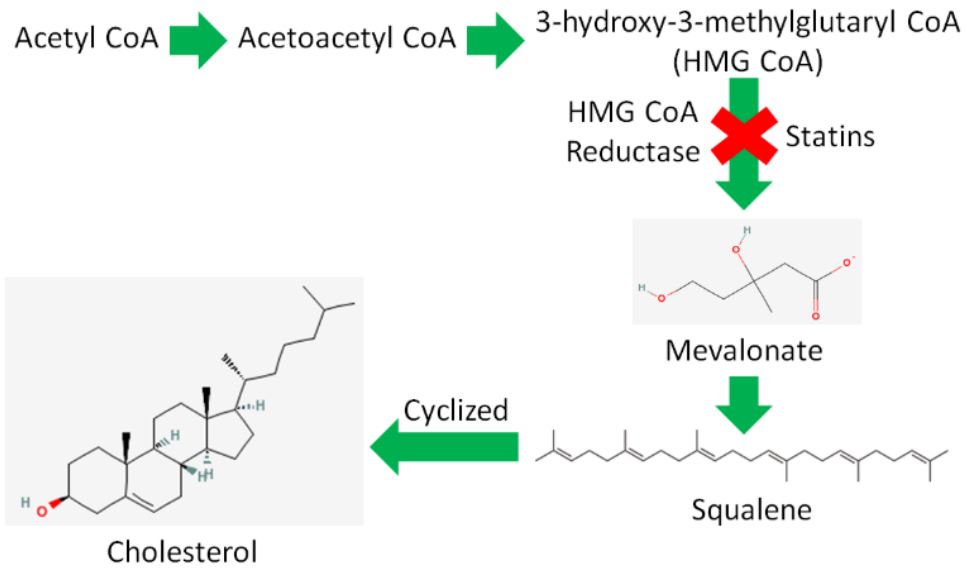


Figure 6.3.14: Cholesterol synthesis simplified[11]

A rate-limiting enzyme is like a bottleneck in a highway, as shown below, that determines the flow of traffic past it.

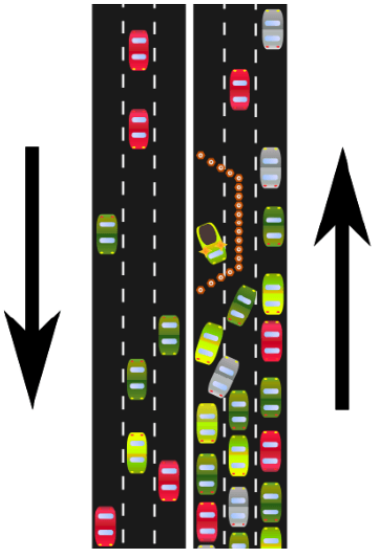


Figure 6.3.15: Bottleneck in traffic12

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Rate-limiting enzymes limit the rate at which a metabolic pathway proceeds. The pharmaceutical industry has taken advantage of this knowledge to lower people's LDL levels with drugs known as statins. These drugs inhibit HMG-CoA reductase and thus decrease cholesterol synthesis. Less cholesterol leads to lower LDL levels, and hopefully a lower risk of cardiovascular disease.

The brand name of the statins approved for use in the US are13:

- Lipitor
- Lescol
- Mevacor
- Pravachol
- Crestor
- Zocor
- Livalo

The cholesterol guidelines have changed dramatically from the previous focus on LDL and HDL target levels. Now statins are prescribed at set therapeutic doses based on assessed cardiovascular risk rather than based off LDL and HDL target levels. It is also recommended that only statins that have been shown to decrease cardiovascular disease risk be used, some have only been shown to improve LDL/HDL levels. The link below is to the online calculator that can be used to estimate an individual's risk.

Web Link

Check.Change.Control Heart Attack & Stroke Risk Calculator

The body synthesizes approximately 1 g/day, whereas it is recommended that we consume less than 0.3 g/day. A number of tissues synthesize cholesterol, with the liver accounting for ~20% of synthesis. The intestine is believed to be the most active among the other tissues that are responsible for the other 80% of cholesterol synthesis1.

Query 6.3.10

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6.4: Protein Metabolism

Section 2.2 described how proteins are synthesized. Thus, this section will focus on how proteins and amino acids are broken down. There are four protein metabolic pathways that will be covered in this section

Transamination, Deamination & Ammonia Removal as Urea

The first step in catabolizing, or breaking down, an amino acid is the removal of its amine group (-NH_3). Amine groups can be transferred or removed through transamination or deamination, respectively.

Transamination

Transamination is the transfer of an amine group from an amino acid to a keto acid (amino acid without an amine group), thus creating a new amino acid and keto acid as shown below.

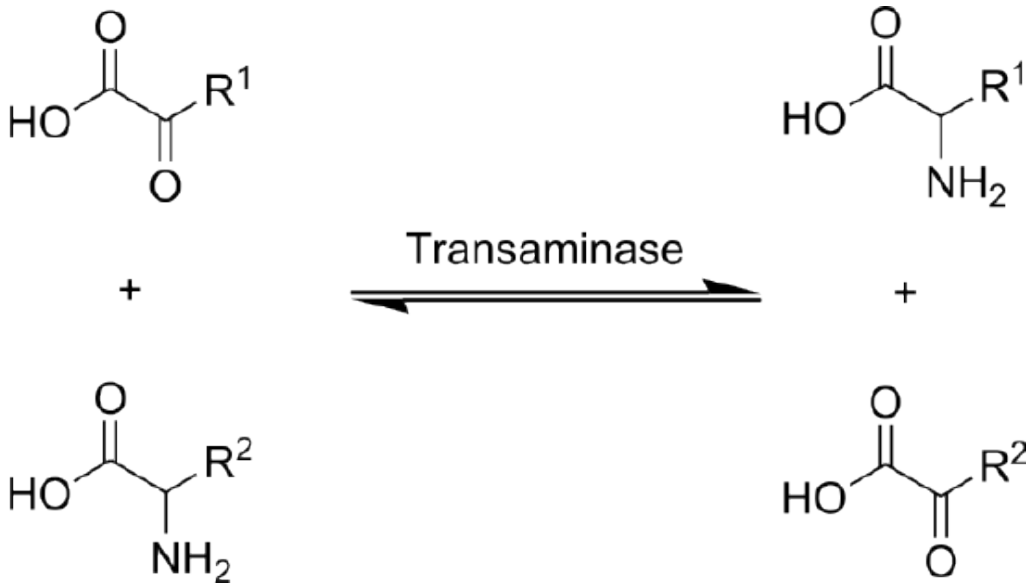


Figure 6.4.1: Generic transamination reaction where the top keto acid is converted to an amino acid, while the bottom amino acid is converted to a keto acid1

Keto acids (also known as carbon skeletons) are what remains after amino acids have had their nitrogen group removed by deamination or transamination. Transamination is used to synthesize nonessential amino acids.

Deamination

Deamination is the removal of the amine group as ammonia (NH_3), as shown below.

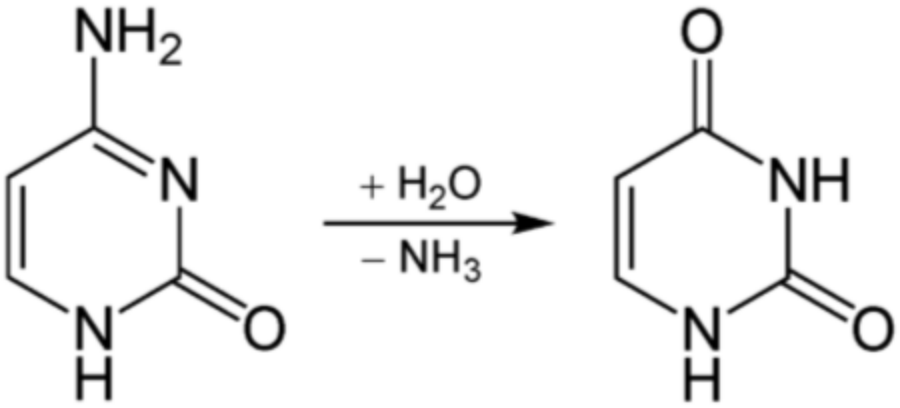


Figure 6.4.2: Deamination of cytosine to uracil (nucleotides, not amino acids)2

The potential problem with deamination is that too much ammonia is toxic, causing a condition known as hyperammonemia. The symptoms of this condition are shown in the following figure.

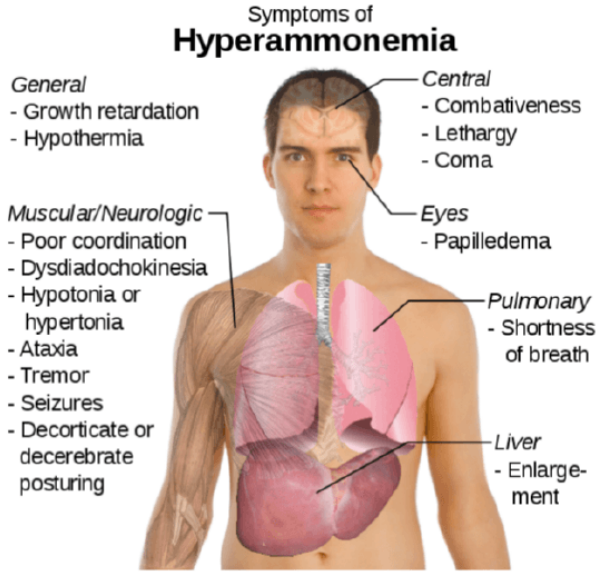


Figure 6.4.3: Symptoms of Hyperammonemia3

Our body has a method to safely package ammonia into a less toxic form to be excreted. This safer compound is urea, which is produced by the liver using 2 molecules of ammonia (NH_3) and 1 molecule of carbon dioxide (CO_2). Most urea is then secreted from the liver and incorporated into urine in the kidney to be excreted from the body, as shown below.

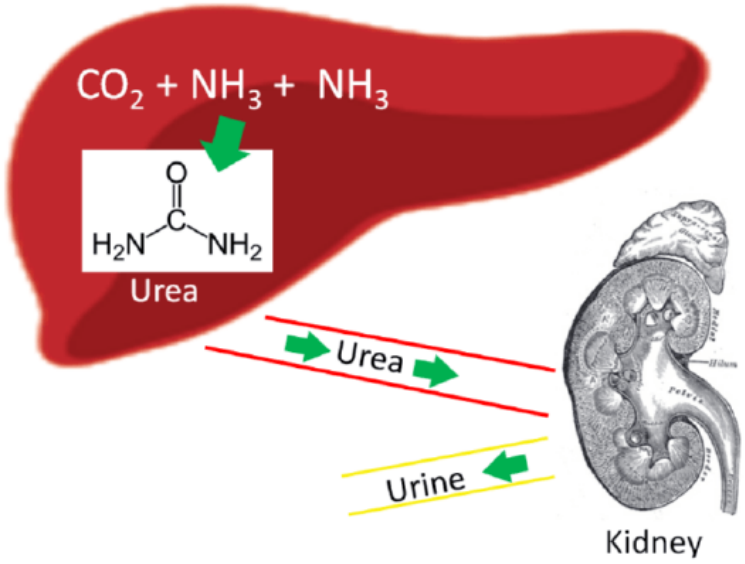


Figure 6.4.4: Production of urea helps to safely remove ammonia from the body4-6

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Gluconeogenesis

Gluconeogenesis is the synthesis of glucose from noncarbohydrate sources. Certain amino acids can be used for this process, which is the reason that this section is included here instead of the carbohydrate metabolism section. Gluconeogenesis is glycolysis in reverse with an oxaloacetate workaround, as shown below. Remember oxaloacetate is also an intermediate in the citric acid cycle.

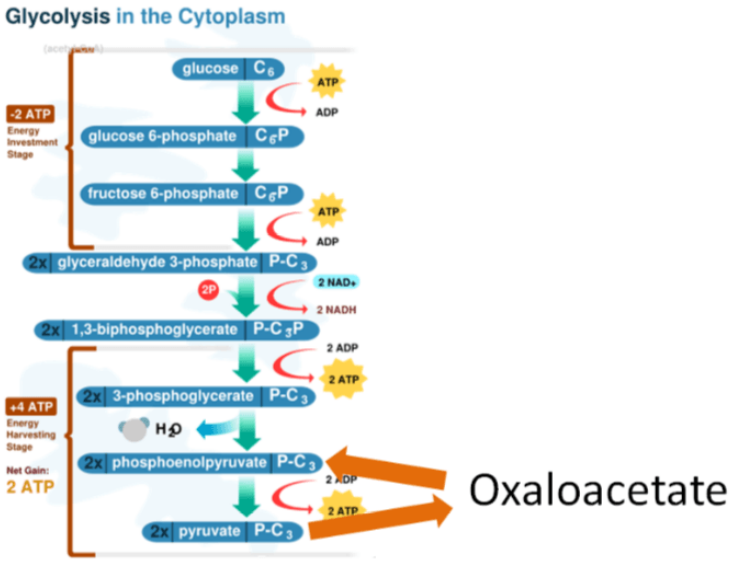


Figure 6.4.5: Gluconeogenesis is glycolysis in reverse with an oxaloacetate workaround7

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Not all amino acids can be used for gluconeogenesis. The ones that can be used are termed glucogenic (red), and can be converted to either pyruvate or a citric acid cycle intermediate. Other amino acids can only be converted to either acetyl-CoA or acetoacetyl-CoA, which cannot be used for gluconeogenesis. However, acetyl-CoA or acetoacetyl-CoA can be used for ketogenesis to synthesize the ketone bodies, acetone and acetoacetate. Thus, these amino acids are instead termed ketogenic (green).

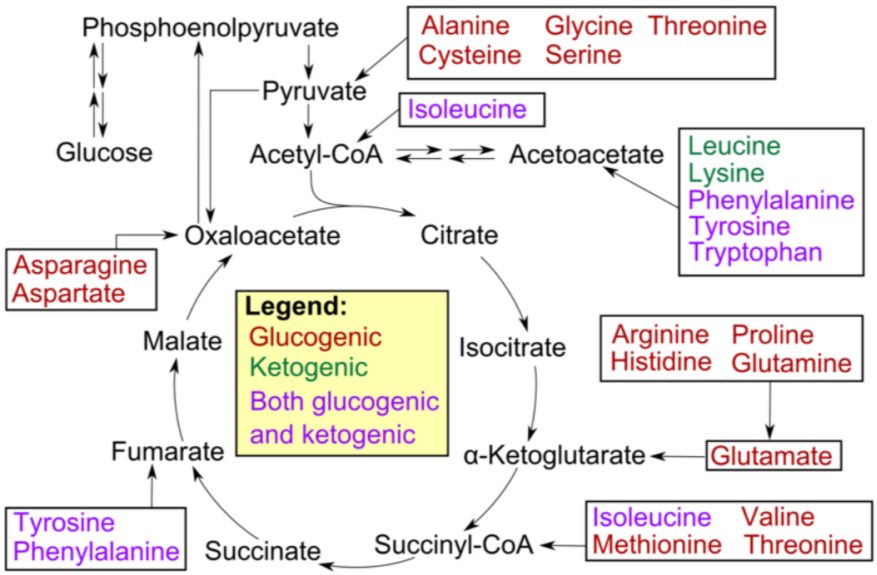


Figure 6.4.6: Glucogenic (red), ketogenic (green), and glucogenic and ketogenic amino acids8

Fatty acids and ketogenic amino acids cannot be used to synthesize glucose. The transition reaction is a one-way reaction, meaning that acetyl-CoA cannot be converted back to pyruvate. As a result, fatty acids can't be used to synthesize glucose, because beta-oxidation produces acetyl-CoA. Even if acetyl-CoA enters the citric acid cycle, the carbons from it will eventually be completely oxidized and given off as $\mathrm{CO_2}$. The net result is that these carbons are not readily available to serve as keto-acids or carbon skeletons for amino acid synthesis. Some amino acids can be either glucogenic or ketogenic, depending on how they are metabolized. These amino acids are referred to as glucogenic and ketogenic (pink).

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Protein Turnover/Degradation

Proteins serve a number of functions in the body, but what happens when cells, enzymes, etc. have completed their lifespan? They are recycled.

Proteins are broken down into amino acids that can be used to synthesize new proteins. There are 3 main systems of protein degradation:

1. Ubiquitin-proteasome degradation
2. Lysosome degradation
3. Calpain degradation

Ubiquitin-Proteasome Degradation

Proteins that are damaged or abnormal are tagged with the protein ubiquitin. There are multiple protein subunits involved in the process (E1-E3), but the net result is the production of a protein (substrate) with a ubiquitin tail, as shown below.

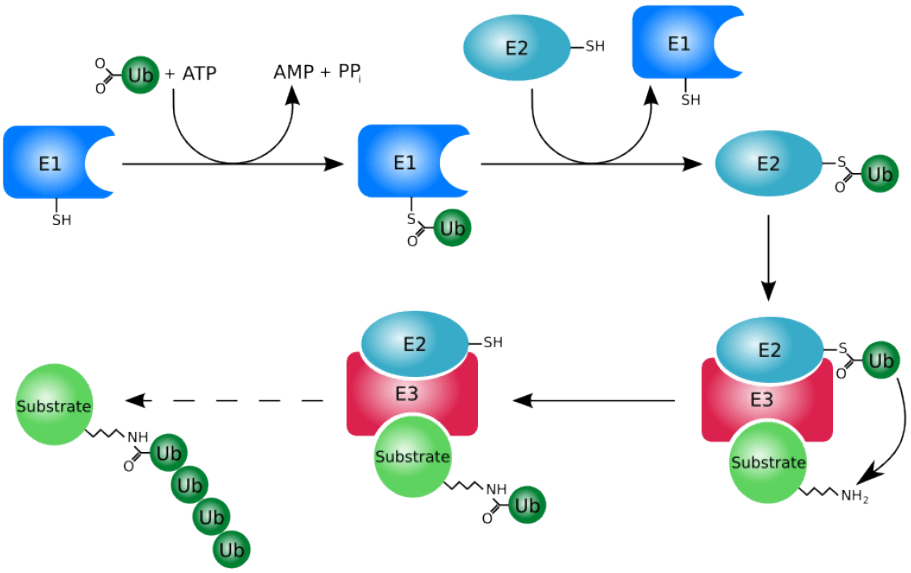


Figure 6.4.7: Ubiquitination of a protein (substrate)[9]

This protein then moves to the proteasome for degradation. Think of the proteasome like a garbage disposal. The ubiquitinated "trash" protein is inserted into the garbage disposal where it is broken down into its component parts (primarily amino acids). The

following video illustrates this process nicely.

YouTube Video

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Video 6.4.1: Proteasomes are large protein complexes located in the nucleus and the cytoplasm.The main function of the proteasome is to degrade unneeded or damaged proteins by proteolysis, a chemical reaction that breaks peptide bonds. https://www.youtube.com/watch?v=w2Qd6v-4IIc

Lysosome Degradation

The lysosomes are organelles that are found in cells. They contain a number of proteases that degrade proteins.

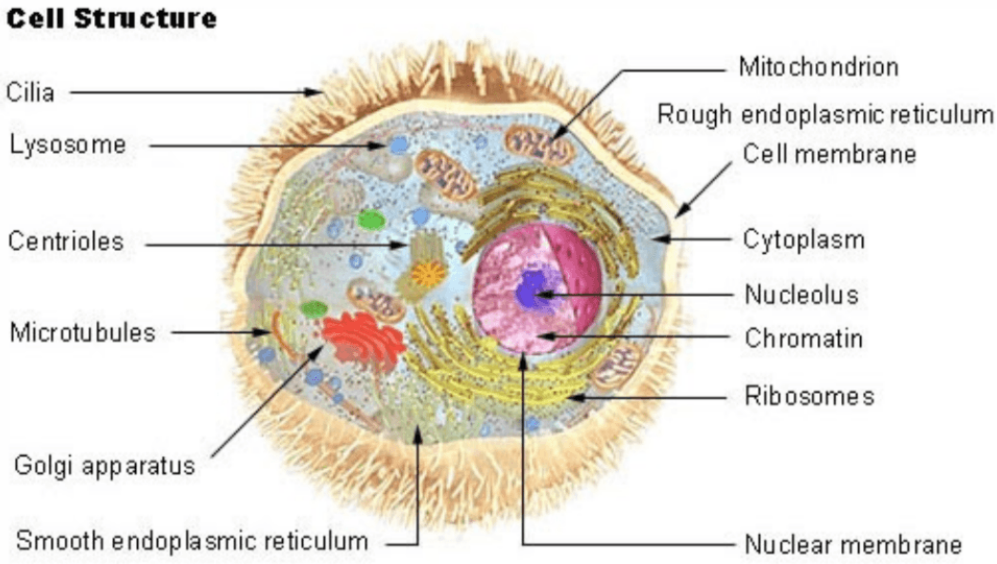


Figure 6.4.8: Lysosomes are organelles within the cell[10]

Calpain Degradation

The last degradation system is the calpain system, which is not as well understood, but does require calcium.

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2. en.Wikipedia.org/wiki/File:De...ierungCtoU.png
3. en.Wikipedia.org/wiki/File:Sy...rammonemia.svg
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6.5: Alcohol Metabolism

The other energy source is alcohol. The alcohol we consume contains two carbons and is known as ethanol.

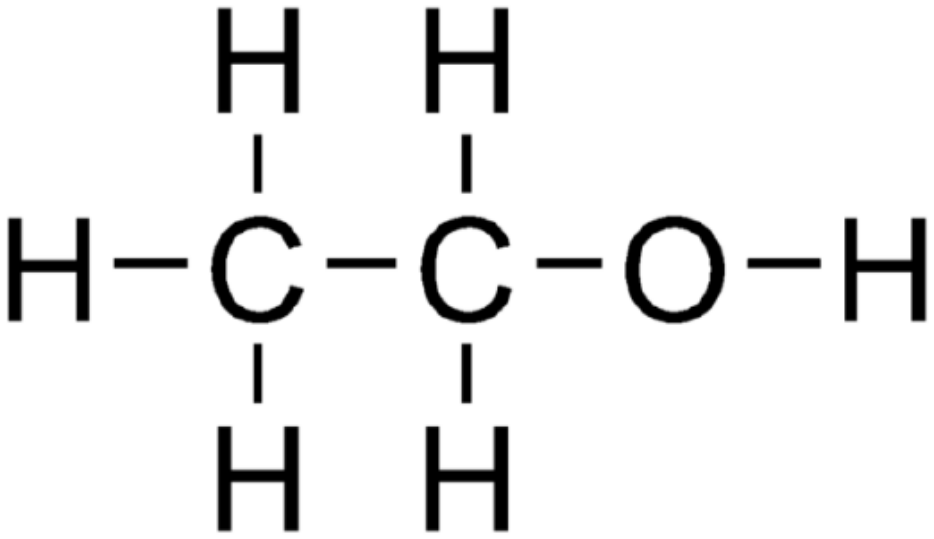


Figure 6.5.1: Structure of ethanol[1]

Ethanol is passively absorbed by simple diffusion into the enterocyte. Ethanol metabolism occurs primarily in the liver, but 10-30% is estimated to occur in the stomach[2]. For the average person, the liver can metabolize the amount of ethanol in one drink (1/2 ounce) per hour[3]. There are three ways that alcohol is metabolized in the body.

1. Catalase - an enzyme that we will cover again in the antioxidants section. Catalase is estimated to metabolize less than 2% of ethanol, so it is not in the figure below or discussed further[4].
2. Alcohol dehydrogenase (ADH) - This is the major ethanol-metabolizing enzyme that converts ethanol and NAD to acetaldehyde and NADH, respectively. Aldehyde dehydrogenase (ALDH) uses NAD, CoA, and acetaldehyde to create acetyl-CoA and to produce another NADH. The action of ADH is shown in the figure below.

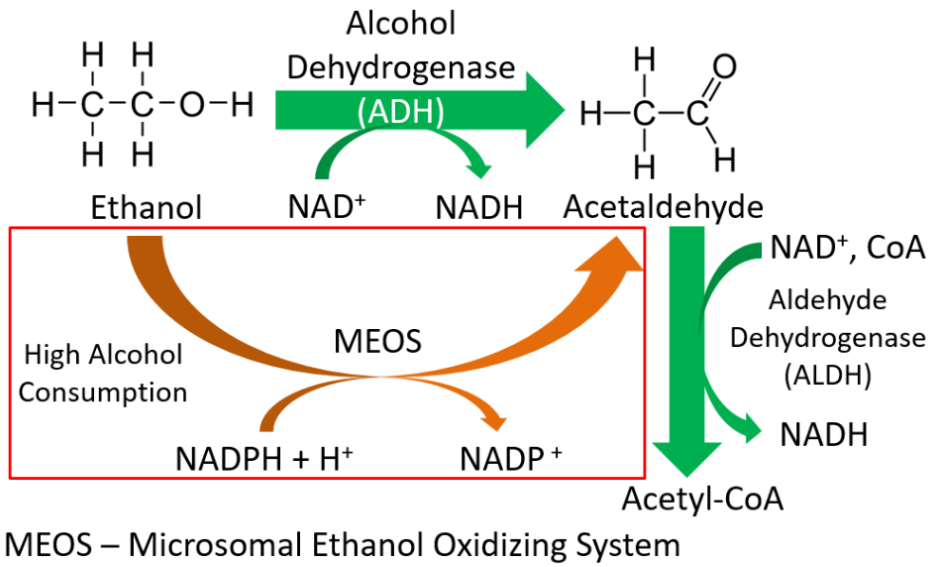


Figure 6.5.2: Ethanol Metabolism[1,5]

3. Microsomal ethanol oxidizing system (MEOS) - When a person consumes a large amount of alcohol the MEOS, is the overflow pathway, which also metabolizes ethanol to acetaldehyde. It is estimated that the MEOS metabolizes 20% of ethanol3, and it differs from ADH in that it uses ATP to convert reduced nicotinamide adenine dinucleotide phosphate ($\mathrm{NADPH} + \mathrm{H}^{+}$) to NADP^{+}. The action of the MEOS is shown in the figure above.

At high intakes or with repeated exposure, there is increased synthesis of MEOS enzymes resulting in more efficient metabolism, also known as increased tolerance. ADH levels do not increase based on alcohol exposure. MEOS also metabolizes a variety of other compounds (drugs, fatty acids, steroids) and alcohol competes for the enzyme's action. This can cause the metabolism of drugs to slow and potentially reach harmful levels in the body3.

Females have lower stomach ADH activity and body $\mathrm{H_2O}$ concentrations. As a result, a larger proportion of ethanol reaches circulation, thus, in general, females have a lower tolerance for alcohol. About 50% of Taiwanese, Han Chinese, and Japanese populations have polymorphisms in ALDH which cause the enzyme to have low activity6. This leads to acetaldehyde buildup and undesirable symptoms such as: flushing, dizziness, nausea, and headaches2. The following animation explains what happens when the MEOS system gets involved in alcohol metabolism.

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Query 6.5.2

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7: INTEGRATION OF MACRONUTRIENT METABOLISM

Understanding the different metabolic pathways is an important step. However, an integrated understanding of the interconnectedness and tissue specificity of metabolism is where this knowledge really becomes powerful. To this end, you will first learn how the different pathways integrate with one another and then talk about the metabolic capabilities of the different tissues in the body. We will then discuss what happens metabolically during different conditions or when consuming certain diets.

7.1: Integration of Macronutrient Metabolism and Alcohol Metabolic Pathways

7.2: Liver Macronutrient and Alcohol Metabolism

7.3: Extrahepatic Macronutrient Metabolism

7.4: Metabolic Conditions

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7.1: Integration of Macronutrient Metabolism and Alcohol Metabolic Pathways

If you were to draw all the macronutrient and alcohol metabolic pathways covered in chapter 6, hopefully it would look something like the figure below.

The following color scheme is used in this figure:

- Carbohydrate pathways are orange
- Triglyceride/fatty acid pathways are purple
- Protein/amino acid pathways are green
- Nonclassified pathways are gray

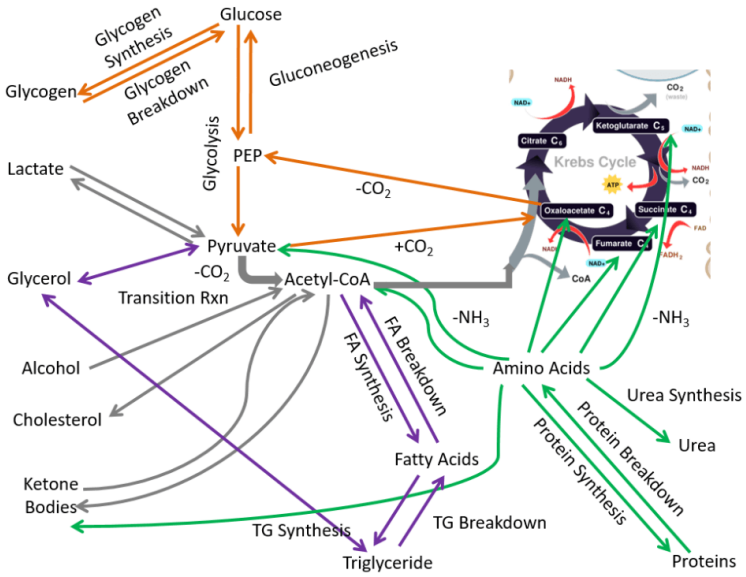


Figure 7.1.1: Integrated macronutrient and alcohol metabolism

To simplify, we are going to remove the glycerol and cholesterol pathways so that we can focus on integrating the other pathways in macronutrient and alcohol metabolism.

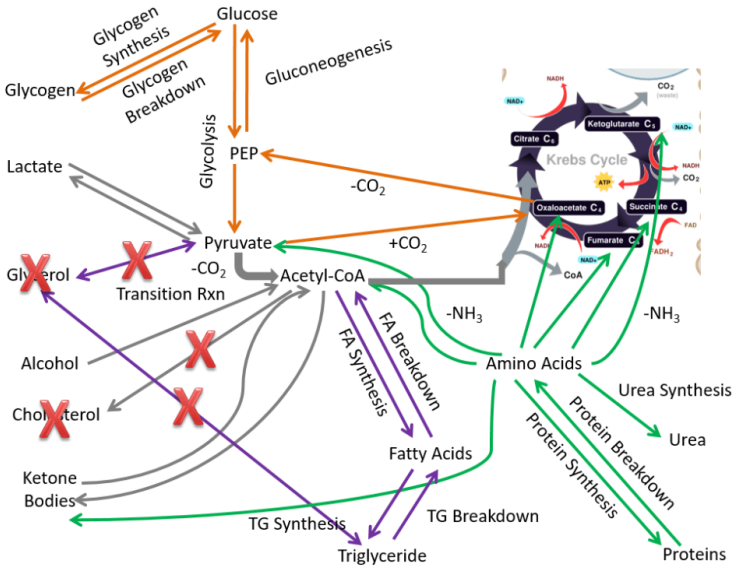


Figure 7.1.2: Removal of glycerol and cholesterol pathways[1]

Thus, we are left with the following simplified figure:

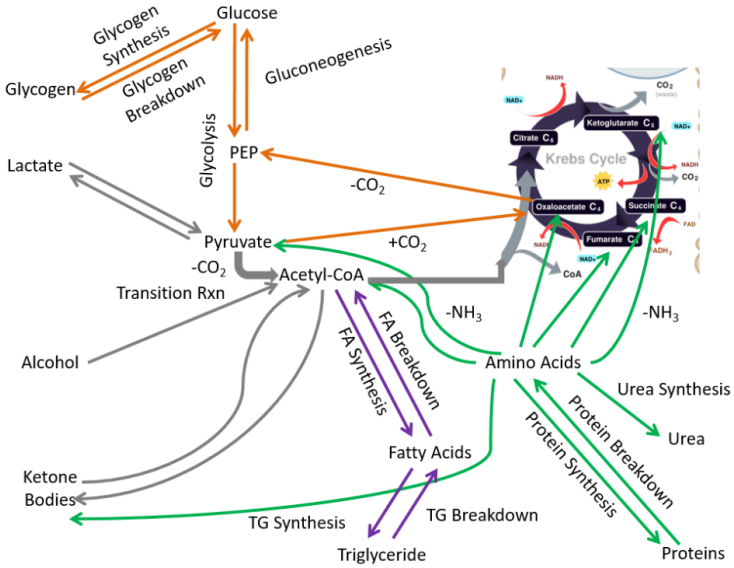


Figure 7.1.3: Simplified integrated macronutrient and alcohol metabolism[1]

Notice that acetyl-CoA is the central metabolite in integrated metabolism that connects many different pathways. For example, carbohydrates can be broken down to acetyl-CoA that can then be used to synthesize fats and ultimately triglycerides.

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References

1. en.Wikipedia.org/wiki/File:CellRespiration.svg

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7.2: Liver Macronutrient and Alcohol Metabolism

The liver is the organ that has the greatest macronutrient metabolic capability; there are a number of metabolic functions that only the liver performs. However, there are two major macronutrient metabolic processes, lactate synthesis and ketone body breakdown, that the liver will not normally perform, as shown in the figure below.

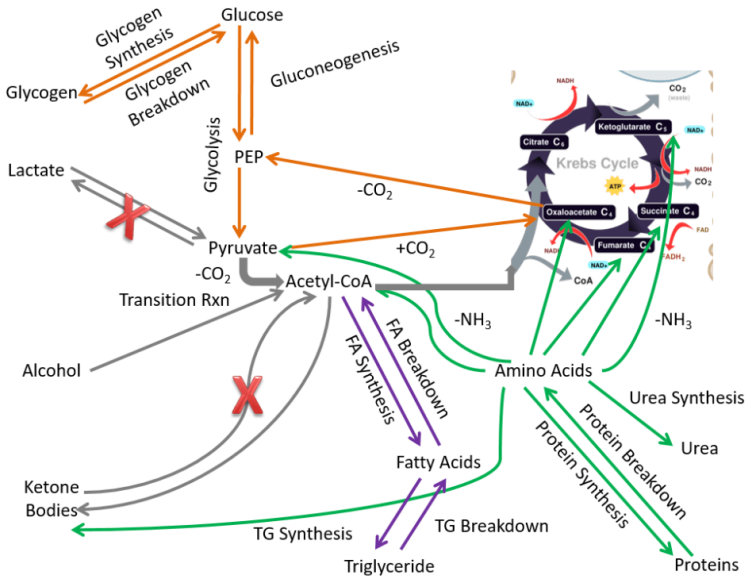


Figure 7.2.1: Ketone body breakdown and lactate synthesis are major macronutrient metabolic pathways that the liver does not normally perform[1]

But aside from those two pathways, the liver performs all the other metabolic pathways that you have learned about that are listed and shown below:

- Glycogen synthesis and breakdown
- Glycolysis
- Gluconeogenesis
- Alcohol oxidation
- Ketone body synthesis
- Fatty acid synthesis and breakdown
- Triglyceride synthesis and breakdown
- Protein synthesis and breakdown
- Urea synthesis
- VLDL synthesis
- Glucose-6-phosphatase

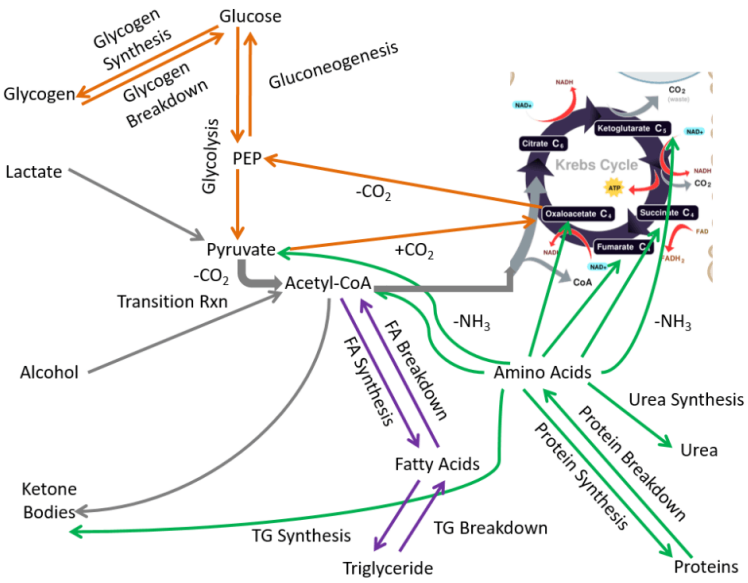


Figure 7.2.2: Metabolic capability of the liver[1]

The liver is the only tissue that performs the following functions:

- Ketone body synthesis
- Urea synthesis
- VLDL synthesis

The liver is also the primary, but not exclusive site, of the following functions:

- Alcohol oxidation (also occurs in the stomach)
- Gluconeogenesis (also occurs in the kidney(s))
- Glucose-6-phosphatase activity (also occurs in the kidney(s))
- Lactate breakdown (also occurs in muscle)[2]

Glucose-6-phosphatase is important because it removes the phosphate from glucose-6-phosphate so that glucose can be released into circulation. Kidneys have glucose-6-phosphatase and can perform gluconeogenesis. However, it is estimated that 90% of glucose formed from gluconeogenesis is produced by the liver; the remaining 10% is produced by the kidney(s). It is also important to note that the muscle does not have this enzyme, so it cannot release glucose into circulation[3].

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1. en.Wikipedia.org/wiki/File:CellRespiration.svg
2. Phypers B, Pierce JMT. (2006) Lactate physiology in health and disease. Continuing Education in Anaesthesia Critical Care & Pain, 6(3).
3. Stipanuk MH. (2006) Biochemical, physiological, & molecular aspects of human nutrition. St. Louis, MO: Saunders Elsevier.

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7.3: Extrahepatic Macronutrient Metabolism

Because the liver is so important in metabolism, the term extrahepatic has been defined to mean "located or occurring outside of the liver[1]". We are next going to consider extrahepatic tissue metabolism.

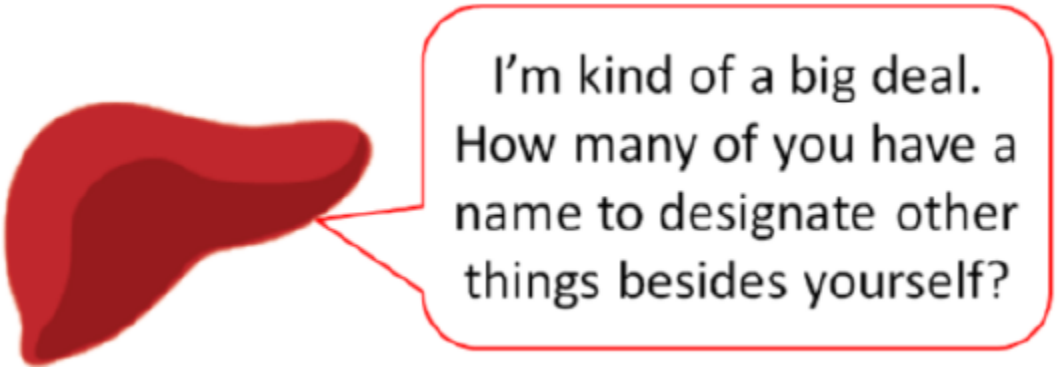


Figure 7.3.1: The liver "is kind of a big deal[2]"

To start considering the metabolic capabilities of the extrahepatic tissues, we start by removing pathways that only or mostly occur in the liver:

- Alcohol oxidation
- Gluconeogenesis
- Ketone body synthesis
- Urea synthesis
- Lactate breakdown
- Glucose-6-phosphatase

These metabolic processes are crossed off in the figure below.

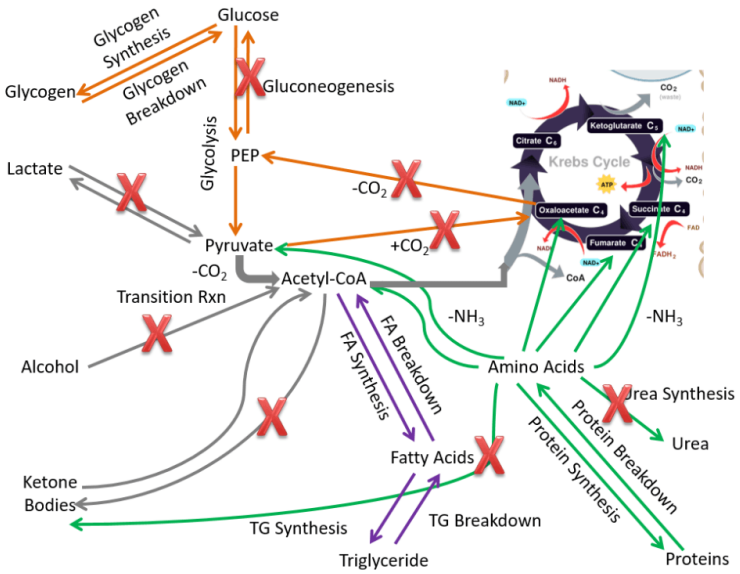


Figure 7.3.2: Removing the pathways that only or mostly occur in the liver[3]

We are left with metabolic capabilities that are listed and shown below.

- Glycogen synthesis and breakdown
- Glycolysis

- Fatty acid synthesis and breakdown
- Triglyceride synthesis and breakdown
- Protein synthesis and breakdown

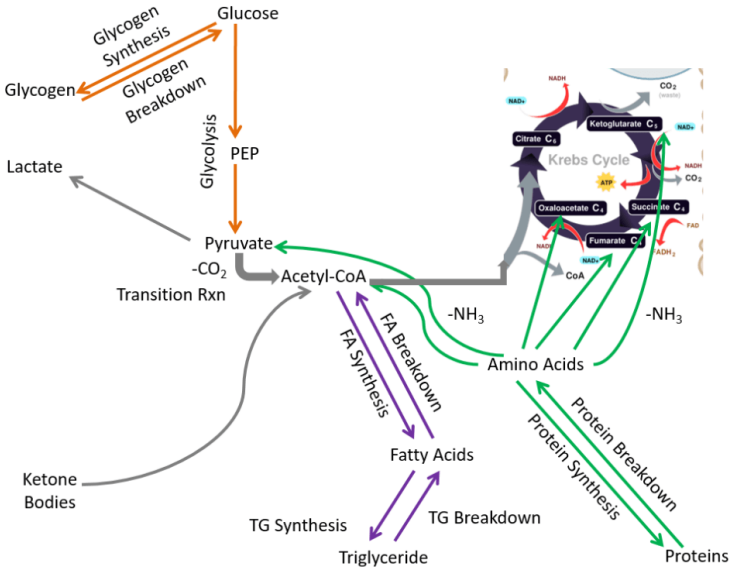


Figure 7.3.3: The metabolic capability of the extrahepatic tissues[3]

We will use this figure as the base for metabolic capabilities of the different extrahepatic tissues to compare what pathways other tissues can perform versus all the pathways performed by extrahepatic tissues.

In an effort to keep this simple, we are going to focus on four extrahepatic tissues in the following subsections:

- Muscle Macronutrient Metabolism
- Adipose Macronutrient Metabolism
- Brain Macronutrient Metabolism
- Red Blood Cell Macronutrient Metabolism

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Muscle Macronutrient Metabolism

Compared to extrahepatic tissues as a whole, in the muscle the following pathways are not performed or are not important:

- Fatty acid synthesis
- Ketone body breakdown

These pathways are crossed out in the figure below.

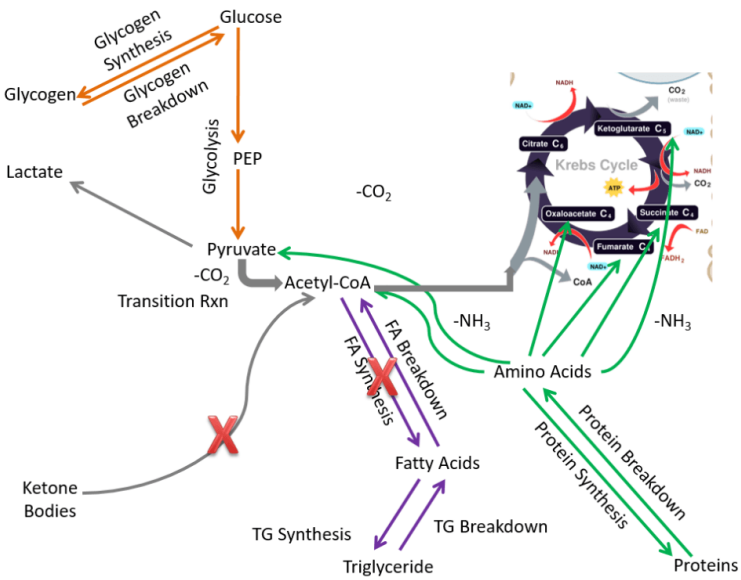


Figure 7.3.4: The metabolic pathways that are not performed or important in the muscle, compared to extrahepatic tissues as a whole[3]

Removing those pathways, the following metabolic pathways make up the muscle metabolic capability:

- Glycogen synthesis and breakdown
- Glycolysis
- Protein synthesis and breakdown
- Triglyceride synthesis and breakdown
- Fatty acid breakdown
- Lactate synthesis

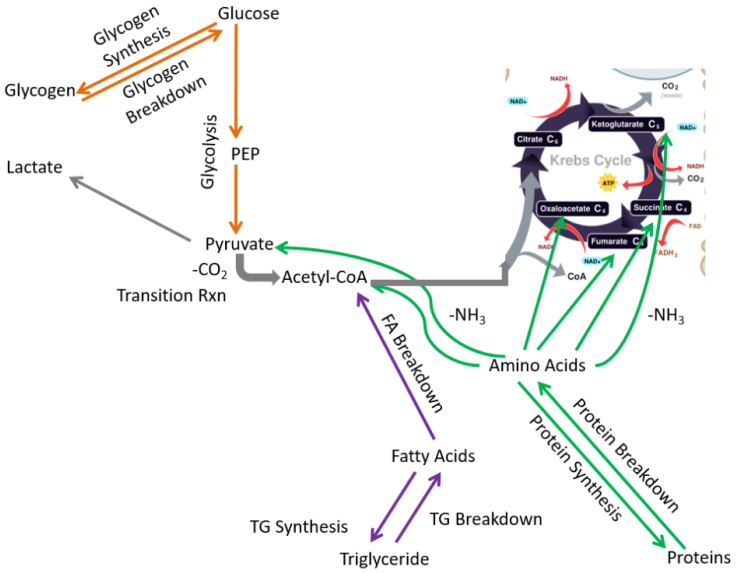


Figure 7.3.5: Muscle metabolic capability[3]

Muscle is a major extrahepatic metabolic tissue. It is the only extrahepatic tissue with significant glycogen stores. However, unlike the liver, the muscle cannot secrete glucose after it is taken up (no glucose-6-phosphatase). Thus, you can think of the muscle as being selfish with glucose. It either uses it for itself initially or stores it for its later use.

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Adipose Macronutrient Metabolism

It probably does not surprise you that the major function of the adipose is to store energy as triglycerides. Compared to extrahepatic tissues as a whole, in the adipose the following pathways are not performed or are not important:

- Glycogen synthesis and breakdown
- Lactate synthesis
- Ketone body breakdown
- Fatty acid breakdown
- Protein synthesis and breakdown
- Citric acid cycle (not much since it is not an active tissue needing energy)

These pathways are crossed out in the figure below.

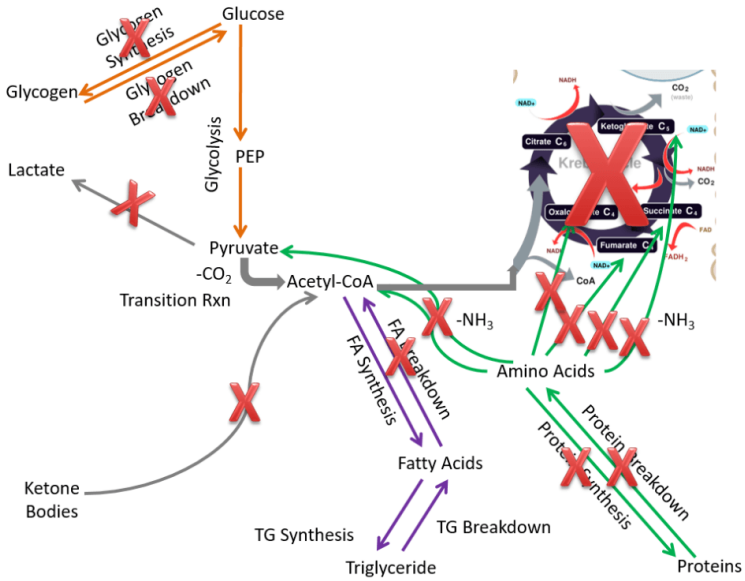


Figure 7.3.6: The metabolic pathways that are not performed or important in the adipose, compared to extrahepatic tissues as a whole are crossed out3

Removing those pathways, we are left with metabolic capabilities listed below and depicted in the following figure:

- Glycolysis
- Fatty acid synthesis
- Triglyceride synthesis and breakdown

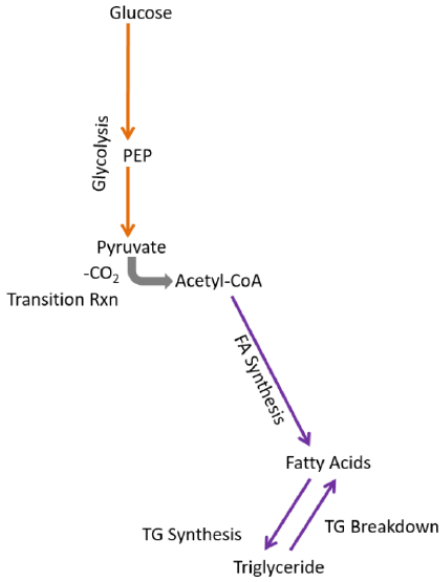


Figure 7.3.7: Adipose metabolic capability

Fatty acid synthesis only occurs in the adipose and liver. In the adipose, fatty acids are synthesized and most will be esterified into triglycerides to be stored. In the liver, some fatty acids will be esterified into triglycerides to be stored, but most triglycerides will be incorporated into VLDL so that they can be used or stored by other tissues.

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Brain Macronutrient Metabolism

Fatty acid breakdown does not occur to any great extent in the brain because of the low activity of an enzyme in the beta-oxidation pathway limits the pathway's activity1. Compared to the extrahepatic tissues as a whole, in the brain the following pathways are not performed or are not important:

- Glycogen synthesis and breakdown
- Lactate synthesis
- Fatty acid synthesis and breakdown
- Triglyceride synthesis and breakdown
- Protein synthesis and breakdown

These pathways are crossed out on the figure below.

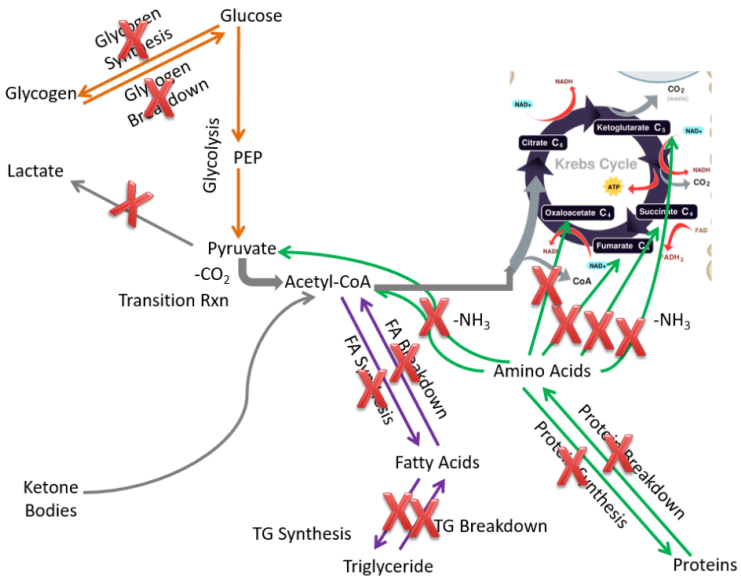


Figure 7.3.8: The metabolic pathways that are not performed or important in the brain compared to extrahepatic tissues as a whole are crossed out[3]

Fatty acid breakdown does not occur to any great extent in the brain because low activity of an enzyme in the beta-oxidation pathway limits the activity of this pathway[4].

By removing those pathways the only pathways left are:

- Glycolysis
- Ketone body breakdown

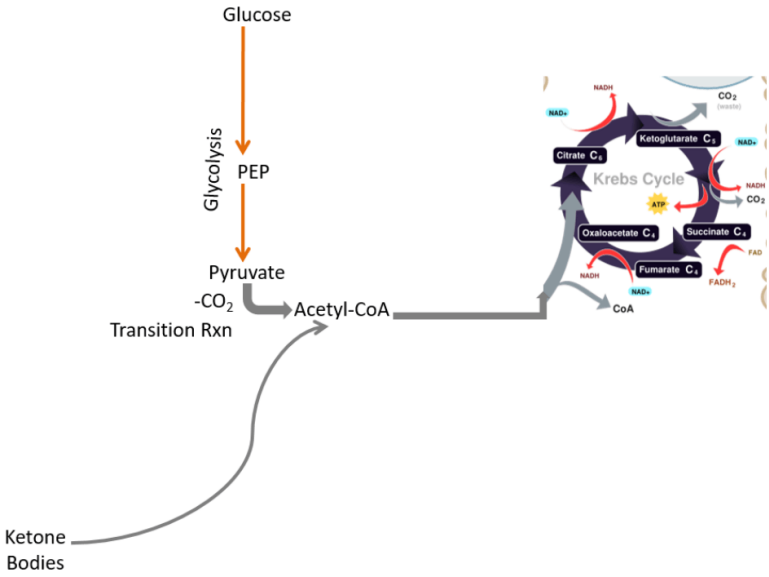


Figure 7.3.9: Brain metabolic capability[3]

Thus, due to its limited metabolic capabilities, the brain needs to receive either glucose or ketone bodies to use as an energy source.

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Red Blood Cell Macronutrient Metabolism

Red blood cells are the most limited of the extrahepatic tissues because they do not contain a nucleus or other cell organelles, most notably mitochondria.

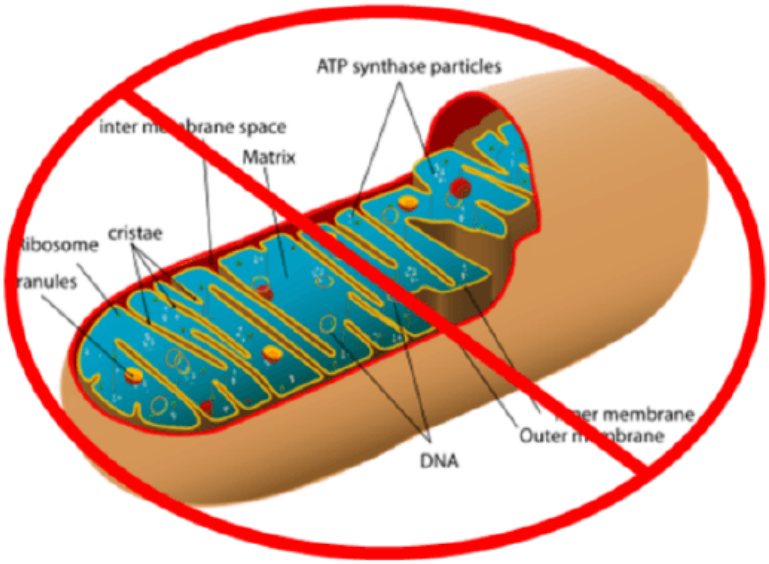


Figure 7.3.10: Red blood cells do not contain mitochondria[8]

As a result, compared to the extrahepatic tissues, in red blood cells the following pathways are not performed or are not important:

- Glycogen synthesis and breakdown
- Lactate breakdown
- Fatty acid synthesis and breakdown
- Triglyceride synthesis and breakdown
- Protein synthesis and breakdown
- Ketone body breakdown

These pathways are crossed off in the figure below.

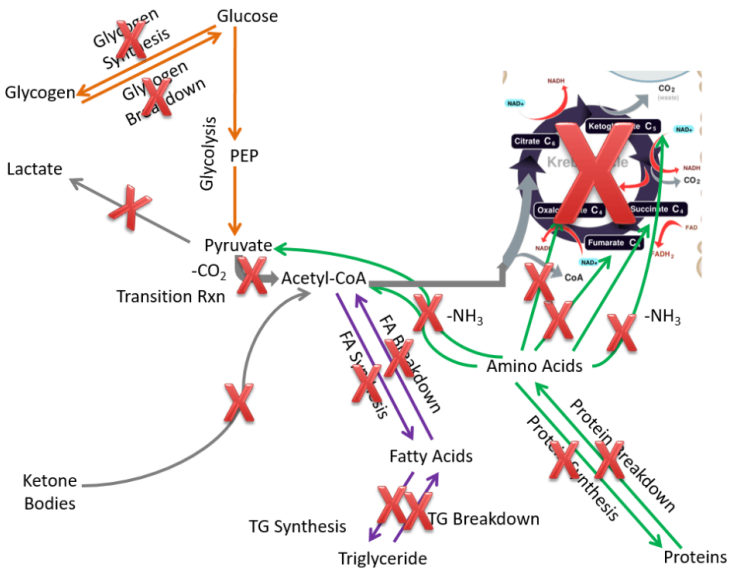


Figure 7.3.11: The metabolic pathways that are not performed or important in the red blood cells, compared to extrahepatic tissues as a whole are crossed off[3]

If all those pathways are removed, only glycolysis is left, where pyruvate is converted to lactate.

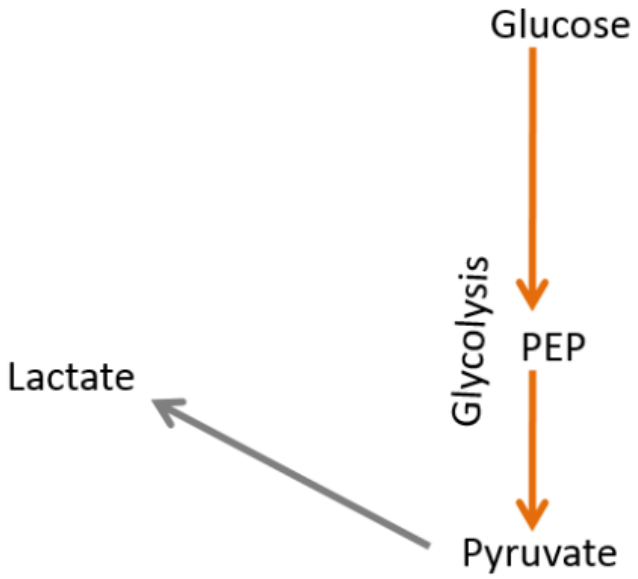


Figure 7.3.12: Red blood cell metabolic capability

Thus, red blood cells are one-trick ponies, only being able to perform glycolysis and produce lactate.

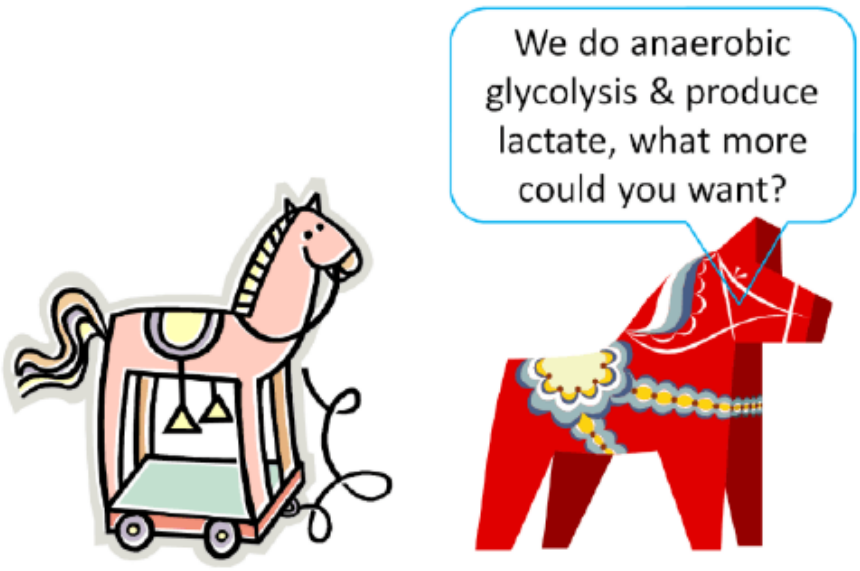


Figure 7.3.13: Red blood cells are one-trick ponies

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2. commons.wikimedia.org/wiki/File:Liver.svg
3. en.Wikipedia.org/wiki/File:CellRespiration.svg
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5. en.Wikipedia.org/wiki/Mitochondrion

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7.4: Metabolic Conditions

You have learned about the pathways and the tissue metabolic capabilities, so now you are going to apply that knowledge to four conditions: fed state, fasting, the Atkins diet, and the Ornish/Pritikin diet, as ways to illustrate how you can use this knowledge. In the fed state, we are going to be considering what is happening metabolically after consuming all 3 macronutrients. In fasting, we're going to be considering what is happening metabolically during a prolonged period without food. The Atkins diet is a carbohydrate-restricted diet, so we are going to consider what happens metabolically when someone is eating a diet that essentially only contains protein and lipids over an extended period of time. Finally the Ornish/Pritikin diet is a very low fat diet, so we're going to consider what happens metabolically when someone is eating a diet that is essentially only carbohydrates and protein over an extended period of time. For each of these conditions, we're going to consider what is happening in the liver, muscle, adipose, and brain.

Now that you should have an understanding of the glycemic response and macronutrient metabolism, you should be able to understand the broader effects of insulin and glucagon that are summarized in the following tables. Knowing what hormone is elevated in the different conditions helps you to understand the metabolism that occurs in different conditions.

Table 7.4.1: Insulin's effects on targets in tissues[1,2]

Effect	Tissue	Target
↑ Glucose Uptake	Muscle, Adipose	↑ GLUT4
↑ Glucose Uptake	Liver	↑ Glucokinase
↑ Glycogen Synthesis	Liver, Muscle	↑ Glycogen Synthase
↓ Glycogen Breakdown	Liver, Muscle	↓ Glycogen Phosphorylase
↑ Glycolysis, ↑ Transition Reaction	Liver, Muscle	↑ Phosphofructokinase-1 ↑ Pyruvate Dehydrogenase Complex
↑ Fatty Acid Synthesis	Liver	↑ Fatty Acid Synthase
↑ Triglyceride Synthesis	Adipose	↑ Lipoprotein Lipase

Table 7.4.2: Glucagon's effects on targets in tissues[2]

Effect	Tissue	Target
↑ Glycogen Breakdown	Liver	↑ Glycogen Phosphorylase
↓ Glycogen Synthesis	Liver	↓ Glycogen Synthase
↑ Gluconeogenesis	Liver	Multiple Enzymes
↓ Glycolysis	Liver	↓ Phosphofructokinase-1
↑ Ketone Body Synthesis	Liver	↑ Acetyl-CoA Carboxylase
↑ Triglyceride Breakdown	Adipose	↑ Hormone-Sensitive Lipase

The final subsection is a summary table that summarizes some pertinent details for these 4 conditions along with 100% protein, 100% carbohydrates, and 100% fat (triglyceride) diets.

Fed State

In this condition, assume a person just consumed a meal containing carbohydrates, protein and fat. As a result, this person is in an anabolic state with high blood glucose levels, meaning the pancreas will secrete insulin.

The liver will take up glucose and synthesize glycogen until its stores are filled. After these stores are full, glucose can be broken

down through glycolysis to pyruvate, then form acetyl-CoA in the transition reaction. Because we are in the fed or anabolic state, acetyl-CoA will be used for ATP generation, but some acetyl-CoA will also be used for fatty acid synthesis. Chylomicron remnants will also be taken up and fatty acids from them will also be used for triglyceride synthesis (along with fatty acids synthesized) to contribute to the pool of triglycerides found in the liver. Triglycerides from this pool will be packaged into VLDL and secreted from the liver. Amino acids will also be taken up and used for protein synthesis as needed. Because there is plenty of glucose, gluconeogenesis and ketone body synthesis will not be operating to any great extent.

Query 7.4.1

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The muscle will take up glucose and synthesize glycogen until those stores are filled. Some glucose will go through glycolysis to produce pyruvate, then form acetyl-CoA in the transition reaction. The acetyl-CoA will enter the citric acid cycle, and NADH and $\mathrm{FADH_2}$ produced will enter the electron transport chain to generate ATP. Fatty acids that are cleaved from chylomicrons, VLDL, IDL, and LDL are also going to be taken up. These fatty acids will be used to synthesize triglycerides for storage. Whatever amino acids are taken up will be used for protein synthesis. The muscle will not be secreting anything in this condition.

Query 7.4.2

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The adipose is going to take up glucose that will enter glycolysis, pyruvate will be produced, then acetyl-CoA will be produced in the transition reaction. Because we are in the fed or anabolic state, the acetyl-CoA will be used for fatty acid synthesis. Fatty acids will also be taken up from being cleaved from chylomicrons, VLDL, IDL, and LDL. These fatty acids from both synthesis and cleavage are primarily going to be used to synthesize triglycerides for storage. The adipose will not be secreting anything under this condition.

Query 7.4.3

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The brain will have plenty of glucose available for its use, so it is not going to have to use ketone bodies like it would during fasting and during prolonged Atkins diet consumption.

Fasting

In this condition a person has been fasting for an extended period of time (18 hours or longer). As a result, the person is in a catabolic state with low blood glucose levels, which leads the pancreas to secrete glucagon.

The liver will break down glycogen to secrete glucose for other tissues to use until its stores are exhausted. Amino acids (minimal) and lactate (Cori cycle) from muscle will be used for gluconeogenesis to synthesize glucose that will also be secreted. Glycolysis will not be occurring to any great extent to spare glucose for use by other tissues. From the breakdown of amino acids, there will be an increase in the synthesis and secretion of urea from the liver to safely rid the body of ammonia from the amino acids. Fatty acids that are received from the adipose will be broken down to acetyl-CoA. The acetyl-CoA will then enter the citric acid cycle, and NADH and $\mathrm{FADH_2}$ produced will enter the electron transport chain to generate ATP. The acetyl-CoA will also be used to synthesize ketone bodies that are secreted for tissues, such as the brain, that cannot directly use fatty acids as a fuel.

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The muscle will break down glycogen to glucose until glycogen stores are exhausted, and receive limited glucose from the liver that enters glycolysis, forming pyruvate. Most pyruvate will be converted to lactate to spare glucose (Cori cycle). Limited pyruvate will enter the transition reaction to form acetyl-CoA. Once there isn't enough glucose for the muscle to use, fatty acids taken up from the adipose and from breakdown of muscle triglyceride stores will be broken down to acetyl-CoA. Acetyl-CoA will then enter the citric acid cycle, and NADH and $\mathrm{FADH_2}$ produced will enter the electron transport chain to generate ATP. Amino acids from protein breakdown and lactate (Cori cycle) will be secreted to be used by the liver for gluconeogenesis.

Query 7.4.5

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The adipose tissue will break down triglycerides to fatty acids and release these for use by the muscle and the liver. It will not be taking up anything.

Given the limited glucose levels available, the brain will primarily be using ketone bodies as its fuel.

Atkins Diet

In this condition, assume a person has just started into phase I of the Atkins Diet and he/she has just consumed a meal of all protein and fat with no carbohydrates. As a result, this person is in an anabolic state, but blood glucose levels are low, meaning the pancreas will secrete glucagon.

Liver glycogen stores will be broken down to secrete glucose for other tissues. Glycolysis will not be occurring to any great extent, in order to spare glucose for other tissues. Using amino acids from digestion and lactate from muscle (Cori Cycle), gluconeogenesis will synthesize glucose (minimal) that will also be secreted. From the breakdown of amino acids, there will be an increase in the synthesis and secretion of urea from the liver to safely rid the body of ammonia from the amino acids. Amino acids will also be used for protein synthesis. Fatty acids will be cleaved from chylomicron remnants and broken down to acetyl-CoA and used to synthesize ketone bodies that are secreted for tissues, such as the brain, that cannot directly use fatty acids as a fuel. Fatty acids from them will also be used for triglyceride synthesis to contribute to the pool of triglycerides found in the liver. Triglycerides from this pool will be packaged into VLDL and secreted from the liver.

Query 7.4.6

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The muscle will break down glycogen to glucose, and receive glucose from the liver that enters glycolysis, forming pyruvate. After glycogen is used up, most pyruvate produced by glycolysis is converted to lactate to spare glucose (minimal). Limited pyruvate will enter the transition reaction to form acetyl-CoA. The acetyl-CoA will then enter the citric acid cycle, and NADH and $\mathrm{FADH_2}$ produced will enter the electron transport chain to generate ATP. Once there is not enough glucose for the muscle to use, fatty acids will be cleaved from and taken up from chylomicrons, VLDL, IDL, and LDL and broken down to acetyl-CoA in beta-oxidation. The acetyl-CoA will then enter the citric acid cycle, and NADH and $\mathrm{FADH_2}$ produced will enter the electron transport chain to generate ATP. Amino acids taken up will be used for protein synthesis, and lactate will be secreted for the liver to use for gluconeogenesis (Cori cycle).

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In the adipose, fatty acids that are cleaved from chylomicrons, VLDL, IDL, and LDL are also going to be taken up. These fatty acids will be used to synthesize triglycerides for storage. With glucagon levels high in this condition, hormone-sensitive lipase would be active. However, since this is an anabolic state, the net effect would be uptake of fatty acids after cleavage by lipoprotein lipase. The adipose will not be secreting anything under this condition.

Query 7.4.8

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Given the limited glucose levels available, the brain will primarily be using ketone bodies as its fuel.

Ornish/Pritikin Diet

In this condition, assume a person is on the Ornish/Pritikin diet and just consumed a meal containing carbohydrates, with minimal but adequate amount of protein and no fat. As a result, this person is in an anabolic state with high blood glucose levels, meaning the pancreas will secrete insulin.

The liver will take up glucose and synthesize glycogen until its stores are filled. After these stores are full, glucose will be broken down through glycolysis to pyruvate, then form acetyl-CoA in the transition reaction. Because we are in the fed or anabolic state, acetyl-CoA will be used for fatty acid synthesis, and the fatty acids will be used for triglyceride synthesis. These triglycerides will be packaged into VLDL and secreted from the liver. Amino acids will also be taken up and used for protein synthesis as needed.

Because there is plenty of glucose, gluconeogenesis and ketone body synthesis will not be operating to any great extent.

Query 7.4.9

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The muscle will take up glucose and synthesize glycogen until those stores are filled. Some glucose will go through glycolysis to produce pyruvate, then form acetyl-CoA in the transition reaction. The acetyl-CoA will enter the citric acid cycle, and NADH and $\mathrm{FADH_2}$ produced will enter the electron transport chain to generate ATP. Fatty acids (minimal) that are cleaved from VLDL, IDL, and LDL are also going to be taken up. These fatty acids will be used to synthesize triglycerides for storage. Whatever amino acids are taken up will be used for protein synthesis. The muscle will not be secreting anything in this condition.

Query 7.4.10

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The adipose is going to take up glucose that will enter glycolysis, pyruvate will be produced, then acetyl-CoA will be produced in the transition reaction. Because we are in the fed or anabolic state, the acetyl-CoA will be used for fatty acid synthesis. Fatty acids will also be cleaved from VLDL, IDL, and LDL. Fatty acids from both sources are going to be taken up and primarily used to synthesize triglycerides for storage. The adipose will not be secreting anything under this condition.

Query 7.4.11

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The brain will have plenty of glucose available for its use, so it is not going to have to use ketone bodies like it would during fasting and during prolonged Atkins diet consumption.

Condition Summary

Condition	Uptake			Secretion			Catabolic or Anabolic	Blood Glucose Concentration	Hormone Secreted	Cori Cycle
	Liver	Adipose	Muscle	Liver	Adipose	Muscle				

Condition	Uptake			Secretion			Catabolic or Anabolic	Blood Glucose Concentration	Hormone Secreted	Cori Cycle
Fed State	Glucose, FA (CM Rem), AA	Glucose, FA	Glucose, FA, AA	VLDL	-	-	Anabolic	High	Insulin	-
Fasting	Lactate, AA, FA	-	FA, Glucose (minimal)	Urea, Ketone Bodies, Glucose (minimal), VLDL	FA	Lactate, AA	Catabolic	Low	Glucagon	+
Atkins	Lactate, AA, FA (CM Rem)	FA	AA, FA, Glucose (minimal)	Urea, Ketone Bodies, Glucose (minimal), VLDL	-	Lactate	Anabolic	Low	Glucagon	Low
Ornish	Glucose, AA	Glucose, FA	Glucose, AA, FA (minimal)	VLDL	-	-	Anabolic	High	Insulin	-
100% protein	Lactate, AA	FA (minimal)	Glucose (minimal), AA, FA (minimal)	Urea, Ketone Bodies, Glucose, VLDL (minimal)	-	Lactate	Anabolic	Low	Glucagon	+
100% carbohydrates	Glucose, AA	Glucose, FA	Glucose, FA	VLDL	-	AA	Anabolic	High	Insulin	-
100% triglyceride	Lactate, AA, FA (CM Rem)	FA	Glucose (minimal), FA	Ketone Bodies, Glucose (minimal), VLDL	-	Lactate, AA	Anabolic	Low	Glucagon	Low

-, None; FA, Fatty acid; AA, Amino Acid; CM Rem, Chylomicron Remnant; VLDL, Very Low Density Lipoprotein

Summary Notes

- Adipose only takes up two things: glucose and fatty acid
  - Glucose only when it is consumed (fed state, Ornish, 100% carbohydrates)
  - Fatty acids in every condition except fasting
- Adipose only secretes fatty acids during fasting
- Muscle only takes up three things: glucose, fatty acid, amino acid
  - Fatty acids in all; minimal in: Ornish and 100% protein
  - Glucose in all; minimal in: 1) fasting; 2) no/low carbohydrate (Atkins, 100% protein, 100% triglyceride)
  - Amino acids only when it is consumed in a meal (no other source)
- Muscle only secretes two things: amino acid and lactate
  - Amino acids secreted when protein is not in diet (fasting, 100% carbohydrates, 100% triglyceride)
  - Lactate secreted in: 1) fasting; 2) no/low carbohydrate diets (fasting, Atkins, 100% protein, 100% triglyceride, note these are the same conditions when minimal glucose is taken up)
- Liver takes up four things: glucose, fatty acids (from chylomicron remnants), amino acids, lactate
  - Amino acid in all; source: food or from muscle

    - Glucose only when it is consumed (fed state, Ornish, 100% carbohydrates)
    - Fatty acids in: 1) fasting (adipose); 2) when it is consumed (fed state, Atkins, 100 triglyceride)
    - Lactate (Cori cycle) in: 1) fasting; 2) no/low carbohydrate diets (Atkins, 100% protein, 100% triglyceride)
- Liver secretes four things: VLDL, glucose, urea, ketone bodies
    - VLDL in all scenarios: 1) chylomicron remnants (triglycerides consumed) or 2) glucose ->acetyl-CoA -> FA
    - Glucose is secreted in 100% protein and minimal in: 1) fasting; 2) Other no/low carbohydrate diets (Atkins, 100% triglycerides)
    - Urea is secreted in 1) fasting; 2), high protein/carbohydrate restricted diets (Atkins, 100% protein)
    - Ketone bodies in: 1) fasting, and 2) no/low carbohydrate diets (Atkins, 100% protein, 100% triglyceride)

References

1. Gropper SS, Smith JL, Groff JL. (2008) Advanced nutrition and human metabolism. Belmont, CA: Wadsworth Publishing.
2. jpkc.gmu.cn/swhx/book/shyl/23.pdf

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8: MICRONUTRIENTS OVERVIEW AND DIETARY REFERENCE INTAKES (DRIS)

Micronutrients consist of vitamins and minerals. In this chapter, an overview of vitamins and minerals will be presented followed by a description of the dietary reference intakes (DRIs), which are used as benchmarks of micronutrient intake.

8.1: Vitamins

8.2: Minerals

8.3: Vitamins and Minerals Functional Categories

8.4: Dietary Reference Intakes (DRIs)

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8.1: Vitamins

The name vitamin comes from Casimir Funk, who in 1912 thought vital amines (NH_3) were responsible for preventing what we know now are vitamin deficiencies. He coined the term vitamines to describe these compounds. Eventually it was discovered that these compounds were not amines and the 'e' was dropped to form vitamins[1].

Vitamins are classified as either fat-soluble or water-soluble. The fat-soluble vitamins are:

- Vitamin A
- Vitamin D
- Vitamin E
- Vitamin K

The water-soluble vitamins are vitamin C and the B vitamins, which are shown in the table below.

Table 8.1.1: The B vitamins and their common names

Vitamin	Common Name
B_1	Thiamin
B_2	Riboflavin
B_3	Niacin
B_5	Pantothenic Acid
B_6*	Pyridoxine
B_7	Biotin
B_9	Folate
B_{12}*	Cobalamin

*Normally used instead of common names

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A common question from students about B vitamins is: “Why are there so many B vitamins? It is not like they ran out of letters in the alphabet to name them.”

Before they even knew that vitamins existed, a scientist named E.V. McCollum recognized that a deficiency in what he called ‘fat-soluble factor A’ resulted in severe ophthalmia (inflammation of the eye). In addition, a deficiency in ‘water-soluble factor B’ resulted in beriberi (a deficiency discussed more later)[1].

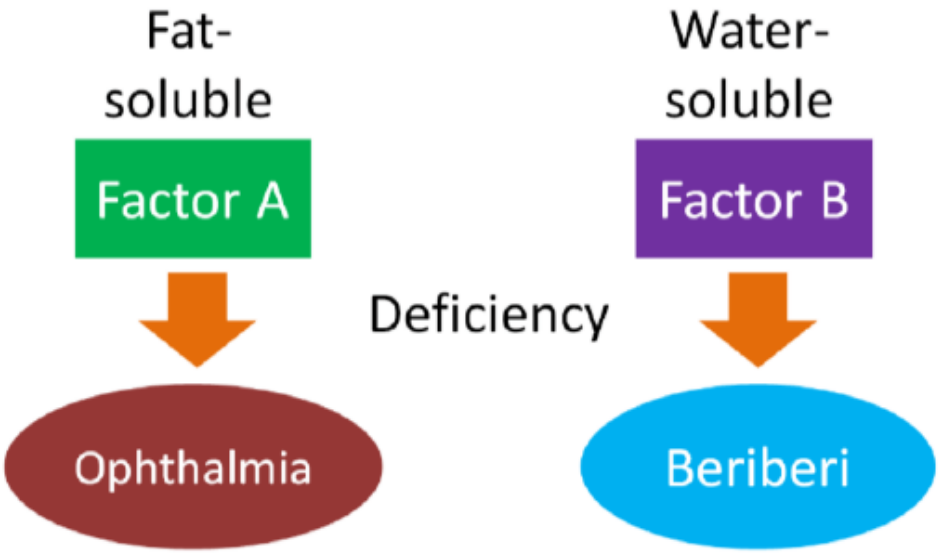


Figure 8.1.1: Factor A deficiency led to ophthalmia, factor B deficiency led to beriberi

Factor A is what we now know as vitamin A. However, researchers soon realized that factor B actually consisted of two factors that they termed B_1 and B_2. Then they realized that there are multiple components in B_2, and they began identifying the wide array of B vitamins that we know today1.

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You might be wondering "why are the B vitamins not in numerical order?" Vitamins B_4, B_8, B_{10}, and B_{11} were discovered and then abandoned leaving us with the B vitamins shown in Table 8.1.1.

Relative to other scientific milestones, the discovery of vitamins is a fairly recent occurrence, as shown in the table below.

Table 8.1.2: Vitamin, year proposed, isolated, structure determined, and synthesis achieved up to 19441

Vitamin	Year Proposed	Isolated	Structure Determined	Synthesis Achieved
Thiamin	1901	1926	1936	1936
Vitamin C	1907	1926	1932	1933
Vitamin A	1915	1939	1942	-
Vitamin D	1919	1931	1932	1932
Vitamin E	1922	1936	1938	1938
Niacin	1926	1937	1937	1867*
Biotin	1926	1939	1942	1943
Vitamin K	1929	1939	1942	1943
Pantothenic Acid	1931	1939	1939	1940
Folate	1931	1939	-	-

Vitamin	Year Proposed	Isolated	Structure Determined	Synthesis Achieved
Riboflavin	1933	1933	1934	1935
Vitamin B6	1934	1936	1938	1939

* Was established long before it was known to be a vitamin

A number of B vitamins serve as cofactors/coenzymes. The following table lists the cofactors/coenzymes formed from B vitamins that will be discussed in more detail in the following subsections.

Table 8.1.3: Cofactors/coenzymes formed from B vitamins

Vitamin	Cofactors/Coenzymes
Thiamin	Thiamin Pyrophosphate (TPP)
Riboflavin	Flavin Adenine Dinucleotide (FAD), Flavin Mononucleotide (FMN)
Niacin	Nicotine Adenine Dinucleotide (NAD), Nicotine Adenine Dinucleotide Phosphate (NADP)
Pantothenic Acid	Coenzyme A
Vitamin B6	Pyridoxal Phosphate (PLP)
Biotin	-
Folate	Tetrahydrofolate (THF)
Vitamin B12	Adenosylcobalamin, Methylcobalamin

Query 8.1.3

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References

1. Carpenter K. (2003) A short history of nutritional science: Part 3 (1912-1944). J Nutr 133(10): 3023-3032

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8.2: Minerals

Minerals are a subset of elements that are essential for body functions that cannot be synthesized in the body. Some people refer to them as elements instead of minerals, and the names can be used interchangeably. However, in the nutrition community, they are more commonly referred to as minerals. Minerals can be divided up into three different categories:

- Macrominerals
- Trace Minerals (aka Microminerals)
- Ultratrace Minerals

There is not an exact, agreed on definition for how the different categories are defined, but in general they are defined by the amount required and found in the body such that:

Macrominerals > Trace Minerals > Ultratrace Minerals

Table 8.2.1: Alphabetical listing of the 20 minerals and their chemical symbols

Macrominerals	Trace Minerals	Ultratrace Minerals
Calcium (Ca)	Chromium (Cr)	Arsenic (As)
Chloride (Cl)[a]	Copper (Cu)	Boron (B)
Magnesium (Mg)	Fluoride (F)	Nickel (Ni)
Phosphorus (P)[b]	Iodine (I)	Silicon (Si)
Potassium (K)	Iron (Fe)	Vanadium (V)
Sodium (Na)	Manganese (Mn)	
	Molybdenum (Mo)	
	Selenium (Se)	
	Zinc (Zn)	

[a] Chlorine ion, Cl-

[b] Phosphate in body, PO4

The table below shows the estimated amount of the macrominerals, trace minerals, and ultratrace minerals found in the body.

Table 8.2.2: Amount of different minerals found in the body1

Macrominerals		Trace Minerals		Ultratrace Minerals	
Calcium	1200 g	Iron	4 g	Silicon	1 g
Phosphorus	780 g	Fluoride	3-6 g	Boron	17 mg
Potassium	110-140 g	Zinc	2.3 g	Nickel	15 mg
Sodium	100 g	Copper	70 mg	Arsenic	7 mg
Chloride	95 g	Selenium	14 mg	Vanadium	0.1 mg
Magnesium	25 g	Manganese	12 mg		
		Iodine	10-20 mg		
		Molybdenum	5 mg		
		Chromium	1-2 mg		

The figure below shows the distribution of minerals in the periodic table, which you should be familiar with from your chemistry education.

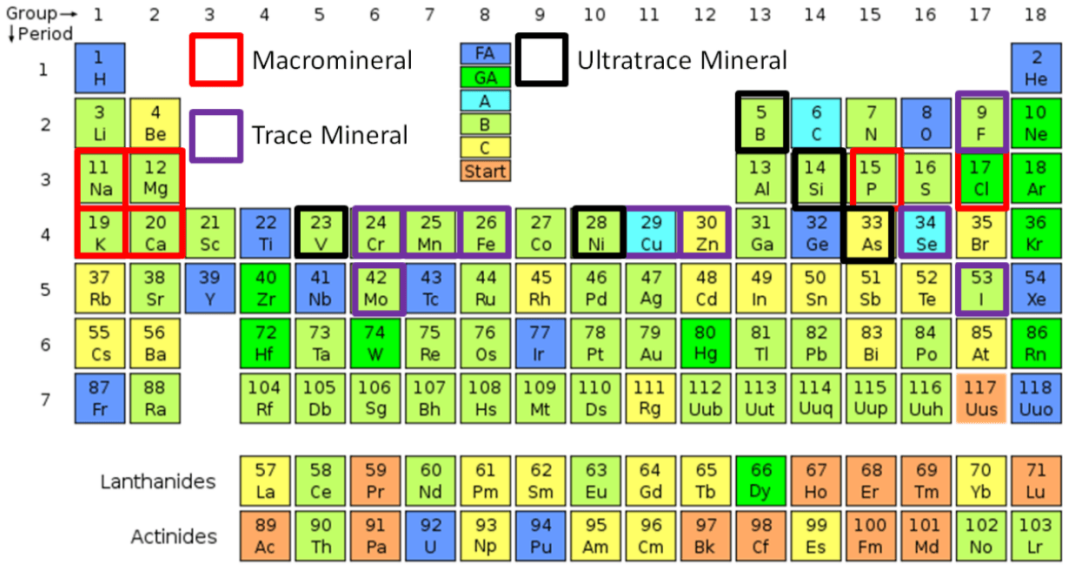


Figure 8.2.1: Minerals are a subset of elements, this figure shows their position within the periodic table[2]

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1. Emsley, John. Nature's building blocks : an A-Z guide to the elements. 2001. Oxford, Oxford University Press.
2. en.Wikipedia.org/wiki/File:Pe...by_Quality.SVG

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8.3: Vitamins and Minerals Functional Categories

There are two common ways to teach about vitamins and minerals in nutrition classes. The traditional way is to start with fat-soluble vitamins and go down through the vitamins alphabetically (i.e. vitamin A, vitamin D, vitamin E, vitamin K). However, this method leads students to learn about vitamins and minerals more individually instead of how they work together. For instance, it makes sense to cover calcium with vitamin D, and iron with copper and zinc. We are going to cover vitamins and minerals based on their function rather than covering them by whether they are a water-soluble vitamin or trace mineral. The hope is that you will gain a more integrative understanding of vitamins and minerals from this approach.

Here are the different functional categories that you are going to learn about. Notice that some micronutrients fit into more than one functional category. Each vitamin and mineral is presented in one section, with some mention of its overlap in other section(s) in certain cases.

Antioxidants	Macronutrient Metabolism	1-Carbon Metabolism	Blood	Bones & Teeth	Electrolytes
Vitamin E	Thiamin	Folate	Vitamin K	Vitamin D	Sodium
Vitamin C	Riboflavin	Vitamin B_{12}	Iron	Calcium	Potassium
Selenium	Niacin	Vitamin B_6	Vitamin B_6	Vitamin K	Chloride
Iron	Pantothenic Acid		Folate	Phosphorus	Phosphorus
Copper	Vitamin B_6		Vitamin B_{12}	Magnesium	Magnesium
Zinc	Biotin		Copper	Fluoride	
Manganese	Vitamin B_{12}		Calcium	Vitamin A	
Riboflavin	Vitamin C			Iron	
	Iodine			Copper	
	Manganese			Zinc	
	Magnesium				

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8.4: Dietary Reference Intakes (DRIs)

Dietary Reference Intakes (DRIs) are more than numbers in the table, even though that is often how many people view them. The link below takes you to the tables that many people commonly associate with the DRIs. These tables have been updated to include the revised RDAs for vitamin D and calcium.

Web Links

DRI Minerals
DRI Vitamins

Most of you are probably familiar with Dietary Guidelines. DRIs and Dietary Guidelines provide different information for different audiences.

Dietary Guidelines provide qualitative advice to the public about diet and chronic disease prevention and maintaining health.

DRIs provide quantitative advice to professionals about amounts of nutrients or food components to be of benefit.

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DRIs are a collective term to refer to these components:

- profe
- Estimated Average Requirement (EAR)
- Recommended Dietary Allowance (RDA)
- Adequate Intake (AI)
- Tolerable Upper Intake Level (UL)
- Chronic Disease Risk Reduction Intakes (CDRR)

A number of people refer to the UL as simply the “upper limit”, leaving off “tolerable”.

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The RDA is the measure that professionals use to assess the quality of people's diets. It is the requirement estimated to meet the needs of 97.5% of the population. But the RDA is calculated using the EAR. Therefore, the EAR needs to be set before an RDA can be set. There must be applicable research in order to set an EAR. An EAR is the estimated requirement for 50% of the population (hence the average in its name), as shown in the figure below. On the left vertical axis is the risk of inadequacy, and on the bottom

of the figure is the observed level of intake that increases from left to right. We will talk about the right axis label in a later figure. Notice that for the EAR, the risk of inadequacy is 0.5 (50%) whereas the RDA the risk of inadequacy is 0.025 (2.5%).

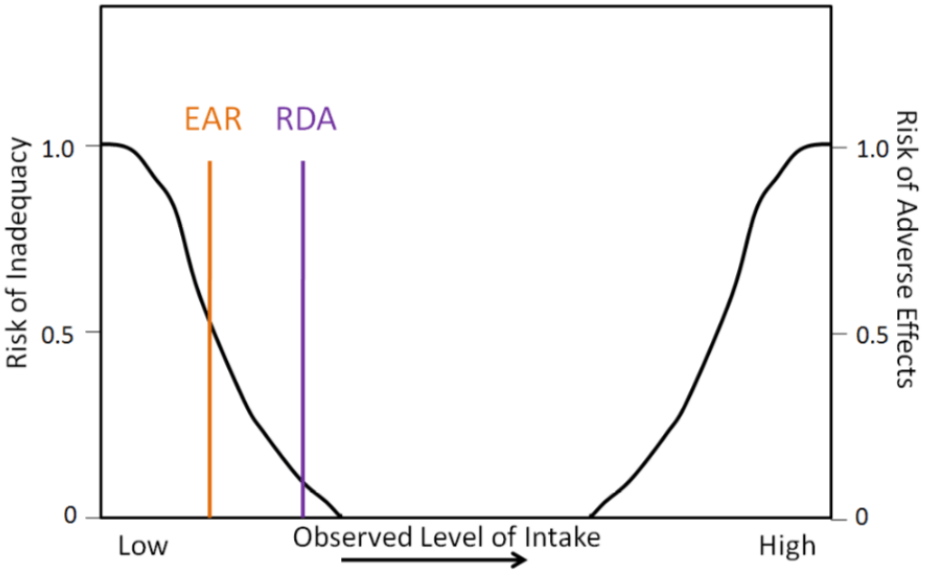


Figure 8.4.1: The EAR meets the needs of 50% of the population, RDA meets the needs of 97.5% of the population.

