ADVANCED NUTRITION - SAN DIEGO MIRAMAR COLLEGE



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Advanced Nutrition | San Diego Miramar College

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Detailed Licensing

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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Licensing

*A detailed breakdown of this resource's licensing can be found in **Back Matter/Detailed Licensing**.*

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

CHAPTER OVERVIEW

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 ($\mathbf{H_2O}$) 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.

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

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.

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.

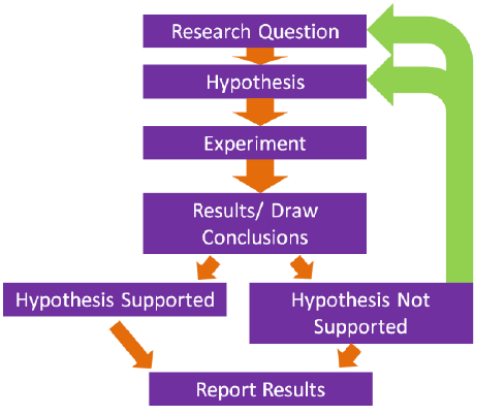


Figure **1.1.1**: The scientific method

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.

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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.

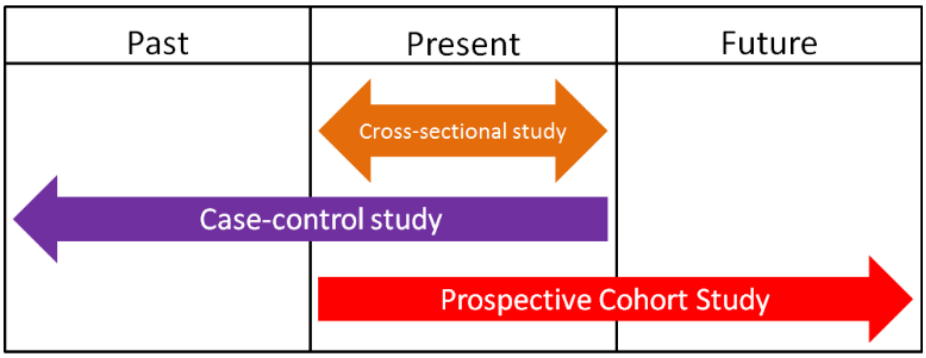


Figure **1.2.1**: Types of epidemiology. Adapted from reference 1.

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.

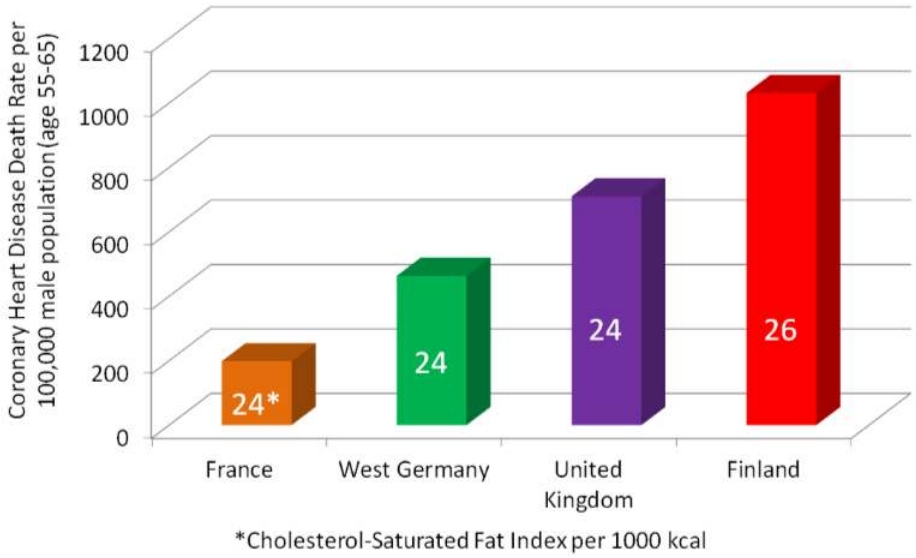


Figure **1.2.2**: An example of a cross-sectional study, "The "French Paradox". The x-axis shows four different European countries with similar cholesterol-saturated fat intakes2 (the numbers shown within the bars), and the y-axis represents coronary heart disease rate.

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.

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.

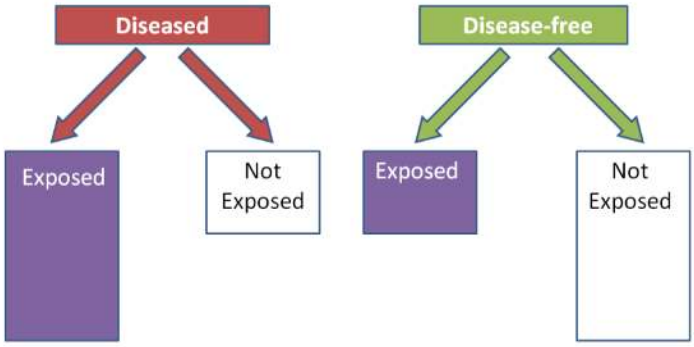


Figure **1.2.3**: An example of a case-control study in which the diseased were more likely to have been exposed than those who were disease-free. Cases are represented by the red box on the left, and the controls are the green box on the right[3].

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

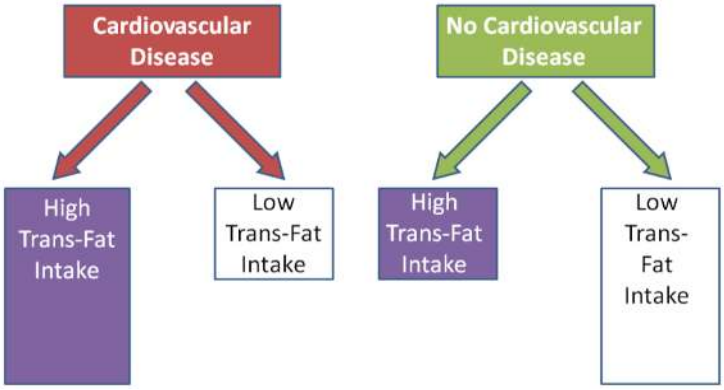


Figure **1.2.4**: An example of a case-control study that indicates that more cases had high trans-fat intake compared to the controls[3]

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

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.

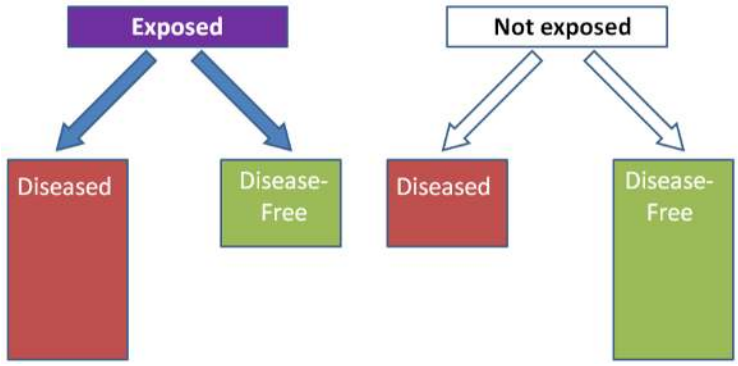


Figure **1.2.5**: An example of cohort study in which those exposed are more likely to develop the disease3

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

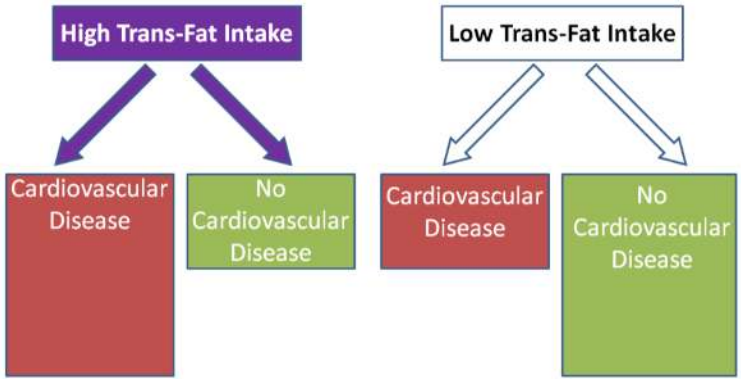


Figure **1.2.6**: An example of a cohort study where higher trans-fat intake is associated with a higher incidence of cardiovascular disease3

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 below4.

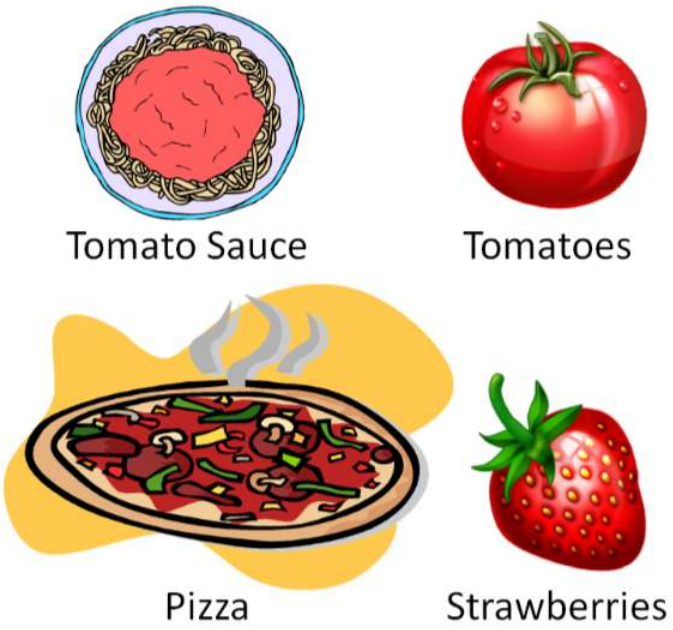


Figure **1.2.7**: Four foods items associated with decreased risk of prostate cancer4

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.

References

1. Levin K. (2006) Study design III: Cross-sectional studies. Evidence - Based Dentistry 7(1): 24.
2. Artaud-Wild SM, Connor SL, Sexton G, Connor WE. (1993) Differences in coronary mortality can be explained by differences in cholesterol and saturated fat intakes in 40 countries but not in france and finland. A paradox. Circulation 88(6): 2771.
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4. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, et al. (1995) Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst 87(23):1767-1776.

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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.

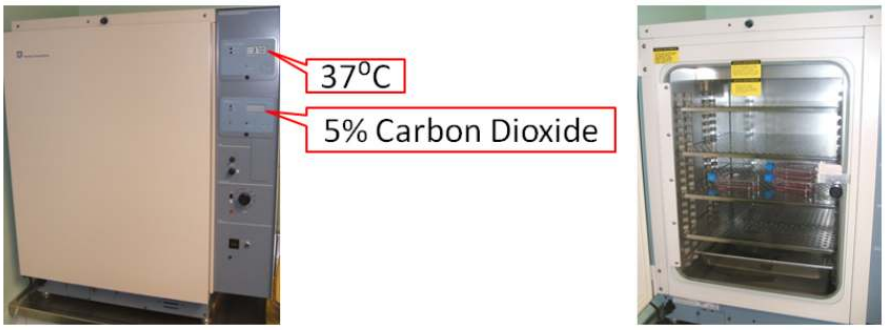


Figure 1.3.2: Outside and inside of an incubator

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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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.

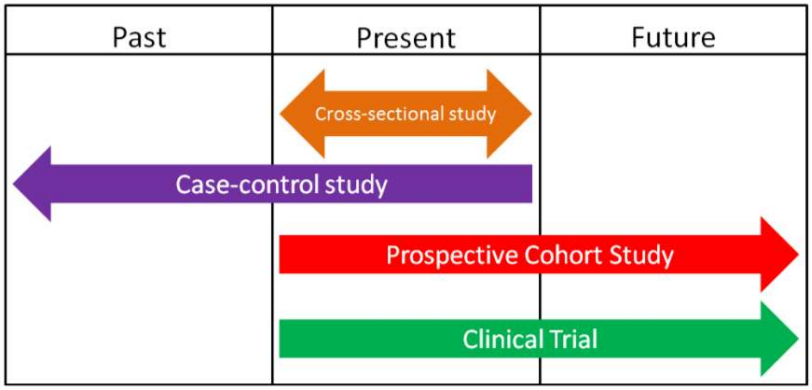


Figure 1.4.1: Clinical trials are prospective. Adapted from reference 1.

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.

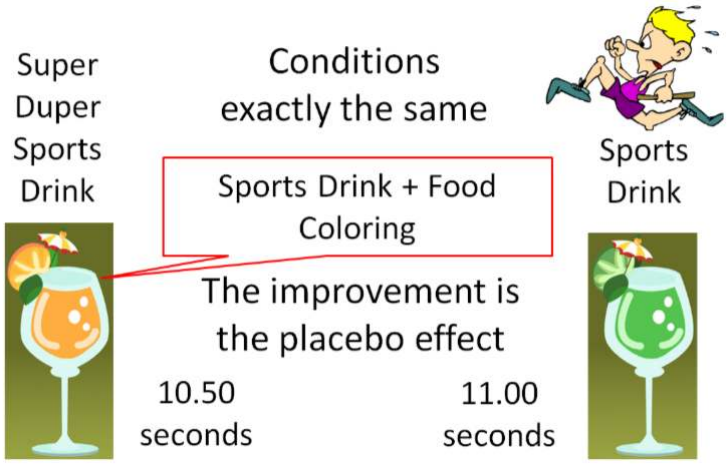


Figure **1.4.3**: Placebo effect example

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

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.

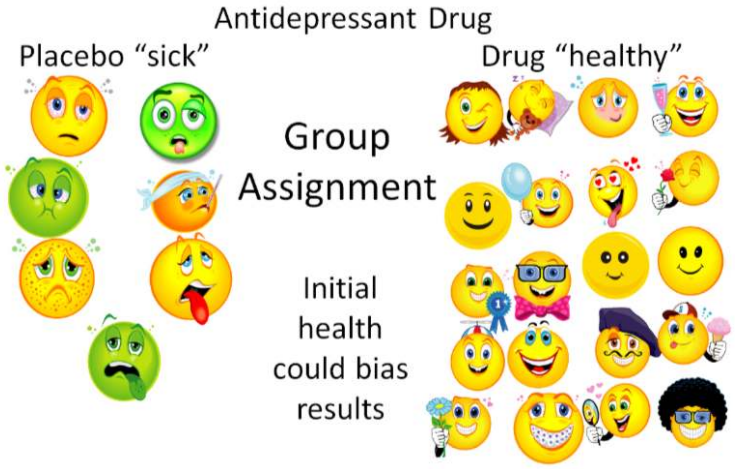


Figure **1.4.4**: Non-randomized antidepressant drug example

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.

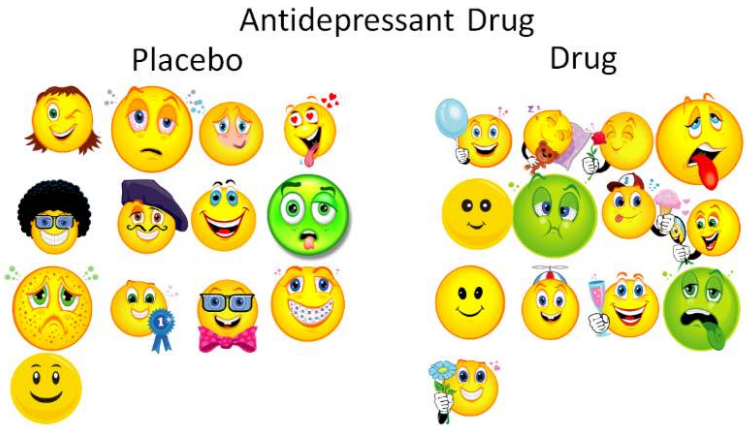


Figure 1.4.5: Randomized antidepressant drug example

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.

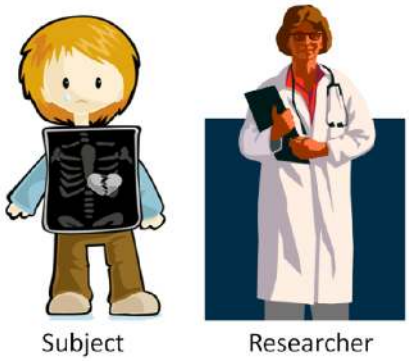


Figure 1.4.6: In an open-label study, both the subject and researcher know what treatment the subject is receiving.

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.

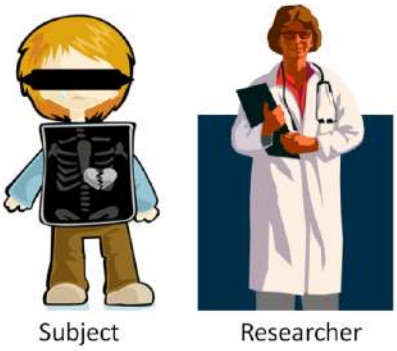


Figure 1.4.7: In a single-blind study, the researcher knows what treatment the subject is receiving, but the subject does not.

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.

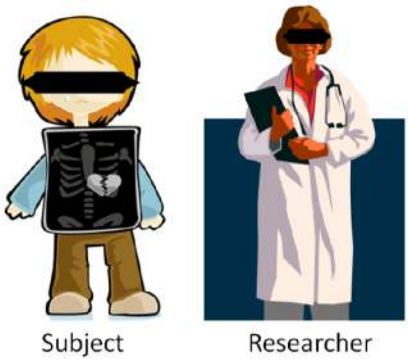


Figure 1.4.8: In a double-blind study, neither the subject nor the researcher know what treatment the subject is receiving.

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.

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.

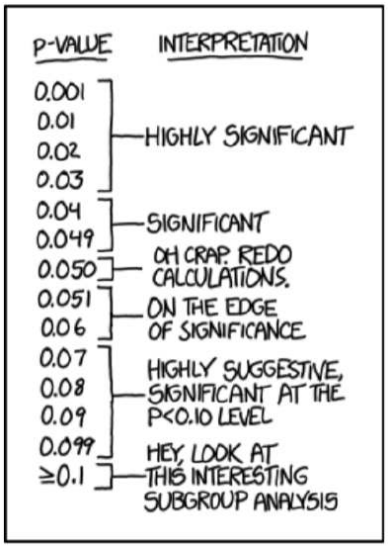


Figure **1.5.1**: ***p***-value interpretation. (CC BY-NC 2.5; xkcd)

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.

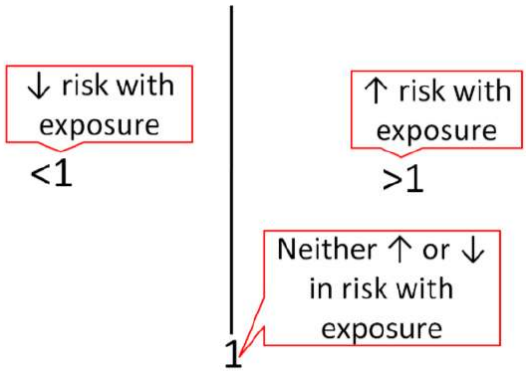


Figure **1.5.2**: Risk in relation to exposure for OR, RR, or HR

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**.

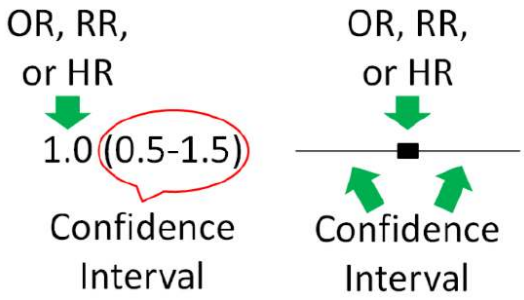


Figure **1.5.3**: Confidence Intervals for OR, RR, or HRs in text form (left) and figure form (right)

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**).

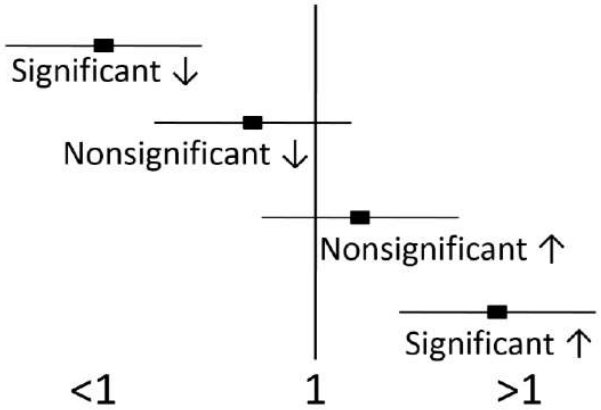


Figure **1.5.4**: Confidence intervals (95%) that include 1 indicate that the value is not significantly different. Confidence intervals above or below 1 without including it indicate that the value is significantly different.

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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 Factor1	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.



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

References

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.



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.

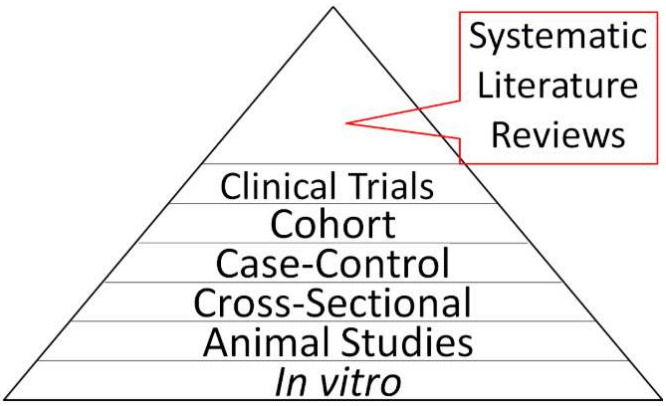


Figure **1.7.2**: Strength of scientific research, a higher position on the pyramid means greater strength of that form of evidence.

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.

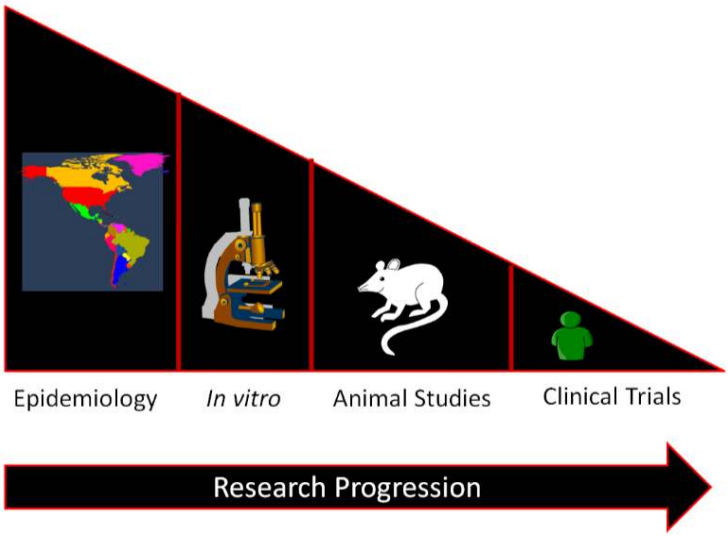


Figure **1.7.3**: The progression of nutrition research. The shape indicates the selection of the most promising and safest hypotheses being moved to the next level. Thus, there is a decrease in the overall number of hypotheses represented by the height of the figure) being investigated by the next form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

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 E[8], and a nonsignificant increase in diabetes among those receiving selenium[9]. 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 effective[10].

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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CHAPTER OVERVIEW

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:

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

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.

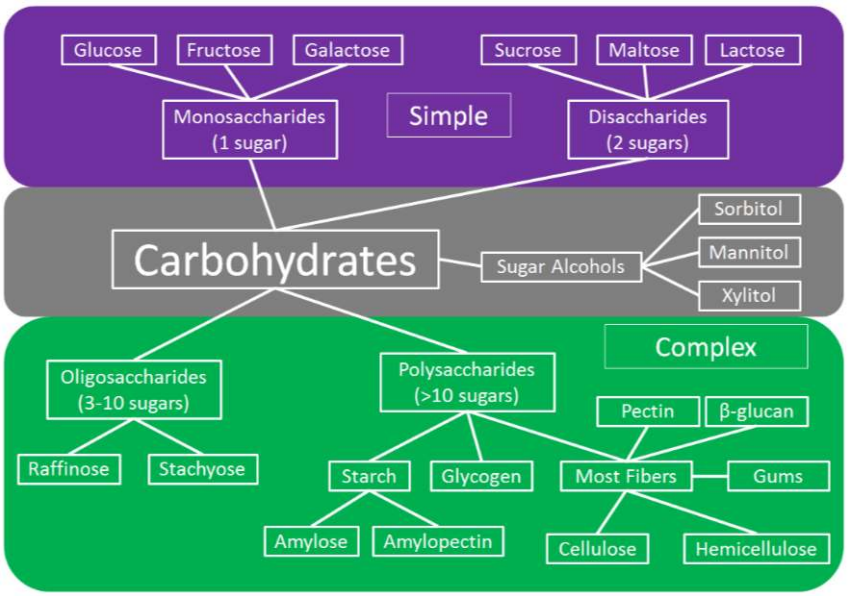


Figure 2.1.1 Different categorizations of carbohydrates

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.

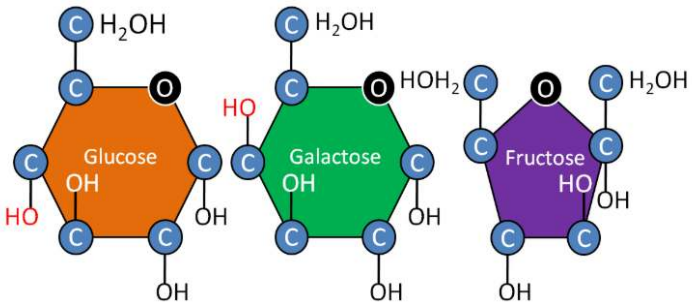


Figure **2.1.2**: The 3 monosaccharides

- **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

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.

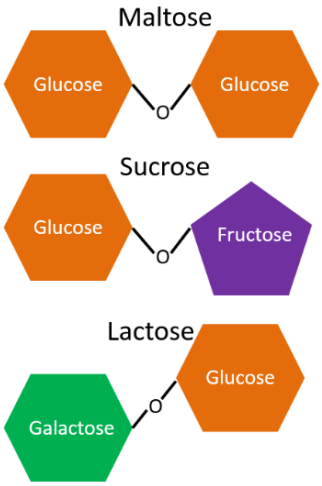


Figure **2.1.3**: The 3 disaccharides

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.

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.

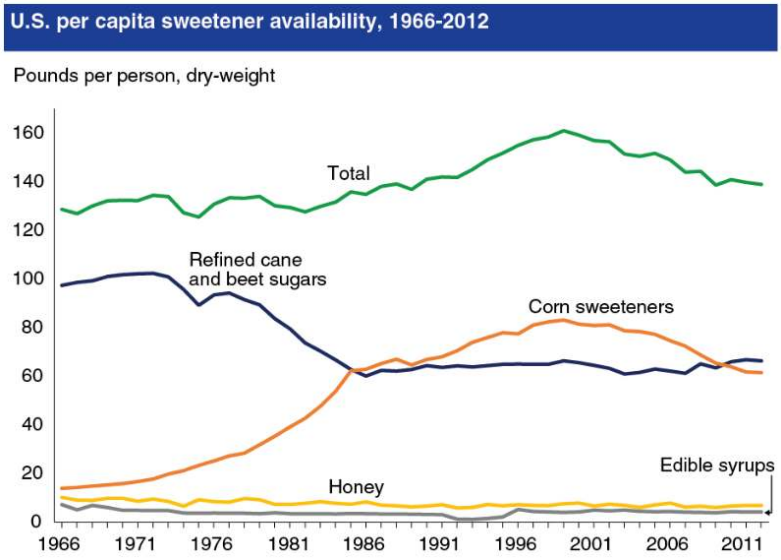


Figure **2.1.4**: U.S. per capita sugar and sweetener consumption[2]

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.

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.

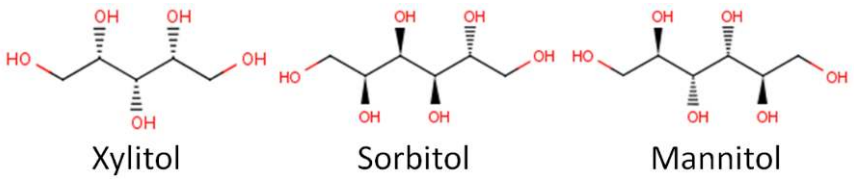


Figure **2.1.5**: Structure of three commonly used sugar alcohols: xylitol, sorbitol, and mannitol[3-5]

Remember that hydroxyl groups are (**–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 alcohols[6,7]

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



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.

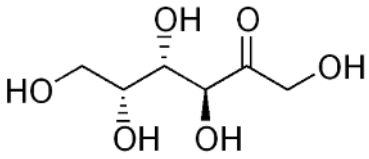


Figure 2.1.6: Structure of tagatose[8]

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].

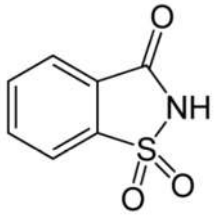


Figure 2.1.7: Structure of saccharin[14]

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].

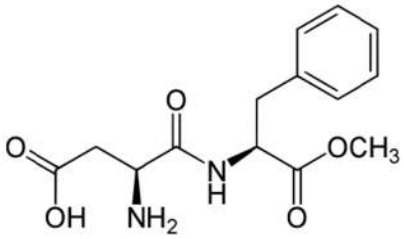


Figure 2.1.8: Structure of aspartame[15]

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].

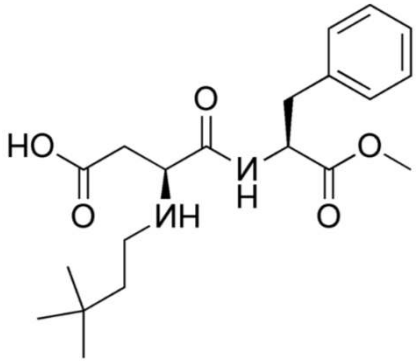


Figure **2.1.9**: Structure of neotame[16]

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.

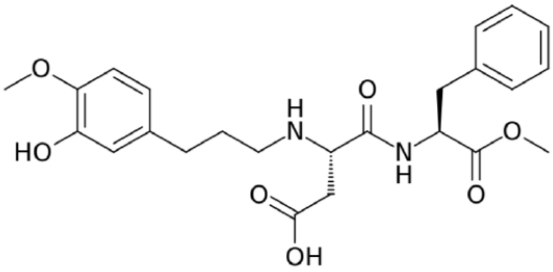


Figure **2.1.10**: Structure of advantame[17]

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.

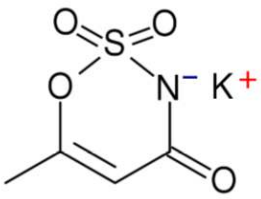


Figure **2.1.11**: Structure of acesulfame-potassium (K)[18]

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.

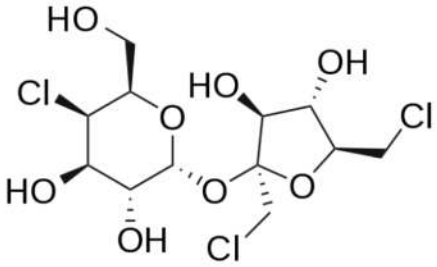


Figure **2.1.12**: Structure of sucralose19

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.

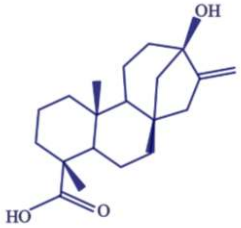


Figure **2.1.13**: Structure of steviol20

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 similar21. The structure of stevioside is shown below as an example.