The figure below shows the EAR on the normal distribution and splits out the different standard deviations as percents. Notice that for 50% of the population, their adequate intake is below the EAR and 50% of the population their adequate intake is above the EAR.

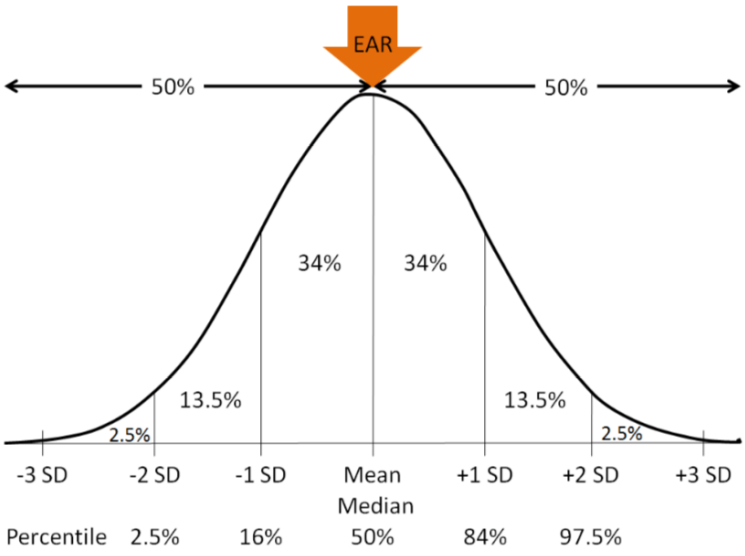


Figure 8.4.2: The EAR meets the needs of 50% of the population as depicted in this normal distribution. SD - standard deviation

If an EAR is set, the formula for setting the RDA is:

EAR + 2 Standard Deviations = RDA

The following figure shows the distribution and how the percentages and standard deviation changes from the EAR. Only 2.5% of the population will have a need above the RDA for a particular nutrient. As you can see, the EAR is adequate for 50% (0.5) of the population and is lower than the RDA. The RDA is adequate for 97.5% (0.025) of the population, and higher than the EAR.

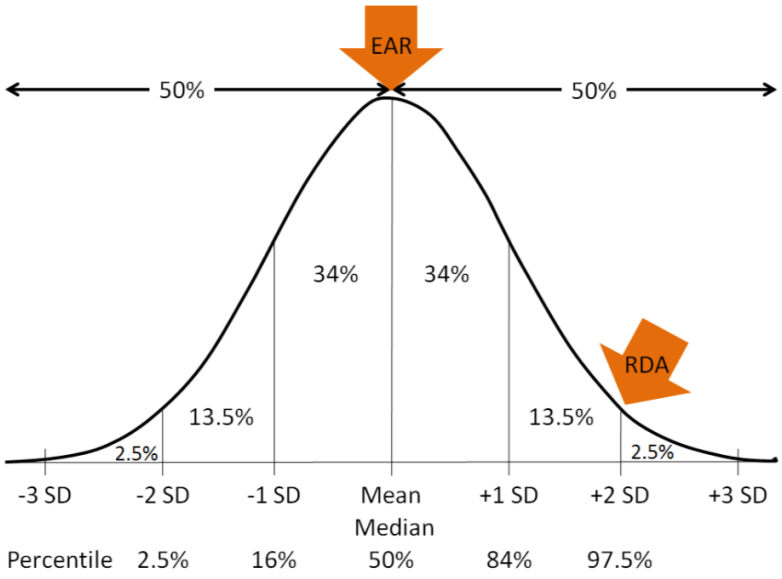


Figure 8.4.3: The RDA meets the needs for 97.5% of the population

For nutrients lacking the research evidence needed to set an EAR, an AI is set instead of an EAR/RDA (thus, there will never be an AI and RDA for the same population class). An AI is a level that appears to be adequate in a defined population or subgroup. Since an EAR/RDA has not been set, it is not known how an AI quantity compares to a RDA/EAR as shown in the figure below, but since an RDA is based on research there is more confidence in it as an indicator than an AI.

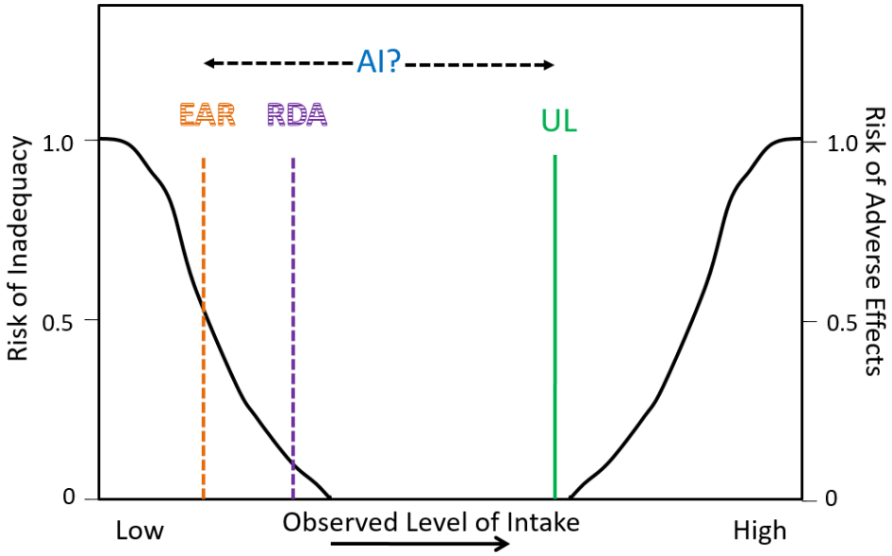


Figure 8.4.4: The AI compared to the other DRI components, the question mark and dotted line are meant to indicate that it is not known exactly where the AI would fall relative to and EAR/RDA if they were set. The dotted EAR/RDA is meant to indicate that these are not set when an AI is set.

The last of the DRIs is the Tolerable Upper Intake Level (UL). This is the highest level of daily nutrient intake that is unlikely to pose a risk of adverse health effects to almost all individuals in the population. To set this, the committee first sets a no observed adverse effect level (NOAEL) and/or the lowest observed adverse effect level (LOAEL). The UL is then set lower based on a number of uncertainty/safety factors off the NOAEL or LOAEL as shown below. The right vertical axis is used to represent the risk of an adverse event. Notice the NOAEL at the point where no adverse effects have been reported. The LOAEL is somewhere above the NOAEL. The UL is set at a level where it is believed that people will not experience the selected adverse effect.

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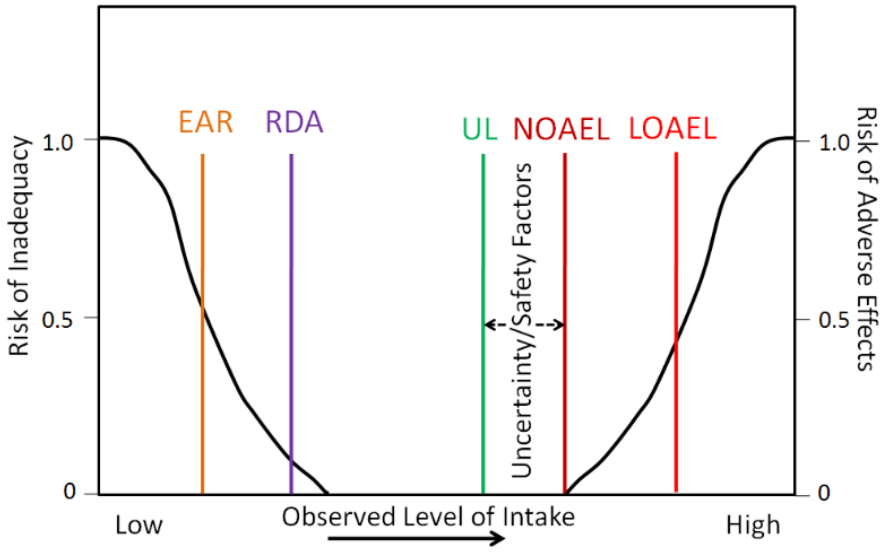


Figure 8.4.5: Setting of the UL

How are Americans doing in meeting the DRIs? The following figure shows the percentage of Americans that are not meeting the EAR for some of the earlier micronutrients that had DRIs set. Keep in mind that the EAR is lower than the RDA.

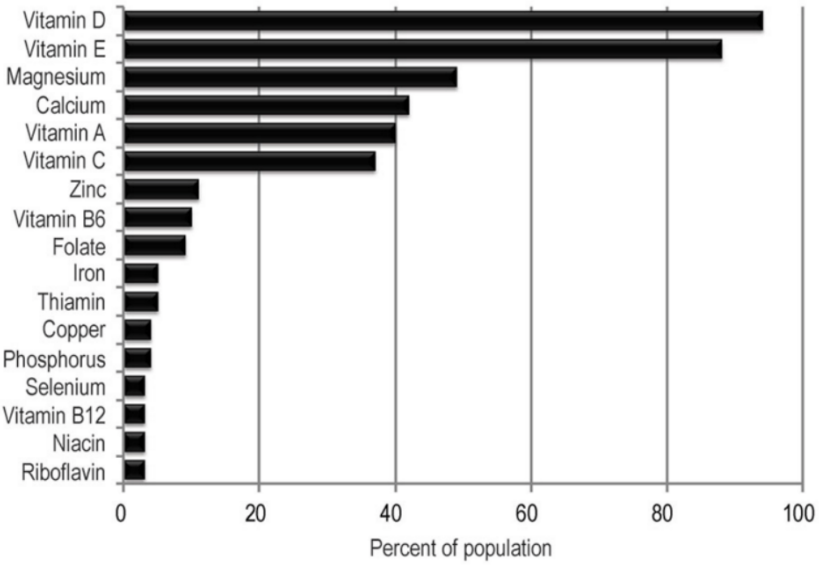


Figure 8.4.6: Percent of Americans with usual intakes below the EAR[1]

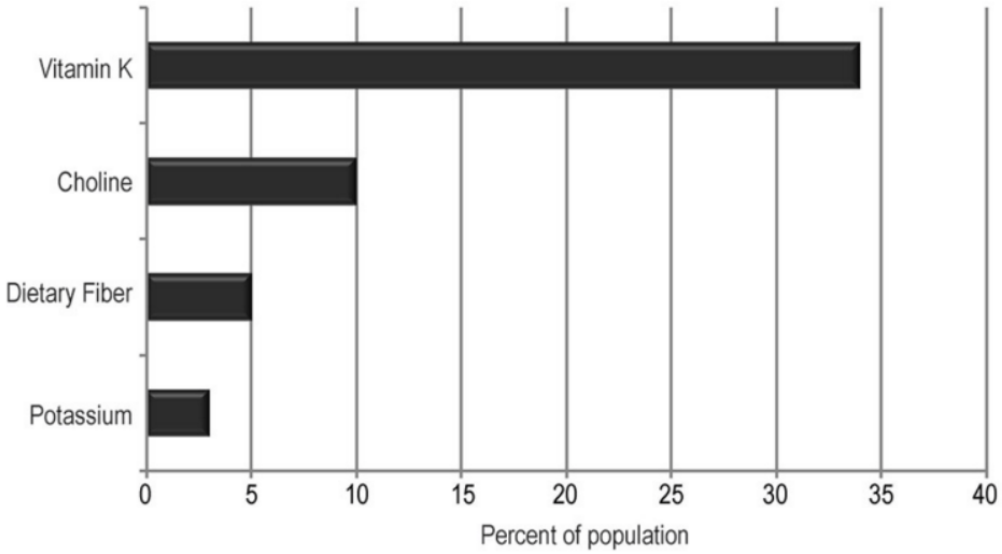


Figure 8.4.7: Percent of Americans with usual intakes exceeding the AI[1]

As you can see, a large percentage of Americans don't meet the EAR for vitamin E, magnesium, vitamin A, and vitamin C. Also, keep in mind that this also does not include micronutrients that have AI instead of EARs and RDAs.

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The Chronic Disease Risk Reduction Intake (CDRR) is the newest of the DRI components, being introduced in 2019 with a CDRR being set for sodium. As the name indicates, the CDRR is an intake that there is evidence reduces the risk of chronic disease. In the case of sodium, intake below the CDRR is associated with beneficial effects on cardiovascular disease risk, hypertension risk, systolic blood pressure, and diastolic blood pressure[2].

References

1. health.gov/dietaryguidelines/...er-1/d1-11.asp
2. National Academies of Sciences, Engineering, and Medicine 2019. Dietary Reference Intakes for Sodium and Potassium. Washington, DC: The National Academies Press. https://doi.org/10.17226/25353.

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9: ANTIOXIDANT MICRONUTRIENTS

This chapter will describe what antioxidants are and then discuss the three major antioxidant micronutrients: vitamin E, vitamin C and selenium.

9.1: Antioxidants

9.2: Vitamin E

9.3: Vitamin C

9.4: Selenium

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9.1: Antioxidants

The antioxidant vitamins and minerals are:

- Vitamin E
- Vitamin C
- Selenium
- Iron
- Copper
- Zinc
- Manganese
- Riboflavin

In this chapter, we are going to cover vitamin E, vitamin C, and selenium in detail because being an antioxidant is their primary function. Iron, copper, zinc, and manganese are cofactors for the antioxidant enzymes catalase and superoxide dismutase, as shown below.

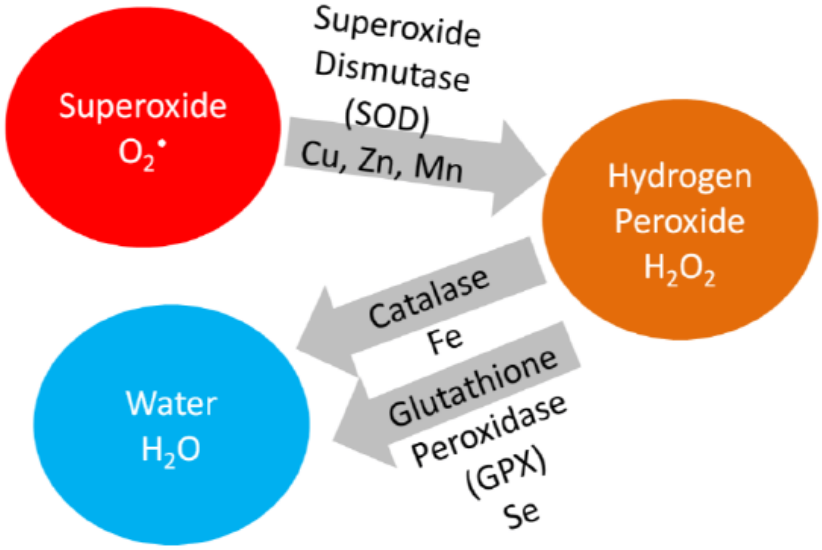


Figure 9.1.1: Antioxidant enzymes that use minerals as cofactors

Superoxide dismutase converts superoxide into hydrogen peroxide. Catalase converts hydrogen peroxide into water. Iron, copper, and zinc will be covered in more detail in the blood, bones, and teeth chapter (Chapter 11). Manganese will be covered in the macronutrient metabolism chapter.

Riboflavin, in the cofactor FAD, is an important cofactor for several antioxidant enzymes, but it will be covered in more depth in the macronutrient metabolism micronutrients chapter (Chapter 10).

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Free Radicals & Oxidative Stress

Before you can understand what an antioxidant is, it is important to have an understanding of oxidants. As you have learned already, oxidation is the loss of an electron as shown below.

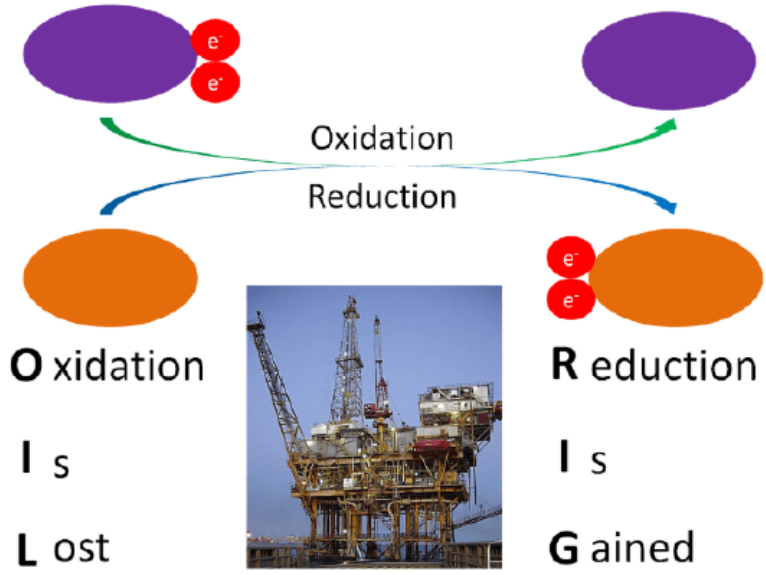


Figure 9.1.2: The purple compound is oxidized; the orange compound is reduced[1]

Some important terms to understand are described in the following sections.

Free Radical

Free Radical a molecule with an unpaired electron in its outer orbital.

The following example shows normal oxygen losing an electron from its outer orbital and thus, becoming an oxygen free radical.

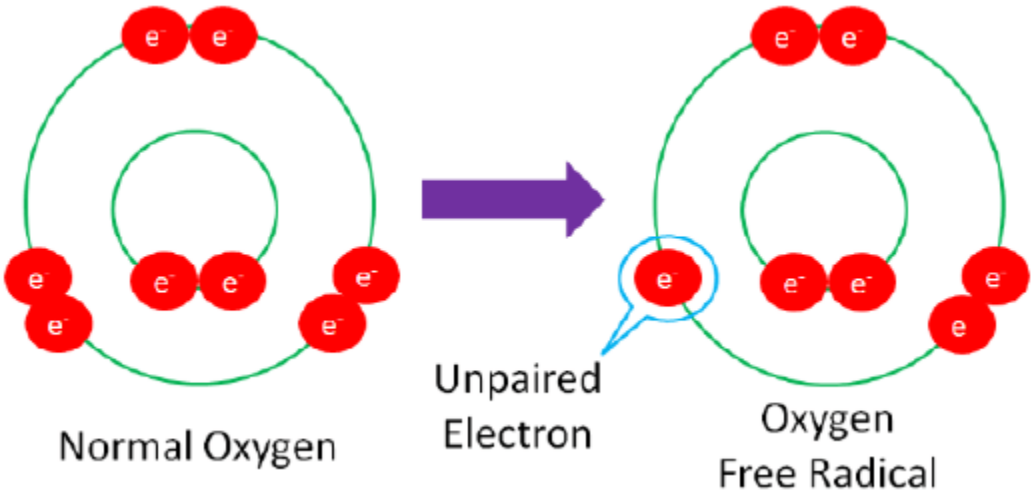


Figure 9.1.3: Normal oxygen is converted to an oxygen free radical by losing one electron in its outer orbital, leaving one unpaired electron

Free radicals are highly reactive because they actively seek an electron to stabilize the molecule.

Reactive Oxygen Species (ROS)

Reactive Oxygen Species (ROS) is an unstable oxygen-containing molecule that seeks out other compounds to react with. Some

ROS have radicals meaning they are oxygen-containing free radicals.

Some of the most common ROS are (● symbolizes radical):

- Superoxide (O_2●)
- Hydroxyl Radical (●OH)
- Hydrogen Peroxide Radical (HO_2●)
- Peroxyl Radical (ROO_2●)
- Alkoxyl Radical (RO●)
- Ozone (O_3)
- Singlet Oxygen ($^1O_2$)
- Hydrogen Peroxide (H_2O_2)

Query 9.1.2

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Oxidative Stress

Oxidative Stress is the imbalance between the production of ROS/free radicals and the body's ability to quench them.

The following video does a good job illustrating how free radicals can be formed and quenched by antioxidants.

YouTube Video

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Video 9.1.1: How free radicals and antioxidants work, watch the first minute. https://www.youtube.com/watch?v=lG3OOXIXvxw

The following figure shows that inflammation caused by hitting your thumb with a hammer, exposure to UV light, radiation, smoking, and air pollution are all sources of free radicals.

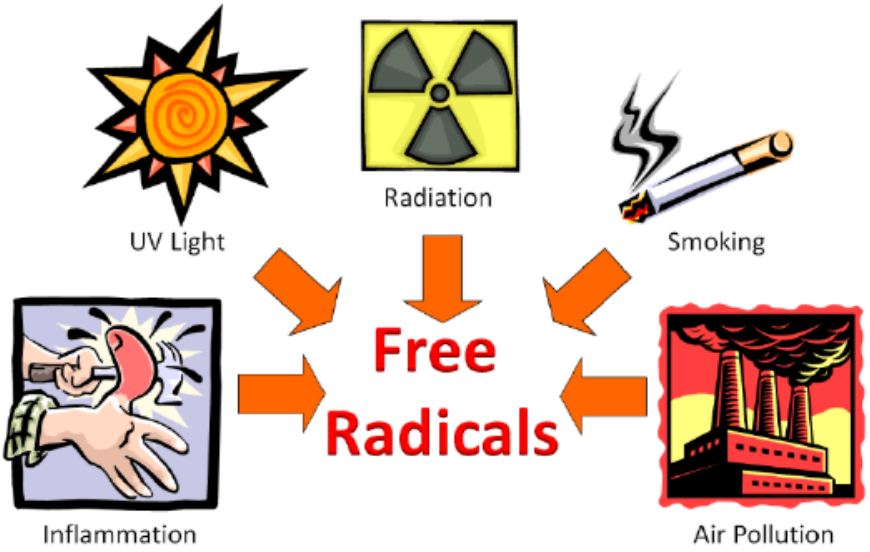


Figure 9.1.4: Some sources of free radicals

Free radicals can be generated by a variety of sources that can be classified as endogenous (within the body) and exogenous sources (outside the body).

So, we have these free radicals searching for an electron, what's the big deal? The problem arises if the free radicals/ROS oxidize LDL, proteins, or DNA as shown below.

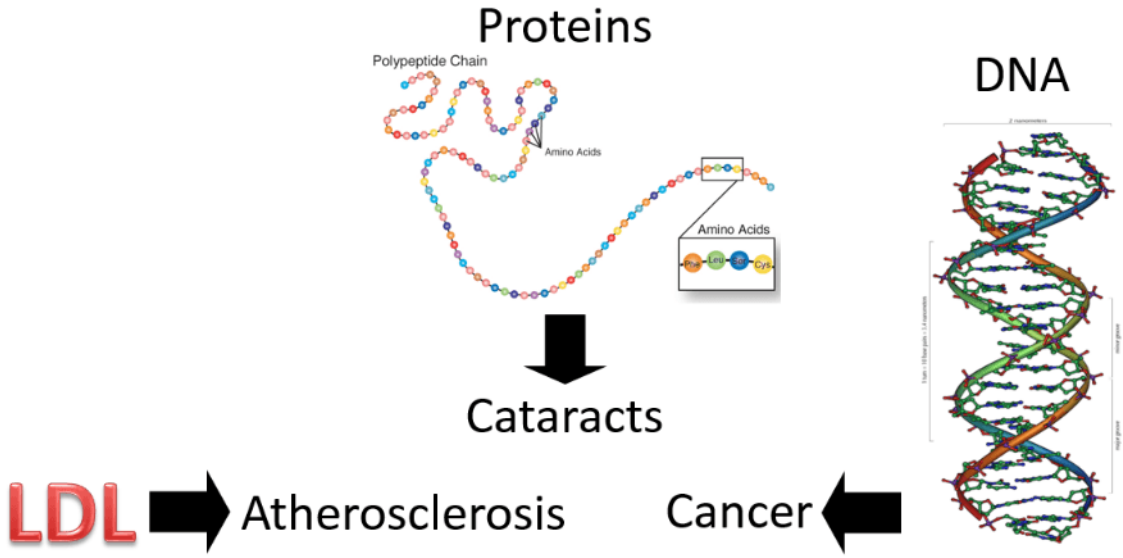


Figure 9.1.5: Free radicals can attack LDL, proteins, and DNA[2,3]

Oxidized LDL is more atherogenic, meaning it is more likely to contribute to atherosclerosis (hardening of the arteries) than normal LDL. Protein oxidation is believed to be involved in the development of cataracts. Cataracts are a clouding of the lens of the eye. If you would like to see what it looks like, see the link below.

Web Link

Cataract Vision Simulator

If a nucleotide in DNA is attacked, it can result in a mutation. A mutation is a change in the nucleotide or base pair sequence of

DNA. Mutations are a common occurrence in cancer.

Query 9.1.3

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What is an Antioxidant?

We are ready to move on to antioxidants, which as their name indicates, combat free radicals, reactive oxygen species (ROS), and oxidative stress. As a humorous introduction, the link below is to a cartoon that shows Auntie Oxidant kicking free radicals out of the bloodstream.

Web Link

Auntie Oxidant

But it is not quite that simple. You have probably heard the saying "take one for the team." Instead of taking one for the team, antioxidants "give one for the team." The 'giving' is the donation of an electron from the antioxidant to a free radical, in order to regenerate a stable compound, as shown below.

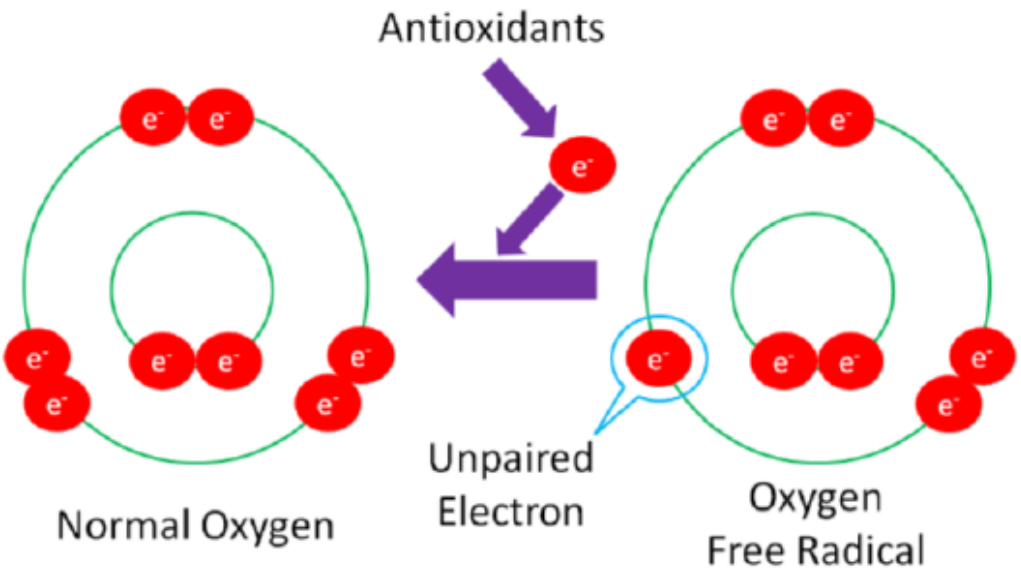


Figure 9.1.7: Regeneration of normal oxygen from oxygen free radical by the donation of an electron from an antioxidant

Donating an electron is how vitamins act as antioxidants. Minerals, on the other hand, are not antioxidants themselves. Instead, they are cofactors for antioxidant enzymes.

These antioxidant enzymes include:

- **Superoxide dismutase (SOD)**: uses copper, zinc, and manganese as cofactors (there is more than one SOD enzyme); converts superoxide to hydrogen peroxide and oxygen4.
- **Catalase**: uses iron as a cofactor; converts hydrogen peroxide to water4.
- **Glutathione peroxidase (GPX)**: is a selenoenzyme that converts hydrogen peroxide to water. It can also convert other

reactive oxygen species (ROSs) to water4.

The action of these enzymes is shown below.

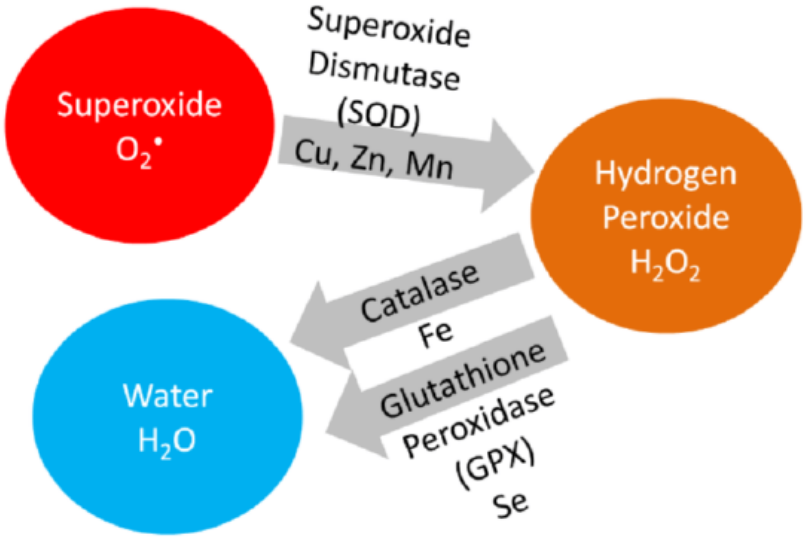


Figure 9.1.8: Antioxidant enzymes that use minerals as cofactors

Query 9.1.4

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Antioxidants are thought to work in concert with one another, forming what is known as the antioxidant network. A theorized antioxidant network is shown below. Here are the steps in this process:

1. Alpha-tocopherol (major form of vitamin E in our body) is oxidized by donating an electron to the reactive oxygen species, thus stabilizing it. This leads to the formation of alpha-tocopherol radical.
2. Ascorbate (vitamin C) is then oxidized, forming dehydroascorbate to regenerate (reduce) alpha-tocopherol.
3. Ascorbate is then regenerated by the selenoenzyme thioredoxin reductase. This theorized network demonstrates how antioxidants can function to regenerate one another so they can continue to function as antioxidants.

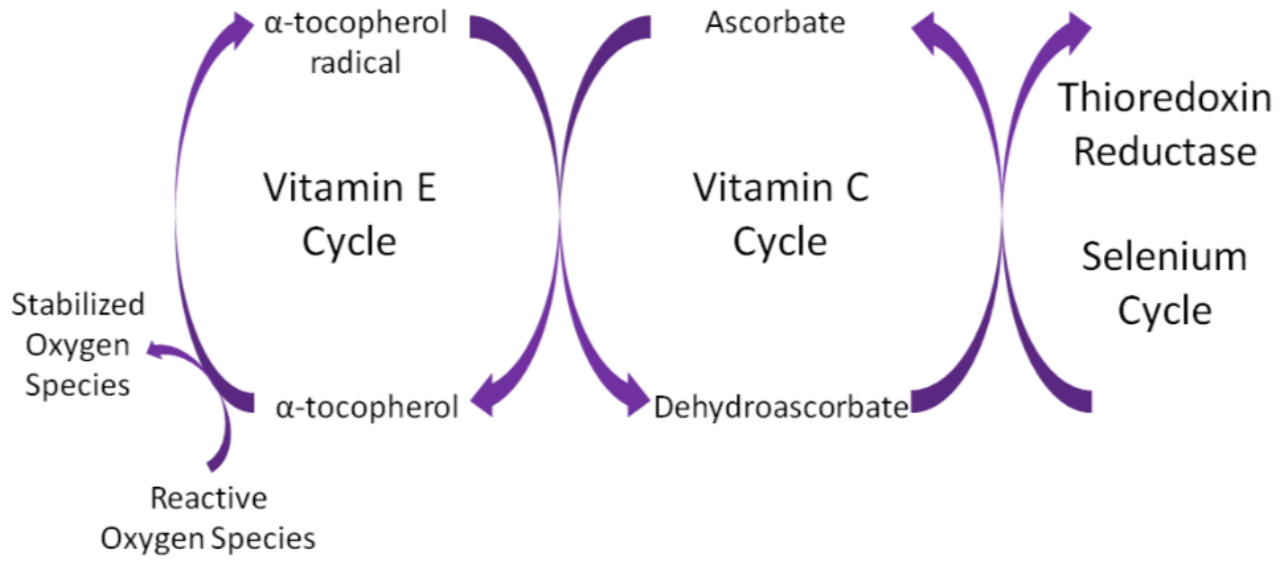


Figure 9.1.9: The theorized antioxidant network[5]. This is to be read from left to right showing the transfer of an electron by oxidation to then be reduced as shown in the description above.

Query 9.1.5

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Meaningful Antioxidant(s)

There is a lot of confusion among the public on antioxidants. For the most part, this is for a good reason. Many food companies put antioxidant numbers on the packages that sound good to consumers, who have no idea how to interpret them. Thus, it is increasingly important to have an understanding of what a meaningful antioxidant actually is.

A meaningful antioxidant has two characteristics (these are based on the assumption that the compound is an antioxidant):

1. Found in appreciable amounts in the right location where there are free radicals/ROS that need to be quenched
2. It is not redundant with another antioxidant that is already serving as an antioxidant

What do these mean? Let's consider the example of lycopene and vitamin E (alpha-tocopherol), which are both fat-soluble antioxidants. In vitro antioxidant assays have found that lycopene is 10-fold more effective in quenching singlet oxygen than alpha-tocopherol[6]. However, when you look at the concentrations found in the body, there is far more alpha-tocopherol than lycopene. For example:

> LDL on average contains 11.6 molecules of alpha tocopherol and 0.9 molecules of lycopene. Thus, if we divide alpha tocopherol by lycopene 11.6/0.9 we find that there is on average 12.9 times more alpha-tocopherol than lycopene[6].

Other examples in the body:

> Prostate - 162-fold higher alpha-tocopherol than lycopene concentrations
>
> Skin - 17 to 269-fold higher alpha-tocopherol than lycopene concentrations
>
> Plasma - 53-fold higher alpha tocopherol than lycopene concentrations[6]

Thus, despite the fact that lycopene is a better antioxidant in vitro, since the concentration of alpha-tocopherol is so much higher in tissues (locations of need), it is likely the more meaningful antioxidant. In addition, if lycopene and alpha-tocopherol have similar antioxidant functions (fat-soluble antioxidants), lycopene's potential antioxidant action is redundant to alpha-tocopherol's antioxidant function and thus, also less likely to be a meaningful antioxidant. Indeed, further examination of the literature has not suggested that lycopene can act as an antioxidant in vivo, even though it is a good one in vitro6.

Query 9.1.6

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The oxygen radical absorbance capacity (ORAC) assay is one of these in vitro antioxidant assays. These values have been used to market the antioxidant potential of food products companies/businesses. The link below is to a database of food ORAC values.

Web Link

ORAC Value Database

USDA removed its database of ORAC values (similar to the one above) "due to mounting evidence that the values indicating antioxidant capacity have no relevance to the effects of specific bioactive compounds, including polyphenols on human health2." However, going back to the two characteristics of meaningful antioxidants, there really is no evidence that shows that a high ORAC score leads to any benefit in vivo. This is because the measure also does not take into account important factors such as bioavailability. Bioavailability is the amount of a compound that is absorbed or reaches circulation. Many of these purported super antioxidants, identified by high ORAC values, have not been shown to be absorbed or maintained in the body in a way that would suggest that they would be meaningful antioxidants. Five years after it was removed, industry and suppliers think it has been a good thing that it is no longer used as indicated in the following article.

Web Link

Saying goodbye to ORAC was a good thing for industry, suppliers say

Query 9.1.7

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Instead some companies are marketing in antioxidants in different ways, like the aggressive approach taken by Welch's grape juice described in the link below.

Web Link

Welch's says grape juice is for men now

Too Much of a Good Thing? Antioxidants as Pro-oxidants

Chapter 1 described a clinical trial that found that high-dose beta-carotene supplementation increased lung cancer risk in smokers. This is an example of findings that support that high doses of antioxidants may be “too much of a good thing”, causing more harm than benefit. The parabolic, or U-shaped, figure below displays how the level of nutrient concentration or intake (x -axis) relates to an antioxidant measure (y-axis). The lowest level of antioxidant intake or tissue concentration results in nutrient deficiency if the antioxidant is essential (vitamins and minerals). Intake levels above deficient, but less than optimal, are referred to as low suboptimal. Suboptimal means the levels are not optimal. Thus, low suboptimal and high suboptimal sandwich optimal. The high suboptimal level is between optimal and where the nutrient becomes toxic.

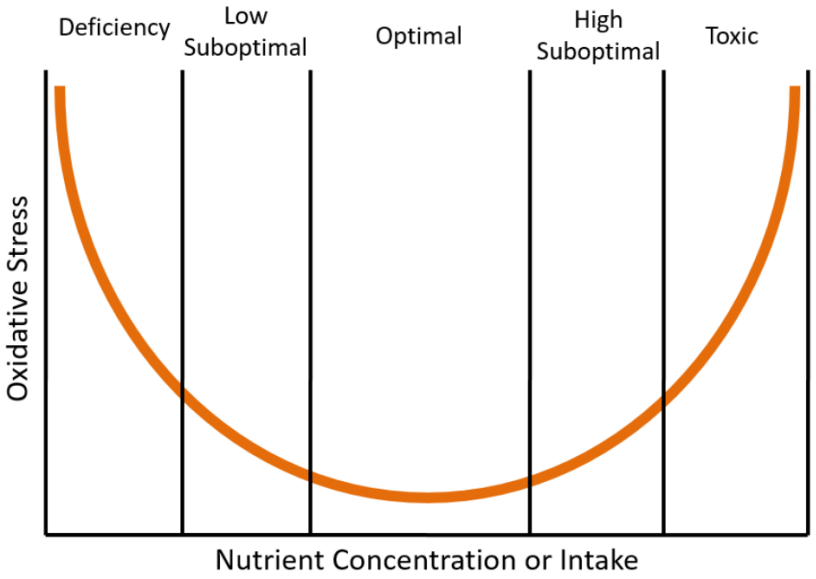


Figure 9.1.10: How the levels of nutrient concentration or intake alters oxidative stress in the body. Going up the y-axis and to the right on the x-axis is higher (or increasing). Adapted from reference8

An example of where this phenomenon has been shown to occur is in the dog prostate with toenail selenium concentrations, which are a good indicator of long-term selenium status8. Researchers found that when they plotted prostate DNA damage (antioxidant measure) against toenail selenium status (nutrient concentration or intake) that it resulted in a U-shaped curve like the one shown above8. Thus, it is good to have antioxidants in your diet, but too much can be counterproductive.

Query 9.1.8

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9.2: Vitamin E

There are 8 different forms of vitamin E: 4 tocopherols and 4 tocotrienols. The difference between tocopherols and tocotrienols is that the former have a saturated tail, while the latter have an unsaturated tail. Within tocopherols and tocotrienols, the difference between the different forms is the position of the methyl groups on the ring. The 4 different forms within the tocopherol and tocotrienols are designated by the Greek letters: alpha, beta, gamma, and delta. The difference in these structures is shown in the figures below.

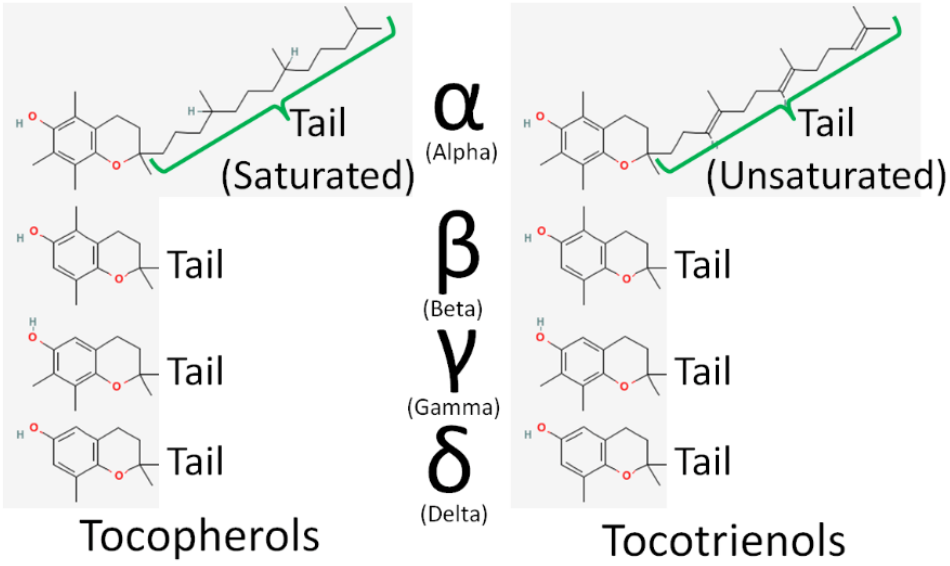


Figure 9.2.1: Structures of the different forms of vitamin E

Query 9.2.1

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Query 9.2.2

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For reasons that will be covered in a later subsection, the primary form of vitamin E found in the body is alpha-tocopherol. The major, and possibly only, function of vitamin E is as an antioxidant. When it serves as an antioxidant it forms an alpha-tocopherol radical, as shown below.

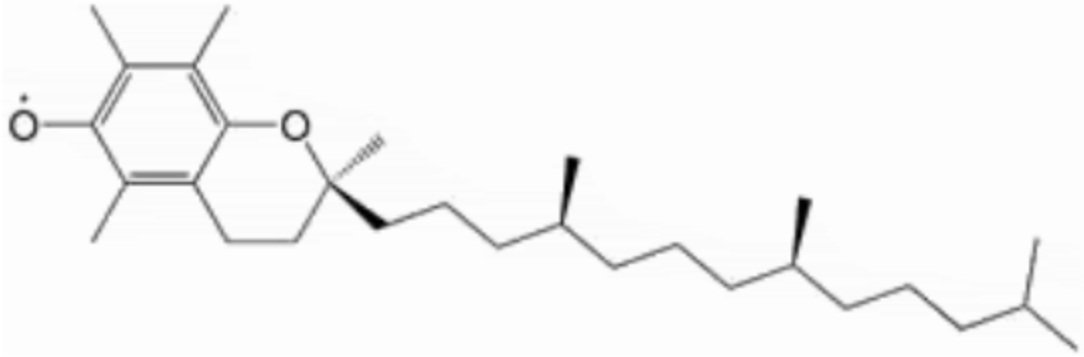


Figure 9.2.2: Alpha-tocopherol radical[1]

Alpha-tocopherol is believed to be the first part of an antioxidant network (shown below) where it is oxidized to donate an electron to stabilize reactive oxygen species. Alpha-tocopherol radical can then be reduced by the donation of an electron from ascorbate.

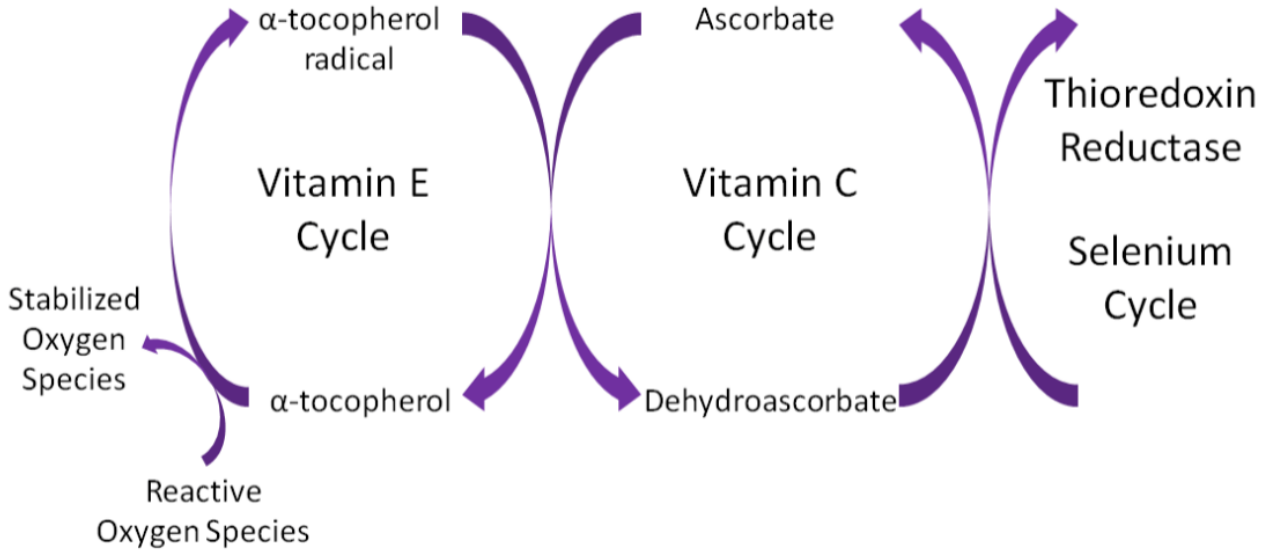


Figure 9.2.3: The theorized antioxidant network[2]

To help protect the antioxidant function of alpha-tocopherol (by preventing the formation of alpha-tocopherol radical) in foods and during digestion, some manufacturers have added compounds to this site of alpha-tocopherol through ester bonds. These are referred to as alpha-tocopherol derivatives or alpha-tocopherol esters. The most common forms are alpha-tocopherol acetate, alpha-tocopherol succinate, and alpha-tocopherol phosphate (Ester-E®). The figures below show the structure of alpha-tocopherol acetate, and the structure of succinic acid.

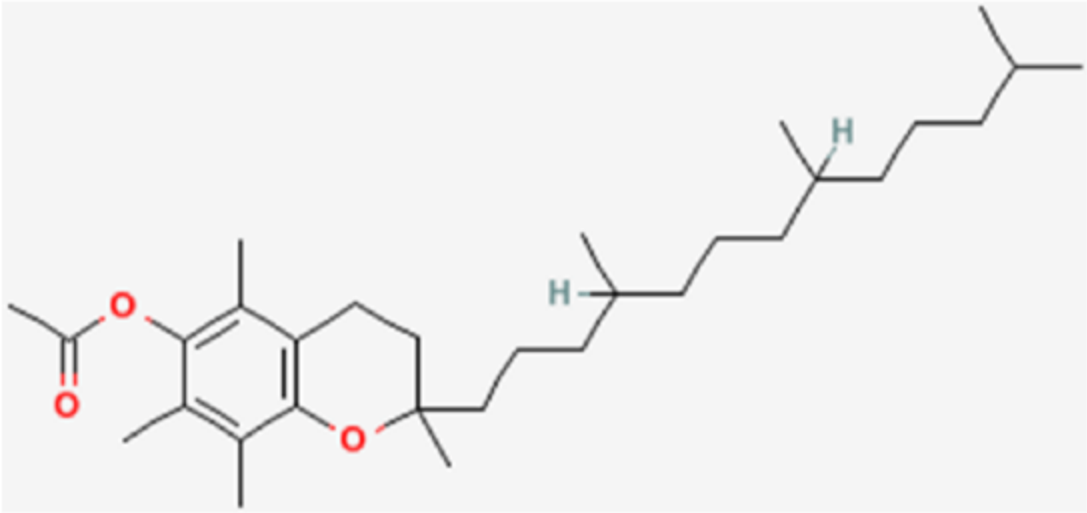


Figure 9.2.4: Alpha-tocopherol acetate

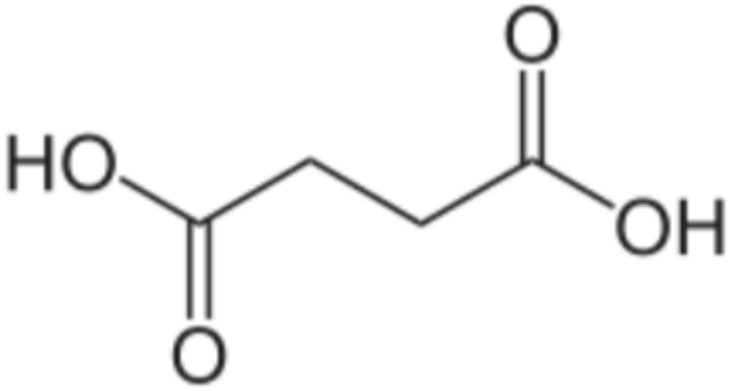


Figure 9.2.5: Succinic acid3

Alpha-tocopherol derivatives, such as acetate in alpha-tocopherol acetate, are cleaved prior to absorption in the small intestine by esterases, meaning that alpha-tocopherol is absorbed, not the alpha-tocopherol derivative.

Query 9.2.3

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Alpha-Tocopherol: Natural vs. Synthetic

In addition to being found naturally in foods, alpha-tocopherol can also be synthesized. It is important to know whether alpha-tocopherol is natural or synthetic because the stereochemistry (spatial arrangement) differs between these forms. In some cases stereochemistry is used to three dimensionally depict whether a molecule is coming out towards you or alternatively away from you. Alpha-tocopherol contains 3 chiral centers (non-superimposable mirror images) designated as R or S.

The 3 chiral centers in alpha-tocopherol are located at the 2, 4', and 8' positions. You can see the full numbering of tocopherols in the link below. In short, the rings are normal numbers and the tail are prime numbers.

Web Link

Tocopherol Numbering

The figure below shows the 3 chiral centers without the other numbers.

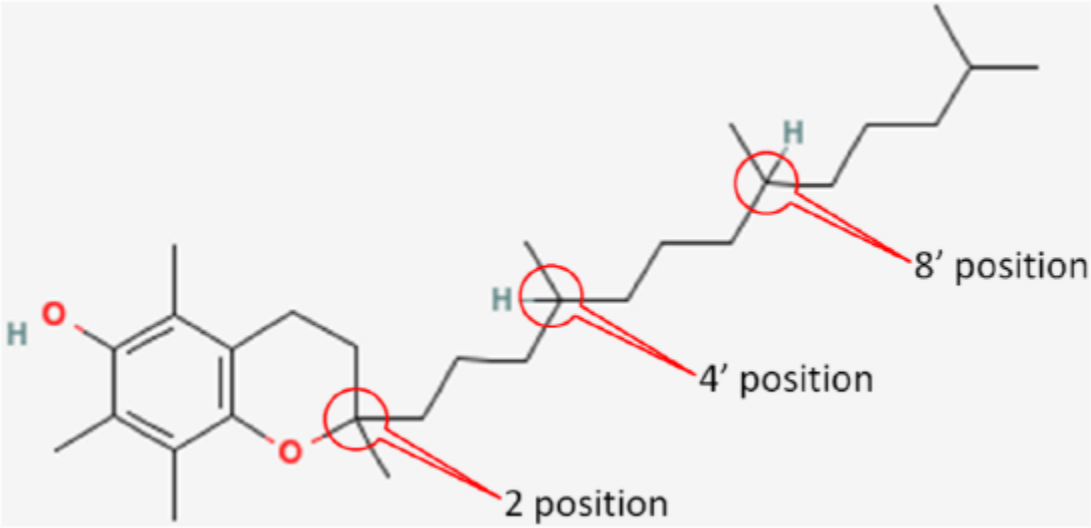


Figure 9.2.6: The 2, 4’, and 8’ positions of alpha-tocopherol are chiral centers

In natural alpha-tocopherol, all 3 chiral centers are in the R configuration. Thus, it is designated RRR-alpha-tocopherol. The R’s represent the 2, 4’, and 8’ positions of alpha-tocopherol, respectively, as shown below4.

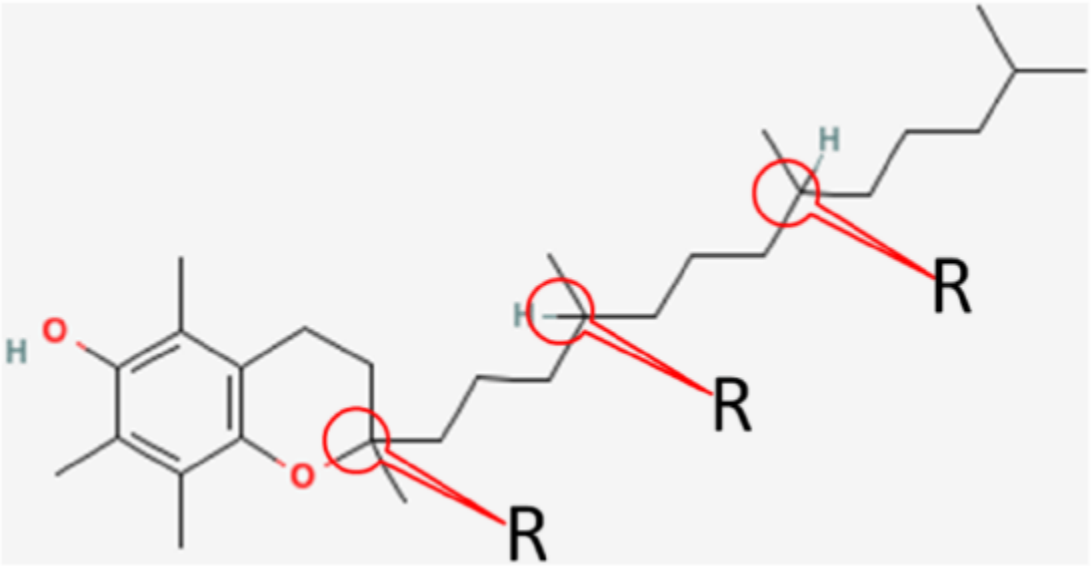


Figure 9.2.7: Natural alpha-tocopherol 2, 4’, and 8’ positions are in the R conformation

Query 9.2.4

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Synthetic alpha-tocopherol is a racemic (equal) mixture of all the different possibilities at the three chiral centers. These are:

RRR

RRS

RSS

RSR

SRR

SSR

SSS

SRS

The two forms of alpha-tocopherol are designated (these are placed before alpha-tocopherol to indicate whether it is natural or synthetic) as listed below:

1. **Natural**

   New designation: RRR-alpha-tocopherol (because all 3 positions are RRR)

   Old designation: d-alpha-tocopherol

2. **Synthetic**

   New designation: all-rac-alpha-tocopherol (because it is a racemic mixture)

   Old designation: dl-alpha-tocopherol

The old d and dl designations were describing the chemical structure that are sometimes still used. Keep in mind the natural and synthetic are describing the stereochemistry of alpha-tocopherol and not whether it is naturally derived. For example, there are natural alpha-tocopherol derivatives where the derivatives are added through synthetic procedures.

Query 9.2.5

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Query 9.2.6

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Vitamin E Absorption, Metabolism, & Excretion

You might be saying to yourself, “who cares about natural versus synthetic alpha-tocopherol.” But the small change in stereochemistry makes a big difference in how alpha-tocopherol is maintained in the body.

All forms of vitamin E (tocopherols, tocotrienols) are absorbed equally. Fat-soluble vitamins are handled like lipids and thus are incorporated into chylomicrons that have triglycerides removed by lipoprotein lipase. The chylomicron remnants containing the different forms of vitamin E are then taken up by the liver. The figure below shows the absorption, metabolism, and excretion of vitamin E.

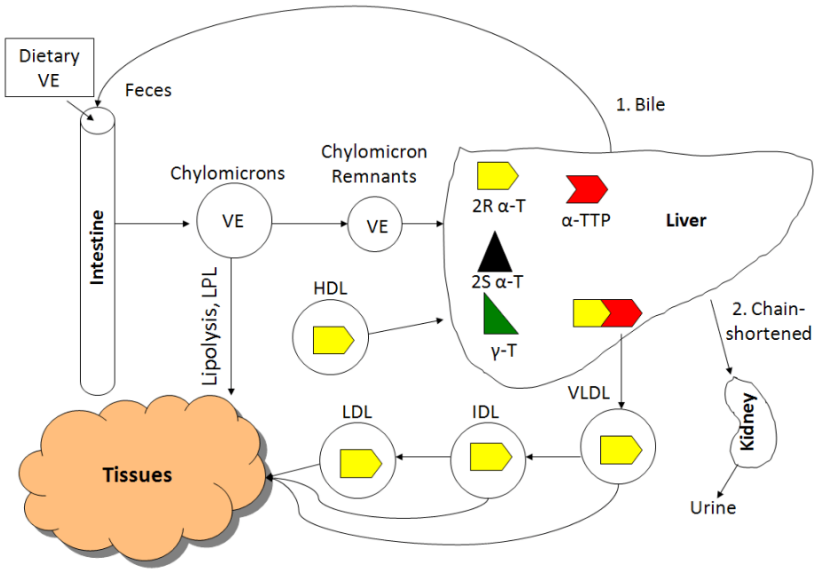


Figure 9.2.8: The absorption, metabolism, and excretion of vitamin E

Query 9.2.7

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The liver contains a protein called alpha-tocopherol transfer protein (alpha-TTP), which is responsible for maintaining higher levels of alpha-tocopherol in the body. Alpha-TTP preferentially binds to 2R alpha-tocopherol and helps facilitate its incorporation into VLDL. 2R means any form of alpha-tocopherol in which the 2 position is in the R conformation. The following table summarizes the forms of alpha-tocopherol that bind well to alpha-TTP, and those that don't bind well to alpha-TTP.

Table 9.2.1: Alpha-tocopherol isomers and binding to alpha-TTP

Do not bind well to alpha-TTP	Bind well to alpha-TTP
SRR	RRR
SSR	RRS
SSS	RSS
SRS	RSR

Query 9.2.8

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Other forms of vitamin E (gamma-tocopherol, tocotrienols) also don't bind well to alpha-TTP and thus, are found in lower levels than alpha-tocopherol in the body. The following graph shows plasma (liquid component of blood) vitamin E levels from a study in which subjects were given 150 mg each of RRR-alpha-tocopherol, all-rac-alpha-tocopherol, or gamma-tocopherol[5].

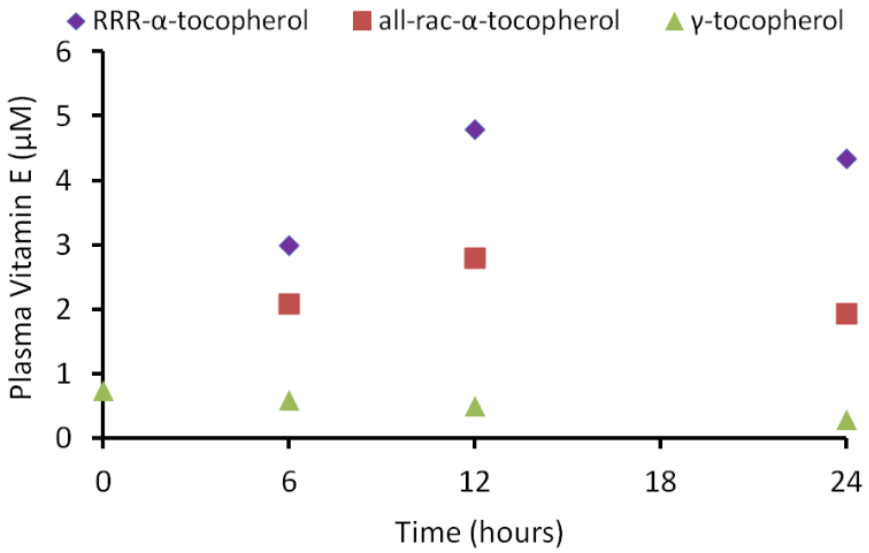


Figure 9.2.9: Plasma vitamin E concentrations in response to a 150 mg dose of RRR-alpha-tocopherol, all-rac-alpha-tocopherol, or gamma-tocopherol. Adapted from reference[5]

As you can see in the figure, there was a greater rise in the plasma alpha-tocopherol levels after receiving RRR-alpha-tocopherol vs. all-rac-alpha-tocopherol. This is not a surprise because approximately 50% of all-rac-alpha-tocopherol is 2R alpha-tocopherol that binds well with alpha-TTP. You can also see that the plasma gamma-tocopherol concentration is much lower than either natural or synthetic alpha-tocopherol.

From VLDL and subsequent lipoproteins, vitamin E reaches tissues, with most vitamin E in the body being found in the adipose tissue. There are 2 main routes of vitamin E excretion. The major route of excretion is through bile that is then excreted in feces. The second route is in the urine after vitamin E is chain-shortened in a process similar to beta-oxidation to make them more water-soluble.

Query 9.2.9

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Dietary Vitamin E & Amounts Found in Body

The best food sources of vitamin E are primarily oils and nuts. As you can see below, the forms of vitamin E that nuts and oils contain varies, with the two major forms being alpha and gamma-tocopherol. Soybean, corn, and flaxseed oils are good sources of gamma-tocopherol. Palm and canola oils contain almost equal amounts of alpha-tocopherol and gamma-tocopherol. Safflower oil, almonds, sunflower oil, and wheat germ oil are good sources of alpha-tocopherol. Beta-tocopherol and delta-tocopherol are found in lower levels in foods. Tocotrienols, for the most part, are not found in high levels in the diet. The amount of tocopherols in different nuts and oils are shown in the figure below.

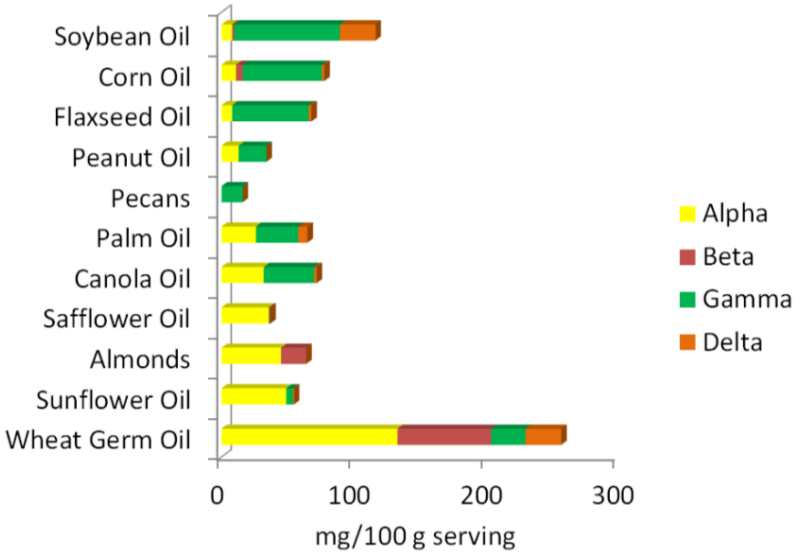


Figure 9.2.10: Tocopherol distribution in plant products6

Three-fourths of the oil Americans consume is soybean oil. As a result, it is estimated that we consume 2-4 times more gamma-tocopherol than alpha-tocopherol. Europeans consume more olive, sunflower, and canola oil and thus are believed to consume at least 2 times more alpha-tocopherol than gamma-tocopherol6.

Despite Americans' higher intake of gamma tocopherol compared to other countries, our serum (liquid portion of blood without coagulation proteins) concentrations do not differ much as illustrated in the table below.

Table 9.2.2: International serum gamma-tocopherol and alpha-tocopherol concentrations (uM/L)6

Location	Gamma-tocopherol	Alpha-tocopherol
USA 1*	2-7	15-20
USA 2	5.4	22.3
USA 3	2.5	21.8
Costa Rica	2.7	28.6-31.8
France	1.05-1.28	26.7

Location	Gamma-tocopherol	Alpha-tocopherol
Ireland	1.74-1.87	26.3
The Netherlands	2.3	23.9-25.5
Spain	0.88-1.14	27.4-28.3
Italy	1.29	24.3
Sweden	3.2	23.8
Lithuania	1.64	21.7
Austria	1.48	21.1

There are 3 different studies that have reported serum levels in the United States.

Tissue concentrations, for the most part, also indicate a greater accumulation of alpha-tocopherol than gamma-tocopherol as shown in the table below.

Table 9.2.3: Tissue gamma-tocopherol and alpha-tocopherol concentrations (nM/g)6

Tissue	Gamma-tocopherol	Alpha-tocopherol
Skin	180	127
Adipose	176	440
Muscle	107	155

Query 9.2.10

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Vitamin E Deficiency & Toxicity

Vitamin E deficiency is extremely rare. Depletion studies require years on a vitamin E-deficient diet to cause deficiency7. Deficiency primarily occurs in people with lipid malabsorption problems or Ataxia with Isolated Vitamin E Deficiency (AVED). Individuals with AVED have a mutation in their alpha-TTP that prevents it from functioning correctly. The primary symptoms of vitamin E deficiency are neurological problems.

Query 9.2.11

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High levels of vitamin E intake do not result in a noted toxicity. However, higher levels of intake of alpha-tocopherol (like achieved by taking supplements) are associated with decreased blood coagulation. In particular, hemorrhagic stroke has been linked to high alpha-tocopherol intake levels. The link below shows that in this condition a blood vessel ruptures or leaks in the brain.

Web Link

Hemorrhagic Stroke

It is believed that this increased bleeding risk is due to a alpha-tocopherol metabolite that has anti-vitamin K activity. This potential antagonism will be described more in the vitamin K section.

Query 9.2.12

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Vitamin E DRI & IUs

Before 2001, all forms of vitamin E contributed to the RDA, using a measure called alpha-tocopherol equivalents. This indicator essentially provided a value for all forms relative to alpha-tocopherol. In 2001, the Dietary Reference Intake (DRI) committee decided only 2R forms of alpha-tocopherol should be used to estimate the requirement, because these forms bind to alpha-TTP. Thus, other forms of vitamin E (gamma-tocopherol, tocotrienols etc.) do not count toward the requirement and the unit is now mg of alpha-tocopherol. As a result, soybean, corn, and flaxseed oils, which are good sources of gamma-tocopherol, are no longer considered to be good sources of vitamin E. The figure below is a reminder of the tocopherol content of different nuts and oils.

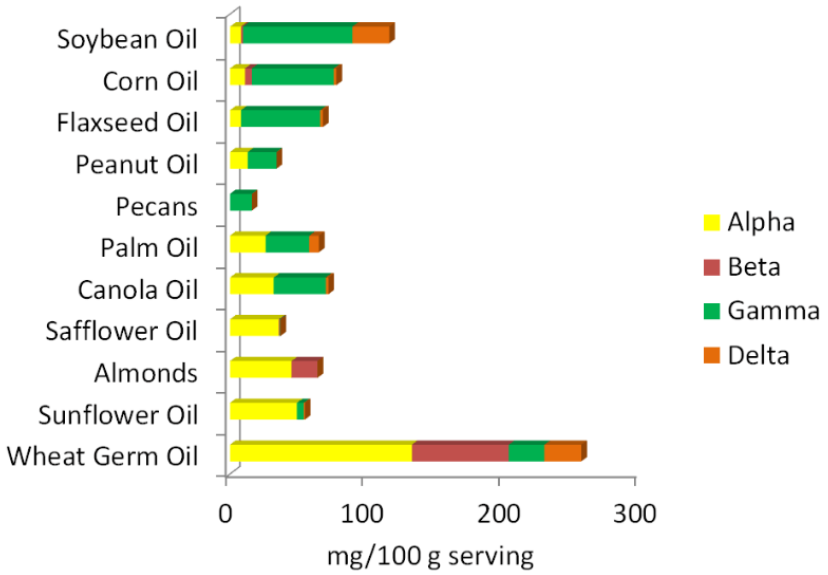


Figure 9.2.11: Only the yellow bars count toward the 2001 DRI requirement6

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Another level of complexity is added by international units (IU). IUs are a unit that are used to describe the bioactivity of different compounds, including 4 vitamins: A, D, E, and C. You might be wondering why these 4 vitamins, it is because these are the ones that were chosen by those who set IUs. Most likely because these vitamins are commonly included in supplements. It would be less confusing if these units were not used. However, most supplements use IUs, IUs are not as common on food items.

For vitamin E, IUs are specific for alpha-tocopherol and adjusted for the molecular weight of the different forms (alpha-tocopherol acetate etc.). The conversion factors for converting IU to mg of alpha-tocopherol are:

0.67 for RRR-alpha-tocopherol (and its esters)

0.45 for all-rac-alpha-tocopherol (and its esters)

Here are some example calculations showing how to use these conversion factors:

Example 1

For a supplement containing 100 IU of RRR-alpha tocopherol:

100 IU X 0.67 = 67 mg alpha-tocopherol

Example 2

For a supplement containing 100 IU of all-rac-alpha tocopherol:

100 IU X 0.45 = 45 mg alpha-tocopherol[7,8]

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9.3: Vitamin C

Vitamin C is well-known for being a water-soluble antioxidant. Humans are one of the few mammals that do not synthesize vitamin C, making it an essential micronutrient. Other mammals that do not synthesize vitamin C include primates, guinea pigs, and other less prevalent species1. This means that some species like rats, mice, dogs and cats are not great options for human vitamin C research since it is not an essential nutrient for them.

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Vitamin C's scientific names are ascorbic acid or ascorbate and the oxidized form is dehydroascorbic acid or dehydroascorbate. The structure of vitamin C is shown below.

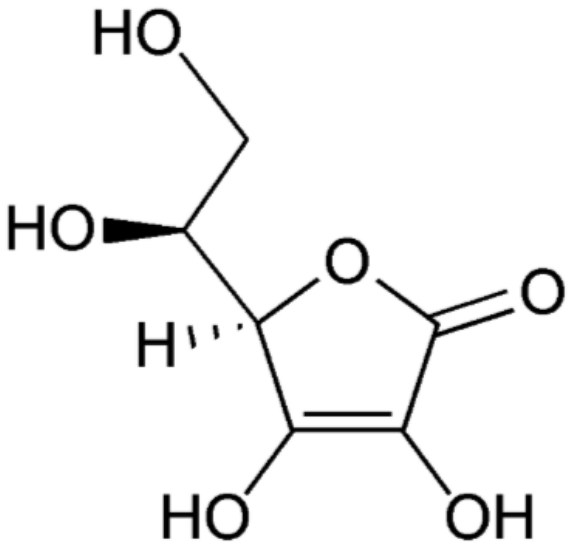


Figure 9.3.1: Structure of ascorbic acid2

When ascorbic acid is oxidized, it forms semidehydroascorbate (1 degree of oxidation) and then dehydroascorbate (2 degrees of oxidation). The structure of dehydroascorbic acid is shown below.

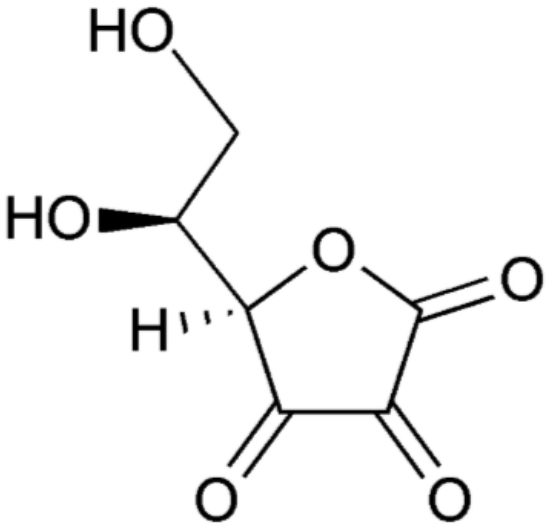


Figure 9.3.2: Structure of dehydroascorbic acid3

The figure below shows the reaction through which ascorbic acid can stabilize or quench 2 free radicals. The 2 circled hydrogens are lost and replaced by double bonds when ascorbic acid is oxidized to dehydroascorbic acid. Reducing dehydroascorbic acid back to ascorbic acid is the opposite reaction.

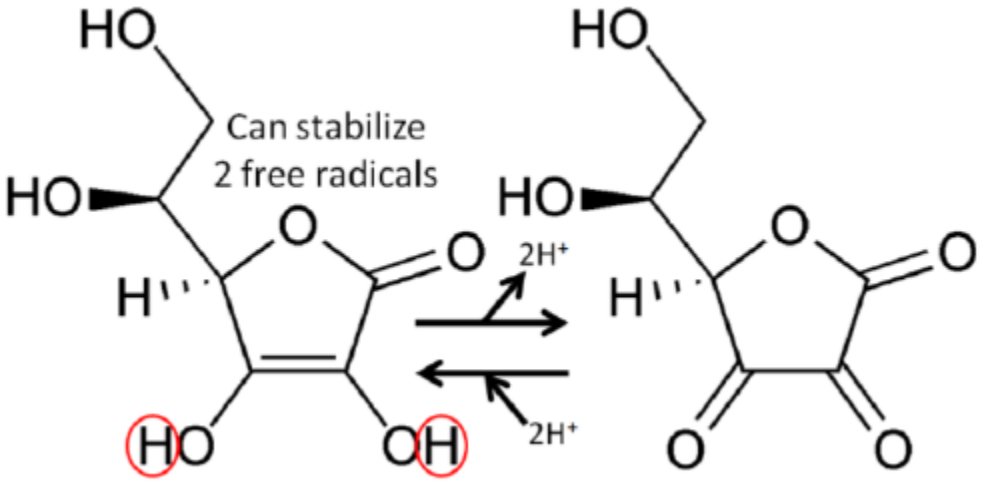


Figure 9.3.3: The oxidation-reduction reaction between ascorbic acid (left) and dehydroascorbic acid (right)2,3

Ascorbic acid is believed to be a part of an antioxidant network (shown below) where it is oxidized to reduce alpha-tocopherol radicals. Dehydroascorbic acid can be reduced by thioredoxin reductase, a selenoenzyme, to regenerate ascorbic acid.

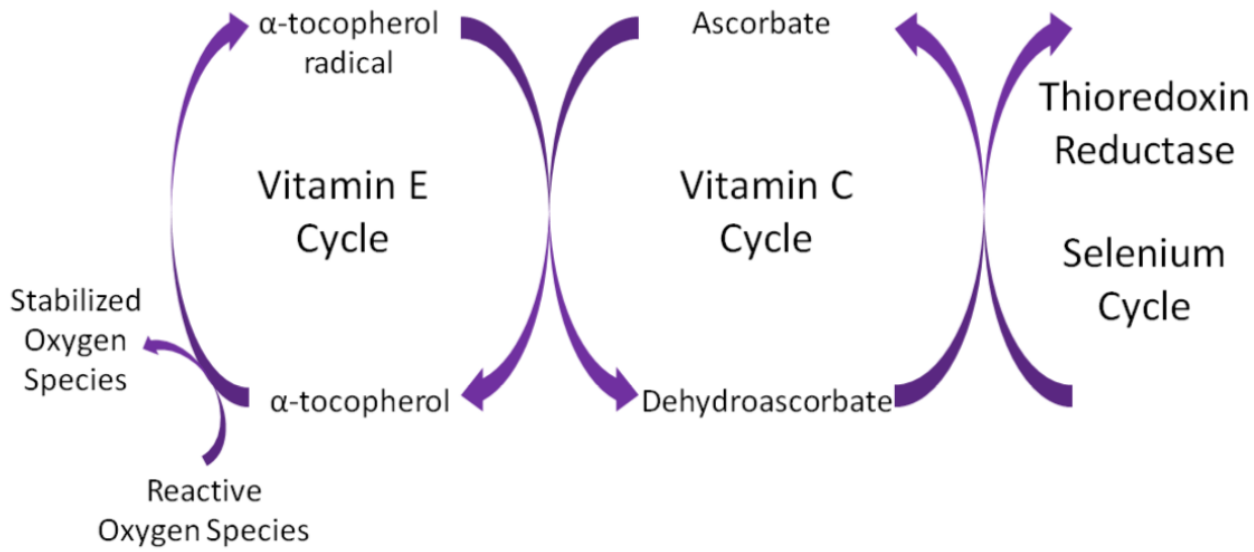


Figure 9.3.4: The theorized antioxidant network[4]

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Vitamin C Absorption & Tissue Accumulation

Vitamin C is found in foods primarily as ascorbic acid (80-90%), but dehydroascorbic acid (10-20%) is also present. The bioavailability of vitamin C is high at lower doses as shown below, but drops to less than 50% at higher doses.

Table 9.3.1: Bioavailability of vitamin C[5]

Dose (mg)	% Bioavailability
200	112
500	73
1250	49

Ascorbic acid is actively absorbed by the sodium vitamin C cotransporter (SVCT) 1. This active transport is driven by the sodium electrochemical gradient created by sodium-potassium ATPase. Ascorbic acid then diffuses into the capillary and ultimately enters general circulation. Vitamin C generally circulates as ascorbic acid.

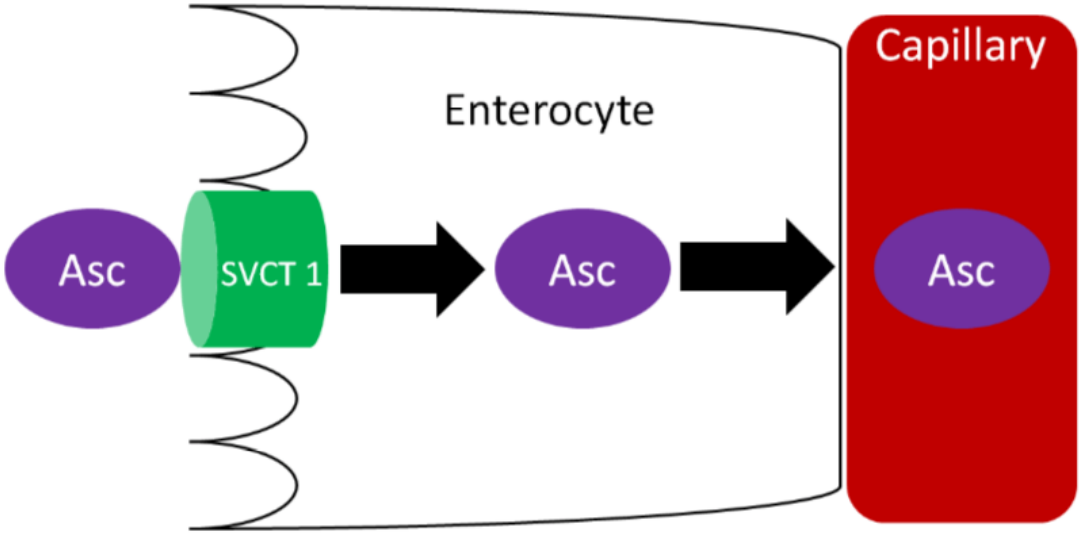


Figure 9.3.5: Ascorbic acid (Asc) absorption

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Accumulation

Most water-soluble vitamins are not stored in the body. Vitamin C is not stored, but is accumulated in certain tissues in the body where it can be 5-100 times higher than found in the plasma[1]. The table below shows the concentrations of vitamin C in different tissues and fluids.

Table 9.3.2: Human tissue & fluid ascorbic acid concentrations[5]

Organ/Tissue	Vitamin C Concentration*	Organ/Tissue	Vitamin C Concentration*
Pituitary Gland	40-50	Lungs	7
Adrenal Gland	30-40	Skeletal Muscle	3-4
Eye Lens	25-31	Testes	3
Liver	10-16	Thyroid	2
Brain	13-15	Cerebrospinal Fluid	3.8
Pancreas	10-15	Plasma	0.4-1
Spleen	10-15	Saliva	0.1-9.1
Kidneys	5-15		

* mg/100 g wet tissue, mg/100 mL fluids

How does the body accumulate such high levels of vitamin C? There are 2 primary mechanisms:

1. Ascorbic Acid (Ascorbate) uptake using sodium-dependent vitamin C transporter (SVCT) 1 or 2

2. Ascorbic Acid (Ascorbate) Recycling

Ascorbic Acid (Ascorbate) transport using sodium-dependent vitamin C transporter (SVCT) 1 or 2

As shown below, SVCT 1 and SVCT 2 transport ascorbic acid or ascorbate into the cell against the concentration gradient (represented by the orange wedge in the figure below). Like absorption, this uptake is driven by the action of sodium-potassium ATPase. This mechanism is saturable, meaning that at high concentrations it reaches a threshold where it cannot take up ascorbic acid any faster. Thus, there is a limit to how much can be taken up through this mechanism7.

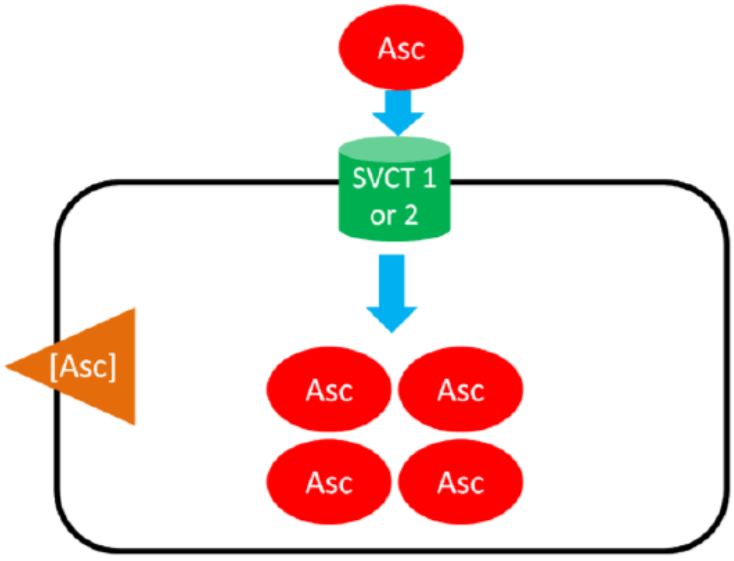


Figure 9.3.6: Ascorbic acid (Asc) uptake using SVCT 1 and 2 against the ascorbic acid concentration gradient7

Ascorbic Acid (Ascorbate) Recycling

In ascorbic acid recycling, ascorbic acid is oxidized to dehydroascorbic acid (DHA). DHA is then transported into the cell moving with its concentration gradient using GLUT1 or 3. Once inside the cell, DHA is reduced back to ascorbic acid, thus maintaining the DHA gradient. As a result, the cell is able to accumulate high levels of ascorbic acid6. The figure below depicts ascorbic acid recycling.

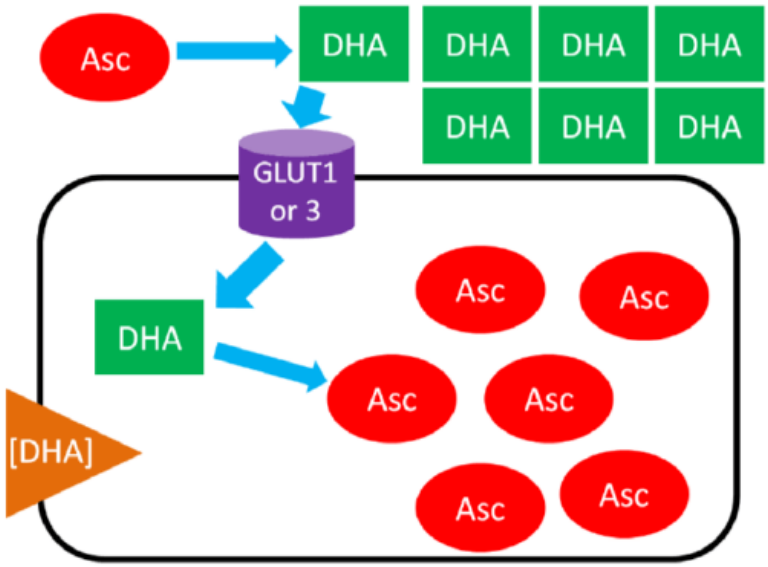


Figure 9.3.7: Ascorbic acid (Asc) recycling7. Ascorbic acid is oxidized to dehydroascorbic acid (DHA) outside the cell. DHA concentration {DHA} is higher outside the cell than inside the cell as represented by the orange wedge, whose wide side is outside the cell and narrow point is inside the cell. Thus, DHA is taken up through GLUT1 or 3 through facilitated diffusion. Once inside the cell DHA is reduced back to Asc, thus maintaining the DHA concentration gradient.

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Enzymatic Functions

In addition to its antioxidant function, vitamin C is also a cofactor for a number of enzymes or contributes to reducing a cofactor in others. Proline hydroxylase and lysyl hydroxylase are two enzymes that vitamin C is needed for them to carry out their catalytic function. These enzymes are important in the formation of the protein collagen. Hydroxylase means that the enzymes add alcohol (hydroxyl, $-\mathrm{OH}$) to the amino acids proline and lysine, as shown below.

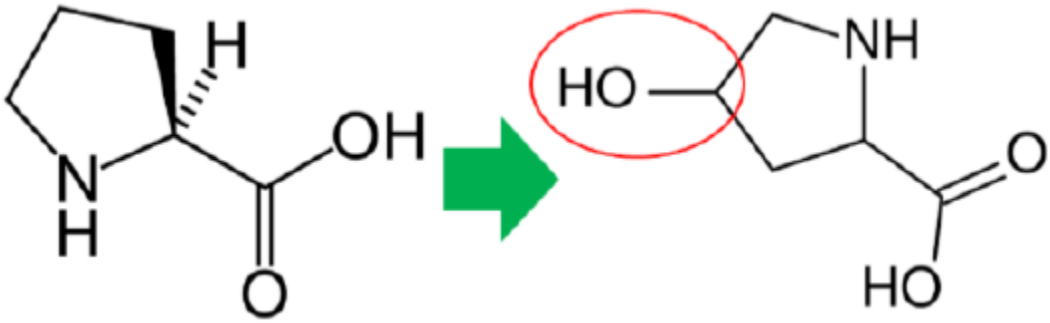


Figure 9.3.8: Prolyl hydroxylase adds an alcohol group (circled) to proline forming hydroxyproline7,8

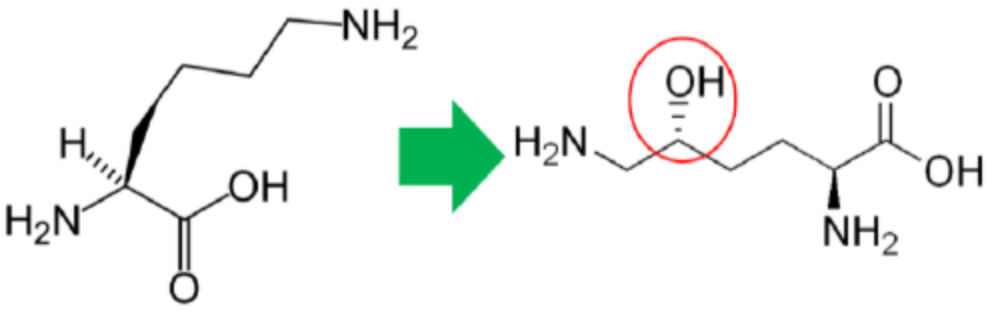


Figure 9.3.9: Lysyl hydroxylase adds an alcohol group (circled) to lysine forming hydroxylysine[9,10]

As shown below, prolyl and lysyl hydroxylases require ferrous iron (Fe^{2+}) to function. But in the course of the hydroxylating proline or lysine, ferrous iron (Fe^{2+}) is oxidized to ferric iron (Fe^{3+}). Ascorbic acid is required to reduce Fe^{3+} to Fe^{2+}, forming semidehydroascorbic acid in the process. With Fe^{2+}, the enzyme is then able to continue to hydroxylate proline and lysine.

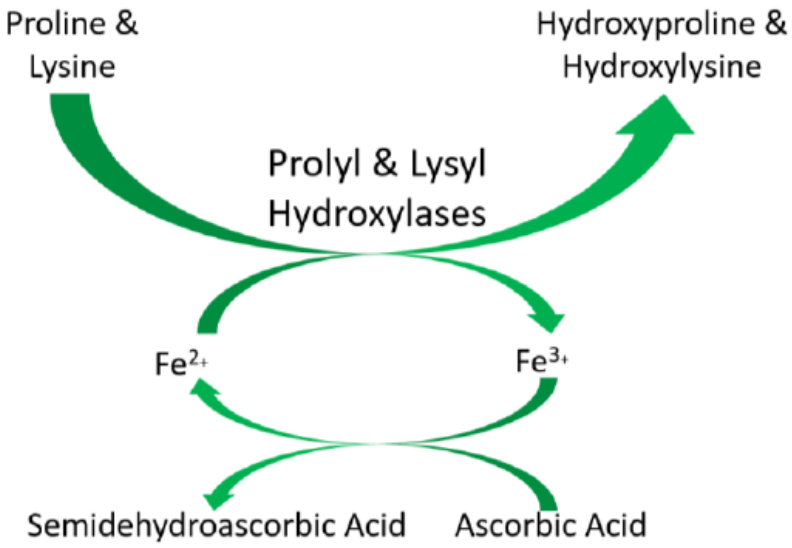


Figure 9.3.10: Ascorbic acid reduces iron so that it can continue to serve as a cofactor for prolyl and lysyl hydroxylases

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Why should you care about collagen formation? Because collagen is estimated to account for 30% or more of total body proteins11. Collagen contains a number of hydroxylated prolines and lysines that are needed for collagen strands to properly cross-link. This cross-linking is important for collagen to wind together like a rope, forming the strong triple helix known as tropocollagen. This process is shown in the following animation, as well as in the figure below.

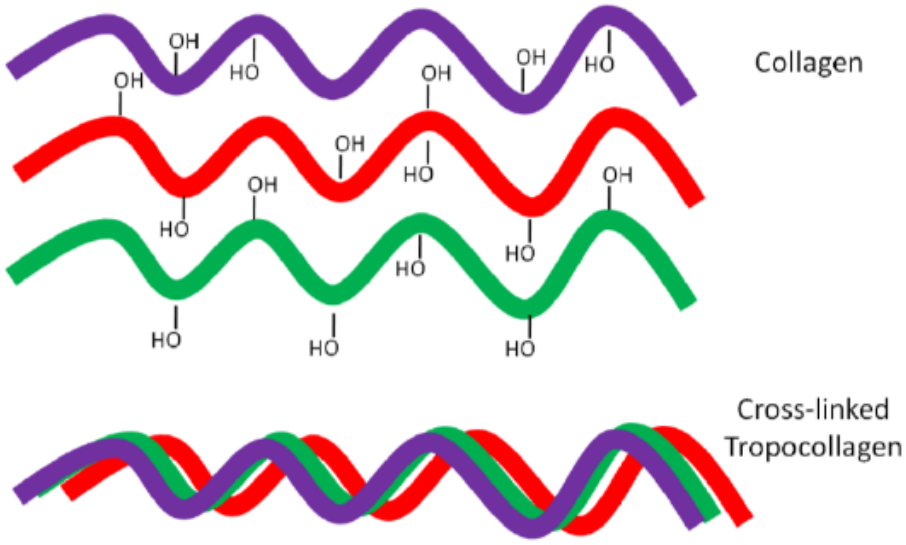


Figure 9.3.11: Production of cross-linked tropocollagen in the presence of adequate vitamin C

But if there is not enough ascorbic acid available, the collagen strands are underhydroxylated and instead of forming strong tropocollagen, the underhydroxylated collagen is degraded as shown below.