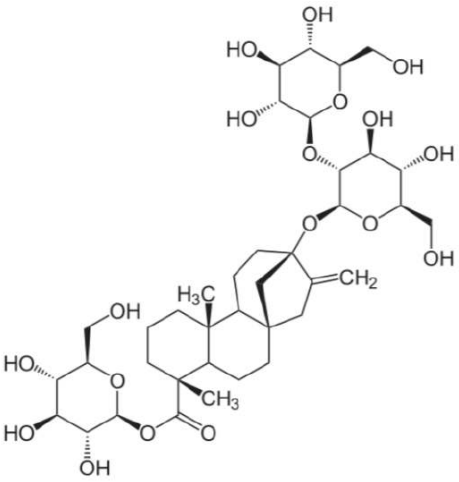


Figure **2.1.14**: Structure of stevioside22

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.

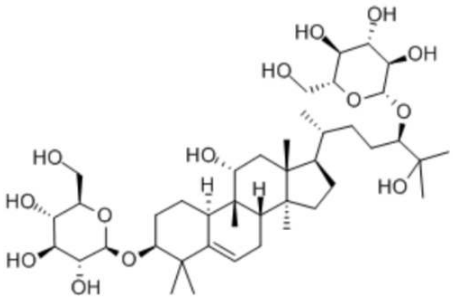


Figure **2.1.15**: Structure of a mogroside[23]

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 wheat[11]. 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.

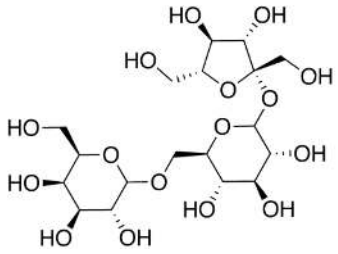


Figure **2.1.16**: Structure of raffinose[24]

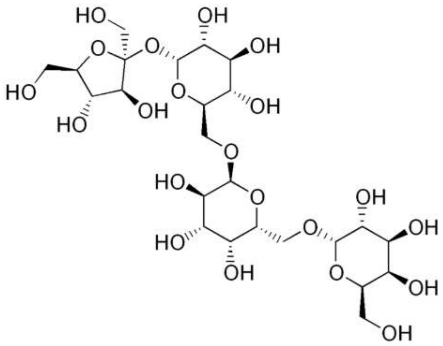


Figure **2.1.17**: Structure of stachyose[25]

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.

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**.

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.

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.

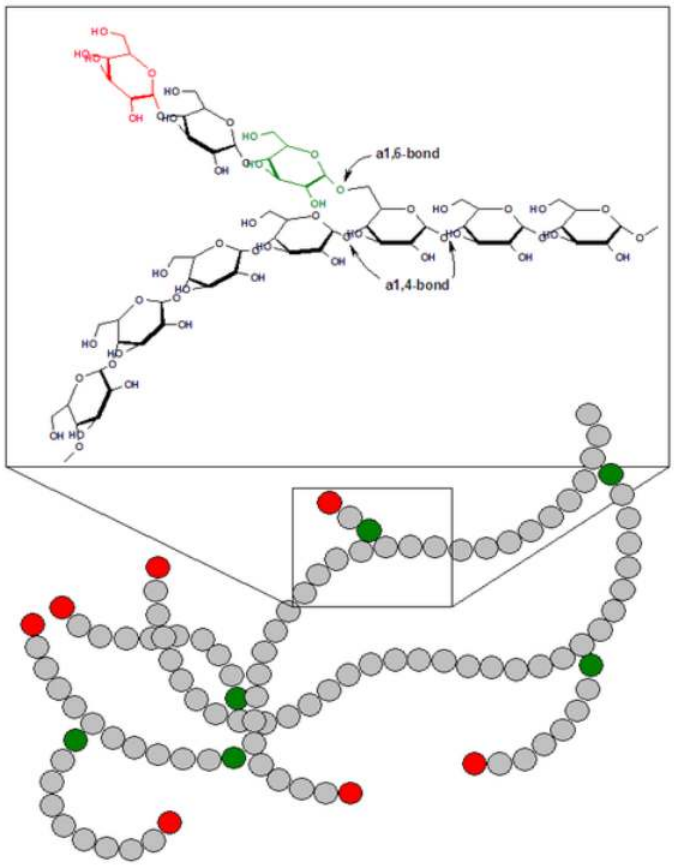


Figure **2.1.21**: Structure of glycogen[27]

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].

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.

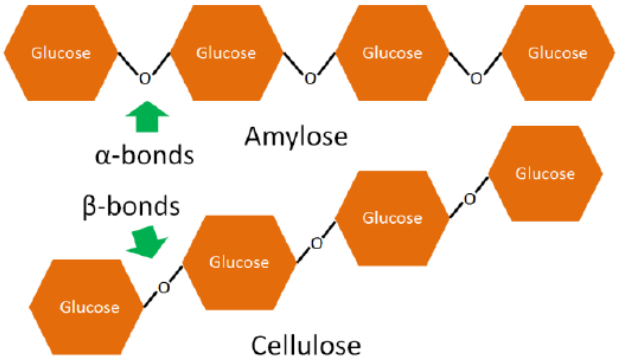


Figure **2.1.2**: Structures of amylose and cellulose

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

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
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 ($\mathbf{NH_2}$) and carboxylic acid (**COOH**) groups. The only structural difference in the 20 amino acids is the side group represented by the **R** below.

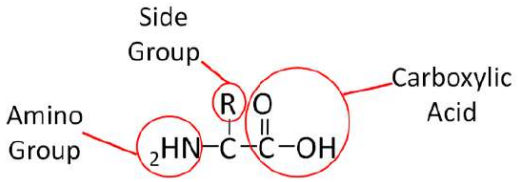


Figure **2.2.1**: Structure of an amino acid

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 ($\mathbf{CH_3}$). The structures of these two amino acids are shown below.

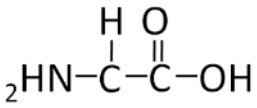


Figure **2.2.2**: Structure of glycine

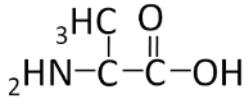


Figure **2.2.3**: Structure of alanine

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

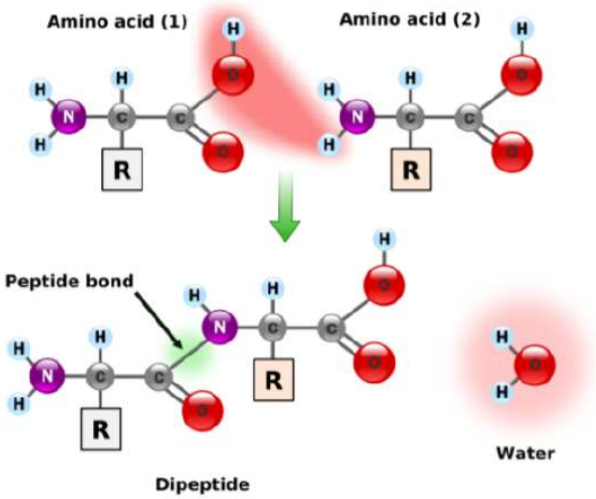


Figure **2.2.4**: Peptide bond formation[1]

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.

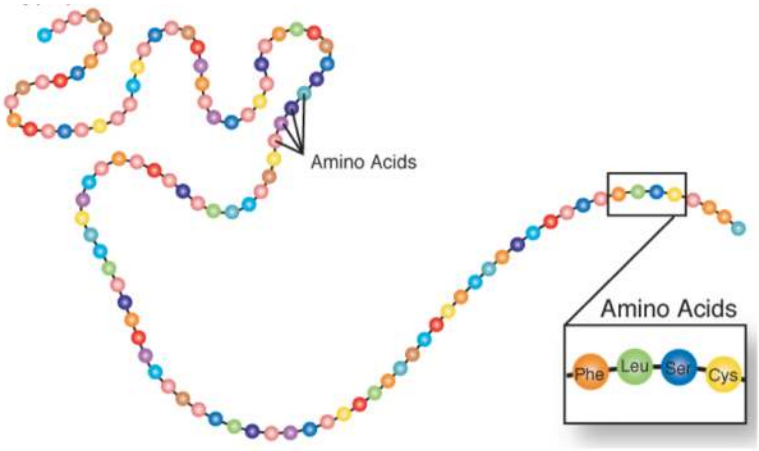


Figure **2.2.5**: A polypeptide chain2

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.

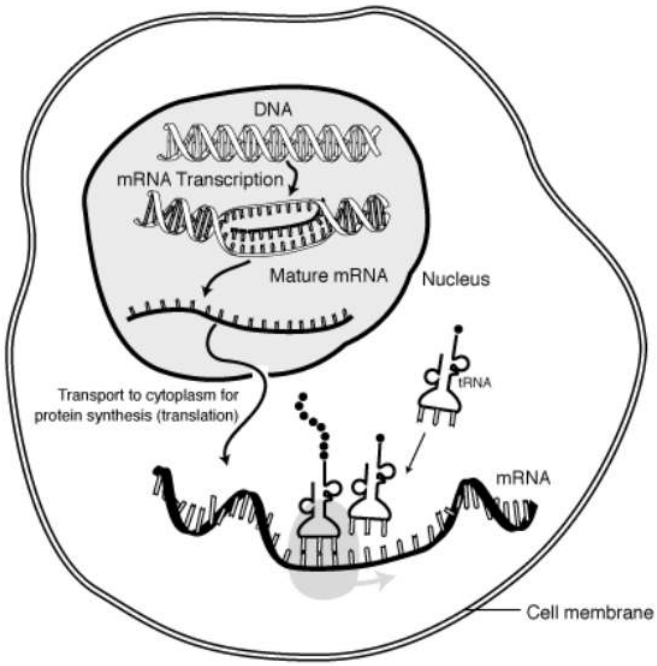


Figure **2.2.6**: The process of creating a polypeptide3

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).

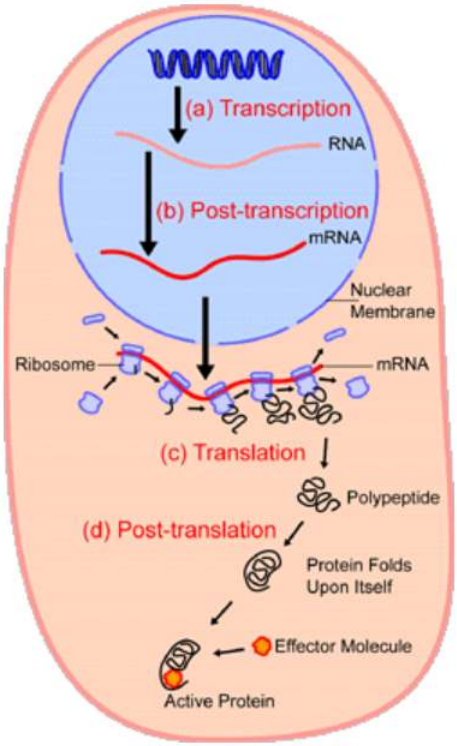


Figure **2.2.7**: Protein synthesis and processing[4]

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



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



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

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.

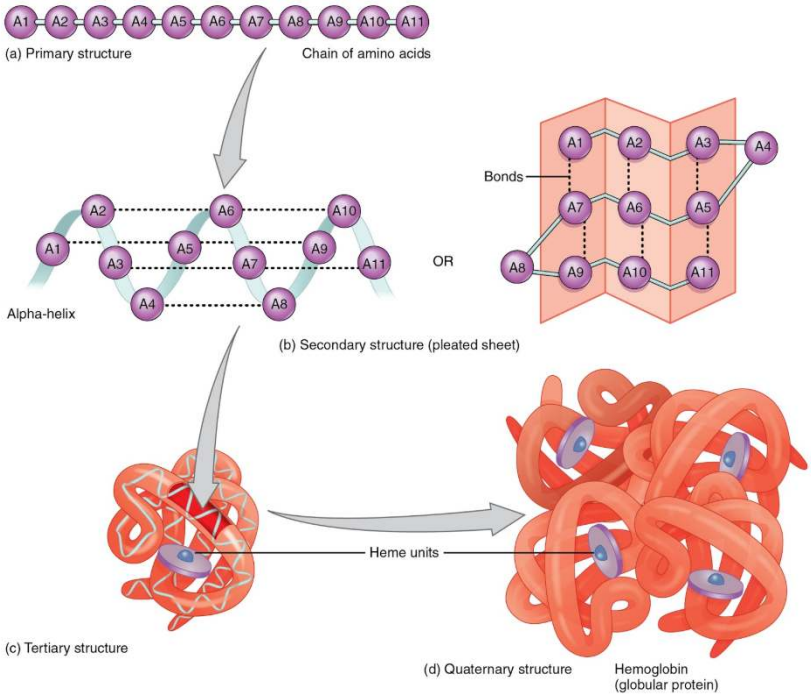


Figure **2.2.8**: Different Protein Structures[5]

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



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

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.

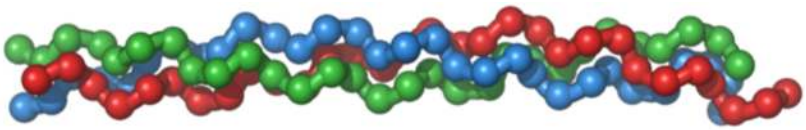


Figure **2.2.9**: Triple-helix structure of collagen6

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.

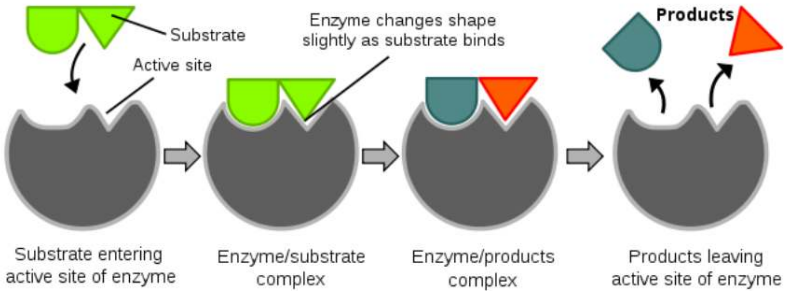


Figure **2.2.10**: The function of enzymes7



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.



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.

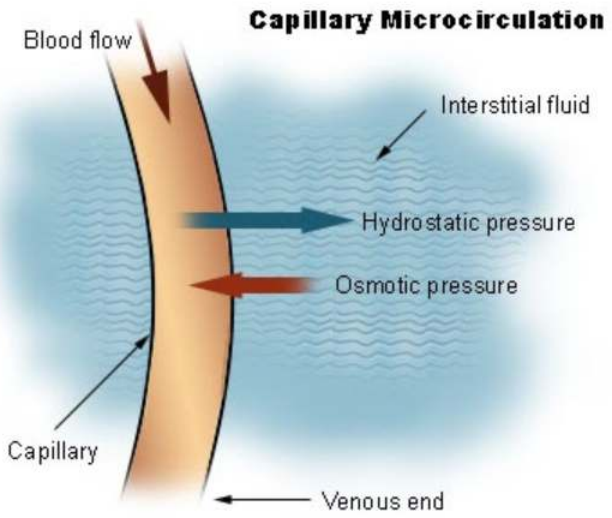


Figure **2.2.11**: Interstitial Fluid and plasma[8]

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.

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.

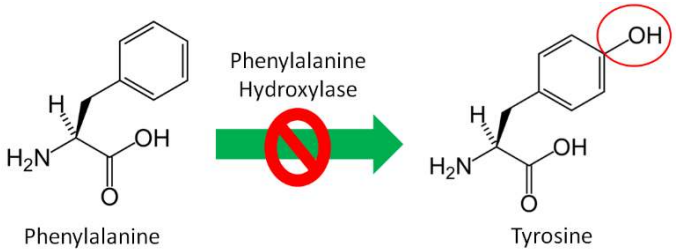


Figure **2.2.12**: Phenylketonuria (PKU) results from a mutation in the enzyme phenylalanine hydroxylase[10,11]

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.

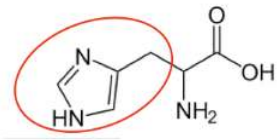
Web Link

Kuvan

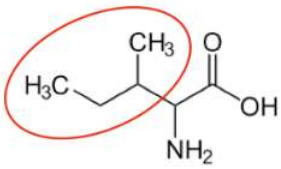
Amino Acid Structures

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

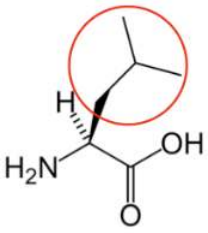
talking about an amino acid. Each amino acid differs only by its side group, which is circled in red in each figure below. Also, the more familiar you become with chemical structures, the more prepared you will be for later classes.



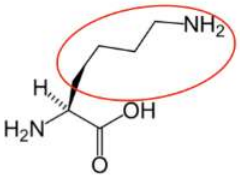
Histidine[12]



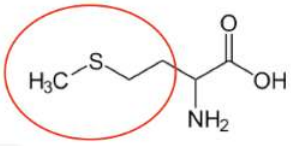
Isoleucine[13]



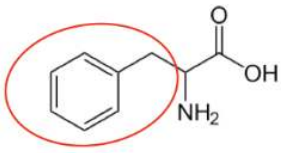
Leucine[14]



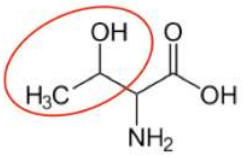
Lysine[15]



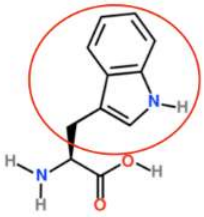
Methionine[16]



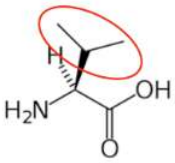
Phenylalanine[17]



Threonine[18]



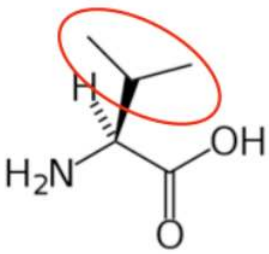
Tryptophan[19]



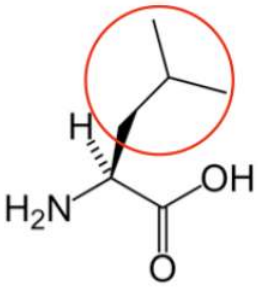
Valine [20]

Figure **2.2.13**: Essential amino acids12-20

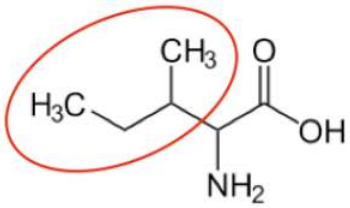
You may hear someone talk about the branch chain amino acids, which are all essential amino acids, but they are singled out in the figure below. These amino acids have branched carbons in their side chains.



Valine[20]

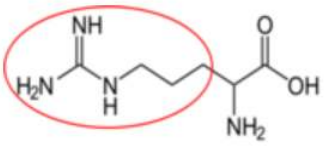


Leucine[14]

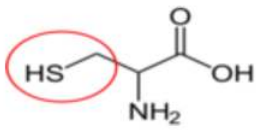


Isoleucine[13]

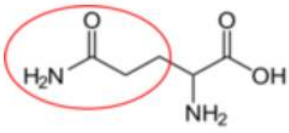
Figure **2.2.14**: Branched chain amino acids20,14,13



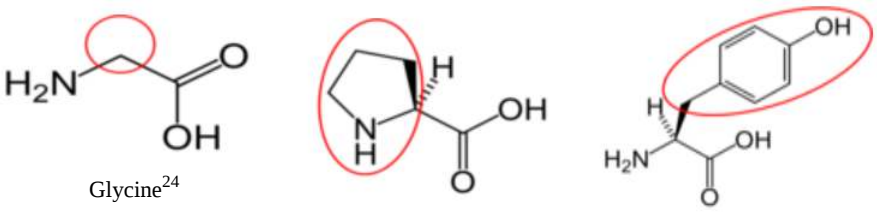
Arginine[21]



Cysteine[22]

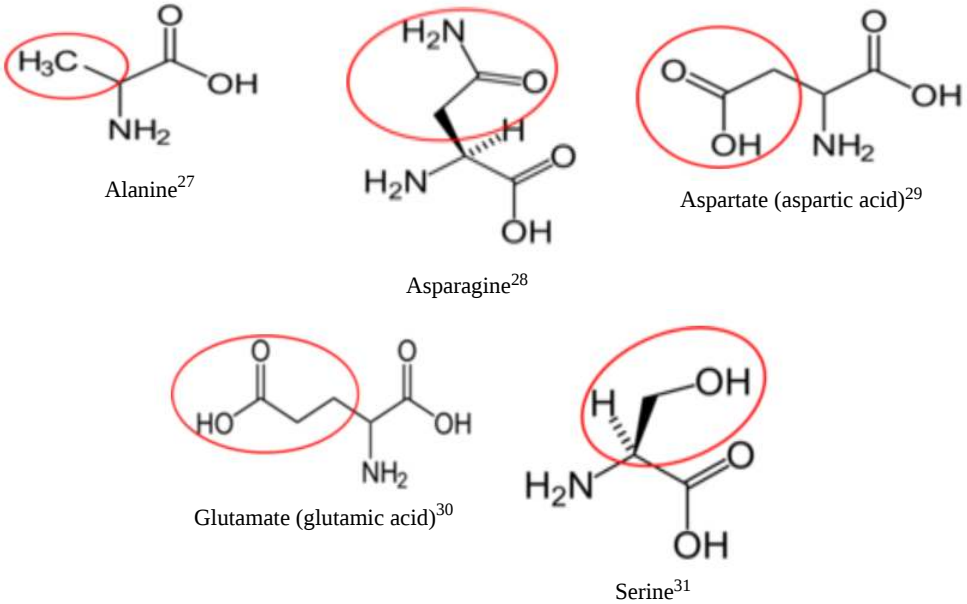


Glutamine[23]



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

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
Vegetables	Methionine, Lysine

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.

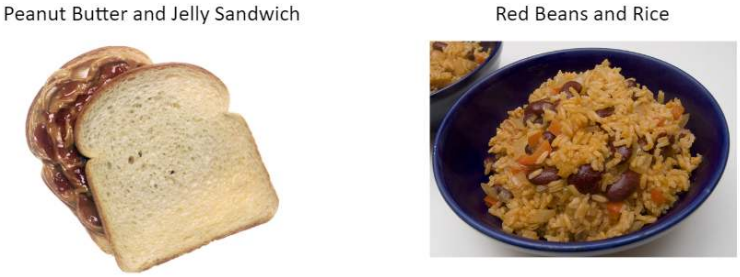


Figure **2.2.18**: Two complementary protein examples33,34

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 another35.

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 recently36,37.

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

Table **2.2.3**: Measures of protein quality36

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

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.

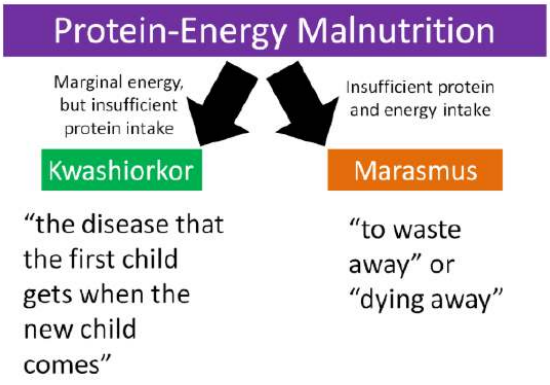


Figure **2.2.19**: The 2 types of protein-energy malnutrition

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.



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.

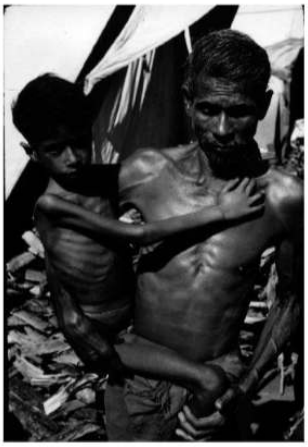


Figure **2.2.21**: Two individuals suffering from marasmus[41]

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14. en.Wikipedia.org/wiki/Leucin...e_Nonionic.svg
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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.

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 ($\mathbf{CH_3}$) 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.

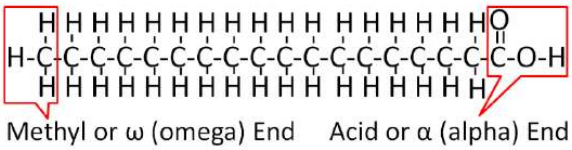


Figure **2.3.1**: Structure of a saturated fatty acid

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.

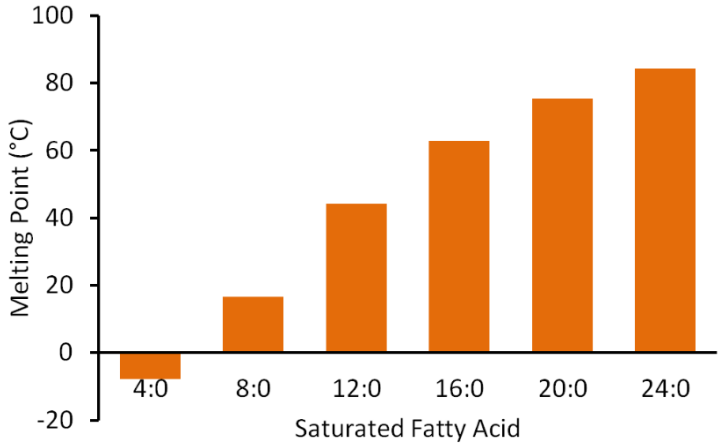


Figure **2.3.2**: The melting point of saturated fatty acids of varied lengths[1]

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).

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.

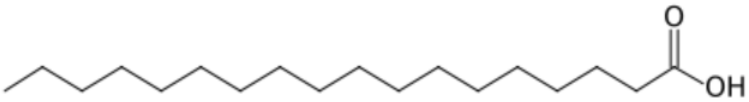


Figure **2.3.3**: A simplified view of 18 carbon saturated fatty acid stearic acid[2]. Each inflection point the zigzag pattern represents a carbon, and the hydrogens are not shown to allow quicker recognition of the carbon chain

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).

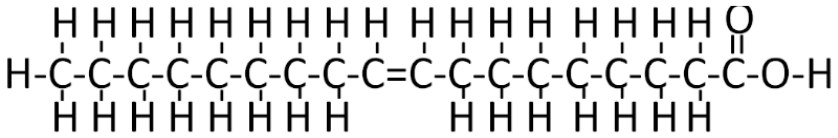


Figure **2.3.4**: Structure of the monounsaturated fatty acid (oleic acid)

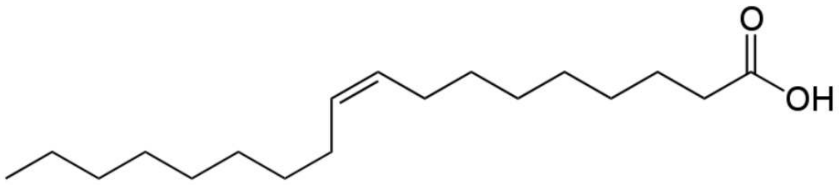


Figure **2.3.5**: The simplified structure of the monounsaturated fatty acid (oleic acid)3

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).

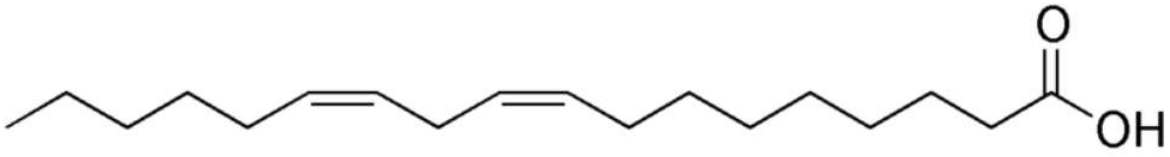


Figure **2.3.6**: Structure of the polyunsaturated fatty acid linoleic acid, a polyunsaturated fatty acid with two carbon-carbon double bonds4

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.

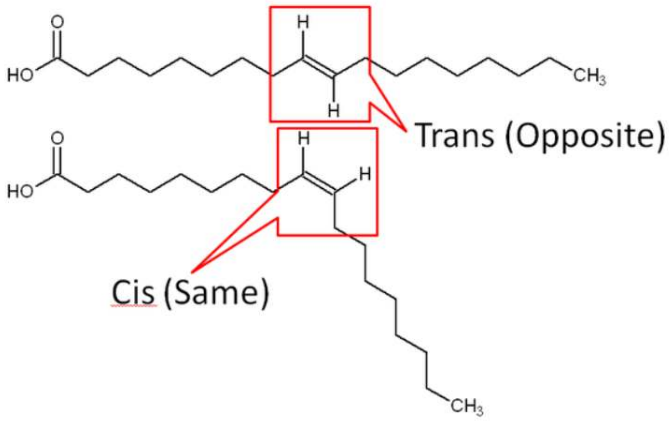


Figure **2.3.7**: Cis and trans structural conformations of a monounsaturated fatty acid

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.

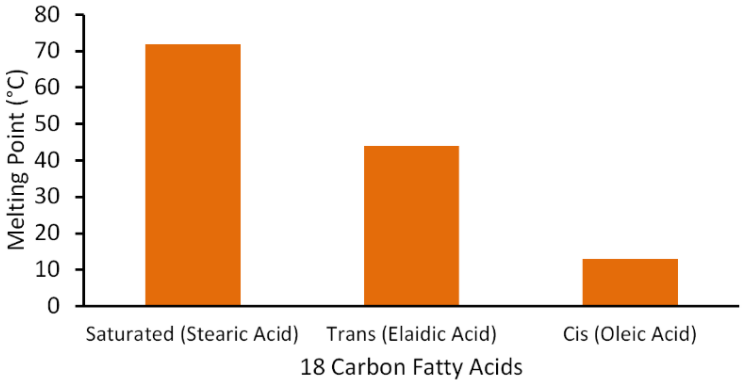


Figure **2.3.8**: The melting point of saturated, trans, and cis 18 carbon monounsaturated fatty acids[1]

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.

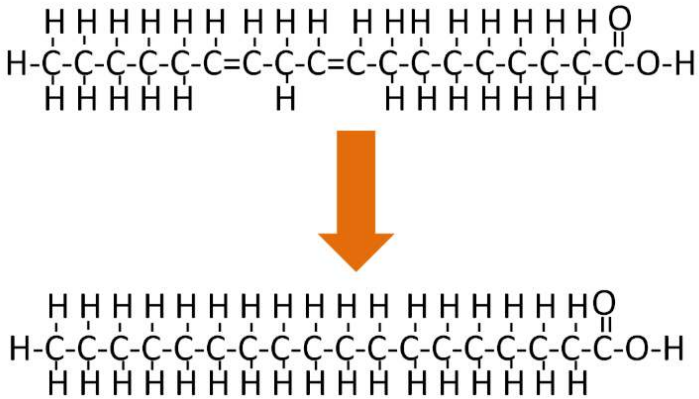


Figure **2.3.9**: Fatty acid hydrogenation

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

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.

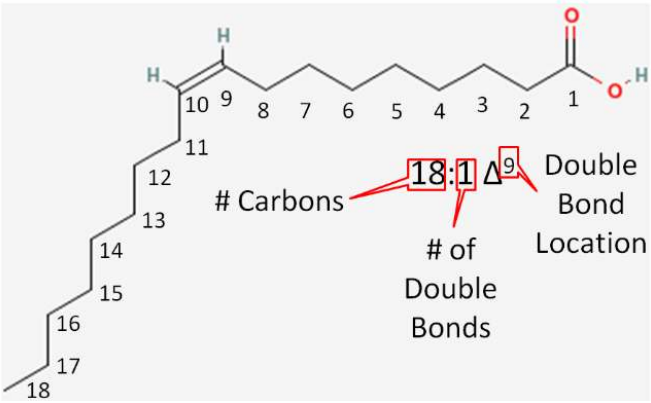


Figure **2.3.10**: Delta Nomenclature

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**.