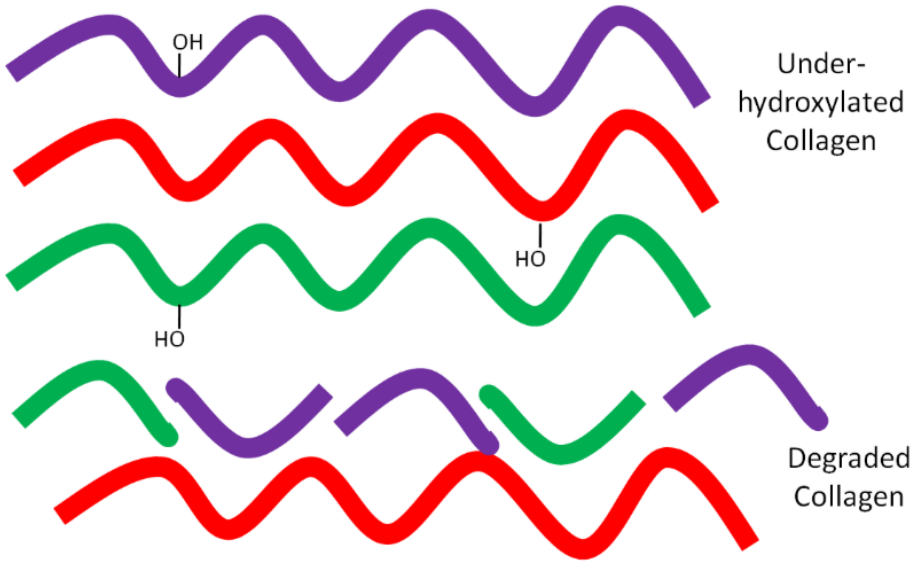


Figure 9.3.12: Production of underhydroxylated collagen

This weak collagen then results in the symptoms seen in the vitamin C deficiency, scurvy, that will be discussed in the next subsection.

Ascorbic Acid is also needed for:

- Carnitine synthesis
- Tyrosine synthesis and catabolism
- Serotonin (neurotransmitter) synthesis
- Other hormone and neurotransmitter synthesis12

The figure below shows how ascorbic acid is needed for dopamine hydroxylase, which ultimately produces the hormone epinephrine.

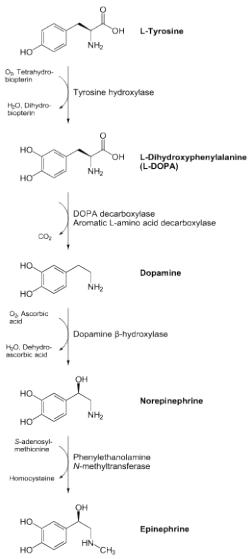


Figure 9.3.13: Dopamine beta-hydroxylase requires ascorbic acid to produce norepinephrine[13]

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Vitamin C Deficiency (Scurvy)

Why should you care about the details of prolyl and lysyl hydroxylases and their actions on collagen hydroxylation and tropocollagen formation? Because they explain the symptoms of vitamin C deficiency. While it is rare in the United States, vitamin C deficiency, known as scurvy, displays symptoms that are a result of weak tropocollagen, that in turn, weakens connective tissue throughout the body. Symptoms of scurvy include bleeding gums, pinpoint hemorrhages, and corkscrew hairs as shown in the figure and link below.



Figure 9.3.14: Bleeding gums that occur in scurvy[14]

Web Link

Corkscrew Hairs

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Additional symptoms include impaired wound and fracture healing, easy bruising, and loose or decaying teeth. Scurvy can be fatal if not treated. Scurvy was the first discovered nutrition deficiency in 1746 by James Lind, who is shown below[12].



Figure 9.3.15: Dr. James Lind discovered that scurvy was caused by a nutrition deficiency[15]

Keep in mind as you read the description below that suggesting scurvy was due to a diet deficiency, at that time, sounded like flu was caused by not consuming green beans. Sounds pretty crazy, right? Because the concept of vitamines and compounds that would become vitamins were not proposed until around 150 years later.

Lind was a surgeon on a British navy ship. Frequently during voyages the sailors would develop scurvy for reasons that were not understood at the time. It was known that citrus fruits could cure or prevent scurvy, but it was believed this was due to their acidity. Lind performed clinical trials comparing citrus juice to dilute sulfuric acid and vinegar and found that only citrus juice caused the sailors to recover, as depicted in the link below. As a result of the discovery, the British sailors became known as "Limeys" because they would drink lime juice to prevent the development of the disease[16].

Web Link

Curing Scurvy

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Vitamin C Toxicity, Linus Pauling & the Common Cold

Vitamin C does not have a toxicity per se, but in some people over 2 grams/day can lead to diarrhea and gastrointestinal distress. In addition, high intake of vitamin C increases excretion of uric acid (urate) and oxalic acid (oxalate). The structure of these 2 compounds are shown below.

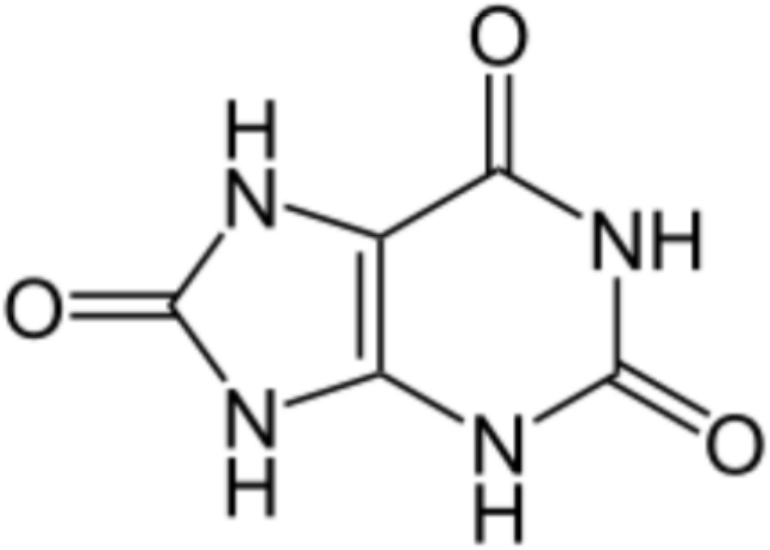


Figure 9.3.16: Structure of uric acid17

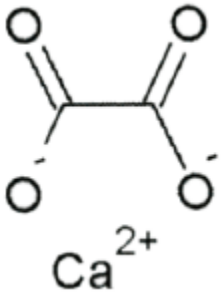


Figure 9.3.17: Structure of calcium oxalate18

These compounds are the primary components of 2 types of kidney stones21. The figures below show the most common sites of pain in someone with kidney stones.

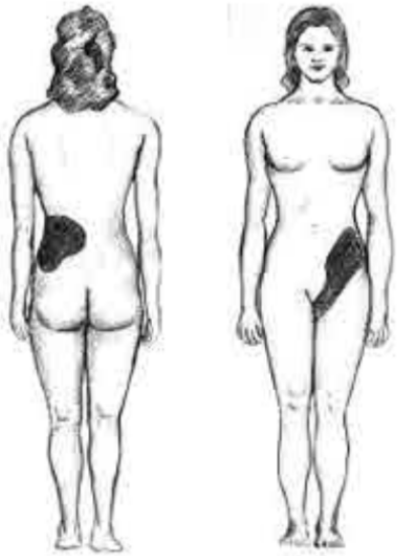


Figure 9.3.18: Kidney stones normally cause pain in the shaded areas19

The following video describes what kidney stones are and the symptoms that can occur if someone has kidney stones. The link shows some pictures of kidney stones.

YouTube Video

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Video 9.3.1: Researchers have found that riding roller coasters may help pass kidney stones! But what are kidney stones and what causes them? https://www.youtube.com/watch?v=2ntH5PqSSlI

Web Link

Kidney Stones

Calcium oxalate is one of the primary forms of kidney stones with uric acid stones being more rare[20]. However, a link between excretion of these compounds and actual stone formation has not been established. Nevertheless, high-dose vitamin C supplementation should be approached with some caution, since it is not clear whether it increases the risk of forming kidney stones[21].

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Linus Pauling and the Common Cold

The person who popularized taking megadoses of vitamin C was Dr. Linus Pauling. Dr. Pauling was a chemist, and is the only person to receive 2 unshared Nobel Prizes. The Nobel Prize is a prestigious award, and Dr. Pauling was close to solving the structure of DNA. This would have likely netted him another Nobel prize, but Watson and Crick beat him to it.



Figure 9.3.19: Linus Pauling22

Later in his life Pauling became convinced that megadoses of vitamin C could prevent the common cold. In 1970 his book Vitamin C and the Common Cold was released and became a bestseller. Later he came to believe that vitamin C could prevent cardiovascular disease, cancer, and combat aging23. However, critics of his beliefs countered that all megadose supplementation was doing was creating "expensive urine". This refers to the fact that the RDA is only 75-90 mg/day for adults and Pauling recommended taking 1-2 grams of vitamin C daily24. Thus, with vitamin C being water-soluble, most of the vitamin C that people on the regimen were paying to consume was being excreted in the urine, thus making it “expensive”.

A review of vitamin C and colds found that that routine megadoses of vitamin C do not reduce the risk of the common cold in most individuals. However, there is some evidence that it might benefit people exposed to brief periods of severe physical exercise (marathon runners) or cold environments (skiers and soldiers in subarctic conditions). There has been little research conducted in children, so it is not known whether vitamin C supplementation is beneficial in this age group25.

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9.4: Selenium

Selenium can be divided into 2 categories: organic and inorganic. The organic forms contain carbon, while the inorganic forms do not. The primary inorganic forms of selenium are selenite (SeO_3) and selenate (SeO_4). Selenite and selenate are not commonly found alone in nature; they are usually complexed with sodium to form sodium selenite (Na_2SeO_3) and sodium selenate (Na_2SeO_4)[1].

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Selenomethionine is the most common organic form of selenium. The structure of selenomethionine is shown above the structure of the amino acid methionine in the figure below.

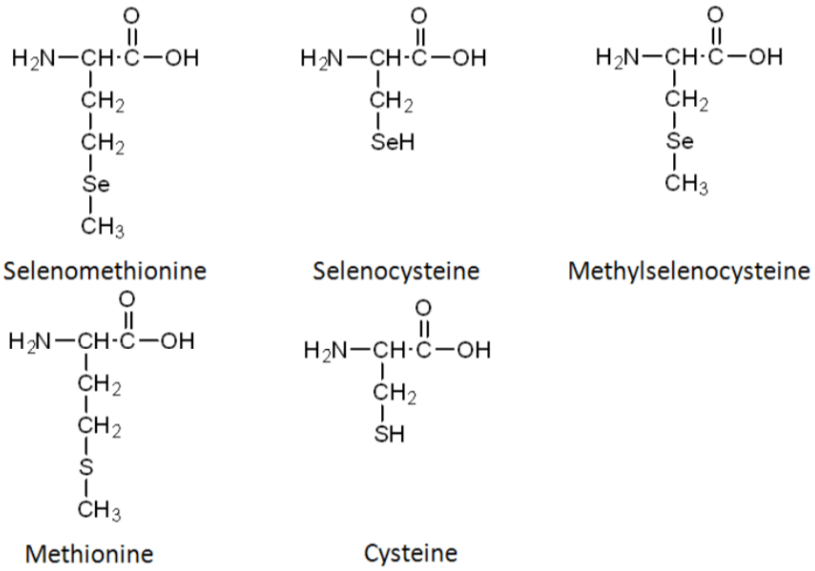


Figure 9.4.1: Structures of organic forms of selenium and similar sulfur-containing amino acids

In comparing the structures of selenomethionine or methionine, you can see that the only difference is that selenium has been substituted for sulfur (S) in methionine. Selenocysteine is considered the 21st amino acid by some, because there is a codon that directs its insertion into selenoproteins. Like selenomethionine versus methionine, the only difference between selenocysteine and cysteine is the substitution of selenium for sulfur. The last organic form is methylselenocysteine (aka Se-methylselenocysteine). Notice that its structure is like selenocysteine, but with a methyl group added (like the name suggests).

The selenium content of plants is dependent on the soil where they are grown. As shown below, soil selenium levels vary greatly throughout the United States, meaning that the selenium content of plant foods also vary greatly.

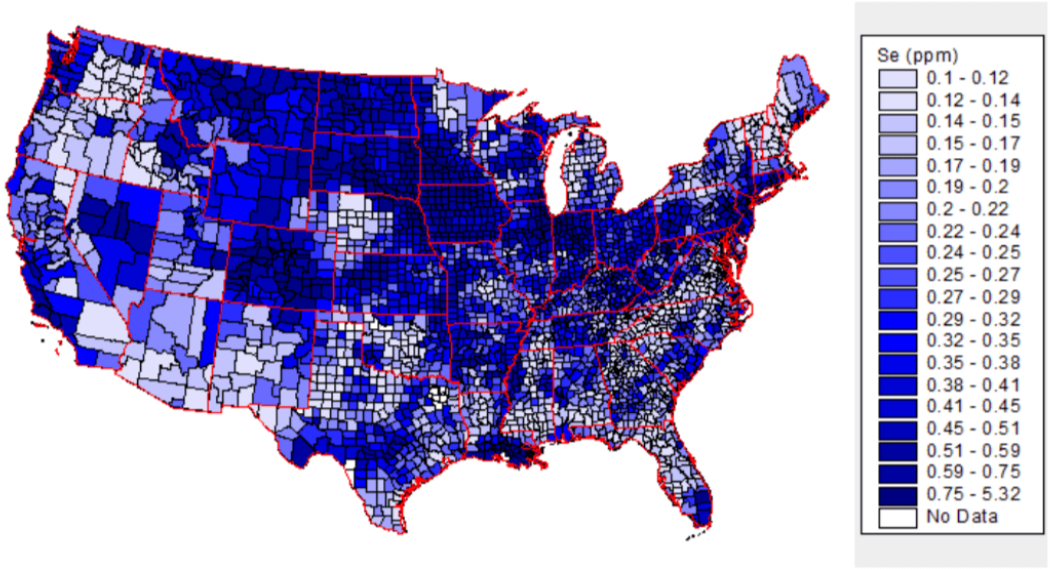


Figure 9.4.2: United States soil selenium levels2

The above map is interactive, so to see the soil selenium levels in a certain county or state, click on it in the link below.

Web Link

USGS Soil Selenium Levels

Inorganic forms of selenium are commonly used in supplements. Selenomethionine is the most common organic form of selenium in supplements and food. It is found in cereal grains such as wheat, corn, and rice as well as soy. Yeast are typically used to produce selenomethionine for supplements.

It should be noted that selenomethionine accumulates at much higher concentrations in the body than other forms of selenium. This is because it can be nonspecifically incorporated into body proteins in place of methionine. However, despite accumulating at higher levels, selenomethionine is less effective than the methylselenocysteine in decreasing cancer incidence or growth in animal models3. However, methylselenocysteine is not commonly consumed, because it is a form that plants accumulate to prevent selenium from becoming toxic to themselves. Thus, plants need to be grown in the presence of high selenium levels to accumulate meaningful amounts of methylselenocysteine.

Query 9.4.2

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Selenoproteins

As mentioned earlier, selenium's antioxidant function is not due to the mineral itself, but a result of the action of selenoenzymes. Selenoenzymes is a term used to describe the subset of selenoproteins that are enzymes. This is illustrated in the figure below, where the different colored circles represent amino acids in the crescent shaped enzyme. In most enzymes, the mineral is a cofactor that is external to the enzyme, as shown on the left. Selenoenzymes contain selenocysteine as an amino acid in the active site of the enzyme. Thus, in selenoenzymes, selenium does not serve as a cofactor, which is different than most minerals

required for enzyme function.

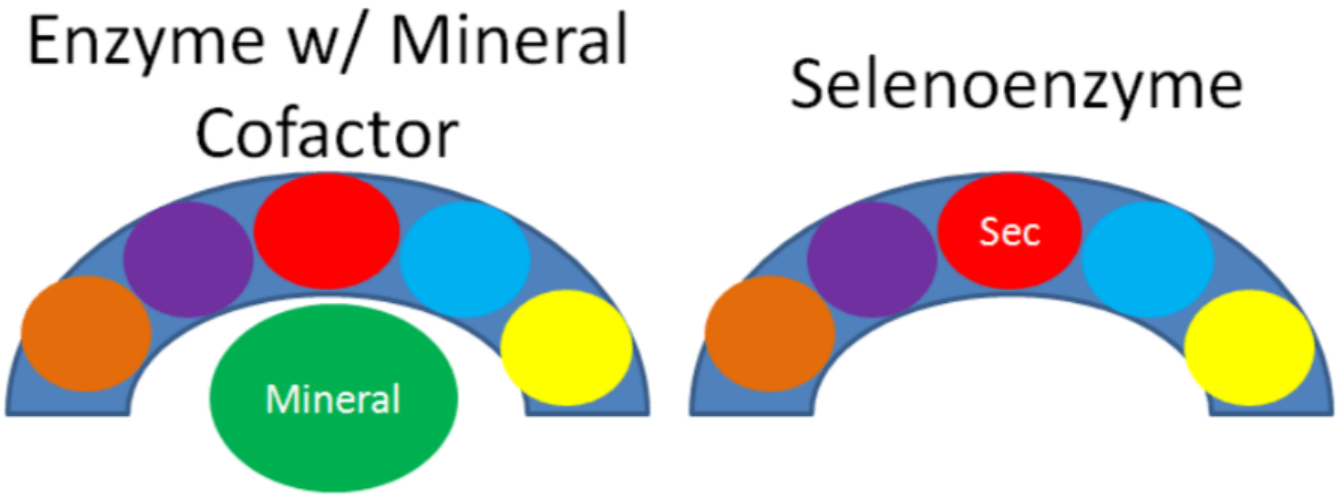


Figure 9.4.3: Enzyme with a mineral cofactor versus a selenoenzyme with selenocysteine as an amino acid in its active site.

Query 9.4.3

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25 human selenoproteins, containing the amino acid selenocysteine, have been identified. The following table lists these selenoproteins along with their function.

Table 9.4.1: The 25 Human Selenoproteins[1,4]

Selenoprotein	Function
Glutathione peroxidase 1 (GPX1)	Cytosolic glutathione peroxidase
Glutathione peroxidase 2 (GPX2)	Gastrointestinal glutathione peroxidase
Glutathione peroxidase 3 (GPX3)	Plasma glutathione peroxidase
Glutathione peroxidase 4 (GPX4)	Phospholipid hydroperoxide glutathione peroxidase
Glutathione peroxidase 6 (GPX6)	Olfactory glutathione peroxidase
Iodothyronine 5'-deiodinase-1 (DI1)	Thyroid hormone-activating iodothyronine deodinase
Iodothyronine 5'-deiodinase-2 (DI2)	Tissue-specific thyroid hormone-activating iodothyronine deodinase
Iodothyronine 5'-deiodinase-3 (DI3)	Tissue-specific thyroid hormone-deactivating iodothyronine deodinase
Thioredoxin reductase (TR1)	Reduction of cytosolic thioredoxin
Thioredoxin reductase (TR2)	Testis-specific thioredoxin reductase
Thioredoxin reductase (TR3)	Reduction of mitochondrial thioredoxin
Selenophosphate synthetase 2 (SPS2)	Selenophosphate synthesis
15 kDa Selenoprotein (Sep15)	Quality control of protein folding in the Endoplasmic Reticulum
Selenoprotein H (SelH)	Unknown

Selenoprotein	Function
Selenoprotein I (SelI)	Unknown
Selenoprotein K (SelK)	Endoplasmic Reticulum-associated degradation
Selenoprotein M (SelM)	Unknown
Selenoprotein N (SelN)	Involved in muscle development
Selenoprotein O (SelO)	Unknown
Selenoprotein P (SelP)	Se transport
Methionine-R-sulfoxide reductase R (SelR)	Reduction of oxidized methionine residues
Selenoprotein S (SelS)	Endoplasmic Reticulum-associated degradation
Selenoprotein T (SelT)	Unknown
Selenoprotein V (SelV)	Unknown
Selenoprotein W (SelW)	Unknown

Hopefully from looking at the table, you see that the glutathione peroxidase enzymes and thioredoxin reductases are antioxidant enzymes. The iodothyronine 5'-deiodinases are involved in the metabolism of thyroid hormones, which will be discussed further in the iodine section. For the vast majority of the other selenoproteins, their function is not known, so they were named selenoprotein and given a letter. As described earlier and shown below, glutathione peroxidase converts hydrogen peroxide into water.

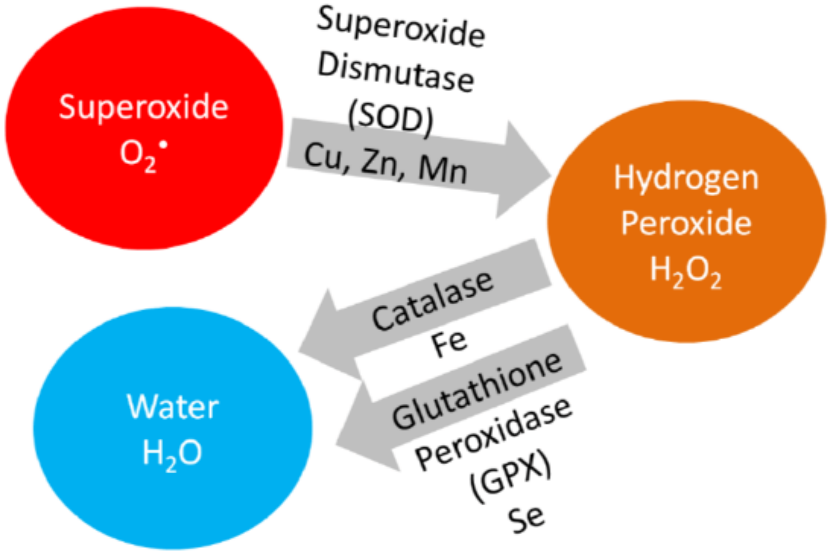


Figure 9.4.4: Antioxidant enzymes that use minerals as cofactors

Remember that thioredoxin reductase can regenerate ascorbate from dehydroascorbate in the theorized antioxidant network (shown below).

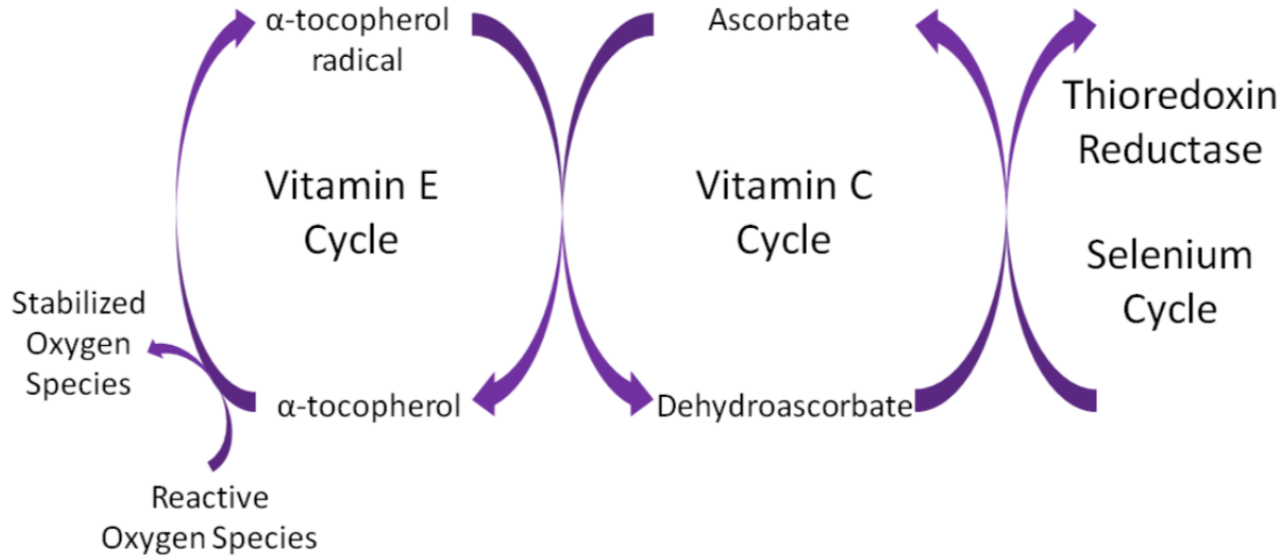


Figure 9.4.5: The theorized antioxidant network[5]

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Selenium Absorption, Excretion, Toxicity & Its Questionable Deficiency

Selenium is highly absorbed. Thus, selenium levels in the body are not regulated by absorption, but rather by urinary excretion. Organic selenium forms may be absorbed slightly better than inorganic forms, as one study found that 98% of a dose of selenomethionine was absorbed, compared to 84% of selenite[1].

Selenium is primarily excreted in the urine, but at high levels it can be expired, producing garlic odor breath.

Selenium toxicity can be a problem, especially for animals living in or around a body of water in an area with high soil selenium levels. This is because runoff from the soil causes selenium to collect in the water in high levels and then starts working its way up the food chain and causing problems, as shown in the following link.

Web Link

Selenium Toxicity

In humans, the initial symptoms are nausea, fatigue, and diarrhea. If continued, the person may develop hair and nail brittleness, rash or skin lesions, and nervous system abnormalities.

There are two questionable selenium deficiency diseases, Kashin-Beck disease and Keshan disease. Kashin-Beck disease is a disorder of the cartilage, bone, and joints that results in deformity and stunted growth. These disabling symptoms result in restricted movement and joint enlargement. The etiology of Kashin-Beck disease remains controversial as it is seen primarily in Tibet and other parts of China, Siberia, and North Korea. The main controversy with Kashin-Beck disease being linked to Selenium deficiency is that the pathogenesis is likely multifactorial in nature. Specifically, selenium deficiency alone cannot cause the occurrence of this disease. However, in combination with other health issues, it has been shown to be linked with Selenium

deficiency6.

The second controversial disease is Keshan disease. This disease occurred primarily in the mountainous regions of China, causing heart lesions. Below is a topographical map of China to give you an idea of what areas are mountainous.

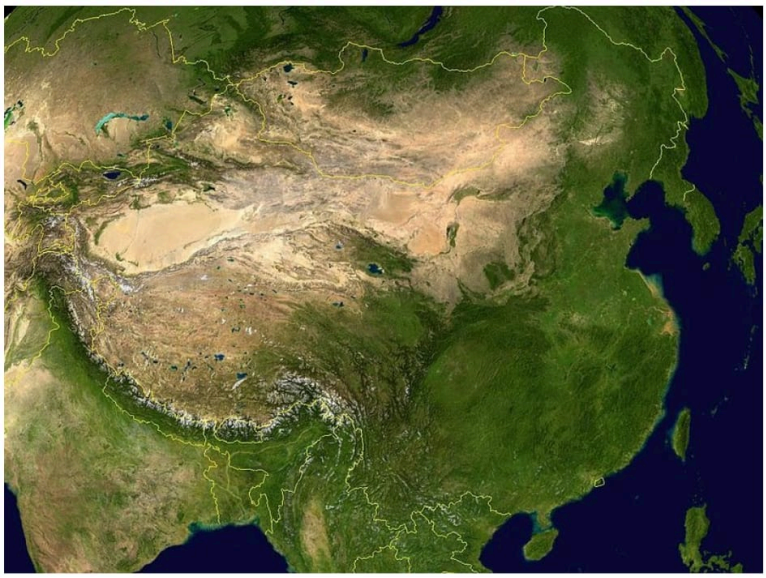


Figure 9.4.6: Topographical map of China7

You can see in the link below the areas where Keshan disease occurred. For the most part, you can see that these 2 areas overlay.

Web Links

Distribution of Keshan Disease

However, sodium selenate supplementation failed to totally eradicate Keshan disease like you would expect if it was caused by selenium deficiency. The incidence of Keshan disease also fluctuated seasonally and annually, which is unusual for a deficiency and more consistent of an infectious disease. Research found coxsackievirus in the heart of Keshan disease victims. They isolated this virus and used it to perform the experiment illustrated below.

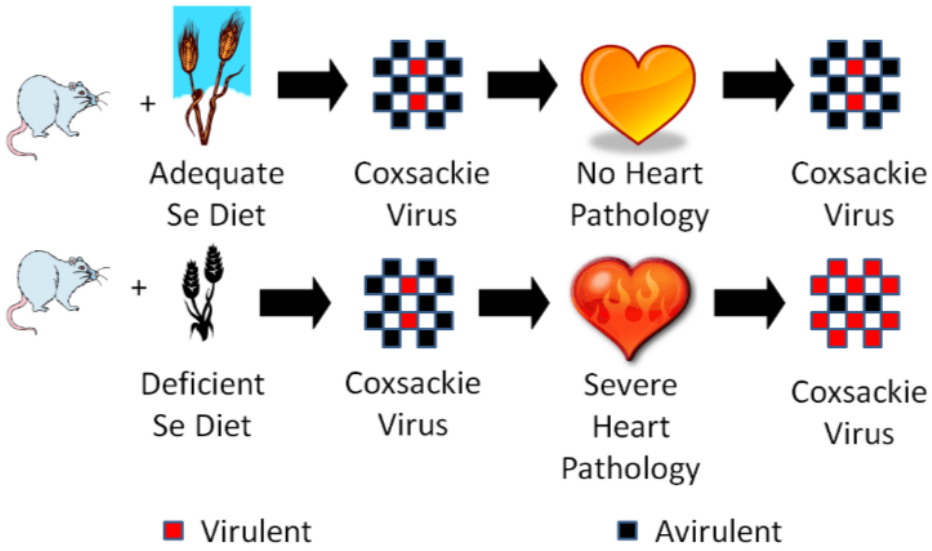


Figure 9.4.7: Keshan disease experiment8

One group of mice was fed an adequate selenium diet and another group a deficient selenium diet. They were then infected with coxsackievirus that was mostly avirulent, but also contained some virulent viruses. A virulent virus is one that causes a disease, and an avirulent virus is one that does not cause a disease (some vaccines use avirulent viruses). After a period of time, they found that the selenium deficient animals developed severe heart pathology, while the selenium adequate animals did not develop heart pathology. They then isolated the virus from the hearts of the mice from both groups and found that the coxsackievirus from the deficient animals' hearts had become mostly virulent7. They then took it one step further as shown in the figure below.

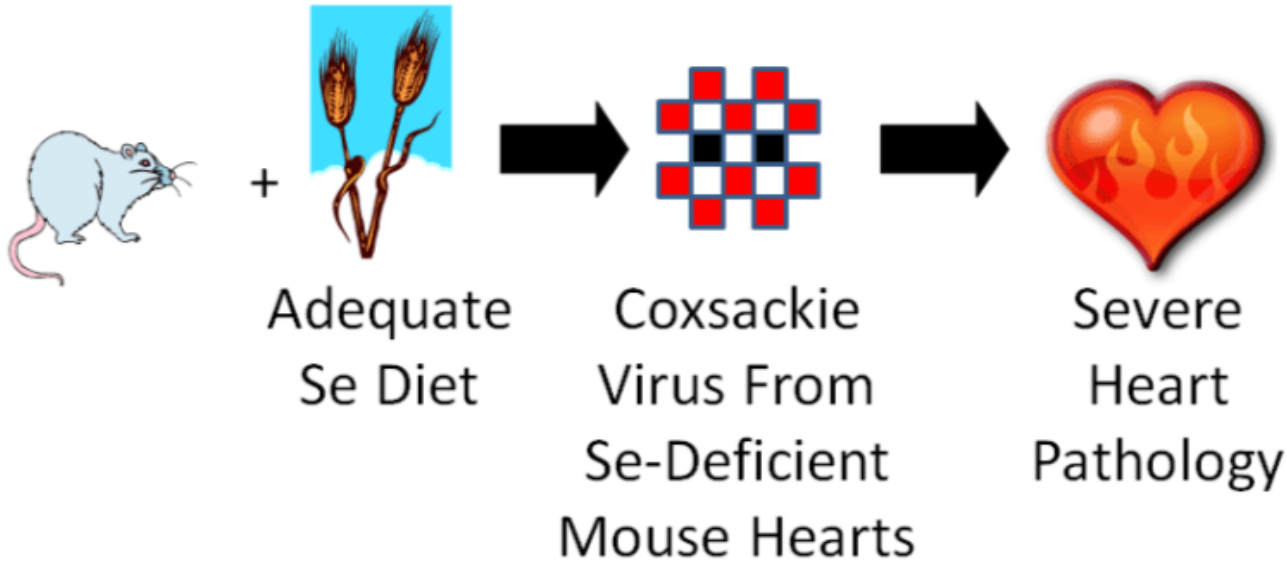


Figure 9.4.8: Keshan disease experiment continued8

They took the isolated virus from the selenium-deficient mouse hearts and infected selenium adequate animals with it. The selenium adequate animals developed severe heart pathology like the selenium-deficient animals had previously.

What's going on? They found mutations in the virus from the selenium-deficient animals that they believe caused it to become virulent. They believe that high oxidative stress, as a result of inadequate antioxidant selenoenzymes, in these animals leads to mutations in the virus causing it to become virulent8.

Who cares? Research has found similar results with vitamin E. Researchers are also examining the effects on other viruses such as influenza (flu) and HIV. If they find a similar phenomenon occurring in other viruses, it means that you and your friend who eats a horrible diet (eats no fruit and vegetables) could be exposed to a virus. You don't know you were exposed because your immune system fights off the virus. However, your friend gets sick. He/she can serve as a host in which the virus mutates making it more virulent, which when you're exposed a second time, may make you sick.

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10: MACRONUTRIENT METABOLISM MICRONUTRIENTS

The macronutrient metabolism vitamins and minerals are:

- Thiamin
- Riboflavin
- Niacin
- Pantothenic Acid
- Vitamin B_6
- Biotin
- Vitamin B_{12}
- Vitamin C
- Iodine
- Manganese
- Magnesium

All but three of these will be covered in this section. You will learn about vitamin B_{12} in the one-carbon metabolism chapter and magnesium in the electrolyte chapter. You have learned about vitamin C in the antioxidant chapter. We are left with iodine, manganese, and many of the B vitamins. You will learn about the 2 minerals followed by the B vitamins in the next sections.

10.1: Iodine

10.2: Manganese

10.3: Thiamin

10.4: Riboflavin

10.5: Niacin

10.6: Pantothenic Acid

10.7: Vitamin B_6

10.8: Biotin

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10.1: Iodine

Why is iodine first in this chapter? Partly because it is a mineral (but so is manganese), but there is also a connection between iodine and selenium (last antioxidant in the previous chapter). Iodine's only, yet critical, function is that it is required for thyroid hormone synthesis. The figure below shows that the thyroid gland is a butterfly-shaped organ found in the neck. The parathyroid glands are also found within the thyroid gland.

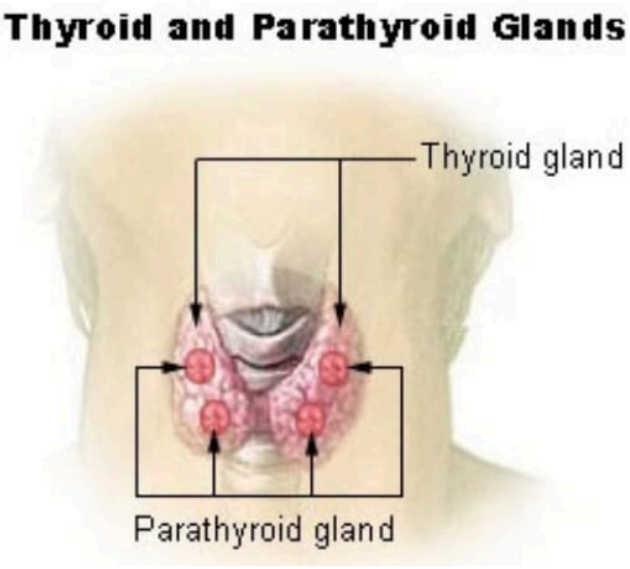


Figure 10.1.1: Location of thyroid and parathyroid glands[1]

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Iodine is found in foods primarily as iodide (I^-), some bread dough has iodate (IO_3^-) added to help with gluten cross-linking[2]. This used to be more commonly used in the past than it is now. Like selenium, iodide concentrations of the soil vary greatly, causing food concentrations to greatly fluctuate. Sea water is high in iodine, thus foods of marine origin, such as seaweed and seafood, are good dietary sources of iodine. Dairy products also tend to be good sources of iodide because it is added to cattle feed. Cattle receive iodine-containing medications, and iodide-containing sanitizing solutions are used in dairy facilities[3,4].

For most Americans, we consume ample iodine through the consumption of iodized salt. Consumption of 1/2 teaspoon of iodized salt meets the RDA for iodine. There is a global logo for iodized salt. However, I must admit that I do not recall ever seeing it myself.

The other link below is to a page that contains a scorecard map that depicts access to iodized salt worldwide. It also contains a Youtube video that displays the reduction in iodine deficiency over the last 2 decades.

Web Link

Global Iodized Salt Icon

Global Iodine Scorecard

Query 10.1.2

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Salt is iodized with either potassium iodide (KI) or potassium iodate ($\mathrm{KIO_3}$). The positives of each are:

Potassium iodide

- Less expensive
- Higher iodine content (76% vs. 59% for $\mathrm{KIO_3}$)
- More soluble

Potassium Iodate

- More stable

The U.S. uses potassium iodide, but the form, and amount, used varies from country-to-country. Most Americans' salt intake comes from processed foods, many of which are made with non-iodized salt. Iodine is well absorbed (~90%). Some dietary compounds interfere with thyroid hormone production or utilization. These compounds are known as goitrogens. However, it is not believed that goitrogens are of clinical importance unless there is a coexisting iodine deficiency[5].

Some examples of foods that contain goitrogens are[3,4,6]:

Cassava

The cassava plant is cultivated as an annual crop in tropical and subtropical regions for its edible starchy tuberous root. It is often called yuca in Spanish America and in the United States.



Figure 10.1.2: (left) Cassava plants are typically grown in tropical and subtropical environments.[6] (center) The cassava roots are what are typically eaten, but first they must be peeled. These are unprocessed[7] (right) Peeled cassava roots[8]

Millet

Millets are important crops in the semiarid tropics of Asia and Africa (especially in India, Mali, Nigeria, and Niger).



Figure 10.1.3: (left) Millet growing in a field9 (right) Millets10

Cruciferous Vegetables (broccoli, cabbage, Brussels sprouts)

Cruciferous vegetables are vegetables of the family *Brassicaceae* with many species being raised for food production including

- Onions
- Garlic
- Soybeans
- Peanuts

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Thyroid Hormone

The thyroid accumulates most absorbed iodine, keeping it for use to synthesize thyroid hormone. The following video shows the thyroid and describes its function.

YouTube Video

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View this YouTube Video online

Video 10.1.1: In this animation thyroid gland, its structure and function along with the hormones produced are described. https://www.youtube.com/watch?v=xKQa-MbZUPY

As mentioned in the video, the two primary forms of thyroid hormone are triiodothyronine (T3) and thyroxine (T4).

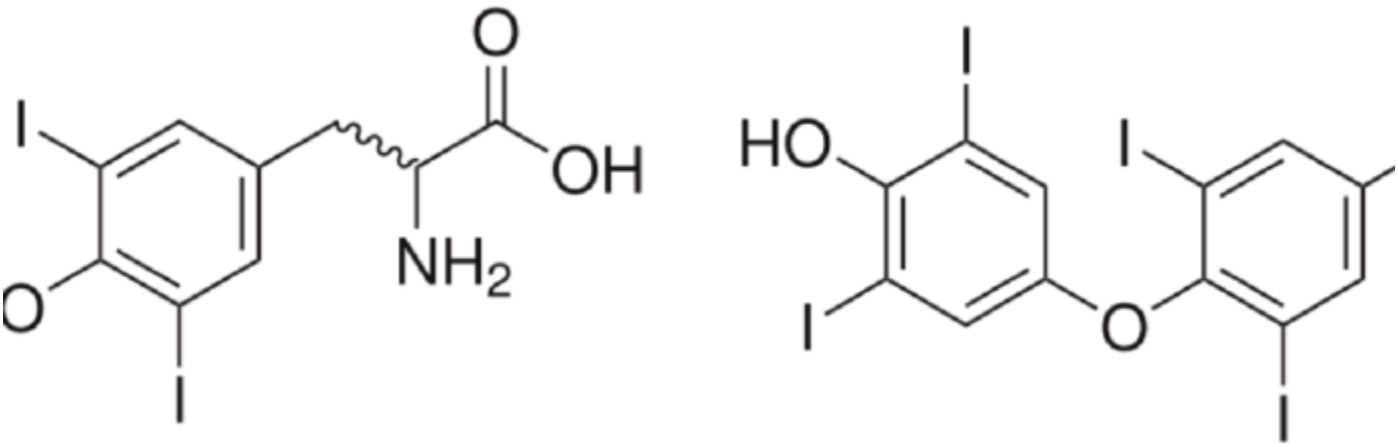


Figure 10.1.4: (left) The structure of triiodothyronine (T3)11 and (right) The structure of thyroxine (T4)12

T4 is the primary circulating form, and is really a prohormone that is converted to the active T3 form.

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The enzymes that metabolize thyroid hormones are known as deiodinases. There are three deiodinases (Type I , Type II, Type III) that are selenoenzymes whose location and function are summarized in the table below.

Table 10.1.1: Location and function of the three deiodinases13

Enzyme	Tissues	Function
Deiodinase Type I (DI1)	Liver, kidney, thyroid gland	Plasma T3 production
Deiodinase Type II (DI2)	Brain, pituitary, brown adipose	Local T3 production
Deiodinase Type III (DI3)	Brain, placenta	T3 degradation

Thyroid hormone regulates the basal metabolic rate and is important for growth and development. Thyroid hormone is particularly important for brain development, but hypothyroidism (low thyroid hormone) also leads to decreased muscle mass and skeletal development[13].

Query 10.1.5

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Iodine Deficiency & Toxicity

There are two iodine deficiency disorders (IDD): goiter and cretinism (also known as congenital hypothyroidism and congenital iodine deficiency syndrome). Goiter is a painless deficiency condition that results from the enlargement of the thyroid to help increase its ability to take up iodine. A couple of pictures of goiter are shown below.



Figure 10.1.5: Pictures of women with goiters[14,15]

A more serious consequence of iodine deficiency occurs during pregnancy to the fetus. Iodine deficiency during this time can lead to cognitive impairment and stunted growth and is known as cretinism. This condition is characterized by severe hypothyroidism, speech loss, and paralysis[13,16]. Proposed mechanisms have been attributed to the chronic consumption of poorly detoxified cassava, selenium deficiency, and the immune system causing thyroid dysfunction[17]. The following links show some examples of individuals with cretinism.

Web Link

Cretinism

The World Health Organization calls iodine deficiency "the world's most prevalent, yet easily preventable, cause of brain damage[18]." By saying it is easily preventable, they are referring to the ability of salt iodization to prevent brain development problems. The following New York Times article talks about how salt iodization may be the cheapest way to raise the world's IQ.

Web Link

In Raising the World's I.Q., the Secret's in the Salt

Iodine toxicity is rare, but like iodine deficiency, it can result in thyroid enlargement, and hypothyroidism or hyperthyroidism. Acute toxicity results in gastrointestinal irritation, abdominal pain, nausea, vomiting, and diarrhea2.

Query 10.1.6

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10.2: Manganese

We know far less about manganese than many other minerals. Like many minerals it serves as a cofactor for a number of enzymes that are discussed in more detail below.

The enzyme superoxide dismutase uses manganese as a cofactor to convert superoxide to hydrogen peroxide as shown below.

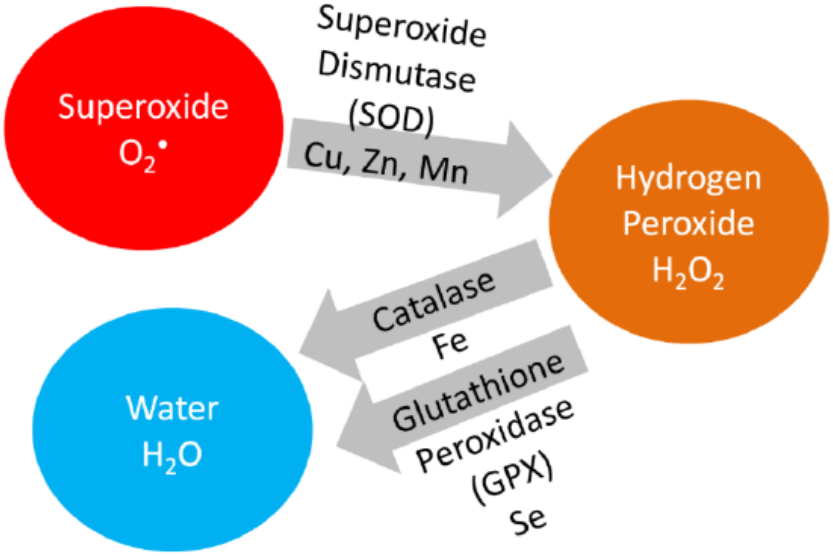


Figure 10.2.1: Antioxidant enzymes that use minerals as cofactors

In addition, both the enzymes involved in the gluconeogenesis oxaloacetate workaround use manganese as cofactors as shown below.

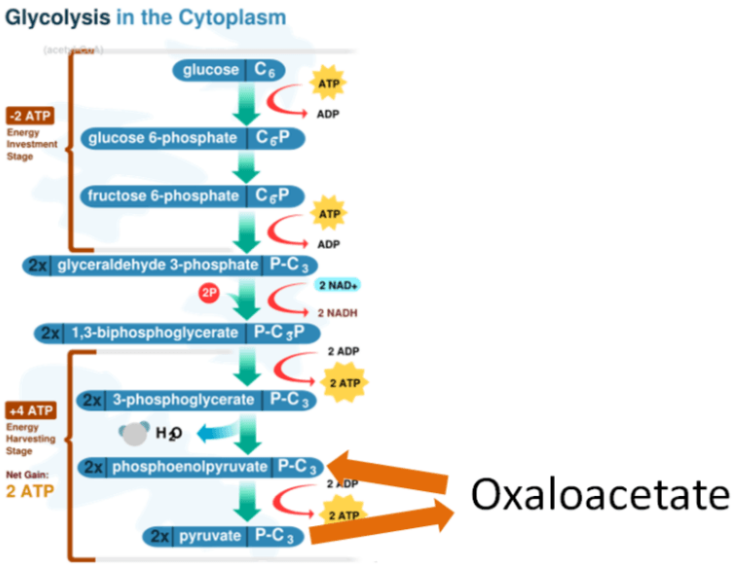


Figure 10.2.2: Both enzymes of the oxaloacetate workaround in gluconeogenesis use manganese as cofactors (Cc BY-SA 3.0; via Wikipedia)

One enzyme in the urea cycle uses manganese as a cofactor.

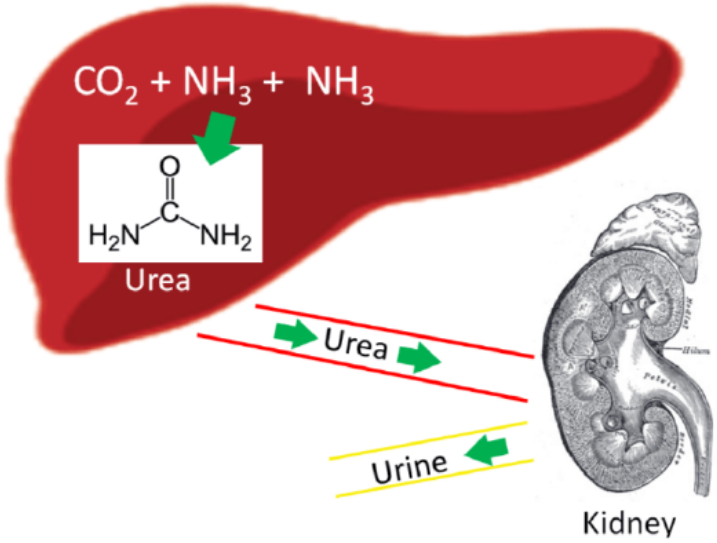


Figure 10.2.3: Production of urea helps to safely remove ammonia from the body2-4

Enzymes critical to the production of proteoglycans, which are essential components of cartilage and bone, use manganese as a cofactor5.

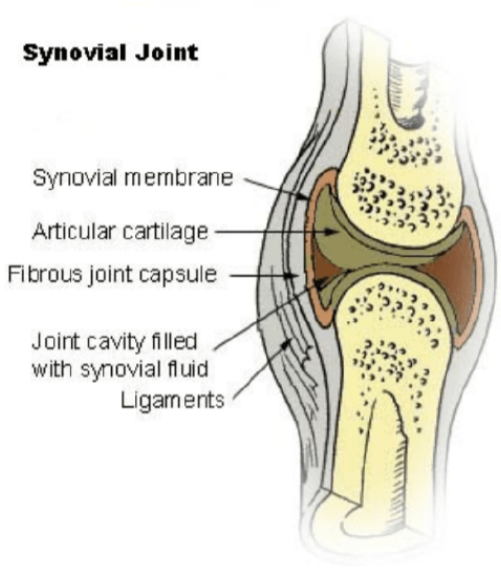


Figure 10.2.4: Cartilage serves as a cushion between joints6

Absorption of manganese is not well understood but is believed to be pretty low (<5%). It is mainly excreted (90%) through bile/feces5. Deficiency and toxicity of manganese is extremely rare. The deficiency is so rare in humans that there isn't much information available on the symptoms of the condition. Symptoms in those who were deliberately made deficient include vomiting, dermatitis, changes in hair color, & skeletal defects5. Toxicity symptoms include neurological disorders similar to schizophrenia and Parkinson's disease. In Chilean miners exposed to Mn-containing dust the toxicity was named Manganese Madness7,8. Some research suggests manganese toxicity is associated with iron deficiency because low iron levels allows for increased absorption of manganese9.

Query 10.2.1

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10.3: Thiamin

Thiamin (Vitamin B_1) structurally consists of 2 rings that are bridged together as shown below.

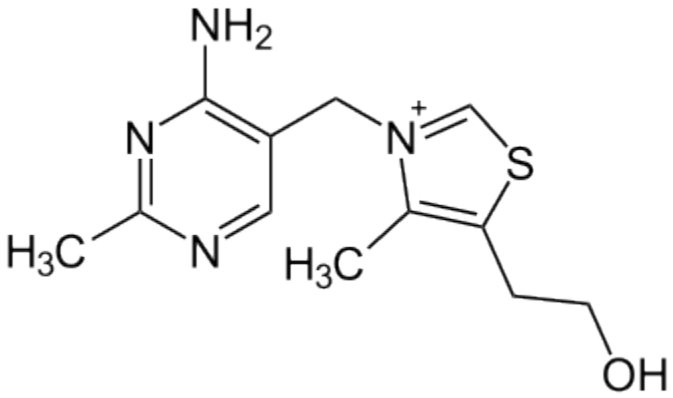


Figure 10.3.1: Structure of thiamin[1]

Since it was one of the original vitamins, (remember it was the primary part of Factor B), it was originally named thiamine (consistent with vitamine). The -e has since been dropped in its spelling. Thiamin is sensitive to heat, so prolonged heating causes the cleavage of thiamin between the 2 rings destroying its activity[2].

Like most of the B vitamins, thiamin's primary function is as a cofactor for enzymes. It is not thiamin alone that serves as a cofactor but instead thiamin diphosphate (thiamin + 2 phosphates), which is more commonly referred to as thiamin pyrophosphate (TPP). The structure of thiamin pyrophosphate is shown below.

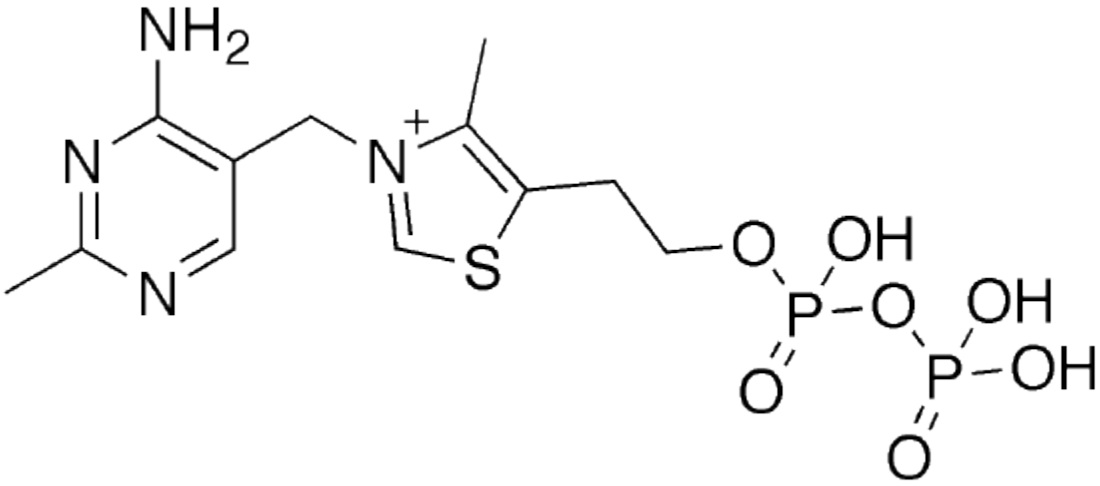


Figure 10.3.2: Structure of thiamin pyrophosphate (aka thiamin diphosphate)[3]

In plants, thiamin is found in its free form, but in animals it is mostly thiamin pyrophosphate. These phosphates must be cleaved before thiamin is taken up into the enterocyte[4].

Thiamin uptake and absorption is believed to be an efficient process that is passive when thiamin intake is high and active when thiamin intakes are low[4]. There are two thiamin transporters (THTR), THTR1 and THTR2, that are involved in thiamin uptake and absorption. THTR1 is found on the brush border and basolateral membrane, while THTR2 is only found on the brush border membrane as shown below[5].

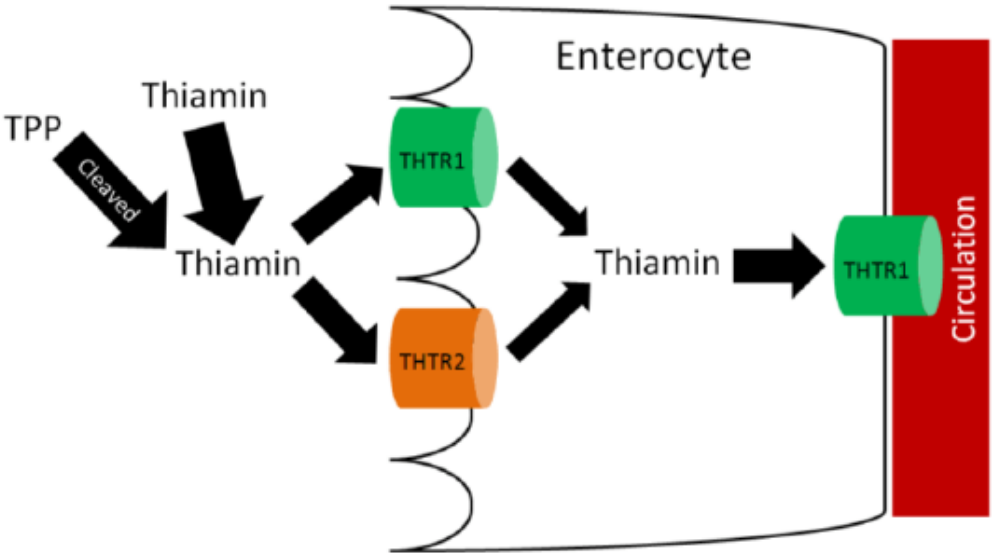


Figure 10.3.3: Thiamin uptake and absorption

Like most water-soluble vitamins there is little storage of thiamin.

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Thiamin Functions

There are three functions of thiamin[4]:

1. Cofactor for decarboxylation reactions (TPP)
2. Cofactor for the synthesis of pentoses (5-carbon sugars) and NADPH (TPP)
3. Membrane and nerve conduction (Not as a cofactor)

Decarboxylation Reactions

A decarboxylation reaction is one that results in the loss of carbon dioxide (CO_2) from the molecule as shown below.

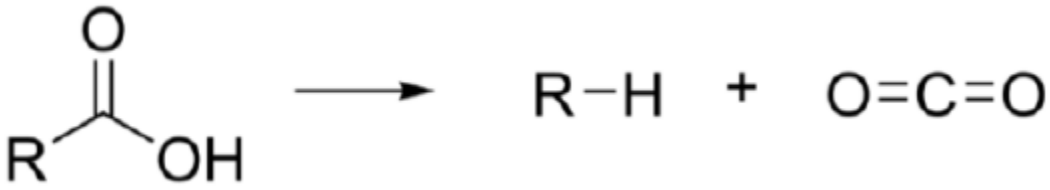


Figure 10.3.4: Decarboxylation reaction[6]

The transition reaction and one reaction in the citric acid cycle are decarboxylation reactions that use TPP as a cofactor. The figure below shows the transition reaction and citric acid cycle.

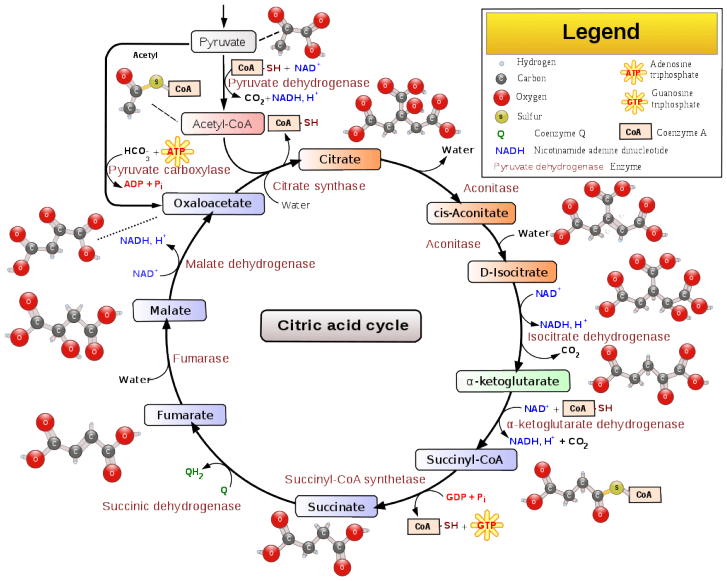


Figure 10.3.5: The transition reaction and citric acid cycle7

As shown below the conversion of pyruvate to acetyl CoA in the transition reaction is a decarboxylation reaction that requires TPP as a cofactor. CO_2 (circled) is produced as a result of this reaction.

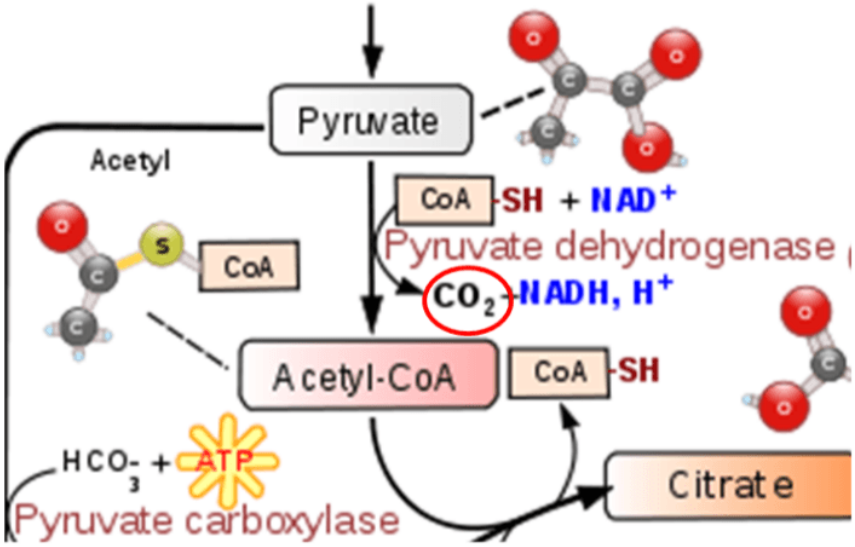


Figure 10.3.6: The transition reaction requires TPP as a cofactor7

A similar TPP decarboxylation reaction occurs in the citric acid cycle converting alpha-ketoglutarate to succinyl-CoA . CO_2 (circled) is given off as a result of this reaction.

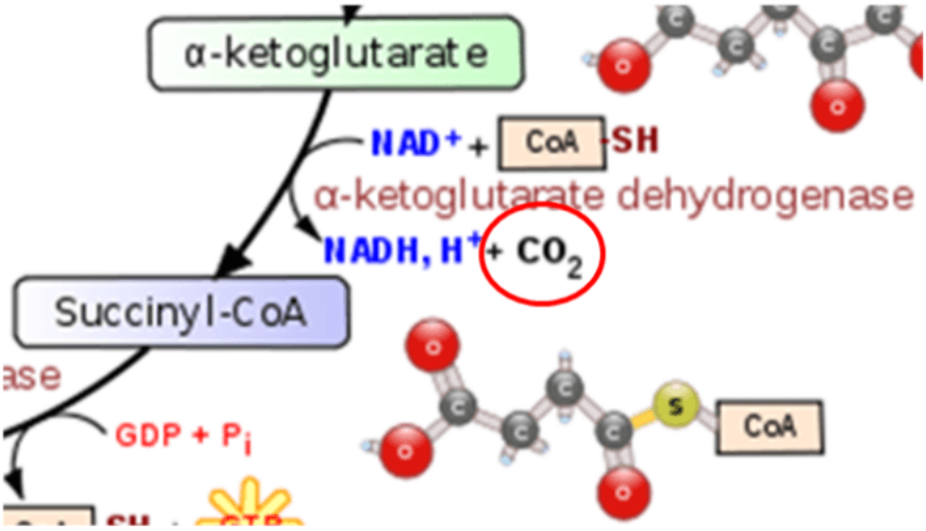


Figure 10.3.7: Alpha-ketoglutarate dehydrogenase requires TPP as a cofactor[7]

TPP also functions as a cofactor for the decarboxylation of valine, leucine, and isoleucine (branched-chain amino acids)[4].

Synthesis of Pentoses and NADPH

TPP is a cofactor for the enzyme transketolase. Transketolase is a key enzyme in the pentose phosphate (aka hexose monophosphate shunt) pathway. This pathway is important for converting 6-carbon sugars into 5-carbon sugars (pentose) that are needed for synthesis of DNA, RNA, and NADPH. In addition, pentoses such as fructose are converted to forms that can be used for glycolysis and gluconeogenesis[8]. Transketolase catalyzes multiple reactions in the pathway as shown below.

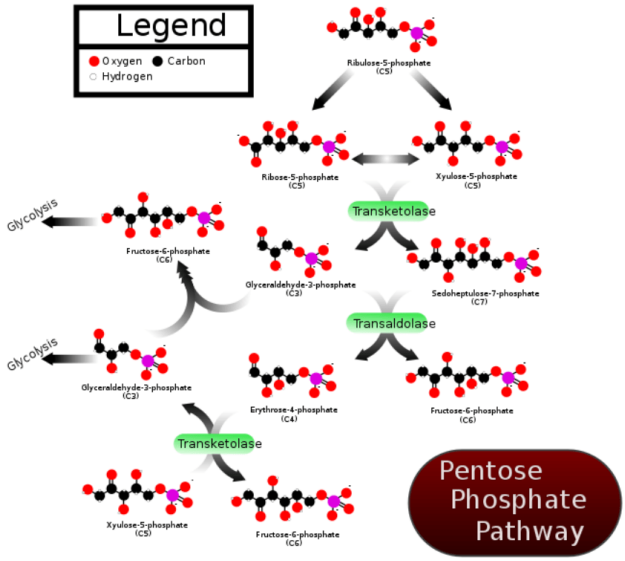


Figure 10.3.8: Transketolase in the pentose phosphate pathway uses TPP as a cofactor[9]

Membrane and Nerve Conduction

In addition to its cofactor roles, thiamin, in the form of thiamin triphosphate (TTP, 3 phosphates), is believed to contribute in some unresolved way to nervous system function[6].

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Thiamin Deficiency & Toxicity

Thiamin deficiency is rare in developed countries, but still occurs in poorer countries where white (aka polished) rice is a staple food. During the polishing process, thiamin, and many other nutrients, are removed. Some people also have a mutation in THTR1 that causes them to become thiamin deficient[10]. Thiamin deficiency is known as beriberi, which, when translated, means "I can't, I can't." The symptoms of beriberi are illustrated in the link below.

There are two major forms of beriberi: dry and wet. Dry beriberi affects the nervous system, with symptoms such as loss of muscle function, numbness, and/or tingling. Wet beriberi affects the cardiovascular system resulting in pitting edema, along with enlargement of the heart[10]. A picture of a person with beriberi is shown below.

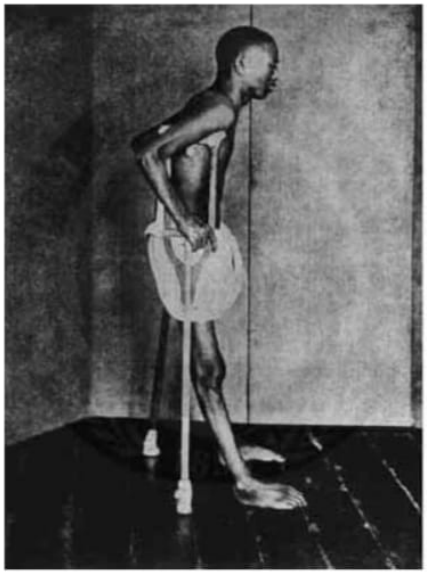


Figure 10.3.9: A person suffering from beriberi[11]

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Another group that is at risk for thiamin deficiency is alcoholics. There are three reasons why alcoholics are prone to becoming deficient[12]:

1. Alcohol displaces foods that are better sources of thiamin
2. Liver damage decreases TPP formation

3. Increased thiamin excretion

The thiamin deficiency found in alcoholics is known as Wernicke-Korsakoff Syndrome. Symptoms of this condition include paralysis or involuntary eye movement, impaired muscle coordination, memory loss and confusion3. The following video shows some of the symptoms of this condition.

YouTube Video

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Video 10.3.1: Wernicke-Korsakoff Syndrome (First 1:50). https://www.youtube.com/watch?v=wDcyBXJAZNM

Thiamin toxicity has never been reported as a result of oral intake. Thus, there is little worry about thiamin toxicity13.

Query 10.3.4

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10.4: Riboflavin

A student once asked this question:

> *"I started taking the Mega Man Sport Multi-vitamin from GNC and about an hour or two after consumption, with a meal, my pee is bright, practically neon yellow. What does that mean?"*

Since this question is leading off the riboflavin section, you have probably surmised that riboflavin is somehow involved. Indeed, flavin means yellow in Latin, and riboflavin is bright yellow as shown in Figure 10.4.1.



Figure 10.4.1: Riboflavin in solution[1]

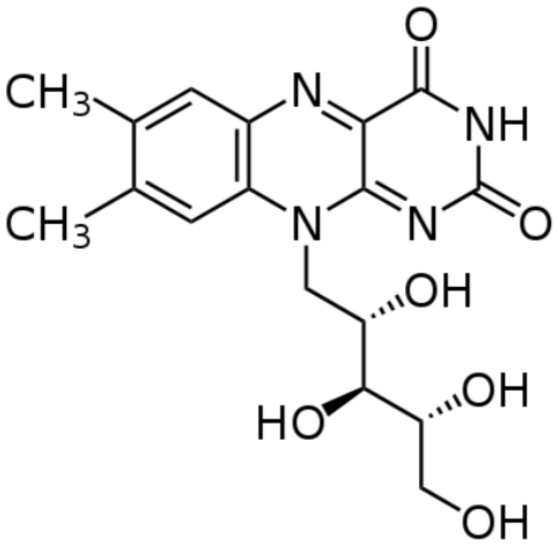


Figure 10.4.2: Structure of riboflavin[2]

Riboflavin is a water-soluble B vitamin, so the student was excreting large amounts of riboflavin in his urine, leading it to become "bright, practically neon yellow." The structure of riboflavin is shown in Figure 10.4.2.

Riboflavin is important for the production of two cofactors: flavin adenine dinucleotide (FAD) & flavin mononucleotide (FMN).

FAD has been introduced before, but structurally you can see where riboflavin is within the compound below.

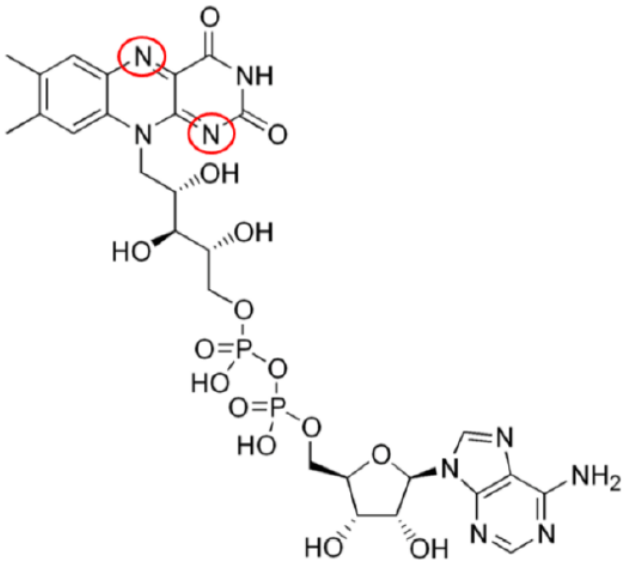


Figure 10.4.3: Structure of FAD[3]

The 2 circled nitrogens are the sites that accept hydrogen to become $FADH_2$ as illustrated below.

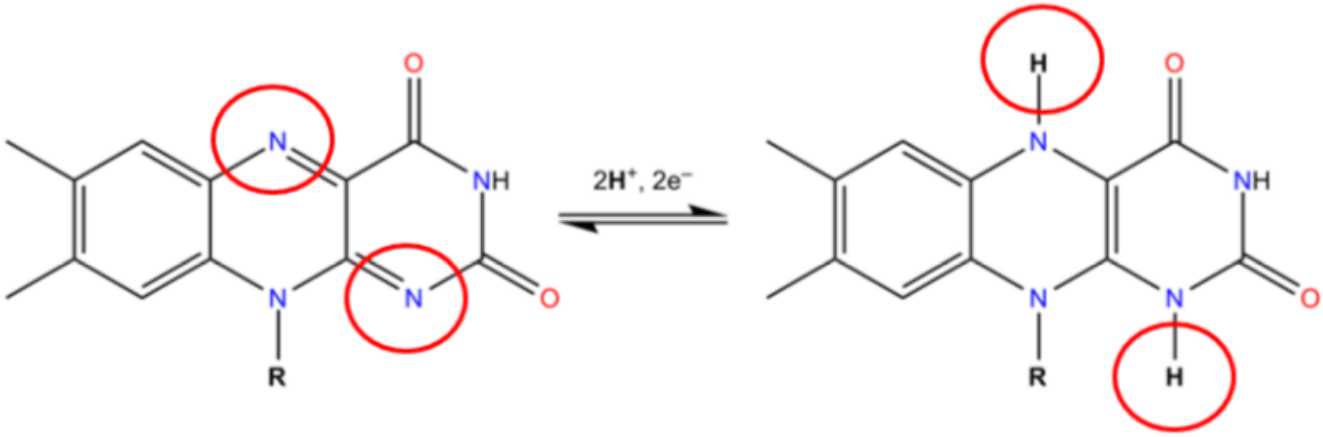


Figure 10.4.4: Addition of two hydrogens to the rings of FAD to form $FADH_2$[4]

The structure of FMN as shown below, is similar to FAD, except that it only contains one phosphate group (versus 2) and doesn't have the ring structures off the phosphate groups that are found in FAD.

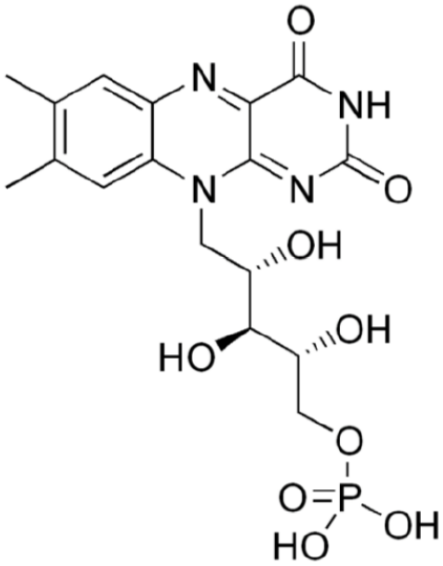


Figure 10.4.5: The structure of FMN[5]

Riboflavin is photosensitive, meaning that it can be destroyed by light. This was a problem in the old days when the milkman delivered milk in clear glass bottles. These have now been replaced by cartons or opaque plastic containers to help protect the riboflavin content of the milk.



Figure 10.4.6: Milk is no longer packaged in clear glass bottles to help protect its riboflavin from light destruction

Riboflavin in foods is free, protein-bound, or in FAD or FMN. Only free riboflavin is taken up so it must be cleaved, or converted before absorption[6]. Riboflavin is highly absorbed through an unresolved process, though it is believed that a carrier is involved[7]. As you would guess from the description above, riboflavin is primarily excreted in the urine.

Query 10.4.1

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Riboflavin Functions

Riboflavin is required for the production of FAD and FMN. Below are some of the functions of FAD and FMN6:

Citric Acid Cycle

FAD is reduced to $FADH_2$ in the citric acid cycle when succinate is converted to fumarate by succinic dehydrogenase as circled below.

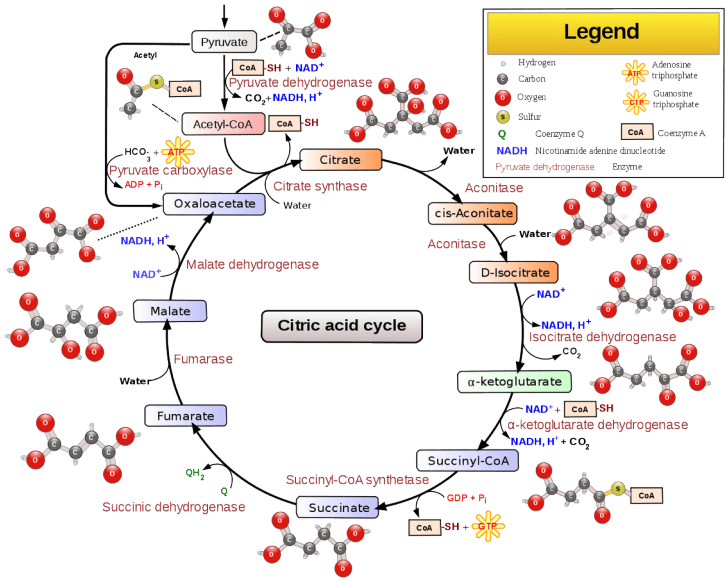


Figure 10.4.7: The citric acid cycle requires FAD8

Electron Transport Chain

Under aerobic conditions, the electron transport chain is where the $FADH_2$ is used to produce ATP. Complex I of the electron transport chain includes an FMN molecule. The electron transport chain is shown below.

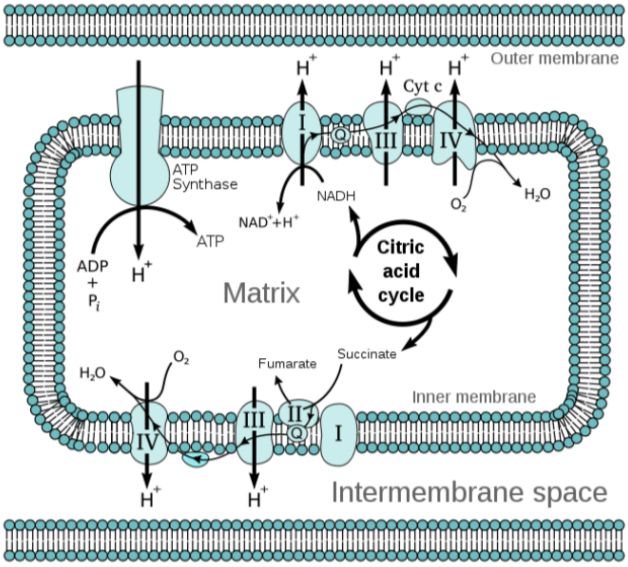


Figure 10.4.8: Complex I in the electron transport chain contains FMN9

Fatty Acid oxidation

During fatty acid oxidation FAD is converted to $FADH_2$ as shown below.

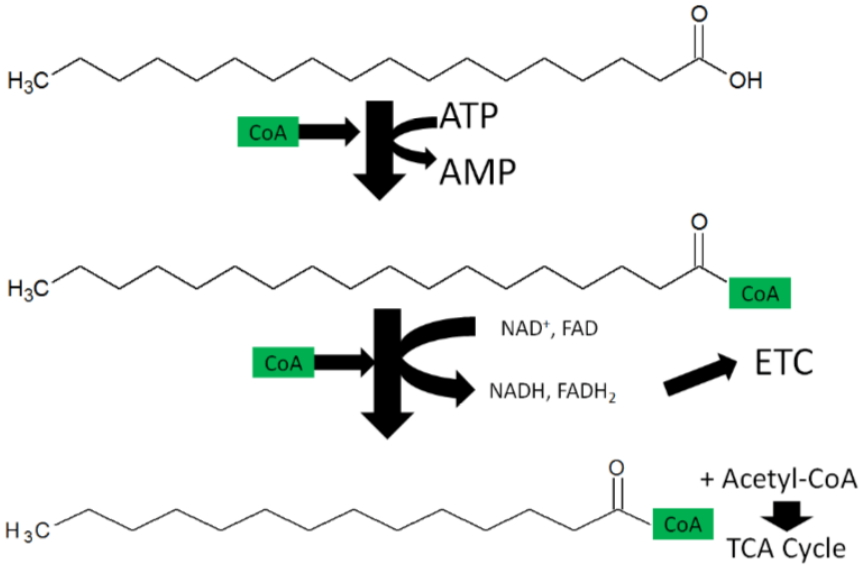


Figure 10.4.9: Fatty acid oxidation requires FAD

Niacin synthesis

As you will hear more about in the niacin section, niacin can be synthesized from tryptophan as shown below. An intermediate in this synthesis is kynurenine, and one of the multiple steps between kynurenine to niacin requires FAD.

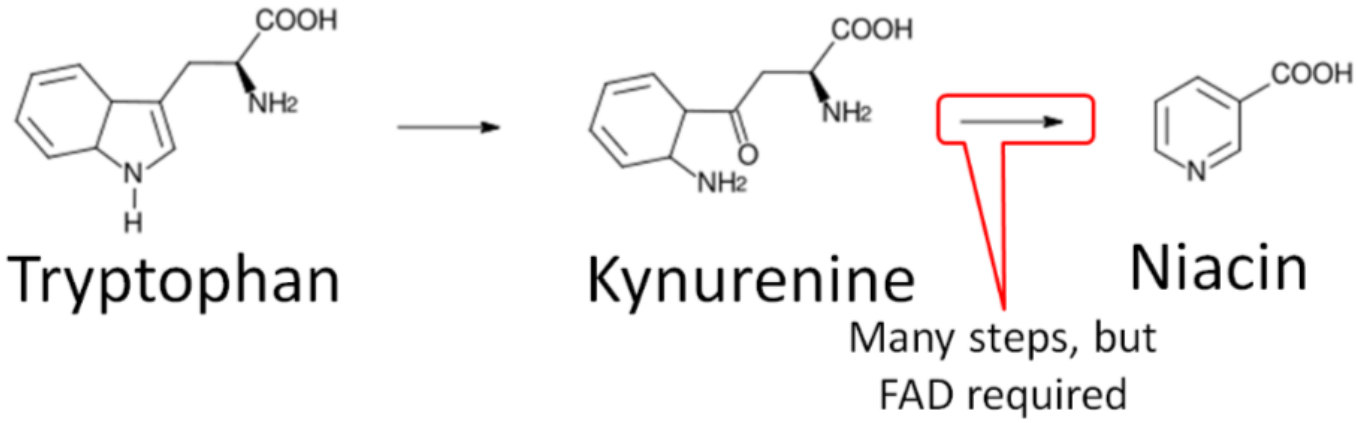


Figure 10.4.10: Niacin synthesis from tryptophan requires FAD[10]

Vitamin B_6 Activation

The enzyme that creates the active form of vitamin B_6 (pyridoxal phosphate) requires FMN.

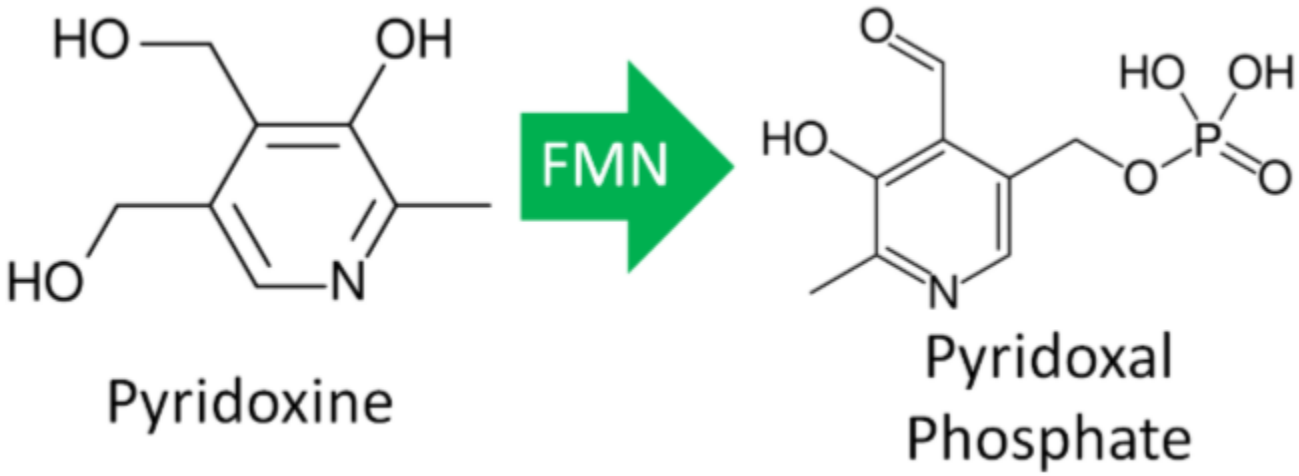


Figure 10.4.11: Vitamin B_6 activation requires FMN[11,12]

Neurotransmitter Catabolism

The enzyme monoamine oxidase (MAO) requires FAD. This enzyme shown below is important in the catabolism of neurotransmitters such as dopamine and serotonin.

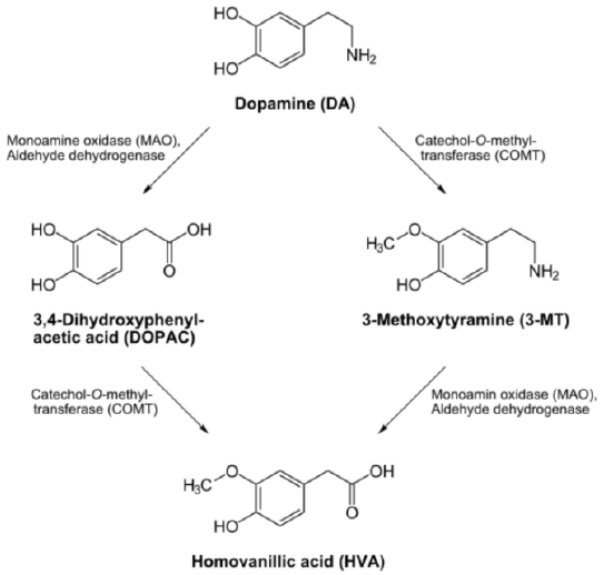


Figure 10.4.12: Catabolism of dopamine involves monoamine oxidase, an enzyme that requires FAD13

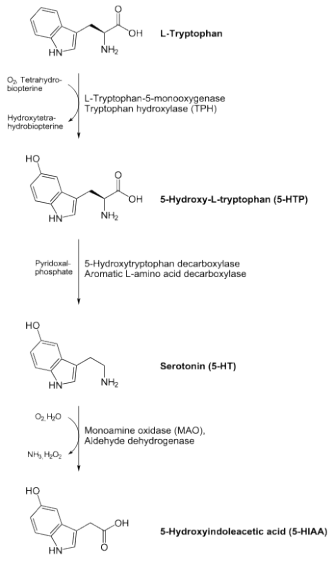


Figure 10.4.13: Catabolism of serotonin involves monoamine oxidase, an enzyme that requires FAD14

Antioxidant Enzymes

The antioxidant enzymes glutathione reductase and thioredoxin reductase both require FAD as a cofactor. Thioredoxin reductase is a selenoenzyme. The function of glutathione reductase is shown in the following link. Glutathione reductase can reduce glutathione that can then be used by the selenoenzyme glutathione peroxidase to convert hydrogen peroxide to water.

Web Link

The Glutathione Oxidation Reduction (Redox) Cycle

In addition to the functions listed above, FAD is also used in folate activation, choline catabolism, and purine metabolism6.

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Riboflavin Deficiency & Toxicity

Ariboflavinosis, riboflavin deficiency, is a rare condition that often occurs with other nutrient deficiencies. The symptoms of this condition are shown in the figure below.

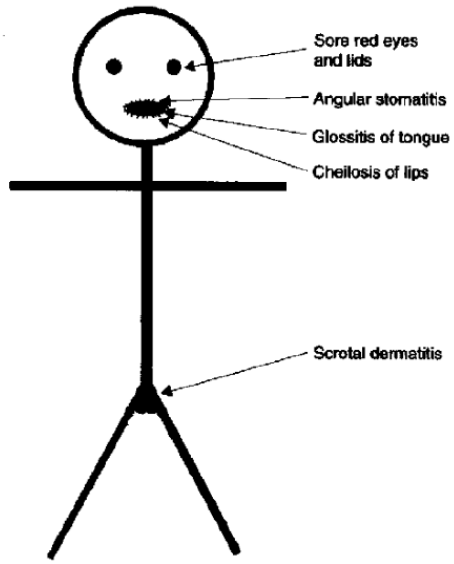


Figure 10.4.14: The symptoms of riboflavin deficiency15

The most notable symptoms include angular stomatitis (aka angular cheilitis, cheilosis), which is a lesion or cracking that forms at the corners of the mouth as shown below.

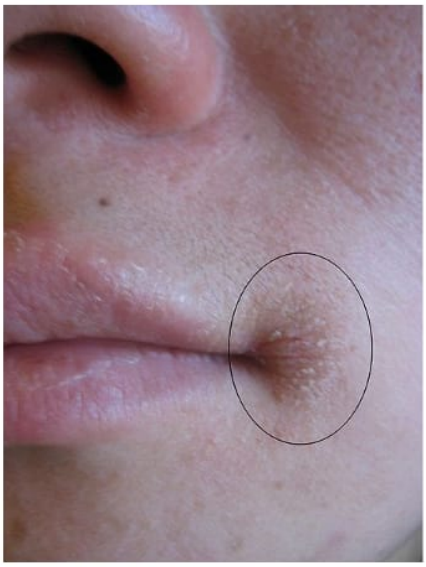


Figure 10.4.15: Angular Cheilitis[16]

Glossitis is the inflammation of the tongue, which can be accompanied by redness or inflammation of the oral cavity. Dermatitis (skin inflammation) is also frequently a symptom[6,17]. Rare reports of riboflavin toxicity has resulted in optic problems[18].

Query 10.4.3

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12. https://courses.lumenlearning.com/suny-nutrition/chapter/10-7-vitamin-b6/
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10.5: Niacin

There are two forms of niacin: nicotinic acid and nicotinamide (aka niacinamide), that have a carboxylic acid group or amide group, respectively. The structure of nicotinic acid and nicotinamide are shown below.

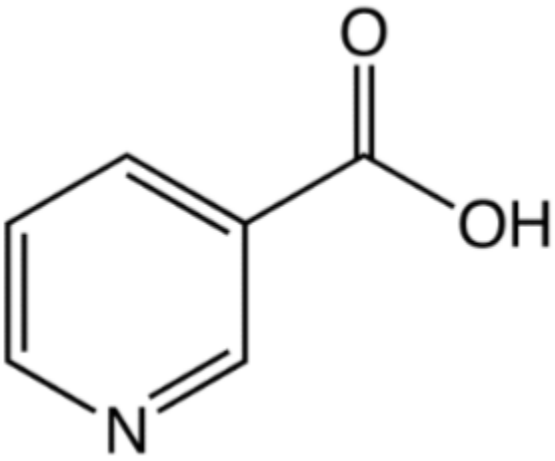


Figure 10.5.1: Structure of nicotinic acid[1]

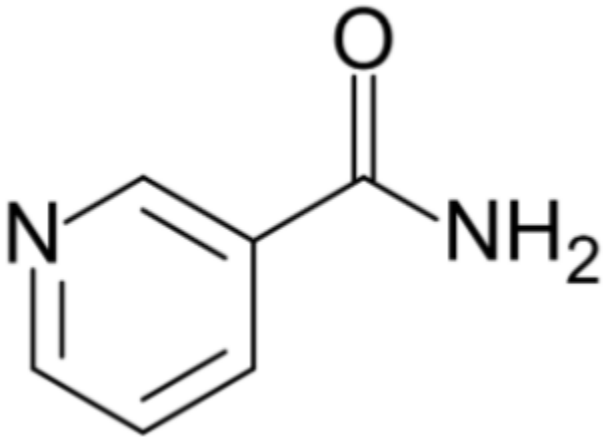


Figure 10.5.2: Structure of nicotinamide[2]

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Niacin is important for the production of two cofactors: nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate ($NADP^+$). The structure of NAD is shown below; you can clearly see the nicotinamide at the top right of the molecule.

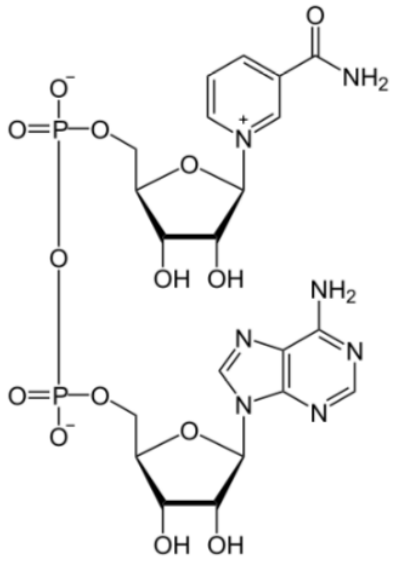


Figure 10.5.3: Structure of NAD[3]

NAD is reduced to form NADH, as shown below.

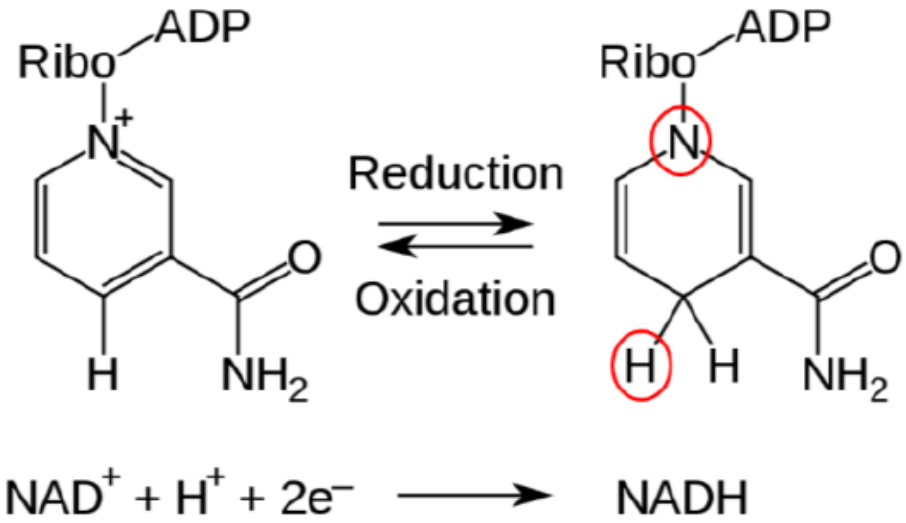


Figure 10.5.4: Reduction of NAD to NADH[4]

The structure of $NADP^+$ is exactly the same as NAD, except it has an extra phosphate group off the bottom of the structure, as shown below.

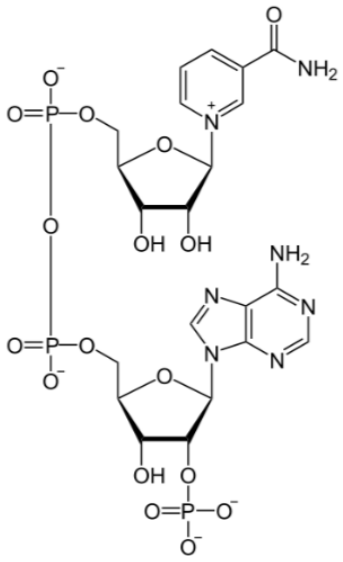


Figure 10.5.5: Structure of $NADP^+$[5]

Like NAD, $NADP^+$ can be reduced to NADPH.

Query 10.5.2

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Niacin is unique in that it can be synthesized from the amino acid tryptophan as shown below. An intermediate in this synthesis is kynurenine. Many reactions occur between this compound and niacin, and riboflavin and vitamin B_6 are required for two of these reactions.



Figure 10.5.6: Tryptophan can be used to synthesize niacin[6]

To account for niacin synthesis from tryptophan, **niacin equivalents (NE)** were created by the DRI committee to account for the amount of niacin in foods as well as their tryptophan content. It takes approximately 60 mg of tryptophan to make 1 mg of niacin. Thus, the conversions to niacin equivalents are:

$$1\,mg\,\text{Niacin} = 1\,NE \tag{10.5.1}$$

$$60\,mg\,\text{Tryptophan} = 1\,NE \tag{10.5.2}$$

The tryptophan levels of most foods is not known, but a good estimate is that tryptophan is 1% of amino acids in protein[7]. Thus, lets take peanut butter, smooth style, with salt as an example[8].

Example 10.5.1: Peanut Butter

The peanut butter contains 13.403 mg of niacin and 25.09 g of protein[8].

Step 1: Calculate the amount of tryptophan:

$$25.09\,g \times 0.01(\text{the numerical value of } 1 = 0.2509\,g \text{ of tryptophan}$$

Step 2: Convert Grams to Milligrams

$$0.2509\,g \times 1000\,mg/g = 250.9\,mg \text{ of tryptophan}$$

Step 3: Calculate NE from tryptophan (Equation 10.5.2)

$$\frac{250.9\,mg \text{ of tryptophan}}{60\,mg \text{ of tryptophan}/1NE} = 4.182\,NE$$

Step 4: Add NEs together

$$13.403\,NE\,(\text{from niacin}) + 4.182\,(\text{from tryptophan}) = 17.585\,NE$$

Query 10.5.3

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Most niacin we consume is in the form of nicotinamide and nicotinic acid[9], and in general is well absorbed using an unresolved carrier[10]. However, in corn, wheat, and certain other cereal products, niacin bioavailability is low. In these foods, some niacin (~70% in corn) is tightly bound, making it unavailable for absorption. Treating the grains with a base frees the niacin and allows it to be absorbed. After absorption nicotinamide is the primary circulating form[7,9].

Query 10.5.4

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Niacin Functions

Approximately 200 enzymes require NAD or NADP^+. We will go through some selected functions of NAD and NADP^+. The following figures and legends show and describe the functions of NAD and NADP^+.

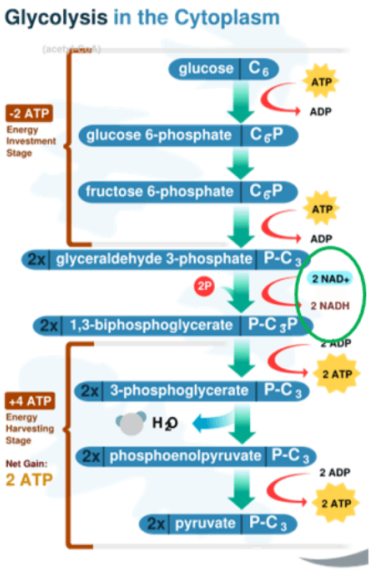


Figure 10.5.7: NAD is required for glycolysis[11]

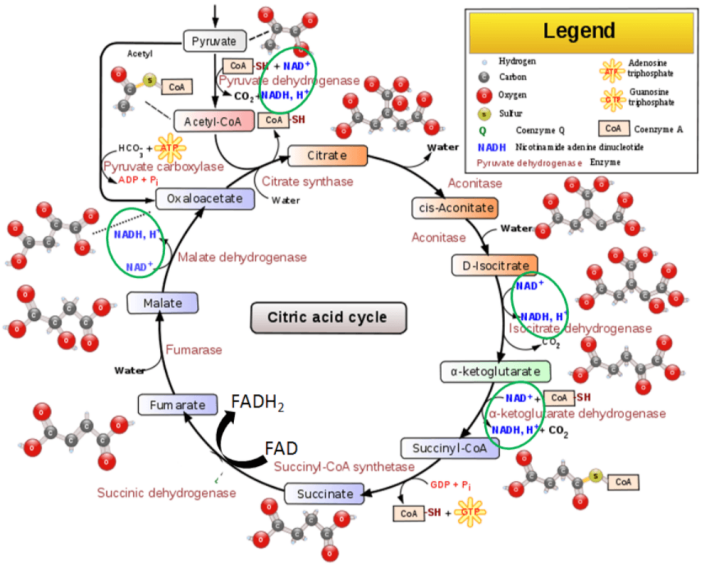


Figure 10.5.8: NAD is required for the transition reaction and at three different points in the citric acid cycle[12]

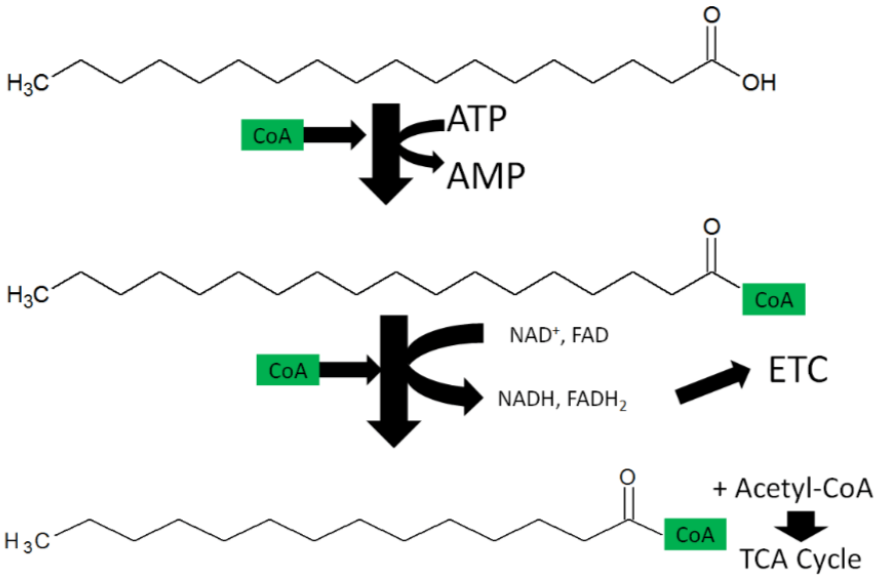
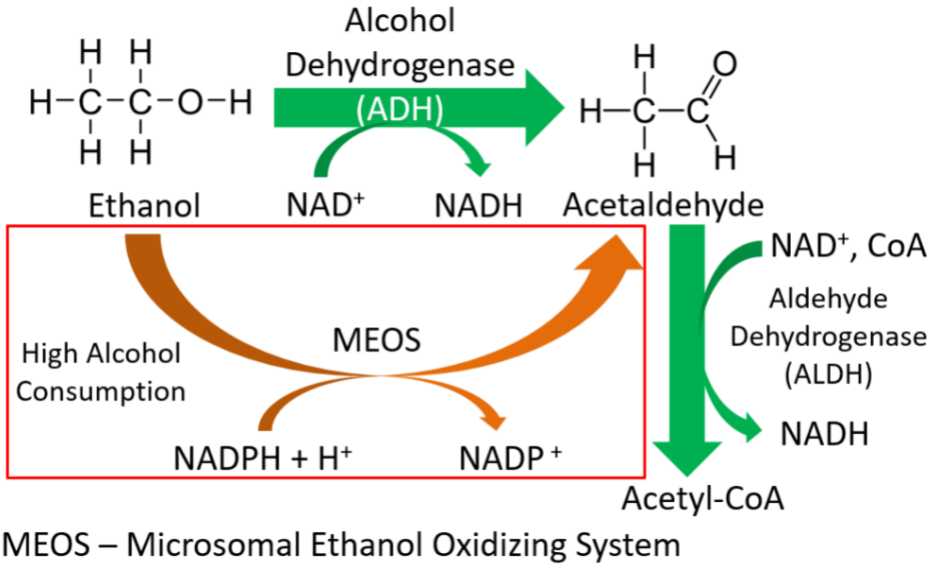


Figure 10.5.9: NAD is required for fatty acid oxidation



MEOS – Microsomal Ethanol Oxidizing System

Figure 10.5.10: Alcohol oxidation; NAD is required by alcohol dehydrogenase, and the MEOS uses NADPH[13,14]

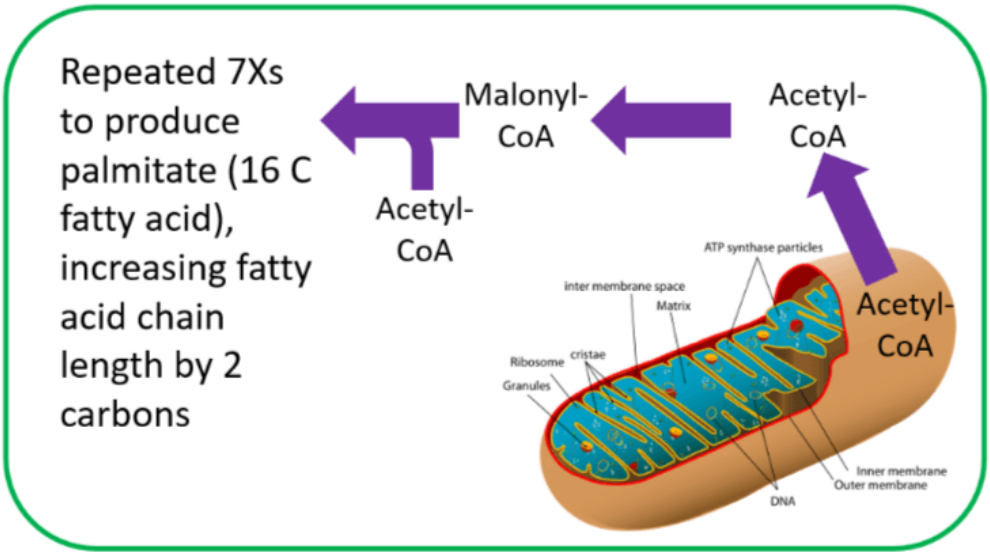


Figure 10.5.11: Fatty acid synthesis uses NADPH[15]

HMG CoA reductase, the rate-limiting enzyme in cholesterol synthesis, uses NADPH. NADPH is also used by the antioxidant enzyme glutathione reductase as shown in the link below[9].

Web Link

The Glutathione Oxidation Reduction (Redox) Cycle

Query 10.5.5

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Niacin Deficiency & Toxicity

Pellagra is a niacin deficiency. This is no longer a common deficiency in developed countries, but was in the U.S. in the early 1900s. This was because corn was a staple crop, meaning it was what people primarily consumed. The bioavailability of niacin from corn is poor unless treated with a base to release the bound niacin. The symptoms of pellagra are the 3 D's:

- Dementia
- Dermatitis
- Diarrhea

Some refer to 4 D's in which the 4th D is death if the condition is not managed. The following pictures show the symptoms of pellagra.

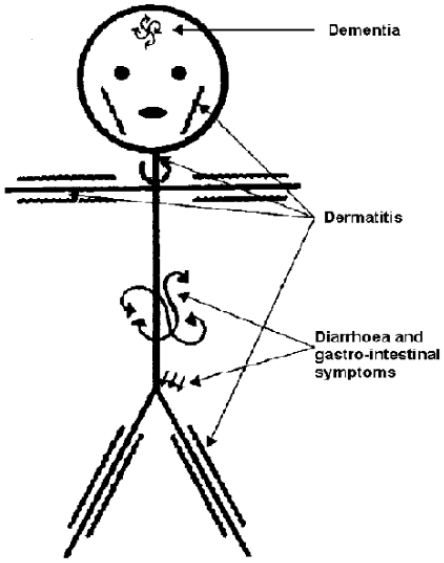


Figure 10.5.12: The 3 D's of pellagra[16]



Figure 10.5.13: A man with pellagra; notice the dermatitis on his arms[17]

The link below shows another picture of a person suffering from dermatitis as a result of pellagra.

Web Link

Pellagra

Query 10.5.6

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Dietary niacin toxicity is rare. However, nicotinic acid (not) can improve people's lipid profiles when consumed at levels far above the RDA. For instance the RDA and upper limit (UL) is 14 or 16 (women & men) and 35 mg (both), respectively. Many people are taking 1-2 grams (up to 6 g/day) to get the benefits in their plasma lipid profiles as shown in the table below[7,9.]

Table 10.5.1: Effects of nicotinic acid (>1.5 g/day) on plasma lipid profile[18]

Measure	Change
VLDL	↓ 25-40%
LDL	↓ 6-22%
HDL	↑ 18-35%
Total Cholesterol	↓ 21-44%
Triglycerides	↓ 21-44%

It should be pointed out that there are special supplements for this purpose that include a slower release nicotinic acid that helps prevent the toxicity symptoms (nicotinamide is not toxic). A slow (aka long or extended) release form of niacin for people with atherosclerosis is Niaspan®. The link below is to Niaspan's site.

Web Link

Niaspan®

A study found that Niaspan plus a statin was no better than a statin alone in preventing heart attacks, despite improvements in HDL and triglyceride concentrations. This result challenged the understanding of the importance of HDL and triglyceride concentrations to heart attack risk. The link below explains this study's results.

Web Link

Niacin Drugs Don't Reduce Heart Attack Risk

The most well known of the toxicity symptoms is "niacin flush", which is a dilation of capillaries accompanied by tingling that can become painful. This symptom is noted to occur at lower levels than the other toxicity symptoms[19]. Other symptoms include:

- Gastrointestinal Distress
- Liver Damage

A nicotinic acid receptor GPR109A, which is present in adipocytes and immune cells, is believed to mediate niacin flush, but the beneficial effects on lipid profiles do not appear to be mediated by it[20,21]. It is not clear at this time the mechanism of action for the improvements in lipid profiles[20]. However, it appears that the nicotinic acid receptor stated above (GPR109A) increases glucose uptake in the intestine. Pharmacological levels of 1-3g of nicotinic acid administration has been found to result in a rapid reduction of high levels of blood lipids[22]. However, the increased glucose uptake and rapid reduction in lipid levels has been suggested to lead to a prediabetic state when ingesting these high pharmacological levels more than 100 times the RDA. Thus, nicotinic acid administration needs to be carefully prescribed and monitored by a physician.

Based on the benefits of nicotinic acid supplementation on blood lipid level, you might think this is an ideal candidate for treatment of diabetes or cardiovascular disease. Research investigating nicotinic acid supplementation on both of these disease states has found positive and negative impacts on participants. Although, at first glance nicotinic acid supplementation appears very promising, the detrimental effects on the glucose system are too great for nicotinic acid to be a long term cure. Several clinical trials have investigated the impacts of nicotinic acid supplementation in diabetic patients and patients with cardiovascular disease. The primary outcome of improved lipid levels was observed, however, at the cost of glucose response. Multiple studies observed an increase in the risk of developing diabetes following nicotinic acid supplementation. The lipid levels were corrected, albeit at the expense of poor glucose function. This research has shown the importance of nicotinic acid in improving lipid levels and therefore is currently used in combination with other drugs to improve lipid levels in patients[23].

Query 10.5.7

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10.6: Pantothenic Acid

Pantothenic acid has two roles in the body:

1. It is part of coenzyme A (CoA), this is its major role
2. It is part of acyl carrier protein

Coenzyme A

The structure of pantothenic acid is shown alone below and circled within coenzyme A.

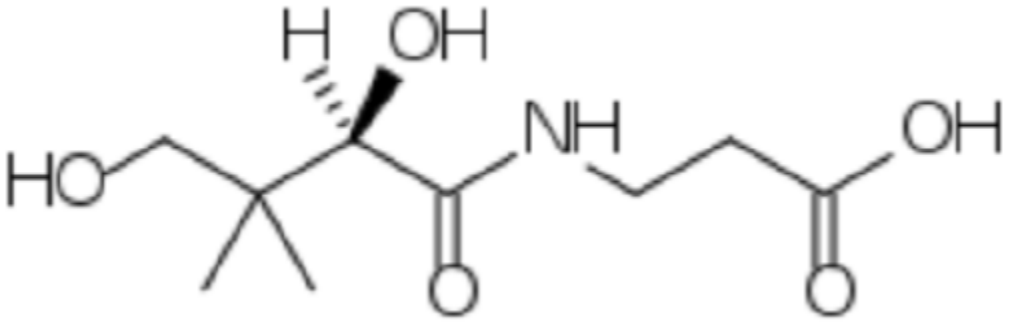


Figure $10.6.1$: The structure of pantothenic acid[1]

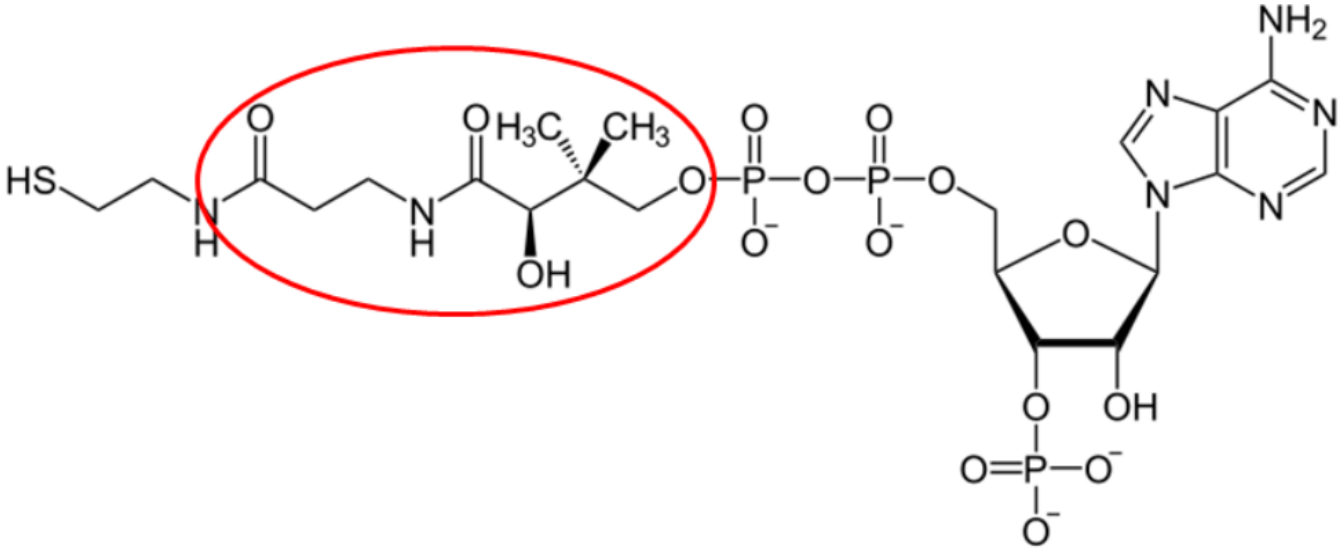


Figure $10.6.2$: The structure of coenzyme A (CoA) with pantothenic acid circled[2]

The functions of CoA are shown and described below[3].

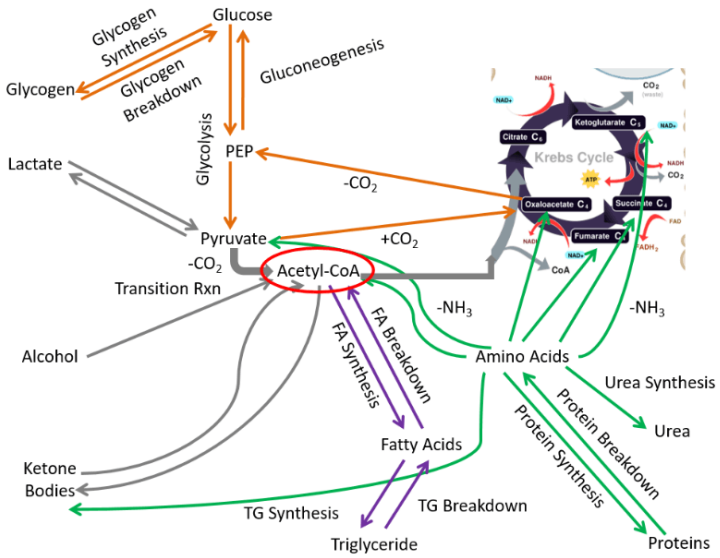


Figure 10.6.3: Acetyl-CoA is a central point in metabolism, and contains CoA[4]

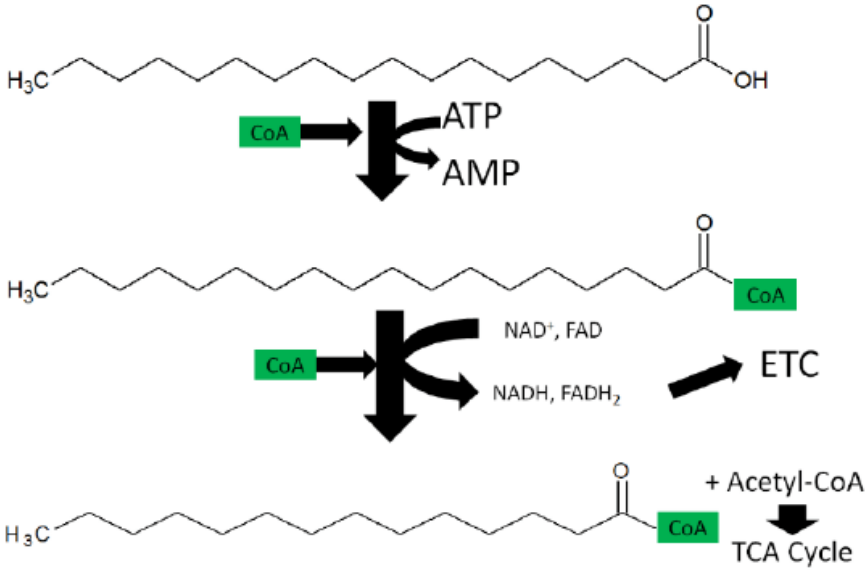


Figure 10.6.4: CoA is used in fatty acid oxidation. The fatty acid is activated by adding CoA, forming acyl-CoA.

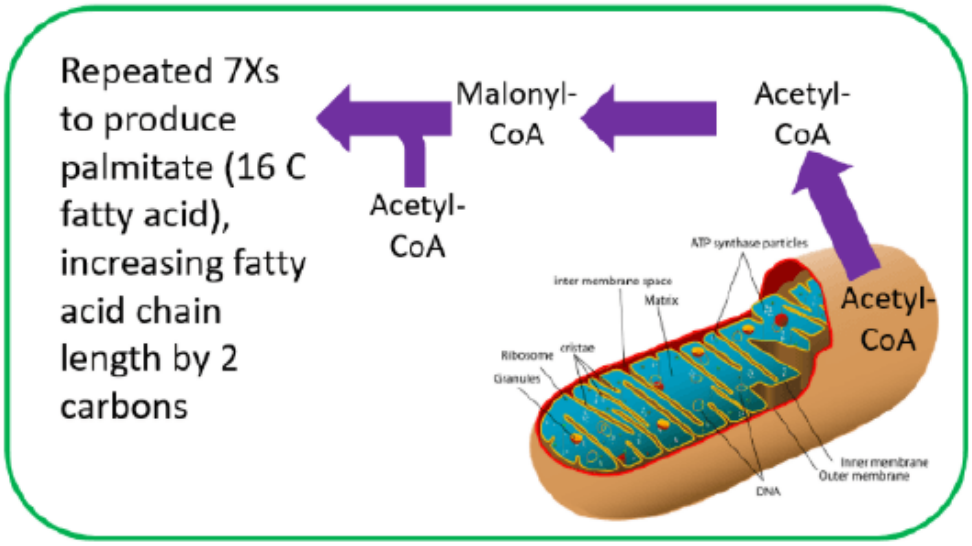


Figure 10.6.5: Fatty acid synthesis uses CoA5

Acyl Carrier Protein

Acyl carrier protein, is also important in fatty acid synthesis3.

Most pantothenic acid in food is found as CoA, which is cleaved prior to absorption. It is then taken up into the enterocyte through the sodium-dependent multivitamin transporter (SMVT) as shown below. Approximately 50% of pantothenic acid is absorbed; it is excreted primarily in urine3.

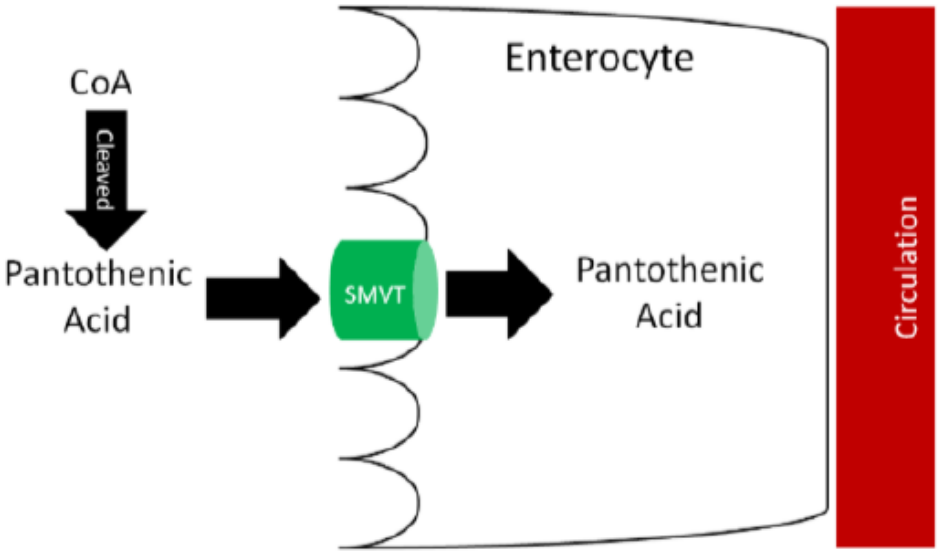


Figure 10.6.6: The absorption of pantothenic acid

Deficiency of pantothenic acid is very rare. Pantothenic acid supplementation did relieve the symptoms (burning feet and numbness of toes) of "burning feet syndrome" in prisoners in World War II6. It is believed that pantothenic acid deficiency was the cause of this syndrome. Other symptoms noted are vomiting, fatigue, weakness, restlessness, and irritability3. No toxicity has been reported.

Query 10.6.1

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References

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10.7: Vitamin B_6

Vitamin B_6 is composed of three compounds: pyridoxine, pyridoxal, and pyridoxamine. Pyridoxine contains a methylhydroxyl group ($-\mathrm{CH_3OH}$), pyridoxal an aldehyde ($-\mathrm{CHO}$), and pyridoxamine an aminomethyl group ($-\mathrm{CH_3NH_2}$), as shown below.

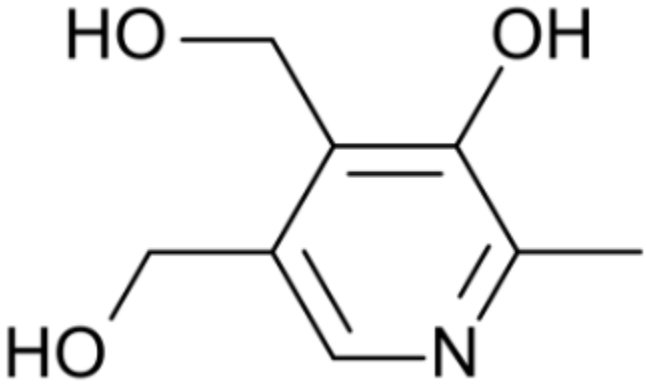


Figure $10.7.1$: Structure of pyridoxine[1]

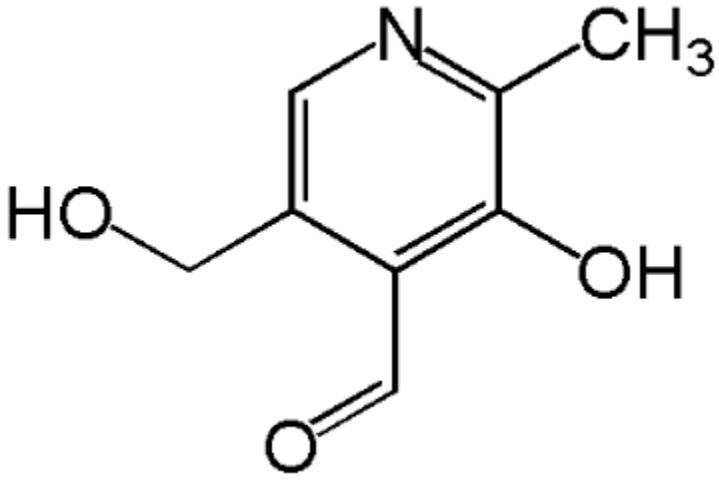


Figure $10.7.2$: Structure of pyridoxal[2]

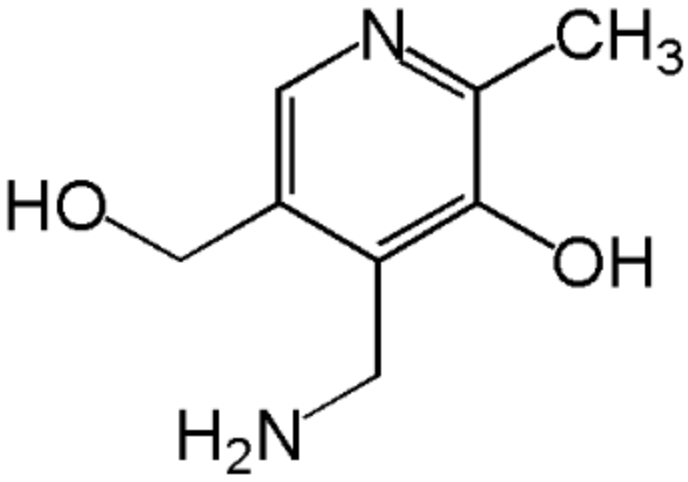


Figure 10.7.3: Structure of pyridoxamine3

Query 10.7.1

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All three forms can be activated by being phosphorylated. The phosphorylated forms can be interconverted to the active, or the cofactor form of vitamin B_6, pyridoxal phosphate (PLP). This active form has a phosphate group added in place of a hydroxyl group. The enzyme that catalyzes this reaction requires FMN (riboflavin cofactor), as shown below.

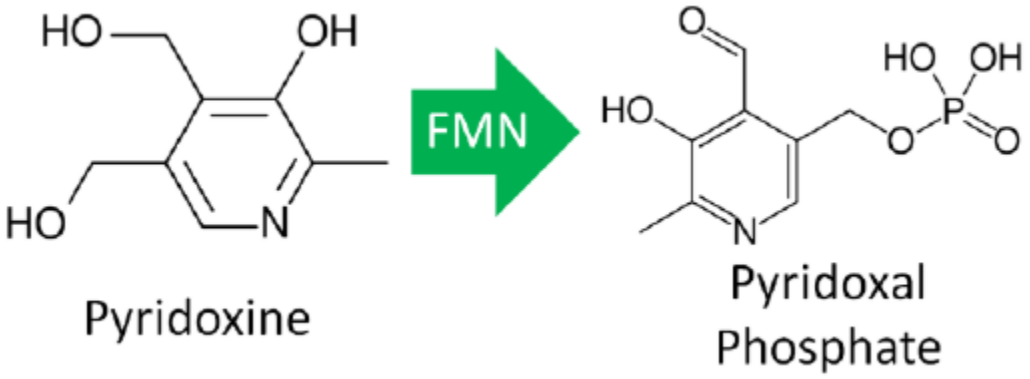


Figure 10.7.4: Vitamin B_6 activation1,4

In animal products, vitamin B_6 is found in its cofactor forms, PLP and pyridoxamine phosphate (PMP). The latter cofactor is less common than PLP. In plants, vitamin B_6 is primarily found as pyridoxine, with up to 75% being pyridoxine glucoside, which is believed to be the plant storage form6. Pyridoxine glucoside has a glucose added to pyridoxine as shown below.

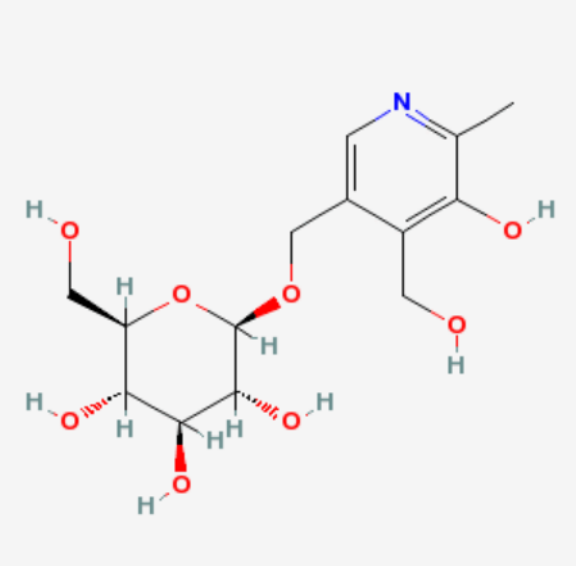


Figure 10.7.5: Structure of pyridoxine glucoside[5]

Vitamin B_6 is well absorbed from foods (~75%) through passive diffusion. PLP and PMP are dephosphorylated before uptake into the enterocyte. Some of the pyridoxamine glucoside is cleaved to form free pyridoxine, but some pyridoxine glucoside is absorbed intact. Pyridoxine glucoside absorption is lower (~50%) than pyridoxine alone. The primary circulating forms of vitamin B_6 are pyridoxal and PMP. Vitamin B_6 is primarily excreted in the urine, and like many other B vitamins, vitamin B_6 is destroyed during cooking or heating[6].

Query 10.7.2

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Vitamin B_6 Functions

PLP is a cofactor for over 100 different enzymes, most are involved in amino acid metabolism. In fact, without PLP, all amino acids would be essential because we would not be able to synthesize nonessential amino acids. Below are some of the functions of PLP and PMP[7]:

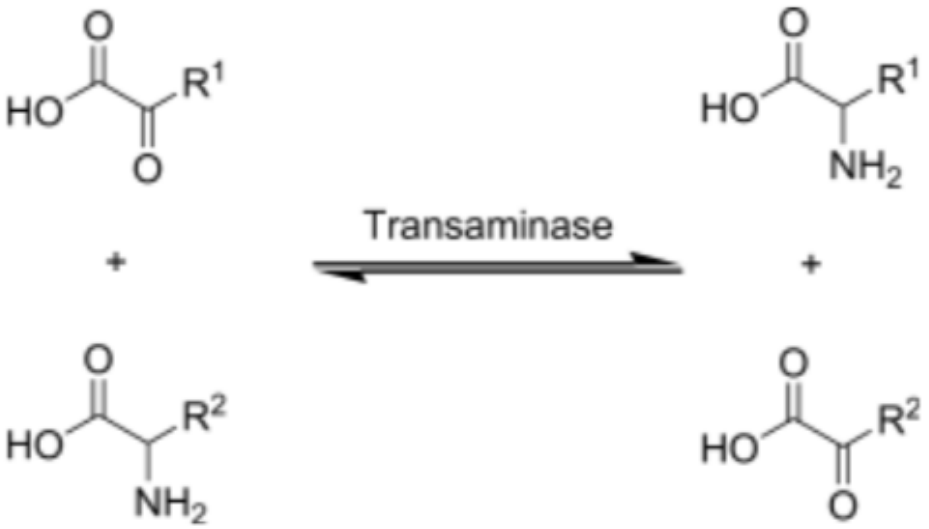


Figure 10.7.6: Transaminases require PLP or PMP[8]

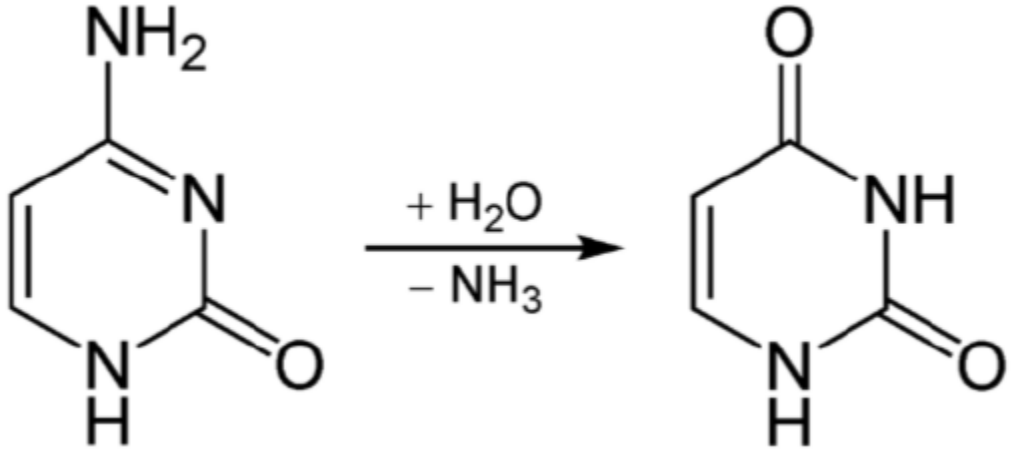


Figure 10.7.7: Some deaminases require PLP[9]

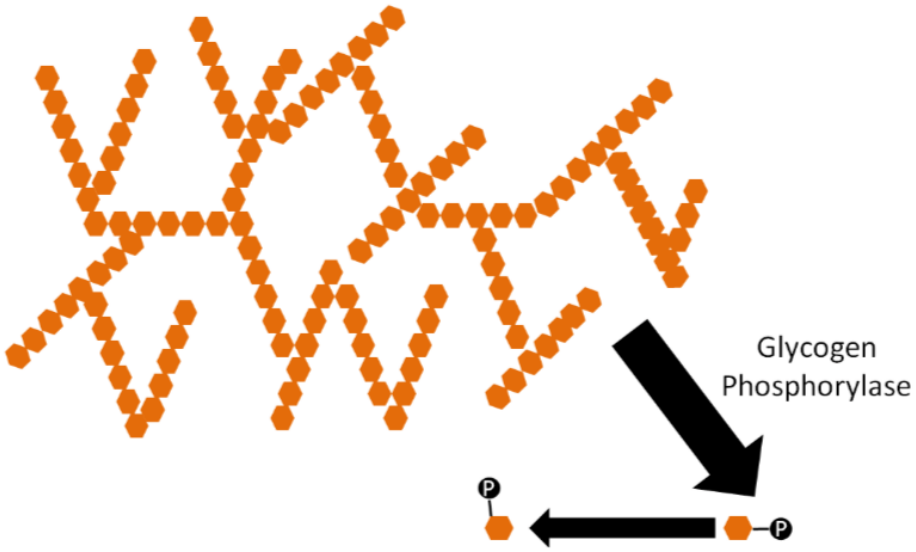


Figure 10.7.8: Glycogen phosphorylase (glycogenolysis) requires PLP

PLP is required for decarboxylase enzymes that are involved in the synthesis of the neurotransmitters GABA, serotonin, histamine, and dopamine. As an example, DOPA decarboxylase uses PLP to convert L-DOPA to dopamine as shown below7.

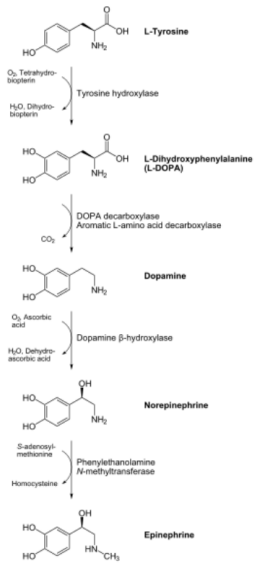


Figure 10.7.9: DOPA decarboxylase uses PLP to synthesize dopamine10

PLP is also required by gamma-aminolevulinic acid (ALA) synthetase that is involved in heme synthesis, as shown below. Heme will be discussed in more detail in the iron section.

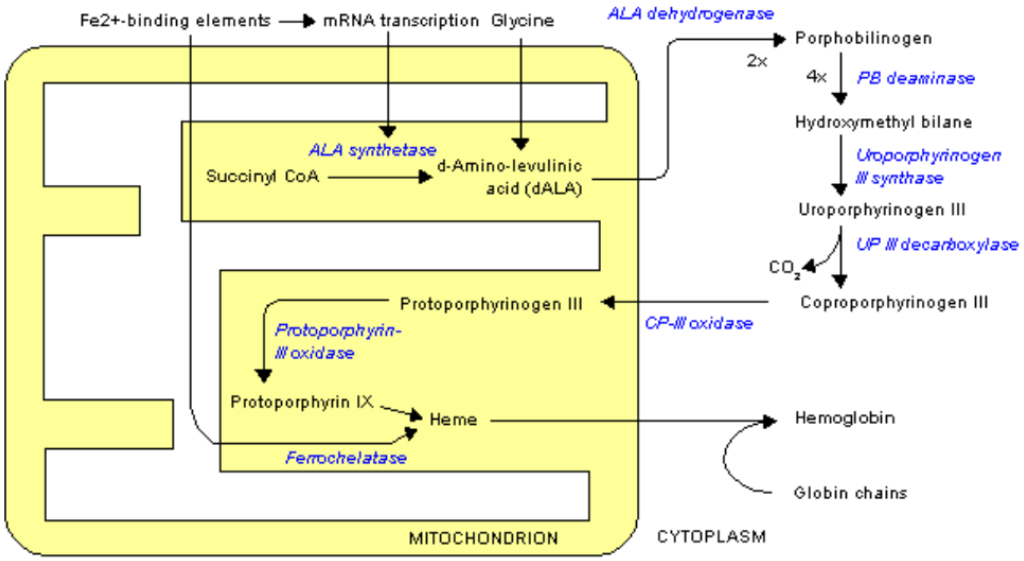


Figure 10.7.10: ALA synthetase uses PLP in the heme synthesis pathway11

PLP is also used in one of the multiple reactions that occurs between kynurenine and niacin in its synthesis from tryptophan.



Figure 10.7.11: PLP is required for niacin synthesis from tryptophan[12]

In addition, PLP is also involved in:

- Carnitine Synthesis
- 1-Carbon Metabolism

Query 10.7.3

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Vitamin B_6 Deficiency & Toxicity

Vitamin B_6 deficiency is rare, but symptoms include:

- Skin or scalp ailments (seborrheic dermatitis)
- Microcytic hypochromic anemia (small cells, low color)
- Convulsions
- Depression
- Confusion

Given what we know about the functions of vitamin B_6 most of these symptoms make sense. The microcytic hypochromic anemia is a result of decreased heme synthesis. The neurological symptoms are due to the decreased production of neurotransmitters[13].

Vitamin B_6, unlike many of the B vitamins, can produce toxicity. High doses of vitamin B_6, taken for an extended period of time, can lead to neurological damage[13]. There are some potential uses of vitamin B_6 supplementation that are important to be done with consultation with a physician. The levels at which vitamin B_6 is supplemented for these uses is usually nearing its UL, which is why care should be taken in how this is done.

Carpal tunnel syndrome is a condition that some people take a vitamin B_6 supplement for. The following video does a nice job of explaining and showing how this condition occurs.

YouTube Video

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View this YouTube Video online

Video 10.7.1: Carpal Tunnel Syndrome. https://www.youtube.com/watch?v=rewDQgqU5Hg

While the evidence is not conclusive, it appears that vitamin B_6 supplementation may be beneficial to those suffering from carpal tunnel syndrome and may be tried alone, or in combination with other complementary treatments, before surgery is undertaken14,15.

Morning sickness (hyperemesis gravidarum) that occurs early in pregnancy is another condition where vitamin B_6 supplementation is utilized. The evidence again is not clear on whether it is beneficial16,17, but The American College of Obstetricians and Gynecologists suggests that vitamin B6 may be tried first to treat nausea and vomiting during pregnancy18. In 2013, the FDA approved doxylamine-pyridoxine (Diclegis) for use in pregnancy19. It is not known exactly what causes morning sickness, but it is believed that lower circulating vitamin B6 levels are associated with increased morning sickness severity20.

The last condition that vitamin B6 is commonly supplemented for is premenstrual syndrome (PMS). A systematic literature review found that it is inconclusive whether vitamin B_6 supplementation is beneficial in managing PMS21.

Query 10.7.4

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10.8: Biotin

The 2 primary dietary forms of biotin are free biotin and biocytin (aka biotinyllysine)1. The structure of biotin is shown below.

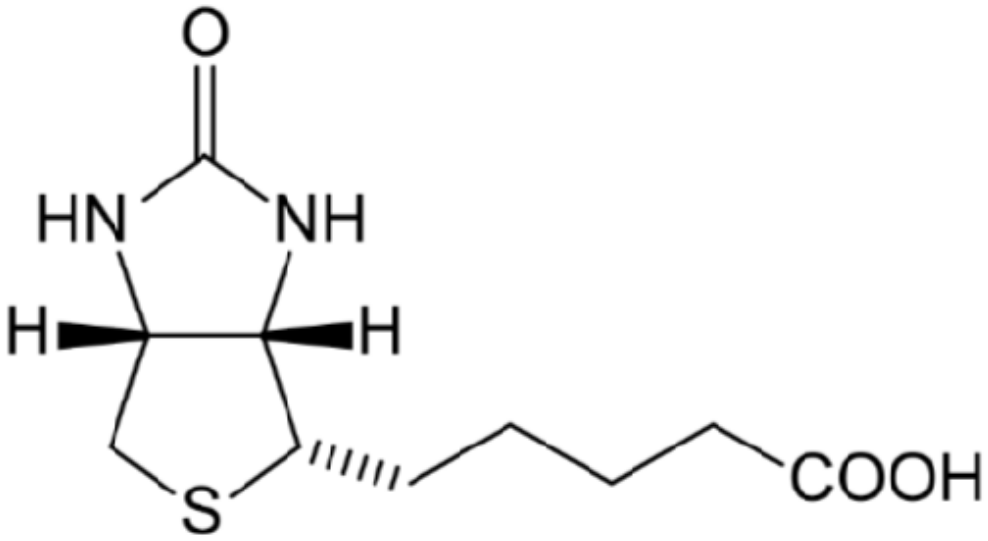


Figure 10.8.1: Structure of biotin2

Biocytin is biotin bound to the amino acid lysine as seen in its structure below.

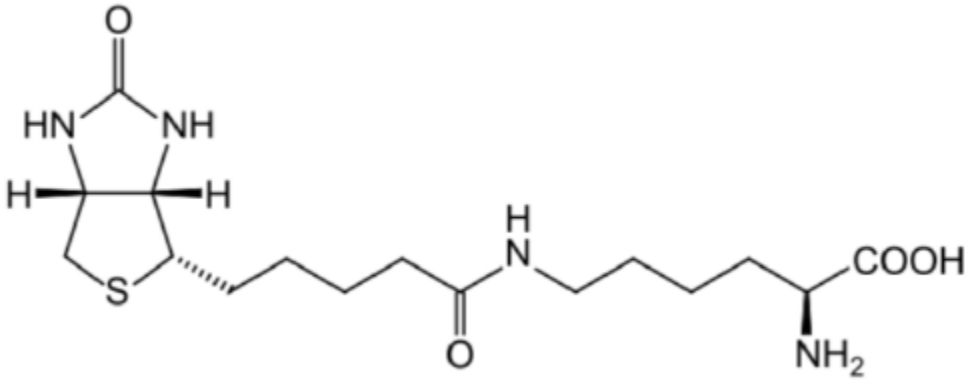


Figure 10.8.2: Structure of biocytin3

Free biotin is believed to be highly absorbed. Before uptake, biocytin is acted on by the enzyme biotinidase, forming free biotin and lysine. Free biotin is then taken up into the enterocyte through the sodium-dependent multivitamin transporter (SMVT), as shown below1,4,5.

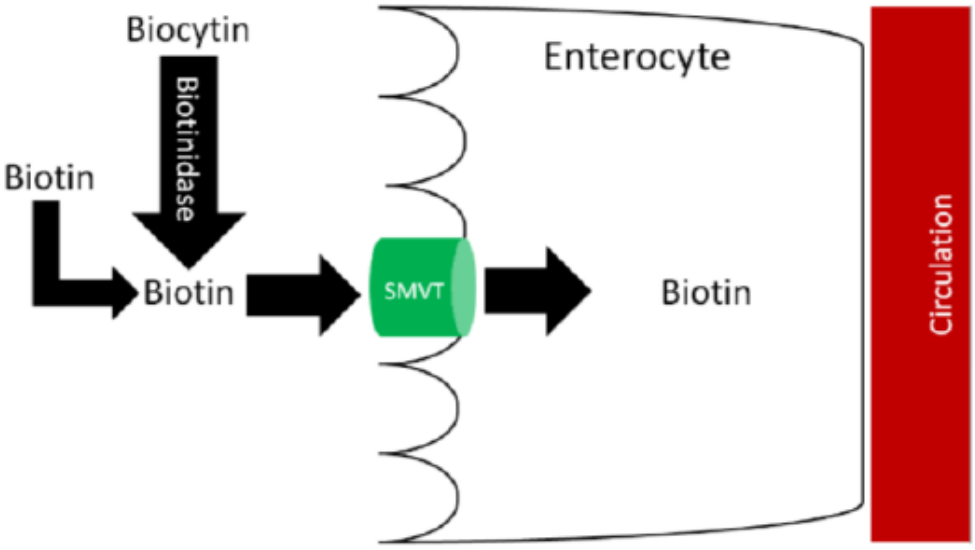


Figure 10.8.3: Free biotin is taken up into the enterocyte by the SMVT.

Most biotin is excreted in the urine.

Query 10.8.1

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Biotin Functions

Biotin is an important cofactor for carboxylase enzymes. As the name sounds, these enzymes add carboxylic acid groups ($-\mathrm{COOH}$) to whatever compound they act on. In fatty acid synthesis, biotin is required by the enzyme that forms malonyl-CoA from acetyl-CoA, as shown below1.

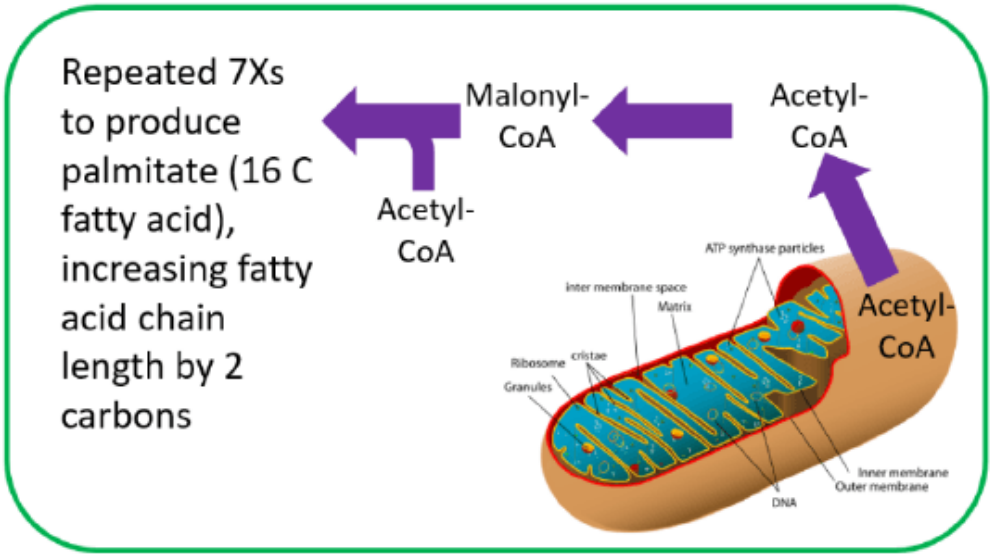


Figure 10.8.4: The conversion of acetyl CoA to malonyl CoA in fatty acid synthesis requires biotin[6]

Another biotin-requiring carboxylase is one that converts pyruvate to oxaloacetate in gluconeogenesis as shown below[1].

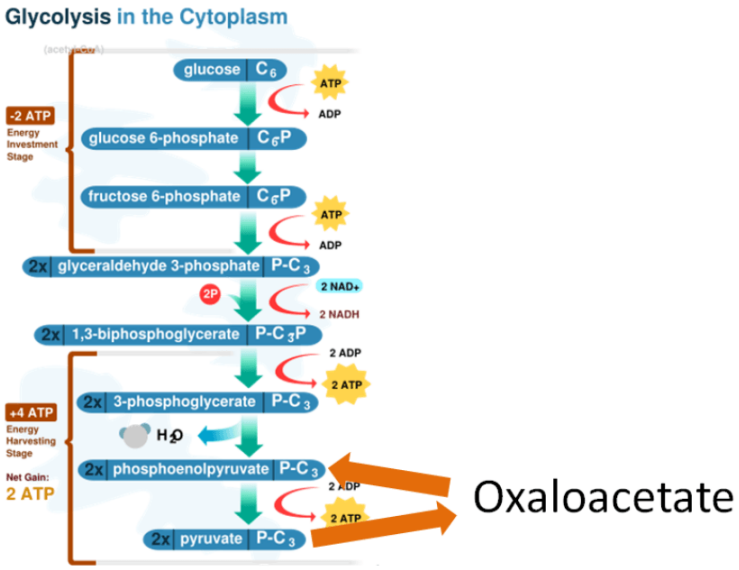


Figure 10.8.5: Biotin is required for conversion of pyruvate to oxaloacetate in the oxaloacetate workaround of gluconeogenesis (like glycolysis in reverse with oxaloacetate workaround)[7]

In addition to these two functions, biotin is also important for histone biotinylation and the breakdown of isoleucine, leucine, methionine, and threonine[1]. Histone biotinylation is an epigenetic modification that is described in the next section.

Biotin is an effective treatment for brittle nail syndrome, but it has not been shown to improve healthy nails[8]. There is little evidence to suggest that biotin improves healthy hair as well[9].

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Epigenetics

What is epigenetics? Epigenetics means "above the genome." To use a computer analogy, if the DNA sequence is the hardware, epigenetics can be viewed as the software. The nucleotide sequence of the human genome is known, and there is surprisingly little difference between individuals. However, the 2 main epigenetic modifications play a major role in determining what genes are expressed:

- DNA methylation
- Histone modification

These epigenetic modifications are illustrated in the following figure.

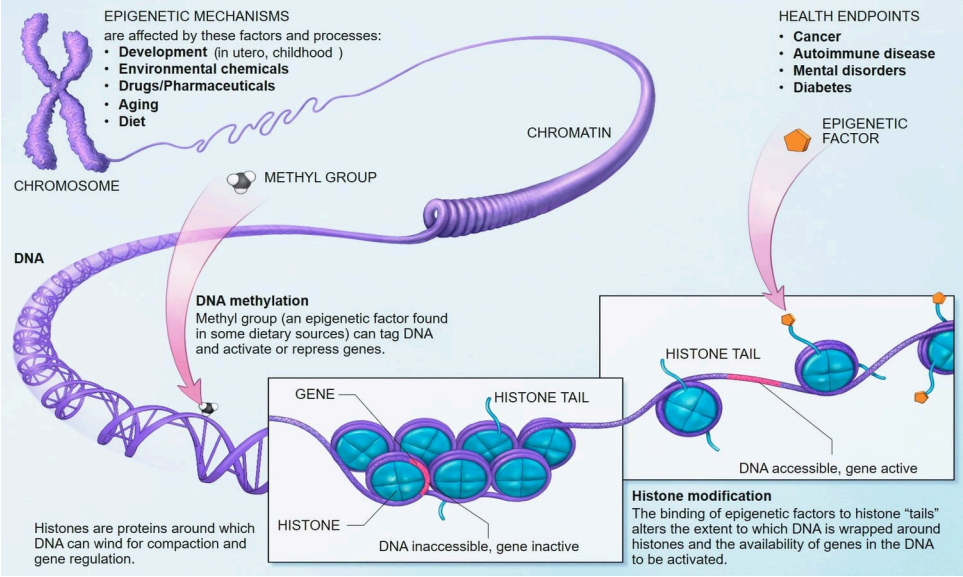


Figure 10.8.6: DNA methylation and histon modification epigenetic modification[10]

DNA methylation is the addition of a methyl group to a DNA base, which decreases gene transcription. Conversely, demethylation increases gene transcription.

DNA does not exist simply as long strands of double helix, instead it is packaged and shaped so that it can fit in the nucleus of our cells. The first part of this packaging is that DNA is wrapped around proteins called histones as shown below.

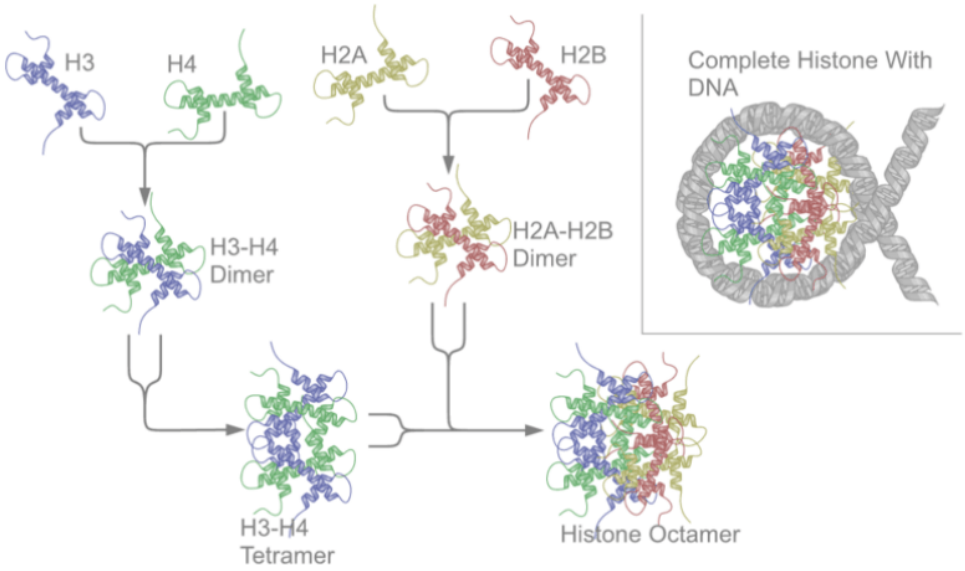


Figure 10.8.7: DNA is wrapped around histones[11]

Histone modification occurs when there are additions or subtractions to the histones themselves. The most common is acetylation (addition of an acetyl group) or deacetylation of histones. The structure of acetyl is shown below.

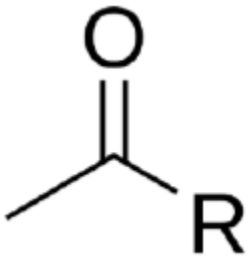


Figure 10.8.8: Structure of acetyl[12]

Histone acetylation causes the DNA structure to open up so that transcription can occur. Histone deacetylation causes the DNA to become more tightly packed, preventing transcription from occurring.

Together, these modifications to DNA and histones are known as the epigenetic code. The following two videos do a good job explaining epigenetics and tying together its two different methods of modification. The Tale of 2 Mice describes how great an impact that the methylation status (whether it is methylated or unmethylated) of the agouti gene has on physical characteristics of genetically identical mice. The second video illustrates how histone modifications impact gene transcription.

YouTube Video

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Video 10.8.1: A Tale of Two Mice. https://www.youtube.com/watch?v=OOiCu5kzGxg

YouTube Video

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View this YouTube Video online

Video 10.8.2: Chromatin, histones and modifications. https://www.youtube.com/watch?v=eYrQ0EhVCYA

How does this relate to biotin? Histones can be biotinylated, or have biotin added to the histone. However, it should be noted that histone biotinylation is rare (<0.001% of human histones H3 and H4), so it is questionable how much impact this action has13.

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Biotin Deficiency & Toxicity

Biotin deficiency is very rare. Symptoms of biotin deficiency include14:

- Skin rash
- Hair loss
- Neurological Impairments

There are a couple of ways that a person could develop a deficiency in biotin. First, a very small number of people are born with a mutation in biotinidase that results in them not being able to cleave biocytin for absorption1. Another way is through the consumption of raw eggs. Drinking raw eggs is not something that most people do. However, some people do it to imitate Sylvester Stallone's movie character Rocky, who consumed them as part of his boxing training regimen. If you are not familiar with this movie the link below shows you how Rocky consumed his raw eggs.

YouTube Video

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View this YouTube Video online

Video 10.8.3: Rocky drinks eggs. https://www.youtube.com/watch?v=NhkdLHSKo9s

The potential problem with consuming raw eggs routinely is that raw egg whites contain a protein called avidin which binds biotin and prevents its absorption. However, it would take more than two dozen egg whites consumed daily over many months to cause a deficiency, making this an unlikely occurrence15. Cooking denatures avidin and prevents it from binding biotin, meaning that cooked eggs are not a concern.

No toxicity of biotin has been reported.

Query 10.8.4

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11: ONE-CARBON METABOLISM MICRONUTRIENTS

Three B vitamins are involved in what is known as 1-carbon metabolism. This is the movement of 1 carbon units, generally methyl groups (CH_3). It is similar to the movement of the amino group that occurs in transamination. As shown in the figure below, folate, vitamin B_{12}, and vitamin B_6 are the B vitamins involved in 1-carbon metabolism.

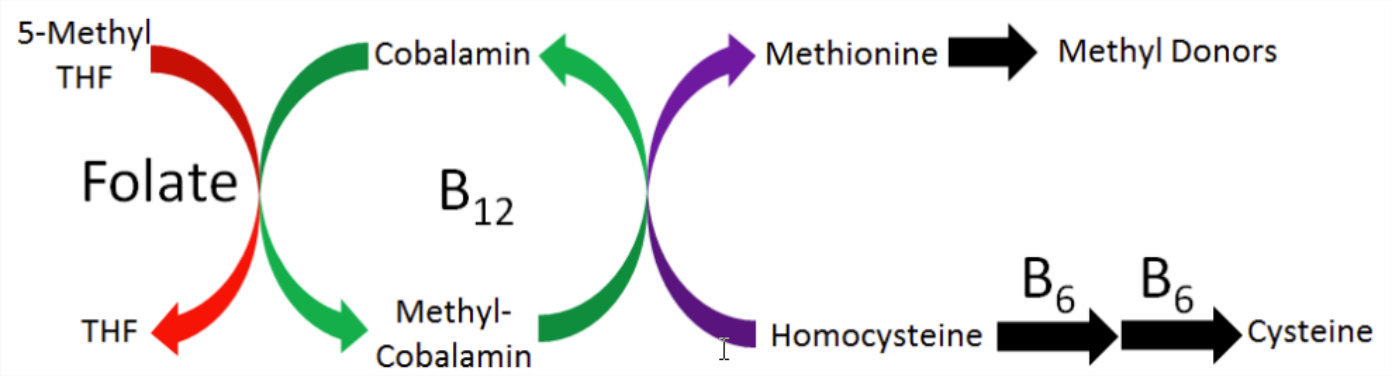


Figure 11.1: One-carbon metabolism depiction. 5-methyltetrahydrofolate (THF) donates a methyl group to cobalamin forming methylcobalamin. Methylcobalamin donates a methyl group to homocysteine, forming methionine (an amino acid). Alternatively, vitamin B_6 can be utilized to convert homocysteine into cysteine.

Vitamin B_6 has been described in the previous chapter, so this chapter is going to focus on folate and vitamin B_{12}. We will examine this figure in pieces, so that hopefully by the time this chapter is completed, you will understand the role of all these vitamins in 1-carbon metabolism.

Query 11.1

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11.1: Folate and Folic Acid

11.2: Vitamin B_{12}

11.3: B Vitamins, Homocysteine and Cardiovascular Disease

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11.1: Folate and Folic Acid

Folate is a B vitamin that exists in either its reduced form (folate) or oxidized form (folic acid). When folate is used in this section, we are referring to the reduced form, not the vitamin itself. Another key distinction between the 2 terms is that folic acid refers to the synthetic form, while folate refers to the natural form. Folic acid is only found in certain foods because they have been fortified with it, not because they produce it. The structure of folic acid is shown below.

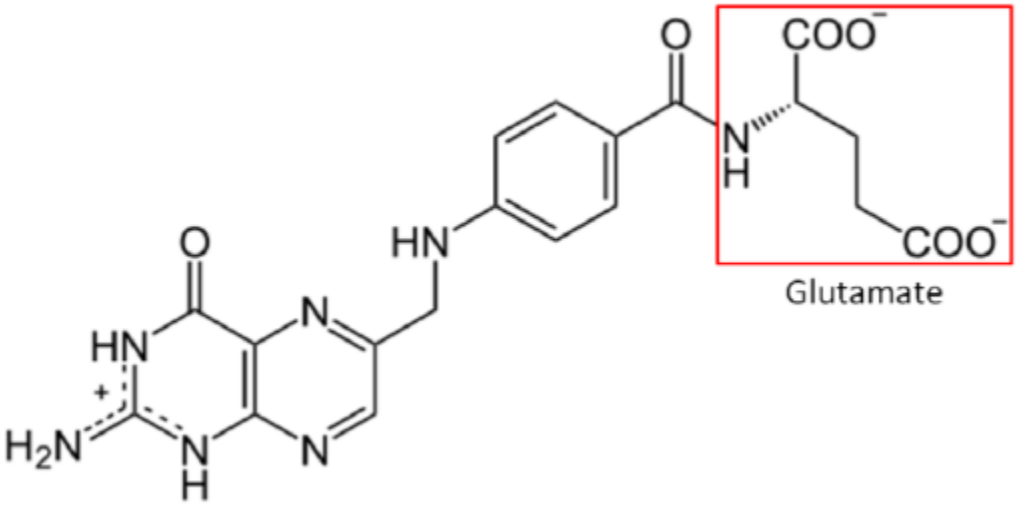


Figure 11.1.1: Structure of Folic Acid[1]

Another key difference between folate and folic acid is the number of glutamates in their tails. Notice that glutamate is boxed in the structure of folic acid above. Folic acid always exists as a monoglutamate, meaning it only contains 1 glutamate. On the other hand, about 90% of the folate found in foods are polyglutamates, meaning there is more than 1 glutamate in their tail. Folic acid is more stable than folate, which can be destroyed by heat, oxidation, and light[2]. Table 11.1.1 summarizes the key differences between folate and folic acid.

Table 11.1.1: Comparison of folate to folic acid

Folate	Folic Acid
Reduced Form	Oxidized Form
Natural	Synthetic
Polyglutamate	Monoglutamate
	More Stable

Query 11.1.1

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Query 11.1.2

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The bioavailability of folate was believed to be much lower than folic acid.3 To account for these differences, the DRI committee created dietary folate equivalents (DFEs) to set the DRIs4. DFEs are defined as follows:

1 DFE = 1 ug food folate = 0.6 ug food folic acid = 0.5 ug folic acid on an empty stomach

DFE = ug food folate + (ug folic acid X 1.7)

The 1.7 came from research suggesting that folic acid from food was 85% bioavailable, compared to 50% for folate (85%/50% = 1.7)4. This was established in 1998 by the DRI committee, but there is newer evidence suggesting folate's bioavailability from food is higher (80% of folic acid) than previously believed3. With this data, a revised conversion factor for folic acid would be 1.25 (100%/80%). This conversion factor means that food folate levels are probably contributing more towards our dietary needs than currently being estimated by the DFE, but the DRI for folate/folic acid has not been updated.

Recent research investigating various food with different folate levels found variable responses in human subjects to both the food and the folate bioavailability. Thus, this research suggests that the bioavailability of folate is dependent on the individual as well as the food source5.

Query 11.1.3

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Before folate (polyglutamates) can be taken up into the enterocyte, the extra glutamates must be cleaved prior to uptake into the enterocyte by the reduced folate transporter (RFT, aka reduced folate carrier)6-8. Folic acid, because it is a monoglutamate, requires no cleavage for uptake before it is taken up through the RFT. Once inside the enterocyte, the monoglutamate form is methylated and transported into circulation through an unresolved carrier5. This series of events is depicted in the figure below.

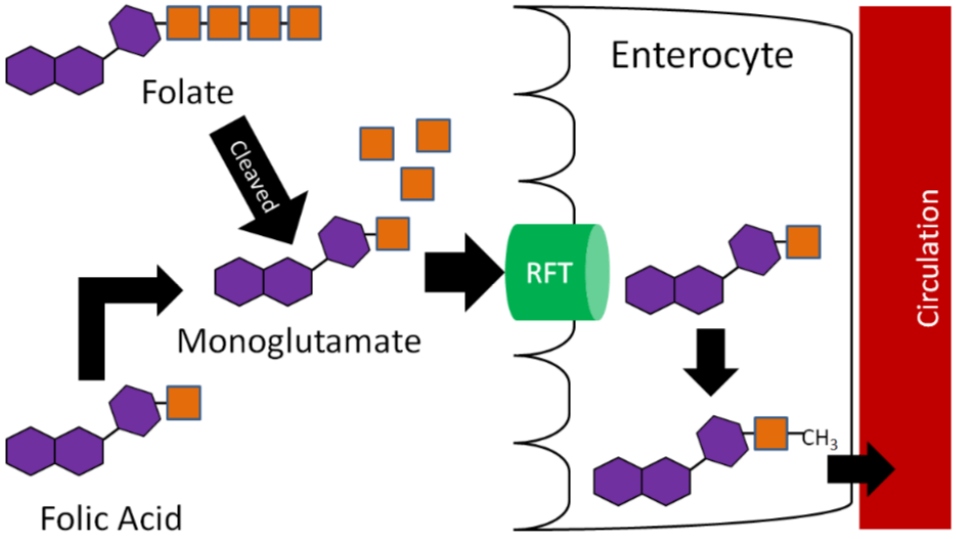


Figure 11.1.2: The uptake and absorption of folate and folic acid (orange boxes represent glutamate)

Thus, the methylated monoglutamate form is the circulating form. This is transported to the liver where it is converted back to the polyglutamate forms THF and 5-methyl THF for storage. Folate is excreted in both the urine and feces6.

Query 11.1.4

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Folate Functions

The major function of folate is that it participates in 1-carbon metabolism. As described earlier, this is the transfer of 1-carbon units from 1 compound to another. The cofactor form of folate is tetrahydrofolate (THF). As is shown in the figure below, in order for THF to be formed, a methyl group is transferred to cobalamin (vitamin B_{12}) from 5-methyl THF (THF plus a methyl group), forming methyl-cobalamin. You can see this on the left side of the figure below.

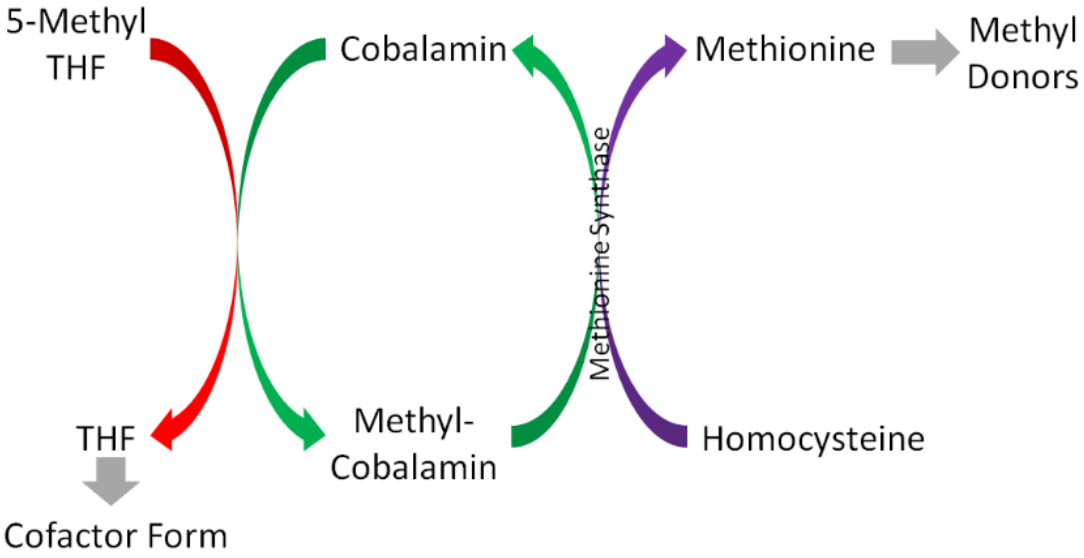


Figure 11.1.3: One-carbon metabolism

There are 2 major cofactor functions of THF[7]:

DNA Base Synthesis

THF is required for the synthesis of DNA bases (purines and pyrimidines)[7]. As shown in the link below, N^{10}-formyl-THF (a form of THF) is needed in 2 reactions (3 and 9) in purine synthesis.

Web Link

Purine Synthesis

Amino Acid Metabolism

THF is a cofactor for enzymes that metabolize histidine, serine, glycine, and methionine[7]. The following link shows that THF is a cofactor for serine hydroxymethyltransferase, the enzyme that converts serine to glycine.

Web Link

Serine to Glycine

Query 11.1.5

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Folate Deficiency & Toxicity

Folate deficiency affects some Americans. The hallmark symptom of folate deficiency is megaloblastic (aka macrocytic) anemia. Megaloblastic anemia, as the name suggests, is characterized by large, nucleated (most red blood cells do not have a nucleus), immature red blood cells. This occurs because folate is needed for DNA synthesis; without it red blood cells are not able to divide properly[2]. As a result, fewer and poorer functioning red blood cells are produced that cannot carry oxygen as efficiently as normal red blood cells[9].

Query 11.1.6

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A maternal folate deficiency can lead to neural tube defects in infants. The exact cause of neural tube defects is unknown, but folate/folic acid supplementation has been shown to decrease the incidence of neural tube defects[8]. The most common of these neural tube defects is spina bifida (1 out of 2500 babies born in the United States), which is a failure of the neural tube to close and the spinal cord and its fluid protrude out the infant's back, as shown below[10,11]. Recent research suggests the defect may not be a result of a deficiency, rather a need for extra folate for some women at the time of increased cell division during embryonic development[12].

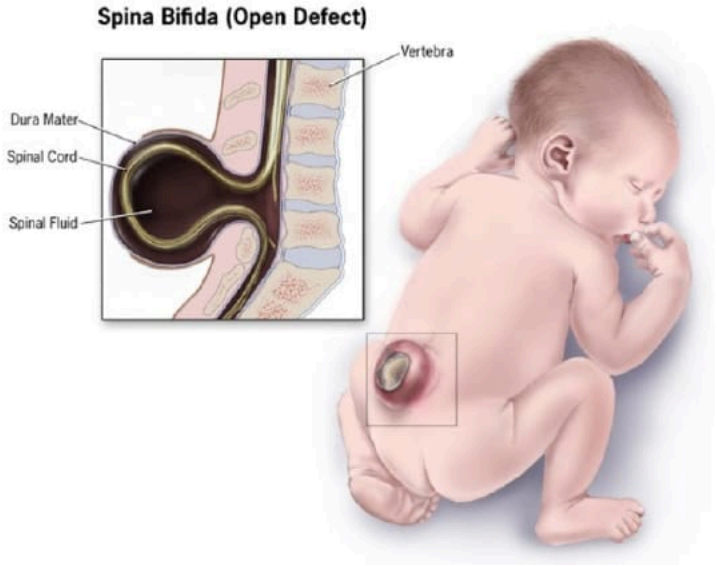


Figure 11.1.4: Spina bifida[13]

The following video illustrates and describes spina bifida.

YouTube Video

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Video 11.1.1: Neural tube defects (Watch first 36 seconds). https://www.youtube.com/watch?v=OpTX8WZbtvc

The neural tube closes 24-28 days after conception12, and with 50% of pregnancies estimated to be unplanned, many women are not aware they are pregnant during this period2,8. It is recommended that women of childbearing age consume 400 ug of folic acid daily8. However, to expect all women to do this through supplements would likely be most difficult for those at most risk (women of low socioeconomic status, young mothers) because they might not be able to afford or not know to take the supplement. In addition, in 1998 the FDA mandated that all refined cereals and grains be fortified with 140 ug folic acid /100 grams of product7. As you can see below, spina bifida prevalence rates declined during the optional fortification years and declined further once fortification became mandatory in the United States.

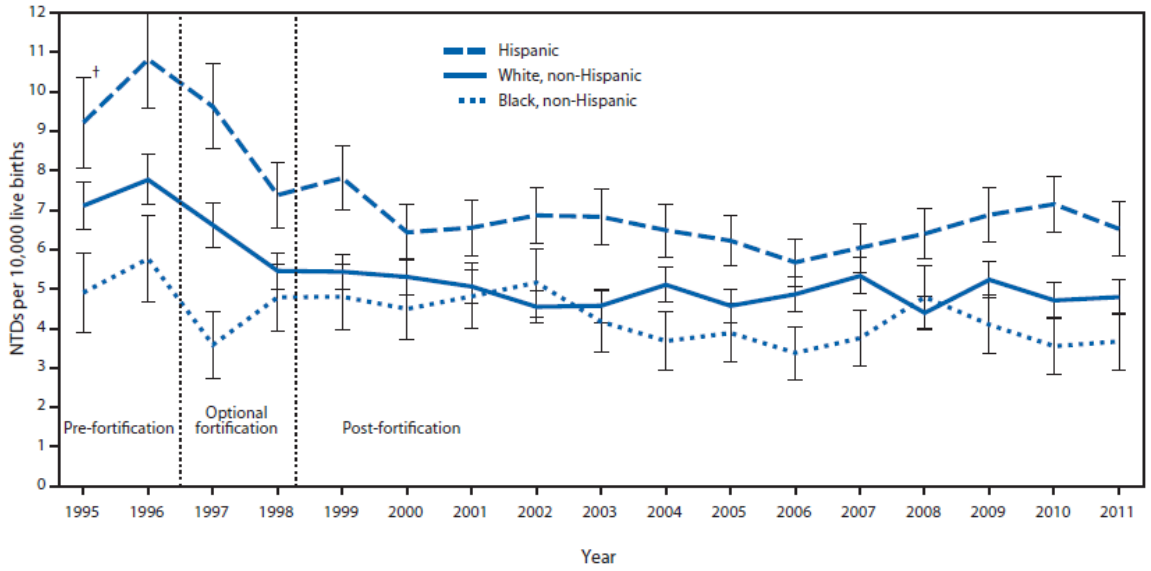


Figure 11.1.5: Neural tube defect prevalence 1995-201114

However, more recent research has found that folic acid supplementation begun before conception reduced the occurrence and severity of neural tube defects15.

The following link is an interesting account of the history that led up to the folic acid fortification. It is not clear whether folic acid fortification was fully responsible for the decrease in spina bifida rates shown above, but the rates are lower than they were pre-fortification. However, you would think that the hope was that the impact would be greater than it has been thus far. The second link is to the announcement that in 2016 the FDA approved the fortification of corn masa flour.

Web Link

- Folic Acid Fortification: Fact and Folly
- FDA Approves Folic Acid Fortification of Corn Masa Flour

Folate/Folic acid is not toxic, but it can mask a vitamin B_{12} deficiency and prevent its diagnosis. This effect will be discussed further in the vitamin B_{12} deficiency section. To put this in perspective, oral intakes of several hundred times the DRI are safe to consume due to the specificity and limited absorption of folic acid16.

Query 11.1.7

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Query 11.1.8

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11.2: Vitamin B_{12}

Vitamin B_{12} is unique among vitamins in that it contains an element (cobalt) and is found almost exclusively in animal products. Neither plants nor animals can synthesize vitamin B_{12}. Instead, vitamin B_{12} in animal products is produced by microorganisms within the animal that the products came from. Animals consume the microorganisms in soil or microorganisms in the GI tract of ruminant animals produce vitamin B_{12} that can then be absorbed1. Some plant products, such as fermented soy products (tempeh, miso) and the sea algae supplement, spirulina, are advertised as being good sources of B_{12}. However, fermented soy products are not a reliable vitamin B_{12} source2 and spirulina contains a pseudovitamin B_{12} compound that is not bioavailable3. For vegans, supplements, nutritional yeast, and fortified products like fortified soy milk can help them meet their vitamin B_{12} needs4.

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Vitamin B_{12}'s scientific name is cobalamin, which makes sense when you consider it contains cobalt and many amine groups, as shown in the figure below.

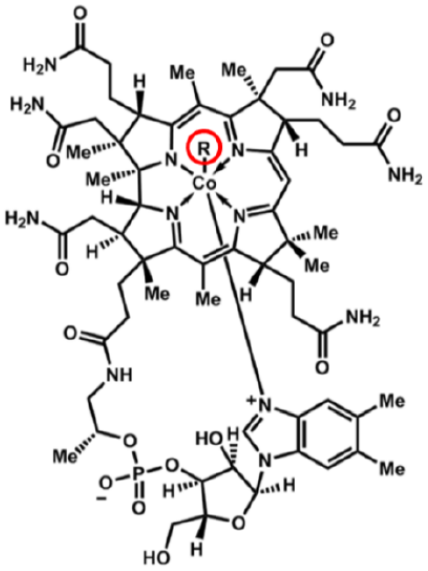


Figure 11.2.1: Structure of vitamin B_{12} (cobalamin)5

The other feature that is important in cobalamin is the circled R group. This is what differs between the different cobalamins, whose names and R groups are shown in the following table.

Table 11.2.1: Different cobalamin forms

R Group	Name
CN	Cyanocobalamin
OH	Hydroxocobalamin
H_2O	Aquocobalamin

R Group	Name
NO_2	Nitritocobalamin
5'-deoxyadenosyl	Adenosylcobalamin*
CH_3	Methylcobalamin*

*Cofactor Forms

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The 2 cofactor forms are adenosylcobalamin and methylcobalamin. We can convert most cobalamins into these 2 cofactor forms. Most foods contain adenosylcobalamin, hydroxocobalamin, or methylcobalamin[6]. The most common form found in supplements is cyanocobalamin, with some also using methylcobalamin[7]. Cyanocobalamin is a synthetic form of vitamin B_{12}.

The uptake, absorption, and transport of vitamin B_{12} is a complex process. The overall bioavailability of vitamin B_{12} is believed to be approximately 50%[3], with the different cobalamin forms having similar bioavailabilities[7]. Sublingual supplements of vitamin B_{12} have been found to be equally efficacious as oral supplements[7]. Excretion occurs mostly through bile, with little loss in urine[6]. The following descriptions and figures explain and illustrate, respectively, these processes.

Vitamin B_{12} is normally bound to protein in food. Salivary glands in the mouth produce haptocorrin (formerly known as R protein), which travels with the food into the stomach. In the stomach, acid converts pepsinogen into pepsin, and the protein intrinsic factor is released from the parietal cells[1,8].

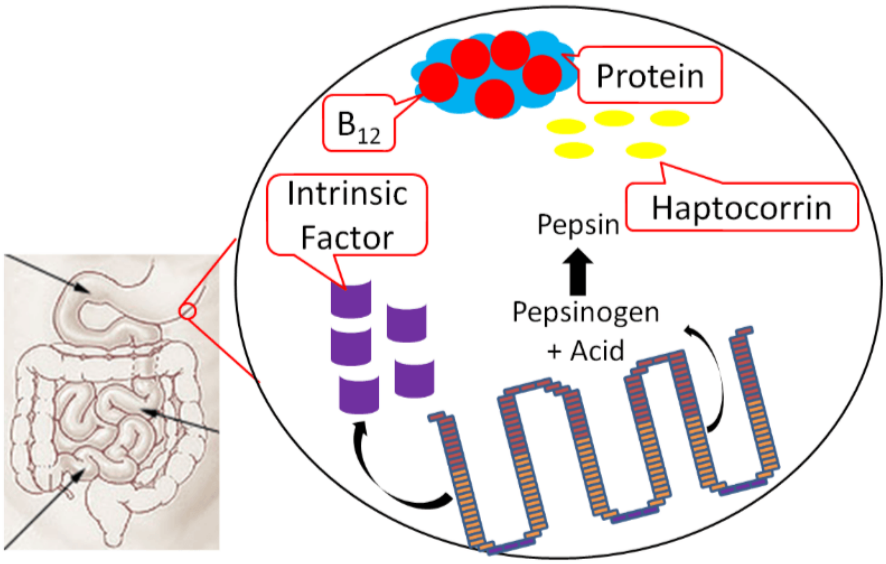


Figure 11.2.2: Vitamin B_{12} in the stomach part 1[8,9]

As pepsin frees B_{12} from protein, haptocorrin binds to the newly freed vitamin B_{12} (haptocorrin + B_{12}). Intrinsic factor escapes digestion and, along with haptocorrin + B_{12}, exits the stomach and enters the duodenum[1,8].

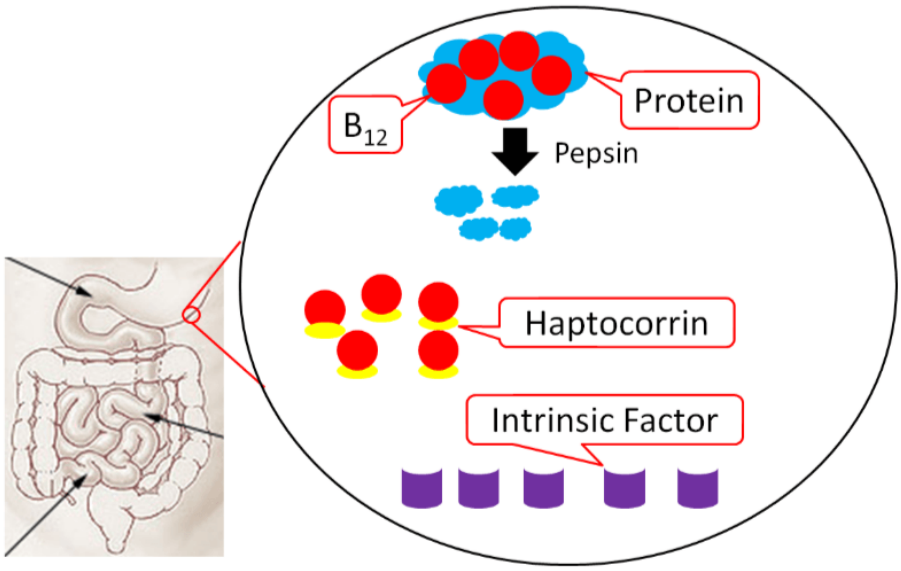


Figure 11.2.3: Vitamin B_{12} in the stomach part 2[8,9]

In the duodenum, pancreatic proteases break down haptocorrin, and again vitamin B_{12} is freed. Intrinsic factor then binds vitamin B_{12} (intrinsic factor + B_{12}); intrinsic factor + B_{12} continues into the ileum to prepare for absorption[1,8].