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.

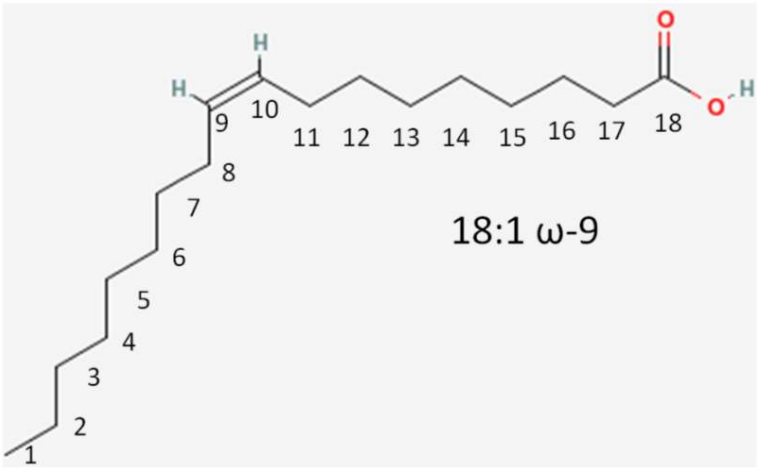


Figure **2.3.11**: Omega Nomenclature

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.

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.

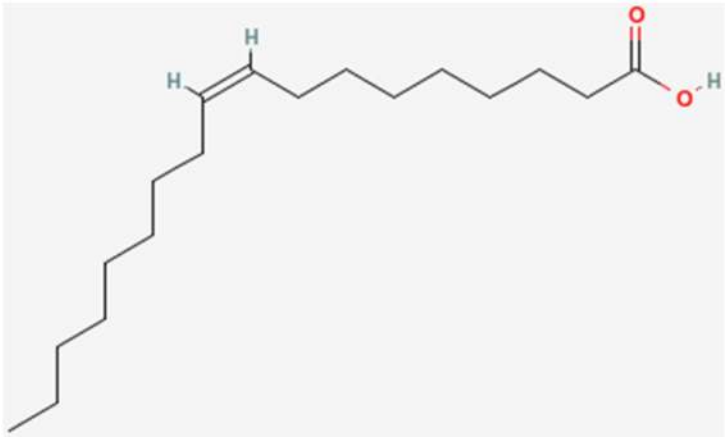


Figure **2.3.12**: Oleic acid

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.

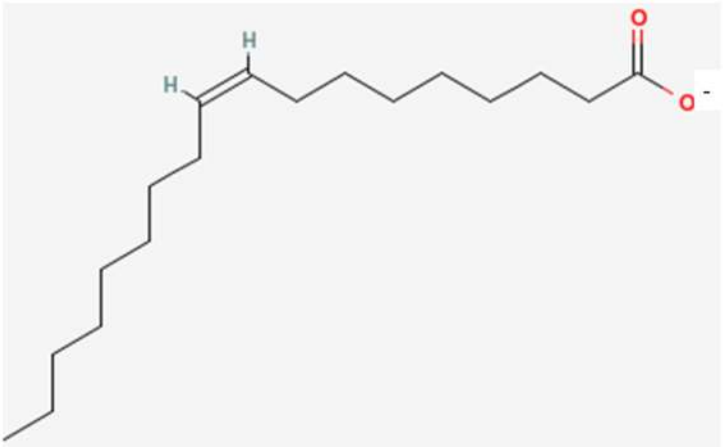


Figure **2.3.13**: Oleate

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
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

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.

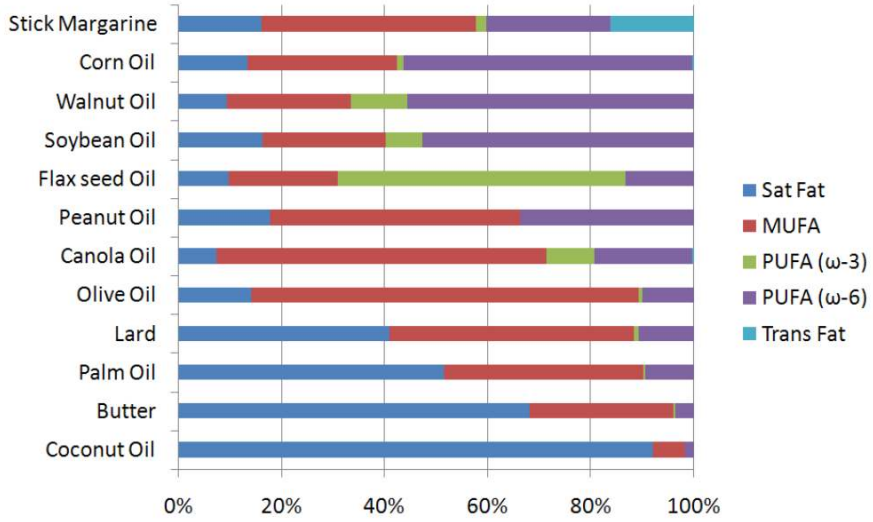


Figure **2.3.14**: Fatty acid composition of foods and oils6

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.

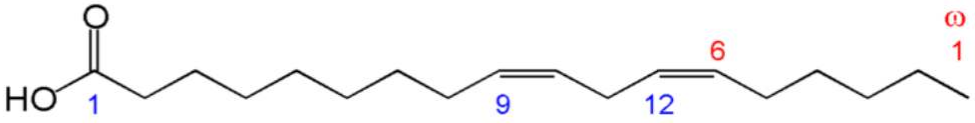


Figure **2.3.15**: Linoleic acid7

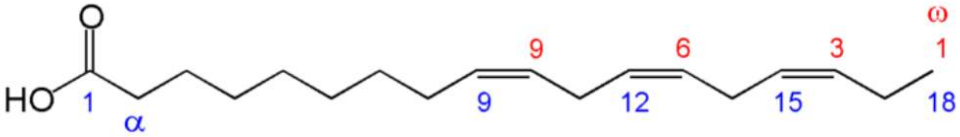


Figure **2.3.16**: Alpha-linolenic acid8

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.

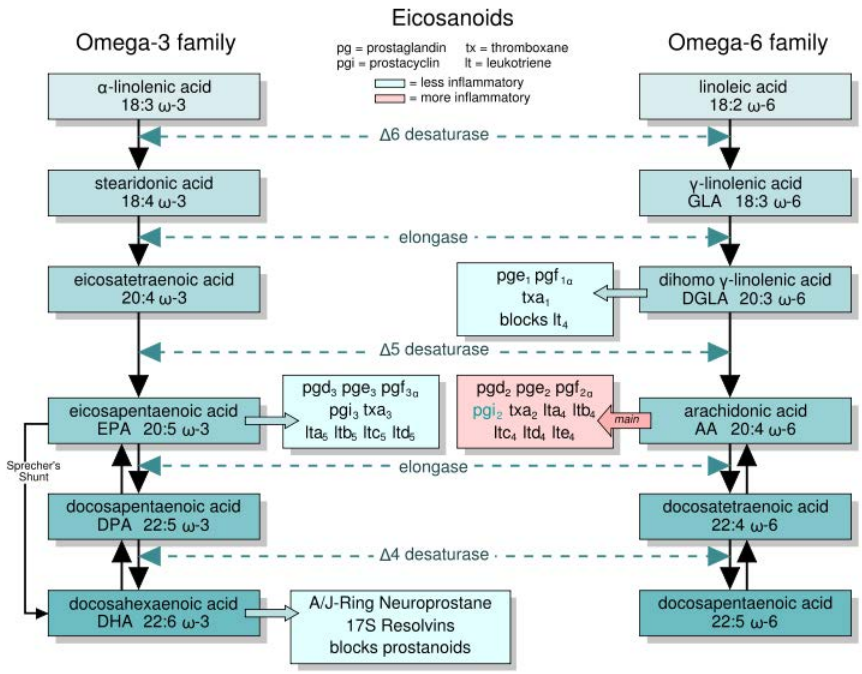


Figure **2.3.17**: Omega-3 and omega-6 fatty acids and eicosanoid production9

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:

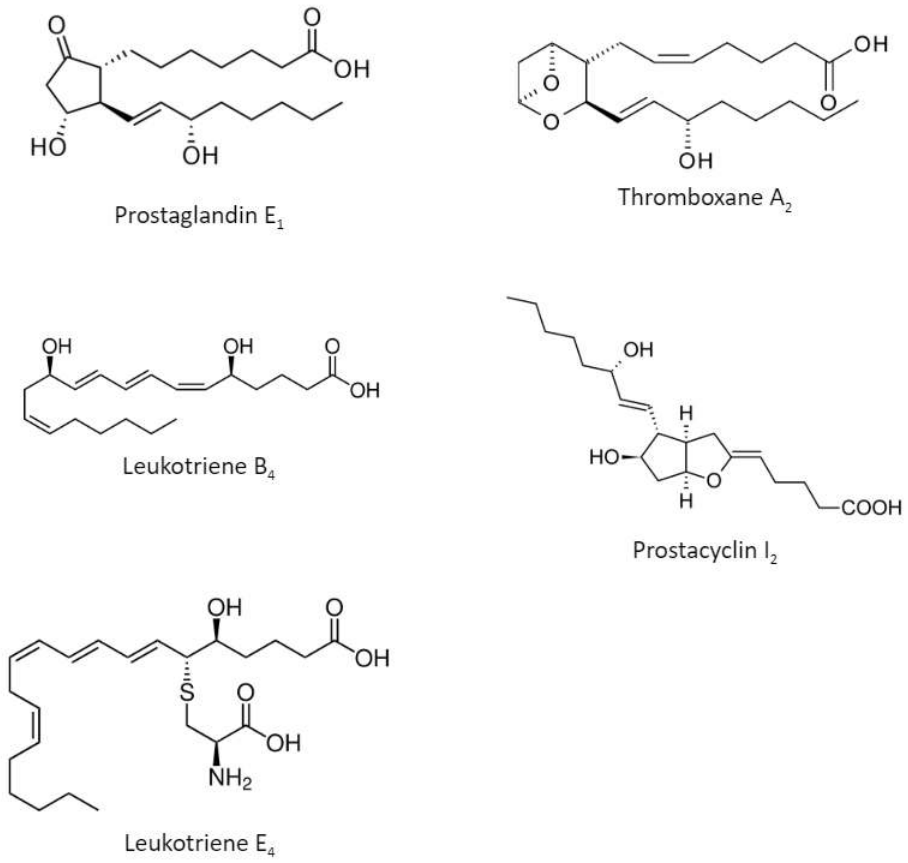


Figure **2.3.18**: Eicosanoid structures10-14

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.

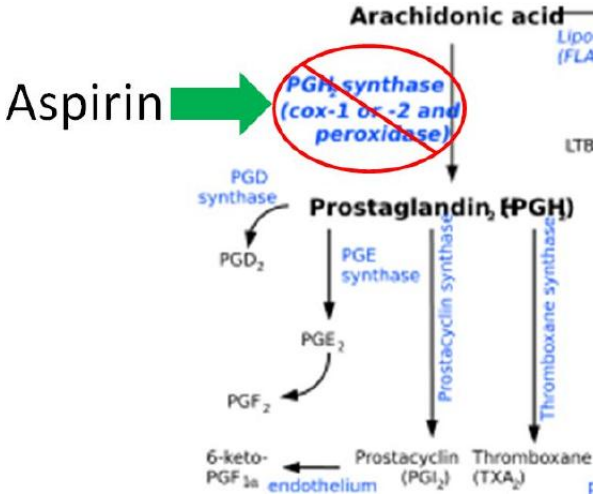


Figure **2.3.19**: Aspirin inhibits Cox-1 and Cox-215

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

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.

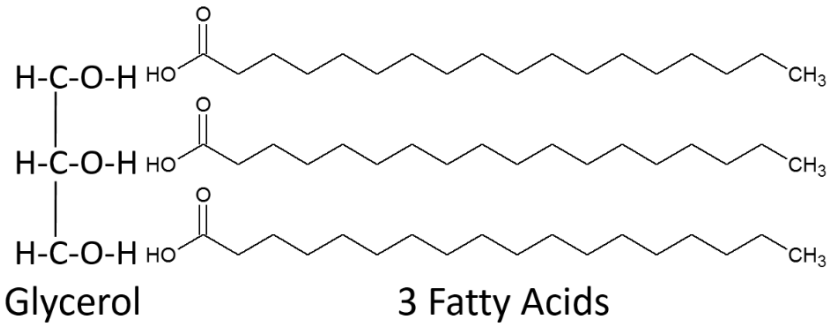


Figure **2.3.20**: Triglyceride formation

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.

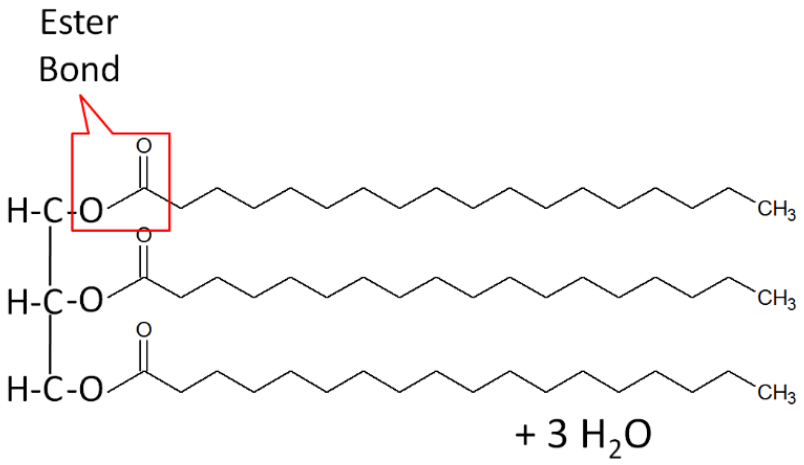


Figure **2.3.21**: Esterification of three fatty acids to glycerol

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.

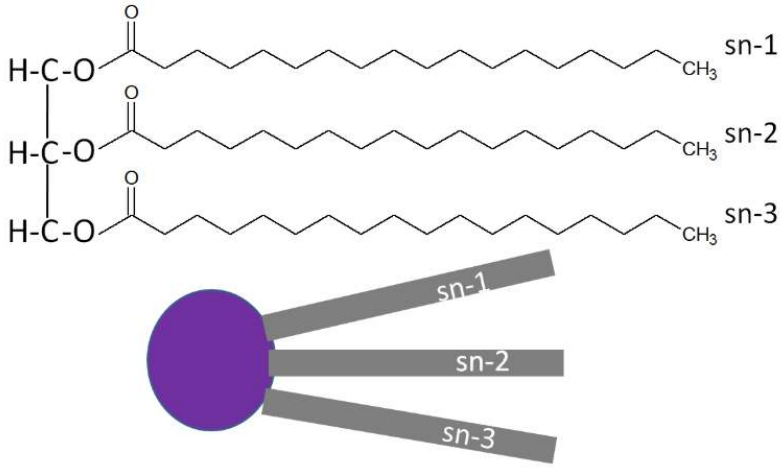


Figure **2.3.22**: Stereospecific numbering (sn) of triglycerides

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.

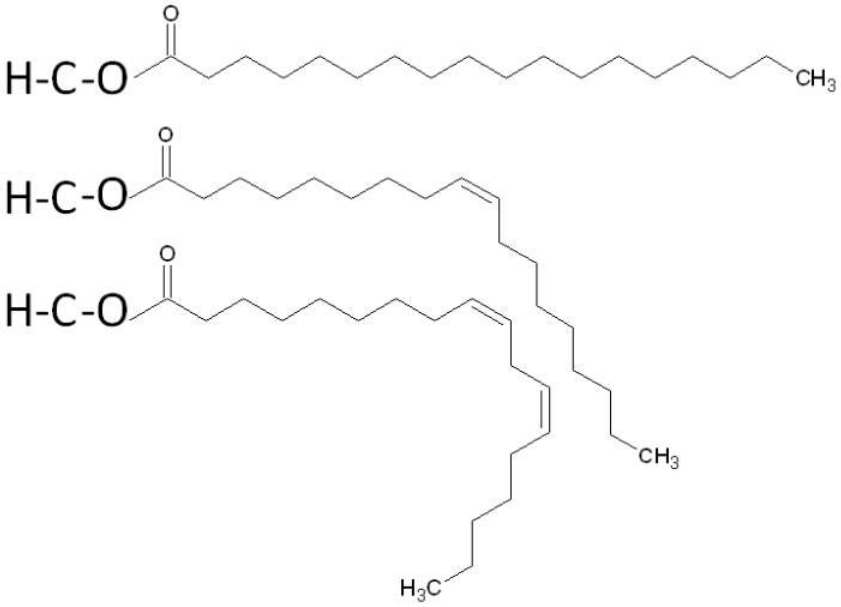


Figure **2.3.23**: Structure of a mixed triglyceride

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.

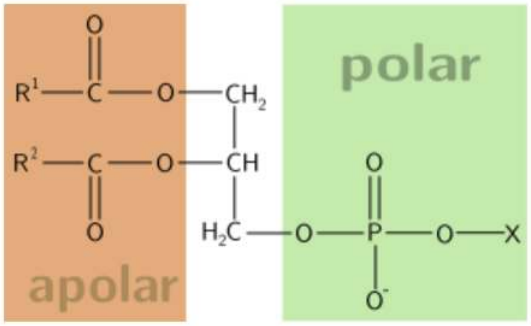


Figure **2.3.24**: Structure of a phospholipid, R represents the different fatty acids, X represents the nitrogen-containing compound off of the phosphate group[19]

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.

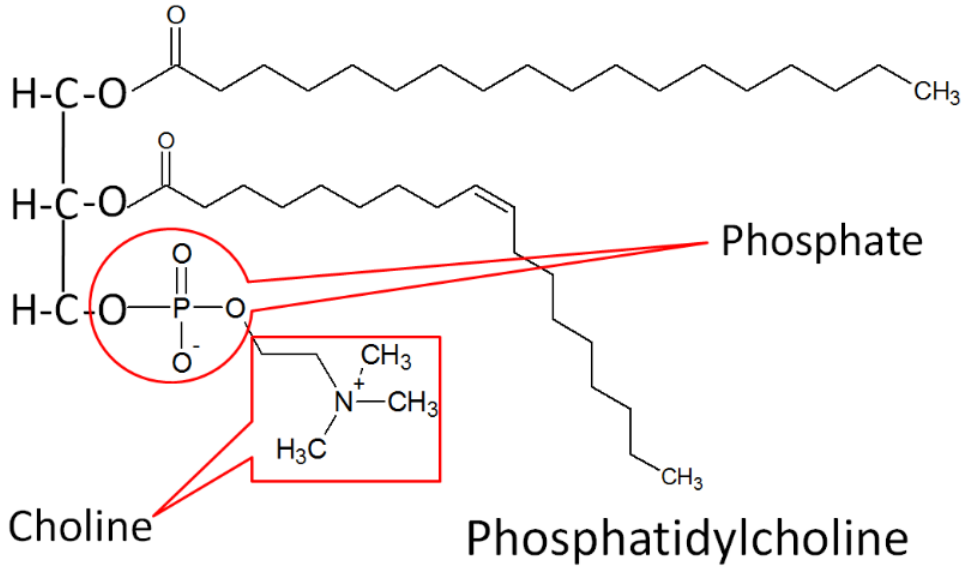


Figure 2.3.25: Structure of phosphatidylcholine (lecithin)

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.

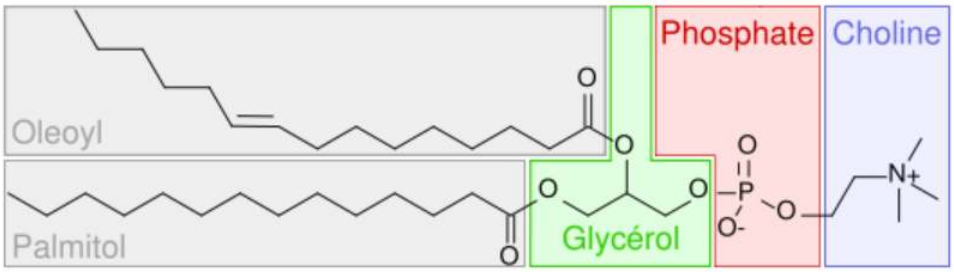


Figure 2.3.26: Structure of phosphatidylcholine (lecithin)20

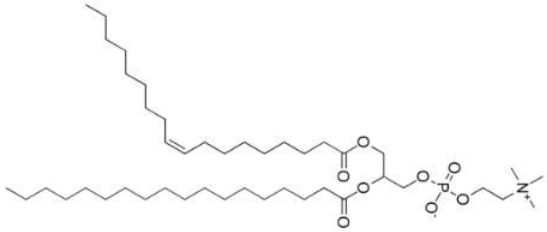


Figure 2.3.27: Structure of phosphatidylcholine (lecithin)21

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

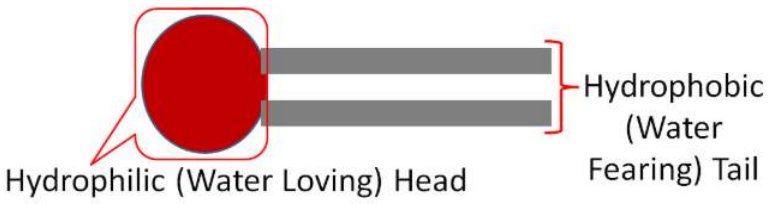


Figure 2.3.28: Schematic of a phospholipid

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.

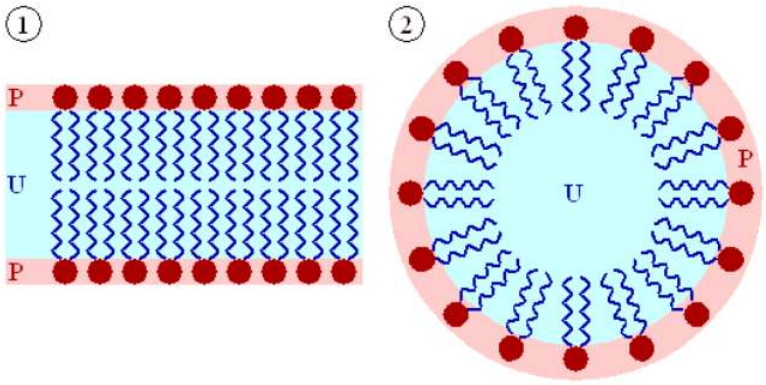


Figure **2.3.29**:, 1 - lipid bilayer, 2 - micelle22

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.

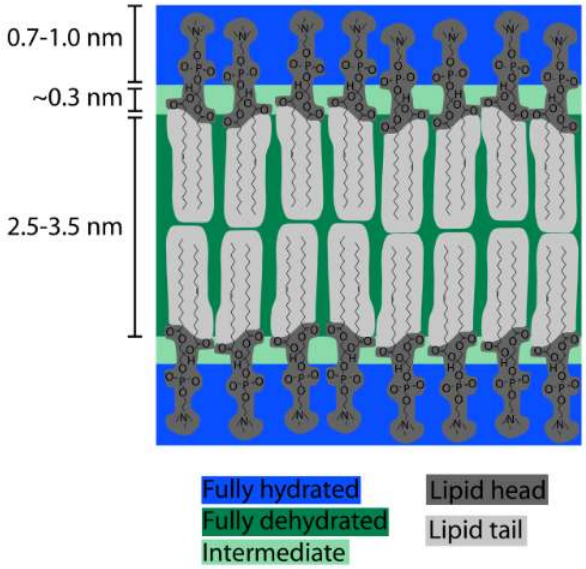


Figure **2.3.30**: Phospholipids in a lipid bilayer. The blue represents the watery environment on both sides of the membrane, while the dark green represents the hydrophobic environment in between the membranes23

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.

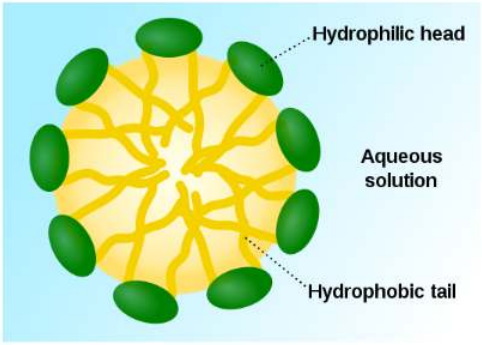


Figure **2.3.31**: Structure of a micelle24

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

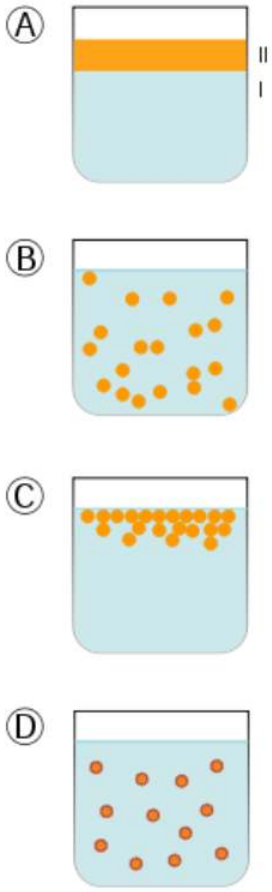


Figure **2.3.32**: How an emulsion can allow the dispersion of a hydrophobic substance (II) into a hydrophilic environment (I) as shown in D25

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).

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.

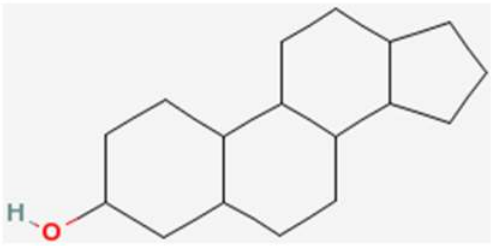


Figure **2.3.33**: Generic structure of a sterol

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

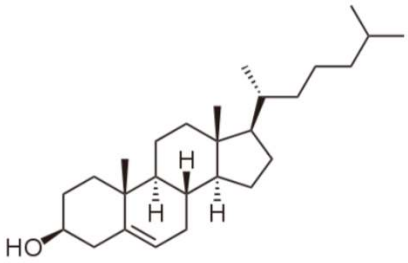


Figure **2.3.34**: The carbon ring structure of cholesterol[27]

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.

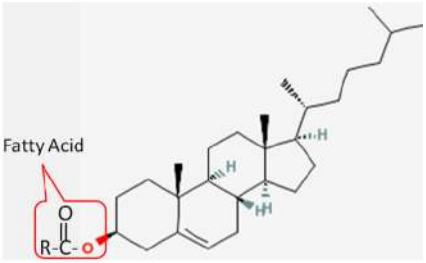
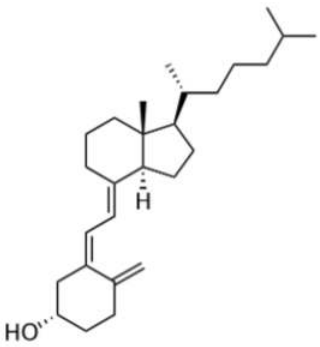


Figure **2.3.35**: Structure of a cholesterol ester

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.



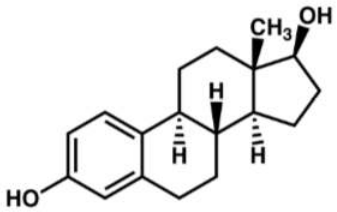


Figure **2.3.36**: Structures of vitamin D3 and estradiol (a form of estrogen)[28,29]

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.

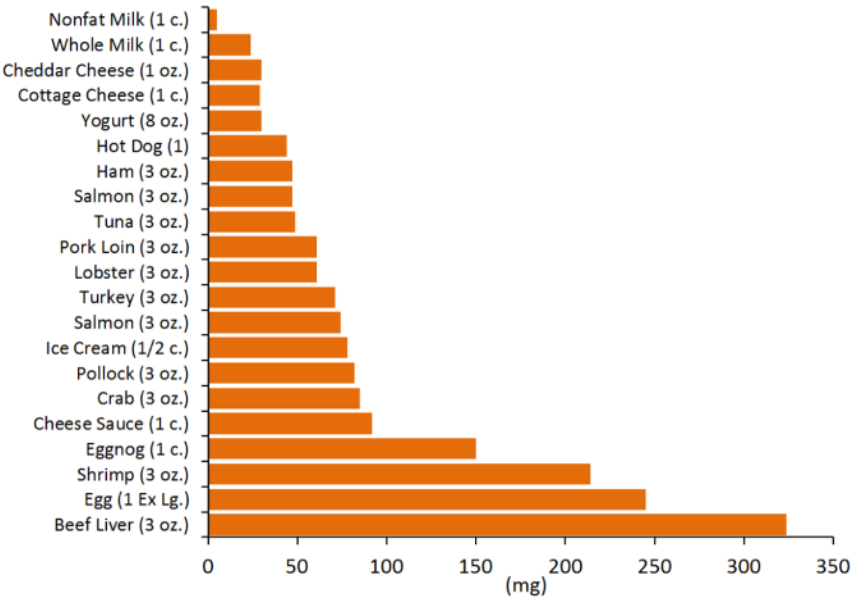


Figure **2.3.37**: The cholesterol content (mg) of foods30

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.

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12. en.Wikipedia.org/wiki/File:Leukotriene_B4.svg
13. en.Wikipedia.org/wiki/File:Pr...glandin_I2.png
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CHAPTER OVERVIEW

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.

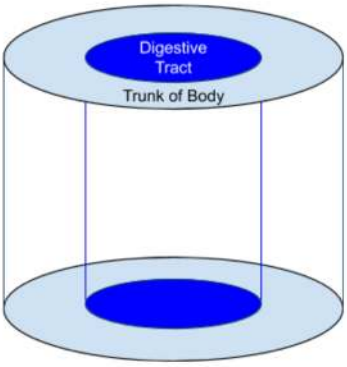


Figure **3.1.1**: The digestive tract, also known as the gastrointestinal tract, is a "tube within a tube"

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

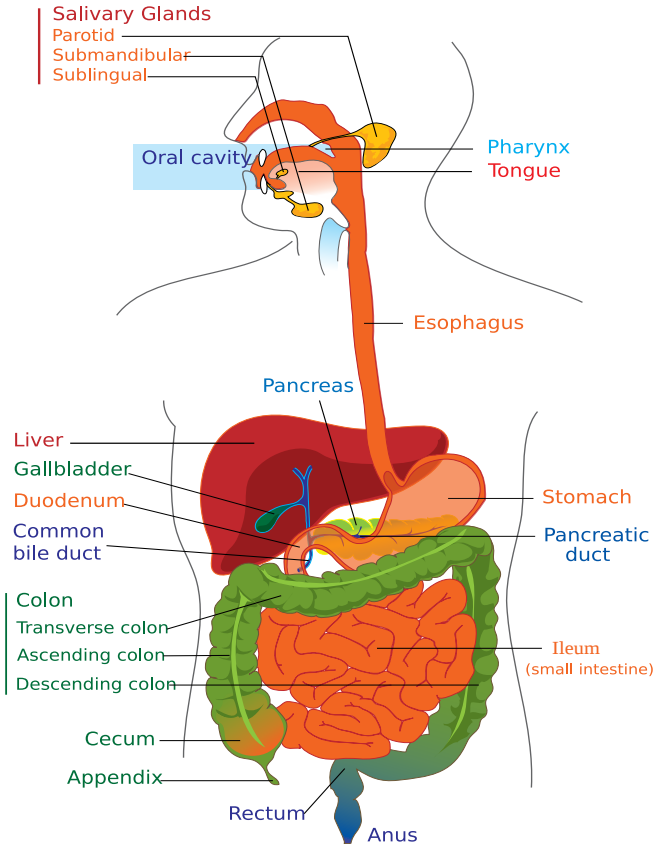


Figure **3.1.2**: The digestive system. (Public Domain; via WPClipart)

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**).