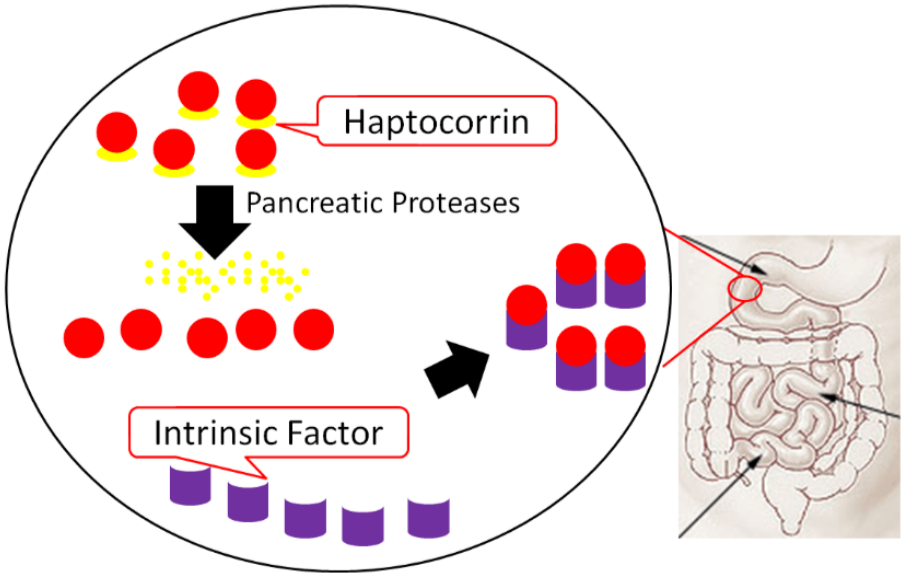


Figure 11.2.4: Vitamin B_{12} in the duodenum[8,9]

In the ileum, intrinsic factor + B_{12} is believed to be endocytosed by intrinsic factor binding to cubulin (aka intrinsic factor receptor), forming an endosome inside the enterocyte. Intrinsic factor is broken down in the enterocyte, freeing vitamin B_{12}. The free vitamin B_{12} is then bound to transcobalamin II (TC II + B_{12}); TC II + B_{12} moves into circulation[8].

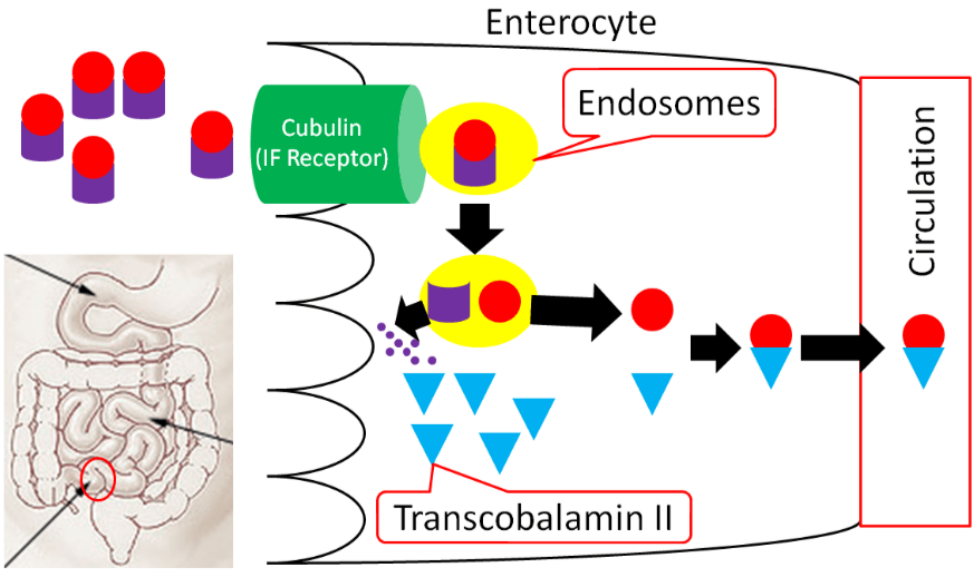


Figure 11.2.5: Vitamin B_{12} absorption8,9

The liver is the primary storage site for vitamin B_{12}. Unlike most other water-soluble vitamins, the liver is able to maintain significant stores of vitamin B_{12}. Uptake into the liver occurs through the binding of TC II + B_{12} to the TC II Receptor and the endocytosis of both the compound and the receptor8. Vitamin B_{12} is once again freed after degradation of TC II. Vitamin B_{12} is primarily stored in the liver as adenosylcobalamin6,8.

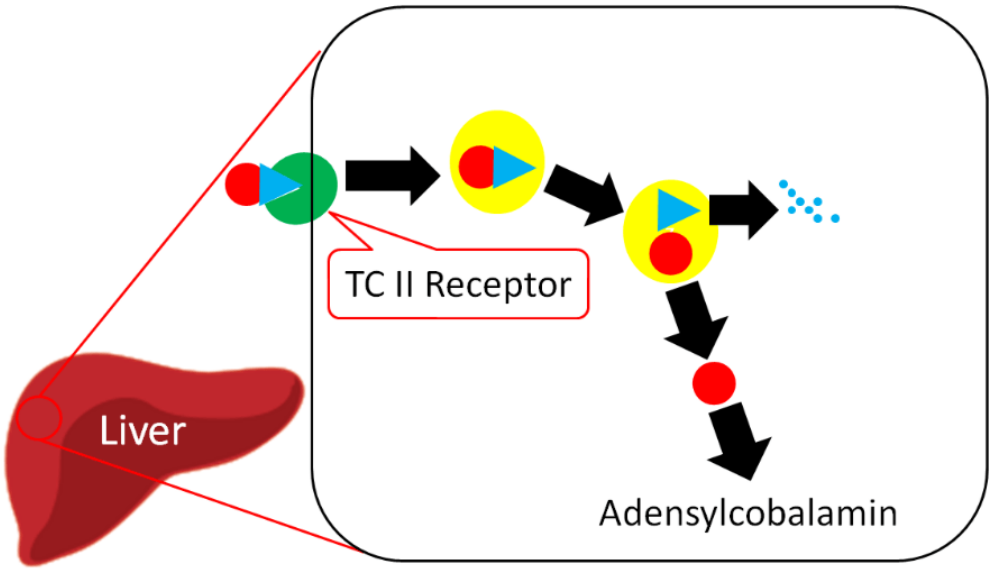


Figure 11.2.6: Hepatic uptake and storage of vitamin B_{12}9

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Vitamin B_{12} Functions

Vitamin B_{12} is a cofactor for 2 enzymes and is also important for neuron function as described further below.

Methionine Synthase

Methionine synthase is an important enzyme in 1-carbon metabolism that uses methylcobalamin as its cofactor and converts homocysteine to methionine by adding a methyl group. Methionine is then converted to other compounds that serve as methyl donors, as shown below1.

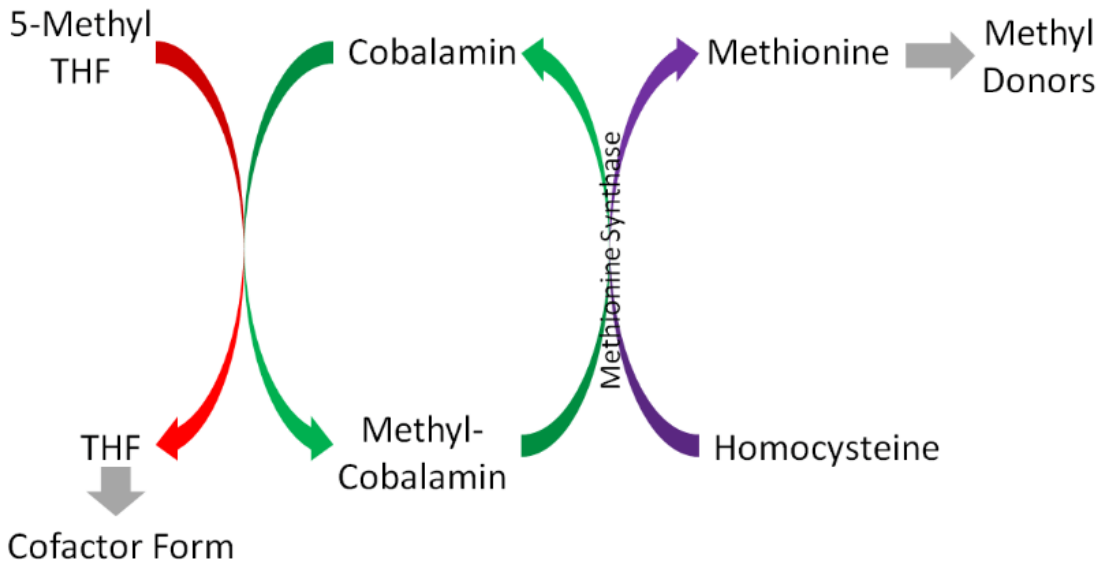


Figure 11.2.7: One-carbon metabolism

These methyl donors can donate methyl groups for methylating DNA, an epigenetic modification1.

Methymalonyl mutase

This enzyme uses adenosylcobalamin as its cofactor, and is important in the breakdown of odd chain fatty acids (5 carbons etc.). As you know, odd chain fatty acids are less common than even chain fatty acids, but this enzyme is required to properly handle these less common fatty acids1.

Demyelination

In addition to its role as a cofactor for enzymes, vitamin B_{12} is also important for preventing degradation of the myelin sheath that surrounds neurons, as shown below.

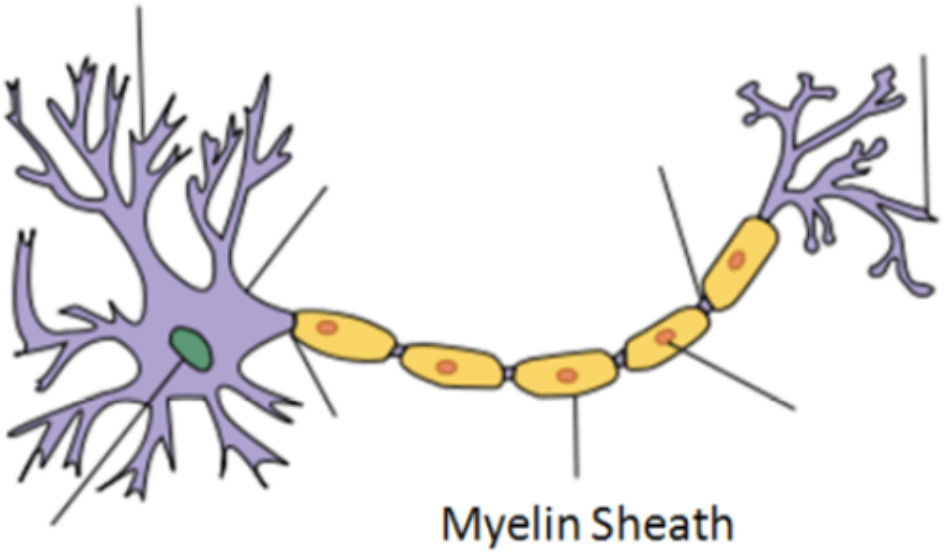


Figure 11.2.8: Vitamin B_{12} is needed to maintain the myelin sheath that surrounds neurons[10]

The mechanism by which vitamin B_{12} prevents demyelination is not known[11].

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Vitamin B_{12} Deficiency & Toxicity

There are 2 primary symptoms of vitamin B_{12} deficiency:

- Megaloblastic (Macrocytic) Anemia
- Neurological Abnormalities

Megaloblastic (Macrocytic) Anemia

This is the same type of anemia that occurs in folate deficiency that is characterized by fewer, enlarged, immature red blood cells. In vitamin B_{12} deficiency, this can occur because there is not enough cobalamin to convert 5-methyl THF to THF as it normally would as illustrated below.

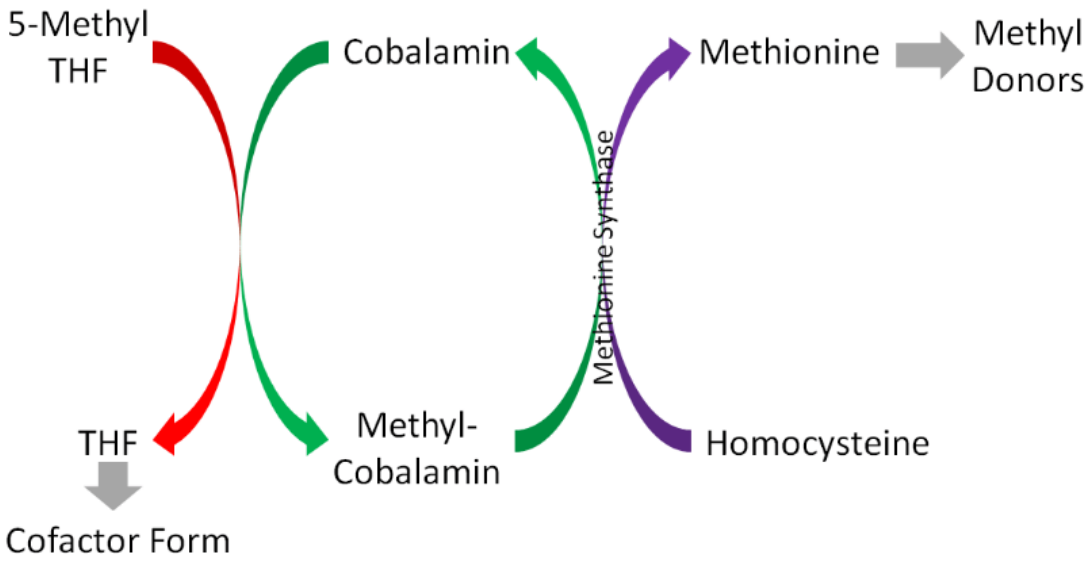


Figure 11.2.9: One-carbon metabolism

Thus, THF is not available for normal DNA synthesis and the red blood cells do not divide correctly.

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Neurological Abnormalities

Vitamin B_{12} deficiency also results in nerve degeneration and abnormalities that can often precede the development of anemia. These include a decline in mental function and burning, tingling, and numbness of legs. These symptoms can continue to worsen and deficiency can be fatal1.

The most common cause of vitamin B_{12} deficiency is pernicious anemia, a condition of inadequate intrinsic factor production that causes poor vitamin B_{12} absorption. This condition is common in people over the age of 50 because they have the condition atrophic gastritis12. Atrophic gastritis is a chronic inflammatory condition that leads to the loss of glands in the stomach, as shown in the figure in the following link.

Web Link

Atrophic Gastritis

The loss of glands leads to decreased intrinsic factor production. It is estimated that ~6% of those age 60 and over are vitamin B_{12} deficient, with 20% having marginal status12. In addition to the elderly, vegans are also at risk for vitamin B_{12} deficiency because they do not consume animal products. However, the deficiency may take years to develop in adults because of stores and recycling of vitamin B_{12}13. Deficiency has the potential to occur much quicker in infants or young children on vegan diets because they do not have stores that adults do1.

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Folate/Folic Acid masking vitamin B_{12} deficiency

As mentioned above, folate and vitamin B_{12} lead to the same megaloblastic (macrocytic) anemia. If high levels of folate or folic acid (most of the concern is with folic acid since it is fortified in foods and commonly taken in supplements) is given during vitamin B_{12} deficiency, it can correct this anemia. This is referred to as masking because it does not rectify the deficiency, but it "cures" this symptom. Folate/folic acid can do this by providing so much folate that there is enough THF for red blood cell division to occur even without having the cobalamin normally needed to accept a methyl group from 5-methyl THF. This is problematic because it does not correct the more serious neurological problems that can result from vitamin B_{12} deficiency. There are some people who are concerned about the fortification of cereals and grains with folic acid because people who are B_{12} deficient might not develop macrocytic anemia, which makes a vitamin B_{12} deficiency harder to diagnose12.

No toxicity of vitamin B_{12} has been reported.

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11.3: B Vitamins, Homocysteine and Cardiovascular Disease

Homocysteine is a sulfur containing, non-proteinogenic (not used for making proteins) amino acid whose structure is shown in the figure below.

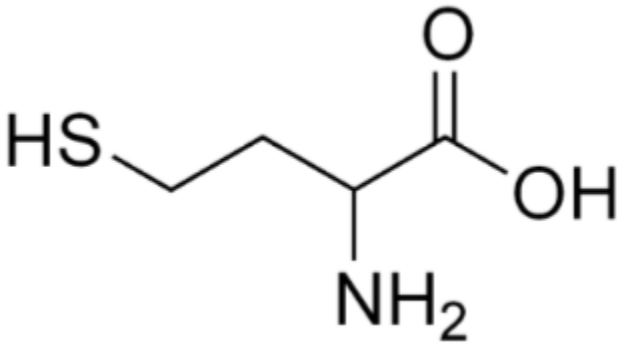


Figure 11.3.1: Structure of homocysteine[1]

Elevated circulating homocysteine levels have been found in people with cardiovascular disease. Folate, vitamin B_6, and vitamin B_{12} contribute to the conversion of homocysteine to methionine by providing methyl groups, thereby decreasing homocysteine concentrations, as illustrated in the figure below. Thus, based on these facts, it was hypothesized that intake of these B vitamins may decrease the risk of cardiovascular disease.

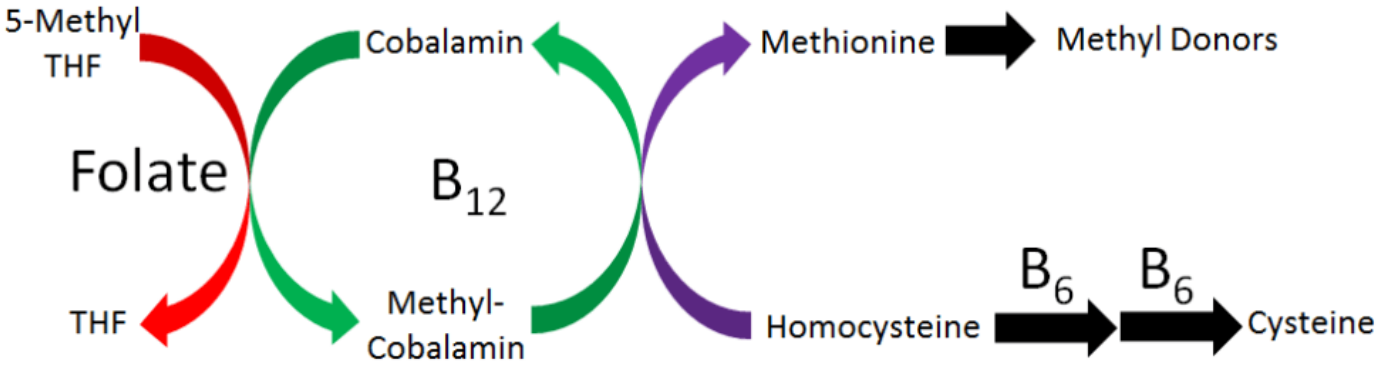


Figure 11.3.2: One-carbon metabolism

Research has found that intake of these B vitamins does decrease circulating homocysteine concentrations. However, most studies have not found that it results in improved cardiovascular disease outcomes[2-4]. It is debated why B vitamin intake has not resulted in improved outcomes. Some think it is because the studies have not focused on individuals with elevated homocysteine levels[2], while others believe that homocysteine is a biomarker or indicator of cardiovascular disease, not a causative or contributing factor to cardiovascular disease development[3].

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12: BLOOD, BONES AND TEETH MICRONUTRIENTS

This chapter is a collection of vitamins and minerals that are involved in the structure or function of blood, bones and teeth.

12.1: Vitamin D

12.2: Calcium

12.3: Phosphorus

12.4: Fluoride

12.5: Vitamin K

12.6: Vitamin A

12.7: Iron

12.8: Zinc

12.9: Copper

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12.1: Vitamin D

Vitamin D is unique among the vitamins in that it is part vitamin, part hormone. It is considered part hormone for two reasons: (1) we have the ability to synthesize it, and (2) it has hormone-like functions. The amount synthesized, however, is often not enough to meet our needs. Thus, we need to consume this vitamin under certain circumstances, meaning that vitamin D is a conditionally essential micronutrient.

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There are two major dietary forms of vitamin D: the form produced mainly by plants and yeast is vitamin D_2 (ergocalciferol), and the form mainly made by animals is vitamin D_3 (cholecalciferol). The main terms in the previous sentence are because lichens, a symbiotic relationship between 2 bacteria and a fungus, are able to synthesize vitamin D_3, and are being utilized some now commercially as described in the following article.

Web Link

Veggie D3 maker explores novel production process to secure future funding supplies

The structures of these two forms are shown below. Notice that the only difference is the presence of a double bond in D_2 tail that is not in D_3.

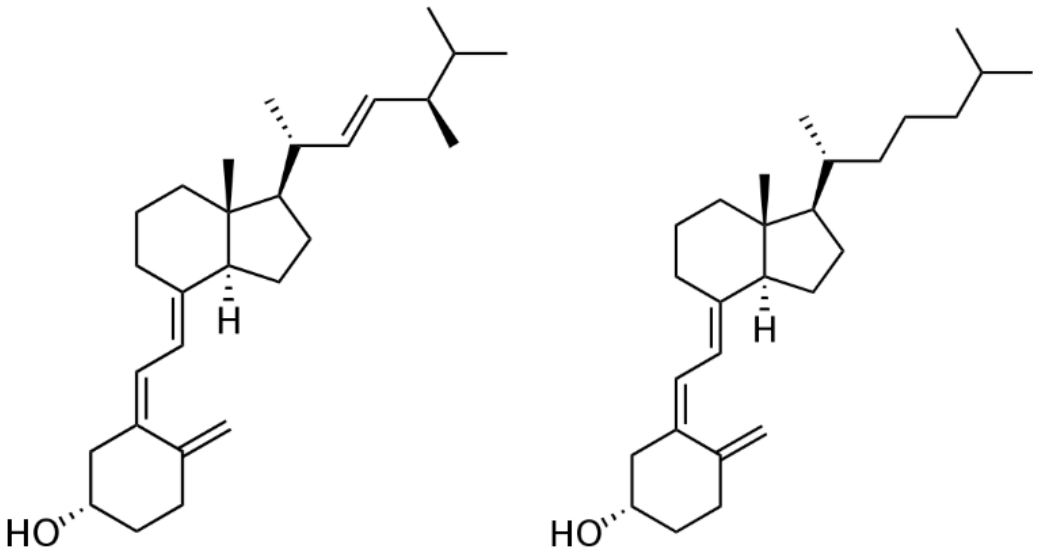


Figure 12.1.1: Structure of vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol)[1,2]

We synthesize vitamin D_3 from cholesterol, as shown below. In the skin, cholesterol is converted to 7-dehydrocholesterol. In the presence of UV-B light, 7-dehydrocholesterol is converted to vitamin D_3. Synthesized vitamin D will combine with vitamin D-binding protein (DBP) to be transported to the liver. Dietary vitamin D_2 and D_3 is transported to the liver via chylomicrons and then taken up in chylomicron remnants. Once in the liver, the enzyme 25-hydroxylase (25-OHase) adds a hydroxyl ($-\mathrm{OH}$) group at

the 25th carbon, forming 25-hydroxy vitamin D (25(OH)D, calcidiol). This is the circulating form of vitamin D, thus 25(OH)D blood levels are measured to assess a person's vitamin D status. The active form of vitamin D is formed with the addition of another hydroxyl group by the enzyme 1alpha-hydroxylase (1alpha-OHase) in the kidney, forming 1,25 hydroxy vitamin D (1,25(OH)2D). The synthesis and activation of vitamin D is shown in the figures below.

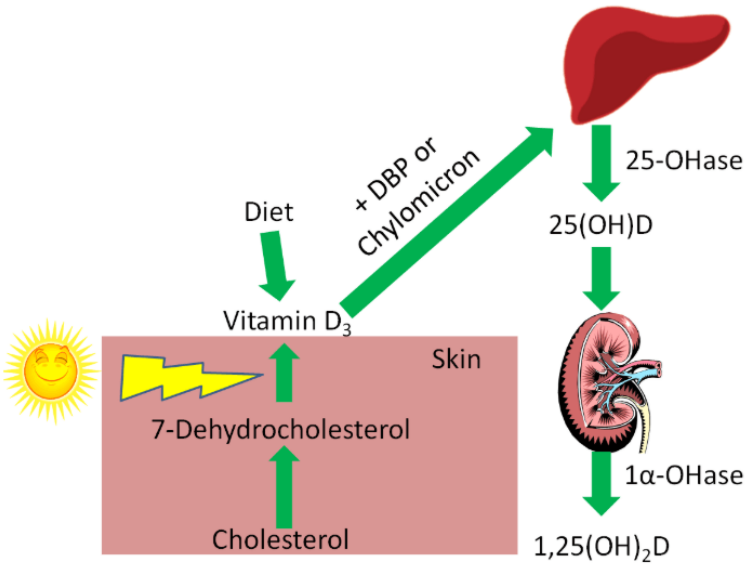


Figure 12.1.2: Vitamin D synthesis and activation[3,4]

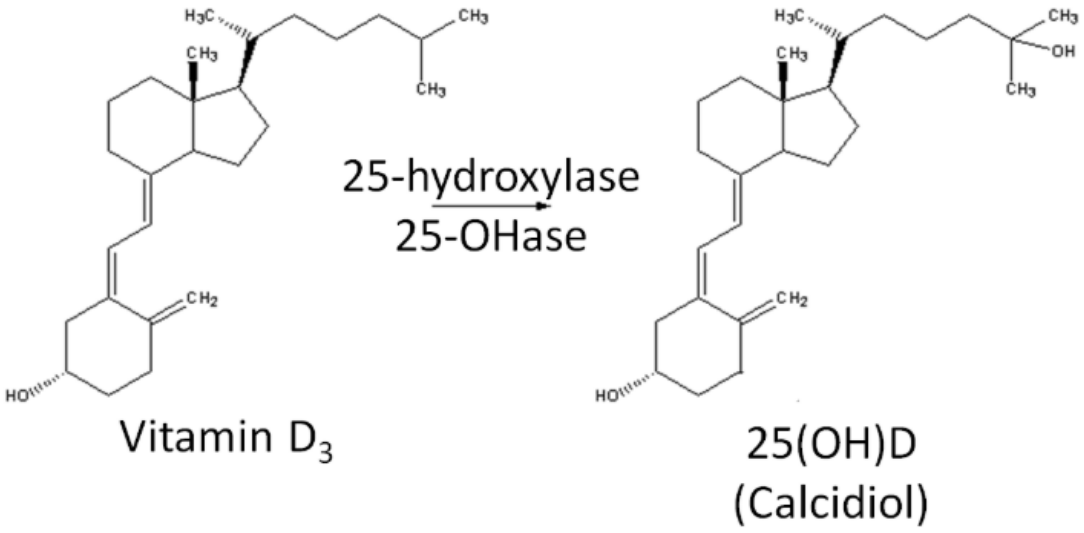


Figure 12.1.3: Synthesis of 25(OH)D (calcidiol) from vitamin D_3 by 25-hydroxylase[5,6]

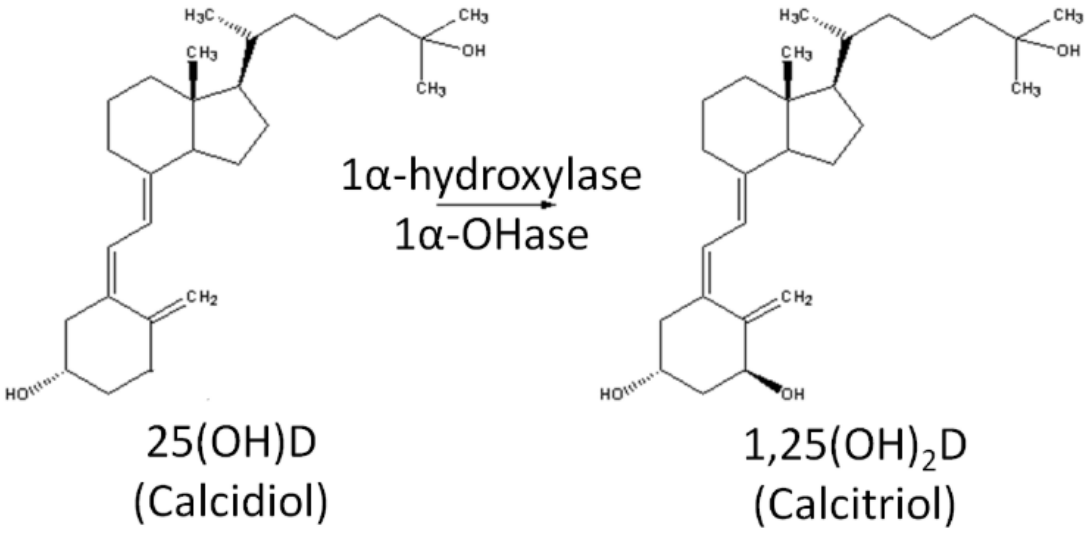


Figure 12.1.4: Synthesis of 1,25(OH)2D (calcitriol) from 25(OH)D by 1alpha-hydroxylase6

However, there are a number of other tissues that have been found to have 1alpha-hydroxylase activity. Therefore, these tissues can activate circulating 25(OH)D to 1,25(OH)2D for their own use.

Vitamin D_2 and D_3 were once thought to be equivalent forms of vitamin D, but research has found that D_3 supplementation increases 25(OH)D concentrations more than D_2 supplementation7,8.

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Environmental Factors That Impact Vitamin D3 Synthesis

There are a number of environmental factors that affect vitamin D_3 synthesis:

Latitude

The latitude a person is at affects that person's ability to synthesize vitamin D_3. There is an inverse relationship between distance from the equator and UV light exposure. Thus, with increased distance from the equator (increased latitude), there is decreased UV light exposure and vitamin D_3 synthesis. The link below shows the latitude and longitude lines of the United States.

Web Link

United States Latitude and Longitude Lines

Seasons

Seasons also make a difference in vitamin D_3 synthesis. In Boston (42° N), vitamin D synthesis only occurs from March-October, because during late fall and winter not enough UV-B reaches the earth's surface to synthesize vitamin D_3. However, in Los Angeles (34° N), vitamin D_3 synthesis occurs year round10. The difference is the angle of the sun relative to latitude and how many UV-B photons are absorbed before they reach the earth's surface9.



Figure 12.1.5: Seasons are also an important factor affecting vitamin D_3 synthesis

Time

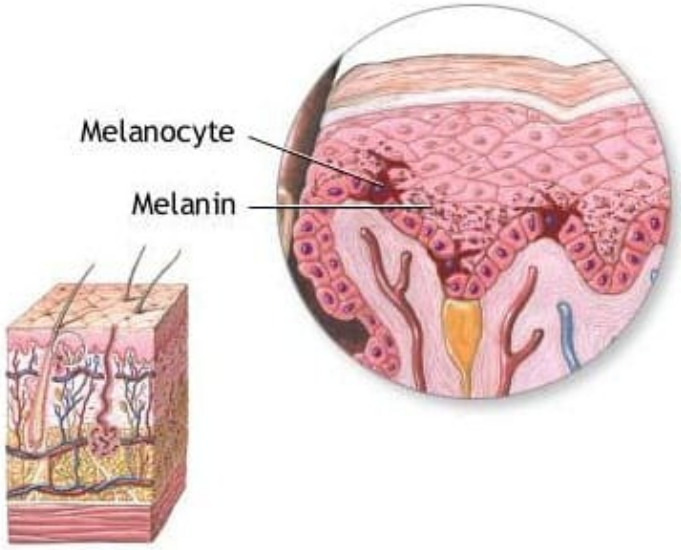
Time of day is also an important factor in affecting vitamin D_3 synthesis. Vitamin D_3 synthesis increases in the morning before peaking at noon, then declines the rest of the day[9].



Figure 12.1.6: Time of day is an important factor for vitamin D_3 synthesis

Skin pigmentation

Another factor that plays an important role in vitamin D_3 synthesis is skin pigmentation. Skin color is the result of increased production of the pigment melanin, as shown in the link below.



Melanin is the natural substance that gives color (pigment) to hair, skin, and the iris. (Public Domain; NIH)

Very dark skin color can provide a sun protection factor (SPF) 8-30 for those individuals who never burn[2]. These individuals will require approximately 5- to 10-times greater sunlight exposure than light-skinned, white individuals to synthesize the same amount of vitamin D_3[10,11].

Age

Age also plays a factor in vitamin D_3 synthesis. Aging results in decreased 7-dehydrocholesterol concentrations in the skin, resulting in an approximately 75% reduction in the vitamin D_3 synthesis capability by age 70[11].



Figure 12.1.7: Aging decreases vitamin D synthesis

Clothing

Clothing is another factor that influences vitamin D_3 synthesis. More clothing means that less sun reaches your skin, and thus less vitamin D_3 synthesis.

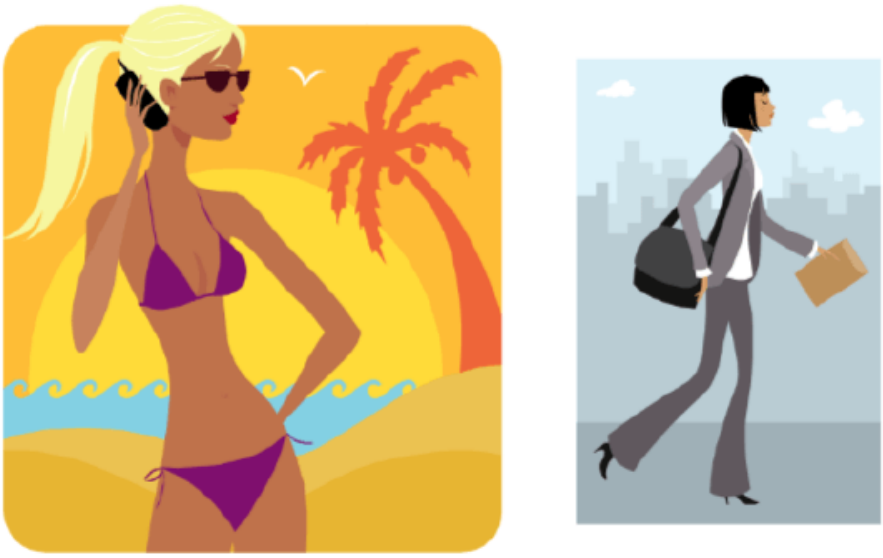


Figure 12.1.8: Which of these 2 do you think is synthesizing less vitamin D?

Sunscreen, "Sensible Sun Exposure", and Tanning

There is quite a spirited debate on sunscreen, sun exposure, skin cancer, and vitamin D synthesis. On one side are the vitamin D researchers, on the other side are dermatologists. Older vitamin D research found that SPF 8 sunscreen almost totally blocked vitamin D_3 synthesis12. However, more recent research as described in the article below suggests that it does occur even with sunscreen use.

Web Link

Sunscreen doesn't prevent vitamin D production in most people, studies find

However, the SPF value equals 1/(# photons that reaches your skin) meaning that SPF 30 means 1/30 UV photons reach your skin. Thus, vitamin D_3 synthesis shouldn't be totally blocked. In addition, studies indicate that consumers apply 1/2 or less of the amount required to get the listed SPF protection4. Researchers recommend sun exposure on the face, arms, and hands for 10-15 minutes 2-3 times per week between 10 AM-3 PM10,13. However, dermatologists do not like "sensible sun exposure" because this is also the peak time for harmful sun exposure. Dermatologists say that "sensible sun exposure" appeals to those who are looking for a reason to support tanning and are at highest risk (primarily young, fair-skinned females) of sun damage. They argue that vitamin D can be provided through supplementation11.

What about tanning beds? Not all tanning beds provide UV-B rays that are needed for vitamin D_3 synthesis. In fact, some advertise that they only use UV-A rays that are safer, even though this is not the case14. Virtually every health organization advises against using tanning beds, because the risks are far greater than the potential benefits14,15.

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Dietary or Supplemental Vitamin D

Because of the possible double-edged sword of sun exposure for synthesizing vitamin D_3, dietary or supplemental vitamin D is another alternative.

However, there are a limited number of foods naturally rich in vitamin D. Good sources of vitamin D are fatty fish (salmon, tuna, etc.) and their oils (such as cod liver oil). The amount of vitamin D in fatty fish varies greatly with wild-caught salmon being the highest. One study showed that farmed salmon contained almost 75% less vitamin D than wild-caught salmon16. It is not known whether this disparity exists between other types of farmed and wild-caught fish varieties.

Table 12.1.1: Vitamin D content of fish16

Fish	Vitamin D (IU/oz)
Blue Fish	280 ± 68
Cod	104 ± 24
Grey Sole	56 ± 36
Farmed Salmon	240 ± 108
Wild Salmon	988 ± 524
Farmed Trout	388 ± 212
Tuna	404 ± 440

Like vitamin C, E, and A, international units (IU) are also used for vitamin D.

For vitamin D the conversions are:

1 ug of D_3 = 40 IU

1 ug of 25-OH-D = 200 IU[17]

Thus, since not many foods contain vitamin D, cow's milk has been voluntarily fortified with vitamin D_2 or D_3 (100 IU/8 oz) since the 1930s[11]. However, the actual measured amount of vitamin D in many brands of cow's milk is far less than stated on their labels[18,19]. Part of this problem stems from a lack of a standardized method for measuring vitamin D in the past. Without standardized analysis, there inevitably was a wide range of variation from lab-to-lab in the reported amount of vitamin D.

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Lactose Intolerance

Another issue with relying on dairy products to provide vitamin D is the common problem of lactose intolerance. Lactose intolerant individuals don't have lactase, the enzyme needed to break down lactose. Common symptoms of this condition include:

- Abdominal Pain
- Abdominal Bloating
- Gas
- Diarrhea
- Nausea[20]

Lactose intolerance is a fairly common problem worldwide, as shown in the map below.

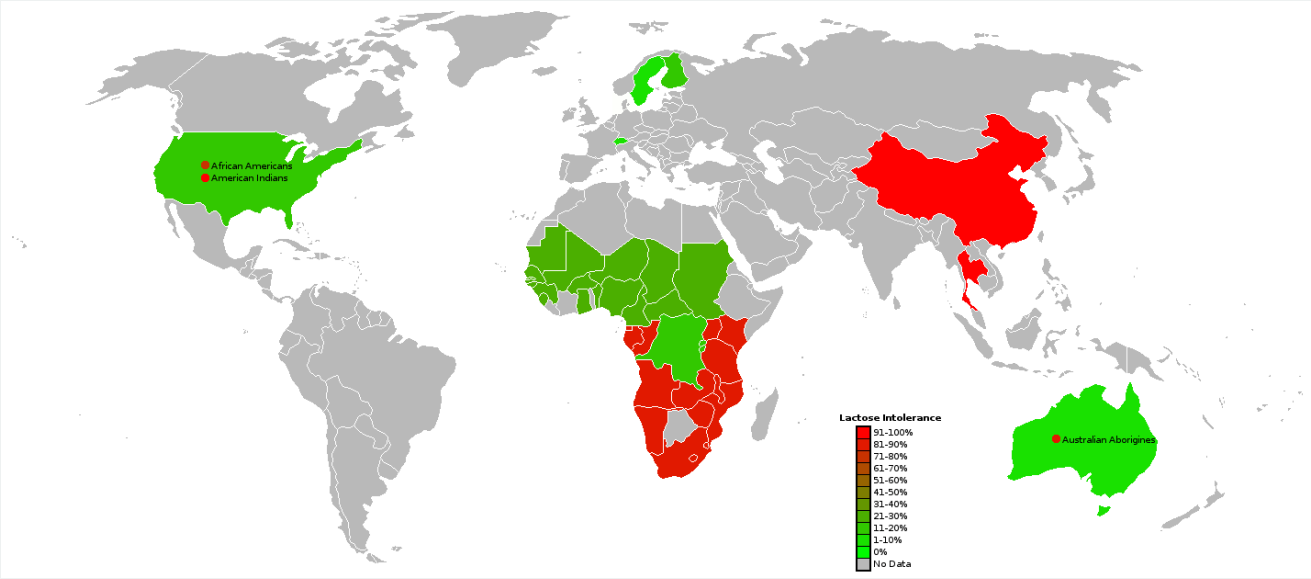


Figure 12.1.9: Lactose intolerance worldwide (red high, green low). (Public Domain; Stevenfruitsmaak via Wikipedia)

The following table shows the percent of people who are lactose intolerant by race:

Table 12.1.2: Lactose intolerance rates[22]

Race or ethnicity	% Lactose Intolerant
Southeast Asian	98%
Native Americans	62-100%[23]
Asian Americans	90%
Alaskan Eskimo	80%
African-American Adults	79%
Mexicans (rural communities)	74%
North American Jews	69%
Greek Cypriots	66%
Cretans	56%
Mexican American Males	55%
Indian Adults	50%
African-American Children	45%
Indian Children	20%
Descendants of N. Europeans	5%

Thus, you can see that many people are lactose intolerant. Coincidentally, many of these people have darker pigmented skin, meaning that they have an increased risk of vitamin D deficiency/insufficiency because they require greater sun exposure to synthesize adequate amounts of vitamin D_3.

Other foods that are sometimes fortified are breakfast cereals and orange juice. Despite the fact that orange juice doesn't contain fat, and vitamin D is fat-soluble, vitamin D is quite bioavailable in orange juice[24].

Vitamin D in supplements is found as vitamin D_2 or D_3. However, based on the recent evidence suggesting that D_2 isn't as beneficial as D_3, many are being reformulated to contain D_3[25].

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Response to Low Blood Calcium

One of the major functions of vitamin D is to assist in maintaining blood calcium concentrations. The other major regulators of blood calcium concentrations are 2 hormones: parathyroid hormone (PTH) and calcitonin, which are released from the parathyroid glands and thyroid glands, respectively. Bone serves as the calcium depot, or reservoir, if there is a sufficient concentration in the body. In bone, calcium is found in hydroxyapatite crystals on a collagen matrix.

The chemical formula of hydroxyapatite is $\mathrm{Ca_{10}(PO_4)_6(OH)_2}$.

Calcium and phosphorus are either jointly deposited (deposition) or jointly liberated (resorption) from bone hydroxyapatite to maintain/achieve blood calcium concentrations. Osteoblasts are bone cells that are responsible for bone formation or depositing hydroxyapatite. Osteoclasts are the bone cells that are responsible for breaking down or resorption of bone. An easy way to remember the function of these cells is:

- **Osteoblasts** "build" bone
- **Osteoclasts** "chew" bone

Bone resorption is the process of liberating calcium and phosphorus from hydroxyapatite. Bone deposition is the process of depositing calcium and phosphorus in bone as hydroxyapatite.

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Response to Low Blood Calcium

The parathyroid senses low blood calcium concentrations and releases PTH. These steps are designed to maintain consistent blood calcium concentrations, but also affects phosphate (phosphorus) concentrations. PTH has 3 effects:

1. Increases bone resorption
2. Decreases calcium and increases phosphorus urinary excretion
3. Increases 1,25(OH)2D activation in the kidney3,14

The first effect of PTH is increased bone resorption. Hydroxyapatite must be broken down to release both calcium and phosphate. This effect is illustrated below.

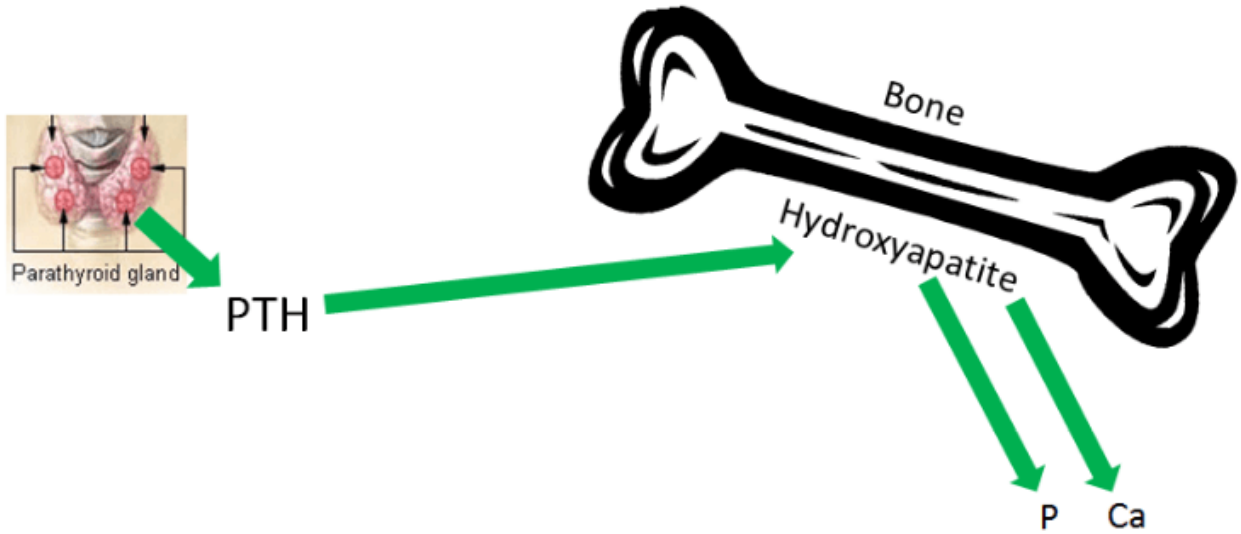


Figure 12.1.10: PTH effect 1: increased bone resorption26

The second effect of PTH is decreased calcium excretion in urine. This is a result of increased calcium reabsorption by the kidney before it is excreted in urine. Kidney phosphate reabsorption is decreased, meaning the net effect is less calcium, but more phosphate in urinary excretion, as shown in the figure below.

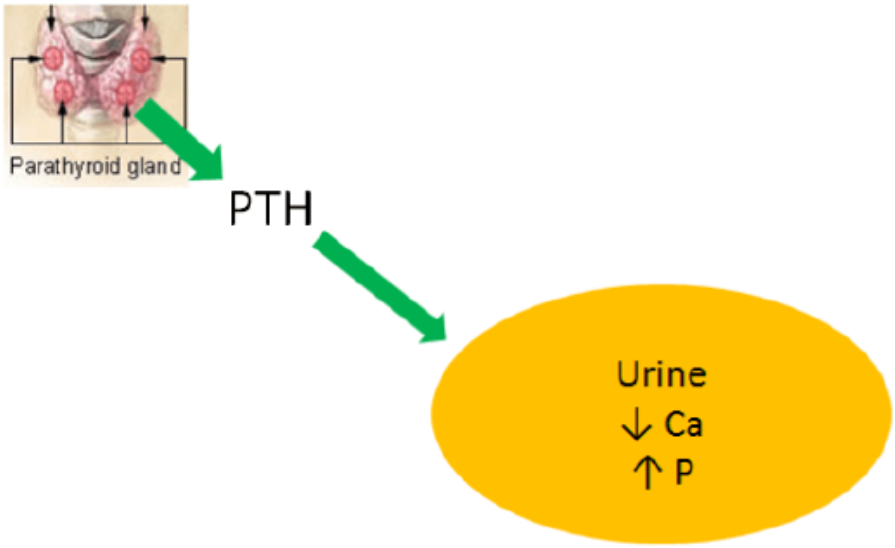


Figure 12.1.11: PTH effect 2: decreased calcium, increased phosphorus excretion[26]

The 3rd effect of PTH is that it increases 1,25(OH)2D activation in the kidney, by increasing 1alpha-hydroxylase levels. The 1,25(OH)2D then increases calcium and phosphorus absorption in the small intestine to help raise blood calcium levels, as shown below. This mechanism will be discussed in more detail in the vitamin D receptor subsection.

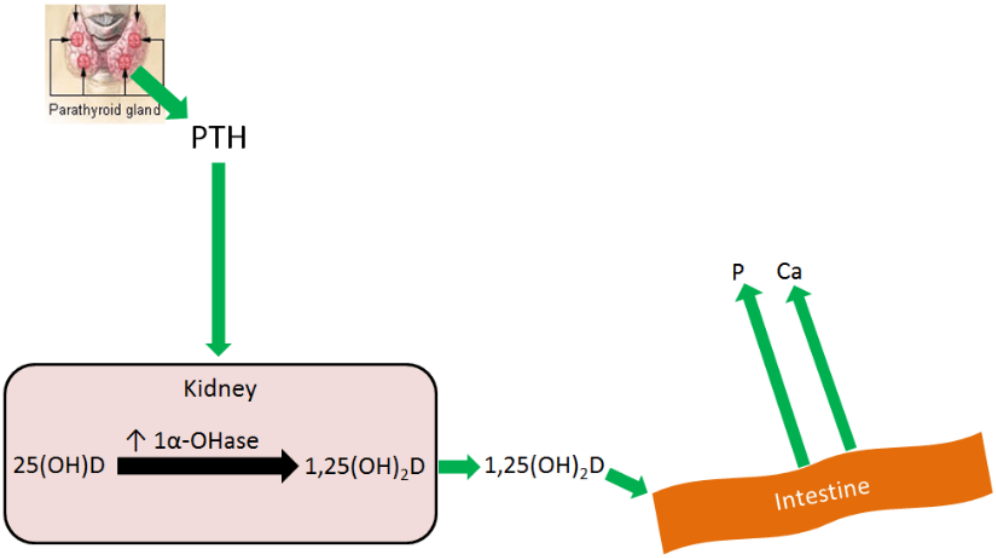


Figure 12.1.12: PTH effect 3: increased 1,25(OH)2D activation[26]

Overall PTH causes more calcium and phosphate to be leached from bone, and absorbed from the intestine into the blood. Coupled with decreased calcium and increased phosphate urinary excretion, means that blood calcium levels rise without a marked rise in phosphate levels, as depicted in the figure below.

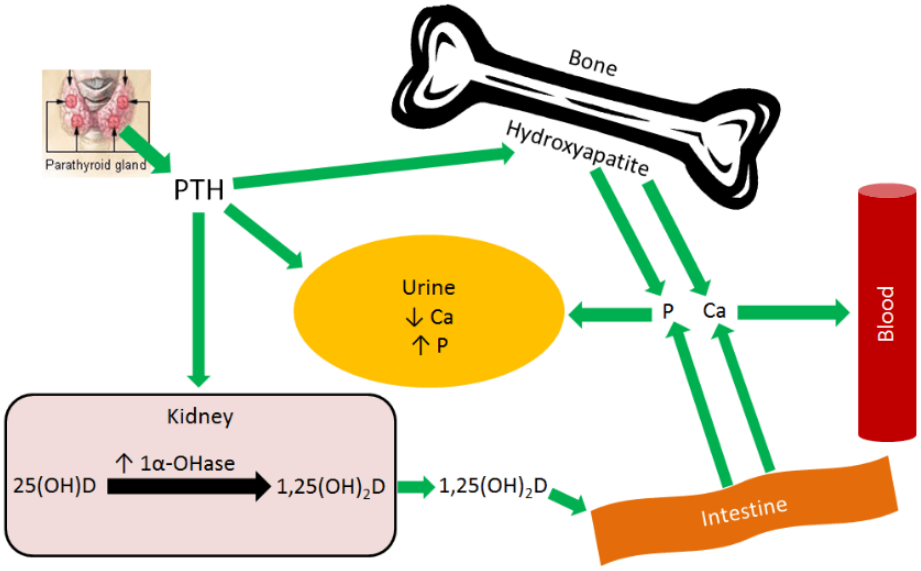


Figure 12.1.13: 1,25(OH)2D increased calcium and phosphorus absorption[26]

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Response to High Blood Calcium

In adults, it is rare for blood calcium concentrations to get too high. However, in infants and young children whose bodies, and thus bones, are not as large, the hormone calcitonin helps to prevent blood calcium levels from getting too high[3].

Response to High Blood Calcium

High blood calcium concentrations are sensed by the thyroid, which releases calcitonin. This response is designed to maintain/achieve normal blood calcium concentrations, but also affects phosphate (phosphorus) levels. Calcitonin has 3 effects[3,14]:

1. Decreases bone resorption, increases bone deposition
2. Increases calcium and phosphorus excretion in urine
3. Decreases 1,25(OH)2D activation in the kidney

The first effect of calcitonin is to inhibit bone resorption, thus promoting the deposition of calcium and phosphorus into bone as hydroxyapatite.

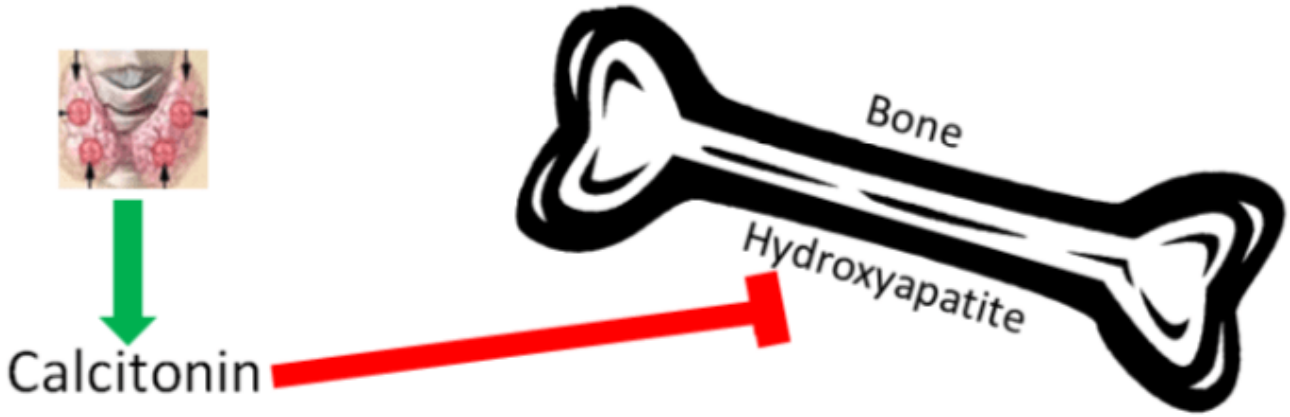


Figure 12.1.14: Calcitonin effect 1: increased bone deposition[26]

The second effect of calcitonin is to increase calcium and phosphorus excretion in urine.

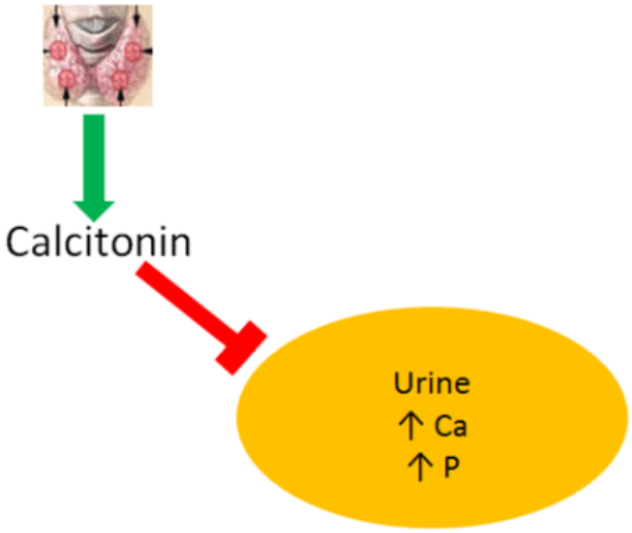


Figure 12.1.15: Calcitonin effect 2: increased calcium and phosphorus excretion[26]

The third effect of calcitonin is to decrease 1alpha-hydroxylase levels, which decreases the activation of 1,25(OH)2D. As a result, the absorption of calcium and phosphorus from the small intestine is decreased, as shown below.

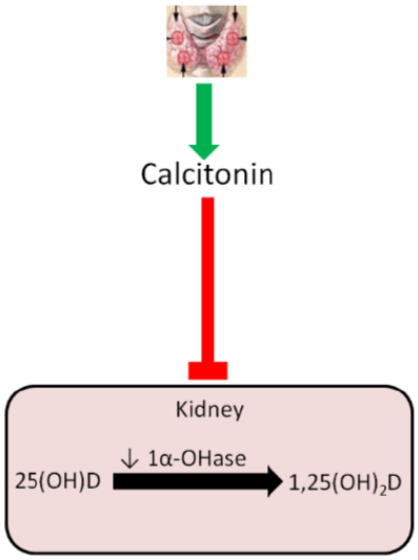


Figure 12.1.16: Calcitonin effect 3: decreased 1,25(OH)2D activation[26]

Overall, calcitonin inhibits the 3 actions that PTH uses to increase blood calcium levels. Thus, more calcium and phosphate are deposited into bones and excreted into urine as shown below. This causes blood calcium levels to decrease.

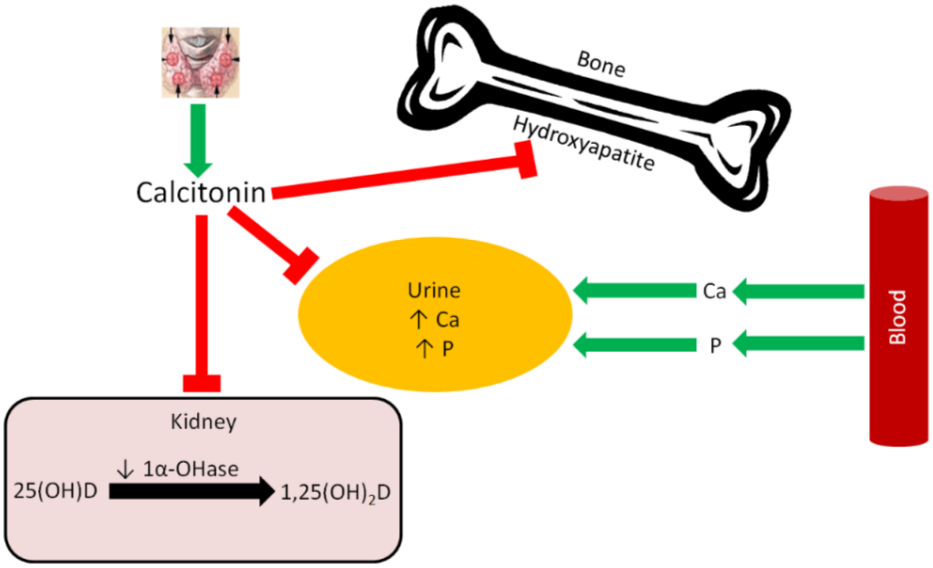


Figure 12.1.17: Response to high blood calcium[26]

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Vitamin D Receptor

Vitamin D, along with vitamin A, are unique among the vitamins in that they have nuclear receptors. Many steroid hormones have nuclear receptors. The following figure illustrates the action of a nuclear hormone receptor.

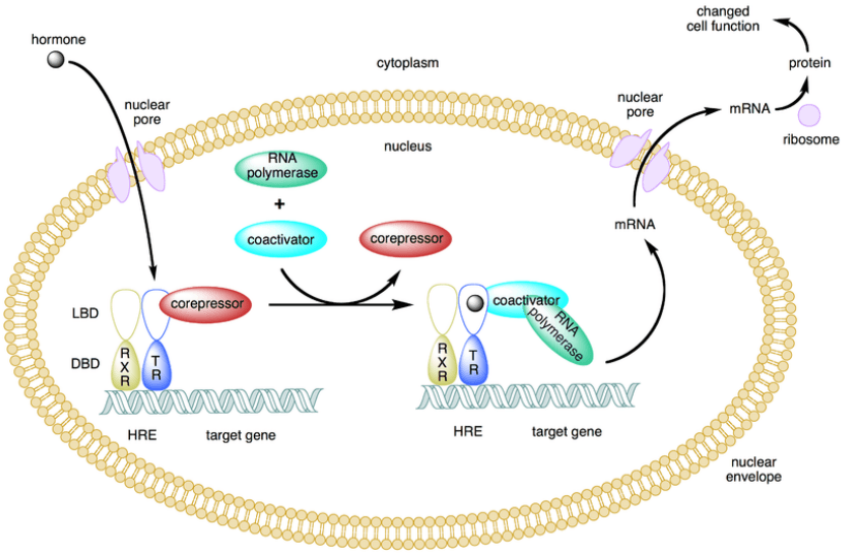


Figure 12.1.18: Nuclear hormone receptors action[27]

In the figure above of the hormone (in this case thyroid hormone) receptor, the receptor's ligand (something that binds to the receptor), enters the nucleus and binds to the thyroid hormone receptor (TR). The TR has paired (formed a dimer) with the retinoid X receptor (RXR) on the hormone response element (HRE) in the promoter (region before a gene in the DNA sequence) of target genes. The HRE for thyroid hormone is the thyroid hormone response element. Target genes are those whose transcription is altered by the hormone binding to its receptor on the response element. The mRNA produced then leaves the nucleus where it is translated into protein.

Vitamin A and D have nuclear receptors that act in the same fashion as nuclear hormone receptors. The video below illustrates and explains the action of a nuclear hormone receptor.

YouTube Video

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Video 12.1.1: Steroid hormone receptors. https://www.youtube.com/watch?v=Dxyq8GAWbpo

Query 12.1.13

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1,25(OH)2D is considered to be the active form of vitamin D because it binds to the vitamin D receptor (VDR). Like the thyroid hormone example above, there is a vitamin D response element (VDRE) in the promoter of specific vitamin D target genes. In the figure below, 25(OH)D, the major circulating form of vitamin D, is usually transported through the blood to a target tissue by vitamin D binding protein (DBP). The kidney converts 25(OH)D to 1,25(OH)2D by use of the enzyme 1alpha-hydroxylase, but this enzyme is also found in other tissues to synthesize 1,25(OH)2D primarily for their own use (rather than secreting like the kidney). The latter scenario is what is being represented in the figure below. 1,25(OH)2D (bound to DBP) moves from the kidney, or the tissue itself, into the nucleus. It then binds to the vitamin D receptor (VDR), that is dimerized to the RXR on the vitamin D response element of the target gene. Consequently, this binding causes increased transcription of mRNA. The mRNA then moves into the cytoplasm to synthesize specific proteins. This process is shown in the figure below.

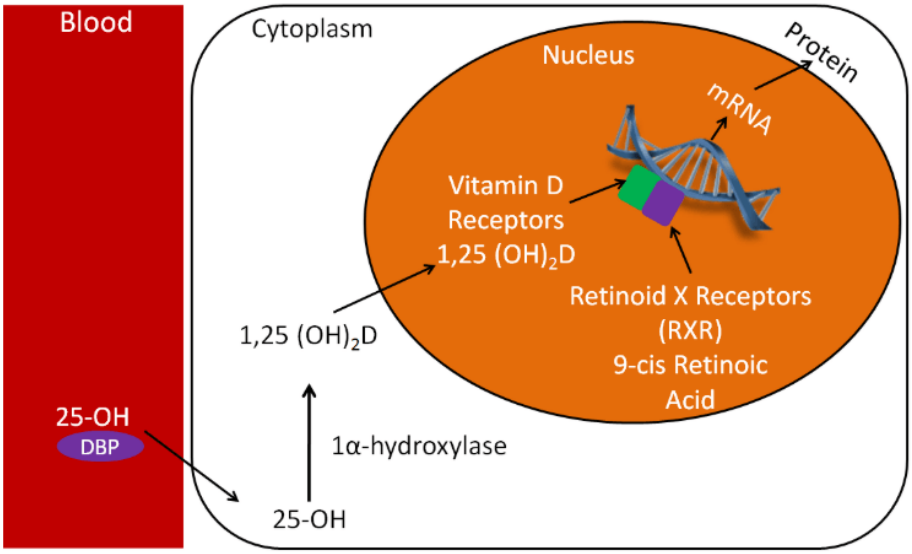


Figure 12.1.19: Vitamin D receptor and a generic target gene

It's through this action that 1,25(OH)2D is able to increase calcium absorption. In this case, the target gene is the calcium-binding protein calbindin. Thus, increased 1,25(OH)2D leads to increased calbindin mRNA. This then leads to increased calbindin protein levels. Calbindin will be discussed in more detail in the calcium section.

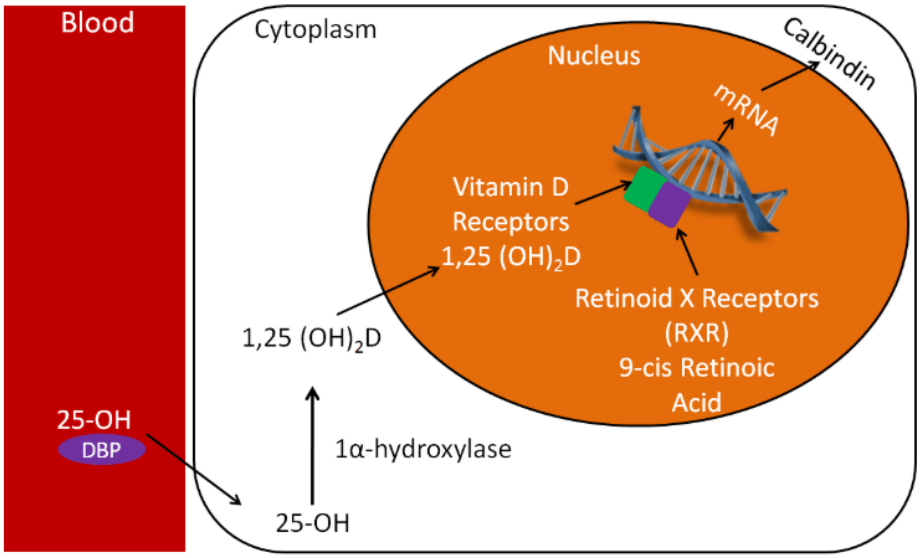


Figure 12.1.20: Vitamin D receptor and calbindin

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Vitamin D Deficiency, Toxicity & Insufficiency

Rickets is a vitamin D deficiency condition in infants and children. A lack of vitamin D leads to decreased bone mineralization, causing the bones to become weak. The bones then bow under pressure, leading to the characteristic bowed legs, as seen below.

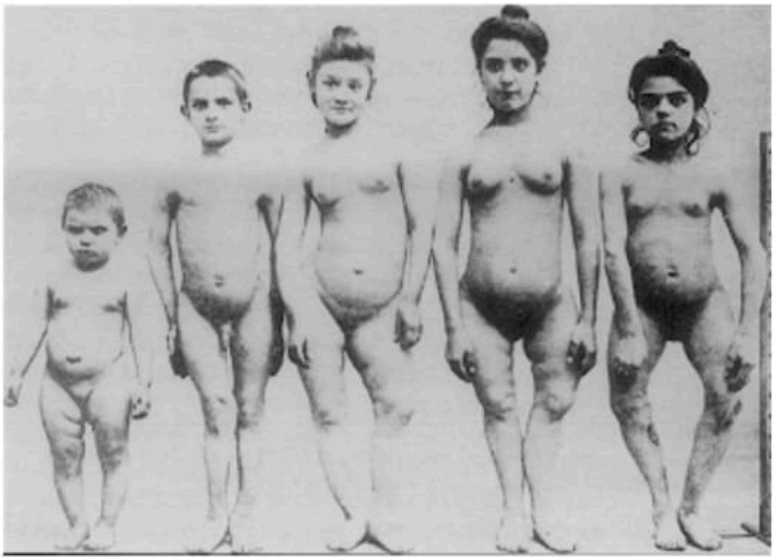


Figure 12.1.21: Children suffering from rickets28

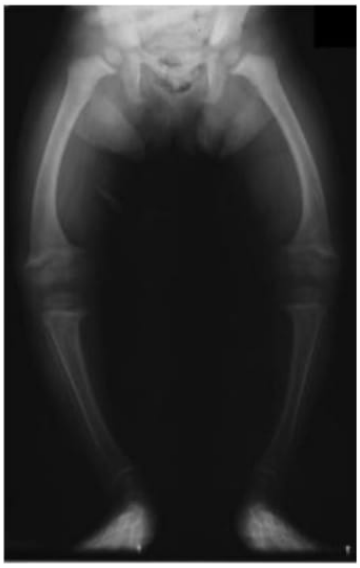


Figure 12.1.22: X-ray from child suffering from rickets29

Another characteristic symptom of rickets is rachitic rosary, or beaded ribs. The beading occurs at the areas where cartilage meets bone on the rib cage, as shown in the link below14.

Web Link

Rachitic Rosary

Osteomalacia is a vitamin D deficiency in adults and results in poor bone mineralization. The bone becomes soft, resulting in bone pain and an increased risk of fractures14.

While rickets and osteomalacia are fairly rare in the United States, it is believed that vitamin D insufficiency might be much more widespread. Insufficiency means that the level of intake, or body status, is suboptimal (neither deficient nor optimal). The figure below illustrates this concept.

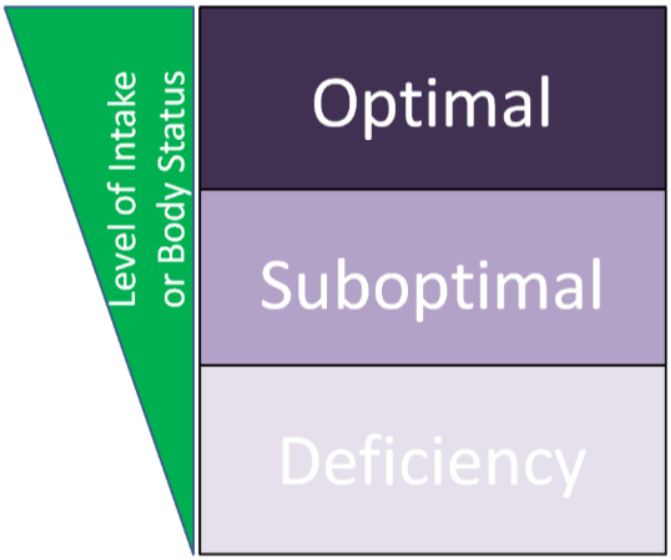


Figure 12.1.23: Illustration of insufficient or suboptimal levels

Suboptimal/insufficient means intake, or status, is higher than deficient, but lower than optimal. This is an important distinction

to understand particularly for vitamin D, because there have been some (like Dr. Michael Holick described in the link below) saying the people are vitamin D deficient when their circulating 25(OH)D concentrations are lower than optimal. This is different from a classical deficiency definition, where there is a condition associated with too low level of intake or body status. What is really being described is that circulating 25(OH)D concentrations might be suboptimal. A lot of the debate about vitamin D deficiency is nicely captured in the article about Dr. Michael Holick, a prominent vitamin researcher.

Web Link

Selling America on Vitamin D - and reaping the profits

Thus, higher intake levels will provide additional benefits. The functions of vitamin D are growing by the day due to increased research discoveries. These functions now include benefits beyond bone health, further supporting the importance of vitamin D. In late 2010, an RDA for vitamin D was established (was an Adequate Intake before). This made it, along with calcium, the first micronutrients to have their DRIs revised30. The RDA for vitamin D is 3 times higher than the previous AI. Many believe these are more reasonable levels, while others think that the new RDA is still not high enough. This belief, that many people's vitamin D intake/status is suboptimal, is challenged by a review described in the first link below that found that vitamin D did not reduce osteoporosis risk. In addition, a recent meta-analysis (second link) concluded that "there is probably no benefit to expect from vitamin D supplementation in normally healthy people."

Web Link

Vitamin D Ineffective for Preventing Osteoporosis

Vitamin D from supplements can become toxic. You cannot develop vitamin D toxicity from sun exposure, because the sunlight degrades a precursor of vitamin D_3 in the skin9. Vitamin D toxicity results in hypercalcemia or high blood calcium levels. These become problematic because it can lead to calcification of soft tissues.

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Query 12.1.16

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12.2: Calcium

Calcium is a macromineral and the most abundant mineral in the body. The reason for calcium's abundance is its distribution in the skeleton, which contains 99% of the calcium in the body.

Calcium Absorption

Calcium is taken up into the enterocyte through Transient Receptor Potential V6 (TRPV6), a calcium channel found on the brush border. Calbindin is the calcium binding protein that facilitates uptake through TRPV6 and transport across the enterocyte. [redacted] — [redacted] ATPase functions to pump calcium out of the enterocyte and into circulation and to pump magnesium into the enterocyte, as shown below1.

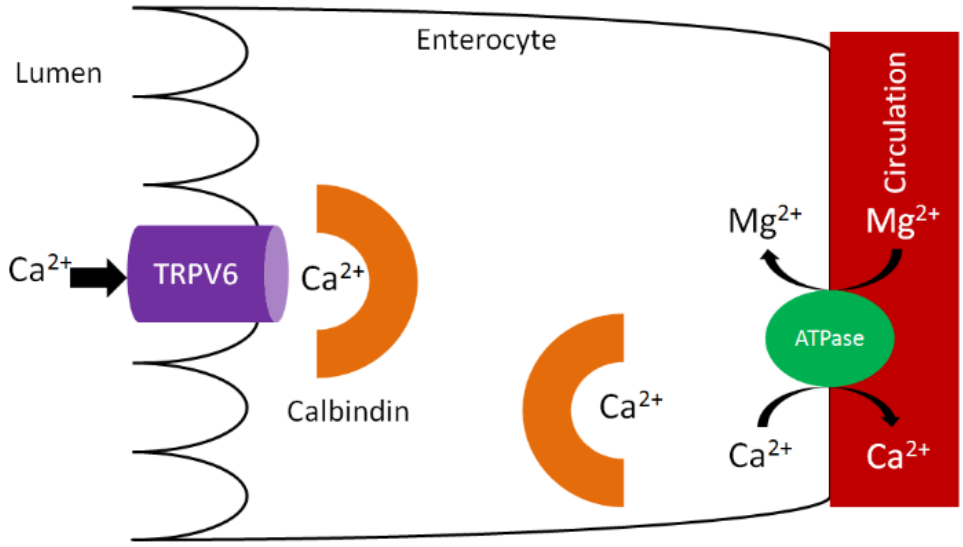


Figure 12.2.1: Calcium uptake and absorption

As we have previously discussed, increased 1,25(OH)2D synthesis in the kidney causes increased binding to the vitamin D receptor, which increases calbindin synthesis. Increased calbindin ultimately increases calcium uptake and absorption.

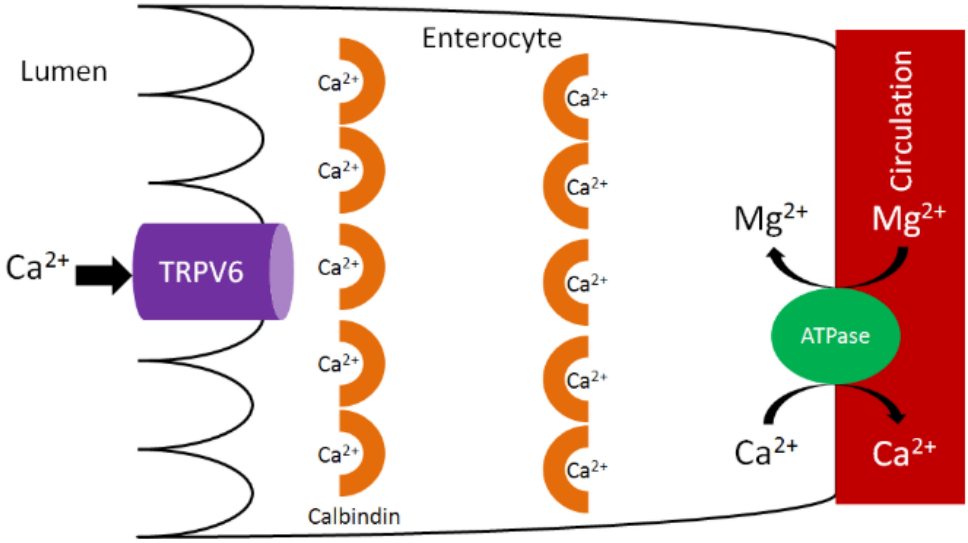


Figure 12.2.2: Increased calbindin increases calcium absorption

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There are a couple of calcium-binding compounds that inhibit its absorption (normally by binding to it). Therefore, even though some foods are good sources of calcium, the calcium is not very bioavailable. Oxalate, found in high levels in spinach, rhubarb, sweet potatoes, and dried beans, is the most potent inhibitor of calcium absorption2. Recall that calcium oxalate is one of the compounds that makes up kidney stones. Based on this understanding, it should not be a surprise that formation of this compound inhibits calcium absorption.

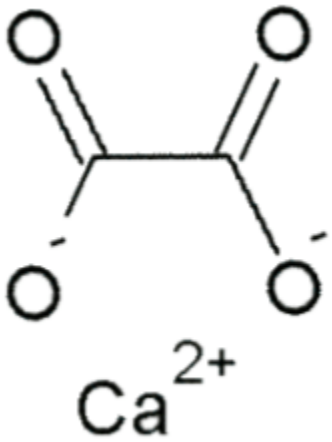


Figure 12.2.3: Structure of calcium oxalate3

Another inhibitor of calcium absorption is phytate. Phytate is found in whole grains and legumes. You will learn more about it in the phosphorus section.

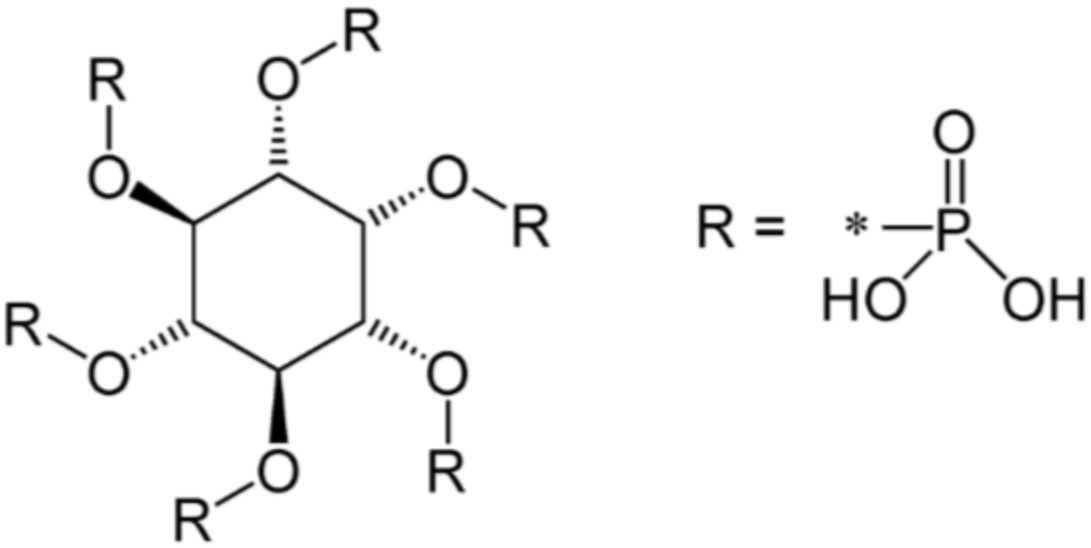


Figure 12.2.4: Structure of phytate[4]

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Calcium Bioavailability

Calcium bioavailability varies greatly from food to food, as shown in the table below. This table gives the serving size, calcium content of that food, and percent absorbed. The calcium content is multiplied by the absorption percentage to calculate the estimated calcium absorbed. Finally, it shows servings of each food needed to equal the estimated calcium absorbed from 1 serving of milk.

Table 12.2.1: Bioavailability of calcium from different foods sources[5-7]

Food	Serving Size (g)	Calcium content (mg)	Absorption (%)	Estimated Calcium Absorbed	Servings needed to equal 240 mL cow's milk
Cow's Milk	240	300	32.1	96.3	1.0
Almonds, dry roasted	28	80	21.2	17.0	5.7
Beans, Pinto	86	44.7	26.7	11.9	8.1
Beans, Red	172	40.5	24.4	9.9	9.7
Beans, White	110	113	21.8	24.7	3.9
Bok Choy	85	79	53.8	42.5	2.3
Broccoli	71	35	61.3	21.5	4.5
Brussel Sprouts	78	19	63.8	12.1	8.0
Cabbage, Chinese	85	79	53.8	42.5	2.3
Cabbage, Green	75	25	64.9	16.2	5.9

Food	Serving Size (g)	Calcium content (mg)	Absorption (%)	Estimated Calcium Absorbed	Servings needed to equal 240 mL cow's milk
Cauliflower	62	17	68.6	11.7	8.2
Cheddar Cheese	42	303	32.1	97.2	1.0
Chinese mustard greens	85	212	40.2	85.3	1.1
Chinese spinach	85	347	8.36	29	3.3
Fruit Punch (CCM)	240	300	52	156	0.6
Kale	85	61	49.3	30.1	3.2
Kohlrabi	82	20	67.0	13.4	7.2
Mustard Greens	72	64	57.8	37.0	2.6
Orange juice (CCM)	240	300	36.3	109	0.8
Radish	50	14	74.4	10.4	9.2
Rhubarb	120	174	8.54	10.1	9.5
Rutabaga	85	36	61.4	22.1	4.4
Sesame seeds, no hulls	28	37	20.8	7.7	12.2
Soy milk (tricalcium phosphate)	240	300	24.0	72.0	1.3
Soy milk (calcium carbonate)	240	300	21.1	66.3	1.0
Spinach	85	115	5.1	5.9	16.3
Sweet Potatoes	164	44	22.2	9.8	9.8
Tofu with Ca	126	258	31.0	80.0	1.2
Turnip Greens	72	99	51.6	51.1	1.9
Watercress	17	20	67.0	13.4	7.2
Yogurt	240	300	32.1	96.3	1.0

Notice that the foods high in oxalate like spinach, rhubarb, sweet potatoes, and dried beans are poorly absorbed. But there are still a number of calcium sources outside of milk.

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The 2 most common forms of calcium found in supplements are calcium carbonate and calcium citrate. As you can see in the figure below, they differ in the amount of elemental calcium they contain. This shows how much of the molecular weight of the compound is calcium.

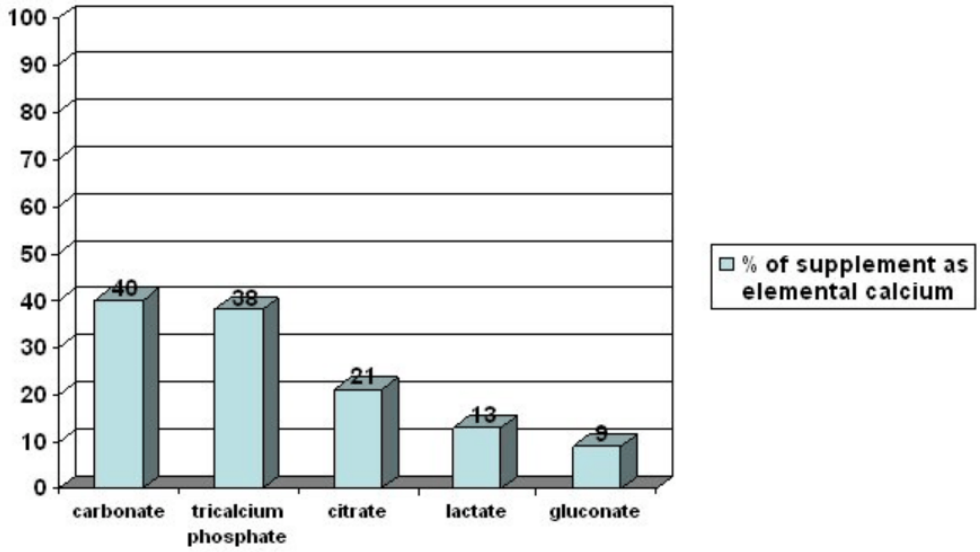


Figure 12.2.5: Percent of calcium supplements that is elemental calcium[8]

The higher the percent elemental calcium, the greater the amount of calcium you will receive per given weight of that compound, versus a compound that has a lower elemental calcium percentage. Both carbonate and citrate forms are well absorbed, but individuals with low stomach acid absorb citrate better. Also, carbonate is best absorbed when taken with food, while for citrate it is equally well absorbed when taken alone[8].

Older research suggested that calcium citrate malate was more bioavailable than other calcium sources. However, a more recent clinical study found no difference in the bioavailability of calcium from calcium citrate malate in orange juice, skim milk, or calcium carbonate supplements[9]. There is some evidence that suggests that even though bioavailability is the same among these different forms, they might not be equally effective in improving bone measures[10].

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Calcium Functions

Calcium in hydroxyapatite is a major component of bones and teeth.

There are also a number of non-bone functions of calcium. Calcium is an intracellular signaling molecule. Because of this, intracellular calcium is tightly controlled, primarily stored within organelles.

Non-bone functions include:

Neurotransmitter release

Neurotransmitter release is stimulated by the opening of voltage-gated Ca^{2+} channels. This stimulates the synaptic vesicle to fuse with the axon membrane and release the neurotransmitter into the synapse, as shown below[11].

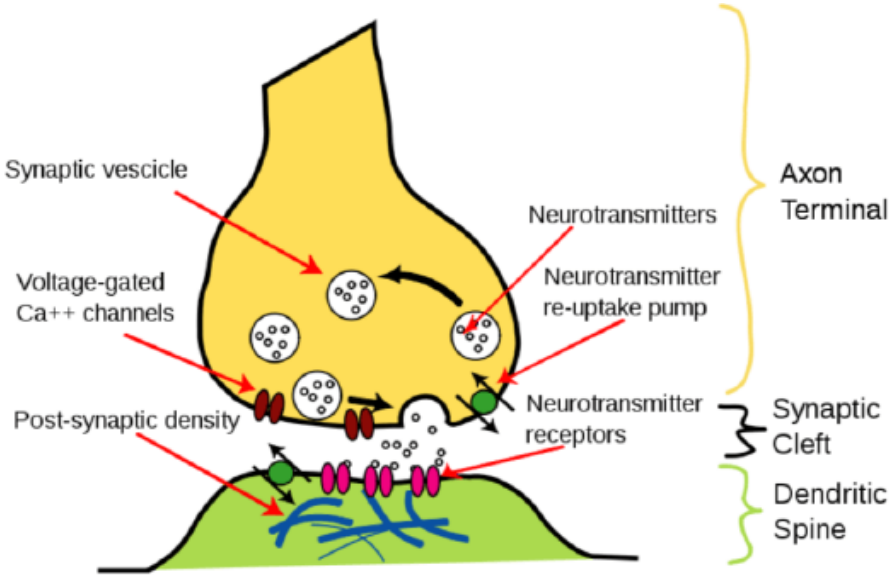


Figure 12.2.6: Calcium regulates neurotransmitter release[12]

Muscle contraction

Calcium is released in muscle cells, where it binds to the protein troponin, changes its shape, and removes the tropomyosin blockade of actin active sites so that contraction can occur[13]. This can be seen in the following figure and video.

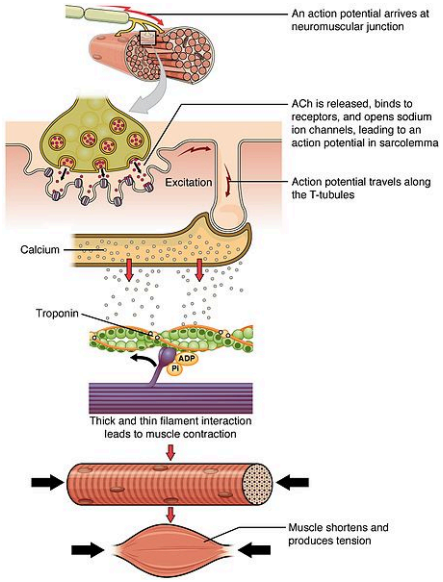


Figure 12.2.7: The role of calcium in muscle contraction[14]

Hormone release

Calcium acts as an intracellular messenger for the release of hormones, such as insulin. The figure below shows how in the beta cells of the pancreas, the opening of voltage-gated calcium channels stimulates the insulin granules to fuse with the beta cell membrane to release insulin.

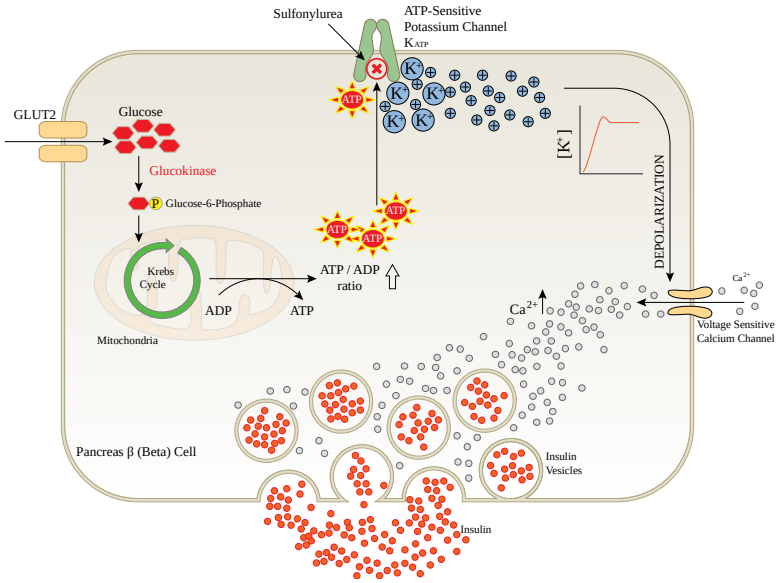


Figure 12.2.8: Calcium signalling insulin release15

Blood Clotting

As will be discussed more in the vitamin K section, calcium binding to activated Gla proteins is important in the blood clotting cascade.

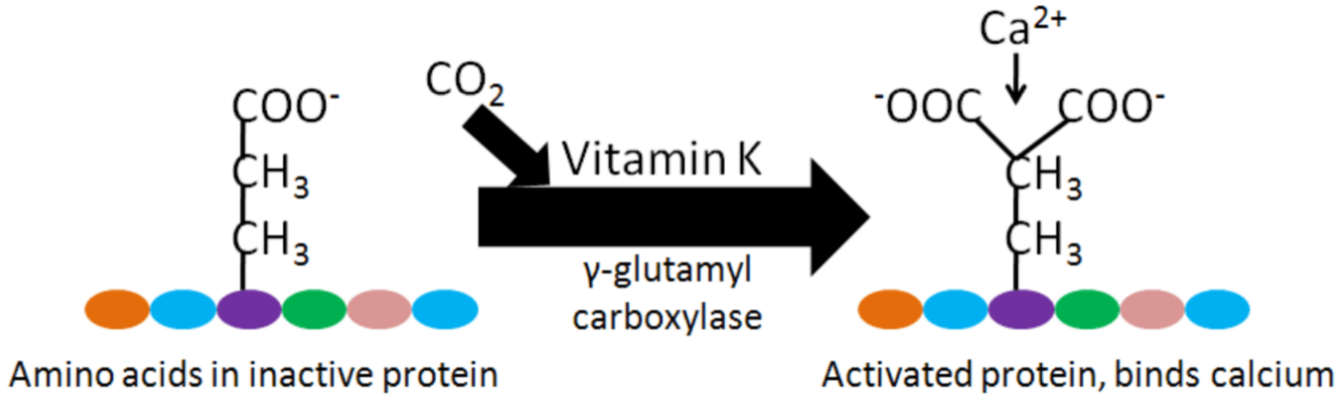


Figure 12.2.9: Calcium bind to Gla proteins. Adapted from reference 1.

Enzyme regulation

The binding of calcium to calcium-binding proteins also regulates the action of a number of enzymes17.

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Calcium Deficiency & Toxicity

Because of the large amount of calcium in bones (which can be mobilized), deficiency is rare[2]. Hypocalcemia (low serum blood calcium concentrations) can result in tetany (involuntary muscle contractions)[1]. In addition, calcium deficiency in children can lead to rickets, the same as occurs in vitamin D deficiency. While not a deficiency, low calcium intake can lead to decreased bone mineral density and the conditions osteopenia and osteoporosis. How these differ from osteomalacia and normal bone is illustrated and described below. There are two different bone components that we will consider to understand what is happening in the bone. Matrix is the protein scaffolding (primarily collagen) onto which mineral is deposited. Mineral is simply the mineral deposited on the matrix.

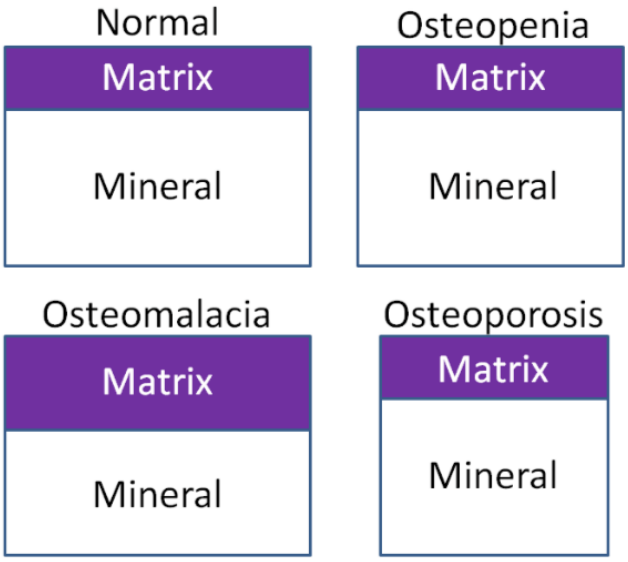


Figure 12.2.10: Bone states; the width of each figure represents the bone mass. The height of the matrix and mineral boxes represents the relative proportion for matrix to mineral in the bone. Adapted from reference 16.

- **Osteomalacia** - Bone mass is normal, but the matrix to mineral ratio is increased, meaning there is less mineral in bone.
- **Osteopenia** - Bone mass is decreased, but the matrix to mineral ratio is not altered from normal bone. This condition is intermediate between normal and osteoporosis.
- **Osteoporosis** - Bone mass is further decreased from osteopenia, but the matrix to mineral ratio is not altered from normal bone[16].

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To prevent osteoporosis it is important to build peak bone mass (the maximum amount that a person will have in their lifetime), 90% of which is built by age 18 and 20 in females and males, respectively, but can continue to increase until age 30. After that time, bone mass starts to decrease. For women after menopause, bone mass decreases dramatically because of the decrease in estrogen production, as shown below[17].

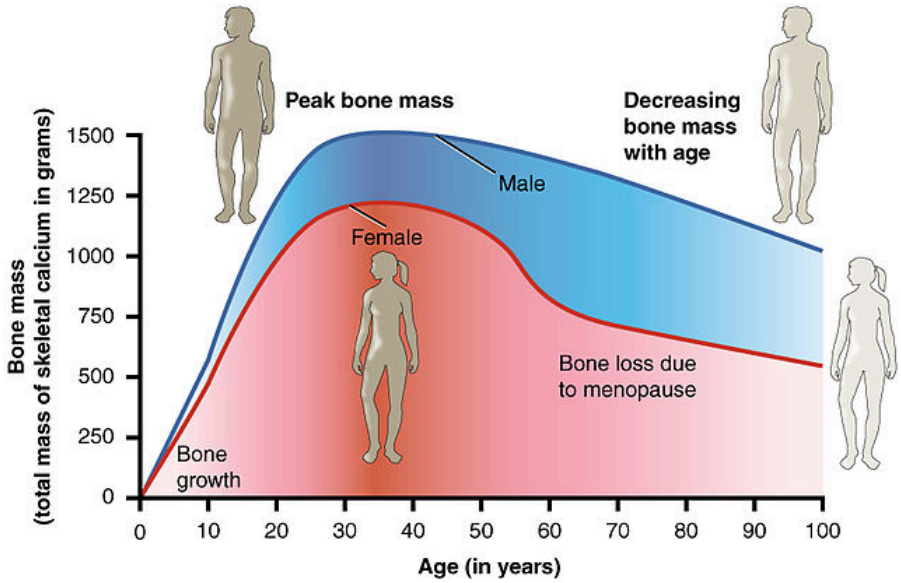


Figure 12.2.11: Age and bone mass[18]

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There is a decrease after menopause in women (estrogen stimulates osteoblasts), that results in a steep decrease in bone mass. Combined with the fact that women have lower peak bone mass to begin with, helps further explain why osteoporosis is more common in females. A measure of bone status is bone mineral density. As the name indicates, bone mineral density is a measure of the amount of mineral in bone. Dual energy X-ray absorptiometry (DEXA) accurately measures bone mineral density using a small amount of radiation. A DEXA is shown in the figure below.



Figure 12.2.12: DEXA scanner[19]

A person lies down on the table and the arm of the machine moves slowly over them.

From the scan, a bone mineral density t-score is generated. These measure your peak bone density compared to a healthy 30-year old adult and give you values of how much higher or lower you are21. The following table summarizes the levels and their scores.

Table 12.2.1: Categories and DEXA bone mineral density t-scores21

Category	T-score
Normal	+1 to -1 SD
Low bone mass (osteopenia)	-1 to -2.5
Osteoporosis	-2.5 or lower

This DEXA measurement cannot distinguish whether the low bone mineral density is due to too little bone (osteoporosis) or too little mineral (osteomalacia)21. There are other methods of measuring bone mineral density, such as peripheral DEXA and ultrasound. These typically are done on the wrist or heel, but are not as accurate because that one area might not reflect the bone mineral density in other parts of the body11.

Calcium toxicity is rare, occurring in those with hyperparathyroidism or high calcium supplementation levels. Like vitamin D, toxicity can lead to calcification of soft tissues11. In addition, a very high intake of calcium can lead to kidney stone formation.

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Query 12.2.9

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20. www.nof.org/patients/diagnos...y-examtesting/
21. https://www.nhs.uk/conditions/dexa-scan/why-its-done/

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12.3: Phosphorus

You have already learned about how blood phosphate levels are regulated in the body by PTH, calcitonin, and 1,25(OH)2D. Animal products are rich sources of phosphate. Plant products contain phosphorus, but some is in the form of phytic acid (phytate, these names are used interchangeably). In grains, over 80% of the phosphorus is phytate. This structure is shown below[1].

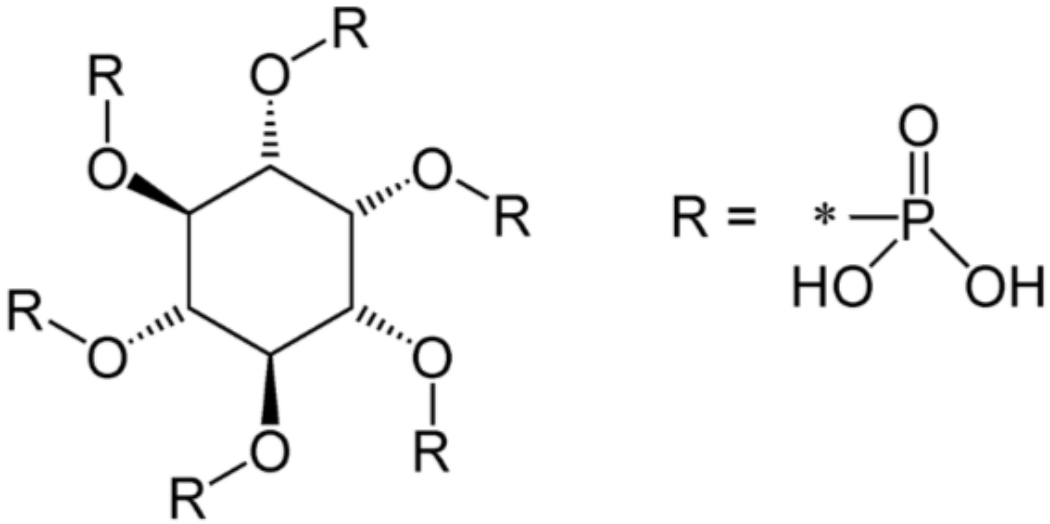


Figure 12.3.1: Structure of phytic acid[2]

The bioavailability of phosphorus from phytate is poor (~50%) because we lack the enzyme phytase that would cleave the phosphorus so it can be taken up[3]. Phytate binds to other minerals and decreases our ability to absorb them (you have learned that it is an inhibitor of calcium uptake, you will learn about it binding other minerals in subsequent sections). Nevertheless, ~50-70% of dietary phosphorus is absorbed[1]. Another source of phosphorus is phosphoric acid that is used to acidify colas. Colas are caramel-colored, carbonated soft drinks that contain caffeine, such as Coca-Cola, Pepsi, etc. Epidemiological studies have found that soft drink consumption is associated with decreased bone mineral densities, particularly in females[4,5]. It has been hypothesized that phosphoric acid plays some role in this effect, but there is limited evidence to support this belief.

Most phosphorus is excreted in the urine.

Phosphorus deficiency is rare, but can hinder bone and teeth development. Other symptoms include muscle weakness, rickets, and bone pain[6]. Toxicity is also rare, but it causes low blood calcium concentrations and tetany[1].

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Phosphorus Functions

Phosphorus has a number of functions in the body[1].

Phosphate is a component of hydroxyapatite in bones and teeth, as described earlier.

Non-bone functions include:

Phosphorylation

Phosphates are used to activate and deactivate a number of proteins. In addition, compounds are also frequently phosphorylated, like the monosaccharides shown below.

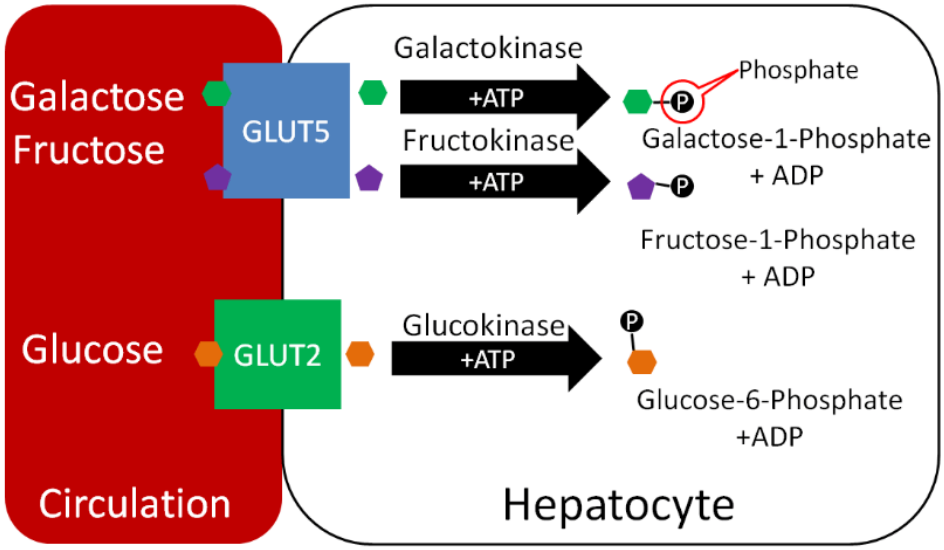


Figure 12.3.2: Uptake of monosaccharides into the hepatocyte

Phospholipids

Phosphates are a component of phospholipids, as shown below.

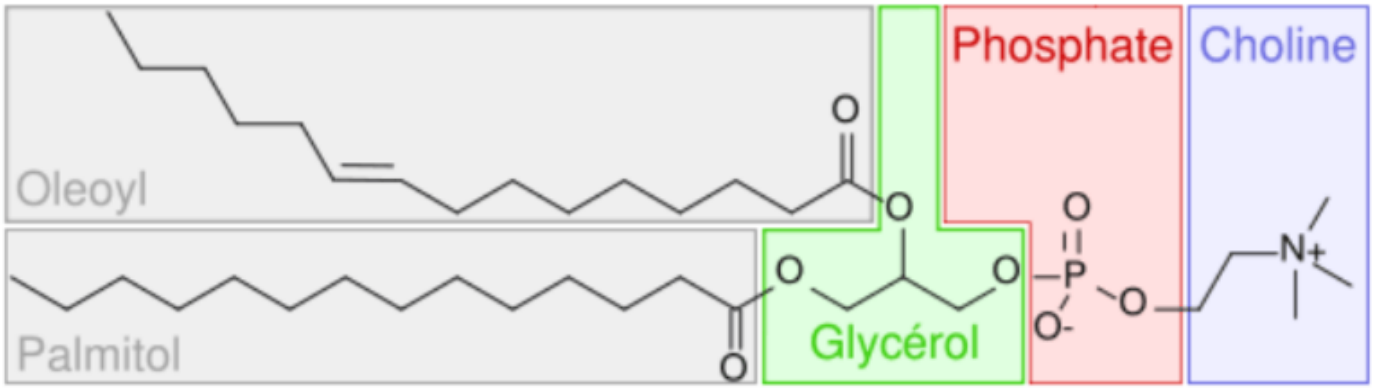


Figure 12.3.3: Structure of phosphatidylcholine (lecithin)[7]

DNA/RNA

DNA/RNA have a phosphate backbone as shown below.

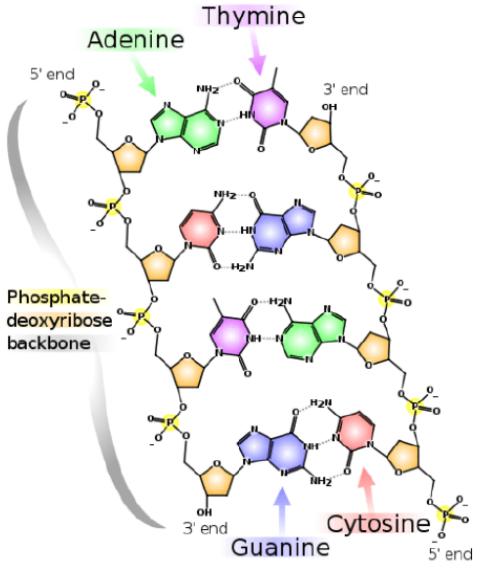


Figure 12.3.4: Structure of DNA[8]

ATP

The major energy currency, ATP, stores energy in its phosphate bonds.

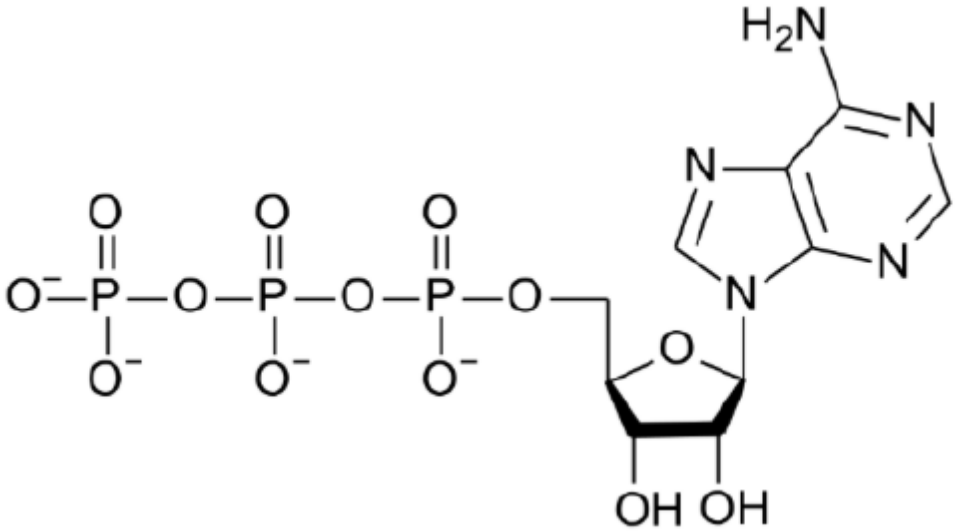


Figure 12.3.5: Structure of ATP[9]

Other functions of phosphate include:

- Intracellular secondary messengers cyclic AMP (cAMP) and inositol triphosphate (IP_3) both contain phosphate
- Acid/Base Balance
- Intracellular Anion

Query 12.3.2

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9. en.Wikipedia.org/wiki/File:ATP_structure.svg

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12.4: Fluoride

Fluoride is a nonessential mineral. It is not required by the body and it is not widely found in the food supply. The majority of what we consume comes from fluoridated water. Other good non-dietary sources are fluoridated toothpaste and dental rinses[1]. Absorption of fluoride is near 100% for both dietary and non-dietary forms and it is rapidly excreted in the urine[2].

Fluoride alters the mineralization of bones and teeth. It does this by replacing hydroxyl (OH) ions in hydroxyapatite ($\mathrm{Ca_{10}(PO_4)_6(OH)_2}$), forming fluorohydroxyapatite. Fluorohydroxyapatite is more resistant to acid degradation than hydroxyapatite, leading to fewer cavities[2].

Since it is a nonessential mineral, there is no fluoride deficiency, but lower levels are associated with higher dental cavity rates. This connection is why so many water supplies are fluoridated. However, fluoride can be quite toxic. Acute toxicity symptoms from large intakes of fluoride include[1]:

- Nausea
- Vomiting
- Diarrhea
- Convulsions

Chronic toxicity results in an irreversible condition known as fluorosis, characterized by the mottling and pitting of teeth as shown below.



Figure 12.4.1: Fluorosis[3]

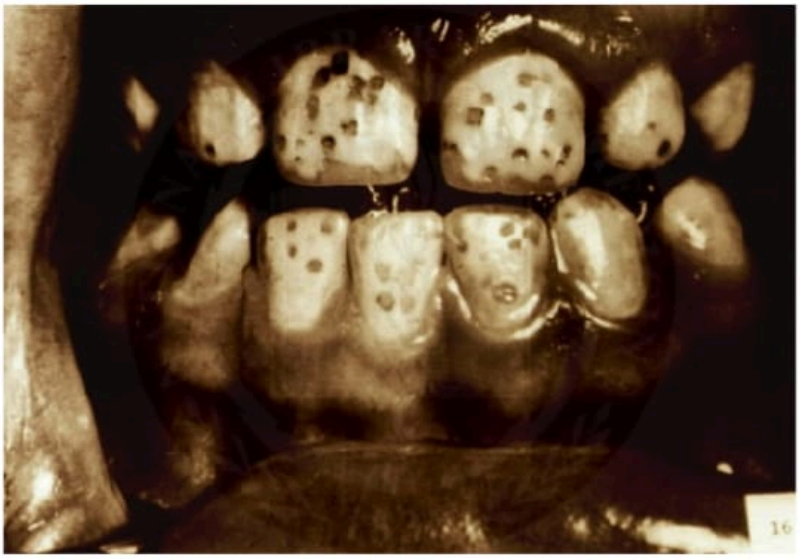


Figure 12.4.2: Severe case of fluorosis[4]

As you can see from the figure below, fluorosis is more prevalent in the United States than most people would probably believe.

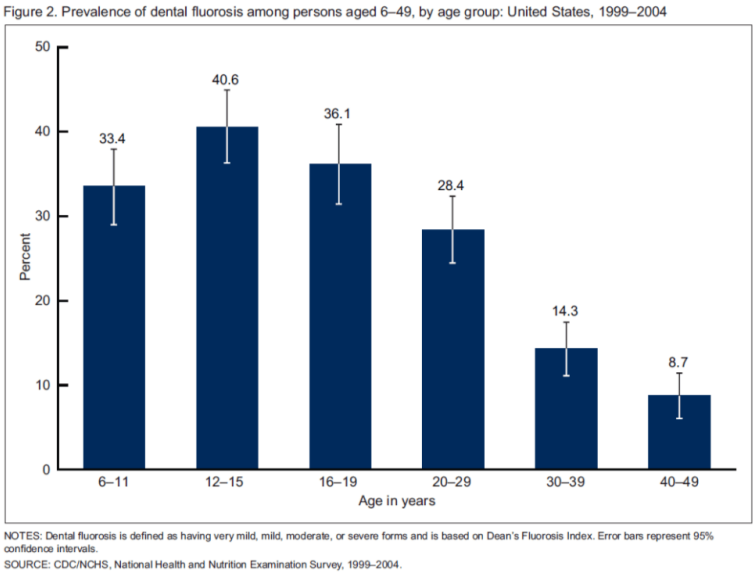
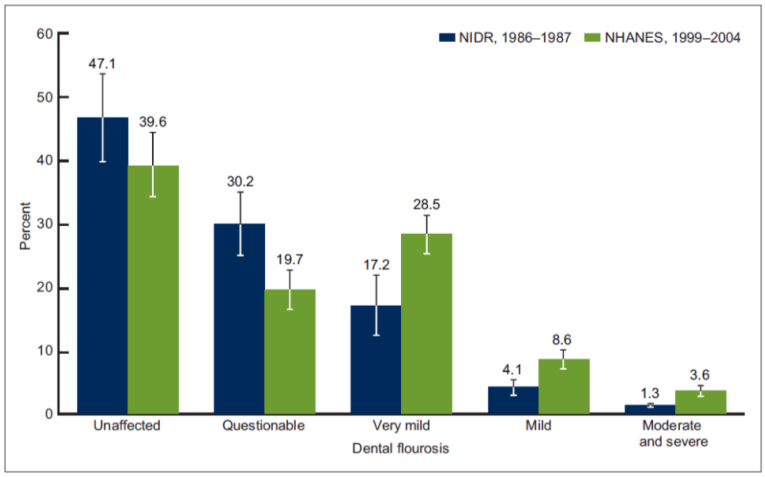


Figure 12.4.3: Fluorosis prevalence by age in the United States[5]

A comparison of the prevalence of fluorosis in US children, ages 12-15, indicates an increase from the late 1980s to the early 2000s[5].

Figure 3. Change in dental fluorosis prevalence among children aged 12–15 participating in two national surveys: United States, 1986–1987 and 1999–2004



NOTES: Dental fluorosis is defined as having very mild, mild, moderate, or severe forms and is based on Dean's Fluorosis Index. Percentages do not sum to 100 due to rounding. Error bars represent 95% confidence intervals.
SOURCES: CDC/NCHS, National Health and Nutrition Examination Survey, 1999–2004 and National Institute of Dental Research, National Survey of Oral Health in U.S. School Children, 1986–1987.

Figure 12.4.4: Change in dental fluorosis in 12-15 year-old US children[5]

There is debate as to whether water should be fluoridated. The following links are examples of just how conflicted the U.S. is. The first is a New York Times article on this topic. There is also an article about Portland's decision to begin fluoridating its water in 2014. The third article is about a bill introduced by a Kansas lawmaker concerned about the effects of water fluoridation. Salina, Kansas, which is home to one of Kansas State University's campuses, voted last November to not rescind its policy of fluoridating its water, as described in the fourth link.

Web Links

- Fluoridation Debate, Redux
- Portland Approves Fluoridation by '14
- Fluoride to Stay in Salina Water

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12.5: Vitamin K

There are 3 forms of vitamin K. Phylloquinone (K1), the plant form of vitamin K, is the primary dietary form of vitamin K. Its structure is shown below.

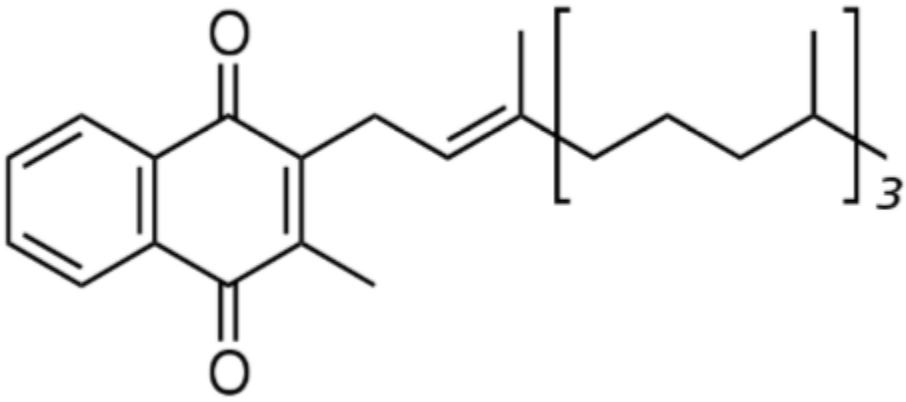


Figure 12.5.1: Structure of phylloquinone (K1), the 3 outside of the brackets indicates that the structural unit inside the brackets is repeated 3 times[1]

Green leafy vegetables, broccoli, Brussels sprouts, and asparagus are foods that are good sources of phylloquinone[2].

Another form of vitamin K, menaquinone (K2), is synthesized by bacteria in the colon (and potentially elsewhere). Menaquinone comprises ~10% of absorbed vitamin K every day and can also be found in small amounts in animal products. Its structure is shown below[3].

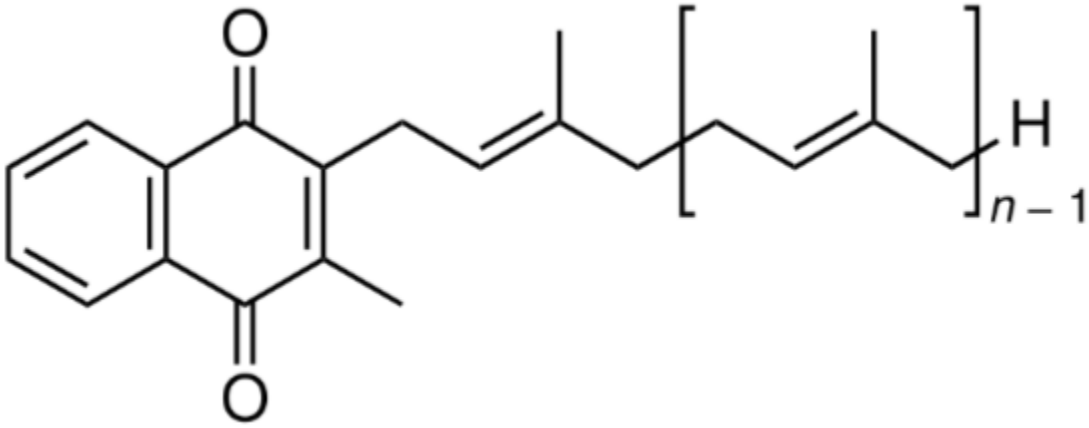


Figure 12.5.2: Structure of menaquinone (K2). Menaquinones have side chains of varying length[4]

In the structure above, if it was menaquinone-8, there would be 7 (8-1) repeating units of the structure inside the brackets above.

The synthetic form of vitamin K is menadione (K3), whose structure is shown below.

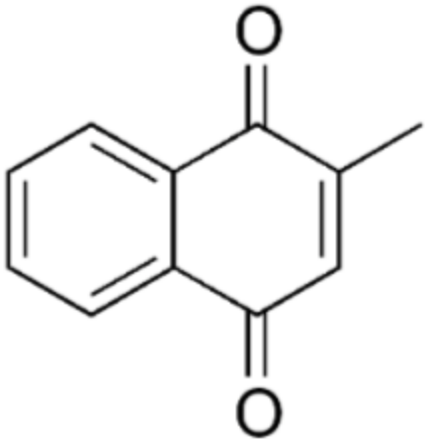


Figure 12.5.3: Structure of menadione (K3)[5]

A tail, similar to the one found in menaquinone, has to be added to menadione for it to be biologically active.

Vitamin K is absorbed like other fat-soluble substances. Approximately 80% of phylloquinone and menaquinone are incorporated into chylomicrons and stored primarily in the liver[2,6]. Once metabolized, vitamin K is primarily excreted via bile in the feces, with a lesser amount excreted in urine[6].

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Vitamin K Functions

Vitamin K is a cofactor for carboxylation reactions that add CO_2 to the amino acid, glutamic acid (glutamate), in certain proteins. The structure of glutamic acid is shown below.

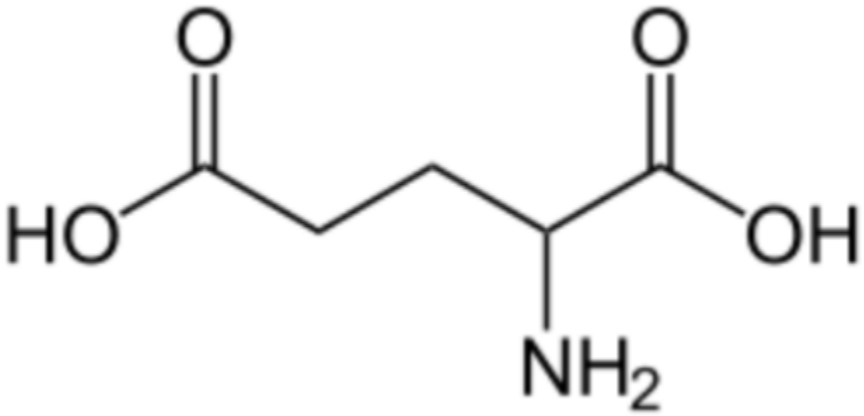


Figure 12.5.4: Glutamic acid structure[7]

The enzyme, gamma-glutamyl carboxylase, uses a vitamin K cofactor to convert glutamic acid to gamma-carboxyglutamic acid

(Gla). In the process of serving as a cofactor, vitamin K is converted to vitamin K epoxide (structure in the figure below).

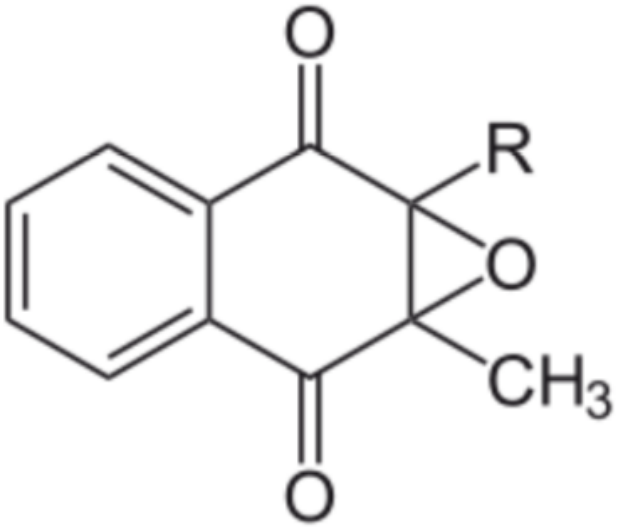


Figure 12.5.5: Vitamin K epoxide structure8

Vitamin K epoxide needs to be converted back to vitamin K to serve as a cofactor again. Gla proteins are those that contain gamma-carboxyglutamic acid(s). This formation of gamma-carboxyglutamic acid allows the 2 positive charges of calcium to bind between the 2 negative charges on the carboxylic acid groups (COO^-) in the Gla. The binding of calcium activates these proteins2,3,6.

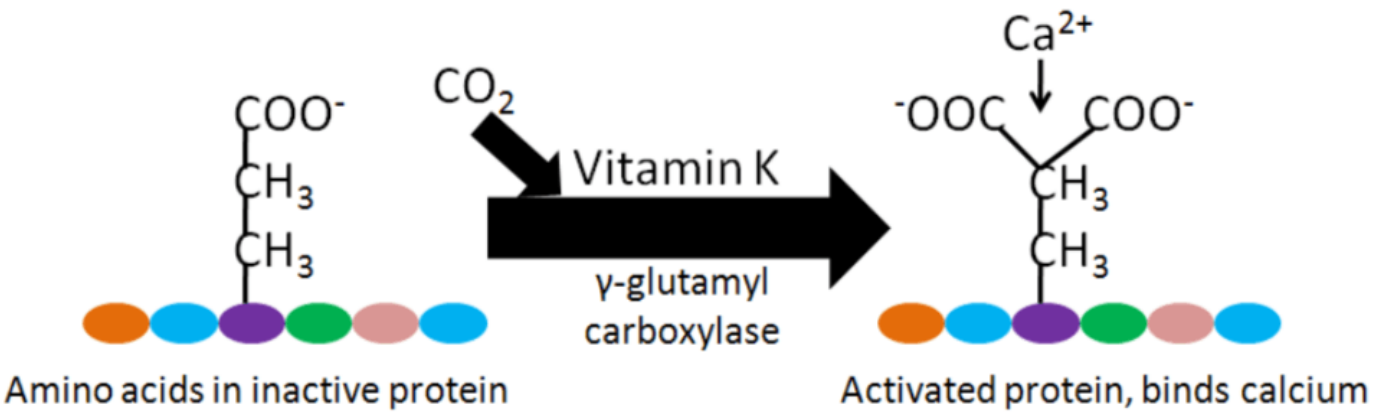


Figure 12.5.6: Gamma-glutamyl carboxylase converts glutamic acid (left) to gamma-carboxyglutamic acid (Gla, right). Proteins containing gamma-carboxyglutamic acid are known as Gla proteins. Binding of calcium activates Gla proteins. Adapted from reference 6.

After being used as a cofactor by gamma-glutamyl carboxylase to produce a Gla protein, vitamin K becomes vitamin K epoxide. Vitamin K epoxide needs to be converted back to vitamin K to serve as a cofactor again. Activated Gla proteins are important in blood clotting. Blood clotting occurs through a cascade of events, as shown in the following video. The first video gives a detailed overview of this, the second video is a fun depiction of the blood clotting cascade.

YouTube Video

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Video 12.5.1: Coagulation Cascade: description of the physiological process of hemostasis including platelet plug formation and about the intrinsic and extrinsic pathways. https://www.youtube.com/watch?v=cy3a__OOa2M&t=1s

YouTube Video

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Video 12.5.2: The clotting cascade. https://www.youtube.com/watch?v=NJm4DE-tVuY&feature=related

Within the blood clotting cascade, there are a number of potential Gla proteins, as shown in the figure below.

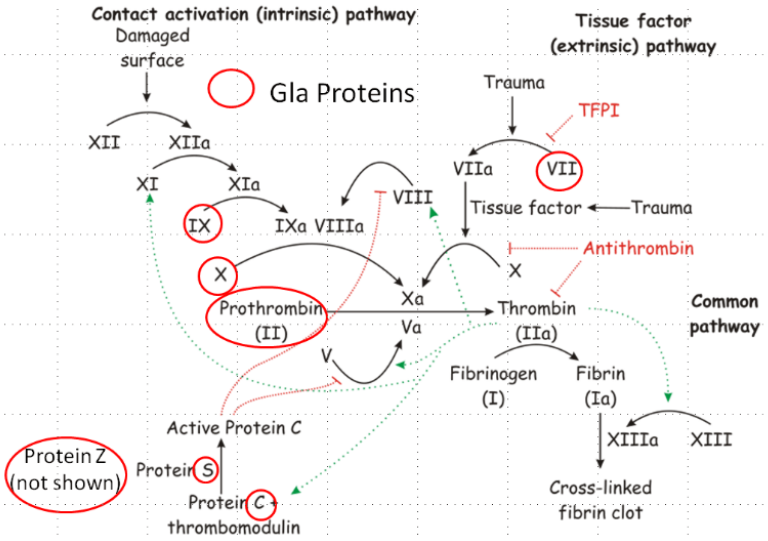


Figure 12.5.7: Blood clotting cascade with potential Gla proteins circled[9]

If these proteins within the blood clotting cascade are not activated Gla proteins, the cascade does not proceed as normal, leading to impaired blood clotting. Warfarin (Coumadin) and dicumarol are a couple of blood thinning drugs that inhibit this regeneration of vitamin K. This reduces the amount of activated Gla proteins in the blood clotting cascade, thus reducing the clotting response[10]. The structure of warfarin and dicumarol are shown below.

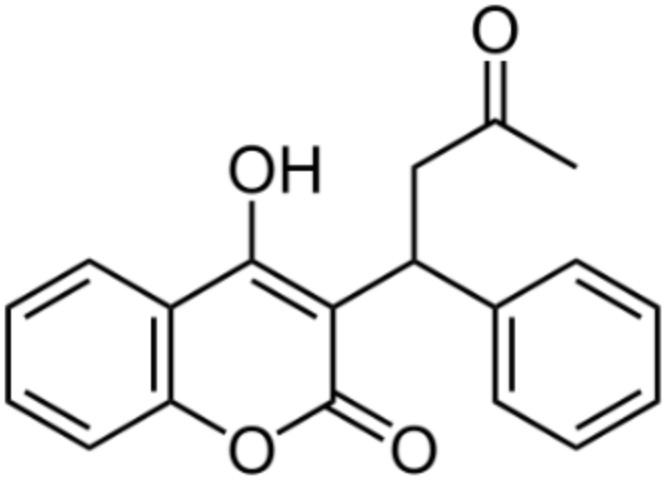


Figure 12.5.8: Structure of warfarin[11]

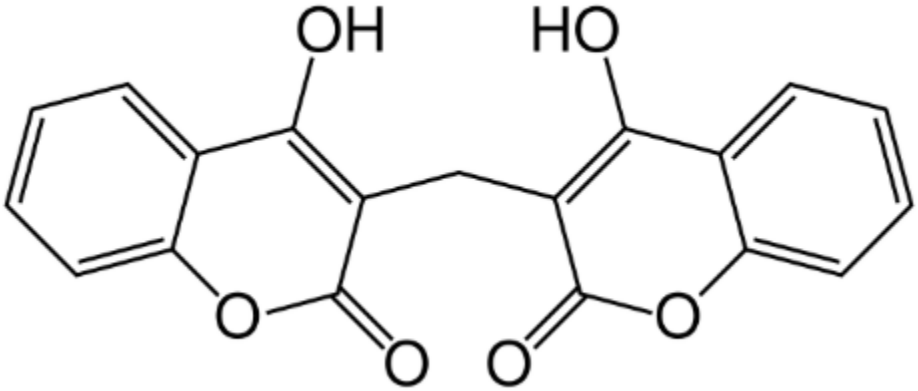


Figure 12.5.9: Structure of dicumarol[12]

The following coumadin rap song video gives further information on warfarin.

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Video12.5.3: Coumadin rap song. https://www.youtube.com/watch?v=Mfk05IFfW48&feature=watch_response

Vitamin K may also be important for bone health. There are 3 Gla proteins found in bone: osteocalcin, matrix Gla protein (MGP), and protein S[10]. Osteocalcin is a major bone protein, constituting 15-20% of all non-collagen proteins in bone. However, overall, the function of these 3 proteins in bone is not known[3,6]. Some research suggests that higher vitamin K status or intake decreases bone loss, but it is still not clear how important vitamin K is for bone health[13].

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Vitamin K Deficiency & Toxicity

Vitamin K deficiency is rare, but can occur in newborn infants. They are at higher risk, because there is poor transfer of vitamin K across the placental barrier (from mother to fetus in utero), their gastrointestinal tracts do not contain vitamin K producing bacteria, and breast milk is generally low in vitamin K (most infant formula is fortified)6. As a result, it is recommended (and widely practiced) that all infants receive a vitamin K injection within 6 hours of birth3.

Prolonged antibiotic treatment (which kills bacteria in the gastrointestinal tract, including those that produce menaquinone) and lipid absorption problems can also lead to vitamin K deficiency2. Vitamin K deficient individuals have an increased risk of bleeding or hemorrhage. Recall that high levels of alpha-tocopherol intake (levels that generally would only be achieved through supplementation) can also interfere with vitamin K's blood clotting function. It is believed that an alpha-tocopherol metabolite, with similar structure to the vitamin K forms you learned about, antagonizes the action of vitamin K.

Phylloquinone and menaquinone have no reported toxicities. However, menadione can cause liver damage6.

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12.6: Vitamin A

There are 3 forms of vitamin A (retinol, retinal, and retinoic acid) that collectively are known as retinoids. Retinol is the alcohol (OH) form, retinal is the aldehyde (COH) form, and retinoic acid is the carboxylic acid ($COOH$) form, as shown in the figure below (areas of difference are indicated by red).

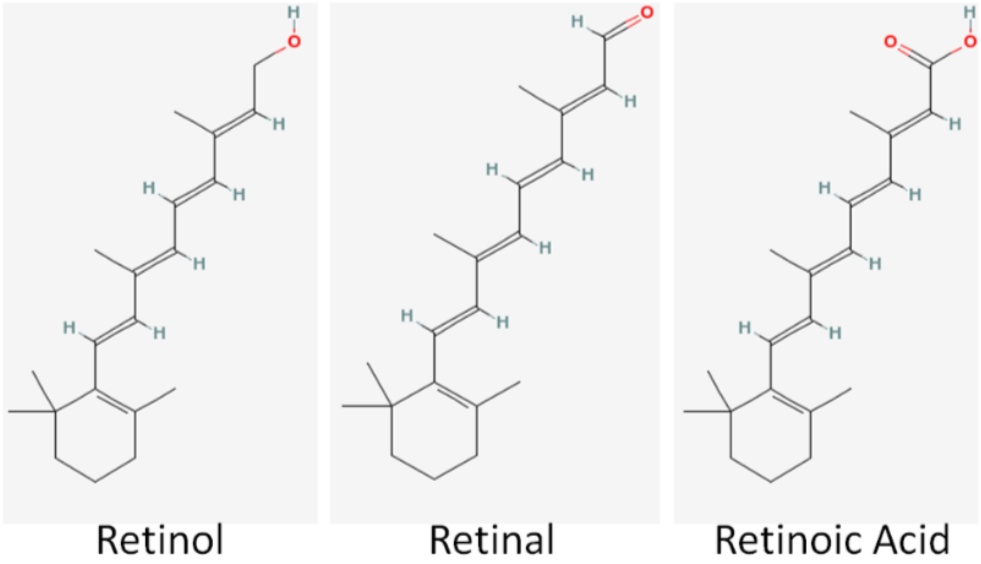


Figure 12.6.1: Structure of the retinoids[1]

Among these different retinoids, retinol and retinal are fairly interchangeable. Either form is readily converted to the other. However, only retinal is used to form retinoic acid, and this is a one-way reaction. Thus, once retinoic acid is formed it can't be converted back to retinal, as shown in the figure below.

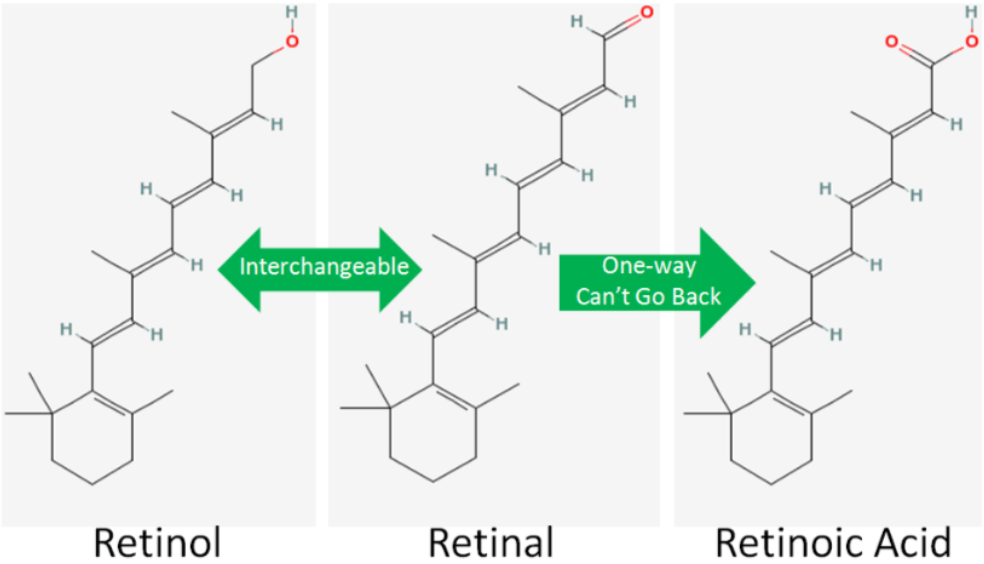


Figure 12.6.2: Metabolism of retinoids[1]

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There are 2 primary dietary sources of vitamin A:

- Retinyl/retinol esters (Animal Products)
- Provitamin A Carotenoids (Plants)

Preformed vitamin A means that the compound is a retinoid. Preformed vitamin A is only found in animal products (carrots are not a good source of preformed vitamin A). Most retinol in animal products is esterified, or has a fatty acid added to it, to form retinyl esters (aka retinol esters). The most common retinyl ester is retinyl palmitate (retinol + the fatty acid palmitate) whose structure is shown below.

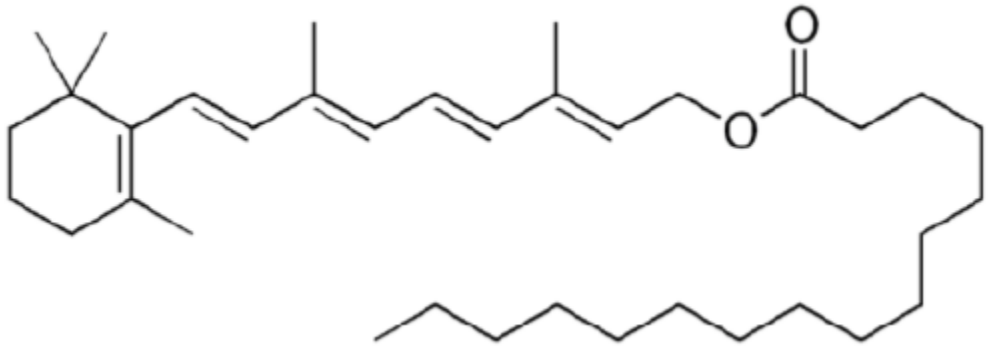


Figure 12.6.3: Retinyl palmitate2

Provitamin A is a compound that can be converted to vitamin A in the body, but currently is not in vitamin A form. The next section will talk about carotenoids, some of which are provitamin A compounds.

International units are also used for vitamin A, such that:

1 IU = 0.3 ug retinol or 0.6 ug beta-carotene

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Carotenoids

Carotenoids are 40-carbon compounds that are found throughout nature. Animals do not produce carotenoids, thus any found in animals (including people) come from consumed plants or microorganisms. There are more than 600 natural carotenoids. However, the 6 main ones found in the diet and in the body are[3]:

- Beta-carotene
- Alpha-carotene
- Beta-cryptoxanthin
- Lutein
- Zeaxanthin
- Lycopene

Many carotenoids are pigments, meaning they are colored. The table below gives the color of some of these carotenoids, as well as some food sources.

Table 12.6.1: Carotenoids' color and food sources

Carotenoid	Color	Food Sources
Beta-carotene/Alpha-carotene	Orange	Carrots, Sweet Potatoes, Leafy Greens
Lycopene	Red	Tomatoes, Watermelon, Pink Grapefruit
Lutein/Zeaxanthin	Yellow	Kale, Corn, Egg Yolks, Spinach

*Beta-cryptoxanthin is orange in color

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Carotenoids can be further classified as provitamin A or non-provitamin A. Provitamin A carotenoids are those that can be cleaved to form retinal, while the non-provitamin A carotenoids cannot. The structure and classification of the 6 major carotenoids are shown below.

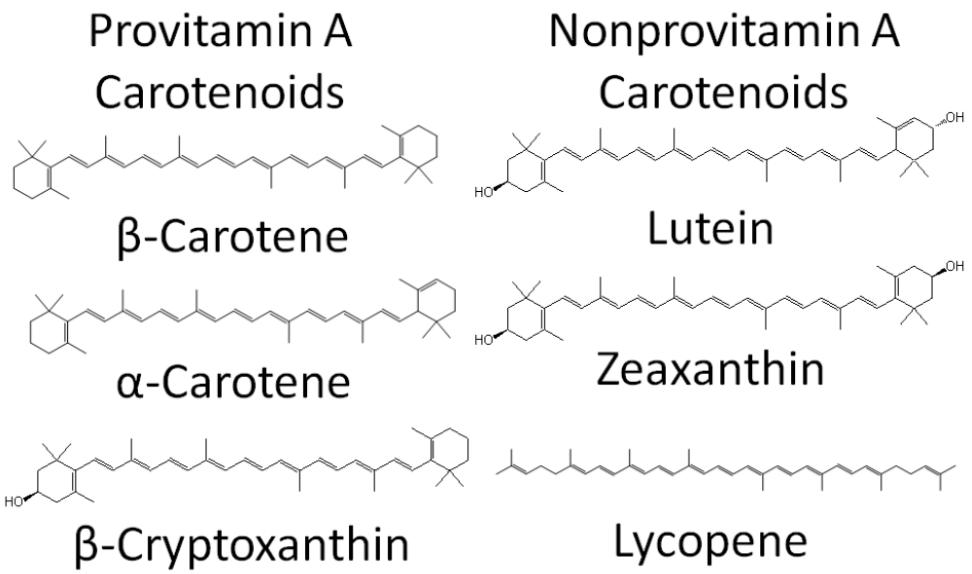


Figure 12.6.4: Structure and classification of the 6 major carotenoids

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After provitamin A carotenoids are taken up into the enterocyte, some are cleaved to form retinal. In the case of symmetrical beta-carotene, it is cleaved in the center to form 2 retinal molecules as shown below.

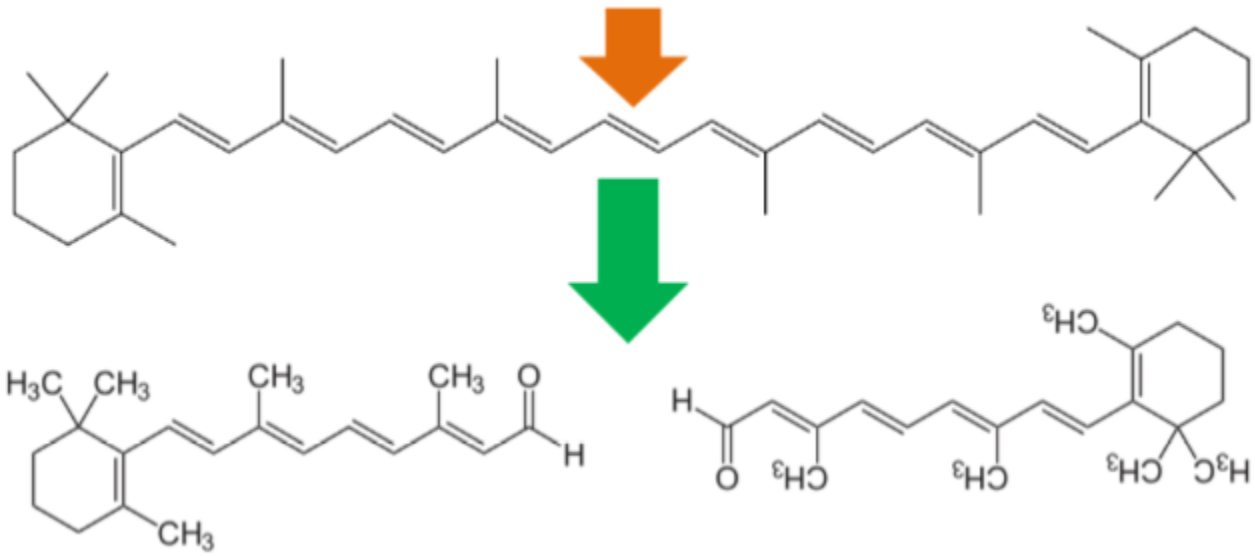


Figure 12.6.5: Cleavage of beta-carotene 2 to retinal molecules[4]

Alpha-carotene and beta-cryptoxanthin are asymmetrical, thus they can be used to form only 1 retinal.

To help account for the fact that retinol can be made from carotenoids, the DRI committee made retinol activity equivalents (RAE) that take into account the bioavailability and bioconversion of provitamin A carotenoids.

1 ug RAE

= 1 ug of retinol

= 2 ug of supplemental beta-carotene

= 12 ug of dietary beta-carotene

= 24 ug of alpha-carotene or beta-cryptoxanthin5

Supplemental beta-carotene is much more bioavailable than dietary beta-carotene found in a natural matrix within plant food components. As a result, you need to consume 6 times more dietary beta carotene to have the same RAE value as supplemental beta-carotene. The RAE difference between the provitamin A carotenoids is due to beta-carotene being cleaved to form 2 retinals, where alpha-carotene and beta-cryptoxanthin are cleaved 1 retinal. As a result, twice as much dietary alpha-carotene and beta-cryptoxanthin needs to be consumed to have the same RAE value as dietary beta-carotene.

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Vitamin A Uptake, Absorption, Transport & Storage

The uptake, absorption, transport, and storage of vitamin A and carotenoids are summarized in the figure below.

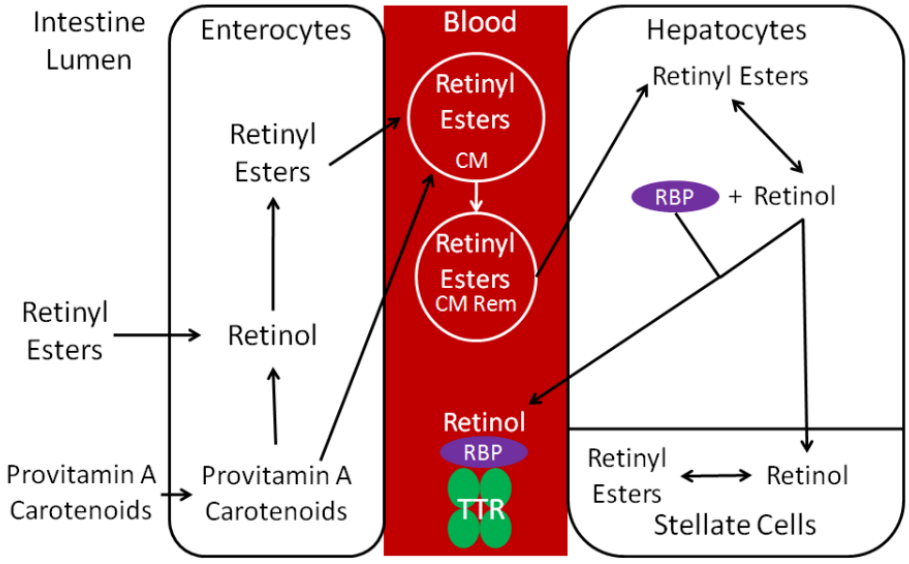


Figure 12.6.6: Vitamin A uptake, absorption, transport, and storage. Adapted from reference6

Esters are removed by esterases so that free retinol can be taken up into the enterocyte. Preformed vitamin A is highly bioavailable (70-90%) if consumed with some fat2. Carotenoids have a much lower bioavailability, which varies based on the

carotenoid and matrix it is in when consumed. Once provitamin A carotenoids are taken up into the enterocytes, they are: (1) cleaved to retinal and then converted to retinol or (2) absorbed intact and incorporated into chylomicrons.

Retinol in the enterocyte is esterified, forming retinyl esters. Retinyl esters are packaged into chylomicrons (CM) and enter the lymph system. Once the chylomicrons reach circulation, triglycerides are cleaved off to form chylomicron remnants (CM Rem). These are taken up by hepatocytes, where the retinyl esters are de-esterified to form retinol. The liver is the major storage site of vitamin A. For storage, the retinol will be transported from hepatocytes to stellate cells and converted back to retinyl esters, the storage form of vitamin A.

If vitamin A is needed to be released into circulation, retinol will combine with retinol binding protein (RBP). Retinol + RBP are then bound to a large transport protein, transthyretin (TTR). It is believed that retinol + RBP would be filtered out by the kidney and excreted in urine if it was not bound to TTR6.

After it is further metabolized, 60% of vitamin A is excreted in the urine, 40% in feces7.

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Vitamin A Nuclear Receptors

Vitamin A, like vitamin D, has a nuclear receptor. Vitamin A technically has two nuclear receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Vitamin A, like polyunsaturated fatty acids, can be found in trans and cis forms, depending on the conformation of its double bonds. The ligand for RARs is all-trans-retinoic acid, and the ligand for RXRs is 9-cis retinoic acid.

As shown in the figure below, all-trans retinol is brought to the cell by RBP and TTR. All-trans retinol is converted to all-trans-retinal, and then to all-trans-retinoic acid. RAR and RXR are paired, or dimerized, on the retinoic acid response element (RARE) in the promoter region of target genes. The binding of all-trans retinoic acid to RAR causes the transcription and ultimately the translation of target proteins. This is why retinoic acid is the active form of vitamin A because all-trans retinoic acid is the ligand for RARs, leading to many of the biologic effects attributed to vitamin A. RXR is primarily a partner receptor for other nuclear hormone receptors and can serve in this role even without its ligand. 9-cis retinoic acid is rarely found in physiologically notable concentrations, so it is role is not entirely clear.

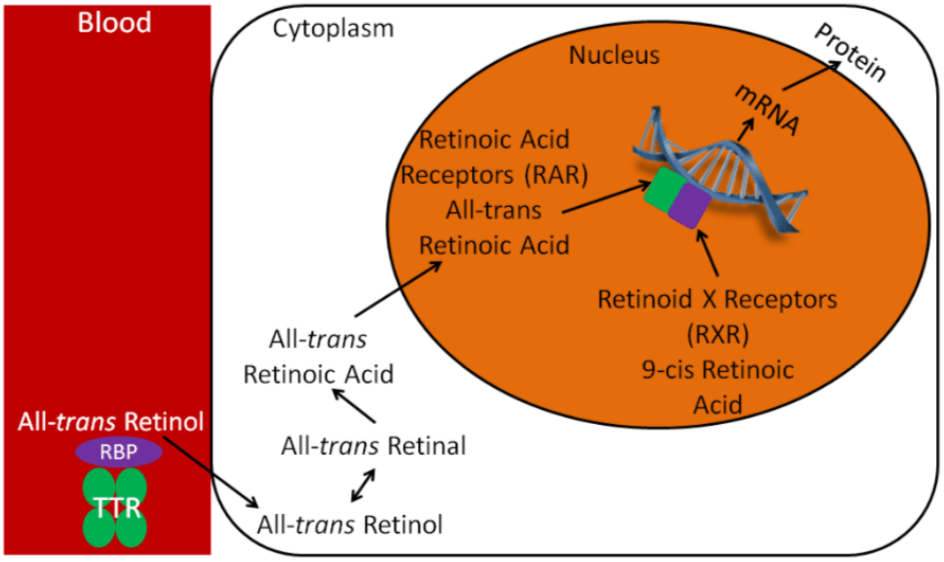


Figure 12.6.7: All-trans retinoic acid and retinoid X receptors

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Vitamin A Functions

Vitamin A has a number of important functions in the body.

Vision

The retina is the inner back lining of the eye that takes visual images and turns them into nerve signals that are sent to the brain to form the images that we "see", as shown in the following figure.

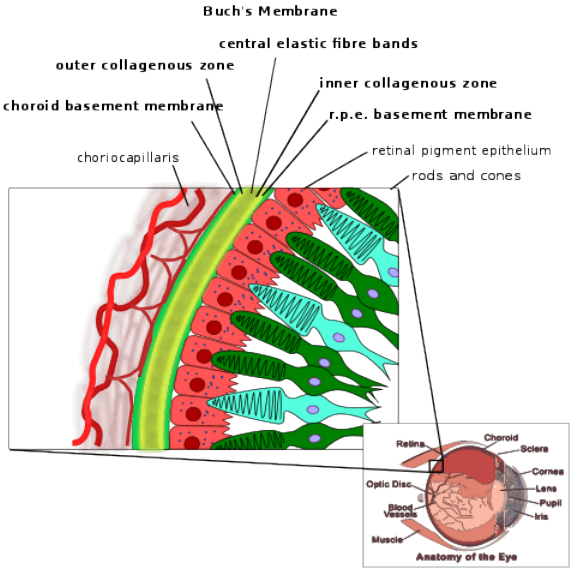


Figure 12.6.8: Retina, rods and cones8.

Inside the retina are the photoreceptor cells, rods and cones. Cones are responsible for color vision, while rods are important for seeing black and white. Within the rods, 11-cis retinal combines with the protein, opsin, to form rhodopsin. When light strikes rhodopsin, the compound splits into opsin and all-trans retinal. This sends a signal to your brain for us to “see” as illustrated below9.

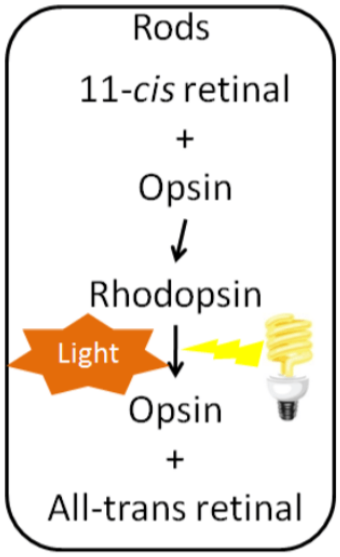


Figure 12.6.8: Vitamin A in the rod

Most all-trans retinal is converted back to 11-cis retinal through a series of steps so it can continue to be used to form rhodopsin. However, this recycling is not 100% efficient. Vitamin A stores, or continued intake, is required to provide the 11-cis retinal needed to continue to form rhodopsin. Normally, our eyes adapt to darkness by increasing the amount of rhodopsin available so we can see under reduced light conditions9. If a person does not have enough rhodopsin he/she will become night blind, meaning his/her eyes do not adjust, or adjust very slowly, preventing he/she from seeing under limited light conditions. The picture below is an example of what night blindness looks like.



Figure 12.6.9: The left is normal vision, the right is what someone with night blindness would see[10].

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Cell Differentiation

Vitamin A, in particular retinoic acid, is important for cell differentiation, or the ability of stem cells to develop into specialized cells.

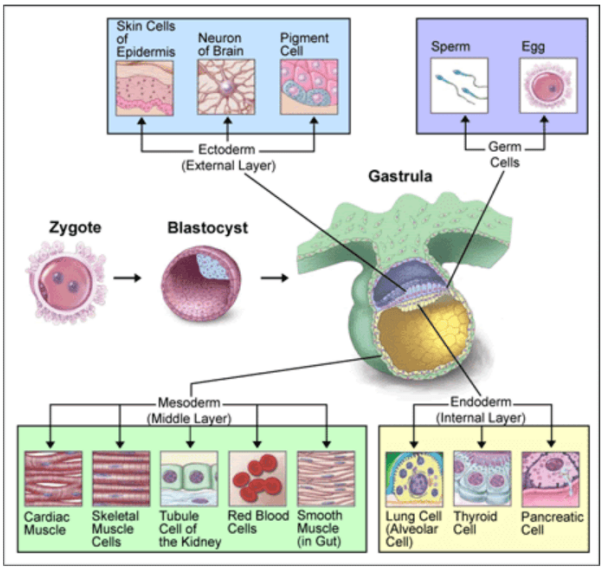


Figure 12.6.10: Cellular differentiation[11]

Other functions that vitamin A is important for include:

- Growth and development
- Reproduction

- Immune function

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Vitamin A Deficiency & Toxicity

Vitamin A deficiency is rare in North America, but is a huge problem in developing countries. In many developing countries, they do not have a stable dietary source of retinoids or provitamin A carotenoids. The figure below gives you an idea of countries where vitamin A deficiency is a problem.

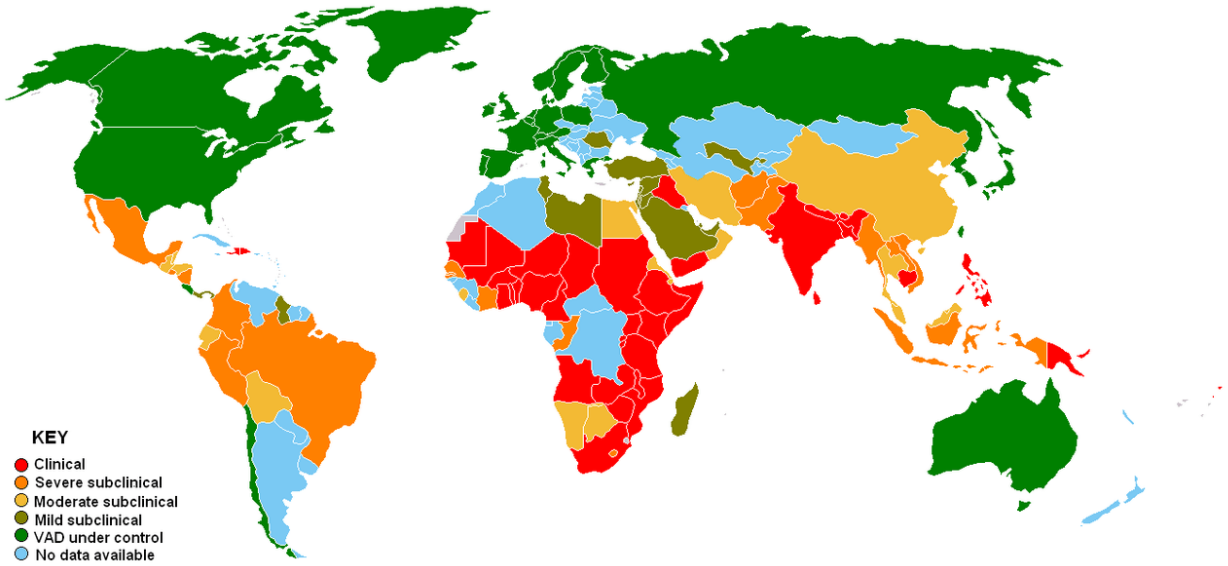


Figure 12.6.11: Prevalence of vitamin A deficiency worldwide. (Public Domain; Petaholmes via Wikipedia)

Often the earliest symptom of vitamin A deficiency is night blindness, due to the insufficient production of rhodopsin. The reason that this is the earliest symptom, is that circulating vitamin A (primary form is retinol) concentrations are homeostatically-controlled, meaning that they do not change until after vitamin A stores are exhausted (because stores are used to maintain circulating concentrations). This means that blood, serum, plasma measurements are going to appear normal until all stores are exhausted. As a result, determining or diagnosing someone as vitamin A deficient can be challenging. It also means that someone can be right on the brink of deficiency and an assessment of the status they would appear the same as someone who has adequate stores. There are further progressively worsening changes to the eye that occur during vitamin A deficiency, collectively referred to as xerophthalmia, which are shown in the link below.

Web Link

The eye signs of vitamin A deficiency

Ultimately the person can become blind. Vitamin A deficiency is the leading cause of blindness in some parts of the world[12].

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Another symptom of vitamin A deficiency is hyperkeratosis. In this condition, cells overproduce the protein keratin, causing the skin to become rough and irritated, as shown in the link below12.

Web Link

Hyperkeratosis

One way to counter vitamin A deficiency in developing countries is for staple crops, like rice and corn, to contain beta-carotene. In the case of rice, Golden Rice was genetically modified to produce beta-carotene. A second generation of golden rice, known as Golden Rice 2, has now been developed. However, politics and regulations have prevented either from being used. This is described in the first link. The second link is a nice figure that details the progress towards Golden Rice being used. The third link describes the issues with how some research with it was conducted. The fourth link is an opinion article that gives you a feel for the opposition to its use.

Web Links

- Golden Rice
- Golden Rice Project
- Golden Rice Not So Golden for Tufts
- Golden Rice Approved as Safe for Consumption in the Philippines

There are also corn varieties that have been bred (not genetically modified) to produce high amounts of beta-carotene, as described in the top link below. The second link describes how it has now been launched in the US.

Web Link

- New Yellow Corn Could Boost Vitamin A, Save Sight
- More nutritious, natural flavor, non-GMO 'orange corn' launches in US markets

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Vitamin A can be very toxic and can cause serious symptoms, such as blurred vision, liver abnormalities, skin disorders, and joint pain9,12. In addition, research has suggested that people who consume high levels of vitamin A are more prone to bone fractures12. Toxic levels of vitamin A are also teratogenic, which means they could cause birth defects.

This is important to keep in mind because a vitamin A derivative isotretinoin (13-cis retinoic acid) was the active ingredient in the oral acne medication, Accutane. Accutane was effective, as you can see in the video below.

YouTube Video

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View this YouTube Video online

Video 12.6.1: The power of Accutane. My isotretinoin experience. https://www.youtube.com/watch?v=r93K-w2saPA

However, due to the number of adverse events reported from its consumption, Accutane was recalled from the US market in 2009[13]. Isotretinoin medications though are still commonly prescribed.

Retin-A is a topical product of all-trans-retinoic acid. Women of childbearing age need to exercise caution when using these products due to the risk of birth defects, should they become pregnant[9]. People should not consume huge doses of vitamin A expecting to get the same effects seen from these 2 medications[14].

It is important to note that you cannot develop vitamin A toxicity from consuming too much beta-carotene or other provitamin A carotenoids. This is prevented because the enzyme cleavage of them is decreased in response to higher vitamin A status. Instead, a nontoxic condition known as carotenodermia occurs when large amounts of beta-carotene are consumed, where the accumulation of the carotenoid in the fat below the skin causes the skin to look orange, as shown in the link below. Excess lycopene consumption leads to a similar condition known as lycopenodermia, which appear more pink or orange.

Web Link

Carotenodermia

Query 12.6.14

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References

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12.7: Iron

There are 2 major dietary forms of iron: heme iron and non-heme iron. Heme iron is only found in foods of animal origin, within hemoglobin and myoglobin. The structure of heme iron is shown below.

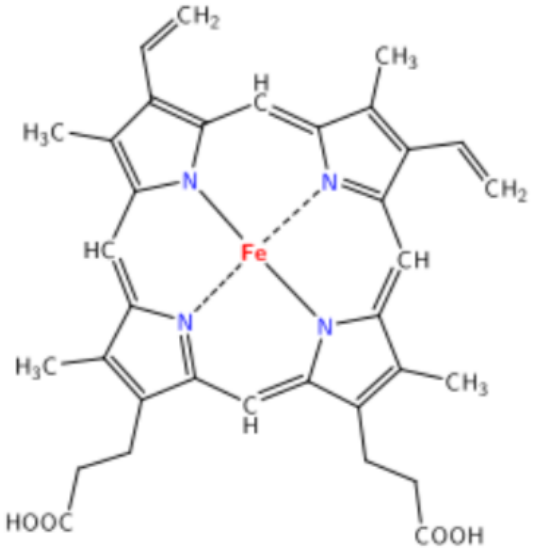


Figure 12.7.1: Structure of heme iron[1]

Approximately 40% of iron in meat, fish, and poultry is heme-iron, and the other 60% is non-heme iron[2].

Non-heme iron is the mineral alone, in either its oxidized or reduced form. The 2 forms of iron are:

- Ferric (Fe^{3+}, oxidized)
- Ferrous (Fe^{2+}, reduced)

It is estimated that 25% of heme iron and 17% of non-heme iron are absorbed[2]. Approximately 85-90% of the iron we consume is non-heme iron[2,3].

In addition to getting iron from food sources, if food is cooked in cast iron cookware, a small amount of iron can be transferred to the food.

Many breakfast cereals are fortified with reduced iron, which looks like iron filings, as the following video shows.

YouTube Video

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View this YouTube Video online

Video 12.7.1: Iron for breakfast. https://www.youtube.com/watch?v=pRK15XSqtAw

While the iron bioavailability of this reduced iron is low, some is absorbed[4].

Supplements

Most iron supplements use ferrous (Fe^{2+}) iron, because this form is better absorbed, as discussed in the next section. The figure below shows the percent of elemental iron in different supplements. This is the percentage of elemental iron that is in each compound.

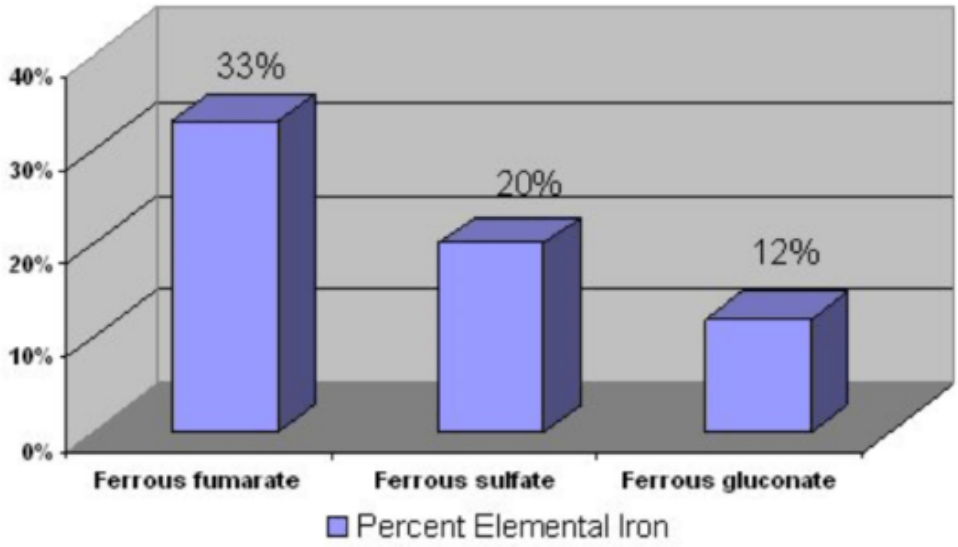


Figure 12.7.2: Elemental iron in different iron supplements3

Iron chelates are marketed as being better absorbed than other forms of iron supplements, but this has not been proven5. It is recommended that supplements are not taken with meals, because they are better absorbed when not consumed with food2.

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Query 12.7.2

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Iron Uptake & Absorption

There are 2 transporters for iron, one for heme iron and one for non-heme iron. The non-heme transporter is the divalent mineral transporter 1 (DMT1), which transports Fe^{2+} into the enterocyte. Heme iron is taken up through heme carrier protein 1 (HCP-1), and then metabolized to Fe^{2+}. Fe^{2+} may be used by enzymes and other proteins or stored in the enterocyte bound to ferritin, the iron storage protein. To reach circulation (and be absorbed), iron is transported through ferroportin5,6. This process is summarized in

the figure below.

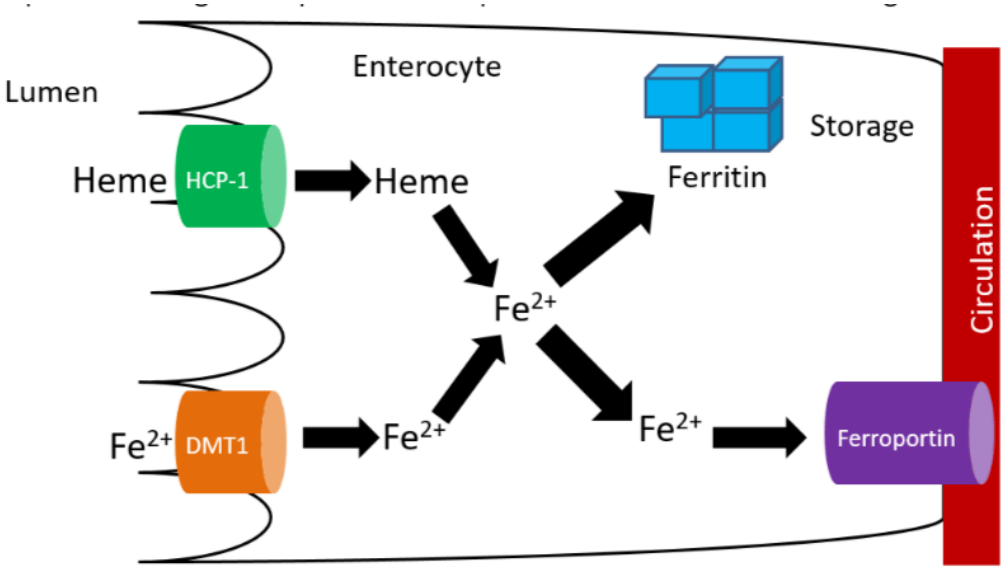


Figure 12.7.3: Iron uptake into the enterocyte

Since only the reduced form of non-heme iron (Fe^{2+}) is taken up, Fe^{3+} must be reduced. There is a reductase enzyme on the brush border, duodenal cytochrome b (Dcytb), that catalyzes the reduction of Fe^{3+} to Fe^{2+}, as shown below. Vitamin C enhances non-heme iron absorption because it is required by Dcytb for this reaction. Thus, if dietary non-heme iron is consumed with vitamin C, more non-heme iron will be reduced to Fe^{2+} and taken up into the enterocyte through DMT1. The exception is that vitamin C does not increase absorption of ferrous supplements because they are already in reduced form.

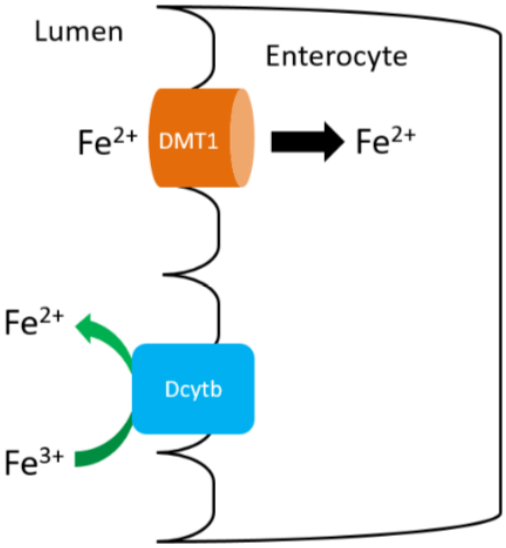


Figure 12.7.4: Reduction of non-heme iron by Dcytb

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In addition to vitamin C, there is an unidentified factor in muscle that enhances non-heme iron absorption if consumed at the same meal7. This unidentified factor is referred to as meat protein factor (MPF). The table shows how MPF can increase non-heme iron absorption.

Table 12.7.1: Non-heme iron absorption from chicken or beef muscle fraction7

Mean Fe Absorption (% of Dose)	Egg Albumin	Whole Muscle	Whole Muscle Protein	Heme-Free Muscle Protein
Chicken	8.41	16.43	26.98	36.81
Beef	11.21	31.52	44.15	38.29

Albumin is a protein, so the egg albumin represents a non-meat protein standard for comparison. You can see that absorption is much higher with whole muscle. When only consuming muscle protein, there is a slight increase from muscle itself, and when they look at heme-free muscle iron, absorption is still higher than egg albumin7.

Inhibitors of non-heme iron absorption typically chelate, or bind, the iron to prevent absorption. Phytates (phytic acid), which also inhibit calcium absorption, chelate non-heme iron decreasing its absorption.

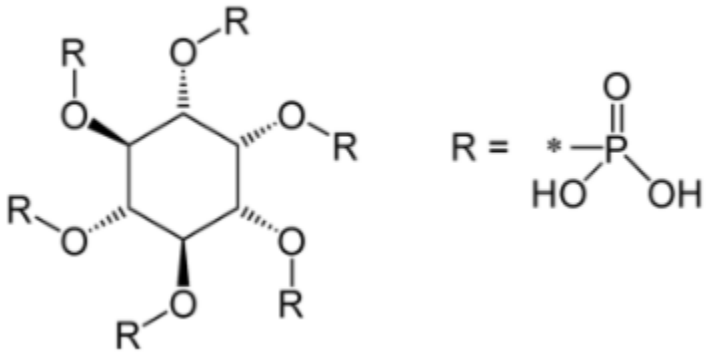


Figure 12.7.5: Structure of phytic acid8

Other compounds that inhibit absorption are:

Polyphenols (coffee, tea)6

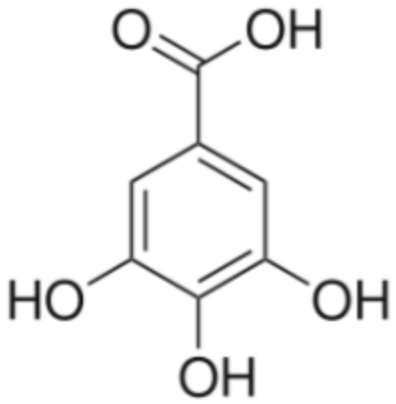


Figure 12.7.6: Structure of gallic acid, a polyphenol[9]

Oxalate (spinach, rhubarb, sweet potatoes, and dried beans)[7]

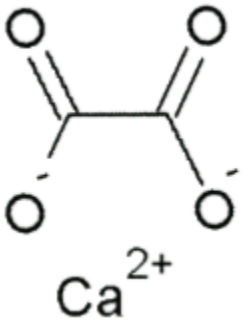


Figure 12.7.7: Structure of calcium oxalate[10]

Calcium is also believed to inhibit iron uptake.

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Iron Transport & Storage

Transferrin is the major iron transport protein (transports iron through blood). Fe^{3+} is the form of iron that binds to transferrin, so the Fe^{2+} transported through ferroportin must be oxidized to Fe^{3+}. There are 2 copper-containing proteins that catalyze this oxidation of Fe^{2+}: hephaestin and ceruloplasmin. Hephaestin is found in the membrane of enterocytes, while ceruloplasmin is the major copper transport protein in blood. Hephaestin is the primary protein that performs this function in a coupled manner (occur together) with transport through ferroportin. This means that the Fe^{2+} being transported through ferroportin is oxidized by hephaestin. Evidence suggests that ceruloplasmin is involved in oxidizing Fe^{2+} when iron status is low[11]. Once oxidized, Fe^{3+} binds to transferrin and is transported to a tissue cell that contains a transferrin receptor. Transferrin binds to the transferrin receptor and is endocytosed, as shown below[5].

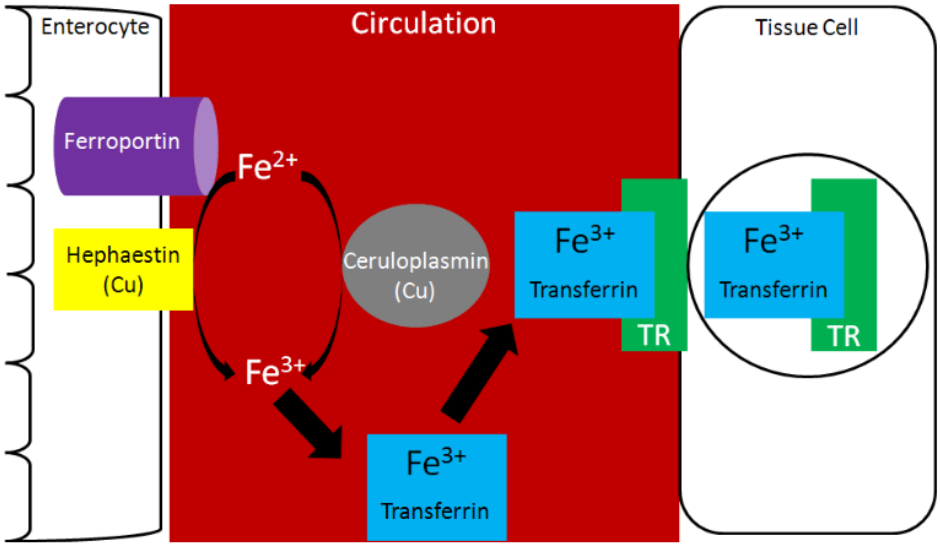


Figure 12.7.8: Transport and uptake of iron

Once inside cells, the iron can be used for cellular purposes (cofactor for enzyme etc.) or it can be stored in the iron storage proteins ferritin or hemosiderin. Ferritin is the primary iron storage protein, but at higher concentrations, iron is also stored in hemosiderin5.

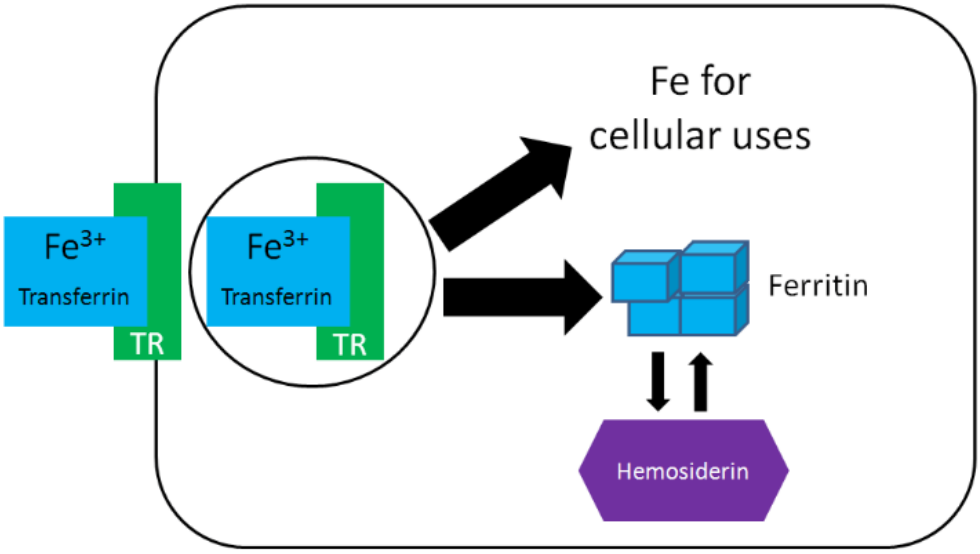


Figure 12.7.9: Fates of iron within cells

Query 12.7.5

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There are 3 major compartments of iron in the body12:

1. Functional Iron
2. Storage Iron
3. Transport Iron

Functional iron consists of iron performing some function. There are 3 functional iron subcompartments.

1. Hemoglobin
2. Myoglobin
3. Iron-containing enzymes

The functions of these subcompartments are discussed in the next section.

Iron Stores consist of:

1. Ferritin
2. Hemosiderin

The liver is the primary storage site in the body, with the spleen and bone marrow being the other major storage sites.

Circulating iron is found in transferrin[12].

The following table shows how much iron is distributed among the different compartments.

Table 12.7.2: Iron Distribution in adults (mg Fe/kg body weight)[12]

	Men	Women
Functional iron		
Hemoglobin	32	28
Myoglobin	5	4
Fe-containing enzymes	1-2	1-2
Storage iron		
Ferritin and hemosiderin	~11	~6
Transport iron		
Transferrin	0.04	0.04

Hopefully you notice that the majority of iron is in the functional iron compartment. The figure below further reinforces this point, showing that most iron is found in red blood cells (hemoglobin) and tissues (myoglobin).

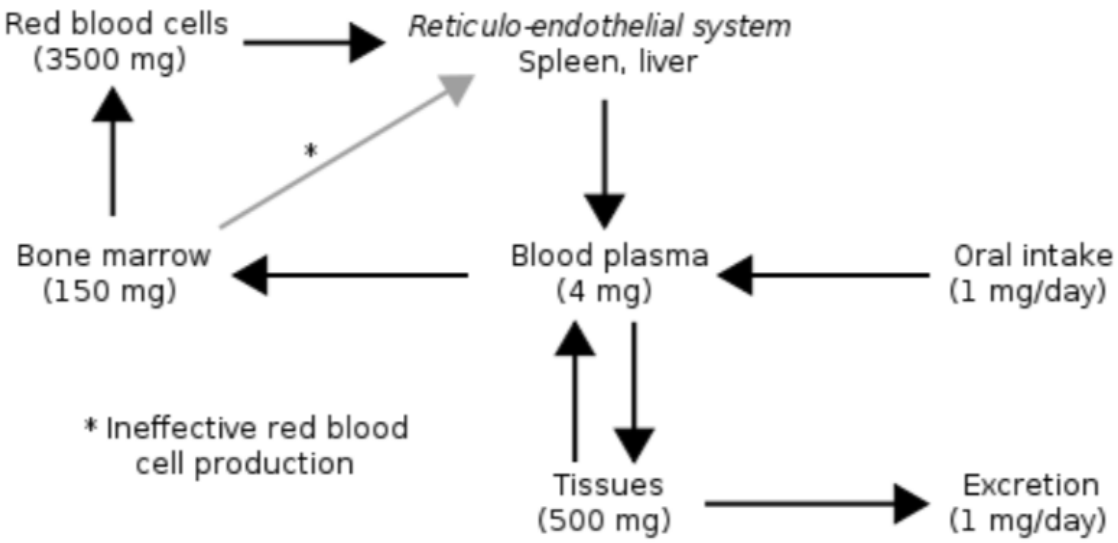


Figure 12.7.10: Iron distribution in different compartments13

Also notice how small oral intake and excretion are compared to the amount found in the different compartments in the body. As a result, iron recycling is really important, because red blood cells only live for 120 days. Red blood cells are broken down in the liver, spleen, and bone marrow and the iron can be used for the same purposes as described earlier: cellular use, storage, or transported to another tissue on transferrin5. Most of this iron will be used for heme and ultimately red blood cell synthesis. The figure below summarizes the potential uses of iron recycled from red blood cells.

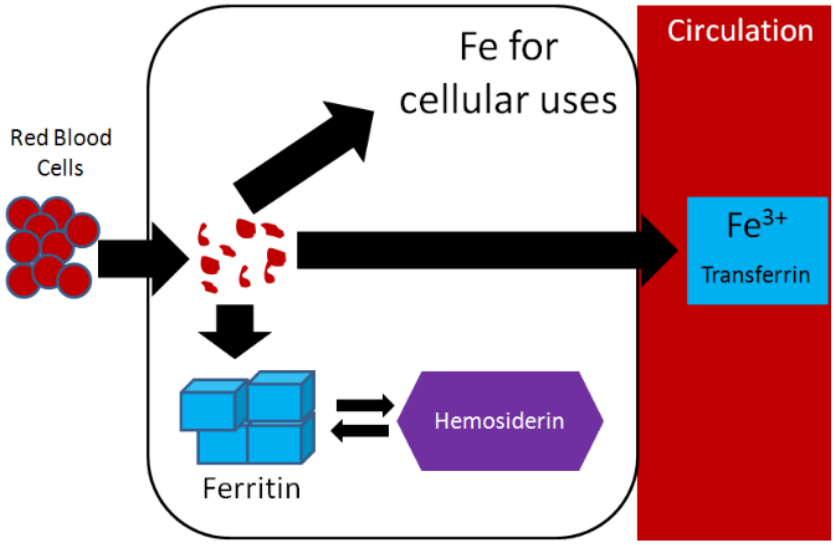


Figure 12.7.11: Iron recycling from red blood cells

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Iron is unique among minerals in that our body has limited ability to excrete it. Thus, absorption is really the only way to regulate iron status. Absorption is controlled by the hormone hepcidin. The liver has an iron sensor so when iron concentrations get high, this sensor signals for the release of hepcidin. Hepcidin travels to the enterocytes where it causes degradation of ferroportin. Thus, the iron is not able to be transported into circulation (since ferroportin is the transporter through which this typically occurs)14.