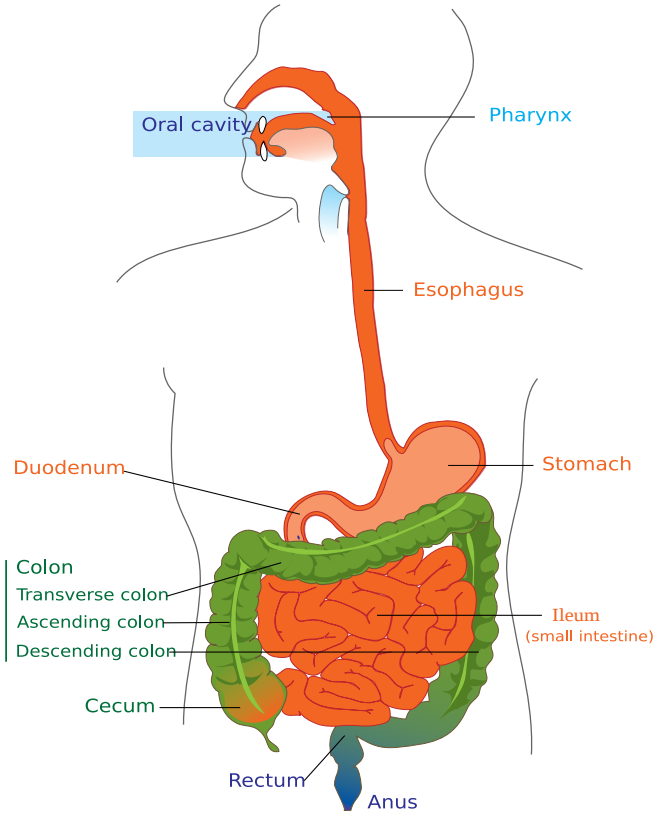


Figure **3.1.3**: The gastrointestinal or digestive tract. (Public Domain; via WPClipart)

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

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.

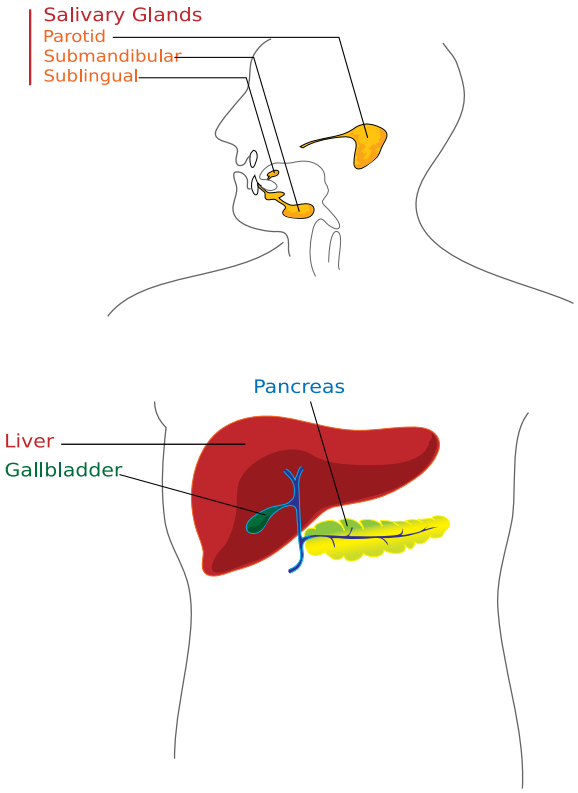


Figure **3.1.4**: Digestion accessory organs. (Public Domain; via WPClipart)

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.

Table **3.1.1**: Digestive enzymes

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

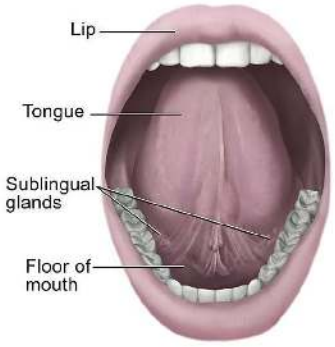


Figure **3.2.1**: The mouth (public Domain; Alan Hoofring (NIH) via Wikipedia)

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.

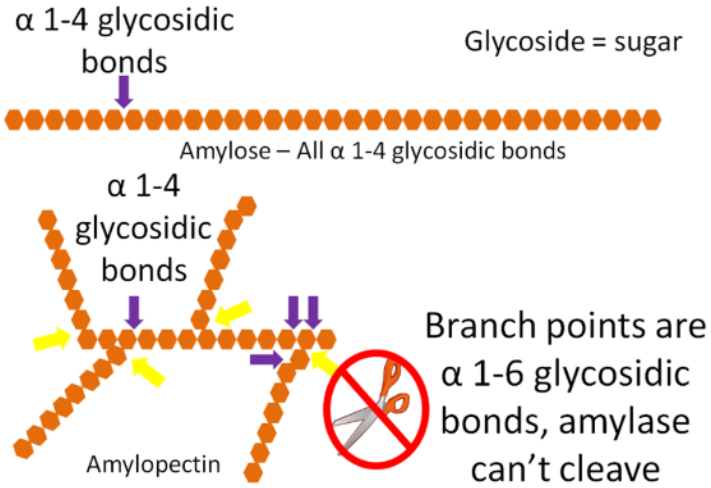


Figure **3.2.2**: Enzymatic action of salivary amylase. Purple arrows point to alpha 1-4 glycosidic bonds that can be cleaved. The yellow arrows point to the alpha 1-6 glycosidic bonds that cannot be cleaved

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.

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.

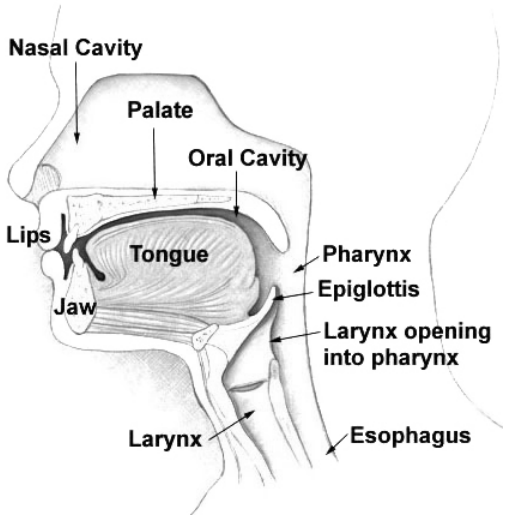


Figure **3.2.3**: Cross section of face. The epiglottis covers the larynx to prevent food and drink from entering the lungs[3]

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.

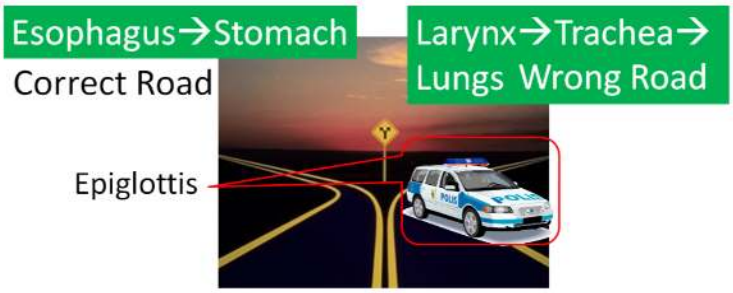


Figure **3.2.4**: Epiglottis is like a traffic cop guiding food down the correct digestion road.

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.



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

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.

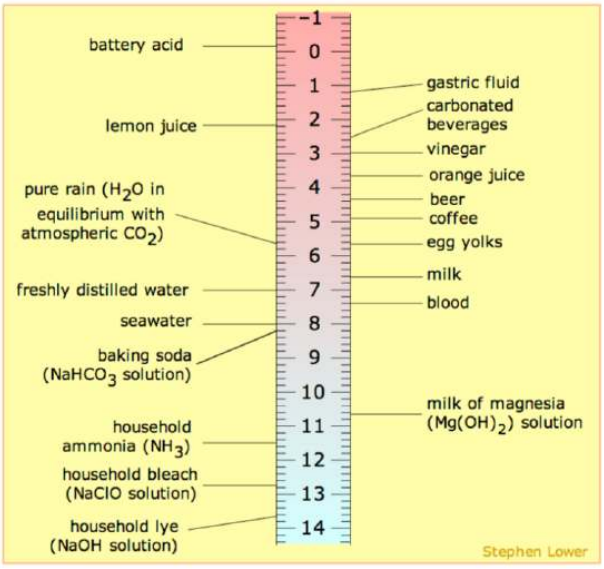


Figure **3.2.5**: pH of some common items4

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.



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



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

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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.

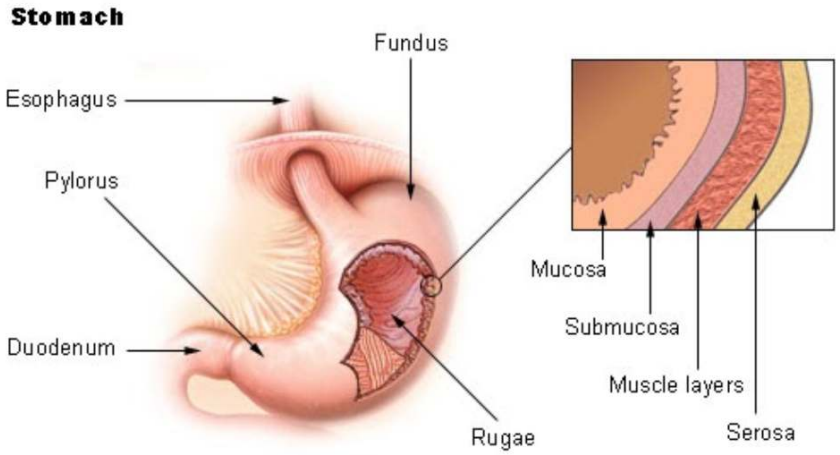


Figure **3.3.1**: The anatomy of the stomach1

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

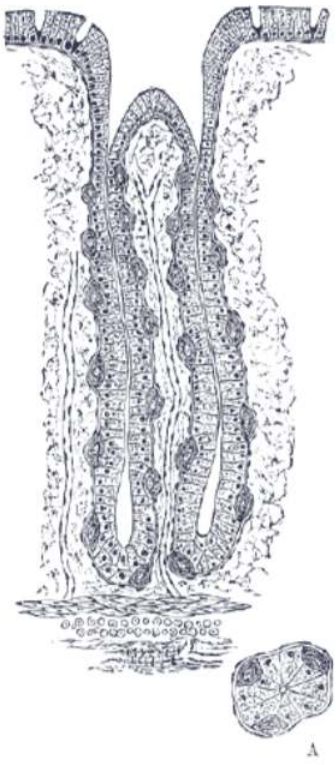


Figure **3.3.2**: Gastric pits2

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

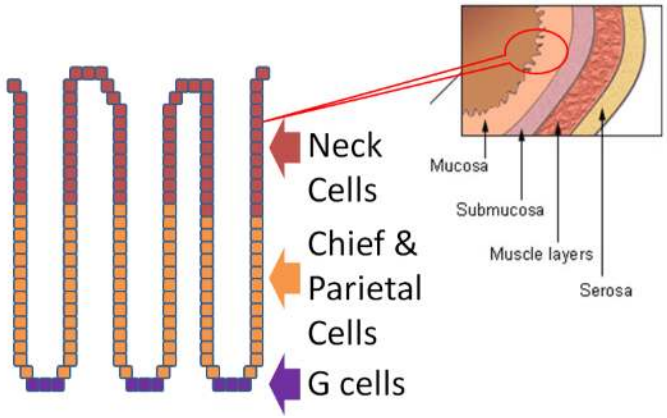


Figure **3.3.3**: Blowup of mucosa to show the structure of gastric pits1

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



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.

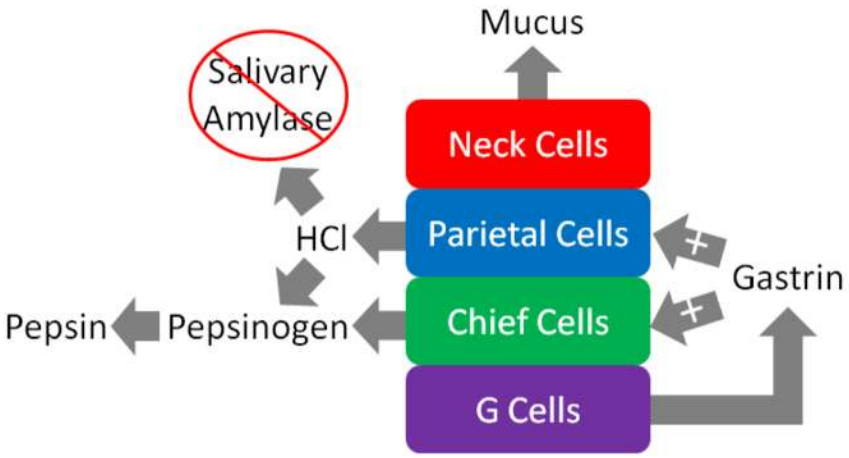


Figure **3.3.4**: The action of gastric secretions in the stomach

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.

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 below4. It is responsible for up to 20% of triglyceride digestion3.

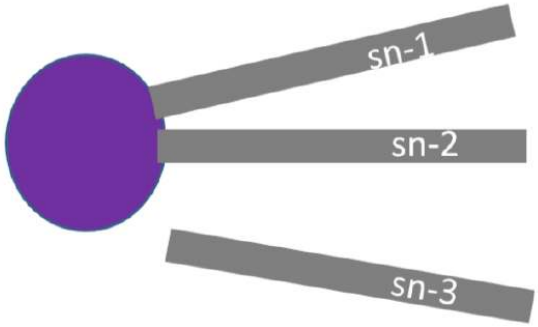


Figure **3.3.5**: Gastric Lipase action results in production of 1,2-diglyceride and a free fatty acid

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

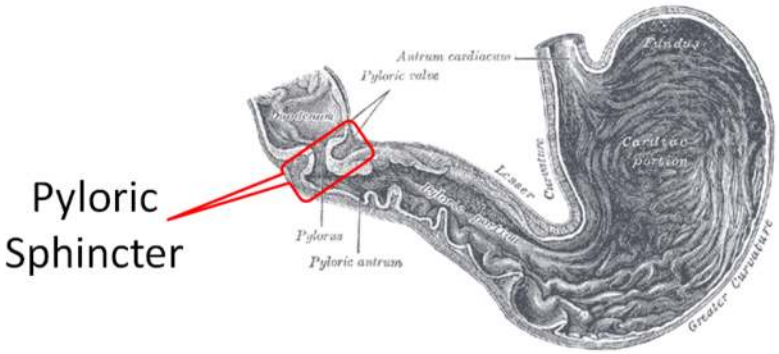


Figure **3.3.6**: Cross section of the stomach showing the pyloric sphincter5

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**
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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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.

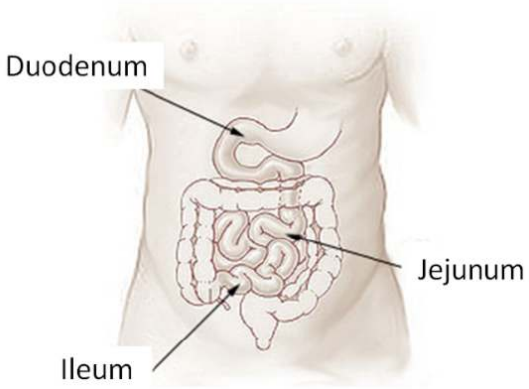


Figure **3.4.1**: Three sections of the small intestine[1]

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

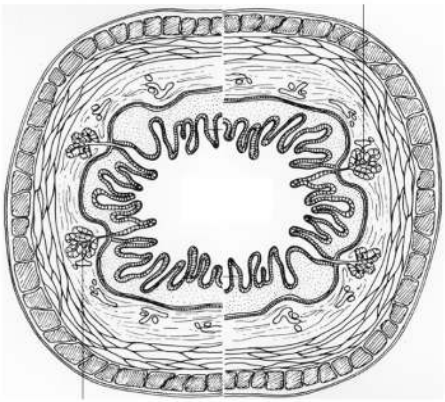


Figure **3.4.2**: Cross section of the small intestine[2]

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.

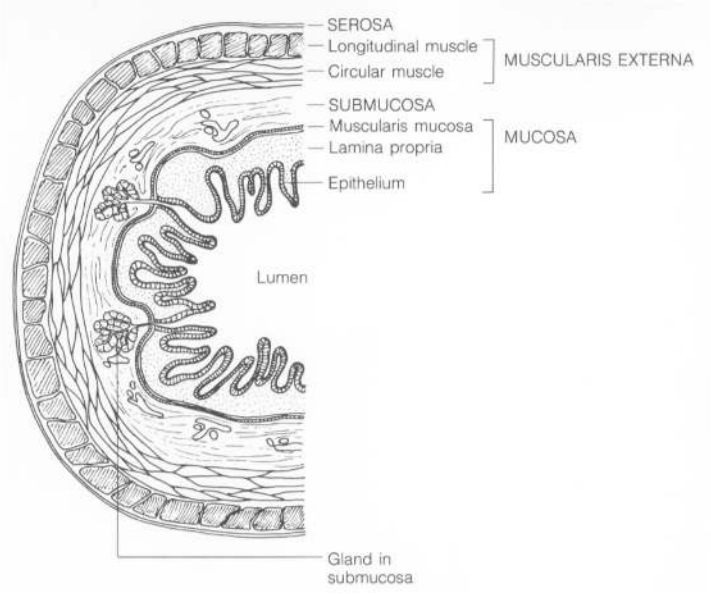


Figure **3.4.3**: Cross section of small intestine with the structures labeled2

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.

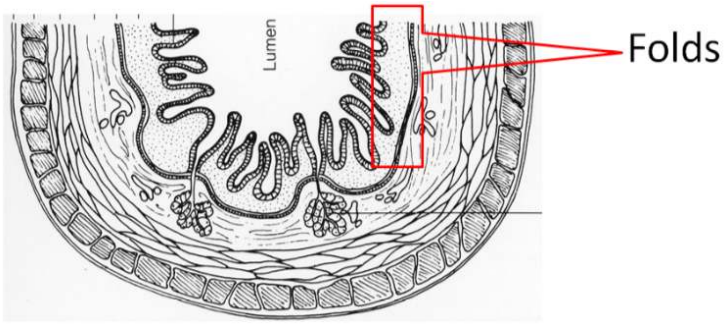


Figure **3.4.4**: Folds in the small intestine2

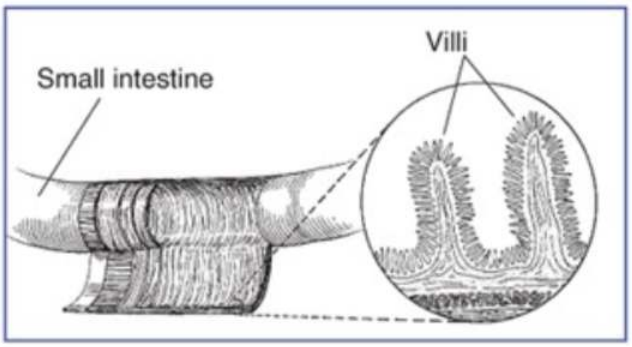


Figure **3.4.5**: Villi in the small intestine3

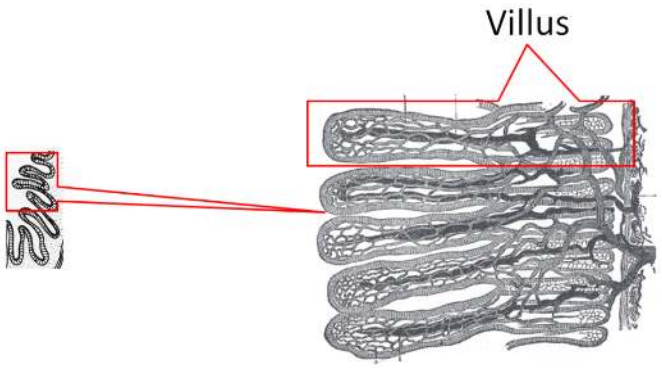


Figure **3.4.6**: Villi line the surface of the small intestine2,4

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.

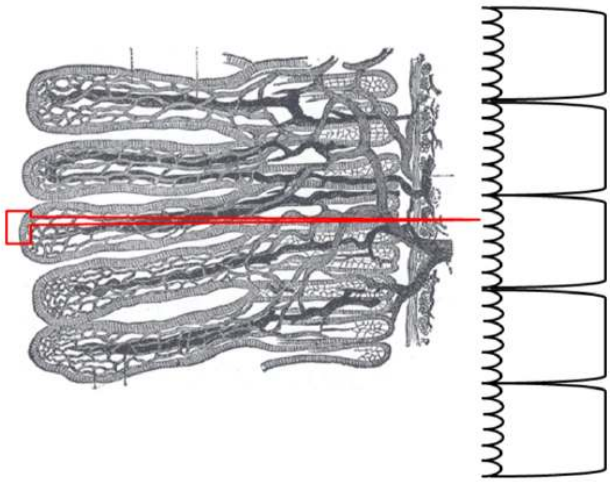


Figure **3.4.7**: Enterocytes line villi4

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.

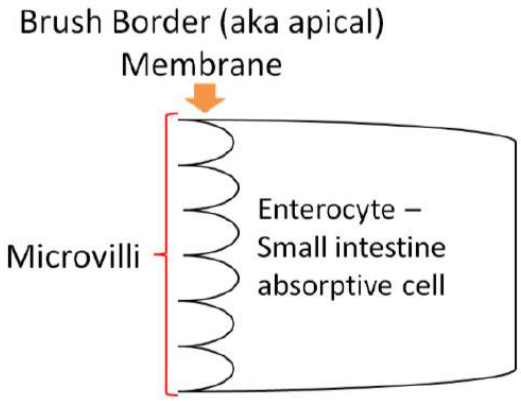


Figure **3.4.8**: Enterocyte, or small intestinal absorptive cell is lined with microvilli. This lined surface is referred to as the brush border membrane.

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.

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.

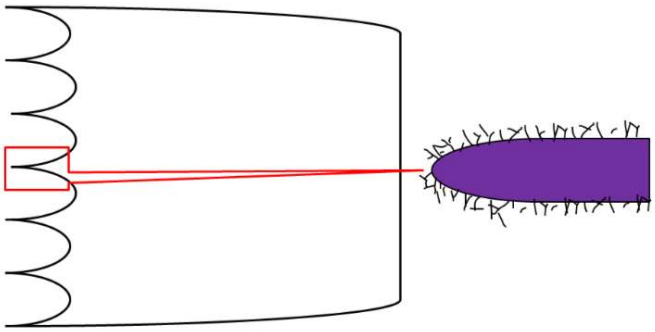


Figure 3.4.9: Glycocalyx lines the microvilli

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

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.

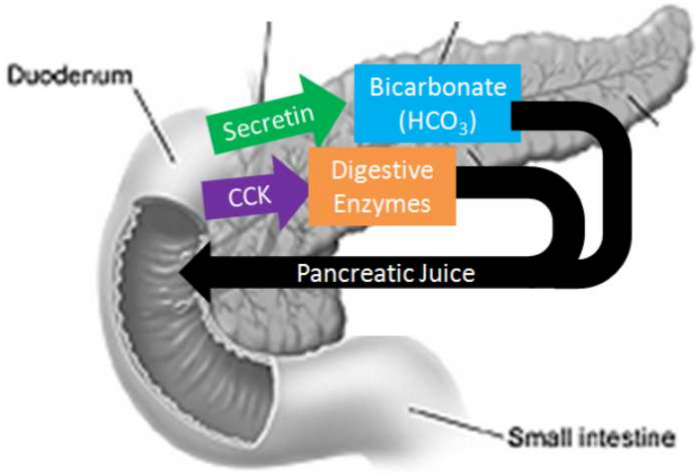


Figure 3.4.10: The hormones secretin and CCK stimulate the pancreas to secrete pancreatic juice[6]

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.



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.

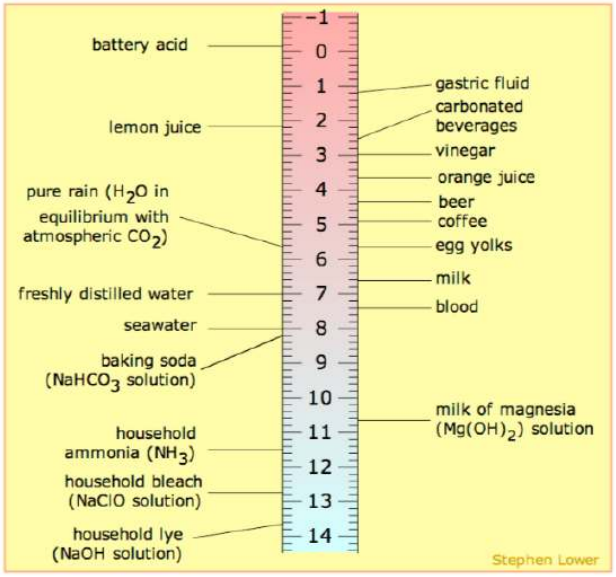


Figure 3.4.11: pH of some common items[7]

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

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.

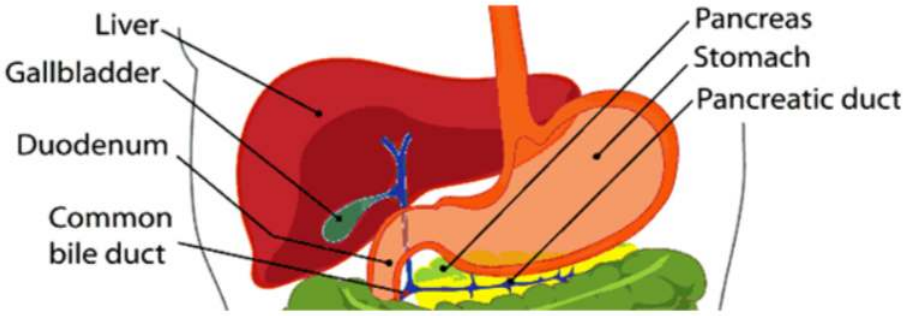


Figure **3.4.12**: Location of digestion accessory organs relative to the stomach[8]

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.

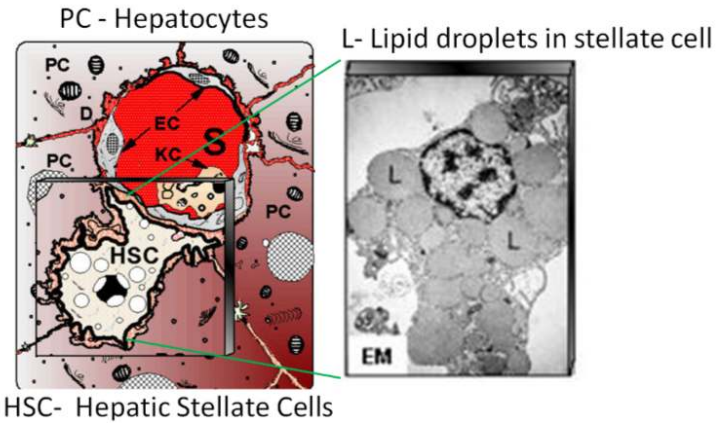


Figure **3.4.13**: Hepatocytes (PC) and hepatic stellate cells (HSC) along with an electron microscope image showing the lipid droplets within a stellate cell[9]

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.

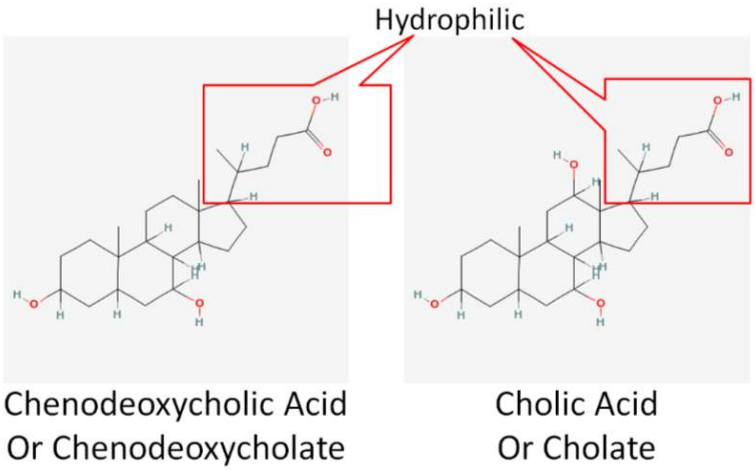


Figure **3.4.14**: Structures of the 2 primary bile acids

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.

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.

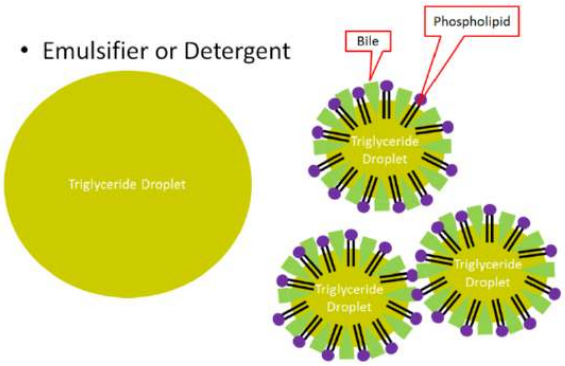


Figure **3.4.16**: Bile acids and phospholipids facilitate the production of smaller triglyceride droplets.

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



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.

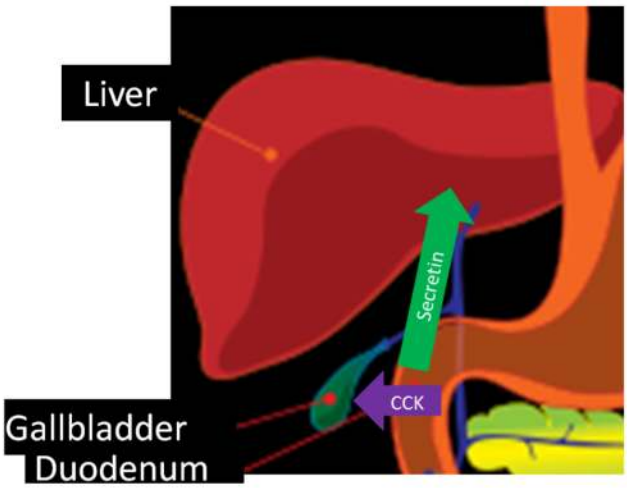


Figure **3.4.17**: Secretion stimulates bile flow from the liver; CCK stimulates the gallbladder to contract[8]

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].

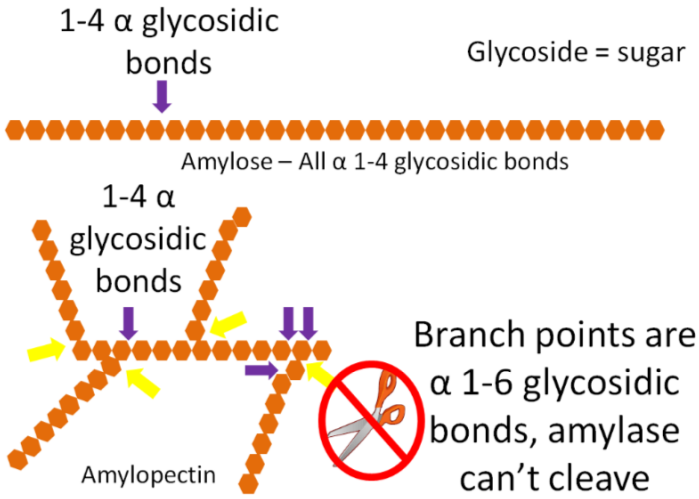


Figure **3.4.18**: The function of pancreatic alpha-amylase



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 enterocyte[10].

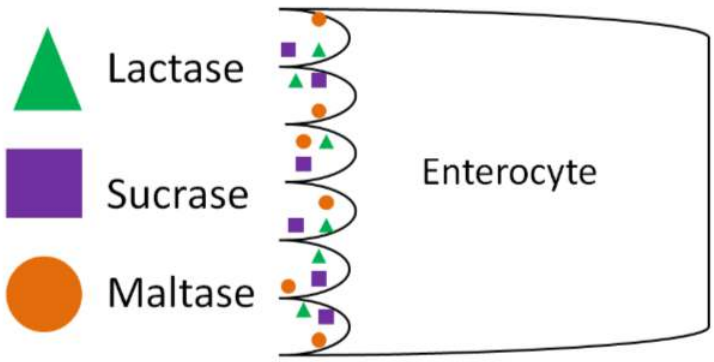


Figure **3.4.20**: Disaccharidases on the outside of the enterocyte.

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.

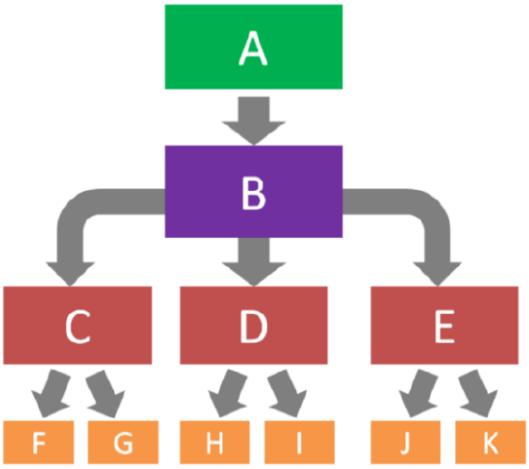


Figure **3.4.21**: An example of a cascade, with one event leading to many more events

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.

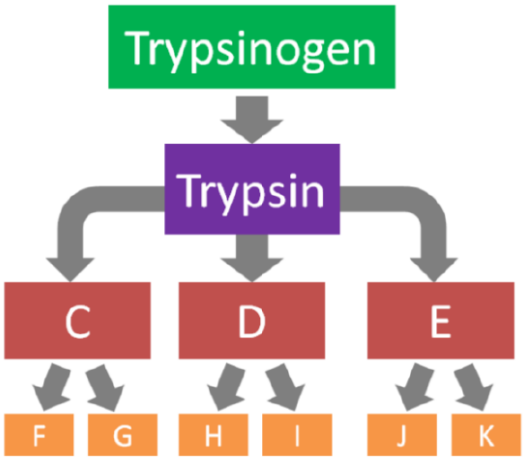


Figure **3.4.22**: Protease/colipase activation cascade

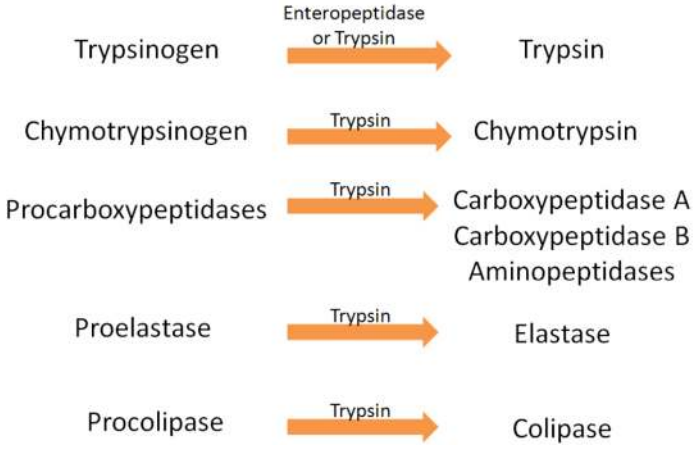


Figure 3.4.23: The protease/colipase activation cascade

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

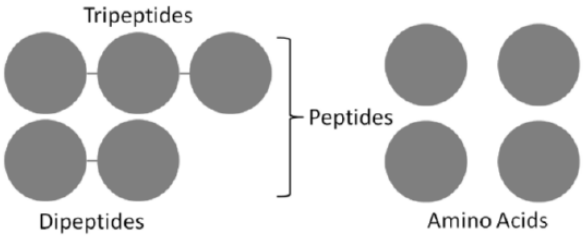


Figure 3.4.24: Products of pancreatic proteases

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 acids10.

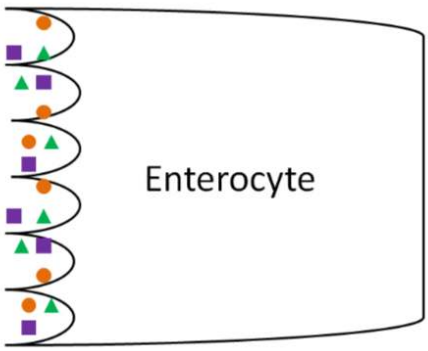


Figure 3.4.25: Peptidases are produced by the brush border to cleave some peptides into amino acids

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.

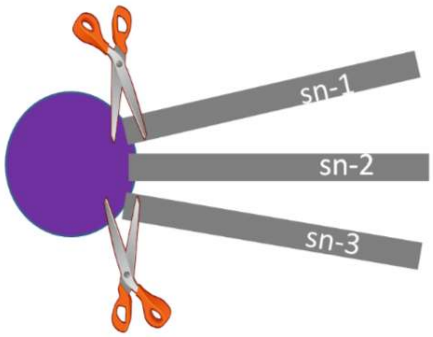


Figure **3.4.26**: Pancreatic lipase cleaves the sn-1 and sn-3 fatty acids of triglycerides

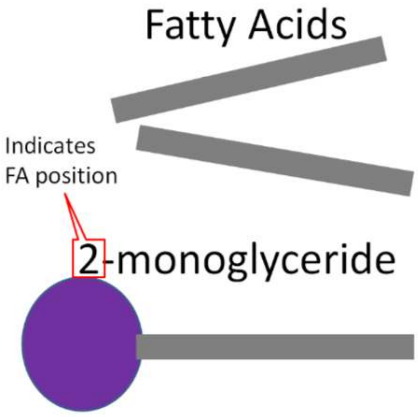


Figure **3.4.27**: The products of pancreatic lipase are a 2-monoglyceride and two free fatty acids

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

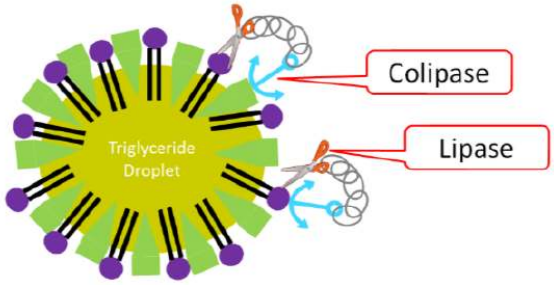


Figure **3.4.28**: Colipase helps anchor lipase to the triglyceride droplet

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

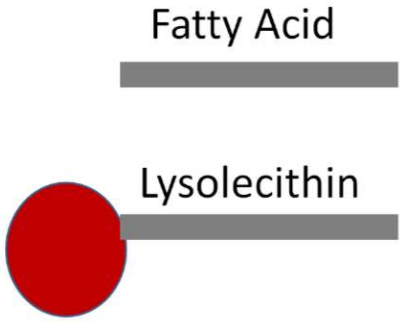


Figure **3.4.30**: Products of phospholipase A_2 cleavage

Cholesterol Esters

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

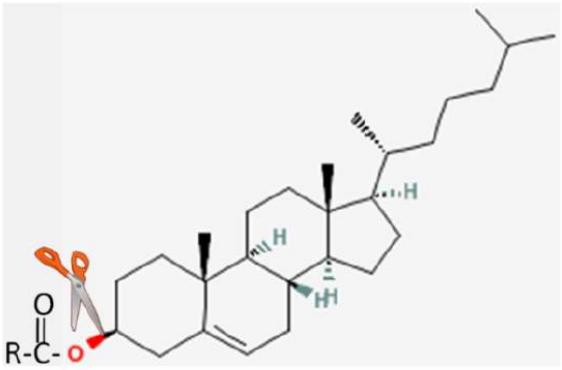


Figure **3.4.31**: Cholesterol esterase cleaves fatty acids off of cholesterol

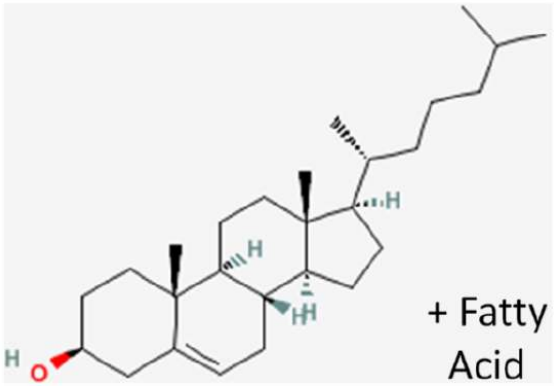


Figure **3.4.32**: Products of cholesterol esterase

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 below10.

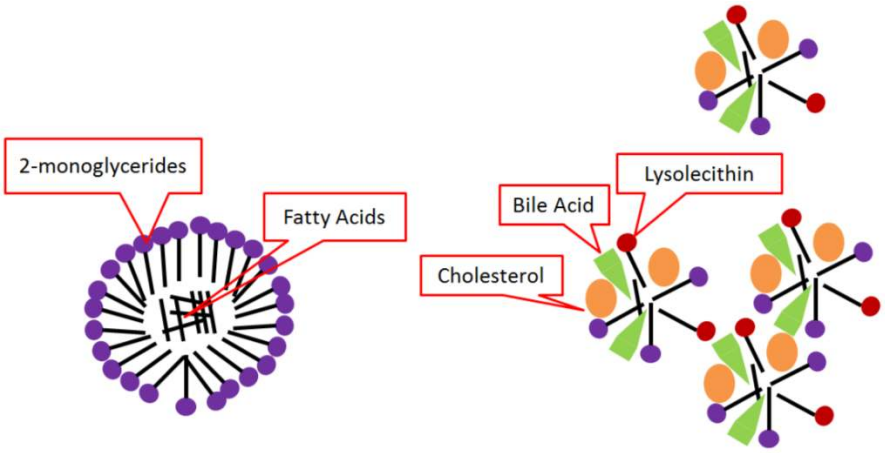


Figure **3.4.33**: Normal (left) and mixed (right) micelles

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

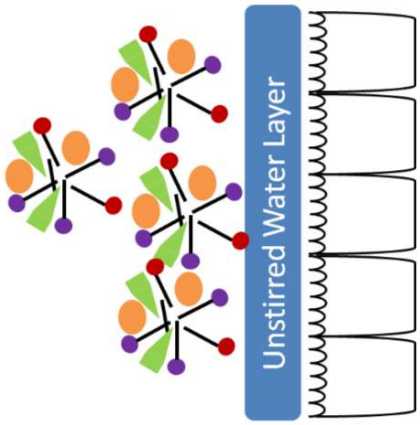


Figure **3.4.34**: Mixed micelles can cross the unstirred water layer for absorption into the enterocytes

References

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2. Author unknown, NCI, http://visualsonline.cancer.gov/deta...m?imageid=1781
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3.5: Macronutrient Digestion Review

The following figures review the digestion of the different macronutrients.

Carbohydrate Digestion

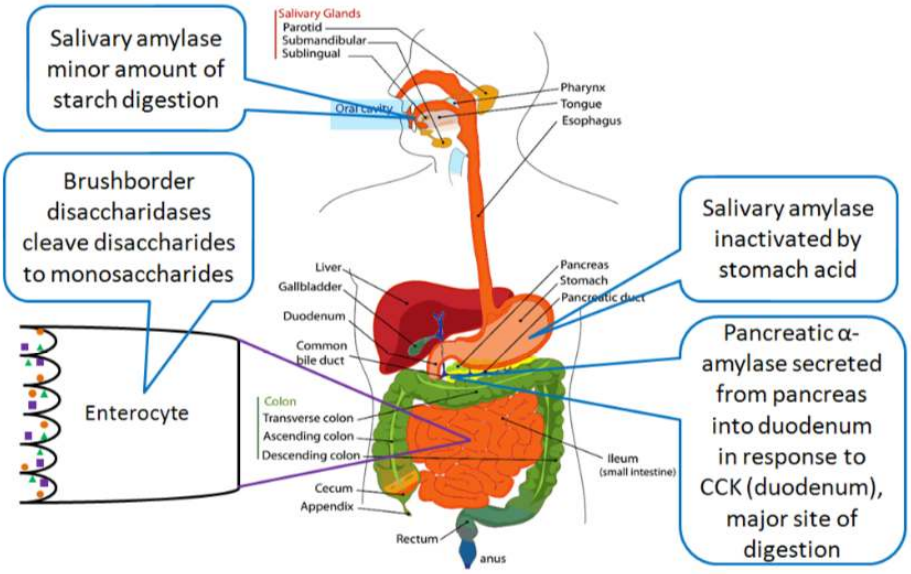


Figure **3.5.1**: Review of carbohydrate digestion[1]

Protein Digestion

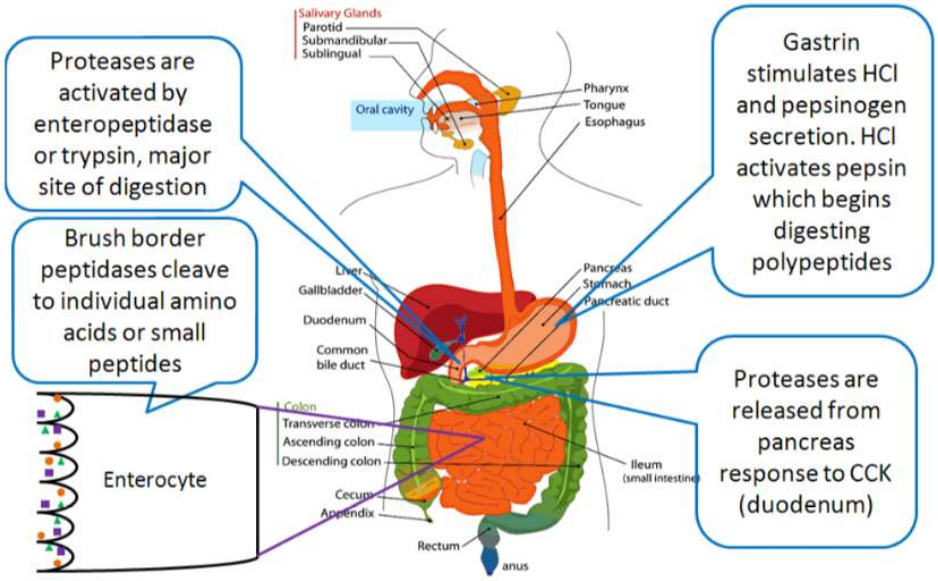


Figure **3.5.2**: Review of protein digestion[1]

Triglyceride Digestion

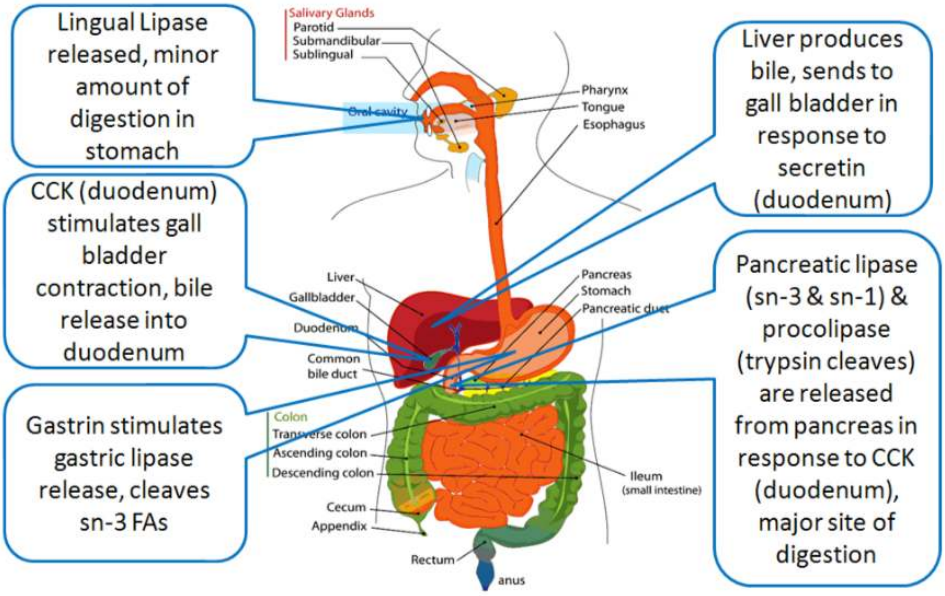


Figure 3.5.3: Review of triglyceride digestion[1]

Cholesterol Ester and Phospholipid Digestion

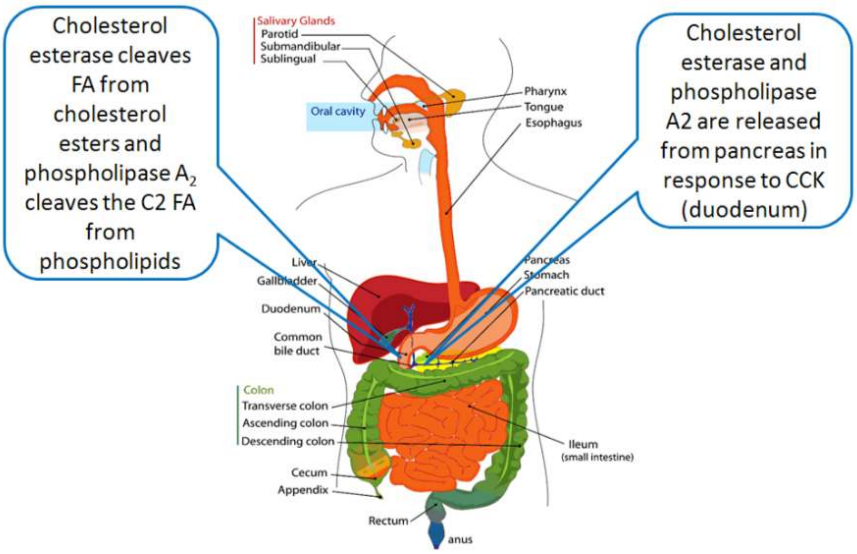


Figure 3.5.4: Review of cholesterol ester and phospholipid digestion[1]

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

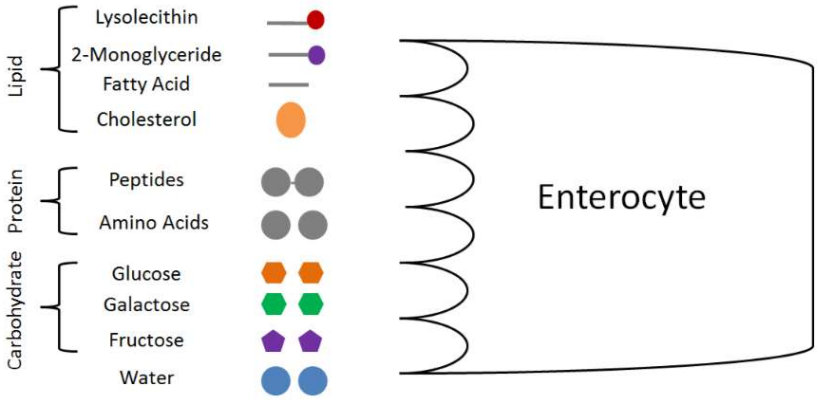


Figure **3.5.5**: Macronutrient digestion products ready for uptake into the enterocyte

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.

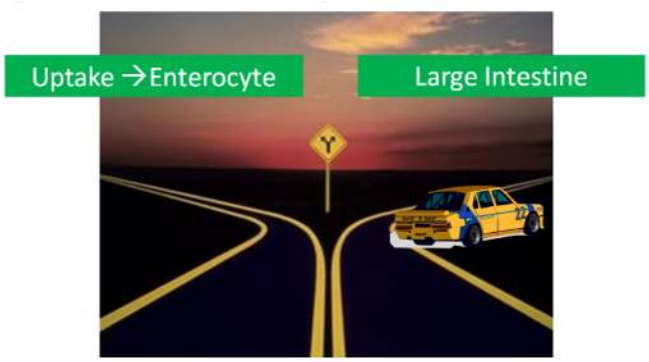


Figure **3.6.1**: The fork in the road between finishing digestion in the colon and absorption into the enterocyte

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.

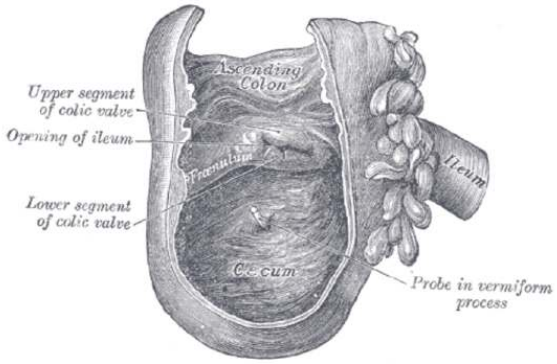


Figure **3.6.2**: The ileocecal valve[1]

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.

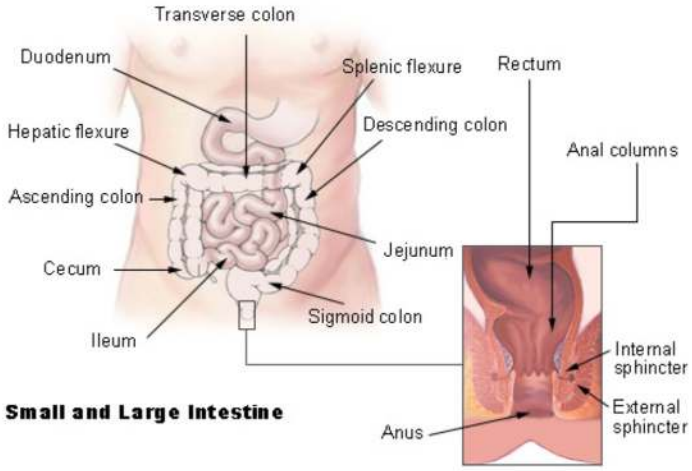


Figure **3.6.3**: Anatomy of the large intestine and rectum[2]

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.

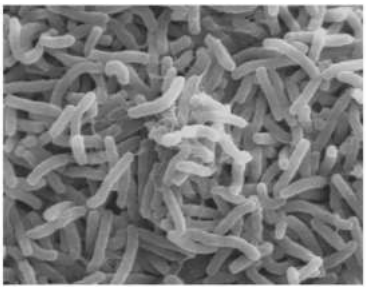


Figure **3.6.4**: Magnified image of bacteria[3]

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 body[4]. As can be seen in the figure below, the density of microorganisms increases as you move down the digestive tract.

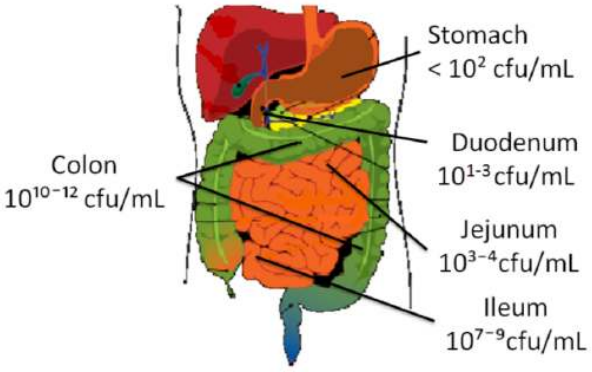


Figure **3.6.5**: Relative amount of bacteria in selected locations of the gastrointestinal tract. cfu/ml = colony forming unit, a measure of the number of live microorganisms in 1 mL of digestive sample[5,6]

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.

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.

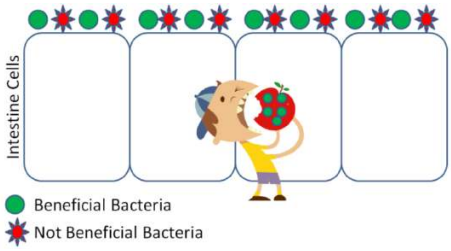


Figure **3.6.6**: Probiotics the consumption of the bacteria itself

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.

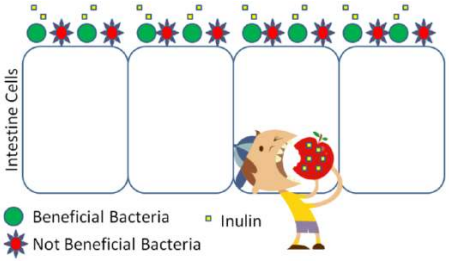


Figure **3.6.7**: Inulin, an indigestible food component that is a commonly used prebiotic

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

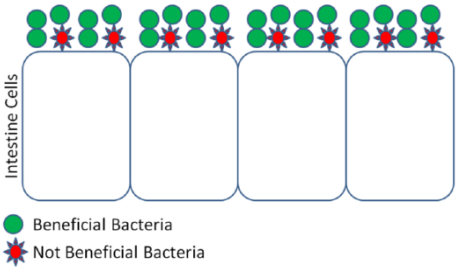


Figure **3.6.8**: An effective prebiotic or probiotic should result in an increase in the beneficial bacteria

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



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.

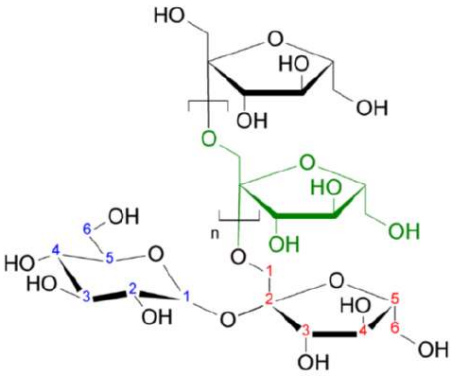


Figure **3.6.9**: Structure of inulin[7]

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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1. commons.wikimedia.org/wiki/File:Gray1075.png
2. en.Wikipedia.org/wiki/Image:Illu_intestine.jpg
3. commons.wikimedia.org/wiki/Im...cteria_SEM.jpg
4. Guarner F, Malagelada J. (2003) Gut flora in health and disease. The Lancet 361(9356): 512.
5. DiBaise J, Zhang H, Crowell M, Krajmalnik-Brown R, Decker , et al. (2008) Gut microbiota and its possible relationship with obesity. Mayo Clin Proc 83(4): 460.
6. Adapted from: http://www.wpclipart.com/medical/ana..._page.png.html

7. en.Wikipedia.org/wiki/File:In...kturformel.png
8. Douglas L, Sanders M. (2008) Probiotics and prebiotics in dietetics practice. American Dietetic Association.Journal of the American Dietetic Association 108(3): 510.

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CHAPTER OVERVIEW

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**.

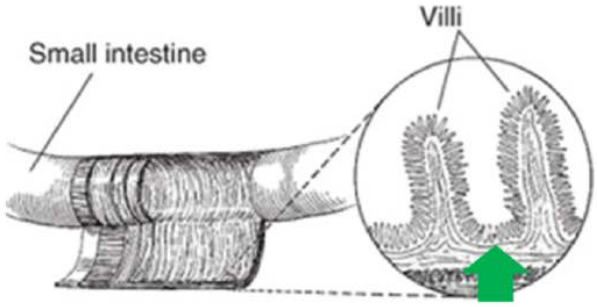


Figure **4.1.1**: A crypt of Lieberkuhn is the pit between the villi in the small intestine as pointed out by the green arrow[1]

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].

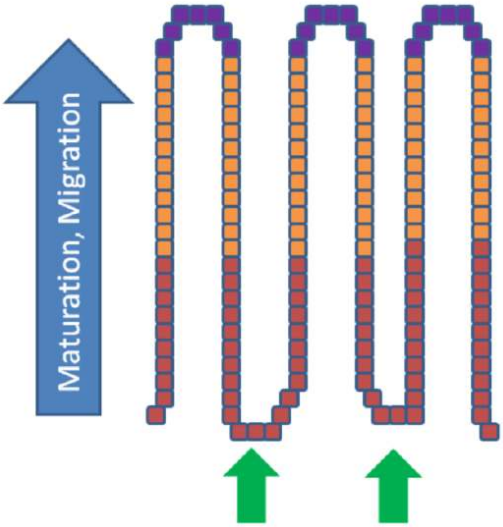


Figure **4.1.2**: Crypts are represented by green arrows, fully mature enterocytes are represented by the purple cells at the top of the villi

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**.

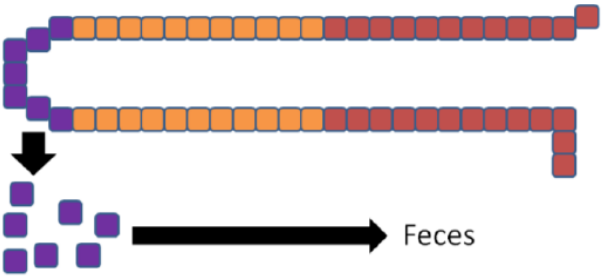


Figure **4.1.3**: Enterocytes sloughed off the villus. Unless these cells are digested and their components are taken up by other enterocytes on the villus, they will be excreted in feces

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.

References

1. digestive.niddk.nih.gov/ddiseases/pubs/celiac/
2. Stipanuk MH. (2006) Biochemical, physiological, & molecular aspects of human nutrition. St. Louis, MO: Saunders Elsevier.
3. Gropper SS, Smith JL, Groff JL. (2008) Advanced nutrition and human metabolism. Belmont, CA: Wadsworth Publishing.

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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.

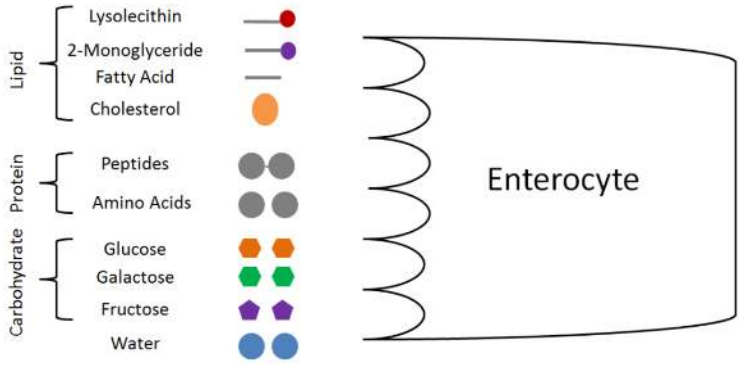


Figure 4.2.1: The macronutrient uptake lineup

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.

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.

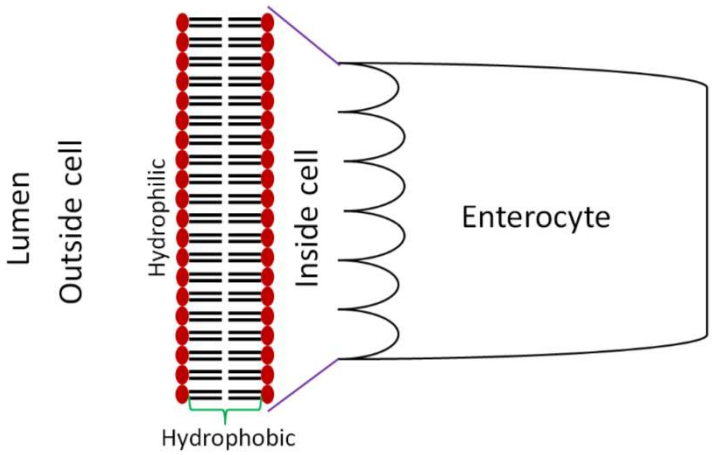


Figure 4.2.2: Plasma membrane of a cell

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.