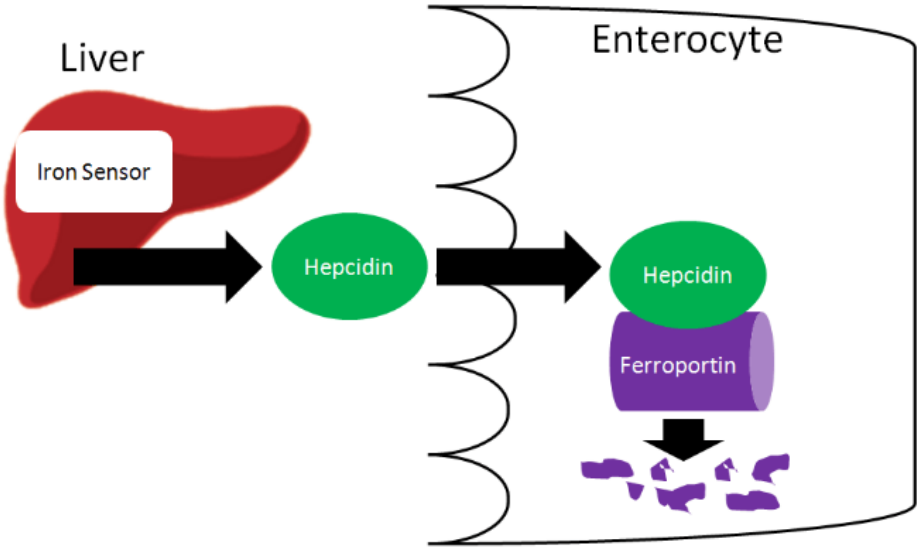


Figure 12.7.12: Action of hepcidin14

The iron is now trapped in the enterocytes, which are eventually sloughed off and mostly excreted in feces (some may be digested for uptake by new enterocytes on the villi). Thus, iron absorption is decreased through the action of hepcidin.

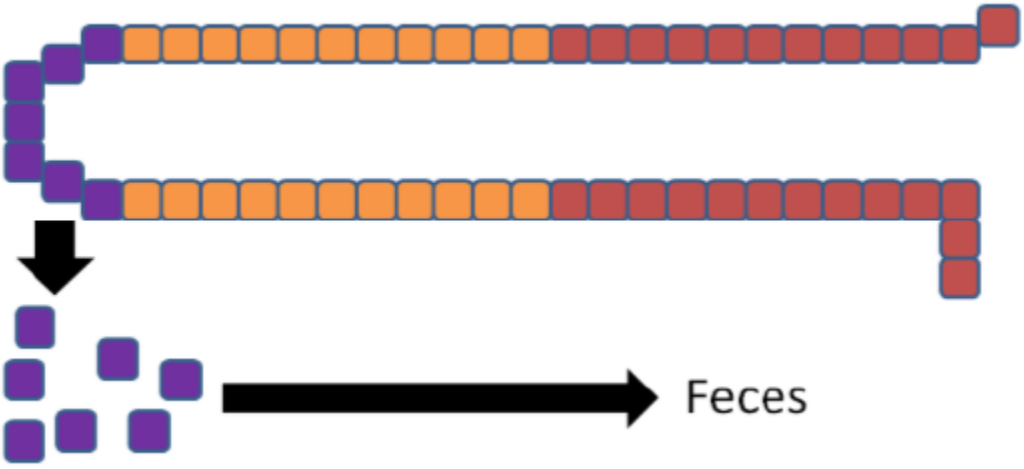


Figure 12.7.13: Enterocytes are sloughed off the villus and unless digested and their components reabsorbed, they will be excreted in feces

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Iron Functions

As we talked about in the previous subsection, there are 3 primary functional iron subcompartments.

1. Hemoglobin
2. Myoglobin
3. Iron-containing enzymes

Hemoglobin contains heme that is responsible for red blood cells' red color. Hemoglobin carries oxygen to tissues. The function of hemoglobin can be seen in the link below.

Web Link

Hemoglobin

Myoglobin is similar to hemoglobin in that it can bind oxygen. However, instead of being found in blood, it is found in muscle. The color of meat products is a result of the state that myoglobin is in, as shown in the link below.

Web Link

Myoglobin & Meat Color

There are a number of enzymes that use iron as a cofactor. We've already talked about two in this class.

Iron is a cofactor for the antioxidant enzyme, catalase, which converts hydrogen peroxide to water, as shown below.

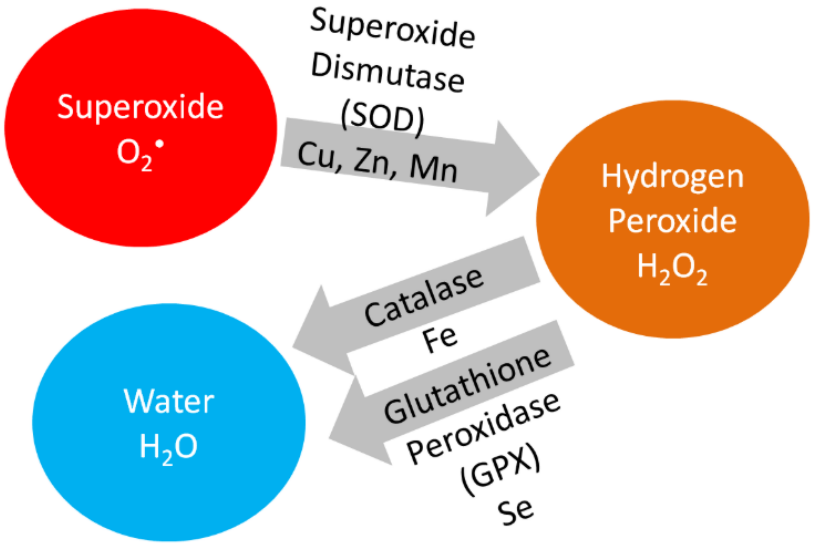


Figure 12.7.14: Catalase uses iron as a cofactor

Iron is also a cofactor for proline and lysyl hydroxylases that are important in collagen cross-linking. This was discussed previously in the vitamin C section. The function of these enzymes is shown below.

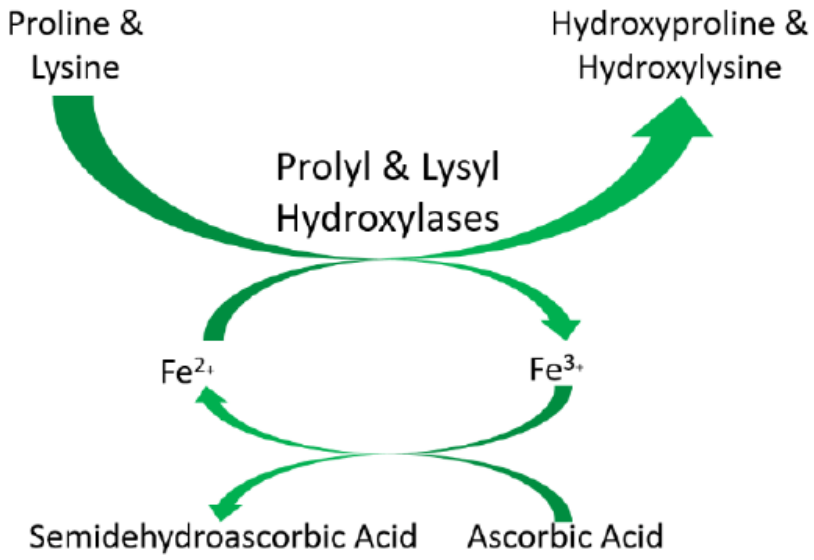


Figure 12.7.15: Importance of ascorbic acid and iron to proline and lysyl hydroxylases

Heme iron is also found in cytochromes, like cytochrome c in the electron transport chain as shown below5.

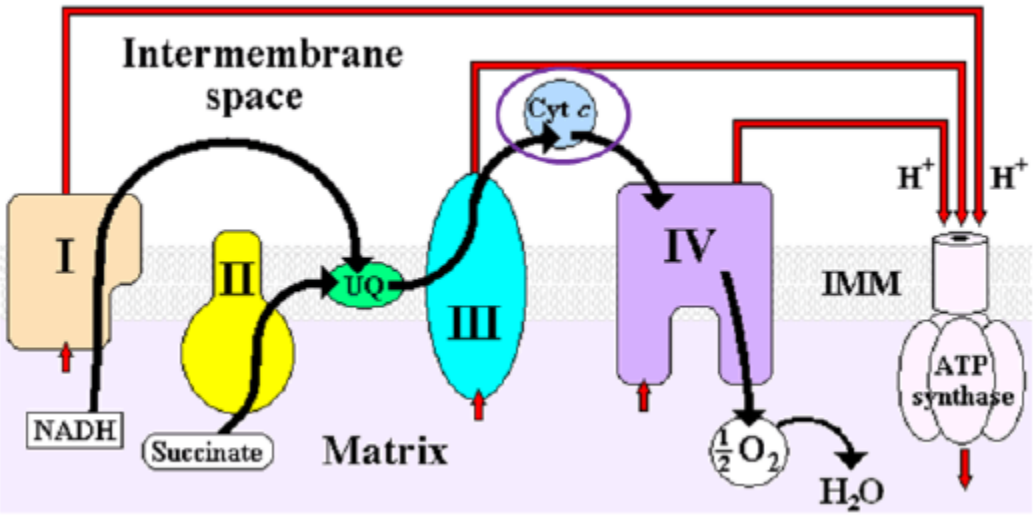


Figure 12.7.16: Cytochrome c in the electron transport chain contains iron15

Query 12.7.8

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Iron Deficiency & Toxicity

The levels of iron in the different compartments is illustrated by the figure below. The red above the table is meant to represent the amount of iron in the different compartments. In early negative iron balance stage, iron stores are slightly depleted. Once

the stores are almost completely exhausted, this state is referred to as iron depletion. In iron deficiency, stores are completely exhausted and the circulating and functional iron levels are also depleted. In iron anemia, the circulating and functional iron levels are further depleted from iron-deficiency.



Measure	Normal	Early Negative Iron Balance	Iron Depletion	Iron-Deficient	Iron Anemia
Bone Marrow Iron[1]	2-3	1+	0-1+	0	0
Plasma ferritin[2] (µg/L)	100±60	<25	20	10	<10
Transferrin iron-binding capacity[3] (µg/dL)	330±30	330-360	360	390	410
Serum Transferrin Saturation (%)	35±15	30	30	<15	<15
Plasma Iron	115±50	<120	115	<60	<40

[1] Great measure, but invasive

[2] Small amount are released from liver, bone, and spleen – proportional to body stores

[3] Also referred to as total iron-binding capacity

Figure 12.7.17: Measures of iron status5,12,16

Query 12.7.9

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The most common measures of iron status are hemoglobin concentrations and hematocrit (described below) levels. A decreased amount of either measure indicates iron deficiency, but these two measures are among the last to indicate that iron status is depressed. This is because, as you can see in the figure above, the functional iron compartment (which contains hemoglobin and is highly correlated to hematocrit values) is not altered until you reach iron deficiency. This is accomplished by using stores to maintain the circulating and functional iron compartments. It is important that you understand the limitations of these indicators so that you can interpret the meaning of their values5.

The hematocrit, as illustrated in the figure below, is a measure of the proportion of red blood cells (erythrocytes) as compared to all other components of blood. The components are separated by a centrifuge. The red blood cells remain at the bottom of the tube. They can be quantified by measuring the packed cell volume (PCV) relative to the total whole blood volume.

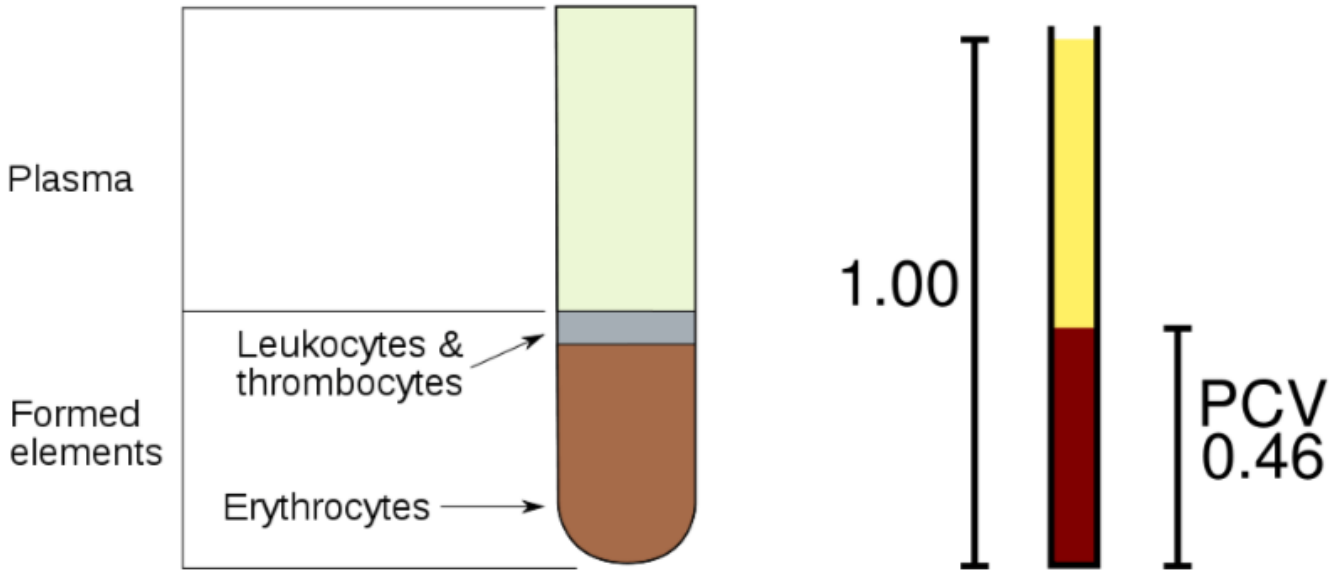


Figure 12.7.18: Hematocrit figures[17,18]

One of the best measures of iron status is bone marrow iron, but this is an invasive measure, and is therefore not commonly used. Plasma ferritin, the iron storage protein, is also found in lower amounts in the blood (plasma) and is a good indicator of iron stores. Thus, it is a sensitive measure to determine if someone is in negative iron balance or iron depleted. It is not as useful of a measure beyond this stage because the iron stores have been exhausted for the most part. Transferrin iron binding capacity (aka total iron binding capacity), as it sounds, is a measure of how much iron transferrin can bind. An increase in transferrin iron binding capacity indicates deficiency (>400 indicates deficiency). But the best measure for deficiency or anemia is either percent serum transferrin saturation or plasma iron. A lower % saturation means that less of the transferrin are saturated or carrying the maximum amount of iron that they can handle. Plasma iron is easily understood as the amount of iron within the plasma[19].

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Query 12.7.11

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Iron deficiency is the most common deficiency worldwide, estimated to affect 1.6 billion people. In the US, it is less common, but an estimated 10% of toddlers and women of childbearing age are deficient. Iron deficiency often results in a microcytic (small cell), hypochromic (low color) anemia, that is a result of decreased hemoglobin production. With decreased hemoglobin, the red blood cells cannot carry as much oxygen. Decreased oxygen leads to slower metabolism. Thus, a person with this anemia feels fatigued, weak, apathetic, and can experience headaches[19]. Other side effects include decreased immune function and delayed cognitive development in children[20].

Those who are particularly at risk are5,20:

- Women of childbearing age - because of losses due to menstruation
- Pregnant women - because of increased blood volume
- Vegetarians/Vegans - because they do not consume heme iron sources
- Infants - because they have low iron stores that can quickly be depleted

To give you a better understanding of these risks, it is helpful to look at how much higher the RDAs are for women of reproductive age and pregnant women compared to men21.

Women of reproductive age 18 mg/day

Pregnancy 27 mg/day

Men 8 mg/day

To put this in perspective, 3 oz of beef contains ~3 mg of iron. Thus, it can be a challenge for some women to meet the requirement. The RDA committee estimates the iron requirements to be 80% and 70% higher for vegans and endurance athletes, respectively. The increased requirement for endurance athletes is based on loss due to "foot strike hemolysis", or the increased rupture of red blood cells due to the striking of the foot on hard surfaces16.

Iron toxicity is rare in adults, but can occur in children who consume too many supplements containing iron. Symptoms of this acute toxicity include nausea, vomiting, and diarrhea20.

50 out of 10,000 newborns in the United States are born with the genetic condition, hemochromatosis. In this condition, there is a mutation in a protein in the enterocyte that prevents the normal decrease of intestinal iron absorption. Without this protein these individuals cannot decrease iron absorption. Since the body cannot excrete iron, it accumulates in tissues, and ultimately can result in organ failure5.

Query 12.7.12

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12.8: Zinc

Many animal products are good sources of zinc and are estimated to account for 70% of the zinc North Americans' consume[1]. An estimated 15-40% of consumed zinc is absorbed[2]. Zinc is taken up into the enterocyte through the Zir-and Irt-like protein 4 (ZIP4). Once inside the enterocyte, zinc can:

1. Bind to the zinc storage protein thionein. Once thionein has bound a mineral (or a metal) it is known as metallothionein.
2. Be used for functional purposes.
3. Bind to the cysteine-rich intestinal protein (CRIP) where it is shuttled to a zinc transporter (ZnT). After moving through the basolateral membrane, zinc primarily binds to the circulating protein albumin[3].

These functions are represented in the figure below.

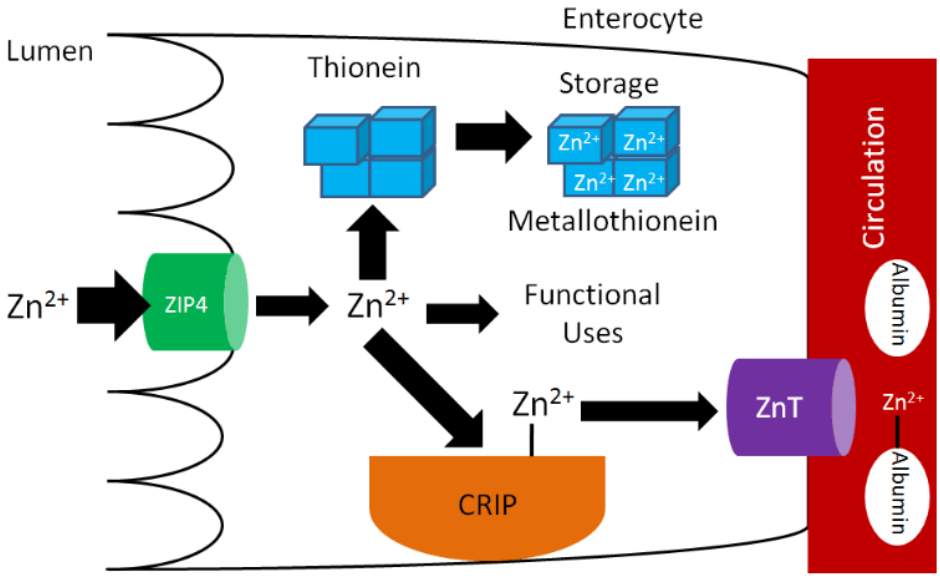


Figure 12.8.1: Fates of zinc once it is taken up into the enterocyte

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The zinc attached to albumin is transported to the liver through the portal vein. There is not a major storage site of zinc, but there are pools of zinc in the liver, bone, pancreas, and kidney[1]. Zinc is primarily excreted in feces.

There are some similarities in how zinc and iron absorption are regulated. Increased zinc consumption results in increased thionein synthesis in the enterocyte. As a result, more zinc is bound to thionein (forming metallothionein) and not used for functional uses or transported into circulation, as represented by the thick and thin arrows in the figure below.

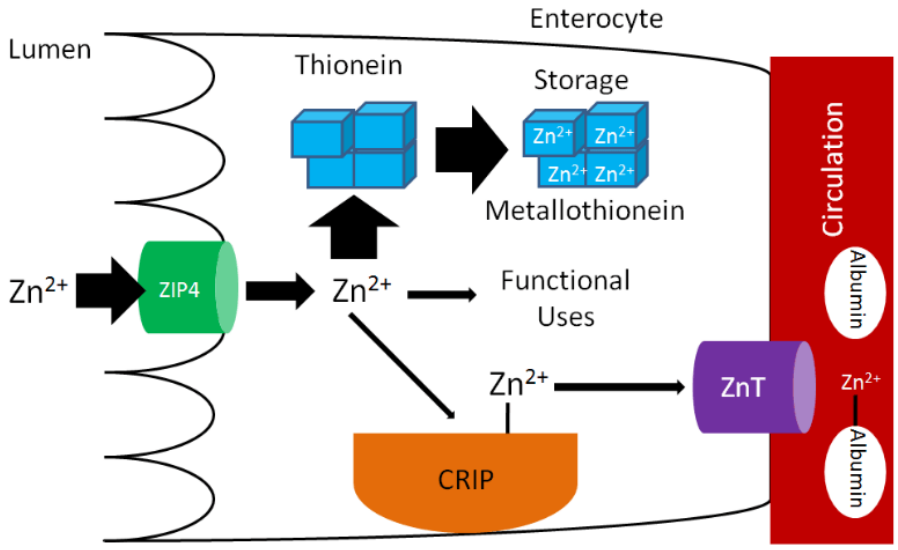


Figure 12.8.2: Fate of zinc under high zinc status

The enterocytes are then sloughed off preventing the bound zinc from being absorbed.

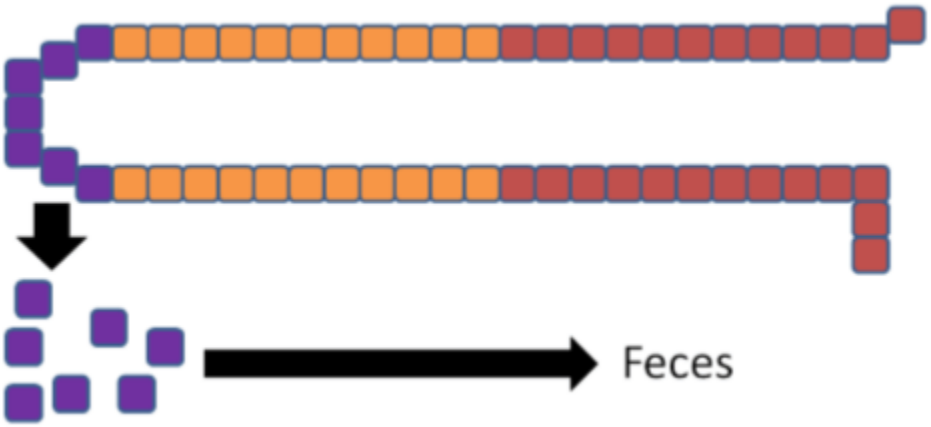


Figure 12.8.3: Enterocytes are sloughed off and excreted in feces.

There are a 3 inhibitors of zinc absorption (same inhibitors you learned about of iron absorption)3:

Phytate (phytic acid)

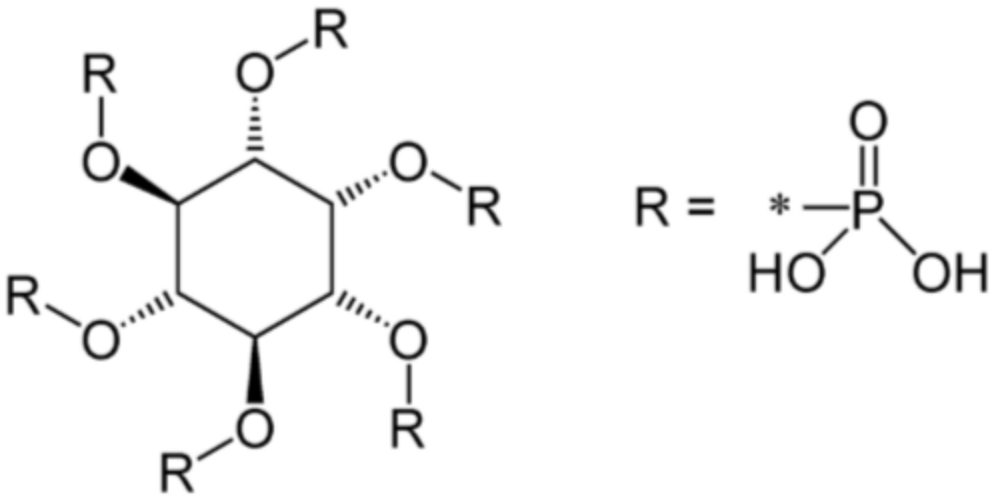


Figure 12.8.4: Phytic acid structure[4]

Polyphenols (coffee, tea)[3]

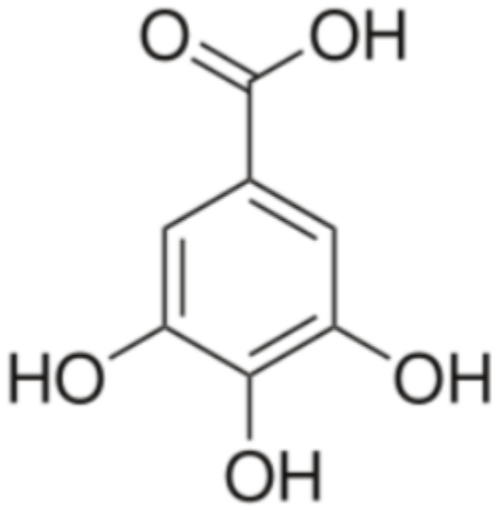


Figure 12.8.5: Structure of the polyphenol gallic acid[5]

Oxalate (spinach, rhubarb, sweet potatoes, and dried beans)[3]

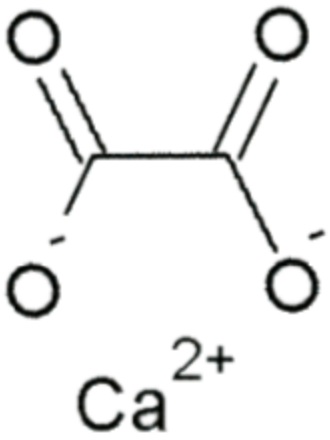


Figure 12.8.6: Structure of calcium oxalate6

Non-heme iron also inhibits zinc absorption.

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In supplements, zinc is found as3,7:

- Zinc oxide - 80% zinc
- Zinc chloride - 23% zinc
- Zinc sulfate - 23% zinc
- Zinc gluconate - 14.3% zinc

Zinc oxide is the least bioavailable form, but since it is 80% zinc, it is commonly used in supplements7.

Query 12.8.3

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Zinc Functions

Zinc is a cofactor for up to 300 enzymes in the body1. Enzymes that use zinc as a cofactor are known as metalloenzymes.

Zinc is a cofactor for the antioxidant enzyme superoxide dismutase that converts superoxide to hydrogen peroxide, as shown below.

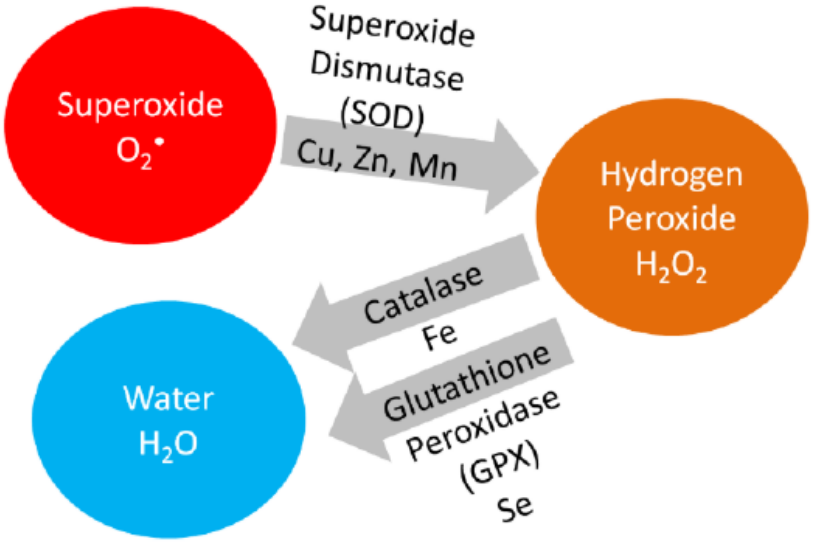


Figure 12.8.7: Superoxide dismutase uses zinc as a cofactor

Alcohol dehydrogenase uses 4 zincs per enzyme. Its role in ethanol metabolism is shown below3.

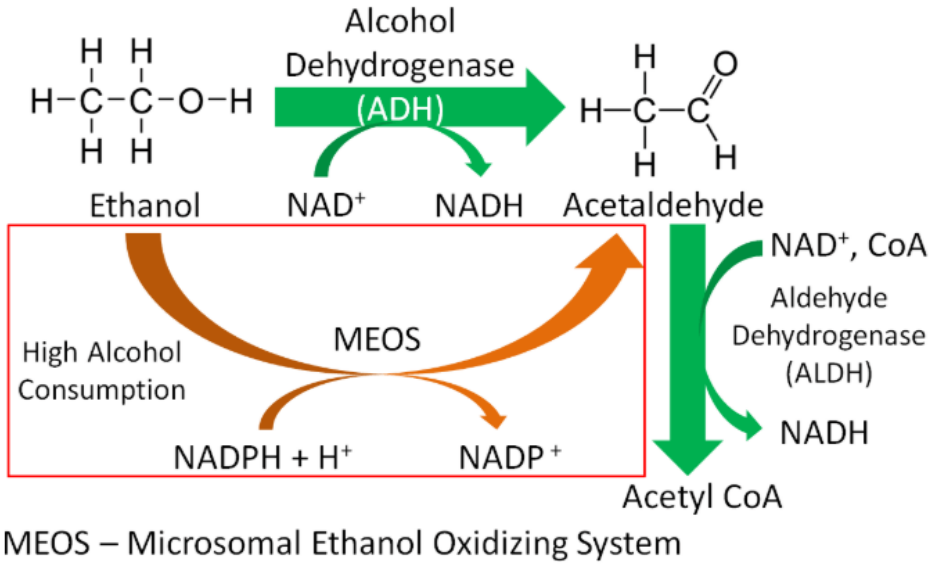


Figure 12.8.8: Ethanol metabolism8,9

Delta-aminolevulinic acid dehydratase (ALA dehydrogenase), which is involved in heme synthesis, uses 8 zincs/enzyme to form porphobilinogen, as shown below3.

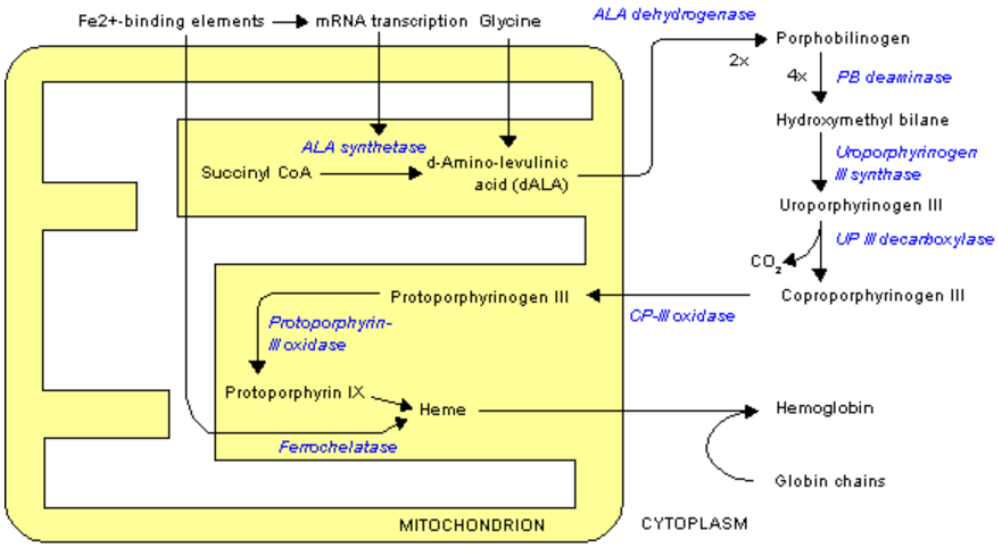


Figure 12.8.9: ALA dehydrogenase requires zinc in the heme synthesis pathway[10]

The enzyme that cleaves the extra glutamates from folate so that it can be taken up into the enterocyte is a metalloenzyme[3]. The cleavage of folate is shown in the figure below.

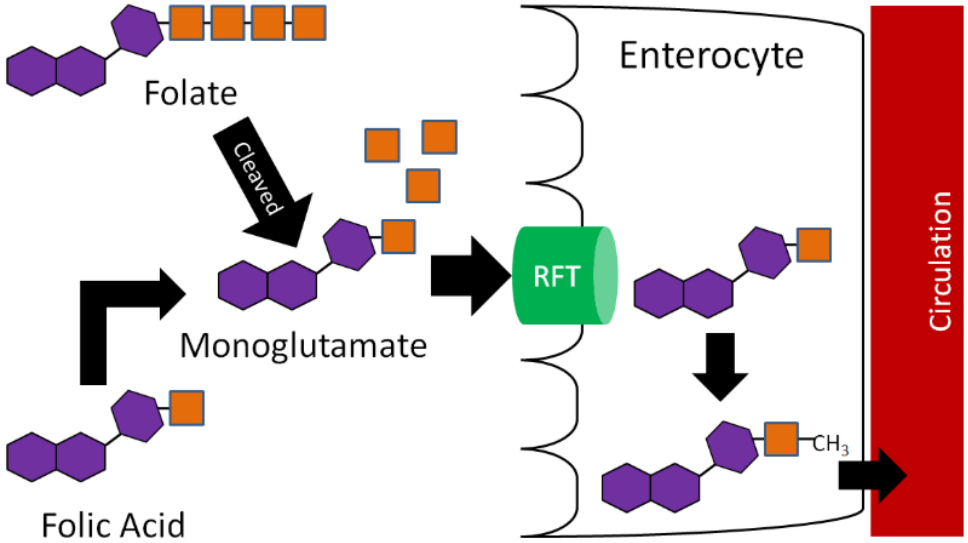


Figure 12.8.10: The absorption of folate and folic acid

Other notable metalloenzymes include DNA and RNA polymerase[3].

Zinc is also important for the formation of zinc fingers in proteins. Zinc fingers help proteins bind to DNA[3].

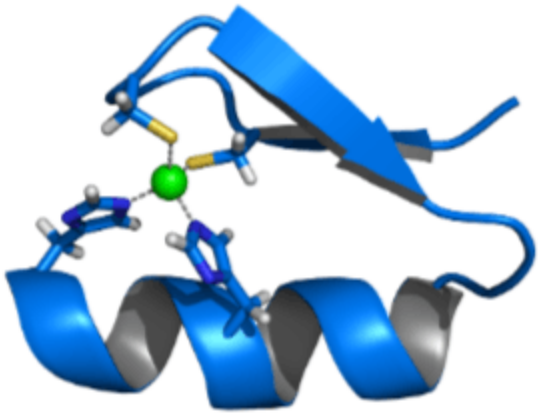


Figure 12.8.11: Structure of a zinc finger, zinc is the green atom bound in the center[11]

Zinc is also important for growth, immune function, and reproduction[9].

A Cochrane systematic review concluded that when taken within 24 hours of the onset of symptoms, that zinc lozenges or syrup results in a significant decrease in the duration and severity of common cold symptoms[12]. Thus, commonly used zinc lozenges may be an effective way to combat the common cold. However, large amounts of zinc consumption can be problematic for copper and ultimately iron levels in the body, as described in the copper section.

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Zinc Deficiency & Toxicity

As can be seen on the bottom map in the link below, the risk of zinc deficiency is low in North America, but there are other places in the world where it is much more common.

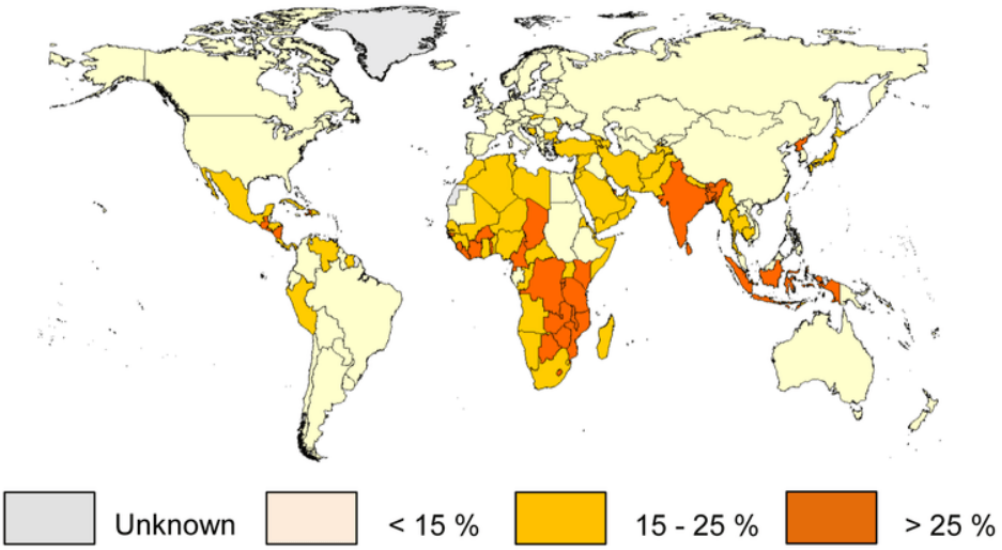


Figure 12.8.12: Worldwide prevalence of zinc deficiency12

At particular risk are children, pregnant women, elderly and the poor13. Symptoms of zinc deficiency include1,3:

- Growth inhibition
- Delayed sexual maturation
- Dermatitis
- Hair loss
- Impaired immune function
- Skeletal abnormalities

In the link below you can see a picture of an infant with dermatitis caused by zinc deficiency.

Web Link

Zinc Deficiency Dermatitis

Another cause of zinc deficiency is mutation of ZIP4 that results in the condition acrodermatitis enteropathica. Without ZIP4, zinc cannot be taken up efficiently into the enterocyte. This condition is managed by administering very high levels of zinc, some of which is absorbed through other mechanisms3.

Zinc toxicity is not common, but an acute toxicity results in1:

- Nausea
- Vomiting
- Intestinal cramps
- Diarrhea

Chronic toxicity can result in copper deficiency, as will be discussed in the copper section3.

Query 12.8.5

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12.9: Copper

Like iron, copper is found in 2 forms:

1. Cupric (Cu^{2+}), oxidized
2. Cuprous (Cu^{1+}), reduced

Cu^{1+} is the form that is primarily absorbed, thus Cu^{2+} is reduced to Cu^{1+} in the lumen. It is believed that, like iron, enzymatic reduction of Cu^{2+} is stimulated by ascorbate. The exact transporter that takes up the copper into the enterocyte is not known. It may be DMT1 that takes up non-heme iron. Once inside the enterocyte, Cu^{1+} can1:

1. Bind to thionein to form metallothionein. While zinc is a better stimulator of thionein levels, copper is actually a more avid binder to this protein.
2. Be used for functional uses as discussed in the next subsection.
3. Transported across the cell by an unknown carrier and then exported by ATP7A, an ATPase transporter.

Like zinc, copper is transported through the portal vein to the liver bound to albumin, as shown below. Albumin has a high affinity for Cu^{2+}, so Cu^{1+} is oxidized before transported to albumin through ATP7A, as illustrated below.

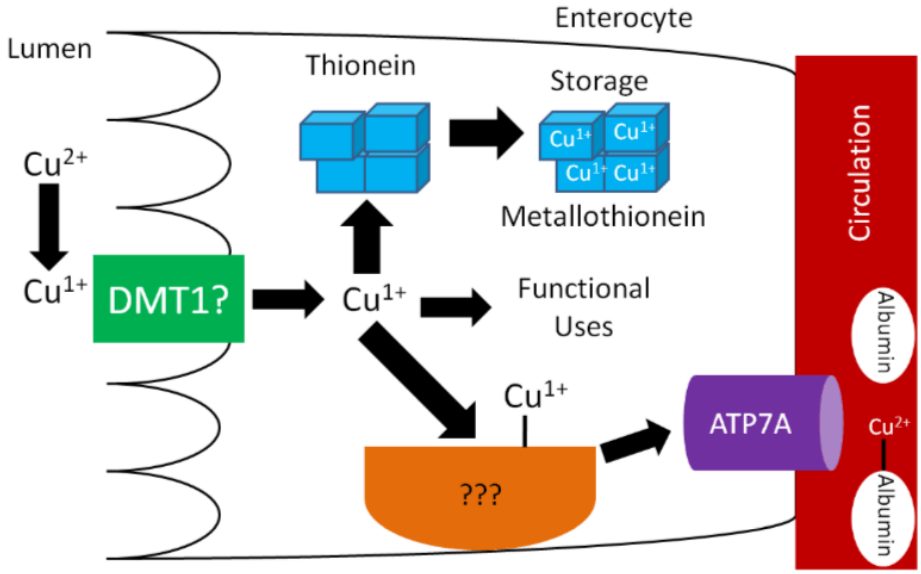


Figure 12.9.1: Copper absorption

Similar to zinc, there is not much storage of copper in the body. The liver is the primary site of storage, where copper is taken up through an unknown transporter. If it is going to be stored, it will bind with thionein to form metallothionein. Copper is transported through circulation by the copper transport protein ceruloplasmin, which can bind 6 coppers/protein as shown below1.

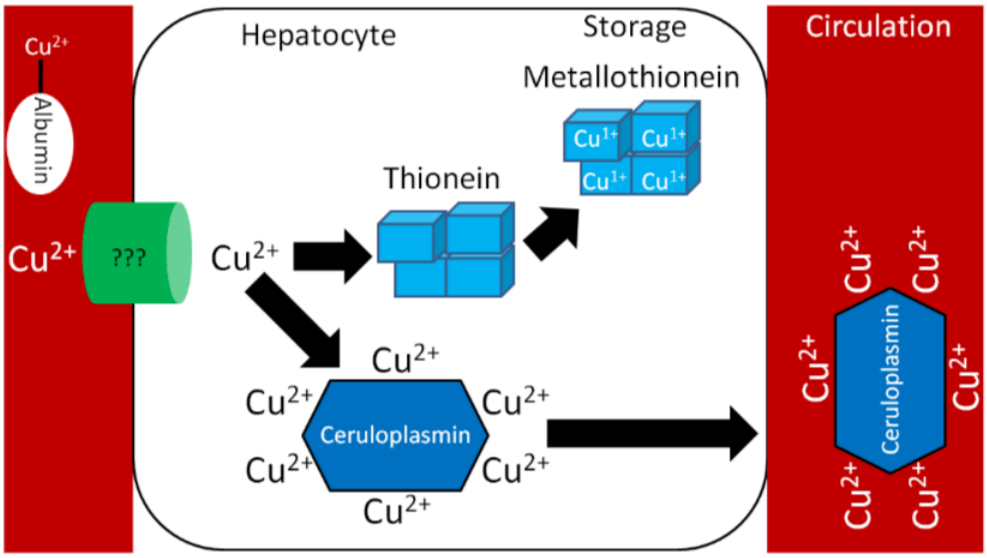


Figure 12.9.2: Copper in the hepatocyte

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Legumes, whole grains, nuts, shellfish, and seeds are good sources of copper[2]. It is estimated that over 50% of copper consumed is absorbed[1]. Copper is primarily excreted in the feces.

There are a number of different forms of copper used in supplements:

- Copper sulfate (25% copper)
- Cupric chloride (47% copper)
- Cupric acetate (35% copper)
- Copper carbonate (57% copper)
- Cupric oxide (80% copper)

All of these forms of copper are bioavailable, except cupric oxide. Assays have shown that it is not absorbed at all. Nevertheless, some supplements still use this form of copper[1,3].

Query 12.9.2

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Copper Functions

Copper has a number of functions that are described and shown below.

Two copper-containing proteins, ceruloplasmin and hephaestin, oxidize Fe^{2+} to Fe^{3+}. Fe^{3+} is the form that binds to transferrin, as shown below1.

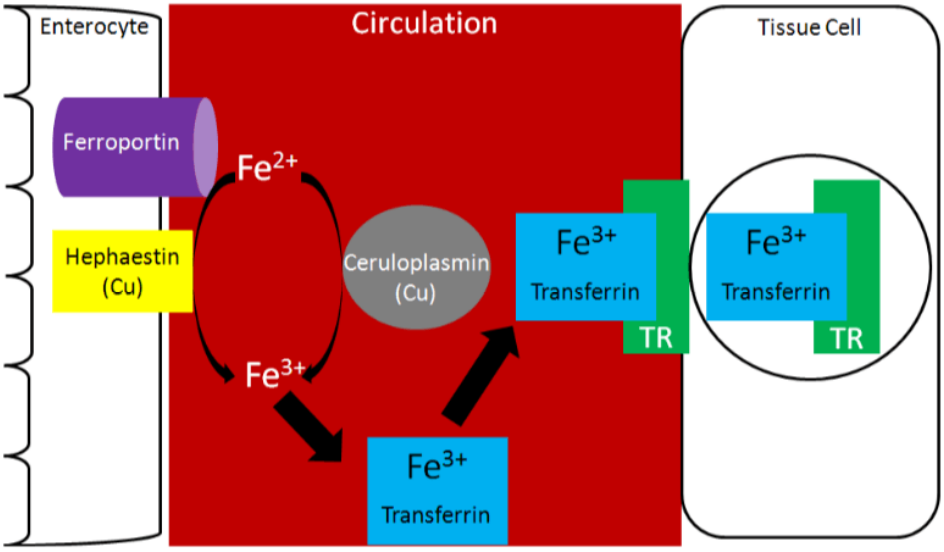


Figure 12.9.3: Transport and uptake of iron

Because copper is needed for this function, it is important for iron absorption.

Copper is also a cofactor for superoxide dismutase, which converts superoxide to hydrogen peroxide, as shown below.

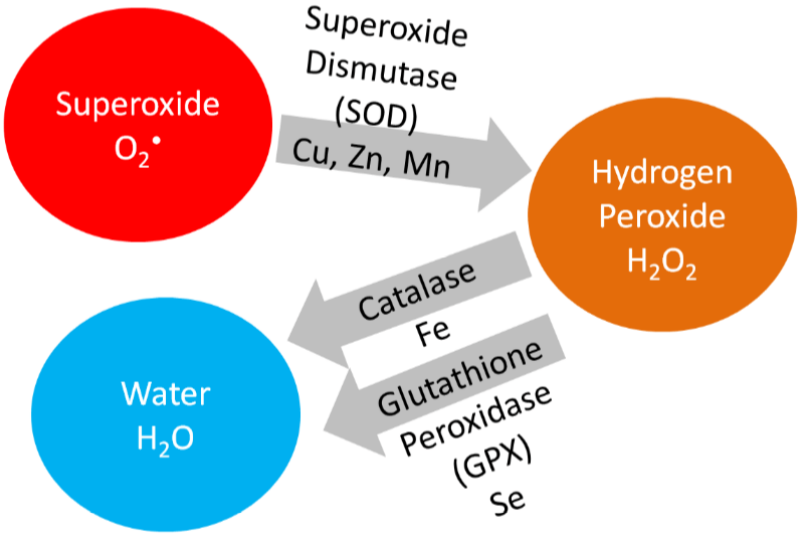


Figure 12.9.4: Superoxide dismutase uses zinc as a cofactor

Copper is also needed for hormone synthesis. For example, it is a cofactor for dopamine beta-hydroxylase, which converts dopamine to norepinephrine, as shown below1.

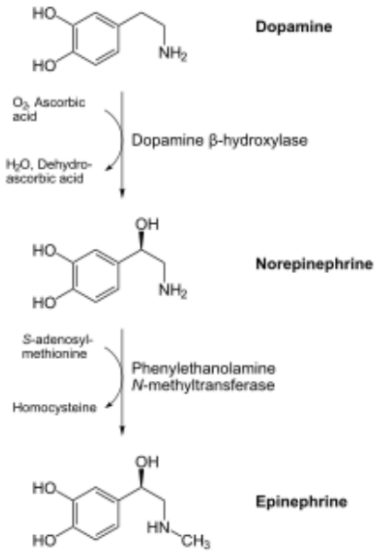


Figure 12.9.5: Dopamine beta-hydroxylase requires copper[4]

Hopefully the following example looks vaguely familiar because we talked about this pathway in the vitamin C functions subsection. Ascorbic acid reduces Cu^{2+} back to Cu^{1+} so that this enzyme can continue to function, as shown below[1]. This is analogous to how ascorbic acid reduces Fe^{3+} back to Fe^{2+} so proline and lysyl hydroxylases can continue to function.

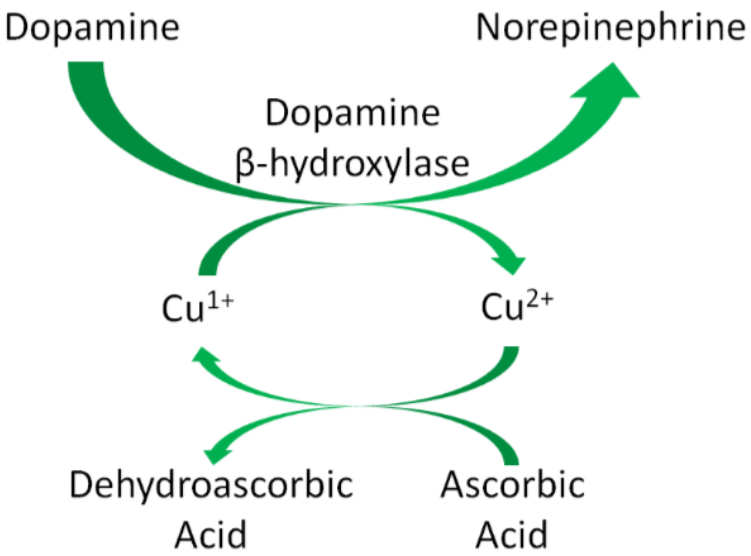


Figure 12.9.6: Dopamine beta-hydroxylase

Cytochrome c oxidase (complex IV) in the electron transport chain is a copper-containing enzyme that reduces oxygen to form water, as shown below[1].

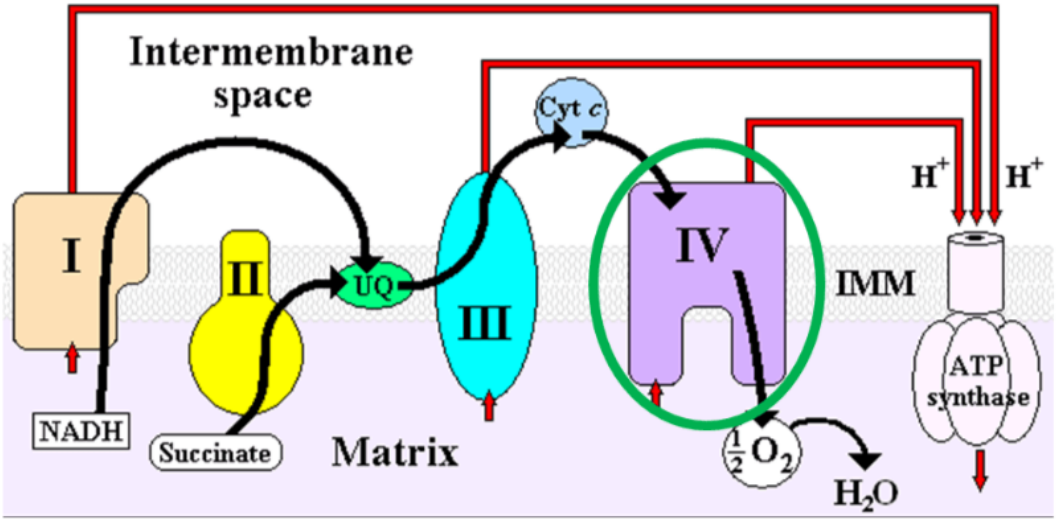


Figure 12.9.7: Cytochrome c oxidase (complex IV)5

Lysyl oxidase, an enzyme that is important for cross-linking between structural proteins (collagen and elastin), requires copper as a cofactor1.

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Copper Deficiency & Toxicity

Copper deficiency is rare in humans, but results in the following symptoms1,6:

- Hypochromic anemia
- Decreased white blood cell counts leading to decreased immune function
- Bone abnormalities

Copper deficiency can result in a secondary iron deficiency, since Fe^{2+} cannot be oxidized to Fe^{3+} to bind to transferrin. This can cause the hypochromic anemia that occurs in iron deficiency.

Menke's disease is a genetic disorder that results in copper deficiency. It is believed that individuals with this disease have a mutation in ATP7A that prevents copper from leaving the enterocyte, thus preventing absorption7.

Copper toxicity is also rare in humans, but acute toxicity results in the following symptoms1,6:

- Nausea, vomiting, diarrhea, abdominal pain

Chronic symptoms include1,6:

- Brain, liver, and kidney damage
- Neurological damage

Wilson's disease is a genetic disorder where a mutation in ATP7B prevents copper excretion, resulting in copper toxicity. One

notable symptom is that individuals with this disease have golden to greenish-brown Kayser-Fleischer rings around the edges of the cornea, as shown in the link below[1,6].

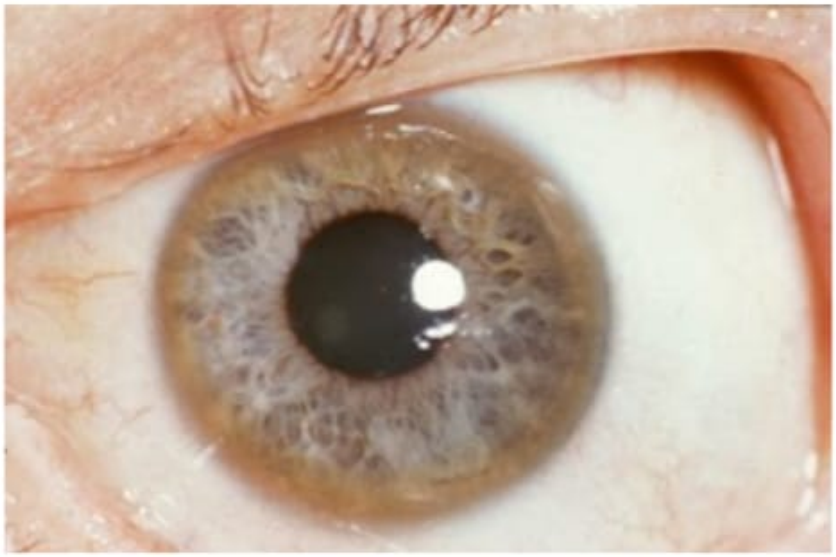


Figure 12.9.8: Kayser-Fleischer ring[7]

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How High Zinc Intake Can Lead to Copper & Iron Deficiencies

As you learned previously, thionein is the storage protein for zinc, but it more avidly binds copper. When it binds a mineral, it becomes metallothionein. High zinc intake results in increased thionein synthesis in the enterocyte. Thus, when an individual is consuming high zinc levels (most likely by supplementation, unlikely from dietary sources), the enterocyte will have high levels of thionein as shown below.

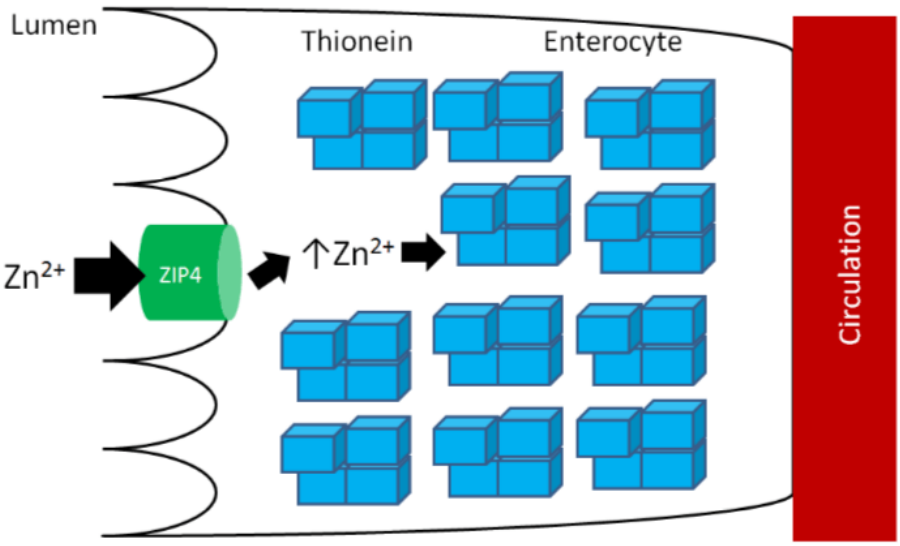


Figure 12.9.9: Zinc increases thionein production

The high levels of thionein will bind any copper that is taken up into the enterocyte (as metallothionein), "trapping" the copper in the enterocyte and preventing it from being absorbed into circulation, as shown below.

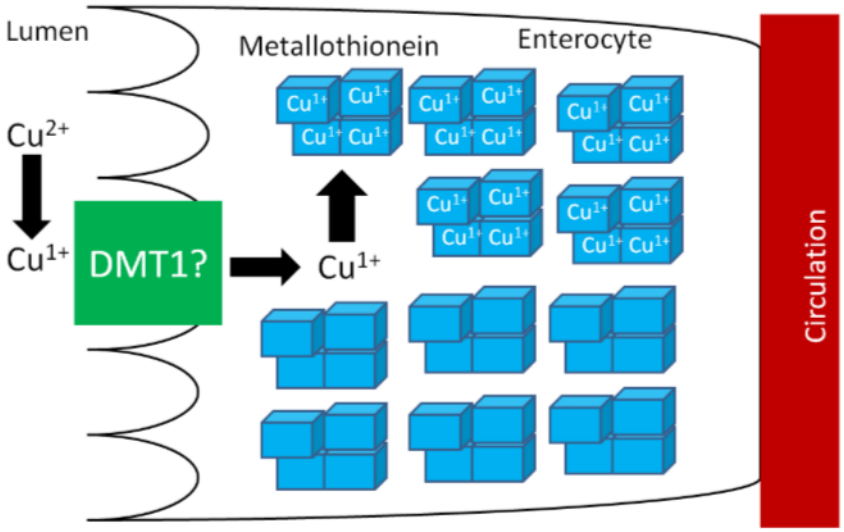


Figure 12.9.10: Copper taken up into the enterocyte is bound to thionein forming metallothionein.

The enterocytes containing the "trapped" copper move up the crypt and are sloughed off and excreted in feces. The copper consumed essentially is lost from the body through this process.

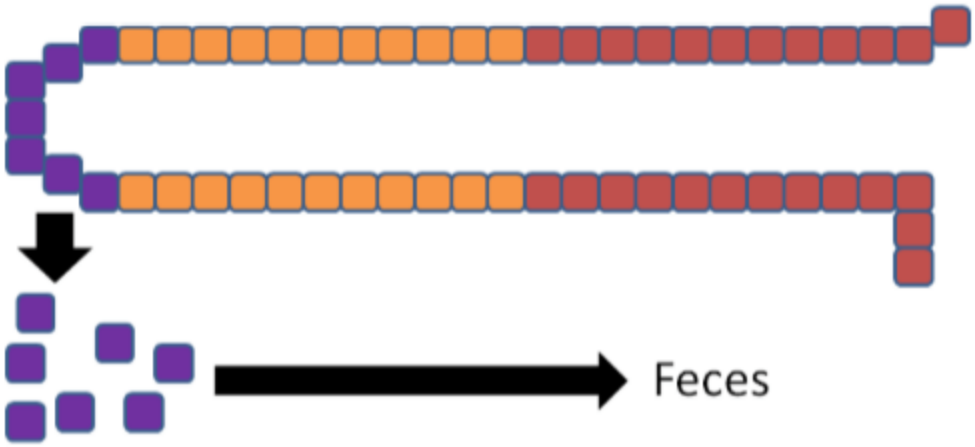


Figure 12.9.11: Enterocytes are sloughed off and excreted in feces

Without adequate copper being transported to the liver, no ceruloplasmin is produced and released into circulation. The lack of copper further influences iron transport by decreasing ceruloplasmin in circulation and hephaestin (another copper-containing protein) on the membrane of the enterocyte. These 2 proteins normally convert $\mathrm{Fe^{2+}}$ to $\mathrm{Fe^{3+}}$ so that iron can bind to transferrin.

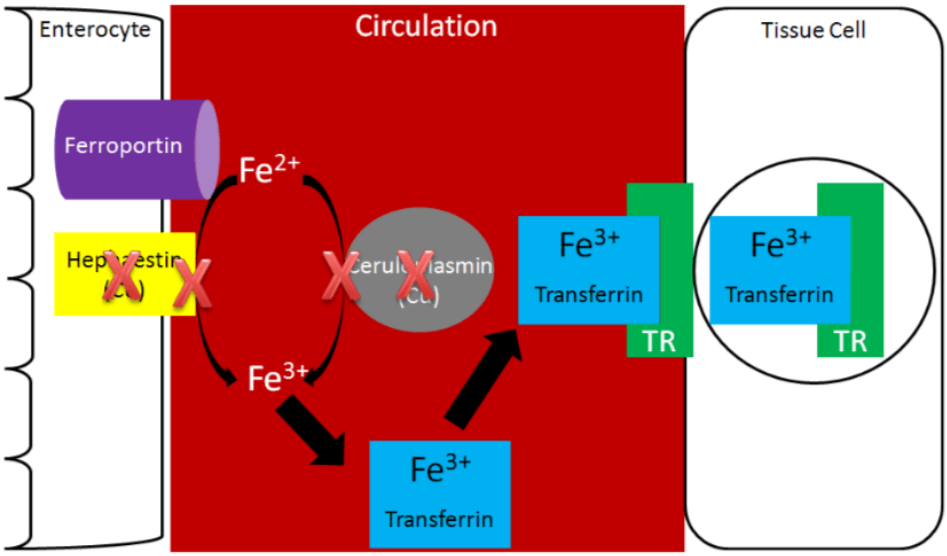


Figure 12.9.12: Lack of copper means that hephaestin and ceruloplasmin aren't available to oxidize $\mathrm{Fe^{2+}}$ to $\mathrm{Fe^{3+}}$

Without hephaestin and ceruloplasmin, $\mathrm{Fe^{3+}}$ is not formed from $\mathrm{Fe^{2+}}$. As a result $\mathrm{Fe^{2+}}$ is "trapped" in the enterocyte because it can't bind to transferrin as shown below.

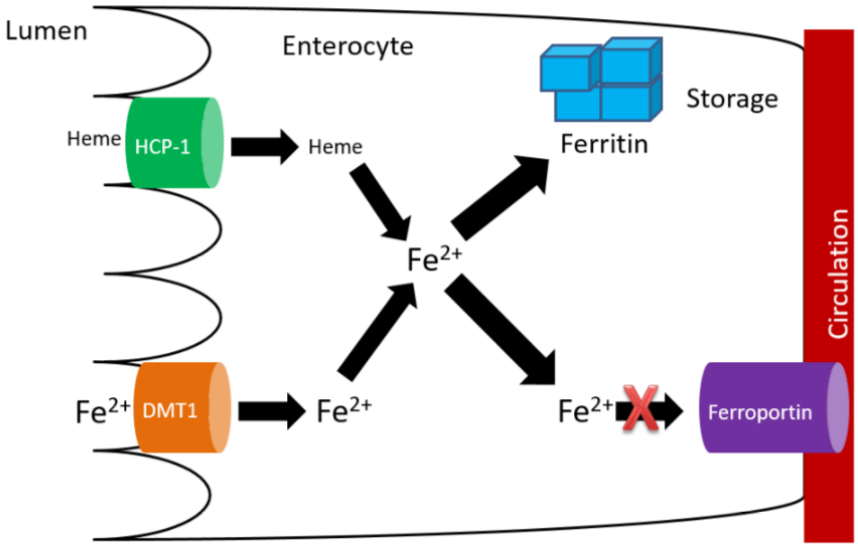


Figure 12.9.13: Fe^{2+} is trapped in the enterocyte

The enterocytes containing the "trapped" iron move up the crypt and are also sloughed off and excreted in feces. The iron consumed essentially is lost from the body through this process.

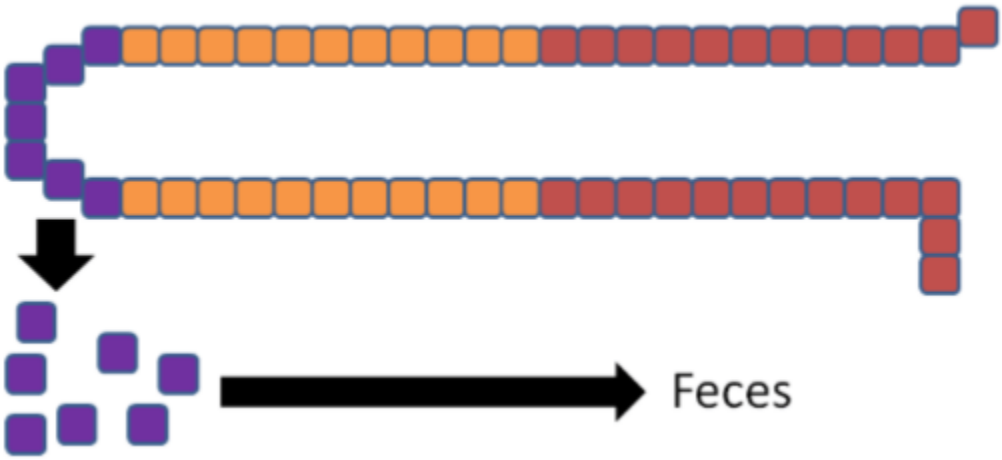


Figure 12.9.14: Enterocytes are sloughed off and excreted in feces

In summary, high zinc intake increases thionein production, which traps all copper; the lack of copper decreases circulating ceruloplasmin and hephaestin, which causes all iron to be trapped as well. This example illustrates the interconnectedness of zinc, copper, and iron.

Query 12.9.5

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1. Gropper SS, Smith JL, Groff JL. (2008) Advanced nutrition and human metabolism. Belmont, CA: Wadsworth Publishing.
2. Whitney E, Rolfes SR. (2011) Understanding nutrition. Belmont, CA: Wadsworth Cengage Learning.
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4. https://s3-us-west-2.amazonaws.com/c...467EB44654.png
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7. By Herbert L. Fred, MD, Hendrik A. van Dijk - http://cnx.org/content/m15007/latest/, CC BY 3.0, commons.wikimedia.org/w/inde...?curid=2746925

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13: ELECTROLYTE MICRONUTRIENTS

In this chapter, electrolytes will be explained before learning more about the 4 electrolyte micronutrients. As a general rule, deficiency and toxicity of these the electrolyte micronutrients are rare, so they are presented in a single subsection rather than multiple subsections like most of the micronutrients that you have learned about. Then, hypertension will be discussed, along with the impact of these micronutrients on the condition.

13.1: Electrolytes

13.2: Sodium

13.3: Chloride

13.4: Potassium

13.5: Magnesium

13.6: Hypertension, Salt-Sensitivity and the DASH Diet

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13.1: Electrolytes

Electrolytes are compounds that separate into ions in water. Electrolytes can be separated into 2 classes:

- **Cations**: ions that have a positive charge
- **Anions**: ions that have a negative charge

The following table summarizes the major intracellular and extracellular electrolytes by giving their milliequivalents (mEq)/L. Milliequivalents are a measure of charge. Thus, a higher value means that the cation or anion is accounting for more charge.

Table 13.1.1*: Major intracellular and extracellular electrolytes (mEq/L)*[1,2]

Intracellular		Extracellular	
Cations	**Anions**	**Cations**	**Anions**
Potassium (K^+) 150	Phosphate (PO^{4-}) 104	Sodium (Na^+) 142	Chloride (Cl^-) 103
Magnesium (Mg^{2+}) 40	Proteins 57		Bicarbonate (HCO^{3-}) 27
	Sulfate (SO_4^{2-}) 20		Proteins 16

The following figure graphically shows the major intracellular and extracellular cations (green) and anions (red).

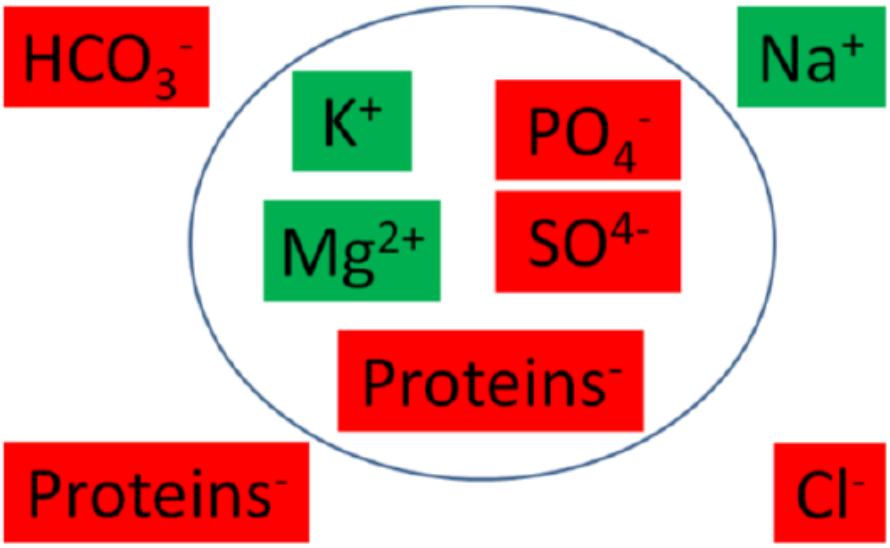


Figure 13.1.1: Major intracellular and extracellular cations (green) and anions (red)[2]

Electrolytes and proteins are important in fluid balance. Your body is 60% water by weight. Two-thirds of this water is intracellular, or within cells. One-third of the water is extracellular, or outside of cells. One-fourth of the extracellular fluid is plasma, while the other 3/4 is interstitial (between cells) fluid. Thus, when considering total body water, around 66% is intracellular fluid, 25% is interstitial fluid, and 8% is plasma[3,4].

Fluid distribution between the different compartments are shown below.

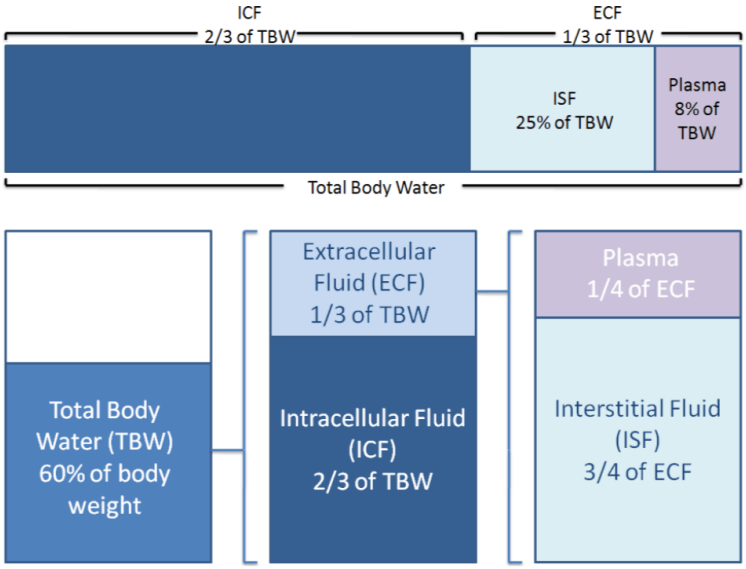


Figure 13.1.2: Distribution of fluid in the body[3,4].

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1. Byrd-Bredbenner C, Moe G, Beshgetoor D, Berning J. (2009) Wardlaw's perspectives in nutrition. New York, NY: McGraw-Hill.
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4. Adapted from http://www.netterimages.com/image/21248.htm

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13.2: Sodium

Salt (NaCl) contributes almost all the sodium that we consume. 75-85% of the salt we consume is from processed foods, 10% is naturally in foods, and added salt contributes 10-15% of total salt intake[1].

95-100% of consumed sodium is absorbed[2]. Sodium is taken up into the enterocyte through multiple mechanisms before being pumped out of the enterocyte by sodium-potassium ($\mathrm{Na^+/K^+}$) ATPase. Sodium-potassium ATPase is an active carrier transporter that pumps 3 sodium ions out of the cell and 2 potassium ions into the cell, as shown below. It is the reason that sodium is the major extracellular cation and potassium is the major intracellular cation.

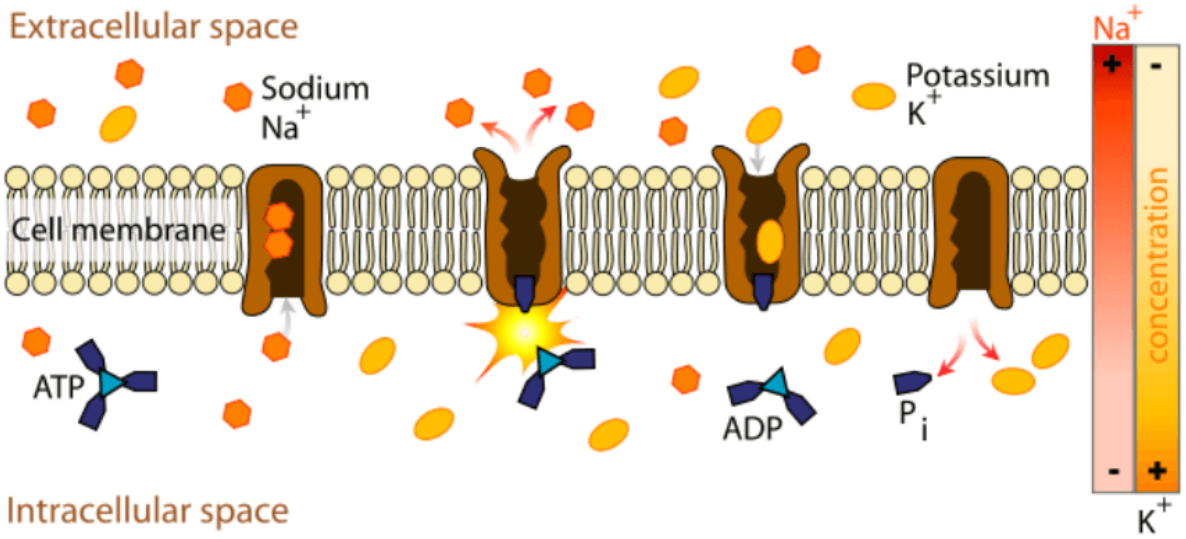


Figure 13.2.1: Sodium-potassium ATPase (aka sodium-potassium pump), an active carrier transporter[3]

Sodium is the major cation in extracellular fluid.

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Sodium has 3 main functions[1]:

1. Fluid balance
2. Aids in monosaccharide and amino acid absorption
3. Muscle contraction and nerve transmission (not discussed further below)

Fluid balance

The body regulates sodium and fluid levels through a series of processes as shown below. A decrease in plasma volume and blood pressure signals the kidney to release the enzyme renin. Renin activates angiotensin that is converted to angiotensin II. Angiotensin II signals the adrenal glands to secrete the hormone aldosterone. Aldosterone increases sodium reabsorption in the kidney, thus decreasing sodium excretion. These actions cause plasma sodium concentrations to increase (these could also be

increased by sodium intake), which is detected by the hypothalamus. The hypothalamus stimulates the pituitary gland to release antidiuretic hormone (ADH) that causes the kidneys to reabsorb water, decreasing water excretion. The net result is an increase in blood volume and blood pressure1.

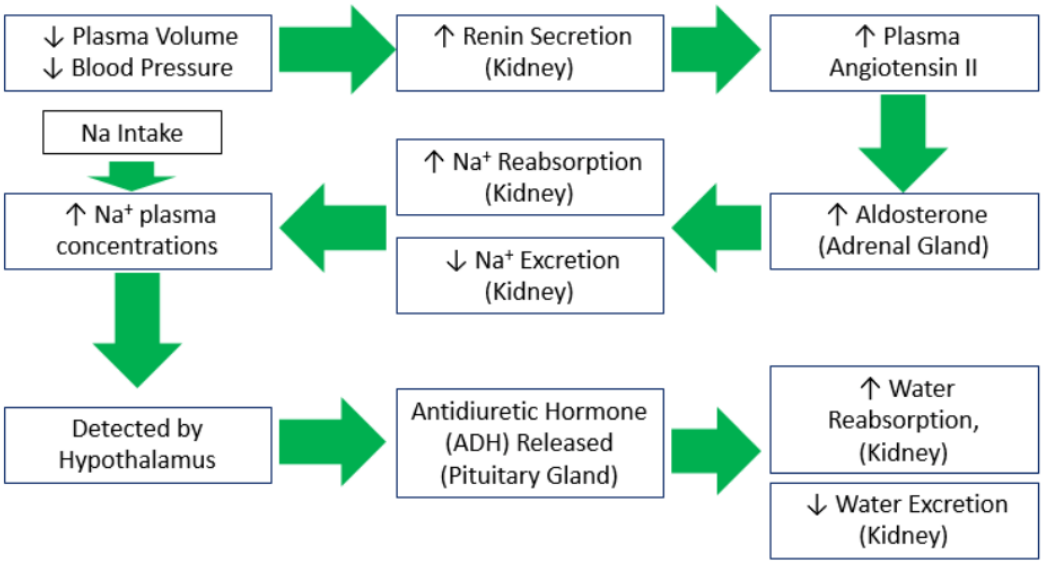


Figure 13.2.2: Response to decreased plasma volume and blood pressure

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Aids in monosaccharide and amino acid absorption

Glucose and galactose are taken up into the enterocyte by sodium-glucose cotransporter 1 (SGLT1), which requires sodium to be transported along with glucose or galactose.

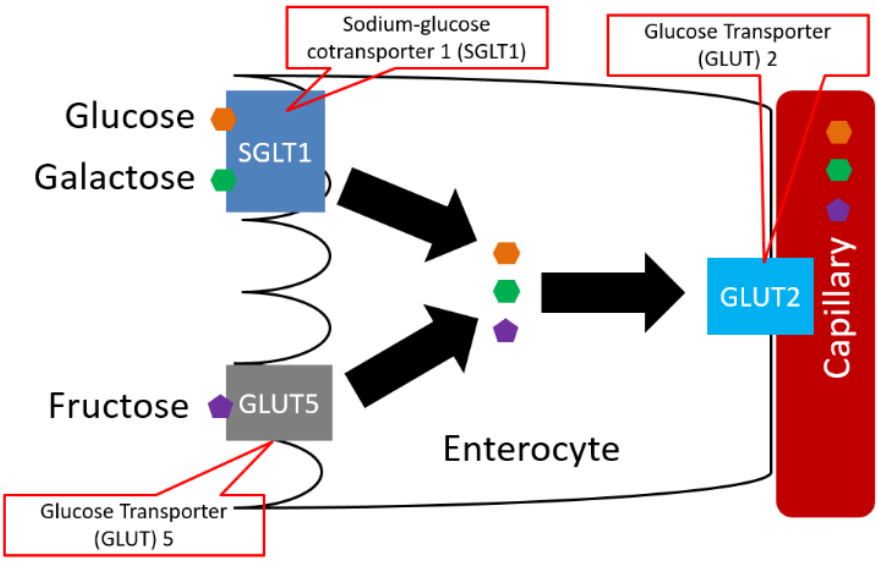


Figure 13.2.3: Monosaccharide Uptake and Absorption

Amino acids are taken up and transported into circulation through a variety of amino acid transporters. Some of these transporters are sodium-dependent (require sodium to transport amino acids).

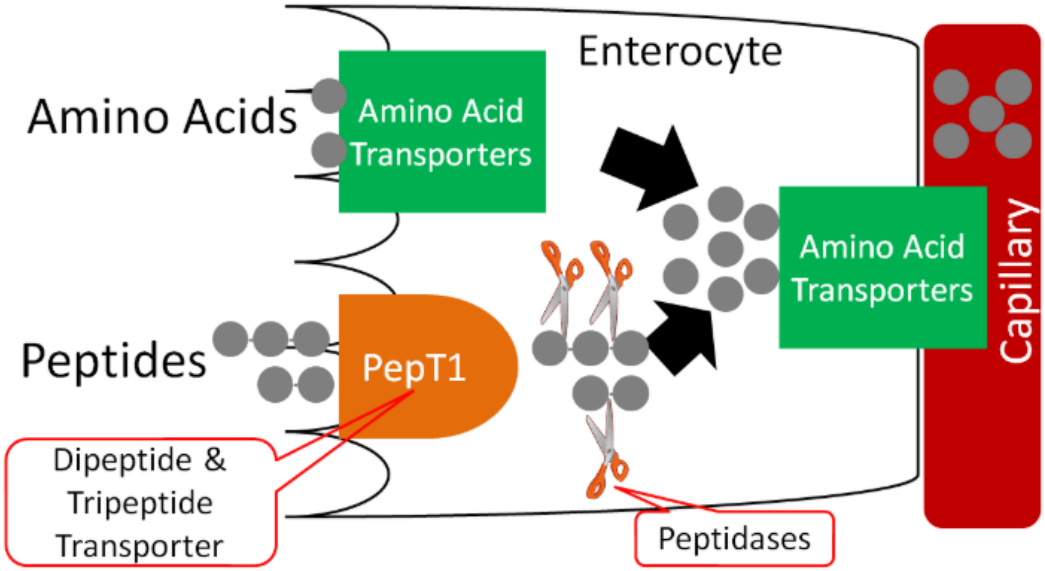


Figure 13.2.4: Protein absorption

Sodium deficiency is rare, and is normally due to excessive sweating. Sweat loss must reach 2-3% of body weight before sodium losses are a concern[1,2]. Losses of this magnitude are uncommon, but can occur in marathon runners and ultra-marathon runners who sweat for many hours straight (without proper liquid intake). But in general some practices like consuming salt pills to replace loss from sweating are not needed. Low blood sodium levels (hyponatremia) can result in[1]:

- Headache
- Nausea
- Vomiting
- Fatigue
- Muscle Cramps

Sodium is not toxic because we can readily excrete it, but higher sodium intake increases the risk of developing high blood pressure. High sodium intake also increases calcium excretion, and a recent meta-analysis has found a positive association between dietary sodium intake and the risk of osteoporosis[4], such that high intakes are associated with a higher risk of

developing osteoporosis. However, hyponatremia (low sodium in the body) has also been associated with an increased risk of developing osteoporosis due to the release of sodium from the bone matrix. The prevalence of hyponatremia is estimated to be between 3-26%5. The extraction of sodium from bone has been hypothesized to affect bone quality, such that the bone is less efficient at healing microfractures which can eventually lead to lower bone density5. High sodium intake may also increase the risk of developing kidney stones (by increasing calcium excretion), because calcium oxalate is the most common form of kidney stone1.

Query 13.2.3

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13.3: Chloride

Sodium's partner in salt, chloride, is the major extracellular anion. Almost all of the chloride we consume is from salt, and almost all chloride is absorbed. It is excreted in urine like sodium.

Chloride has the following functions[1]:

1. Aids in nerve impulses
2. Component of hydrochloric acid (HCl)
3. Released by white blood cells to kill foreign substances
4. Helps maintain acid-base balance

Chloride deficiency is rare, but can occur because of severe diarrhea or vomiting. Other symptoms of this deficiency include[1,2]:

- Weakness
- Diarrhea and vomiting
- Lethargy

Chloride is not toxic (because we readily excrete it), but since it is a part of salt, it is recommended that we restrict our intake to avoid potential increases in blood pressure.

Query 13.3.1

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1. Byrd-Bredbenner C, Moe G, Beshgetoor D, Berning J. (2009) Wardlaw's perspectives in nutrition. New York, NY: McGraw-Hill.
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13.4: Potassium

Potassium is the major intracellular cation. Good sources of potassium include beans, potatoes (with skin), milk products, orange juice, tomato juice, and bananas[1,2]. Potassium, like sodium and chloride, is well absorbed. Greater than 85% of consumed potassium is absorbed. Potassium is primarily excreted in urine (~90%)[3]. As you will learn in a later section, this is an electrolyte that we should try to consume more of rather than limiting like sodium and chloride.

One way to increase intake is through potassium chloride salt, which is an alternative to sodium chloride salt as described in the article below that FDA is proposing changing its name.

Web Link

FDA proposes changing name of healthier alternative to sodium

Potassium is important for:

1. Fluid Balance
2. Nerve transmission and muscle contraction

Increased potassium intake results in decreased calcium excretion. This is the opposite effect of increased sodium intake, which increases calcium excretion[1].

Potassium deficiency is rare but can be fatal. Symptoms include:

- Weakness
- Fatigue
- Constipation
- slow reflexes
- Irregular heartbeat (can be fatal)

Deficiency can occur in individuals that are on diuretics, drugs that increase urine production, and individuals with eating disorders[1].

Toxicity is also extremely rare, only occurring if there is a problem with kidney function that prevents it from being excreted normally. Symptoms of toxicity are irregular heartbeat and even cardiac arrest (likely need to be potassium provided into circulation rather than consumed in some way)[1].

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1. Byrd-Bredbenner C, Moe G, Beshgetoor D, Berning J. (2009) Wardlaw's perspectives in nutrition. New York, NY: McGraw-Hill.
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13.5: Magnesium

Magnesium is an electrolyte, but that is not considered its major function in the body. Green leafy vegetables, beans, nuts, seeds, and whole grains are good sources of magnesium[1,2]. 40-60% of consumed magnesium is absorbed at normal levels of intake. Magnesium is excreted primarily in urine[3]. Like potassium, this is an electrolyte that it is beneficial to consume more of.

55-60% of magnesium in the body is found in bone[3]. Some (30%) of this bone magnesium is believed to be exchangeable, or can be used to maintain blood concentrations, similar to how calcium in bones can be used to maintain blood concentrations.

Magnesium helps to stabilize ATP and nucleotides by binding to phosphate groups. Magnesium plays a role in over 300 enzymes in the body. Here is a list of some of the physiological processes that magnesium participates in[3]:

- Glycolysis
- TCA cycle
- Fatty acid oxidation (beta-oxidation)
- DNA and RNA transcription
- Nucleotide synthesis
- Muscle contraction

Magnesium deficiency is rare, but can be caused by prolonged diarrhea or vomiting. Symptoms include[1]:

- Irregular heartbeat
- Muscle spasms
- Disorientation
- Seizures
- Nausea
- Vomiting

Magnesium toxicity is also rare but can occur from excessive use of magnesium-containing antacids or laxatives. Symptoms include[3]:

- Diarrhea
- Nausea
- Flushing
- Double vision
- Slurred speech
- Weakness
- Paralysis

Magnesium supplements differ in percent of magnesium in different forms, as shown below.

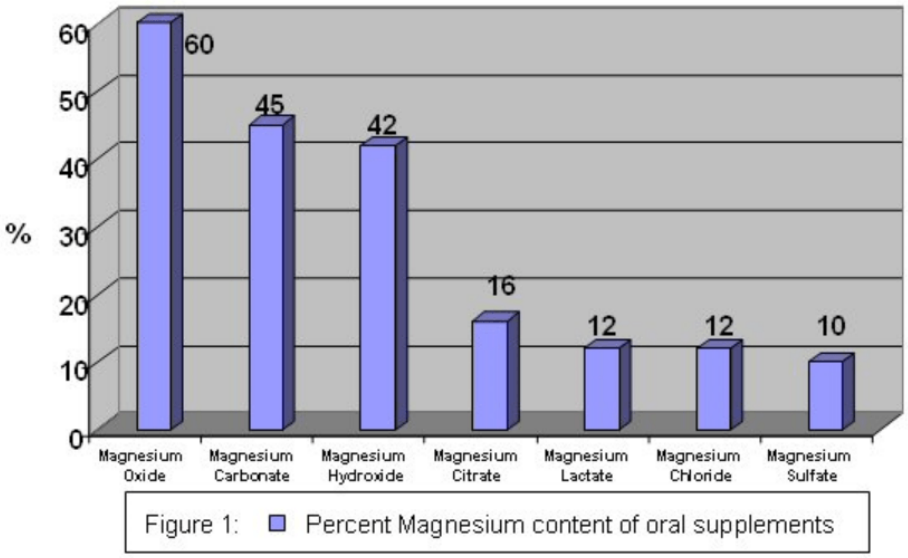


Figure 13.5.1: Percent magnesium in oral supplements[4]

The bioavailability of magnesium oxide is significantly lower than magnesium chloride, magnesium lactate, and magnesium aspartate. The latter 3 are equally bioavailable[4].

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1. Byrd-Bredbenner C, Moe G, Beshgetoor D, Berning J. (2009) Wardlaw's perspectives in nutrition. New York, NY: McGraw-Hill.
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13.6: Hypertension, Salt-Sensitivity and the DASH Diet

Approximately 29% of American adults have hypertension (high blood pressure), which increases their risk of developing cardiovascular disease1. Salt and/or sodium intake is believed to be a major causative factor in the development of hypertension. However, it is now known that not everyone is salt-sensitive. Salt-sensitive means that a person's blood pressure increases with increased salt intake and decreases with decreased salt intake. Approximately 25% of normotensive (normal blood pressure) individuals and 50% of hypertensive individuals are salt-sensitive2. Most others are salt-insensitive, and in a small portion of individuals, low salt consumption actually increases blood pressure1. Unfortunately, there is not a readily employable clinical method to determine whether a person is salt-sensitive. There are some known characteristics that increase the likelihood of an individual being salt-sensitive. They are1:

- Elderly
- Female
- African-American
- Hypertensive
- Diabetic
- Chronic Kidney Disease

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There is some evidence now suggesting that there may be negative effects in some people who restrict their sodium intakes to the levels recommended by some organizations as described in the first link below. The second link describes a couple of studies that had conflicting outcomes as it relates to the importance of salt reduction in decreasing blood pressure and cardiovascular disease. The third link is to a study that found that higher potassium consumption, not lower sodium consumption, was associated with decreased blood pressure in adolescent teenage girls.

Web Links

Report Questions Reducing Salt Intake Too Dramatically
Pour on the Salt? New Research Suggests More Is OK
For Teenagers, Potassium May Matter More Than Salt

This has led to debate because it is quite possible that it is a very real issue whether salt-sensitive individuals can decrease their sodium intake (to concomitantly reduce their blood pressure) in a food environment where there are extremely limited options that do not contain meaningful sodium levels. Thus, the push has been to reduce sodium levels in the food supply overall to provide more options to those who are salt-sensitive. However, this is a push that benefits a minority of the population. Also, further adding to this is the fact that almost no one knows how he/she responds to sodium/salt and there is disagreement over ideal/optimal intake levels.