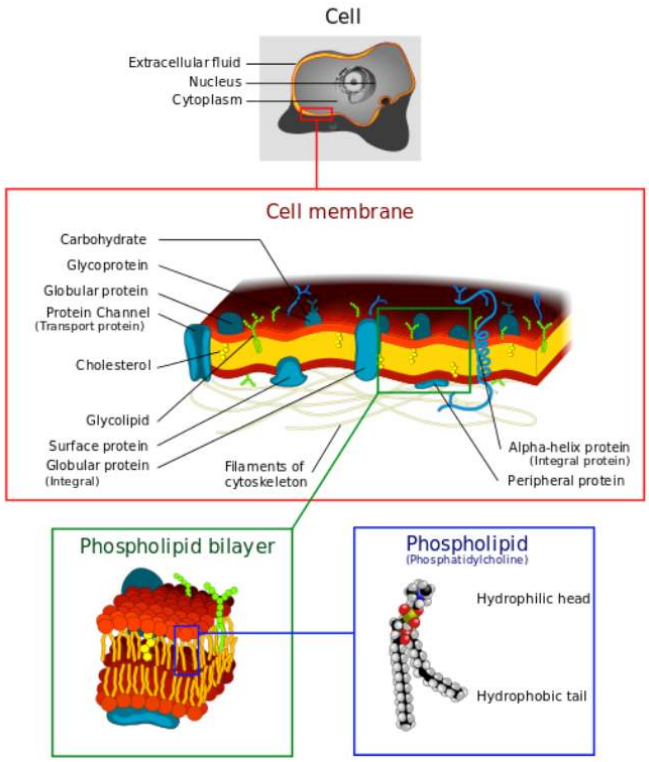


Figure 4.2.3: Cell membrane1



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



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

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.

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.

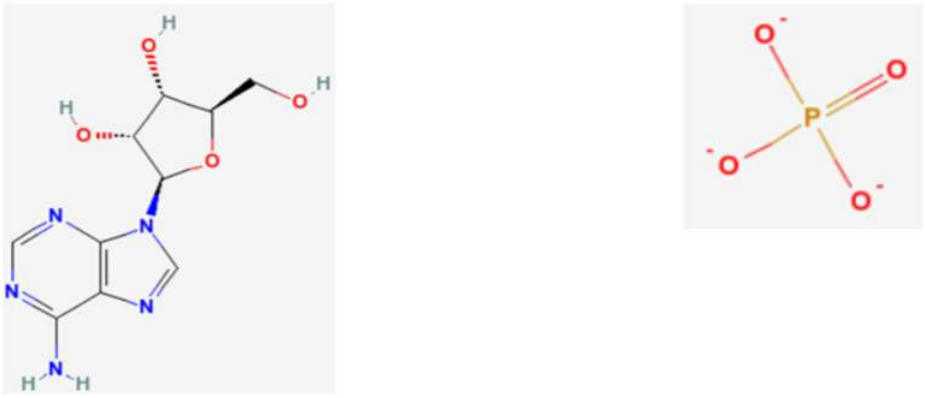


Figure **4.3.1**: Structures of adenosine (left) and phosphate (right)

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

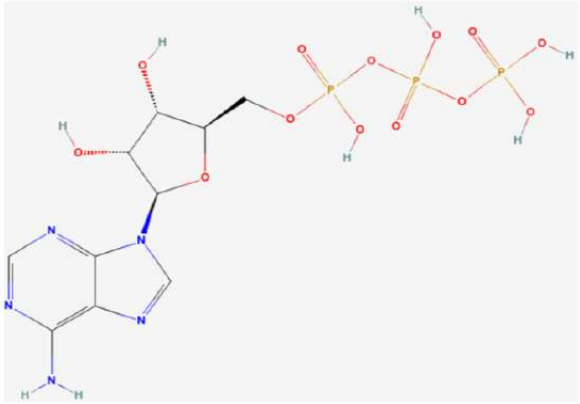


Figure **4.3.2**: Structure of adenosine triphosphate (ATP)

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.

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.

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.

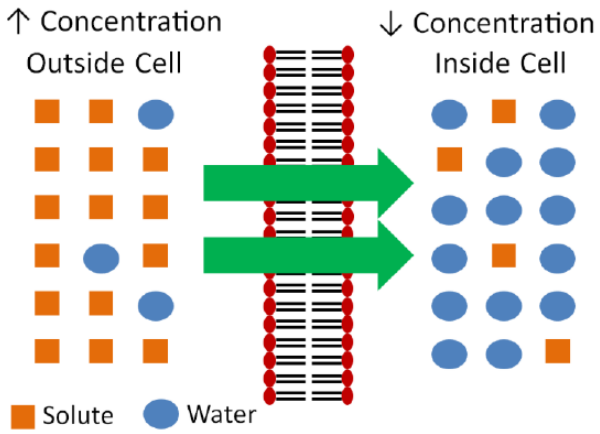


Figure **4.3.3**: Simple diffusion

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.

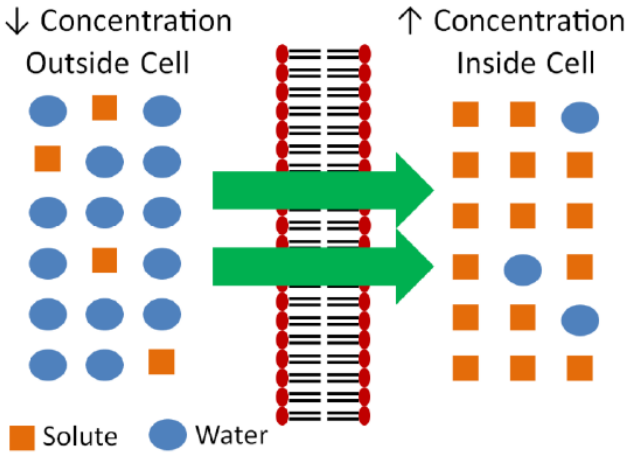


Figure **4.3.4**: Osmosis

The following videos do a nice job of illustrating osmosis.



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



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.

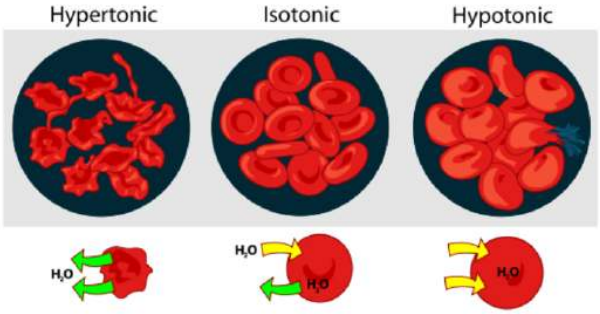


Figure **4.3.5**: Effect of salt solution concentration on red blood cells1

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.

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.

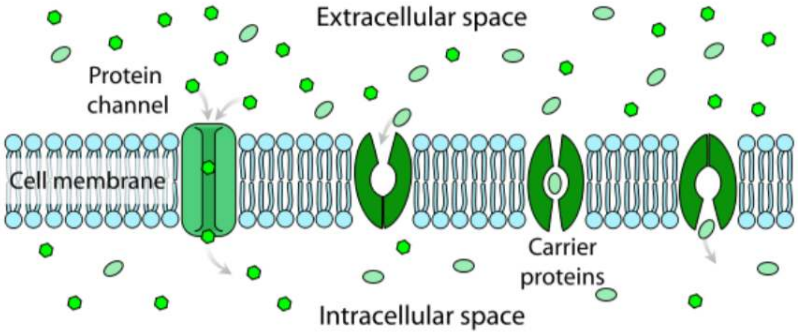


Figure **4.3.6**: Facilitated diffusion examples2



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

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.

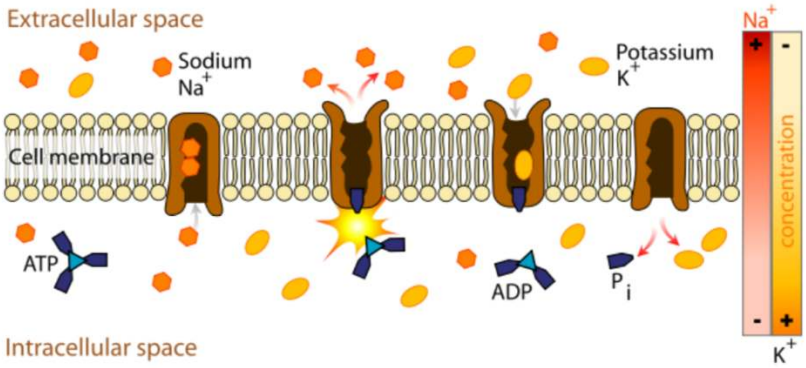


Figure 4.3.7: Sodium-potassium ATPase (aka sodium-potassium pump) an example of active carrier transport3



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

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.

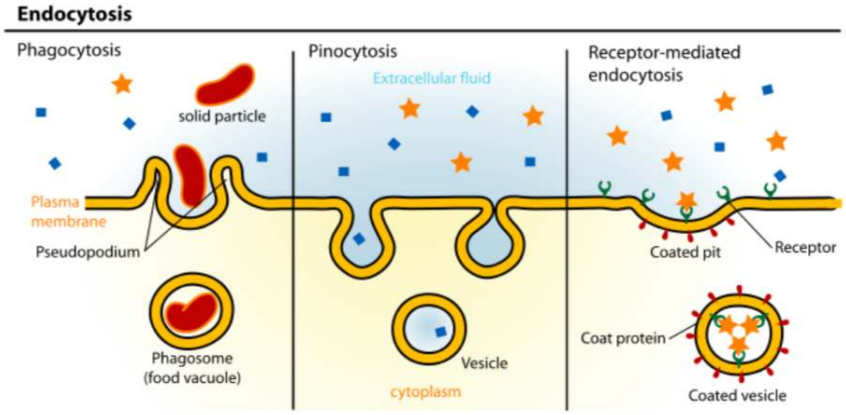


Figure 4.3.8: Different types of endocytosis4

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



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

References

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.

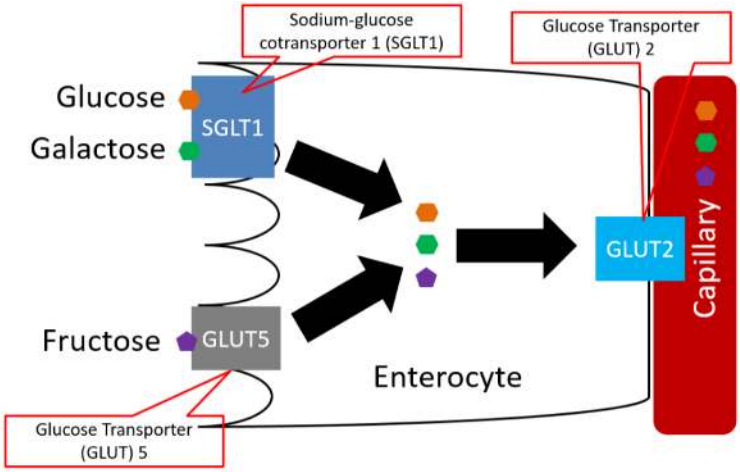


Figure **4.4.1**: Carbohydrate uptake and absorption

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.

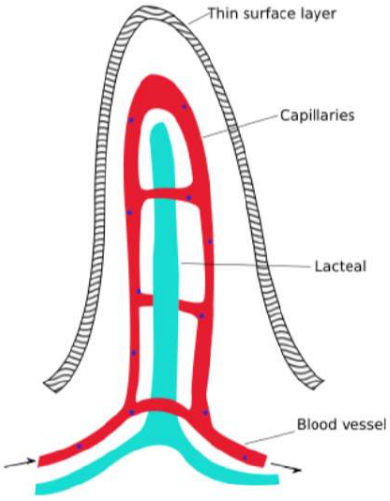


Figure **4.4.2**: Anatomy of a villus2

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



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.

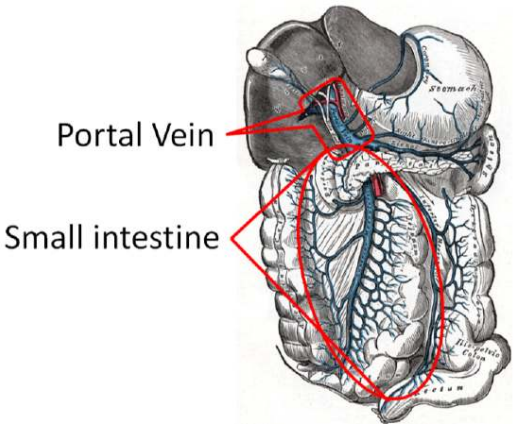


Figure **4.4.3**: The portal vein transports monosaccharides and amino acids to the liver3

The video below shows how hepatic portal circulation flows.

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.

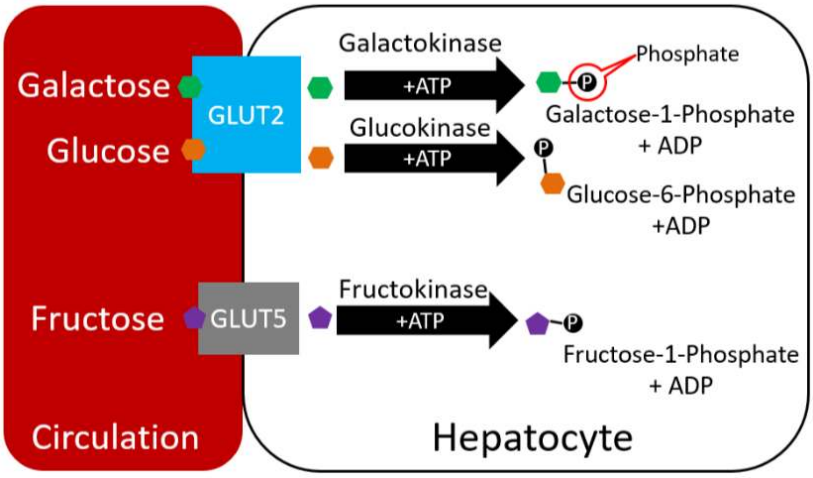


Figure **4.4.4**: Hepatic monosaccharide uptake

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.

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.

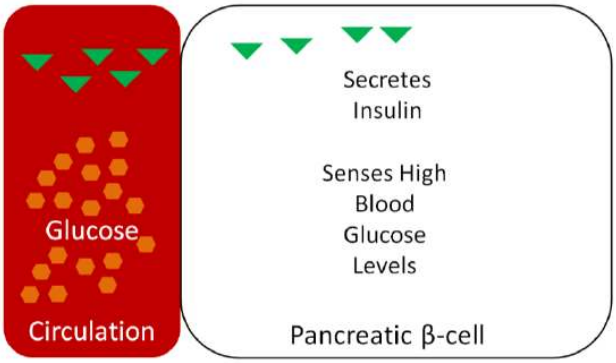


Figure **4.5.1**: Pancreatic beta-cells sense high blood glucose and secrete insulin

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.

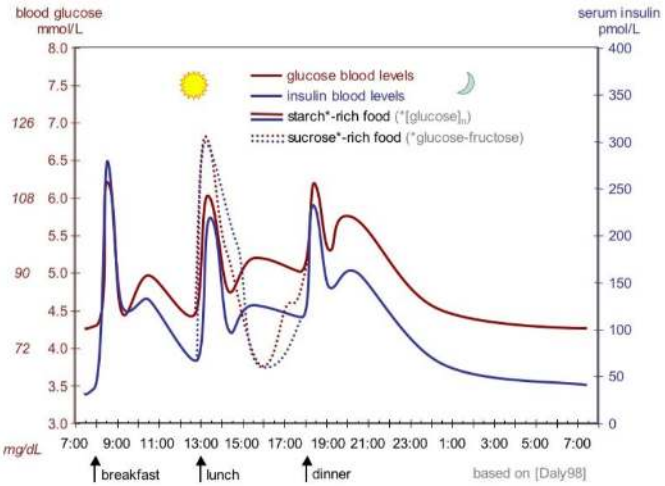


Figure **4.5.2**: Representative figure of blood glucose and insulin levels during a 24-hour period2

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.

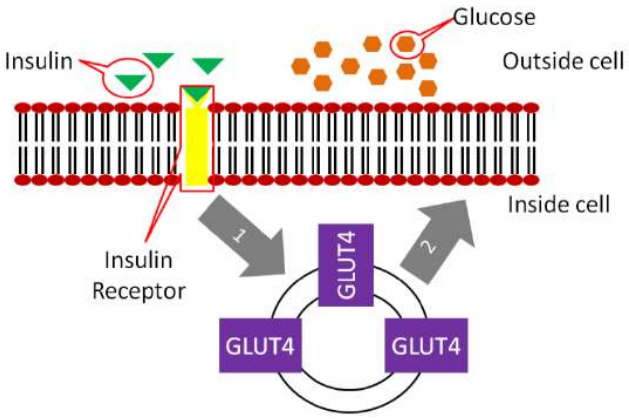


Figure **4.5.3**: Response of muscle and adipose cells to insulin; 1) binding of insulin to its receptor, 2) movement of GLUT4 vesicles to the cell surface.

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.

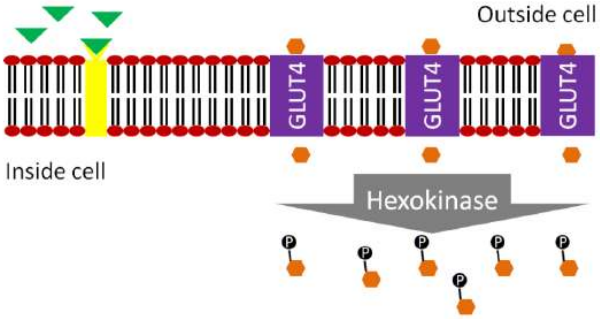


Figure **4.5.4**: Response of muscle and adipose cells to insulin part 2; hexokinase phosphorylates glucose to glucose-6-phosphate

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.

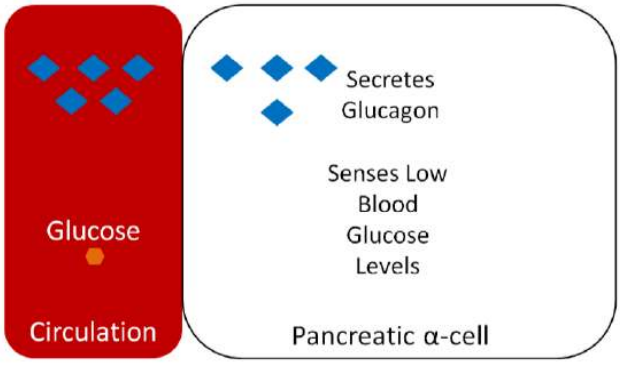


Figure **4.5.5**: Glucagon secretion from pancreatic alpha-cells in response to low blood glucose levels.

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.

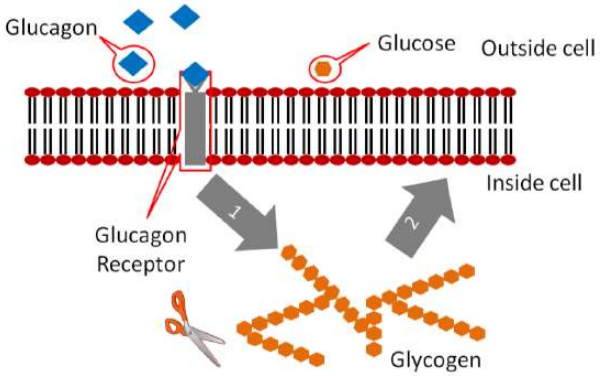


Figure 4.5.6: Glucagon binding to its receptor leads to the breakdown of glycogen to glucose.

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.

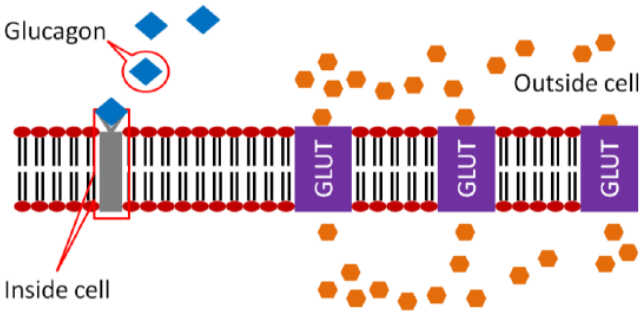


Figure 4.5.7: Glucagon leads to the release of glucose from the liver.

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.

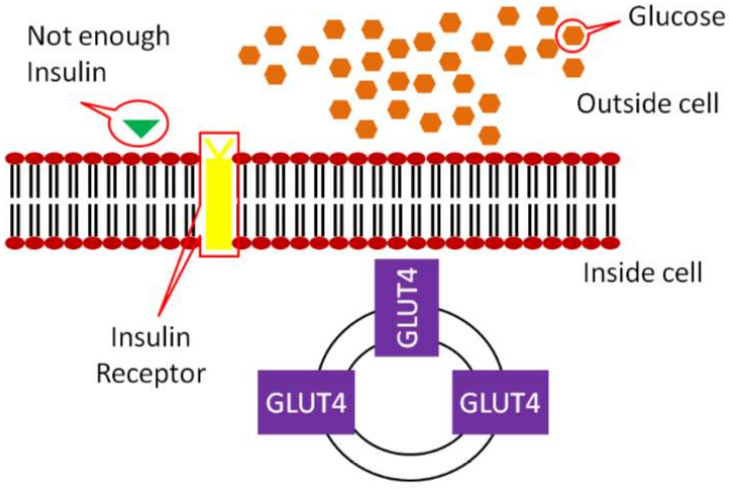


Figure 4.5.8: Type 1 diabetes

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.

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.

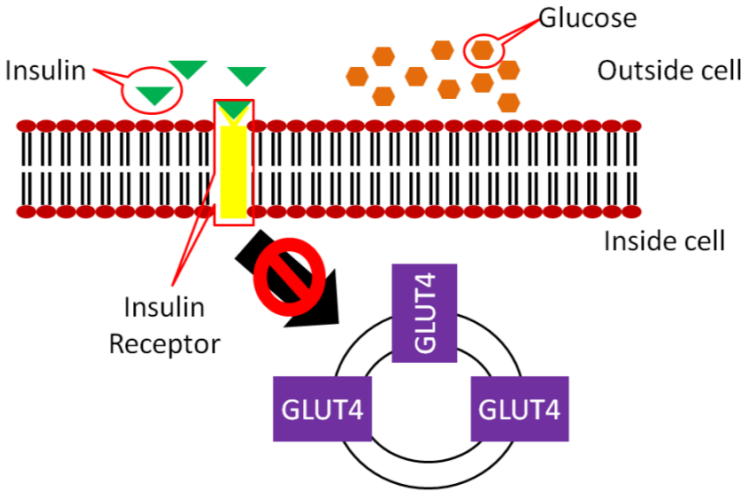


Figure **4.5.9**: Type 2 diabetes

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.



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

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.

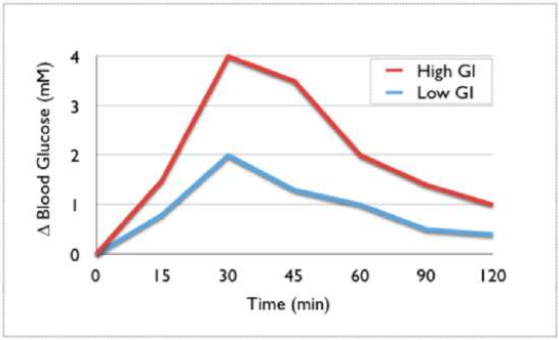


Figure 4.5.10: Blood glucose response to a high glycemic index (GI) food compared to a low glycemic index food4

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 classifications[5]

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 carbohydrate[6]. This is equal to approximately 2.5 cups of popcorn[7]. 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 watermelon[7].

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

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 low[8,9].



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

References

1. Webb , Akbar , Zhao , Steiner . (2001) Expression profiling of pancreatic beta-cells: Glucose regulation of secretory and metabolic pathway genes. Diabetes 50 Suppl 1: S135.
2. http://en.Wikipedia.org/wiki/File:Su...nsulin_day.jpg
3. diabetes.niddk.nih.gov/dm/pub...atistics/#what
4. upload.wikimedia.org/wikipedi...c/Glycemic.png
5. www.glycemicindex.com
6. Foster-Powell K, Holt SHA, Brand-Miller J. (2002) International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr 76(1): 5.
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).

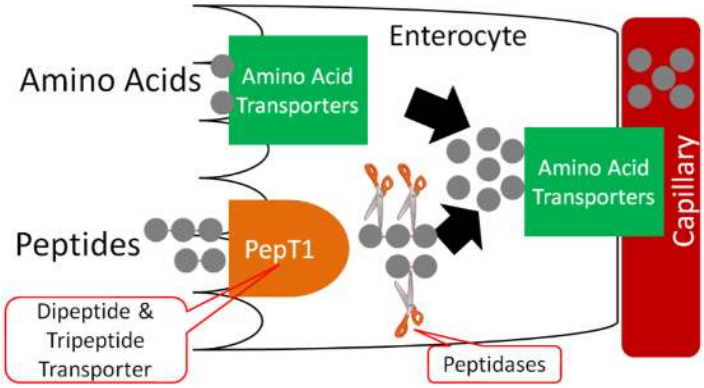


Figure **4.6.1**: Protein uptake and absorption

The capillary inside a villus is shown below.

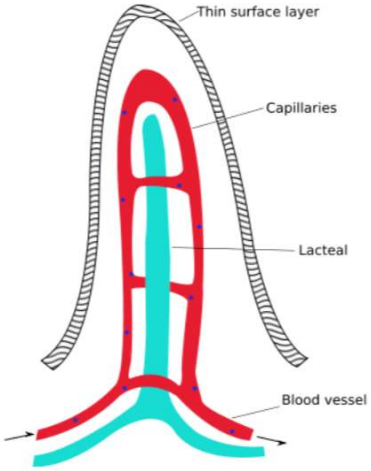


Figure **4.6.2**: Anatomy of a villus[1]

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

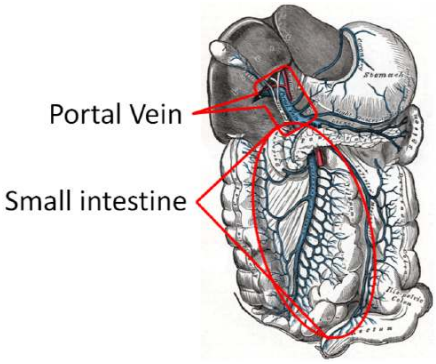


Figure **4.6.3**: The portal vein transports monosaccharides and amino acids to the liver[2]

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.

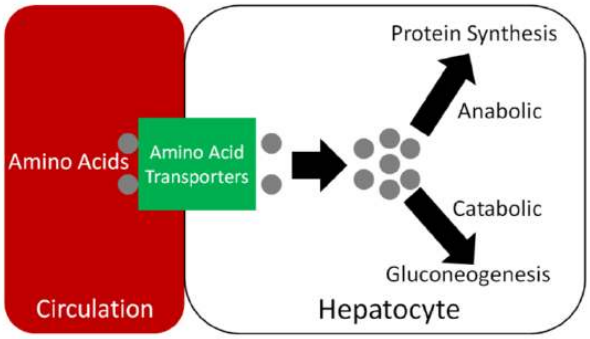


Figure **4.6.4**: Hepatic amino acid uptake

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.

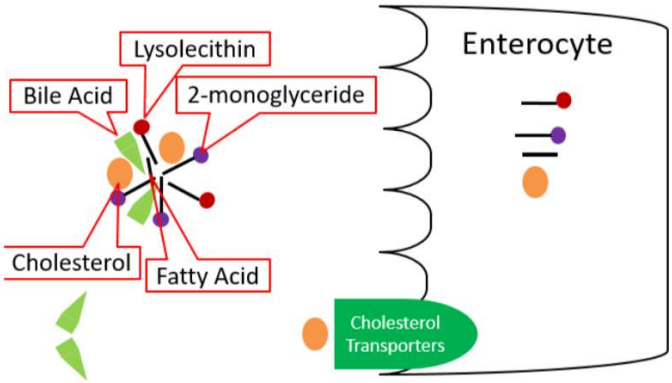


Figure **4.7.1**: Uptake of mixed micelle components into the enterocyte

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.

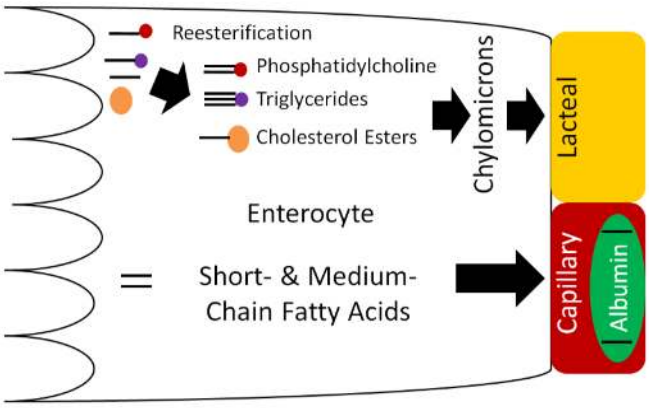


Figure **4.7.2**: Fates of lipids in the enterocyte

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

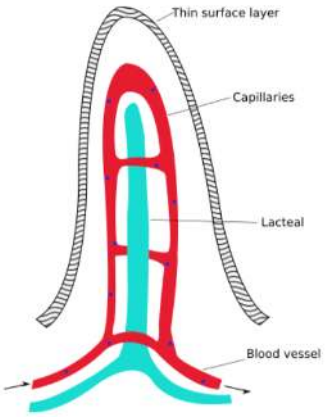


Figure **4.7.3**: Anatomy of a villus, with the lacteal shown in blue[1]

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.

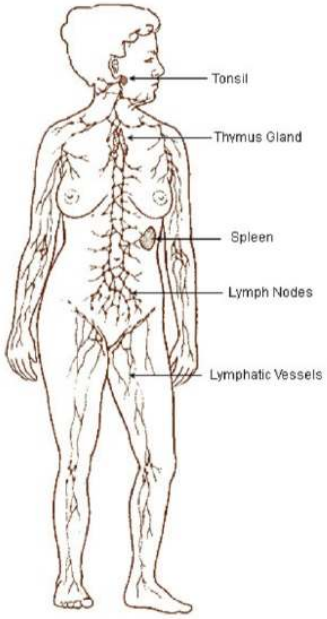


Figure **4.7.4**: The lymphatic system[2]

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



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



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.

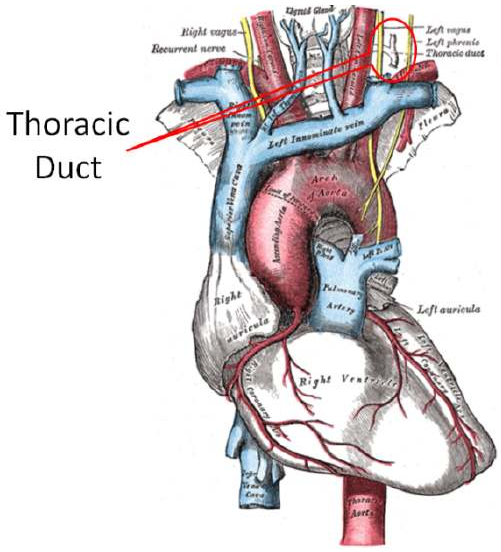


Figure **4.7.5**: The thoracic duct is where the lymphatic system enters circulation3

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

Web Links

Animation: Lipid Digestion, Uptake, and Transport

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.

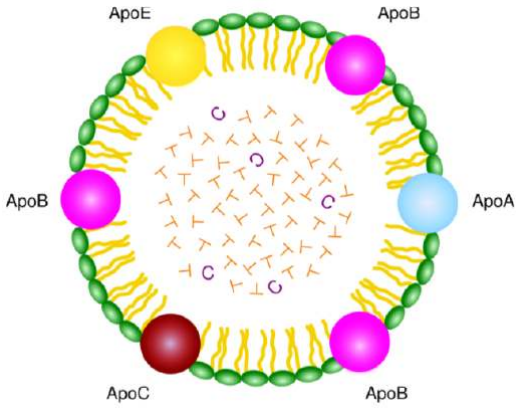


Figure **4.7.6**: Chylomicron structure4

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



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 lipoproteins5

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.

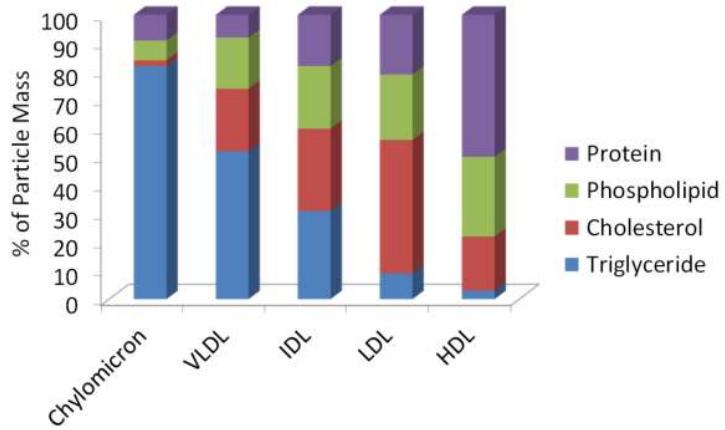


Figure 4.7.7: Composition of lipoproteins6

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.



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

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.

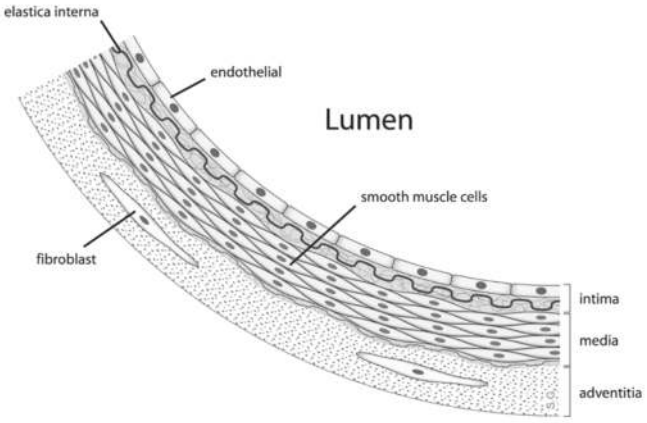


Figure 4.7.8: Lining of a blood vessel. The lumen is where the blood would be flowing, thus endothelial cells are those that are in contact with blood7

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.

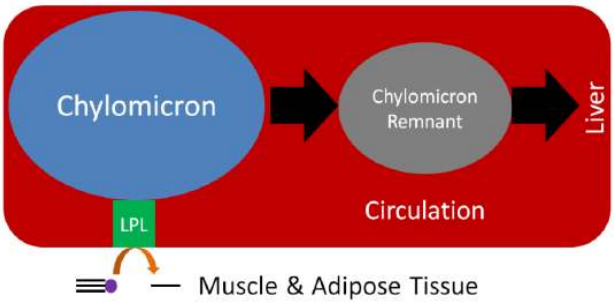


Figure 4.7.9: The cleavage of triglycerides by LPL from a chylomicron leads to the formation of a chylomicron remnant.

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.

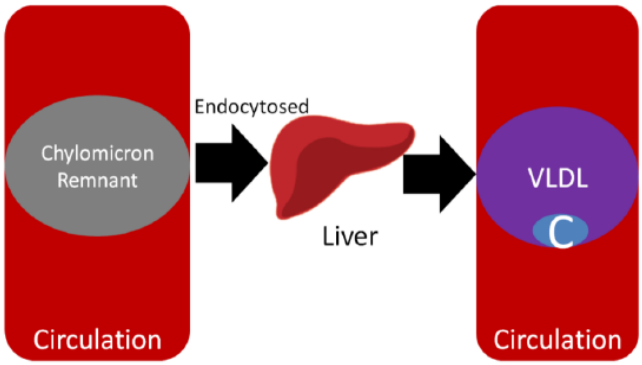


Figure 4.7.10: Chylomicron remnants are taken up by the liver. The liver secretes VLDL that contain cholesterol (C)

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.

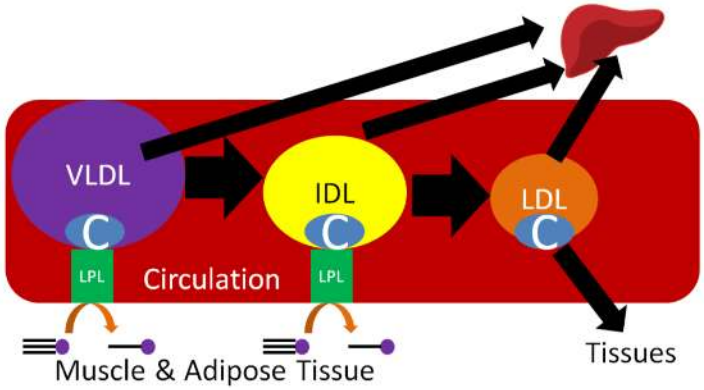


Figure 4.7.11: Formation of IDL and LDL from VLDL

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.

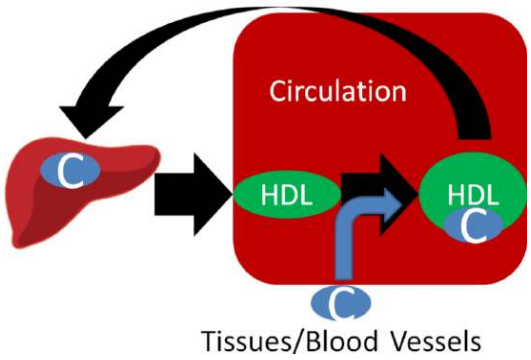


Figure **4.7.12**: HDL is involved in reverse cholesterol transport

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

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.

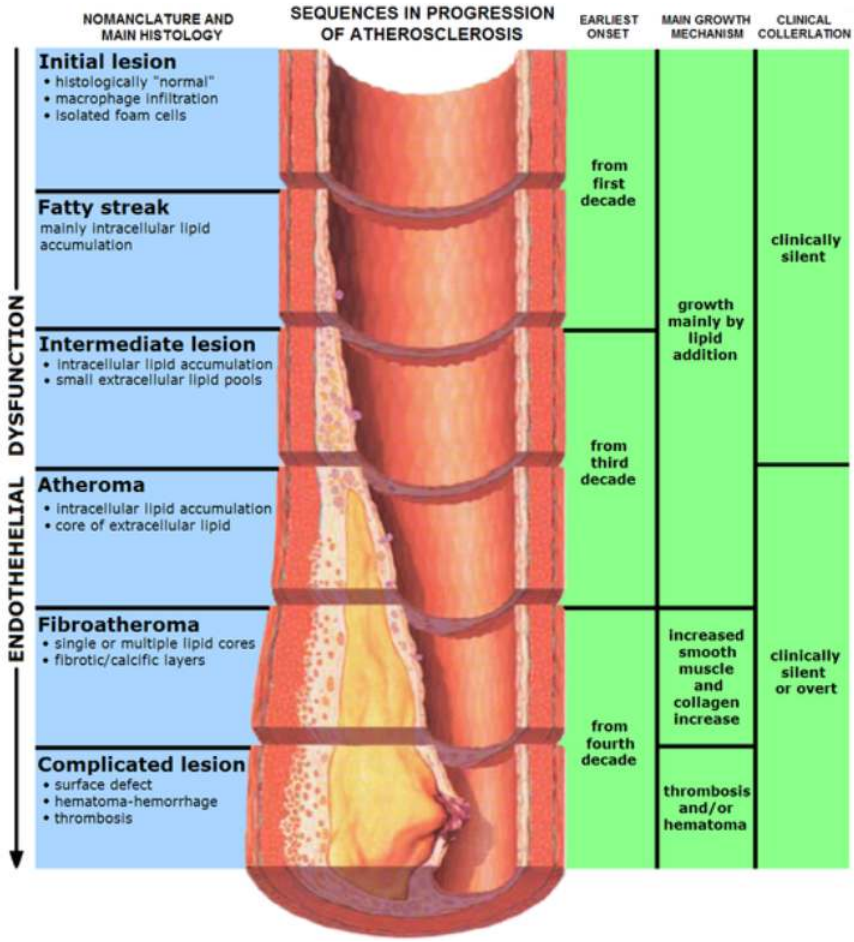


Figure **4.7.13**: The formation of a lesion in an artery[9]

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.



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

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

References

1. en.Wikipedia.org/wiki/File:In...simplified.svg
2. en.Wikipedia.org/wiki/File:Il...tic_system.jpg
3. en.Wikipedia.org/wiki/File:Gray505.png
4. en.Wikipedia.org/wiki/File:Chylomicron.svg
5. Byrd-Bredbenner C, Moe G, Beshgetoor D, Berning J. (2009) Wardlaw's perspectives in nutrition. New York, NY: McGraw-Hill.
6. Gropper SS, Smith JL, Groff JL. (2008) Advanced nutrition and human metabolism. Belmont, CA: Wadsworth Publishing.
7. en.Wikipedia.org/wiki/File:Anatomy_artery.png
8. Erdman JW Jr., MacDonald IA, Zeisel SH, editors. (2012) Present knowledge in nutrition - 10th ed. Ames, IA: Wiley-Blackwell.
9. en.Wikipedia.org/wiki/File:En...ion_Athero.PNG

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CHAPTER OVERVIEW

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
5.8: Macronutrient and Alcohol Metabolism
5.8.1: Metabolism Basics
5.8.2: Carbohydrate Metabolism
5.8.3: Lipid Metabolism Pathways
5.8.4: Protein Metabolism
5.8.5: Alcohol Metabolism

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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.

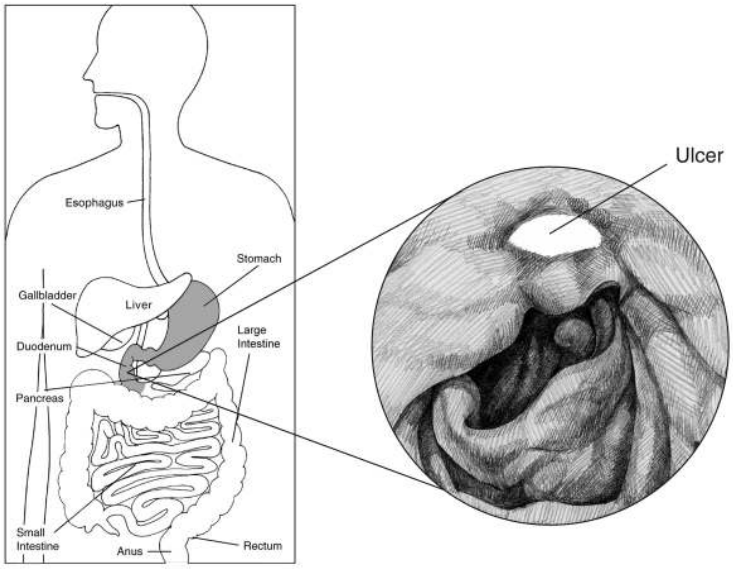


Figure **5.1.1**: A peptic ulcer in the duodenum[1]

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.



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



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

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.



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.

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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https://med.libretexts.org/@go/page/146841

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.

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.

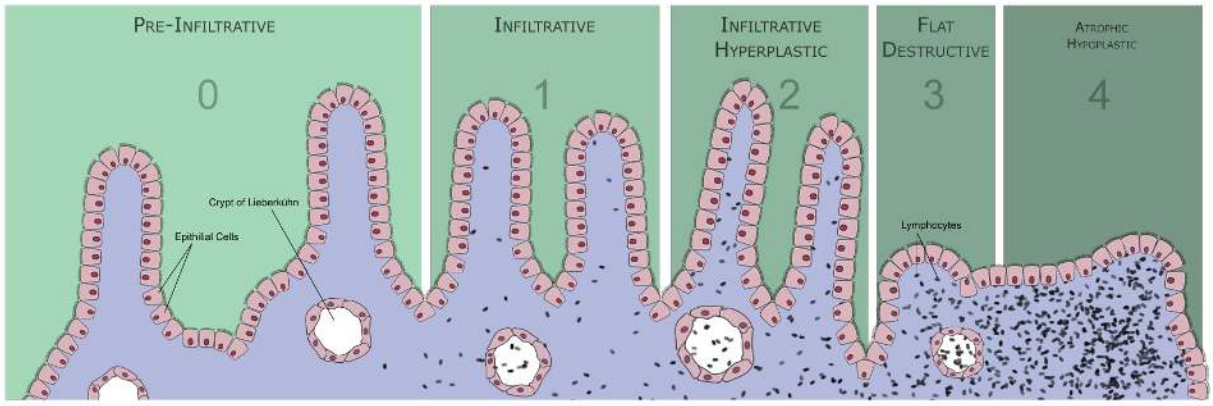


Figure 5.5.1: Different stages of celiac disease[2]

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.

What is gluten?

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

- Wheat
- Barley
- Rye
- Triticale

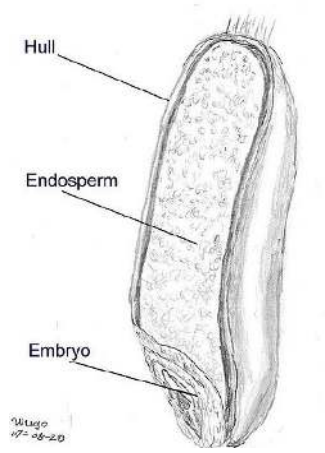


Figure 5.5.2: Parts of a wheat granule[3]

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

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.

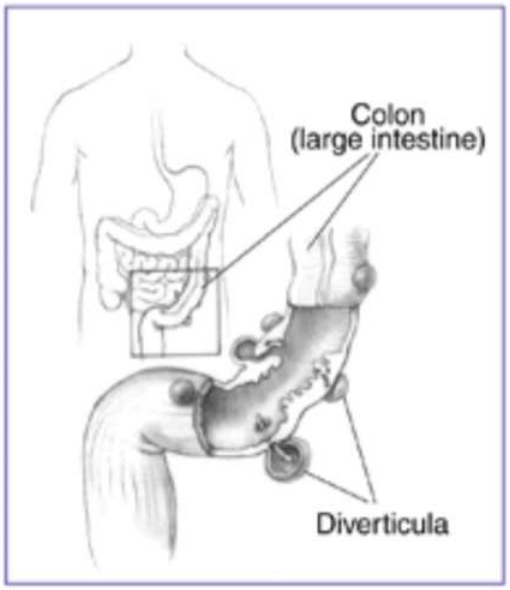


Figure **5.6.1**: Diverticula on the large intestine[1]



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].

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.

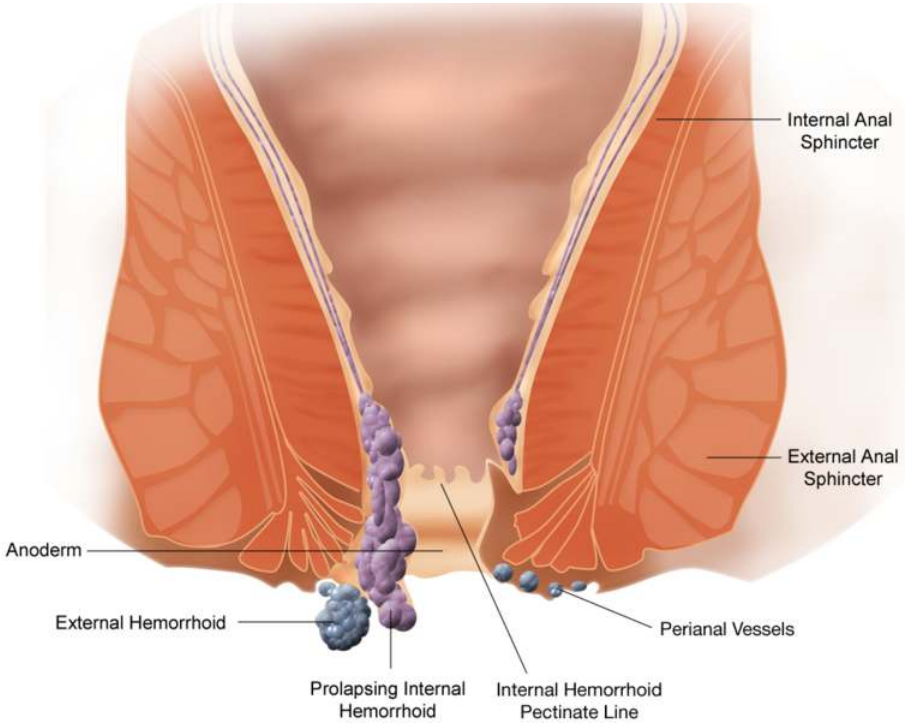


Figure **5.7.1**: Hemorrhoids. (CC BY-SA 3.0 Unported; WikipedianProlific via Wikipedia)

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



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.

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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CHAPTER OVERVIEW

5.8: 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.

5.8.1: Metabolism Basics

5.8.2: Carbohydrate Metabolism

5.8.3: Lipid Metabolism Pathways

5.8.4: Protein Metabolism

5.8.5: Alcohol Metabolism

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5.8.1: 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 **5.8.1.1**: 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.

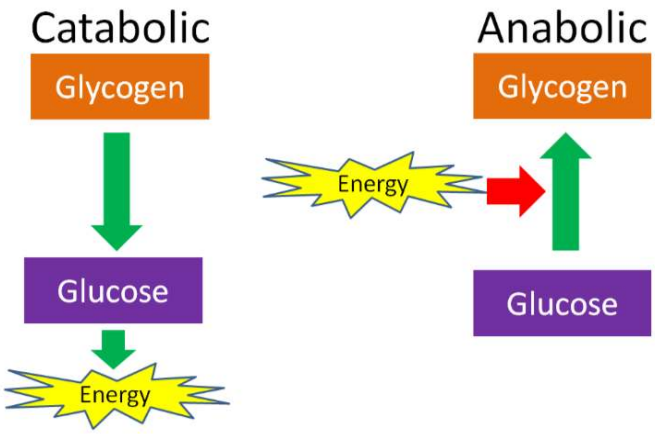


Figure **5.8.1.2**: The breakdown of glycogen to glucose is catabolic. The glucose can then be used to produce energy. The synthesis of glycogen from glucose is anabolic and requires energy.

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.

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.

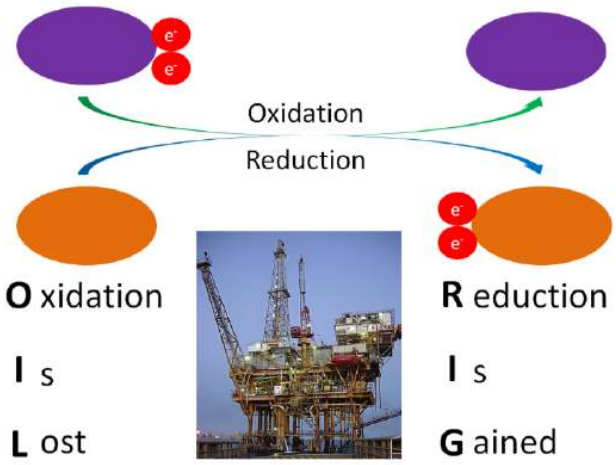


Figure 5.8.1.3: The purple compound is being oxidized, the orange compound is being reduced[1]

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

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.

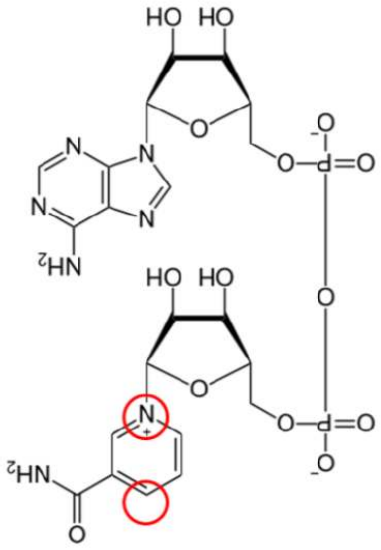


Figure 5.8.1.6

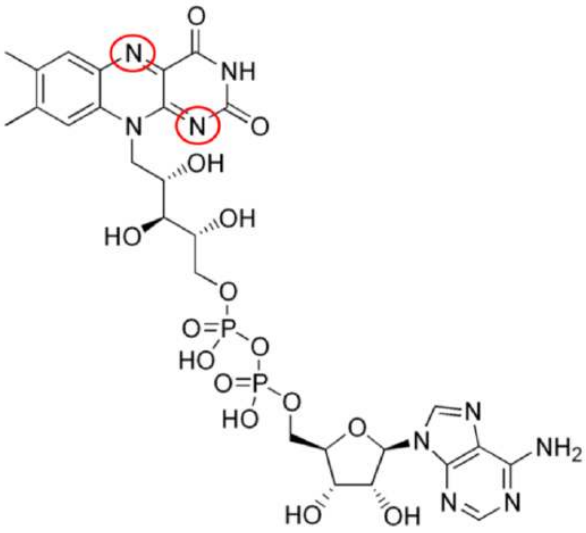


Figure 5.8.1.7

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.

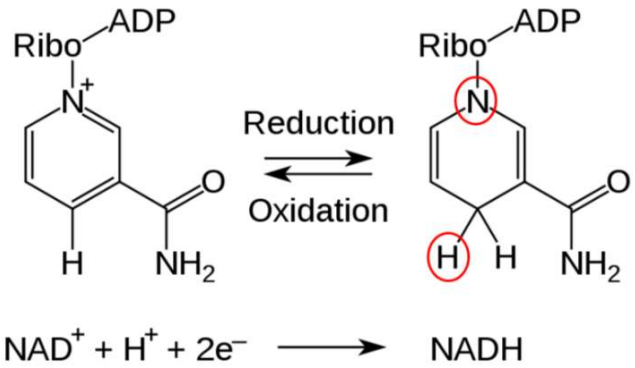


Figure 5.8.1.6: The reduction of **NAD** to form **NADH**[4]

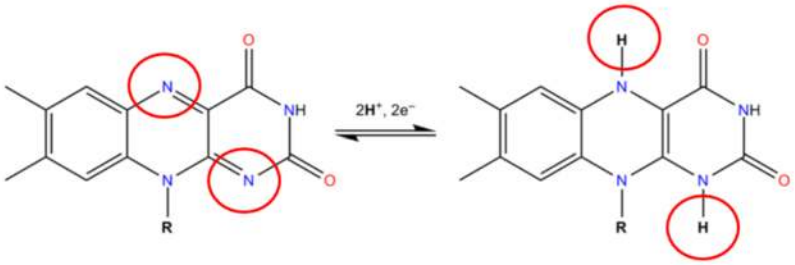


Figure 5.8.1.7: The reduction of FAD to $FADH_2$

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

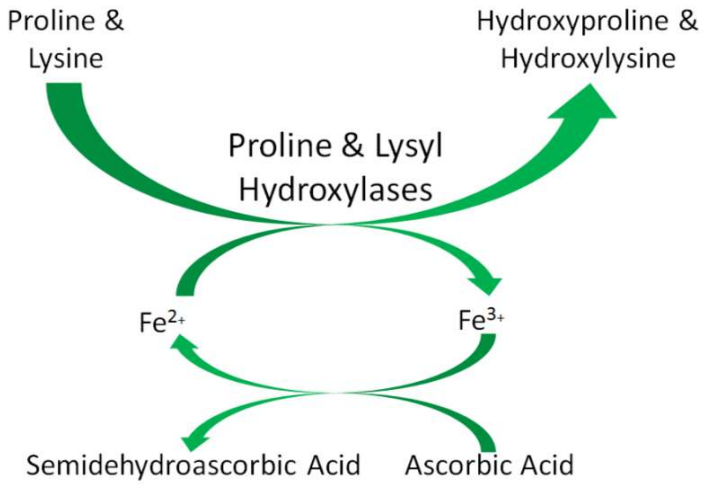


Figure 5.8.1.8: Iron (Fe^{2+}) is a cofactor for proline and lysyl hydroxylases

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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5.8.2: 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 $\mathbf{FADH_2}$ are produced in the cycle
- **Electron Transport Chain:** oxidative phosphorylation, producing ATP from **NADH** and $\mathbf{FADH_2}$

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.

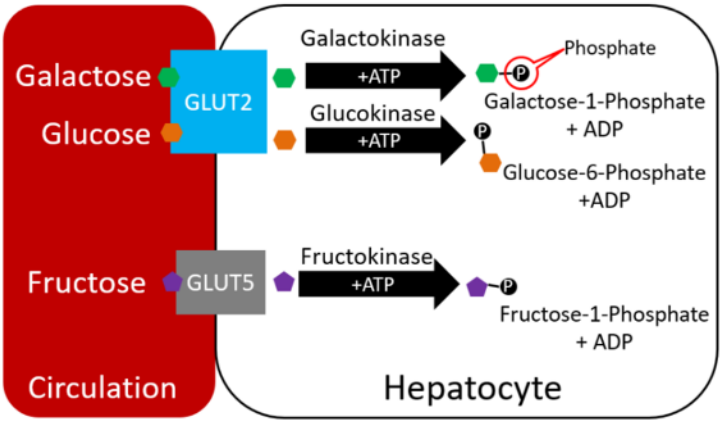


Figure **5.8.2.1**: Uptake of monosaccharides into the hepatocyte

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.

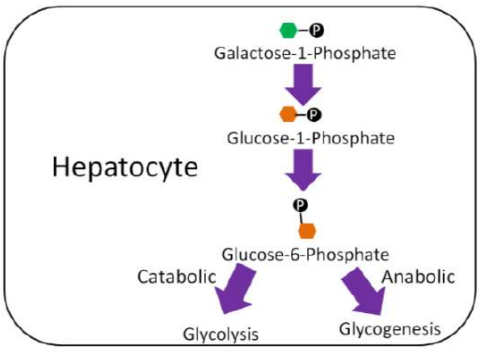


Figure **5.8.2.2**: Conversion of galactose-1-phosphate to glucose-6-phosphate

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.

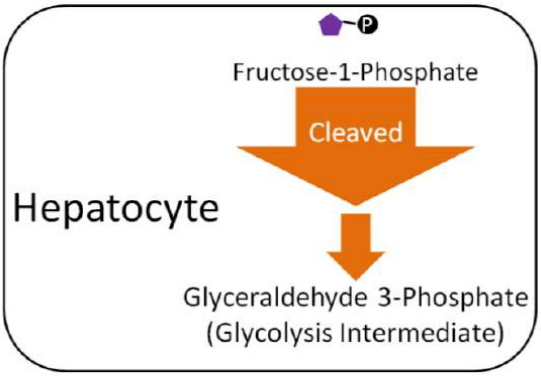


Figure **5.8.2.3**: Conversion of fructose-1-phosphate to glyceraldehyde 3-phosphate

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.

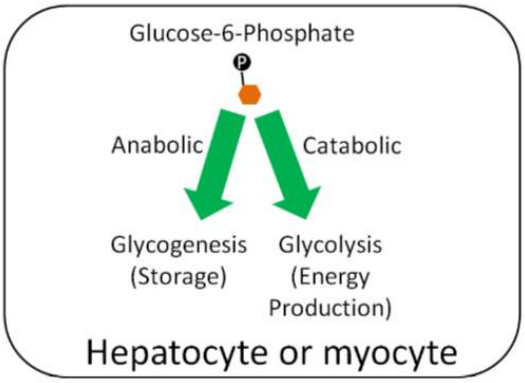


Figure **5.8.2.4**: The "fork in the road" for glucose-6-phosphate

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.

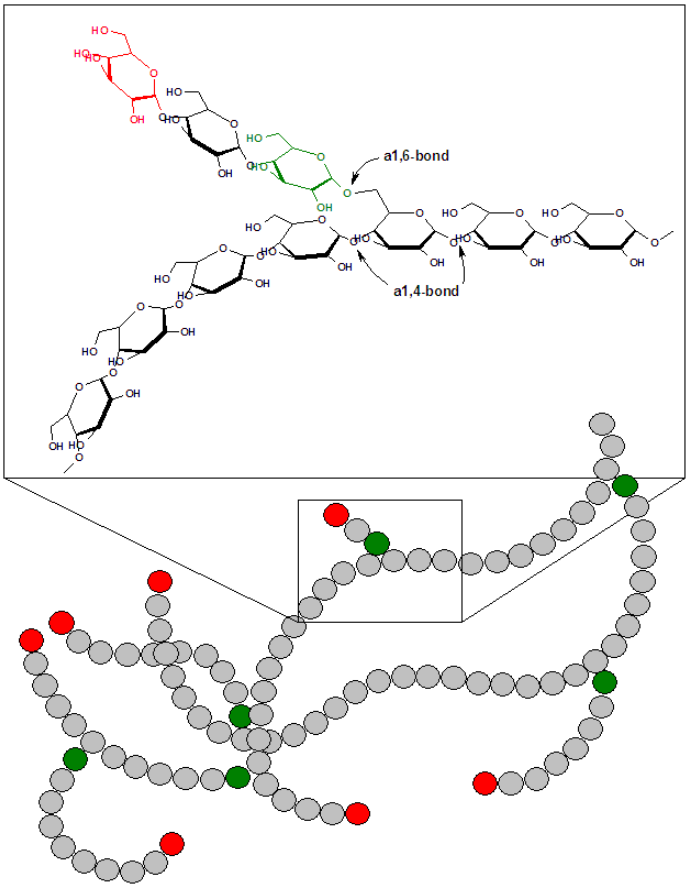


Figure **5.8.2.5**: Structure of glycogen2

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.

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.

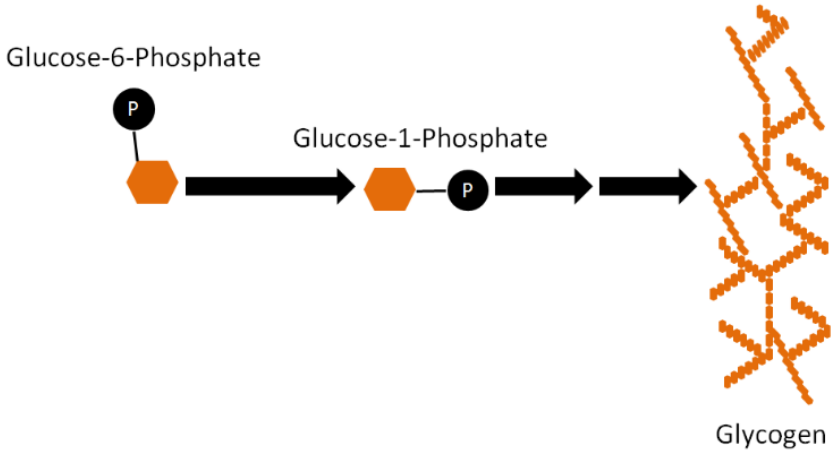


Figure 5.8.2.6: Glycogenesis

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.