To combat hypertension, the Dietary Approaches to Stop Hypertension (DASH) diet was developed. This diet emphasizes:

fruits, vegetables, fat-free/low-fat milk and milk products, whole grain products, fish, poultry, nuts

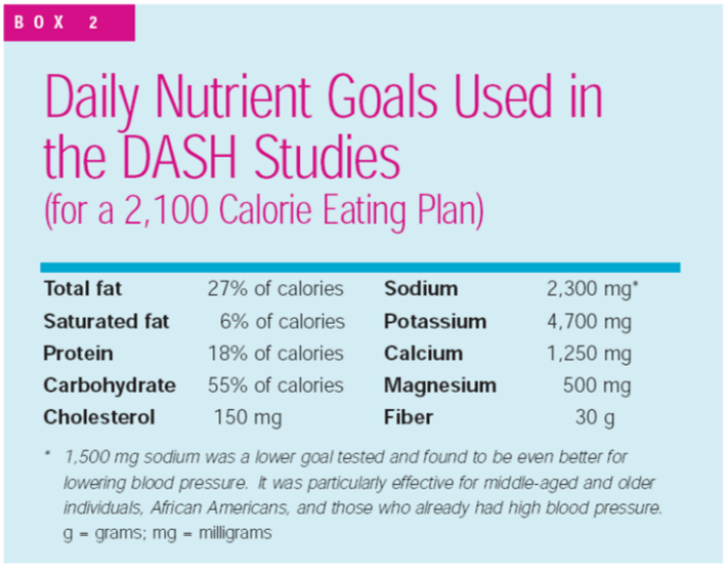
It limits:

red meat, sweets, added sugars, sugar-containing beverages

As a result the diet is high in:

potassium, magnesium, calcium, protein, fiber

The daily goals for the DASH diet are shown below:



BOX 2

Daily Nutrient Goals Used in the DASH Studies (for a 2,100 Calorie Eating Plan)

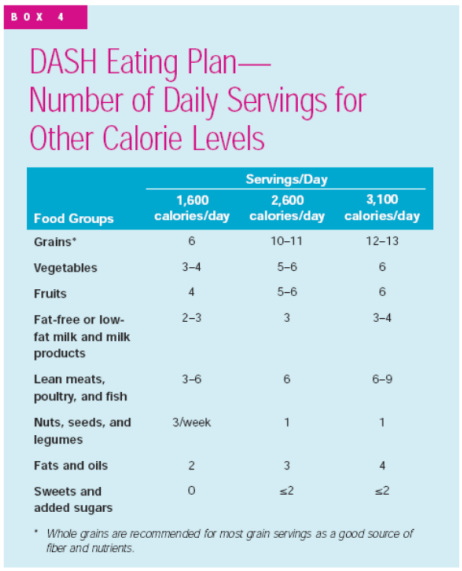
Total fat	27% of calories	**Sodium**	2,300 mg*
Saturated fat	6% of calories	**Potassium**	4,700 mg
Protein	18% of calories	**Calcium**	1,250 mg
Carbohydrate	55% of calories	**Magnesium**	500 mg
Cholesterol	150 mg	**Fiber**	30 g

* *1,500 mg sodium was a lower goal tested and found to be even better for lowering blood pressure. It was particularly effective for middle-aged and older individuals, African Americans, and those who already had high blood pressure.*

g = grams; mg = milligrams

Figure 13.6.1: DASH daily nutrient goals3

To get an idea of what types of foods and how much would be consumed in the diet, an eating plan is shown below.



BOX 4

DASH Eating Plan—Number of Daily Servings for Other Calorie Levels

	Servings/Day		
Food Groups	**1,600 calories/day**	**2,600 calories/day**	**3,100 calories/day**
Grains*	6	10–11	12–13
Vegetables	3–4	5–6	6
Fruits	4	5–6	6
Fat-free or low-fat milk and milk products	2–3	3	3–4
Lean meats, poultry, and fish	3–6	6	6–9
Nuts, seeds, and legumes	3/week	1	1
Fats and oils	2	3	4
Sweets and added sugars	0	≤2	≤2

* *Whole grains are recommended for most grain servings as a good source of fiber and nutrients.*

Figure 13.6.2: DASH eating plan3

The DASH diet has been shown to be remarkably effective in decreasing blood pressure in those with hypertension. Nevertheless, most people with hypertension are not following the DASH diet. In fact, evidence from the National Health and Nutrition Examination Survey found that significantly fewer hypertensive individuals were following the DASH diet in 1999-2004 than during 1988-1994, as shown in the table below4.

Table 13.6.1: Percent of hypertensive subjects in NHANES trial meeting the DASH goals[4]

Variable	NHANES 1988-1994 (n = 4336)	NHANES 1999-2004 (n = 3821)	Absolute Change (%)	p-value
DASH Accordance	29.3 ± 1.5	21.7 ± 1.3	-7.6	<0.001
Total Fat	42.9 ± 1.8	35.9 ± 2.0	-7.0	0.01
Saturated Fat	20.6 ± 1.2	20.4 ± 1.4	-0.2	0.94
Protein	43.7 ± 2.0	47.7 ± 1.9	4.0	0.73
Cholesterol	26.4 ± 2.2	24.3 ± 1.6	-2.1	0.44
Fiber	20.2 ± 1.5	12.3 ± 0.9	-7.9	<0.001
Magnesium	14.2 ± 1.3	6.4 ± 0.8	-7.8	<0.001
Calcium	19.0 ± 1.6	17.6 ± 2.0	-1.4	0.58
Potassium	12.7 ± 0.9	11.7 ± 0.9	-1.0	0.46
Sodium	17.8 ± 1.5	14.6 ± 1.3	-3.2	0.21

The main components that contributed to the decrease in DASH diet accordance (how well the recommendations are being met) were total fat, fiber, and magnesium, as indicated by their high negative absolute changes.

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GLOSSARY

A

Absorption | Absorption from the enterocyte into circulation.

Accordance | How well the recommendations are being met.

Acesulfame-Potassium (K) | Potassium containing, heat-stable alternative sweetener.

Acetaldehyde | 2-carbon ethanol metabolite, which can then be metabolized to acetyl-CoA. Buildup of this metabolite can cause undesirable symptoms such as flushing, dizziness, nausea, and headaches.

Acetyl-CoA | 2-carbon metabolic intermediate.

Acetylation | Addition of an acetyl group.

Acid reflux | A burning sensation cause by gastric fluid refluxing back up the esophagus through a leaky lower esophageal sphincter. Also known as heartburn.

Acini | cluster of cells that resemble a many-lobed "berry (like raspberry).

Acne | An infection of the skin, caused by changes in the sebaceous glands. The redness comes from the inflammation of the skin in response to the infection.

Acrodermatitis enteropathica | Condition that results from a mutation in ZIP4, which prevents the update of zinc into the enterocyte and thus may cause deficiency.

Actin | A muscle protein involved in contraction.

Activate | To make something active.

Active | Requires energy (ATP)

Active carrier transport | Movement of solutes from an area of lower concentration (against the concentration gradient) across a membrane to an area of higher concentration with the help of a protein. Requires energy

Active site | The location within an enzyme where biochemical reactions occur. Also known as the catalytic site.

Acute | Symptoms or signs that begin and worsen quickly; not chronic.

Adenosine triphosphate | Common form of energy currency in the body, energy is stored in phosphate bonds.

Adequate Intake | An intake (not a requirement) that is likely to exceed the actual requirements of almost all individuals in an age, sex, and life-stage group; established when scientific evidence is not sufficient to determine an RDA.

Adipocyte | Adipose cell.

Adipose | Fatty tissue.

Adrenal | A small gland that makes steroid hormones, adrenaline, and noradrenaline. These hormones help control heart rate, blood pressure, and other important body functions. There are two adrenal glands, one on top of each kidney.

Advantame | Similar in structure to aspartame and neotame. Sweeter than aspartame, heat-stable and is not a concern for Phenylketonuria. Higher acceptable daily intake than neotame.

Aerobic | With oxygen.

Aerobic respiration | Metabolism of glucose to carbon dioxide, water, and ATP and involves an electron transport system in which oxygen is the final electron acceptor.

Albumin | The most common of the proteins in the plasma.

Alcohol | From a nutrition perspective traditionally refers to ethanol, which is present in alcoholic beverages. But also a carbon containing compound that includes at least one hydroxyl (-OH) group.

Alcohol dehydrogenase | Primary ethanol metabolizing enzyme, metabolizes ethanol to acetaldehyde reducing its cofactor NAD to NADH in the process. Has limited capacity which can be exceeded.

Aldehyde dehydrogenase | Enzyme that metabolizes acetaldehyde to acetyl-CoA, while reducing cofactor NAD to NADH.

Aldosterone | A steroid hormone made by the adrenal cortex (the outer layer of the adrenal gland). It helps control the balance of water and salts in the kidney by keeping sodium in and releasing potassium from the body.

Alpha 1-4 bonds | An alpha bond between the carbon 1 in the first monosaccharide and carbon 4 of the second monosaccharide. Readily cleaved by digestive enzymes.

Alpha 1-6 bonds | An alpha bond between the carbon 1 in the first monosaccharide and carbon 6 of the second monosaccharide. Not cleaved by digestive enzymes, fermented by microorganisms in colon.

Alpha-bond | A bond formed when both carbons have the same stereochemistry, generally digestive enzymes cleave these

Alpha-carotene | An orange provitamin A carotenoid. It is asymmetrical, so only 1 molecule of retinal is formed when it is cleaved.

Alpha-cell | Pancreatic cells that sense low blood glucose concentrations and secrete glucagon.

Alpha-helix | A type of secondary structure that forms a helix shape.

Alpha-linolenic acid | An essential 18-carbon omega-3 fatty acid with 3 double bonds (18:3 n-3).

Alpha-tocopherol derivative | Alpha-tocopherol with an added compound ester bonded to it.

alpha-tocopherol transfer protein | Protein found in the liver that preferentially binds to 2R-alpha-tocopherol to facilitate its incorporation into VLDL.

Amino acid | Made up of an amino group, a carboxylic acid, and a side group that varies between them all. Are bonded together to form peptides and proteins.

Amino acid score | Test food limiting essential amino acid (mg/g protein) / needs of same essential amino acid (mg/g protein).

Ammonia | Nitrogen with three hydrogens. Can be toxic if concentrations get too high.

Amphipathic | Having both hydrophilic, and hydrophobic properties.

Amylopectin | Branched polysaccharide for of starch with alpha 1-4 bond except at branch points where it contains 1-6 bonds.

Amylose | Linear polysaccharide form of starch. All bonds are alpha 1-4 bonds.

Anabolic | To build. Can relation to metabolic processes or states.

Anaerobic | Without oxygen.

Angular stomatitis | Lesion or cracking at the corners of the mouth.

Anion | An negatively charged ion.

Anonymity | An anonymous state.

Antibody | Proteins made in response to a stimulating molecule called an antigen. The basis for the immune response.

Antidiuretic hormone | A hormone that helps blood vessels constrict and helps the kidneys control the amount of water and salt in the body. This helps control blood pressure and the amount of urine that is made. Antidiuretic hormone is made by a part of the brain called the hypothalamus and is secreted into the blood by the pituitary gland. C

Antigen | A substance that stimulates the body to produce an antibody.

Antioxidant | A substance that protects cells from the damage caused by free radicals and reactive oxygen species. Antioxidants typically donate an electron to stabilize these compounds.

Anus | Final part of the large intestine with an opening to the outside for feces to pass through.

Apathetic | A state of indifference, lack of feeling, emotion, interest, or concern.

Apolipoprotein | A lipid-binding protein that is a constituent of the plasma lipoprotein.

Ariboflavinosis | Riboflavin deficiency.

Ascending colon | After the cecum and before the transverse colon. As name indicates it is portion that is ascending in the body.

Aspartame | Sweetener that breaks down to the amino acids phenylalanine and aspartate and is not heat stable (loses its sweetness). Products containing need Phenylketonuria warning label.

Atherogenic | Contributing to atherosclerosis.

Atherosclerosis | Condition in which lipid builds up inside arteries, eventually causing the lumen inside to narrow and the arterial walls to stiffen.

Atkins diet | Low-carbohydrate or carbohydrate-restricted dietary pattern that consists of multiple phases.

Atrophic gastritis | Chronic inflammatory condition of the gastric mucosa that can lead loss of glands in the stomach. This condition can lead to decreased intrinsic factor production.

Autoimmune response | A condition in which the body's immune system mistakes its own healthy tissues as foreign and attacks them. Most autoimmune diseases cause inflammation that can affect many parts of the body. The parts of the body affected depend on which autoimmune disease a person has. Common signs and symptoms include fatigue, fever, muscle aches, joint pain and swelling, skin problems, abdominal pain, digestion problems, and swollen glands. The symptoms often come and go and can be mild or severe. There are many different types of autoimmune diseases. They are more common in women and can run in families. Also called autoimmune condition.

Avidin | Protein found in raw egg whites that tightly binds to biotin.

Avirulent | Inability of a virus or bacterium to cause damage to its host. Opposite of virulent.

Axon | A long extension from the neuron that carries nerve impulses away from the cell body.

B

Balance | Homeostasis. Negative balance is less than homeostasis, Positive balance is more than homeostasis.

Base | A substance that has a pH greater than 7.

Baseline | The start of a study.

Beriberi | Condition caused by thiamin deficiency. Can be wet or dry.

Beta-bond | A bond formed when both carbons have the different stereochemistry, generally digestive enzymes do not cleave these.

Beta-carotene | An orange provitamin A carotenoid.

Beta-cell | Pancreatic cells that sense high blood glucose concentrations and secrete insulin.

Beta-cryptoxanthin | A red provitamin A carotenoid. It is asymmetrical, so only 1 molecule of retinal is formed when it is cleaved.

Beta-oxidation | Metabolic process that cleaves 2 carbons off, which then after being activated forms acetyl-CoA.

Beta-pleated sheet | A type of secondary structure that forms sheets of molecules.

Bias | Systemic error. Can be selection, misclassification, and/or recall bias.

Bicarbonate | Hydrogen carbonate (HCO3), a base. Baking soda is NaHCO3.

Bile | A basic secretion produced by the liver, commonly concentrated in the gallbladder, which helps break down lipids into small droplets because of its emulsifying properties.

Bile acid | Synthesized from cholesterol, are good emulsifiers in bile given their amphipathic nature.

Bilirubin | Brown pigment secreted into bile by the liver.

Biliverdin | Green bile pigment secreted into bile by the liver.

Bioavailability | The ability to be absorbed and used by the body.

Bioconversion | The amount of retinal formed from the cleaved of the provitamin A carotenoids.

Biological value | (Grams of nitrogen retained / grams of nitrogen absorbed) x 100

Biosafety cabinet | Equipment that can be used to work with cells in a sterile environment.

Biotinidase | Enzyme that cleaves biocytin to biotin and lysine.

Biotinylation | An epigenetic modification where biotin is rarely added to histones.

Blind | The process of obscuring the intervention from either subjects or researchers during a clinical trial/human intervention study.

Bloating | A swelling or feeling of fullness in the abdomen. Bloating is usually the result of gas in the intestines and can be caused by many things, including overeating, lactose intolerance, and constipation.

Blood clot | The process that changes liquid blood to a gelatinous mass.

Bolus | Ball of masticated food and saliva.

Bomb calorimeter | An instrument that measured the energy given off from and item, thereby determining the kilocalories it provides.

Bone | A rigid tissue that constitutes part of the vertebrate skeleton in animals.

Bone marrow | A semi-solid tissue found within the spongy or cancellous portions of bones.

Bone mass | The amount of bone (weight) that a person has.

Bone mineral density | A measure of the amount of minerals (mostly calcium and phosphorous) contained in a certain volume of bone.

Bowel movement | Movement of feces (undigested food, bacteria, mucus, and cells from the lining of the intestines) through the bowel and out the anus. Also called defecation.

Brain | The organ inside the head that controls all body functions of a human being. Made up of billions of nerve cells, the brain is protected by the cranium (the bones that form the head). It is made up of three major parts: the cerebrum, the cerebellum, and the brain stem.

Branch chain amino acids | Valine, leucine, and isoleucine, which have branched side chains in their structures.

Branch point | The point where two branches meet, as in polysaccharides

Brush border | Also known as the microvilli, this membrane of the enterocyte looks like it has the teeth of a comb.

Buffer | A weak acid or a weak base; the pH of a buffer resists change when small amounts of acid or base are added

C

Calbindin | Calcium-binding protein that helps facilitate uptake into, and transport across, the enterocyte, thereby increasing calcium absorption.

Calcification | Deposits of calcium in the tissues.

Calcitonin | A hormone produced in the thyroid gland that when the calcium concentration is too high, calcitonin lowers it.

Calorie | As most commonly used actually refers to a kilocalorie, or the energy content of food.

Calpain | Family of calcium-requiring proteases that degrade proteins.

Capillary | Smallest type of blood vessel that transfers substances between blood and tissues.

Carbohydrate | Macronutrient that provides 4 kilocalories/gram. Made up of carbon, hydrogen, and oxygen.

Carbon dioxide | Carbon with two oxygens. Produce during metabolism and expired.

Carbon skeleton | What is left after an amine group is removed from an amino acid.

Carboxylase | Enzyme that catalyzes the addition of carbon dioxide to form a carboxylic acid group.

Carboxylic acid | A functional group composed of a carbon atom double-bonded to an oxygen atom: C=O and that carbon also containing a terminal hydroxyl (-OH) groups (-COOH).

Cardiovascular disease | A type of disease that affects the heart or blood vessels. The risk of certain cardiovascular diseases may be increased by smoking, high blood pressure, high cholesterol, unhealthy diet, lack of exercise, and obesity. The most common cardiovascular disease is coronary artery disease (narrow or blocked coronary arteries), which can lead to chest pain, heart attacks, or stroke. Other cardiovascular diseases include congestive heart failure, heart rhythm problems, congenital heart disease (heart disease at birth), and endocarditis (inflamed inner layer of the heart). Also called heart disease.

Carnitine | An amino acid derived compound that helps shuttle long-chain fatty acids into the mitochondria.

Carotenodermia | Overaccumulation of beta-carotene below the skin leading it to have an orange color.

Carotenoid | 40 carbon phytochemical or zoochemical compounds. Some are provitamin A. Animals do not synthesize.

Carpal tunnel syndrome | A condition that results from compression of the median nerve by the bones and connective tissue in the wrist.

Carrier protein | A protein that carries and ion or molecule across the membrane by changing shape after binding.

Cartilage | A tough, flexible tissue that lines joints and gives structure to the nose, ears, larynx, and other parts of the body.

Cascade | A series of reactions in which one step activates the next in a sequence that results in the amplification of the response.

Case-control study | An observational study that begins by selecting cases (people with the disease) and then controls from the same target population. Retrospectively then they are asked about the exposures.

Catabolic | To breakdown. Can be relation to metabolic processes or states.

Catabolize | To breakdown.

Catalase | Antioxidant enzyme that uses iron as a cofactor and can convert hydrogen peroxide H2O2 to water. Also metabolizes a minor amount of ethanol (alcohol).

Cataract | A condition in which the lens of the eye becomes cloudy. Symptoms include blurred, cloudy, or double vision; sensitivity to light; and difficulty seeing at night. They may occur in people of all ages, but are most common in the elderly.

Cation | An positively charged ion.

Causality | Cause and effect; an exposure or intervention causes an effect.

Cavity | A hollow area or hole. It may describe a body cavity (such as the space within the abdomen) or a hole in a tooth caused by decay.

Cecum | First part of the colon/large intestine.

Celiac Disease | A digestive disease that is caused by an immune response to a protein called gluten, which is found in wheat, rye, and barley. Celiac disease damages the lining of the small intestine and interferes with the absorption of nutrients from food. A person with celiac disease may become malnourished no matter how much food is consumed.

Cell culture | The growing of cells for normally for research purposes.

Centrifuge | A devise that spins samples to separate various components in a fluid.

Ceruloplasmin | Copper transport protein that takes Cu2+ through circulation. It also serves as the backup protein that oxidizes Fe2+ to Fe3+ so it can bind to transferrin.

Channel | A protein pore that allows molecules to pass in and out of a cell membrane.

Chelate | Bonding of ions and molecules to metal ions.

Chenodoxycholic acid | A primary bile acid that has amphipathic properties.

Chief cells | Cells at the middle of the gastric pit that produce pepsinogen and gastric lipase.

Chiral center | A term chiral used to describe an object that is non-superimposable on its mirror image.

Cholecystectomy | Surgical removal of the gallbladder.

Cholecystokinin | Released from the small intestine in response to chyme entering from stomach. Stimulates secretion of digestive enzymes from the pancreas, and contraction of the gallbladder to secrete bile, into the duodenum.

Cholesterol | Noncaloric lipid from the sterol family. Some hormones are made from it.

Cholesterol ester | Cholesterol is a fatty acid ester bonded to it.

Cholesterol esterase | Cleaves the fatty acid in cholesterol esters forming cholesterol and the fatty acid.

Cholic acid | A primary bile acid that has amphipathic properties.

Chronic | A condition or disease that is persistent or otherwise long-lasting in its effects.

Chronic disease | A disease or condition that usually lasts for 3 months or longer and may get worse over time. Chronic diseases tend to occur in older adults and can usually be controlled but not cured. The most common types of chronic disease are cancer, heart disease, stroke, diabetes, and arthritis.

Chronic Disease Risk Reduction Intakes | The level of intake for which there was moderate strength of evidence of chronic disease risk reduction.

Chylomicron | Large, triglyceride-rich, lipoprotein released from the enterocytes into lacteal. Lowest density of the lipoproteins.

Chylomicron remnant | Lipoprotein left after the action of lipoprotein lipase as a chylomicron moves through general circulation. Ultimately taken up by the liver.

Chyme | Thick, semi-liquid mixture that food in the gastrointestinal tract becomes by the time it leaves the stomach.

Circulating form | Form found in circulation (blood).

Cis | A double bond where the hydrogens are on the same side of the double bond.

Citric Acid Cycle | Acetyl-CoA combines with oxaloacetate to form citrate; ATP, NADH, and FADH2 are produced in this cycle.

Clinical trial | A prospective intervention study.

Codon | In DNA or RNA, a sequence of 3 consecutive nucleotides that codes for a specific amino acid or signals the termination of gene translation (stop or termination codon).

Coenzyme | Organic molecules required by enzymes to function.

Cofactor | Organic or inorganic molecules that are required by enzymes to function.

Cohort | A group of people.

Cola | A carbonated soft drink flavored with vanilla, cinnamon, citrus oils and other flavorings.

Colipase | Assists pancreatic lipase by serving as an anchor point on the triglyceride droplet, helping

Colon | Main part of the large intestine between the small intestine and rectum where water and salts are removed from liquid food wastes to form feces

Compartment | Different segments.

Complementary proteins | Two incomplete proteins that contain differing limiting amino acids such that consuming them in combination the complement one another by supplying the amino acids in in adequate amounts in the other.

Complete protein | A protein that provides adequate amounts of all nine essential amino acids.

Complex carbohydrate | 3 or more sugars bonded together. Oligosaccharides and polysaccharides.

Concentration | Quantitative measure of the relative amounts of solute and solvent in a solution.

Concentration gradient | Relative difference in the concentrations of solute across a membrane. Overall movement is to equalize concentration on both sides with the concentration gradient.

Conception | The beginning of pregnancy, marked by fertilization of an egg by a sperm.

Conditionally essential amino acid | An amino acid that under certain conditions becomes essential and needs to be consumed.

Cone | Photoreceptor cells that can function better in bright light, primarily for seeing color.

Confidence interval | A confidence interval is a range of scores likely to contain the parameter being estimated. Intervals can be constructed to be more or less likely to contain the parameter: 95% of 95% confidence intervals contain the estimated parameter whereas 99% of 99% confidence intervals contain the estimated parameter. The wider the confidence interval, the more uncertainty there is about the value of the parameter.

Constipation | A condition in which stool becomes hard, dry, and difficult to pass, and bowel movements don't happen very often. Other symptoms may include painful bowel movements, and feeling bloated, uncomfortable, and sluggish.

Control | A comparator in a study. Might receive a placebo or no intervention.

Convulsion | A condition in which muscles contract and relax quickly and cause uncontrolled shaking of the body.

Cori cycle | A metabolic cycle that operates under anaerobic and/or glucose sparing situations. In the muscle, glucose is metabolized to pyruvate in glycolysis, than is then converted to lactate which is secreted. The lactate is taken up by the liver and used to synthesize glucose through gluconeogenesis where it is secreted so it can be taken up for use by the muscle again.

Cornea | The transparent front part of the eye that covers the iris, pupil, and anterior chamber.

Cramp | A sharp pain that occurs when a muscle suddenly contracts (tightens up). Cramps commonly occur in the abdomen and legs.

Cretinism | A condition marked by impaired physical and mental development, due to insufficient thyroid hormone (hypothyroidism) often caused by insufficient dietary iodine during pregnancy.

Crohn's disease | A condition in which the gastrointestinal tract is inflamed over a long period of time. Crohn disease usually affects the small intestine and colon. Symptoms include fever, diarrhea, stomach cramps, vomiting, and weight loss. Crohn disease increases the risk of colorectal cancer and small intestine cancer. It is a type of inflammatory bowel disease (IBD). Also called regional enteritis.

Cross-linking | A bond that links one molecule to another.

Cross-sectional study | An observational study design in which one takes sample from a target population and assess their exposure and disease risk at the same time.

Crypts of Liberkuhn | An intestinal gland found between the pits between villi.

Cytochrome | Proteins that are involved in the electron transport chain and reduction-oxidation reactions.

Cytoplasm | The fluid inside a cell but outside the cell's nucleus. Most chemical reactions in a cell take place in the cytoplasm.

D

De novo lipogenesis | Synthesis of fatty acids from acetyl-CoA, by adding 2 carbons to elongate the fatty acid.

Deacetylation | Removal of an acetyl group.

Deamination | Removal of an amine group as ammonia, for instance from an amino acid.

Decarboxylation | Removal of a carboxyl group to release as carbon dioxide.

Deficiency | Shortage of a required substance (usually a nutrient in nutrition) needed by the body.

Degradation | To degrade or breakdown.

Deiodinase | Selenoenzymes that metabolize thyroid hormones.

Delta nomenclature | Used to name fatty acids, counts carbons starting at the acid (alpha) end.

Denature | A structural change in biomolecules such as proteins or deoxyribonucleic acid (DNA), which in most cases is associated with a loss of the biological function of these molecules, although their primary structure remains unchanged. Denaturation can be due to physical or chemical influences.

Density | Ratio of mass to volume for a substance or object.

Dephosphorylation | Removal of a phosphate group, net effect is the release of energy.

Deplete | The use of a resource faster than it can be replenished.

Deposited | To add to.

Depot | A place for storage.

Dermatitis | Inflammation of the skin.

Dermatologist | A doctor who has special training to diagnose and treat skin problems.

Desaturate | To add a double bond.

Descending colon | After the transverse colon and before the sigmoid colon. As name indicates it is portion that is descending in the body.

Dextrins | Oligosaccharide product of digestion containing one or more alpha 1-6 glycosidic bonds.

Diabetes mellitus | Disease caused by problems with the pancreatic hormone insulin, which lead to high blood glucose levels and symptoms such as excessive thirst and urination; includes type 1 and type 2 diabetes.

Diameter | The length of a straight line that extends around a round or spherical shape used to measure the size.

Diarrhea | Frequent and watery bowel movements.

Dietary Fiber | Nondigestible carbohydrates and lignin that are intrinsic and intact in plants.

Dietary Guidelines | Provide qualitative advice on what to eat and drink to meet nutrient needs, promote health, and prevent disease.

Dietary reference intake | A set of reference values used to plan and assess nutrient intakes of healthy people.

Differentiate | Process by which unspecialized cells become specialized into one of many different types of cells, such as neurons or epithelial cells.

Digestible Indispensable Amino Acid Score | 100 x (mg of digestible dietary indispensable amino acid in 1g of dietary protein / mg of the same dietary indispensable amino acid in 1g of the reference protein).

Digestion | The process of breaking down food into substances the body can use for energy, tissue growth, and repair.

Digestion accessory organs | Assist in digestion, but do not come into contact with digestive processes like organs in the gastrointestinal tract. Salivary glands, pancreas, gallbladder, and liver.

Digestive system | Gastrointestinal tract plus the digestion accessory organs.

Dimer | Paired proteins.

Dimerized | The process of forming a dimer or pair.

Dipeptide | 2 amino acids bonded together.

Disaccharide | Two monosaccharides bonded together. Sucrose, lactose and maltose.

Disorientation | A mental state marked by confusion about time, place, or who one is.

Disparity | A notable difference.

Displace | When something take the place of something else.

Disseminate | To communicate, to make widely known.

Diverticula | A small pouch or sac that bulges out from the wall of a hollow organ, such as the colon.

Diverticulitis | Inflammation of one or more pouches or sacs that bulge out from the wall of a hollow organ, such as the colon. Symptoms include muscle spasms and cramps in the abdomen.

Diverticulosis | A condition marked by small sacs or pouches in the walls of a hollow organ, such as the colon. These sacs can become inflamed and cause a condition called diverticulitis.

Dizziness | Having a sensation of whirling, with a tendency to fall; giddy; feeling unbalanced or lightheaded.

Docosahexaenoic acid | 22 carbon omega-3 fatty acid with 6 double bonds (22:6 n-3) commonly found in fatty fish or fish oil.

Double-blind | A study design where neither the researcher nor the subject know what intervention the subject is receiving.

Dry beriberi | Type of thiamin deficiency that affects the nervous system, result in loss of muscle function, numbness, and/or tingling.

Dual energy X-ray absorptiometry | An imaging test that measures bone mineral density (the amount of bone mineral contained in a certain volume of bone) by passing x-rays with two different energy levels through the bone.

Duodenal cytochrome b | A reductase enzyme on the brush boarder, that catalyzes the reduction of Fe3+ to Fe2 using vitamin C.

Duodenum | The first and shortest of three parts of the small intestine where most chemical digestion occurs.

E

Ecologic fallacy | A logical error that stems from applying group-level characteristics to individuals.

Ectoenzymes | Enzymes on the outside of cell walls.

Eicosanoid | 20 carbon fatty acids derivatives that are biologically active locally.

Eicosapentanoic acid | 20 carbon omega-3 fatty acid with 5 double bonds (22:6 n-3) commonly found in fatty fish or fish oil.

Electrolyte | Compounds that separate into ions in water.

Electron | A small particle with a negative charge that is found in all atoms.

Electron carrier | Molecules that accept electrons and donate them in the electron transport chain.

Electron transport Chain | A series of protein complexes that transfer electrons from electron donors to electron acceptors and couples this electron transfer with the transfer of protons (H+ ions) across a membrane as part of oxidative phosphorylation.

Element | a simple substance that cannot be broken down into smaller parts or changed into another substance. Examples of elements are hydrogen, carbon, oxygen, nitrogen, and calcium.

Emulsifier | Amphipathic structure allows it interact with both hydrophilic and hydrophobic substances.

Endocrine | A system of glands that release their hormones into the blood.

Endocytosis | Engulfing of particles, or fluids, to be taken up into the cell in vesicles formed from the cell membrane. Active.

Endogenous | Produced inside an organism or cell. The opposite is external (exogenous) production.

Endoscopy | A procedure that uses an endoscope to examine the inside of the body. An endoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease.

Endosome | A vesicle internalized during endocytosis.

Endothelial | The inside lining of blood vessels, lymph vessels, and the heart.

Enterocyte | Small intestine absorptive cell.

Enteropeptidase | A digestive protease active in the small intestine.

Enzyme | Protein that speeds up biochemical reactions; biological catalyst. Often end in –ase.

Epidemiology | The study of the distribution and determinants of disease or other health-related events in human populations, and the application of that study to prevent and control health problems.

Epigenetic | Epigenetics is an emerging field of science that studies heritable changes caused by the activation and deactivation of genes without any change in the underlying DNA sequence of the organism. The word epigenetics is of Greek origin and literally means over and above (epi) the genome.

Epigenetic code | Chemical compounds that modify, or mark, the genome in a way that tells it what to do, where to do it, and when to do it. Different cells have different epigenetic marks. These epigenetic marks, which are not part of the DNA itself, can be passed on from cell to cell as cells divide, and from one generation to the next.

Epigenetic modification | Changes made to whether genes are expressed without changing the DNA sequence. 2 major types are DNA methylation and histone modifications.

Epiglottis | The cartilage on the top of the larynx that closes the windpipe during swallowing.

Epinephrine | A "fight or flight" hormone and neurotransmitter. Also called adrenaline.

Epithelial | Tissue made up of cells that line inner and outer body surfaces, such as skin and mucous membranes.

Epithelium | Tissue made up of cells that line inner and outer body surfaces, such as skin and mucous membranes.

Esophagus | Long, narrow, tube-like digestive organ through which food passes from the pharynx to the stomach

Essential amino acid | An amino acid that cannot be synthesized by the body and thus needs to be consumed. Also known as indispensable amino acids.

Ester bond | A bond where least one -OH (hydroxyl) group is replaced by an -O-carbon group.

Esterification | Creating ester bonds.

Estimate Average Requirement | Average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular age, sex, and life-stage group.

Estrogen | A type of hormone made by the body that helps develop and maintain female sex characteristics and the growth of long bones.

Ethanol | 2-carbon alcohol, which humans consume and refer to as alcohol.

Exchangeable | Capable of being exchanged.

Excrete | To get rid of waste material from the blood, tissues, or organs by a normal discharge (such as sweat, urine, or stool).

Exogenous | Produced outside an organism or cell. The opposite is internal (endogenous) production.

External hemorrhoid | A hemorrhoid in the skin surrounding the anus.

Extracellular | Outside a cell.

Extracellular fluid | Fluid outside body cells.

Extrahepatic | Located or occurring outside the liver.

F

Facilitated diffusion | Movement of solutes from an area of higher concentration (with the concentration gradient) across a membrane to an area of lower concentration with the help of a protein. Passive.

Fast | To abstain from. Most often used in nutrition to refer to abstain from eating.

Fat | Chemist perspective are solid at room temperature. From a caloric perspective triglycerides, fatty acids and phospholipids that provide 9 kcal/g.

Fatty acid | Made up of carbon, hydrogen and oxygen, with methyl (omega) end and an acid (alpha) end.

Fatty streak | A streak of lipid deposited in a blood vessel. Foam cells contribute to the development. Start of atherosclerosis.

Feces | The material in a bowel movement. Stool is made up of undigested food, bacteria, mucus, and cells from the lining of the intestines.

Fed state | Anabolic state following feeding that is in positive energy balance.

Fenestration | Opening leading into a lacteal through which absorption occurs.

Ferment | In microorganisms, anaerobic breakdown of organic nutrients.

Fermentable | Fiber characterized by being fermented in the colon and for becoming gelatinous in nature in water.

Fermentation | Biochemically used to describe the anaerobic production of ATP from carbohydrates.

Ferritin | Primary iron storage protein.

Ferroportin | Iron transporter in the enterocyte that allows iron to be absorbed into circulation.

Fiber | Branched polysaccharide of glucose bonded by beta bonds.

Final electron acceptor | A substance that accepts the final electron. In the electron transport chain this is oxygen forming water.

Flatulence | The state of having gas, often smelly, trapped (and when released, frequently with noise) in the digestive system of a human and some other animals. Also known as breaking wind; and when released, a flatus, a fart.

Flavin adenine dinucleotide | Riboflavin-containing cofactor that is commonly reduced or oxidized.

Flora | Pertaining to all plant life.

Fluorohydroxyapatite | A molecule where fluoride replaces the hydroxyl molecules in hydroxyapatite. More resistant to acid degradation that hydroxyapatite.

Fluorosis | Toxicity of fluoride that can result in pitting and mottling of teeth.

flush | To become markedly red in the face and often other areas of the skin, from various physiological conditions.

Foam cell | Macrophages that have scavenged and become loaded with LDL, oxidized LDL and other lipids.

FODMAPs | Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols that survive digestion and are prone to being fermented in the colon.

Food frequency questionnaire | An instrument that contains a number of questions designed to determine how frequently foods are consumed.

Fortification | The addition of nutrients to foods.

Fracture | A partial or complete break in bone.

Free radical | A molecule with an unpaired electron in its outer orbital.

Fructose | 5-member ring, sweetest of the monosaccharides.

Functional Fiber | Isolated, nondigestible carbohydrates that have beneficial physiological effects in humans.

Functional food | A food, or a food ingredient, which may provide a health benefit beyond the traditional nutrients (macronutrients and micronutrients) it contains.

G

G cells | Cells at the bottom of the gastric pit that produce gastrin.

Galactose | Monosaccharide similar in structure in glucose, but not normally found alone in nature.

Gallbladder | Sac-like organ that stores bile from the liver and secretes it into the duodenum of the small intestine as needed for digestion.

Gallstone | Solid material that forms in the gallbladder or common bile duct. Gallstones are made of cholesterol or other substances found in the gallbladder. They may occur as one large stone or as many small ones, and vary from the size of a golf ball to a grain of sand.

Gamma-carboxyglutamic acid | Modified version of the amino acid glutamic acid (glutamate) found in Gla proteins that can bind to calcium cause them to activated.

Gamma-glutamyl carboxylase | Enzyme that uses vitamin K as a cofactor, converting it to vitamin K epoxide, while adding a carboxyl group to the amino acid glutamic acid (glutamate) forming gamma-carboxyglutamic acid (Gla).

Gastric | Of or relating to the stomach.

Gastric juice | Fluid in the stomach that includes water, acid and digestive enzymes.

Gastric lipase | Triglyceride digesting enzyme in the stomach that preferentially cleaves fatty acids in the sn-3 position.

Gastric pit | Indentations in the stomach's surface that are lined by four different types of cells.

Gastrin | A hormone, produced by G cells. Stimulates parietal and chief cells to secrete pepsinogen and gastric lipase. Stimulates chief cells to produce hydrochloric acid.

Gastroesophageal reflux disease | A condition where a person experiences heartburn or acid reflux more than twice per week and it is severe.

Gastrointestinal tract | Organs of the digestive system through which food passes during digestion, including the mouth, pharynx, esophagus, stomach, small intestine, large intestines, rectum and anus.

Gene | The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

Genetically modified | Any organism whose genetic material has been altered using genetic engineering techniques.

Genome | The complete set of DNA (genetic material) in an organism. In people, almost every cell in the body contains a complete copy of the

genome. The genome contains all of the information needed for a person to develop and grow. S

Gla protein | Protein containing gamma-carboxyglutamic acid. These activated proteins are needed in the blood clotting cascade for it to function normally.

Gla proteins | Protein that contains gamma-carboxyglutamic acid.

Glossitis | Inflammation of the tongue.

Glucagon | A hormone produced by alpha-cells in the pancreas that increases the level of glucose (sugar) in the blood.

Glucagon receptor | Receptor on the surface of cells that glucagon binds to and ultimately results in the breakdown of glycogen in the liver.

Glucogenic | Amino acids that can be used for gluconeogenesis. Can be converted to pyruvate or citric acid cycle intermediates.

Glucokinase | Enzyme in the liver that phosphorylates glucose to glucose-6-phosphate.

Gluconeogenesis | Synthesis of glucose form a non-carbohydrate source

Glucose | Monosaccharide produced by photosynthesis, major source of energy in body.

Glucose transporter | Facilitated diffusion transporters involved in the monosaccharide uptake and transport into cells.

Glucose-6-phosphatase | Enzyme that cleaves the phosphate from glucose-6-phosphate to glucose. Found in the liver and kidney.

Glucoside | A molecule in which a glucose is bound by a glycosidic bond.

Glutathione peroxidase | An antioxidant selenoenzyme that converts hydrogen peroxide to water.

Gluten | Protein found in wheat, rye, and barley that causes an immune response in those with Celiac disease.

Glycemic index | A measure of the change in blood glucose concentrations caused by eating a 50 grams of a specific tested carbohydrate compared with eating a standard amount of glucose or white bread. A higher glycemic index reflects a higher rise in blood glucose concentrations.

Glycemic load | A measure of the change in blood glucose concentrations that uses the glycemic load multiplies by the number of carbohydrates are in a 100 gram serving. As a result, it better reflects the glycemic response to a serving of food.

Glycemic response | Physiological response to the rise in blood glucose after dietary intake.

Glycerol | 3-carbon molecule that serves as the backbone for triglycerides and phospholipids.

Glycocalyx | Glycoproteins and proteins on the outside of microvilli.

Glycogen | Branched polysaccharide of glucose bonded by alpha bonds. Animal storage of glucose. More branched than amylopectin.

Glycogenesis | Glycogen synthesis.

Glycogenolysis | Glycogen breakdown.

Glycolysis | Metabolic breakdown of glucose to pyruvate.

Glycoprotein | Proteins with carbohydrates attached to them.

Glycosidic bond | A bond between glycosides (aka monosaccharides, sugars).

Goblet cells | Mucus producing cells of primary importance in the GI tract in the small intestine.

Goiter | An enlarged thyroid. It may be caused by too little iodine in the diet or by other conditions.

Goitrogen | Substances that disrupt the production of thyroid hormones by interfering with iodine uptake in the thyroid gland.

Gold standard | The best that is currently available. Not necessarily the most feasible.

Guanosine triphosphate | Similar to ATP, but instead of adenosine contains guanosine. Like ATP is an energy currency.

H

Haptocorrin | Protein released by salivary gland that binds strongly to vitamin B12.

Hazard ratio | A measure of association, similar to odds ratio and relative risk.

Headache | The symptom of pain in the face, head, or neck.

Helicobacter pylori | A type of bacterium that causes inflammation and ulcers in the stomach or small intestine. People with Helicobacter pylori infections may be more likely to develop cancer in the stomach. Also called H. pylori.

Hematocrit | Method of iron status that centrifuges blood and the packed cell volume or the amount of red blood cells that are at the bottom of the tube. Higher packed cell volume means higher iron status.

Heme | A type of iron found primarily in foods of animal origin. Found in hemoglobin, binds to oxygen.

Hemochromatosis | Genetic condition where there is a mutation in a protein in the enterocyte that prevents the normal decrease in iron absorption.

Hemoglobin | Contains heme iron, binds oxygen and carries it through circulation. Is an example of quaternary structure, because it contains multiple polypeptide chains in its structure.

Hemolysis | Rupturing of red blood cells.

Hemorrhage | Loss of blood from damaged blood vessels. A hemorrhage may be internal or external, and usually involves a lot of bleeding in a short time.

Hemorrhagic stroke | A type of stroke that occurs when a blood vessel in the brain or on the surface of the brain leaks or breaks open, causing bleeding in or around the brain. This leads to swelling and pressure, which can damage cells and tissue in the brain.

Hemorrhoids | An enlarged or swollen blood vessel, usually located near the anus or the rectum.

Hemosiderin | Overflow iron storage protein.

Hepatic | Of or relating to the liver.

Hepatocyte | Predominant and major functional cell of the liver.

Hepcidin | Hormone produced in liver response to high iron status that causes degradation of ferroportin, thus preventing iron absorption.

Hephaestin | Copper containing protein found on the membrane of enterocytes that has the primary protein that oxidizes Fe2+ to Fe3+ as it is transported through ferroportin so Fe3+ can bind to transferrin.

Hexokinase | Enzyme in muscle and adipose cells that phosphorylates glucose to glucose-6-phosphate.

High-density lipoprotein | Lipoprotein primarily derived from the liver and intestine that is primarily protein and participates in reverse cholesterol transport.

High-fructose corn syrup | Refined sweetener product that provides either 42% or 55% free fructose with the rest being free glucose.

Histone | A type of protein found in chromosomes that allows DNA to wrap around it.

Homeostatically-controlled | The state of steady internal, physical, and chemical conditions maintained by living systems and resistance to changes to this stable internal environment.

Homocysteine | A sulfur-containing non-proteinogenic amino acid whose concentrations are increased in circulation in cardiovascular disease.

Hormone | A chemical messenger molecule secreted by a gland of the endocrine system into the blood.

Hormone response element | Specific area in the promoter where the nuclear receptor dimers bind.

Hormone-sensitive lipase | Adipose lipolysis enzyme, that cleaves fatty acids from triglycerides so they can be mobilized. Activity increased by glucagon and epinephrine.

Host | An organism harboring another organism or organisms on or in itself.

Hydrogenation | Addition of hydrogen (H2) to reduce a compound.

Hydrophilic | Water loving nature.

Hydrophobic | Water fearing nature.

Hydroxyapatite | How calcium and phosphate are mineralized in bones and teeth. $Ca10(PO4)6(OH)2$.

Hydroxyl | –OH. Composed of oxygen and hydrogen.

Hydroxylate | The process of adding a hydroxyl (-OH) group.

Hyperammonemia | Too high concentrations of ammonia.

Hyperglycemia | Higher than normal amount of glucose in blood. Hyperglycemia can be a sign of diabetes or other conditions. Also called high blood sugar.

Hyperkeratosis | A condition marked by thickening of the outer layer of the skin, which is made of keratin (a tough, protective protein).

Hyperparathyroidism | A condition in which the parathyroid gland (one of four pea-sized organs found on the thyroid) makes too much parathyroid hormone. This causes a loss of calcium from the bones and an increased level of calcium in the blood. Symptoms include bone pain and kidney problems.

Hypertension | A blood pressure of 140/90 or higher. Hypertension usually has no symptoms. It can harm the arteries and cause an increase in the risk of stroke, heart attack, kidney failure, and blindness. Also called high blood pressure.

Hypertensive | Individuals who have hypertension.

Hyperthyroidism | A condition that occurs when the thyroid gland makes more thyroid hormones than the body needs. Signs and symptoms include weight loss, fatigue, rapid or irregular heartbeat, sweating, diarrhea, nervousness, mood swings, shaky hands, trouble sleeping, trouble tolerating heat, muscle weakness, and a goiter (an enlarged thyroid gland that may cause the bottom of the neck to look swollen). Also called overactive thyroid.

Hypertonic | Of higher concentration of solute.

Hypocalcemia | Low blood calcium concentration.

Hypoglycemia | Lower than normal amount of glucose in blood.

Hyponatremia | Lower-than-normal amount of sodium in the blood.

Hypothalamus | The area of the brain that controls body temperature, hunger, and thirst.

Hypothesis | An educated guess about what is expected.

Hypothyroidism | Too little thyroid hormone. Symptoms include weight gain, constipation, dry skin, and sensitivity to the cold. Also called underactive thyroid.

Hypotonic | Of lower concentration of solute.

I

Ileal digestibility | Digestion that occurs by the end of the ileum.

Ileocecal valve | A sphincter between the ileum and the cecum.

Ileum | Final of three parts of the small intestine where vitamin B12 and bile salts are absorbed.

In vitro | Typically refers to research done in cells.

In vivo | In the living. Both humans and animals.

Incomplete protein | A protein that provides inadequate amounts of one or more of the essential amino acids.

Incubator | A chamber that mimics the bodies conditions where cells can be maintained.

Inflammation | Immune response that establishes a physical barrier against the spread of infection and repairs tissue damage while causing redness, swelling, and warmth.

Inflammatory | Causing inflammation.

Inflammatory bowel disease | A general term that refers to the inflammation of the colon and rectum. Inflammatory bowel disease includes ulcerative colitis and Crohn disease.

Inhibition | To prevent or impede.

Inorganic | Not organic or containing carbon.

Insufficiency | Less than a sufficient amount. Inadequate.

Insulin | Endocrine hormone secreted by beta cells of the pancreas that normally helps cells take up glucose from the blood, thereby decreasing the blood glucose concentrations.

Insulin receptor | Receptor on the surface of cells that insulin binds to and ultimately results in GLUT4 moving to the cell surface.

Integrated | Bringing together and uniting of things.

Intermediate | A product that is an intermediate of a metabolic process or pathway.

Intermediate-density lipoprotein | Lipoprotein formed after the action of lipoprotein lipase on very low-density lipoprotein, that is smaller, less triglyceride-rich, but more cholesterol-rich.

Intermembrane space | In the mitochondria, space between the inner membrane and outer membrane.

Internal hemorrhoid | A hemorrhoid within the anus.

International units | Unit of measurement for the amount of some vitamins.

Interstitial fluid | Extracellular fluid surrounding the cells.

Intracellular | Inside a cell.

Intrinsic factor | Protein released in the stomach that binds to vitamin B12 and later is involved in its absorption by binding to its receptor.

Inulin | Fructose-containing oligosaccharide joined by beta bonds. Since it survives digestion it an a commonly used prebiotic.

Invasive | When there is contact with the mucosa, or skin break, or internal body cavity beyond a natural or artificial body orifice.

Inverse | A relationship where if one element increases the other decreases and vice versa.

Ion | A molecule that has gained or lost one or more electrons from its neutral state and therefore possesses a negative or positive electric charge.

Irritable bowel syndrome | A disorder of the intestines commonly marked by abdominal pain, bloating, and changes in a person's bowel habits. This may include diarrhea or constipation, or both, with one occurring after the other. Also called IBS, irritable colon, mucus colitis, and spastic colon.

Isotonic | Of equal concentration of solute.

J

Jejunum | Middle of three parts of the large intestine where most absorption of nutrients occurs.

Journal article | See peer-reviewed journal article.

K

Kashin-Beck disease | Condition associated with selenium deficiency, along with other factors, that affects cartilage, bone, and joints that results in deformity and stunted growth.

Kayser-Fleischer rings | Golden to greenish-brown rings fond on the edges of the cornea that some times are seen in individuals with Wilson's disease.

Keratin | A type of protein found on epithelial cells, which line the inside and outside surfaces of the body. Keratins help form the tissues of the hair, nails, and the outer layer of the skin. They are also found on cells in the lining of organs, glands, and other parts of the body

Keshan disease | Condition associated with selenium deficiency, along with coxsackievirus, which affects the heart.

Keto acid | What is left after an amine group is removed from an amino acid.

Ketoacidosis | Condition of elevated ketone bodies that leads to acidosis or changes in blood pH. More severe than ketosis.

Ketogenic | Amino acids that can be used for ketone body synthesis. Can be converted to acetyl-CoA or acetylacetyl-CoA.

Ketone | The functional group characterized by a carbonyl group (O=C) linked to two other carbon atoms, or a chemical compound that contains a carbonyl group.

Ketone body | Small molecules that are produced from amino acids or fatty acids, that can be used by the brain as an energy source when glucose is limited or not available.

Ketosis | Condition of elevated ketone bodies in blood or urine.

Kidney | One of a pair of organs in the abdomen. The kidneys remove waste and extra water from the blood (as urine) and help keep chemicals (such as sodium, potassium, and calcium) balanced in the body. The kidneys also make hormones that help control blood pressure and stimulate bone marrow to make red blood cells.

Kidney stone | A solid deposit forms in the urinary tract.

Kilocalorie | Amount of energy needed to raise 1 kilogram of water 1 degree Celsius.

Kinase | Enzyme that normally phosphorylate.

Kwashiorkor | Condition that results from inadequate protein intake, but adequate energy intake. Characteristic symptom is a swollen abdomen.

L

Lactase | Disaccharidase that cleaves sucrose to glucose and galactose.

Lactate | 3-carbon metabolic intermediate, can be synthesized from pyruvate.

Lacteal | A lymphatic vessel within the villi of the small intestine.

Lactose | Disaccharide of galactose + glucose by beta bond, primary milk sugar.

Lactose intolerance | An inability to properly digest, and thus absorb, lactose.

Large Intestine | Organ of the digestive system that removes water and salts from food waste and forms solid feces for elimination.

Larynx | Organ of the respiratory system between the pharynx and trachea that is also called the voice box because it contains the vocal cords that allow the production of vocal sounds

Latitude | A geographical term denoting the north–south angular location of a place on the Earth.

Laxative | A substance that promotes bowel movements.

Lesion | An area of abnormal tissue that may be caused by disease or trauma.

Liberated | To remove from.

Lichen | A symbiotic relationship between 2 bacteria and a fungus.

Ligand | A compound that binds to a nuclear receptor.

Lignin | A nondigestible polymer.

Limiting amino acid | An essential amino acid that is found in inadequate amounts in an incomplete protein. The amino acid limits it from being complete.

Lingual lipase | Digestive enzyme released from the salivary glands the preferentially cleaves short-chain fatty acids in the sn-3 position of triglycerides. Believe to be more important in infants.

Linoleic acid | An essential 18-carbon omega-6 fatty acid with 2 double bonds (18:2 n-6).

Lipid | Fatty acids, triglycerides, phospholipids and sterols composed of carbon, hydrogen and oxygen.

Lipid bilayer | Double layer of phospholipid molecules that makes up a plasma membrane of cells.

Lipolysis | Cleave of fatty acids from triglycerides. Triglyceride breakdown.

Lipoprotein | Complexes of lipids and proteins that carry lipids through circulation.

Lipoprotein lipase | Enzyme in endothelial cells of blood vessels, that cleaves off fatty acids from triglycerides in lipoproteins. Typically active in a fed or anabolic state.

Liver | Organ of digestion and excretion that secretes bile for lipid digestion and breaks down excess amino acids and toxins in the blood.

Liver | Digestion accessory organ through producing bile. Central organ in nutrient metabolism.

Local | Act where, or close, to where they are produced.

Long-chain fatty acid | A fatty acid with greater than 12 carbons.

Low-density lipoprotein | Lipoprotein formed after the action of lipoprotein lipase on intermediate-density lipoprotein, that is smaller, contains a minor amount of triglyceride and most is the most cholesterol-rich of the lipoproteins.

Lower esophageal sphincter | Sphincter separating the stomach from the esophagus.

Lumen | A space within an artery, vein, intestine or tube.

Lungs | One of two paired organs of the respiratory system in which gas exchange takes place between the blood and the atmosphere.

Luo Han Guo | Fruit Extracts Sweetener derived from Chinese fruit. Sweetness provide by mogrosides. Heat-stable. Also known as monk fruit extract.

Lutein | Yellow nonprovitamin A carotenoid.

Lycopene | A red, nonprovitamin A carotenoid.

Lycopenodermia | Overaccumulation of lycopene below the skin leading it to have a pink color.

Lymph | Fluid that leaks out of capillaries into spaces between cells and circulates in the vessels of the lymphatic system.

Lymph node | One of many small structures located along lymphatic vessels where pathogens are filtered from lymph and destroyed by lymphocytes (white blood cells).

Lymphatic system | System of the body that produces lymphocytes (a type of white blood cell) and filters pathogens from lymph and blood.

Lysolecithin | Lecithin product after the C-2 fatty acid is cleaved. Only contains 1 ester bonded fatty acid.

Lysosome | A sac-like compartment inside a cell that has enzymes that can break down cellular components that need to be destroyed.

Lysozyme | A non-digestive enzyme that breaks down bacteria cell walls to prevent a possible infection.

M

Macromineral | Minerals that need to be consumed in the greatest quantities.

Macronutrient | A nutrient needed in larger amounts.

Maltase | Disaccharidase that cleaves sucrose to glucoses

Maltose | Disaccharide of glucose + glucose by alpha bond, most commonly found in alcoholic beverage and barley.

Maltotriose | 3 glucoses bonded together.

Marasmus | Condition that results from inadequate protein and energy intake. Results in a skin and bones appearance.

Mastication | Chewing and grinding of food into smaller pieces.

Matrix | Proteins in bones that mineral is deposited on.

Meaningful antioxidant | An antioxidant found in appreciable amounts in the location of need and is not redundant with another antioxidant.

Meat protein factor | The unidentified factor found in meat that enhances non-heme iron absorption.

Media | Solution that provides nutrients to cells that they would normally receive through blood.

Medium-chain fatty acid | A fatty acid containing 6 to 12 carbons.

Megaloblastic anemia | Anemia characterized by large, nucleated, immature red blood cells that do not efficiently carry oxygen.

Melanin | A pigment that gives color to skin and eyes and helps protect it from damage by ultraviolet light.

Melting point | The temperature at which a substance changes state from a solid to a liquid.

Menke's disease | A genetic disorder that may result in copper deficiency believed to be due to ATP7A mutation that prevents copper for leaving the enterocyte, and thus is not absorbed.

Menopause | The time of life when a woman's ovaries stop producing hormones and menstrual periods stop. Natural menopause usually occurs around age 50.

Meta-analysis | A statistical technique that analyzes results from previous studies collectively.

Metabolism | The chemical changes that take place in a cell or an organism. These changes make energy and the materials cells and organisms need to grow, reproduce, and stay healthy. Metabolism also helps get rid of toxic substances.

Metallothionein | Thionein that has bound a mineral or metal.

Methyl | One carbon molecule with only hydrogens bonded to it beyond any carbon-carbon bonds. If only 1 bond -CH3.

Methylate | Adding a methyl group to other molecules. Methylation of proteins or nucleic acids may affect how they act in the body.

Micelle | Tiny spheres that contain amphipathic molecules where the hydrophilic heads are on the exterior near the water environment and hydrophobic tails are on the interior. Other hydrophobic compounds can also be in the interior.

Microbiota | Microorganisms that are found in the gastrointestinal tract.

Microcytic hypochromic anemia | Anemia characterized by small red blood cells, with low color because of decreased hemoglobin. Iron and vitamin B6 deficiency can cause.

Microflora | Incorrectly used term to describe the microbiota.

Micronutrient | A nutrient needed in smaller amounts.

Microorganism | An organism that can be seen only through a microscope. Microorganisms include bacteria, protozoa, algae, and fungi. Although viruses are not considered living organisms, they are sometimes classified as microorganisms.

Microsomal ethanol oxidizing system | Overflow alternative pathway to alcohol dehydrogenase for metabolizing ethanol once its capacity is exceeded. Metabolizes ethanol to acetaldehyde while in the process oxidizing its cofactor NADPH + H+ to NADP+. High intakes or repeated exposures increase the amount of MEOS enzymes available, which increases tolerance. These enzymes also metabolizes drugs, fatty acids and steroids so ethanol competes for their enzymes.

Microvilli | Tiny projections on enterocytes that increases its absorptive surface. Also knowns as the brush border membrane.

Mineral | Elements that are essential for normal physiological processes in the body.

Mitochondria | Small structures in a cell that are found in the cytoplasm (fluid that surrounds the cell nucleus). Mitochondria make most of the energy for the cell and have their own genetic material that is different from the genetic material found in the nucleus. Many diseases are caused by mutations (changes) in the DNA of mitochondria.

Mitochondrial Matrix | Area inside the mitochondrial inner membrane.

Mixed micelle | Micelles that include a mixture of cholesterol, bile acids, lysolecithin, 2-monoglycerides and fatty acids.

Mixed triglyceride | Triglyceride containing at least 2 different fatty acids.

Mobilize | To bring forth, potentially from storage.

Monoglutamate | Containing one glutamate.

Monosaccharide | A single sugar unit carbohydrate. Glucose, fructose or maltose.

Monounsaturated fatty acid | A fatty acid containing one double bond.

Morning sickness | Nausea and vomiting that typically occurs early after pregnancy.

Mottling | A pattern of irregular marks, spots, streaks, blotches or patches of different shades or colors.

Mouth | An opening in the face and is the first part of the gastrointestinal tract. It is the place where food is chewed. Has teeth to help chew/masticate food.

Mucosa | The moist, inner lining of some organs and body cavities (such as the nose, mouth, lungs, and stomach). Glands in the mucosa make mucus (a thick, slippery fluid). Also called mucous membrane.

Mucus | Slimy substance produced by mucous membranes that traps pathogens, particles, and debris.

Muscle | Tissue that is responsible for force and motion.

Muscle contraction | The activation of tension-generating sites within muscle cells. It does not necessarily mean muscle shortening because muscle tension can be produced without changes in muscle length, such as when holding a heavy book or a dumbbell at the same position.

Mutation | Any change in the DNA sequence of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment.

Myocardial infarction | Damage to heart muscle from death of myocardial cells that occurs when blood flow is blocked to part of the heart.

Myocytes | Muscle cell(s).

Myoglobin | An iron- and oxygen-binding protein found in the skeletal muscle tissue.

N

Natural | From nature of made of natural material.

Nausea | A feeling of sickness or discomfort in the stomach that may come with an urge to vomit.

Neck cells | Cells at the top of the gastric pit that produce mucus.

Negative energy balance | The state in which the number of calories consumed is less than the number used. Energy balance is affected by physical activity, body size, amount of body fat and muscle, and genetics.

Neotame | Similar in structure to aspartame and advantame. Sweeter than aspartame, heat-stable and is not a concern for Phenylketonuria. But lower acceptable daily intake than advantame.

Nerve transmission | Neurotransmitters are released by the axon terminal of a neuron (the presynaptic neuron), and bind to and react with the receptors on the dendrites of another neuron (the postsynaptic neuron) a short distance away.

Neural tube | The embryonic precursor to the central nervous system, which is made up of the brain and spinal cord.

Neural tube defect | A group of birth defects in which an opening in the spine or cranium remains from early in human development.

Neurological | Have to do with the nerves or nervous system.

Neurotransmitter | Type of chemical that carries nerve impulses from the axon of a neuron to another cell across the synapse.

Nicotinamide adenine dinucleotide | Niacin-containing cofactor that is commonly reduced or oxidized.

Night blind | A condition making it difficult or impossible to see in relatively low light. Also known as nyctalopia.

Non-heme iron | Forms of iron that are not found in heme.

Nonessential amino acid | An amino acid that can be synthesized by the body in adequate amounts so that it does not need to be consumed. Also known as dispensable amino acids.

Nonfermentable | Fiber characterized by not being fermented in the colon and not becoming gelatinous in nature in water.

Nonsteroidal anti-inflammatory drugs | A drug that decreases fever, swelling, pain, and redness. Also called nonsteroidal anti-inflammatory drug.

Normal distribution | One of the most common continuous distributions, a normal distribution is sometimes referred to as a "bell-shaped distribution."

Nuclear hormone receptor | Receptors found in the nucleus whose ligands are hormones, or hormone-like molecules such as retinoids.

Nucleotide | A molecule consisting of a nitrogen-containing base (adenine, guanine, thymine, or cytosine in DNA; adenine, guanine, uracil, or cytosine in RNA), a phosphate group, and a sugar (deoxyribose in DNA; ribose in RNA). DNA and RNA are polymers comprised of many nucleotides, strung together like beads in a necklace.

Nucleus | In biology, the structure in a cell that contains the chromosomes. The nucleus has a membrane around it, and is where RNA is made from the DNA in the chromosomes.

Nutrient | A compound that provides a needed function in the body

Nutrition | The science of the action of food, beverages, and their components in biological systems.

O

Occurrence | An actual instance when a situation occurs; an event or happening.

Odds ratio | A measure of association, used in study designed that deal with prevalent cases of disease (case-control, cross-sectional). Similar to relative risk and hazard ratio.

Oil | Chemist perspective liquid at room temperature. From a caloric perspective, oils are fats.

Oligopeptide | Medium size peptide, no formal definition unlike oligosaccharide.

Oligosaccharide | 3-10 monosaccharides bonded together. Have alpha 1-6 glycosidic bonds that are not digested.

Omega nomenclature | Used to name fatty acids, counts carbons starting at the methyl (omega) end.

One-carbon metabolism | Movement of 1-carbon units, generally methyl groups.

Open-Label | A study design without blinding, because both the subject and researcher know what intervention the subject is receiving.

Opsin | A light-sensitive protein that is used to form rhodopsin.

Opthalamia | Inflammation of the eye.

Optic | Related to the eye or vision.

Orbital | Places surrounding the nucleus of an atom where the electrons are most likely to be at any given time.

Organ | Structure composed of more than one type of tissue that performs a particular function, such as the brain, kidney, or heart

Organelle | A small structure in a cell that is surrounded by a membrane and has a specific function.

Organic | A natural or synthetic compounds that contains carbon.

Ornish/Pritikin diet | High-carbohydrate, low-fat dietary pattern.

Osmosis | Movement of solvent, water in this case, from a region of lower concentration to higher concentration to dilute it and create equal concentrations on both sides of the membrane. Passive.

Osteoblast | Bone cells that build bone by synthesizing hydroxyapatite.

Osteocalcin | Gla protein that is common in bones and teeth.

Osteoclast | Bone cells that breakdown bone by breaking down hydroxyapatite.

Osteomalacia | A condition in adults in which bones become soft and deformed because they don't have enough calcium and phosphorus.

Osteoporosis | A condition in which there is a decrease in the amount and thickness of bone tissue. This causes the bones to become weak and break more easily. Osteoporosis may be caused by older age, hormone changes, taking certain medicines, and not eating enough foods with calcium and vitamin D. It may also be caused by certain types of cancer and cancer treatment. It is most common in white and Asian women.

Overflow | Exceeding capacity, as if water would overflow a vessel. Can be used to refer to capacity in other ways, like enzyme catalytic capacity.

Oxalate | Compound that binds to and inhibits the absorption of some minerals.

Oxaloacetate | 4-carbon metabolic intermediate.

Oxidation | Loss of electrons. Also can be from gaining oxygen or losing hydrogen.

Oxidative phosphorylation | The metabolic pathway in which cells use the electron transport chain to oxidize nutrients, thereby releasing the chemical energy stored within in order to produce adenosine triphosphate (ATP)

Oxidative stress | imbalance where more ROS/free radicals are produced than the body is able quench.

Oxygen radical absorbance capacity | In vitro antioxidant assay.

P

p-value | A statistical value used to determine statistical significance, if the value is less than 0.05 ($p<0.05$). Lower the value the greater the significance, and less likely is not a true difference.

Packed cell volume | Amount of red blood cell found in the bottom of hematocrit after centrifugation.

Pancreas | Dual endocrine and exocrine gland near the stomach that secretes insulin and glucagon, which regulate blood glucose, as well as enzymes that aid in digestion.

Pancreatic alpha-amylase | Secreted by the pancreas into the duodenum, this is the major carbohydrate digestion enzyme. Cleaves alpha 1-4 glycosidic bonds.

Pancreatic juice | Bicarbonate and digestive enzymes secreted from the pancreas into the duodenum.

Pancreatic lipase | Secreted by the pancreas into the duodenum, this is the major triglyceride digestion enzyme. Cleaves sn-1 and sn-3 fatty acids in triglycerides.

Paradox | A seemingly contradictory relationship.

Paralysis | Loss of ability to move all or part of the body.

Parathyroid glands | One of four pea-sized glands found on the surface of the thyroid. Produces parathyroid hormone.

Parathyroid hormone | A hormone made by the parathyroid gland that helps the body store and use calcium.

Parietal cells | Cells at the middle of the gastric pit that produce hydrochloric acid. Stimulated by gastrin.

Parkinson disease | A progressive disorder of the nervous system marked by muscle tremors, muscle rigidity, decreased mobility, stooped posture, slow voluntary movements, and a mask-like facial expression.

Partially hydrogenated | Not completing hydrogenating, which would completely saturate all compounds. In the case of unsaturated fatty acids, creates some trans fatty acids.

Passive | Not requiring energy (ATP)

Peer reviewer | An expert selected by a journal to review a submitted manuscript.

Peer-reviewed journals | Journals that publish research articles that have been peer reviewed and believed to merit publication.

Pellagra | Niacin deficiency.

Pentose | A 5-carbon monosaccharide.

Pepsin | Protein digesting enzyme in the stomach. A protease. Accounts for a minor amount of protein digestion.

Pepsinogen | Zymogen of pepsin. Activated to pepsin by hydrochloric acid in the stomach.

PepT1 transporter | A di- and tripeptide transporter.

Peptic ulcer | A break on the skin, in the lining of an organ, or on the surface of a tissue. An ulcer forms when the surface cells become inflamed, die, and are shed. Ulcers may be linked to cancer and other diseases.

Peptidases | Brush border enzymes that cleave peptides to amino acids.

Peptide bond | A bond between 2 amino acids.

Peristalsis | Involuntary, wave-like contractions of smooth muscles that push food through the gastrointestinal tract.

Pernicious anemia | Anemia that result from a lack of intrinsic factor.

pH | Scale that is used to measure acidity, on which 7 is neutral, less than 7 is acidic, and greater than 7 is basic.

Phagocytosis | Endocytosis of a particle.

Pharynx | Tubular organ that connects the mouth and nasal cavity with the larynx and through which air and food pass

Phenylketonuria | A condition where a mutation in the enzyme phenylalanine hydroxylase prevents the normal conversion of phenylalanine to tyrosine. Tyrosine is conditionally essential, but phenylalanine and its metabolites can build up can cause adverse brain effects. Needs to limit protein and aspartame intake.

Phosphate | Group composed of phosphorus with bonded to 4 oxygens and negative 3 charge (PO4-3). Ionic form of phosphoric acid.

Phosphatidylcholine | Best known phospholipid, contains a choline off the phosphate group in its head.

Phospholipase A2 | Digestive enzyme that cleaves the C-2 fatty acid in phosphatidylcholine (lecithin) forming lysolecithin.

Phospholipid | Glycerol backbone with 2 ester-bonded fatty acids and a nitrogen containing compound bonded to it. Amphipathic in nature.

Phosphorylation | Addition of a phosphate group, overall requires energy.

Photon | Particles which transmit light.

Photoreceptor cell | A cell found in the retina that is capable of converting light to electrical signals.

Photosensitive | Sensitive to light.

Physiology | Study of the functioning of the human organism.

Phytate | Molecule that contains a number of phosphate groups, whose negative charges can bind to minerals thus inhibiting their absorption.

Phytochemical | Non-nutritive plant compounds that may provide health benefits beyond traditional nutrients.

Pigmentation | Color of tissue. Pigments are responsible for the color of skin, eyes and hair.

Pinocytosis | Endocytosis of fluid.

Pitting | The formation of pits on a surface because of corrosion.

Pitting edema | "Pitting" when, after pressure is applied to a small area, the indentation persists after the release of the pressure.

Pituitary gland | A pea-sized organ attached to the part of the brain called the hypothalamus. It lies at the base of the brain above the back of the nose. The hypothalamus sends signals to the pituitary gland, which then makes hormones that control other glands and many of the body's functions, including growth and fertility.

Placebo | A inert pill or treatment that serves as the control comparison to an active intervention.

Placebo effect | The positive effect that can occur from a subject's belief that they are receiving a treatment that is going to improve their condition, even if they are not receiving an active intervention.

Placental barrier | There is no intermingling of fetal and maternal blood in the placenta.

Plasma | Straw-yellow fluid part of blood that contains many dissolved substances and blood cells.

Plasma membrane | Double layer of phospholipid molecules that makes up the membrane of cells.

Polyglutamate | Containing more than one, or multiple, glutamates.

Polymorphism | Polymorphism involves one of two or more variants of a particular DNA sequence. The most common type of polymorphism involves variation at a single base pair. Polymorphisms can also be much larger in size and involve long stretches of DNA. Called a single nucleotide polymorphism, or SNP (pronounced snip), scientists are studying how SNPs in the human genome correlate with disease, drug response, and other factors.

Polypeptide | Large chain of polypeptides bonded together.

Polyphenol | A large family of naturally occurring organic compounds characterized by multiples of phenol (ringed) units. Inhibits the absorption of some minerals.

Polysaccharide | More than 10 monosaccharides bonded together.

Polyunsaturated fatty acid | A fatty acid contain two or more double bonds.

Portal vein | Blood vessel that transports nutrients directly from the small intestine to the liver.

Positive energy balance | The state in which the number of calories consumed is greater than the number used. Energy balance is affected by physical activity, body size, amount of body fat and muscle, and genetics.

Postbiotic | Metabolites secreted by the microbiota.

Prebiotic | Nondigestible food component that selectively stimulates the growth of beneficial bacteria.

Precipitate | Forming solid in, or settling of solid out of, the solution.

Preformed vitamin A | All ready formed vitamin A. Another way of describing retinoids.

Premenstrual syndrome | A collection of physical and emotional symptoms that occur before menstruation.

Prevalence | A measure of the total number of people in a specific group who have (or had) a certain disease, condition, or risk factor (such as smoking or obesity) at a specific point in time or during a given period of time.

Primary bile acid | Bile acid created directly from cholesterol.

Probiotic | Beneficial bacteria consumed and colonizes in the microbiota in the body.

Procolipase | Zymogen of colipase.

Prohormone | Precursor to a hormone.

Promoter | A regulatory region of DNA usually located upstream of a gene, providing a control point for regulated gene transcription.

Prospective cohort study | An observational study following a select "cohort" of people, assessing their exposure status, and then following them over time looking for incident cases of disease.

Protease | An enzyme that cleaves protein.

Proteasome | A large protein complex that helps destroy other cellular proteins when they are no longer needed.

Protein | Macronutrient that provides 4 kilocalories/gram. Made up of carbon, hydrogen, oxygen and nitrogen.

Protein Digestibility Corrected Amino Acid Score | Amino Acid Score x Digestibility

Protein efficiency ratio | Grams of weight gained / grams of protein consumed. This method is commonly performed in growing rats.

Protein quality | An indication of the quality based off how well it contributes or supports protein use in the body, its amino acid composition, and/or amino acid digestibility.

Protein-energy malnutrition | A condition of inadequate protein intake that can also occur with and without inadequate caloric (energy) intake.

Proteoglycan | A molecule that contains both protein and glycosaminoglycans, which are a type of polysaccharide. Proteoglycans are found in cartilage and other connective tissues.

Proton gradient | Difference in proton concentrations across a membrane. In the electron transport chain there is a higher proton concentration in the intermembrane space than inside the mitochondrial matrix.

Provitamin A | A precursor that can be cleaved to retinal (vitamin A). Used to describe certain carotenoids.

Pseudovitamin | A vitamin-like analogue that is biologically inactive in humans.

Pyloric sphincter | The sphincter separating the stomach from the duodenum.

Pyruvate | 3-carbon metabolic intermediate.

R

Racemic | One that has equal amounts of different possibilities at chiral centers.

Rachitic rosary | Prominent knobs of bone at the costochondral joints (beading of the ribs).

Rancid | Oxidation of fats resulting in objectionable flavor and/or smell.

Randomization | The process of randomly assigning subjects to groups to decrease bias.

Rate-limiting enzyme | Enzyme that limits that rate at which a metabolic pathway proceeds.

Re-esterified | Reforming of ester bonds. Commonly use to reforming of triglycerides, phospholipids and cholesterol esters in the enterocyte after uptake.

Reactive oxygen species | Unstable oxygen-containing molecule that seeks out other compounds to react with. Some ROS have radicals meaning they are oxygen-containing free radicals.

Receptor-mediated endocytosis | Endocytosis that occurs after binding to receptors.

Recommended Dietary Allowance | Average daily nutrient intake level sufficient to meet the nutrient requirement of nearly all (97-98%) healthy

individuals in a particular age, sex, and life-stage group.

Rectum | Short part of the large intestine between the colon and anus where feces is stored until it is eliminated through the anus.

Red blood cell | A type of blood cell that is made in the bone marrow and found in the blood. Red blood cells contain a protein called hemoglobin, which carries oxygen from the lungs to all parts of the body. Checking the number of red blood cells in the blood is usually part of a complete blood cell (CBC) test. It may be used to look for conditions such as anemia, dehydration, malnutrition, and leukemia. Also called erythrocyte and RBC.

Reduction | Gaining of electrons. Also can be from losing oxygen or gaining hydrogen.

Reductionist approach | An approach that seeks to reduce food down to its components so that those potential beneficial components can be consumed individually.

Reflex | An involuntary, unplanned sequence or action and nearly instantaneous movement in response to a stimulus.

Reflux | The backward flow of liquid from the stomach into the esophagus.

Relative risk | A measure of association calculated for studies that observe incident cases of disease (cohort, or clinical trials). Similar to odds ratio and hazard ratio.

Reproduction | The biological process by which new individual organisms – "offspring" – are produced from their "parent" or parents.

Reservoir | A storage place.

Resistant starch | Starch that is resistant to digestion. Thus, it reaches the colon where it is fermented.

Retina | The light-sensitive layers of nerve tissue at the back of the eye that receive images and sends them as electric signals through the optic nerve to the brain.

Retinoic acid receptor | Nuclear hormone receptor whose ligand is all-trans retinoic acid.

Retinoic Acid Response Element | Specific area in the promoter where the Retinoic Acid Receptor-Retinoid X Receptor dimer binds.

Retinoid | Term to refer to retinol, retinal, and retinoic acid.

Retinoid X receptor | Nuclear hormone receptor whose ligand is 9-cis retinoic acid. However, its major function is serving as the dimer partner for other nuclear hormone receptors.

Retinol activity equivalents | Units of vitamin A value that are made to account for the differences in bioavailability and bioconversion of provitamin A carotenoids.

Reverse cholesterol transport | The process of high-density lipoprotein scavenging cholesterol from tissues/blood vessels and returning it to the liver itself or to other lipoproteins returning to the liver.

Rhodopsin | Formed from 11-cis retinal and the protein opsin. Light striking it causes it to split to opsin and all-trans retinal, a signal is sent to brain allow you to see.

Rickets | A condition in children in which bones become soft and deformed because they don't have enough calcium and phosphorus.

Risk | The likelihood or chance of a, most commonly, negative outcome.

Rod | Photoreceptor cells that can function better in low light, primarily for seeing black and white.

Room temperature | Normal room temperature is around 70?F, around 21?C.

S

Saccharin | Older artificial sweetener that triggers both sweet and bitter taste receptors.

Saliva | Fluid secreted by salivary glands that keeps the mouth moist and contains the digestive enzymes salivary amylase and lingual lipase.

Salivary amylase | Digestive enzyme released from the salivary glands that cleaves alpha 1-4 glycosidic bonds in carbohydrates. Accounts for a minor amount of carbohydrate digestion.

Salivary gland | One of many exocrine glands in the mouth that secrete saliva into the mouth through ducts.

Salt | Sodium chloride (NaCl).

Salt-sensitive | Blood pressure is sensitive to salt such that increasing intake increases blood pressure, decreasing intake decreases blood pressure.

Sanitize | Cleaning and disinfecting of the an area or item.

Saturated | Having no double bonds. Completely saturated with hydrogen.

Saturated fat | A fatty acids that is fully saturated, with not double bonds.

Saturation | A clinical measure of the level of fullness of a substance.

Schizophrenia | A group of severe mental disorders in which a person has trouble telling the difference between real and unreal experiences,

thinking logically, having normal emotional responses to others, and behaving normally in social situations.

Scientific method | Procedure of formulating a research question and associated hypothesis, which is then test through an experienced to determine whether the results support the hypothesis.

Scurvy | Condition that can occur because of vitamin C deficiency, characterized by bleeding gums, pinpoint hemorrhages, and corkscrew hairs.

Secondary bile acid | Bile acid created by fermentation of a primary bile acid in the colon.

Secondary messenger | Intracellular signaling molecules released by the cell in response to exposure to extracellular signaling molecules—the first messengers.

Secondary outcome | Outcomes that were not the primary ones that the study was designed to assess, secondary in nature.

Secrete | To form and release a substance. In the body, cells secrete substances, such as sweat that cools the body or hormones that act in other parts of the body.

Secretin | Released from the small intestine in response to chyme entering from stomach, stimulates secretion of bicarbonate from the pancreas into the duodenum and flow of bile from liver to the gallbladder.

Seizure | Sudden, uncontrolled body movements and changes in behavior that occur because of abnormal electrical activity in the brain. Symptoms include loss of awareness, changes in emotion, loss of muscle control, and shaking.

Selenoenzyme | A subset of selenoproteins that have an enzymatic function.

Selenoprotein | Proteins that contain selenocysteine as an amino acid inserted by its codon.

Sensible sun exposure | Sun exposure on the face, arms, and hands for 10-15 minutes 2-3 times per week between 10 AM-3 PM.

Serum | Plasma minus its clotting proteins.

Severity | The degree of something undesirable; badness or seriousness.

Short-chain fatty acid | A fatty acid containing less than 6 carbons.

Sigmoid colon | After the descending colon and before the rectum. As name indicates it is s-shaped.

Significant | Used in research/science communication to indicate statistical significance.

Simple carbohydrate | Monosaccharides and disaccharides (2 or less sugars).

Simple diffusion | Movement of solutes from an area of higher concentration (with the concentration gradient) across a membrane to an area of lower concentration without the help of a protein or energy.

Single-agent | A single compound.

Single-blind | A study design where only the researcher knows what intervention the subject is receiving, the subject does not.

Slough | The act of shedding or casting off.

Small Intestine | Long, narrow, tube-like organ of the digestive system where most chemical digestion of food and virtually all absorption of nutrients take place

Soft drink | A normally carbonated drink that contains sweetener.

Solute | Solution component present in a concentration less than that of the solvent.

Solution | A homogeneous mixture made up of multiple substances generally referred to as solutes and solvents.

Solvent | Solution component present in a concentration that is higher relative to its other components.

Spare | To not use when amounts are limited.

Sphincter | Ring of muscles that can contract to close off an opening between structures, such as between the esophagus and stomach.

Spine bifida | A birth defect in which there is incomplete closing of the spine and the membranes around the spinal cord during early development in pregnancy.

Spleen | The large lymphatic organ near the stomach that stores blood and produces lymphocytes.

Standard deviation | The standard deviation is a widely used measure of variability. It is computed by taking the square root of the variance.

Starch | Polysaccharide of glucose bonded by alpha bonds as either amylose or amylopectin. Plant storage of glucose.

State | Current status, state or condition.

Statins | Pharmaceuticals that inhibit HMG-CoA reductase and thereby decrease cholesterol synthesis. This results in decreased LDL levels.

Statistical significance | Often indicated by $p<0.05$ or through 95% confidence intervals.

Status | State. Typically used to refer to nutrient status (deficient, adequate, excess, toxic).

Stellate cell | Lipid storing cells in the liver.

Stem cell | Undifferentiated cell that can develop into specialized types of cells.

Stereochemistry | The spatial arrangement atoms that form a structure.

Stereospecific numbering | System for numbering based of molecule position.

Steric hindrance | Congestion caused by the physical presence of surrounding atoms in a molecule.

Steroid hormone | Hormones that are synthesized from sterols.

Sterol | Type of lipid with a characteristic 4 ring structure. Does not provide calories unlike other lipids.

Stevia | Sweetener derived from South American shrub. Sweetness provided by steviol glycosides. Heat-stable.

Stomach | Sac-like organ of the digestive system between the esophagus and small intestine in which both mechanical and chemical digestion take place

Stroke | Cerebrovascular accident in which a broken artery or blood clot results in lack of blood flow to part of the brain, causing death of brain cells.

Structure | The spatial arrangement of atoms in a molecule and the chemical bonds that hold the atoms together.

Sublingual | Latin for "under the tongue"

Suboptimal | Less than optimal amount.

Substrate | A substance on which an enzyme acts.

Sucralose | Alternative sweetener similar in structure to sucrose except Chlorine (Cl) replaces the hydroxyl (–OH) groups.

Sucrase | Disaccharidase that cleaves sucrose to glucose and fructose.

Sucrose | Disaccharide of glucose + fructose by alpha bond, table sugar.

Sugar alcohol | An organic compound containing multiple alcohol or hydroxyl groups (-OH). Less sweet than caloric sweeteners, but are not fermented by microorganisms. Also known as polyols and sugar replacers.

Sun protection factor | Indication of the effectiveness of sunscreen, or other protectants, to prevent sunburn or skin damage from UV light. 1 over the number of UV photons that reach skin.

Superoxide Dismutase | Antioxidant enzymes that use copper, zinc, and/or manganese as cofactor to convert superoxide to hydrogen peroxide.

Supplement | Taking nutrients often in a pill or nondietary manner.

Sweat | Fluid excreted by the sweat glands during perspiration.

Symbiotic | A close and long-term biological interaction between two different biological organisms, be it mutualistic, commensalistic, or parasitic.

Synbiotic | A product that contains both a probiotic and a prebiotic.

Synthetic | Not made from natural materials.

Systematic literature review | A systematic process through which a literature review is conducted to answer a specific question.

T

t-score | The number of standard deviations above or below the mean for a healthy 30-year-old adult of the same sex and ethnicity as the patient.

Tagatose | An alternative sweetener that is similar in structure and function to sugar alcohols except is also contains a ketone group.

Teratogen | A substance that can cause birth defects.

Teratogenic | Causing a birth defects.

Tetany | Involuntary muscle contraction.

Thionein | Storage protein for zinc and copper. Zinc is the better inducer, copper the more avid binder.

Thioredoxin reductase | An antioxidant selenoenzyme.

Thoracic duct | Duct where lymph system join general blood circulation.

Throat | Cavity that includes the pharynx and larynx, epiglottis and trachea.

Thyroid | A gland located beneath the larynx (voice box) that makes thyroid hormone and calcitonin. The thyroid helps regulate growth and metabolism.

Thyroxine | The primary circulating form of thyroid hormone (T4). Has 4 iodines.

Tissue | A group or layer of cells that work together to perform a specific function.

Tolerable Upper Intake Level | The highest average daily nutrient intake level likely to pose no risk of adverse health effects for nearly all people in a particular age, sex, and life-stage group.

Tolerance | The amount that can be tolerated without adverse effects. In ethanol, this is impacted by sex, size, and previous metabolic capacity from exposure.

Total Fiber | Dietary fiber + functional fiber.

Toxic | To produce harmful or adverse effects.

Toxicity | The extent to which something is harmful or causes adverse effects.

Trace mineral | Minerals that need to be consumed in less quantities than macrominerals, but more than ultratrace minerals.

Trachea | Tubular organ of the respiratory system that carries air between the larynx and bronchi; also called windpipe.

Trans | A double bond where the hydrogens are on opposite sides of the double bond.

Trans fat | An unsaturated fatty acid that has at least 1 double bond in the trans configuration.

Transamination | Transfer of an amine group from an amino acid to a keto acid.

Transcobalamin II | Vitamin B12 transport protein.

Transcription | The process of synthesizing messenger RNA (mRNA) from DNA.

Transferrin | Iron transport protein that takes Fe3+ through circulation.

Transferrin receptor | Receptor found in tissues that binds to transferrin and cause it to be endocytosed.

Transit time | The amount of time it takes for food to go from the oral cavity through the gastrointestinal tract to the anus.

Transition reaction | Metabolic conversion of pyruvate to acetyl-CoA.

Translation | The process of synthesizing an amino acid sequence (protein product) from the messenger RNA (mRNA) code

Transport proteins | Protein that transport substances through circulation.

Transporter | Protein in a cell membrane that helps other substances cross the membrane to enter or leave the cell.

Transthyretin | Transport protein that carries thyroxine (T4) can complexes with retinol-binding protein through circulation.

Transverse colon | After the ascending colon and before the descending colon. As name indicates it is portion that is moving across the body.

Triglyceride | Glycerol backbone with 3 ester-bonded fatty acids.

Triiodothyronine | The active form of thyroid hormone (T3). Has 3 iodines.

Tripeptide | 3 amino acids bonded together.

Triticale | Hybrid grain of wheat and rye.

Tropocollagen | Three collagen strands wound together forming a strong, cross-linked structure.

Tropomyosin | A muscle protein involved in contraction.

Truncate | To cap, or not allow to exceed.

Trypsin | A digestive protease active in the small intestine.

Trypsinogen | Zymogen of trypsinogen, a digestive protease active in the small intestine.

Type 1 diabetes | Autoimmune disorder in which the immune system destroys insulin-secreting beta cells in the pancreas, leading to loss of glucose control and high blood glucose concentrations.

Type 2 diabetes | Multifactorial disorder in which a combination of insulin resistance and impaired insulin production lead to loss of glucose control and high blood glucose concentrations.

U

Ubiquitin | Any of a class of small protein, or polypeptide, present in the cells, that play a part in modifying and degrading proteins.

Ulcerative colitis | Chronic inflammation of the colon that produces ulcers in its lining. This condition is marked by abdominal pain, cramps, and loose discharges of pus, blood, and mucus from the bowel.

Ultratrace mineral | Minerals that need to be consumed in the lowest quantities.

Unresolved | Not known.

Unsaturated | Having at least 1 double bond. Not completely saturated with hydrogen.

Uptake | Uptake into the enterocyte. Does not always result in absorption from the enterocyte into circulation.

Urea | A substance formed by the breakdown of protein in the liver. The kidneys filter urea out of the blood and into the urine.

UV light | Electromagnetic radiation with a wavelength shorter than that of visible light, but longer than soft X-rays.

UV-A | A spectrum of ultraviolet light with wavelengths ranging from 315-400 nanometers, which does tan skin.

UV-B | A spectrum of ultraviolet light with wavelengths ranging from 280–315 nanometers, which does not tan the skin much. Type of light that leads to vitamin D3 synthesis.

V

Very low-density lipoprotein | Lipoprotein released from the liver that is smaller, is less triglyceride-rich, but more cholesterol-rich than a chylomicron.

Vesicle | A small sac formed by a membrane and filled with liquid. Vesicles inside cells move substances into or out of the cell.

Villi | Microscopic, finger-like projections in a mucous membrane that form a large surface area for absorption.

Virulent | Refers to the ability of a virus or a bacterium to cause damage to its host. Opposite of avirulent.

Vitamin | Organic compounds that are essential for normal physiologic processes in the body.

Vitamin D binding protein | Vitamin D transport protein, that typically transports 25(OH)D2 or 25(OH)D3 through circulation.

Vitamin D receptor | Nuclear hormone receptor whose ligand is 1,25(OH)D2.

Vitamin D response element | Specific area in the promoter where the Vitamin D Receptor-Retinoid X Receptor dimer binds.

Vomit | To eject some or all of the contents of the stomach through the mouth.

W

Warfarin | A drug that prevents blood from clotting. It belongs to the family of drugs called anticoagulants (blood thinners). It prevents the regeneration of vitamin K from vitamin K epoxide.

Water | Noncaloric macronutrient, hydrogen dioxide.

Wet beriberi | Type of thiamin deficiency that affects the cardiovascular system result in pitting edema, and heart enlargement.

Wet weight | Weight with fluid. Alternatively dry weight would be without fluid.

Wilson's disease | A genetic disorder that may result in copper toxicity where a mutation in ATP7B prevents copper excretion, thus potentially resulting in copper toxicity.

X

Xerophthalmia | A destructive dryness of the eye due to dietary vitamin A deficiency. There are multiple stages of this condition.

Z

Zeaxanthin | Yellow nonprovitamin A carotenoid.

Zoomchemical | Non-nutritive animal compounds that may provide health benefits beyond traditional nutrients.

Zymogen | An inactive precursor of an enzyme.

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