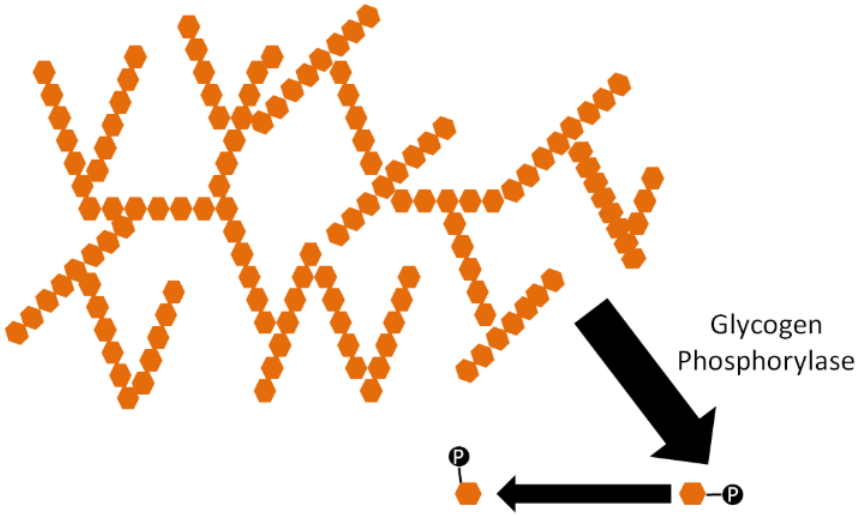


Figure 5.8.2.7: Glycogenolysis

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 **NADH**s are also produced.

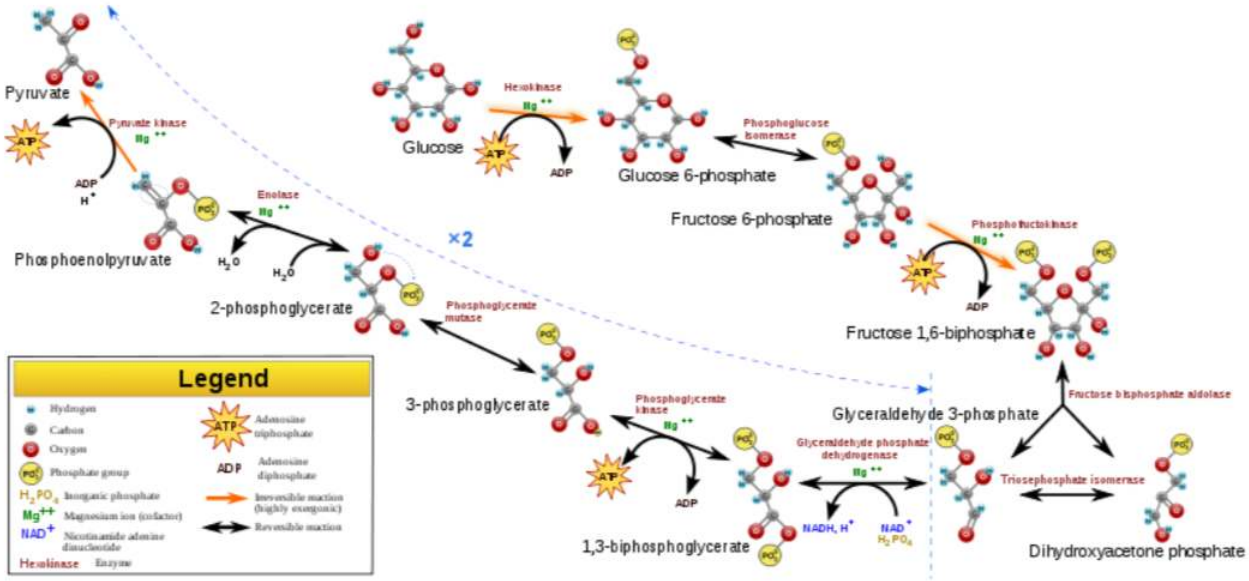


Figure 5.8.2.8: Glycolysis[4]

3 steps of Glycolysis

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

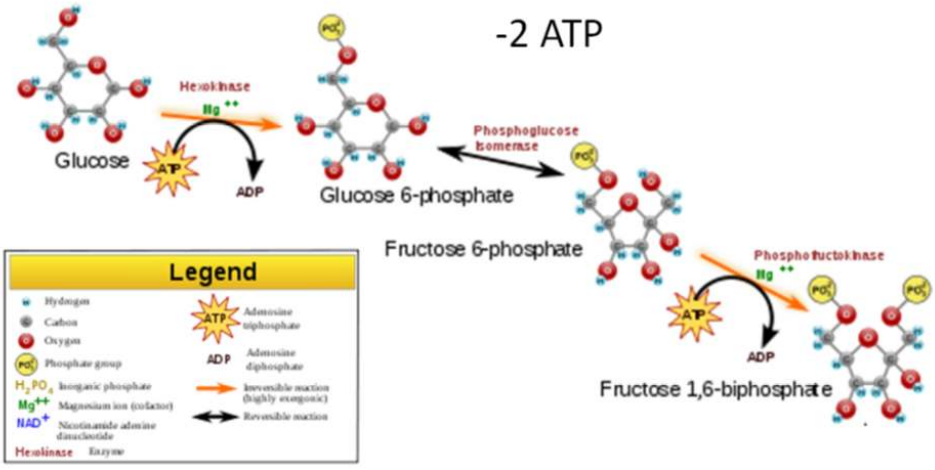


Figure 5.8.2.9: Glycolysis step 1, energy investment[4]

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

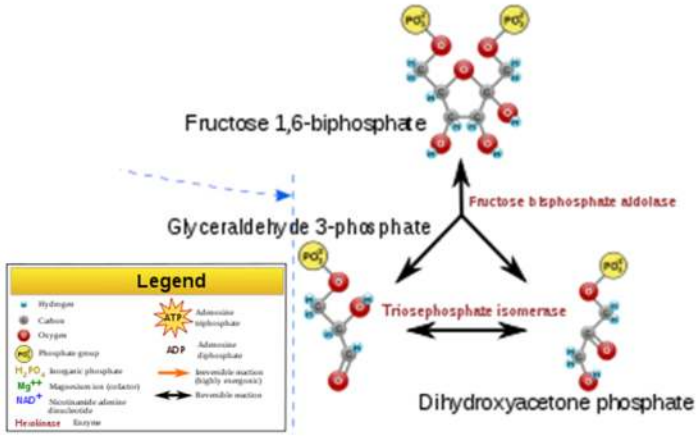


Figure 5.8.2.10: Glycolysis step 2, glucose split4

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.

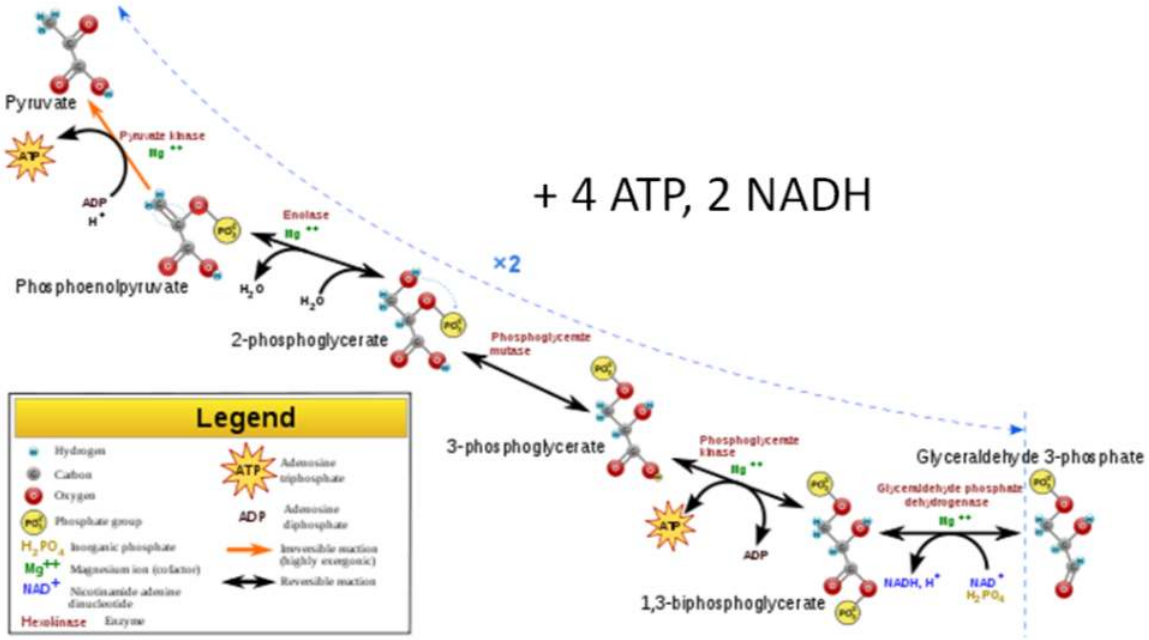


Figure 5.8.2.11: Glycolysis step 3, energy harvesting4

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.



Video 5.8.2.1: 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.

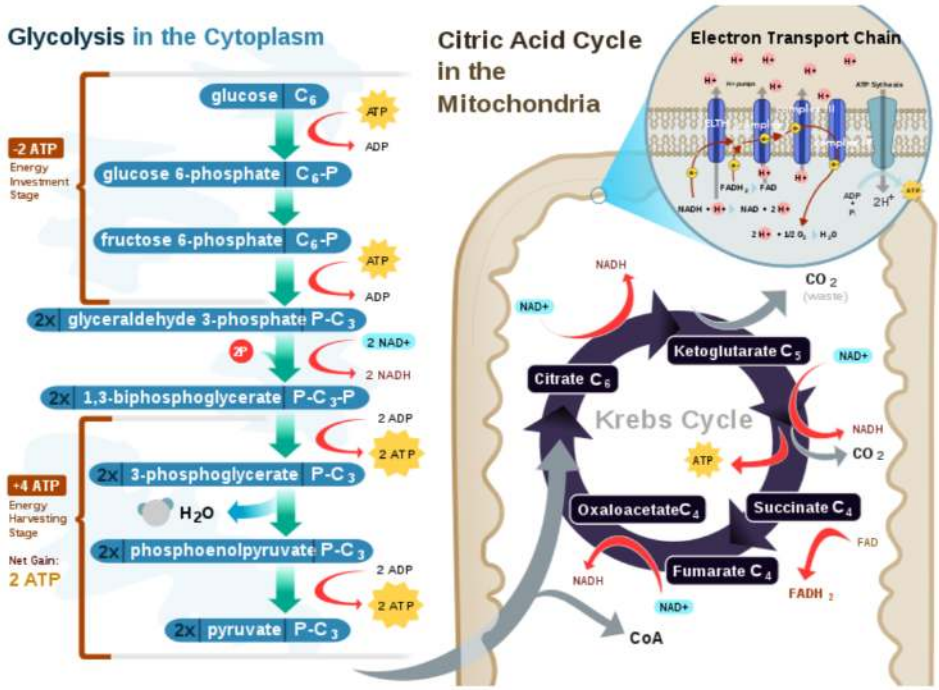


Figure 5.8.2.12: Glycolysis, transition reaction, citric acid cycle, and the electron transport chain5

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.

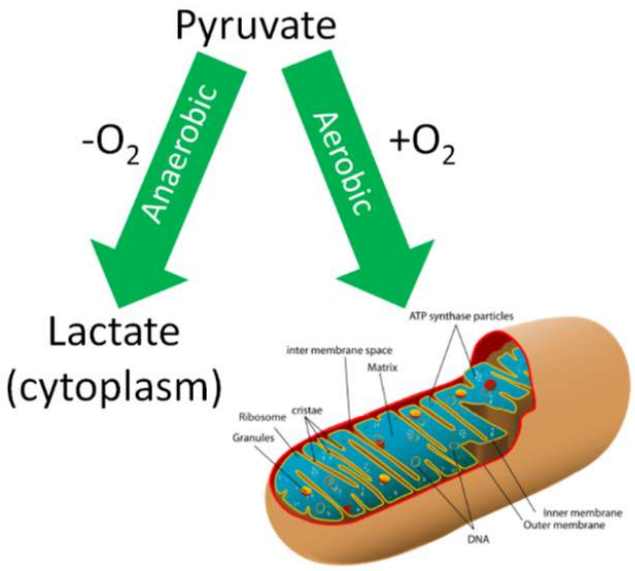


Figure 5.8.2.13: Pyruvate fork in the road. What happens depends on whether it is aerobic or anaerobic respiration6

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.

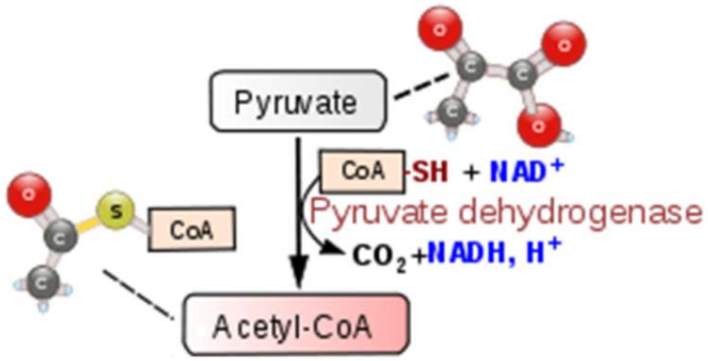


Figure 5.8.2.14: Transition reaction7

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

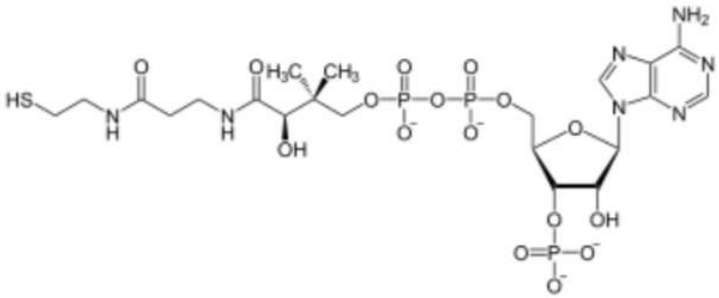


Figure 5.8.2.15: Structure of coenzyme A8

Thus, for one molecule of glucose, the transition reaction produces 2 acetyl-**CoA**s, 2 molecules of CO_2, and 2 **NADH**s.

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.

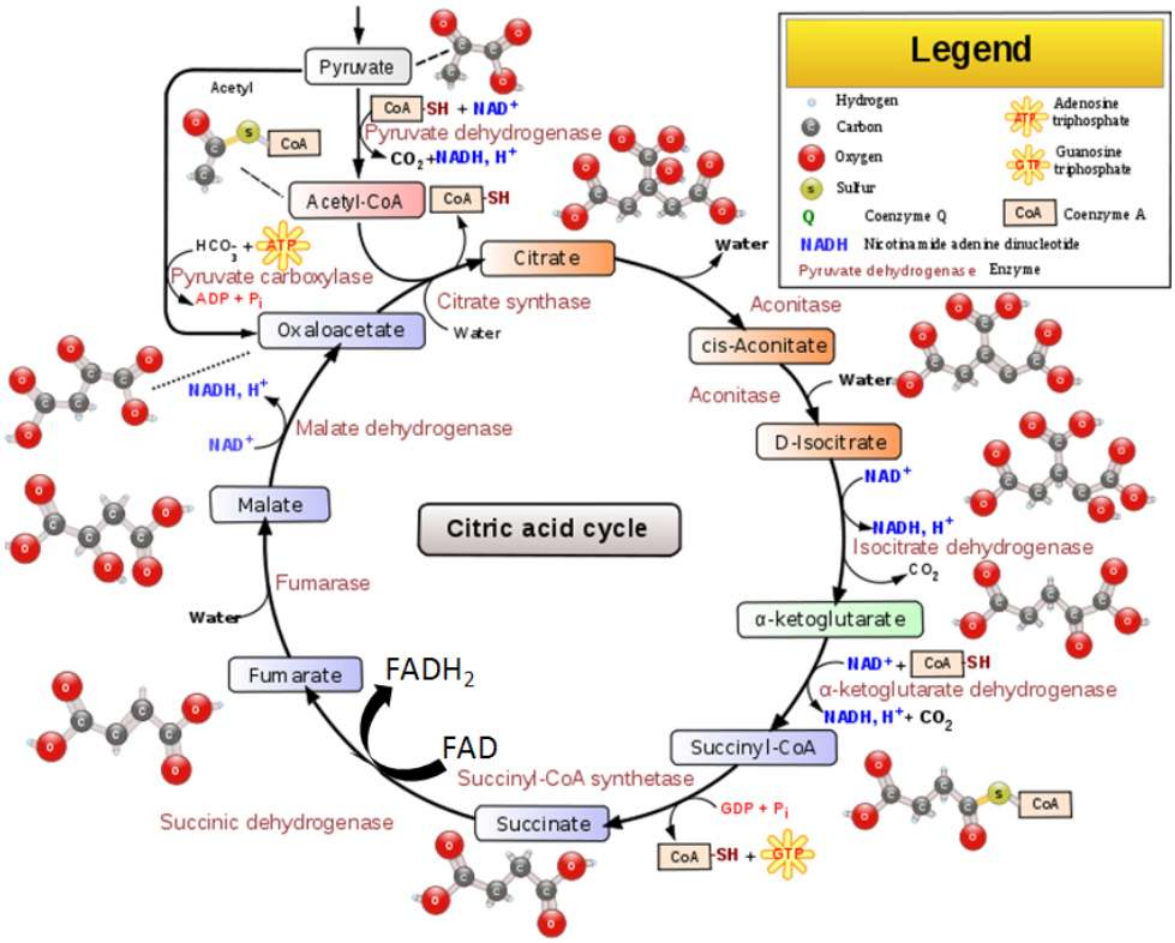


Figure **5.8.2.16**: The citric acid cycle[9]

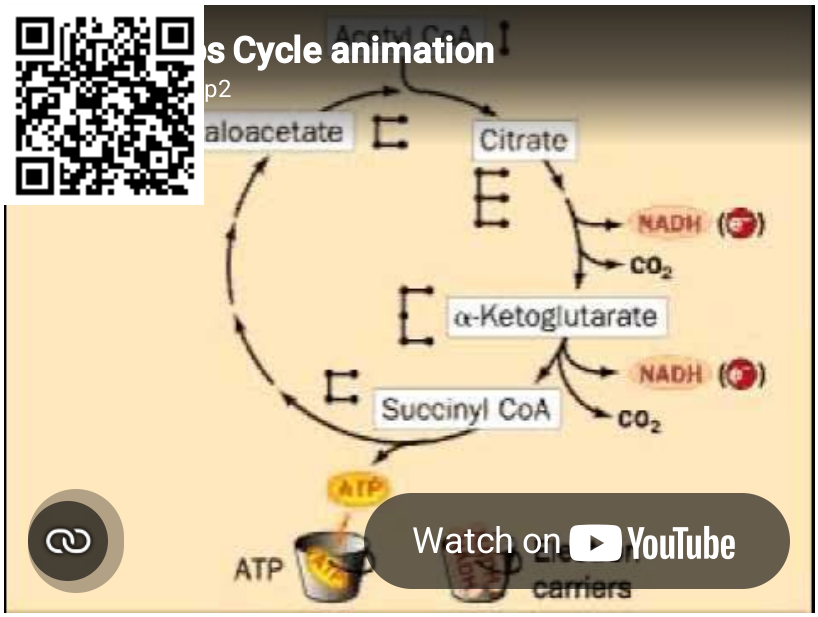
The citric acid cycle begins by acetyl-**CoA** (2 carbons) combining with oxaloacetate (4 carbons) to form citrate (aka citric acid, 6 carbons). A series of transformations occur before a carbon is given off as carbon dioxide and **NADH** is produced. This leaves alpha-ketoglutarate (5 carbons). Another carbon is given off as $\mathbf{CO_2}$ 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 $\mathbf{FADH_2}$ 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 $\mathbf{CO_2}$
- 3 **NADH**
- 1 $\mathbf{FADH_2}$
- 1 GTP (converted to ATP)

The two carbons that are given off as $\mathbf{CO_2}$ 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.



Video 5.8.2.2: Citric acid cycle. https://www.youtube.com/watch?v=hw5nWB0xN0Y



Video 5.8.2.3: 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 CO_2

6 NADH

2 $FADH_2$

2 GTP (converted to ATP)

Through glycolysis, the transition reaction, and the citric acid cycle, multiple NADH and $FADH_2$ 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.

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 $FADH_2$, 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 $FADH_2$ to pump protons (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.

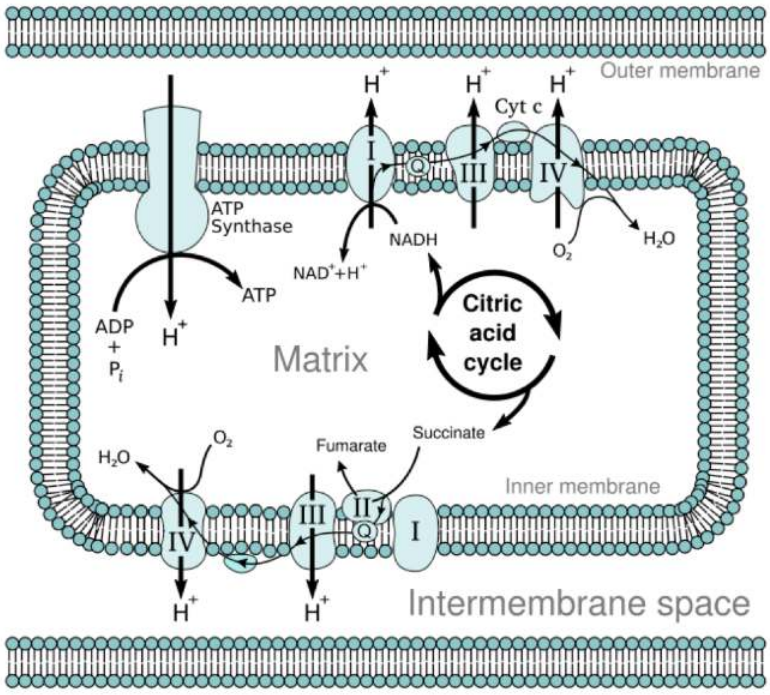


Figure **5.8.2.17**: Location of the electron transport chain in the mitochondria[10]

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

For one molecule of glucose, the preceding pathways produce:

Glycolysis:	**2NADH**
Transition Reaction:	**2NADH**
Citric Acid Cycle:	**6NADH, 2FADH$_2$**
Total:	**10NADH, 2FADH$_2$**

Multiply that by the amount of ATP per **NADH** or $\mathbf{FADH_2}$ to yield:

$$\frac{\mathbf{10NADH \times 2.5ATP}}{\mathbf{NADH}} = \mathbf{25ATP}$$

$$\frac{\mathbf{2FADH_2 \times 1.5ATP}}{\mathbf{FADH_2}} = \mathbf{3ATP}$$

$$\mathbf{Total = 28ATP}$$

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/$\mathbf{FADH_2}$ 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.



Video 5.8.2.4: Electron transport chain. https://www.youtube.com/watch?v=1engJR_XWVU&feature=related



Video 5.8.2.5: Oxidate it or love it/electron to the next one. https://www.youtube.com/watch?v=VCpNk92uswY&feature=response_watch

Aerobic Glucose Metabolism Totals

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

Table 5.8.2.1: 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/$\mathbf{FADH_2}$ are used instead of 2.5 ATP/**NADH** and 1.5 ATP/$\mathbf{FADH_2}$ 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.

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.

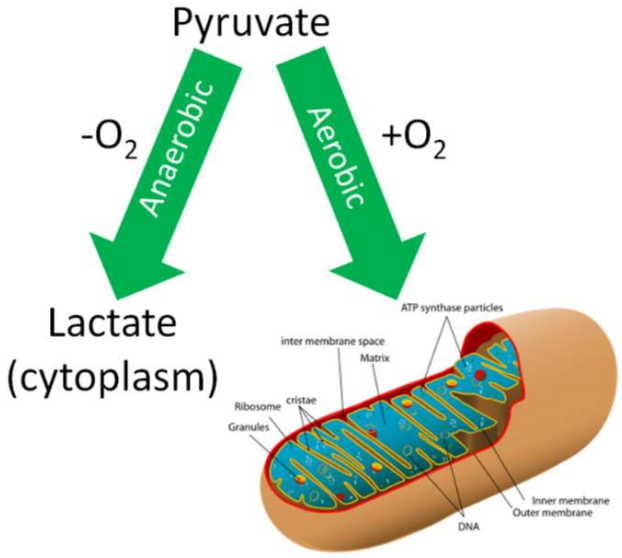


Figure **5.8.2.18**: Pyruvate fork in the road, what happens depends on whether it is aerobic or anaerobic respiration6

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 $\mathbf{FADH_2}$.



Video **5.8.2.6**: What happens in the electron transport chain when you run out of oxygen. https://www.youtube.com/watch?v=StXlo1W3Gvg

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

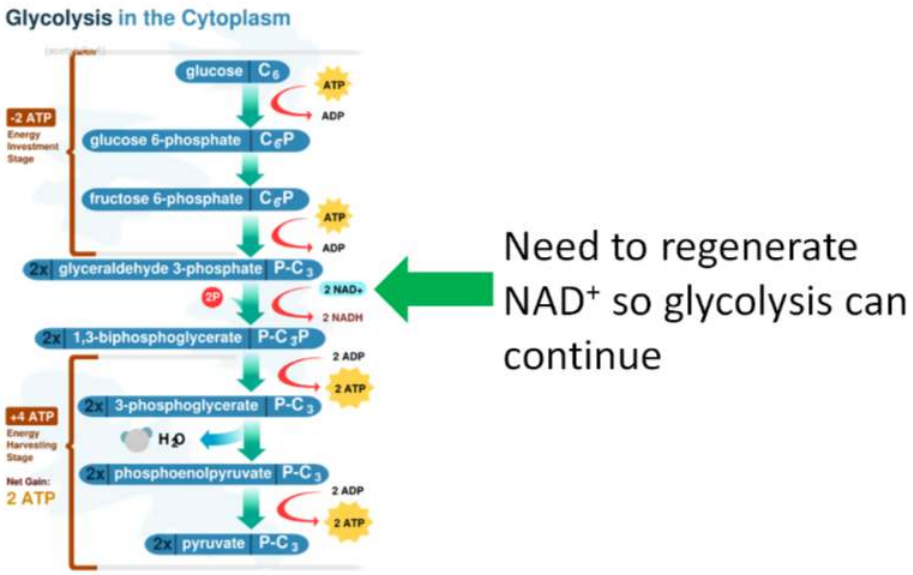


Figure 5.8.2.19: Why **NAD** needs to be regenerated under anaerobic conditions[5]

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

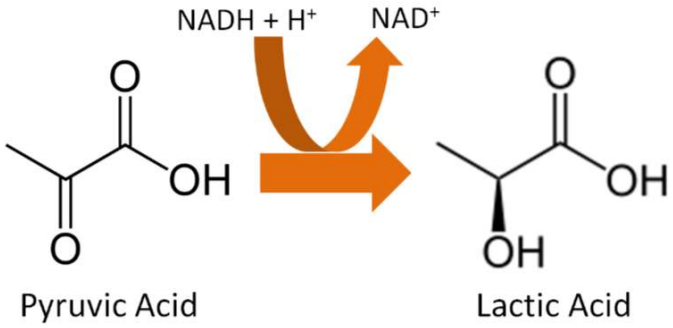


Figure 5.8.2.20: The conversion of pyruvic acid to lactic acid regenerates NAD[12,13]

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.

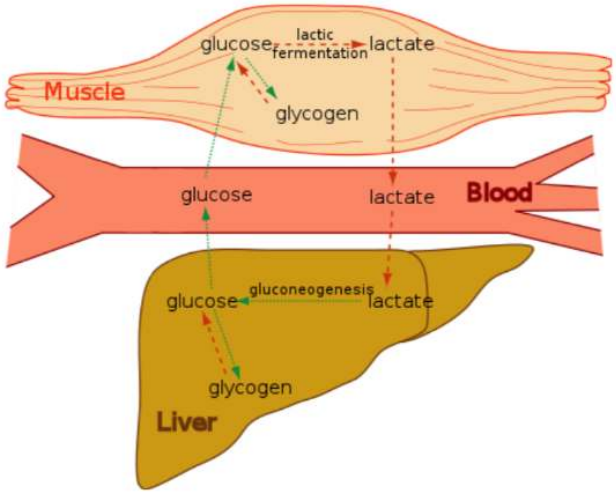


Figure 5.8.2.21: The Cori cycle[14]

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.

References

1. Gropper SS, Smith JL, Groff JL. (2008) Advanced nutrition and human metabolism. Belmont, CA: Wadsworth Publishing.
2. en.Wikipedia.org/wiki/File:Glycogen.png
3. Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ, editors. (2006) Modern nutrition in health and disease. Baltimore, MD: Lippincott Williams & Wilkins.
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5. en.Wikipedia.org/wiki/File:Glycolysis.svg
6. en.Wikipedia.org/wiki/File:CellRespiration.svg
7. simple.Wikipedia.org/wiki/Mi..._en_(edit).svg
8. en.Wikipedia.org/wiki/Image:C...conitate_2.svg
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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5.8.3: 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.

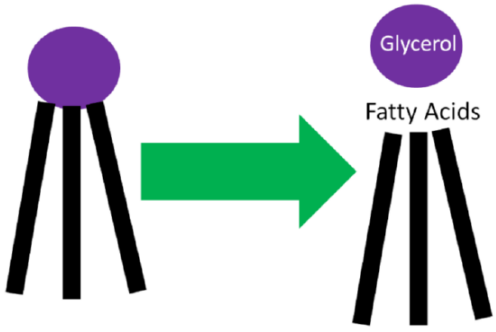


Figure **5.8.3.1**: Lipolysis

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.

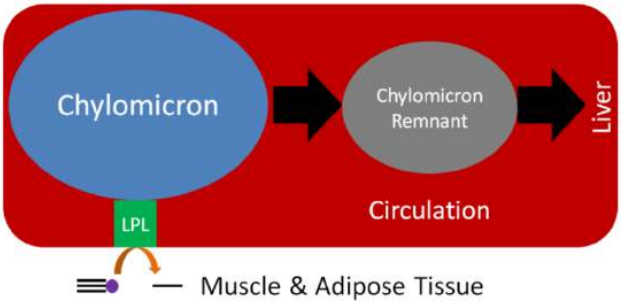


Figure **5.8.3.2**: Lipoprotein lipase cleaves fatty acids from the chylomicron, forming a chylomicron remnant.

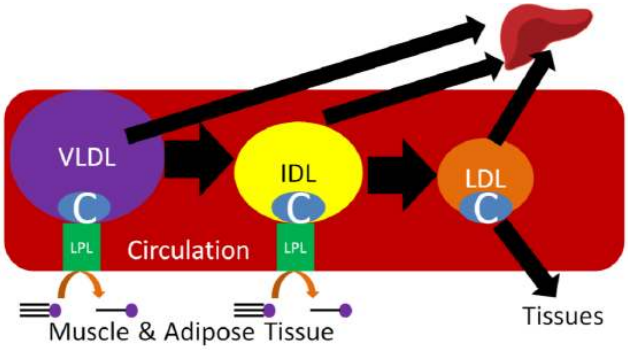


Figure **5.8.3.3**: Lipoprotein lipase cleaves triglycerides from VLDL and IDL, forming subsequent lipoproteins (IDL and LDL) that contain less triglyceride

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 production[1].

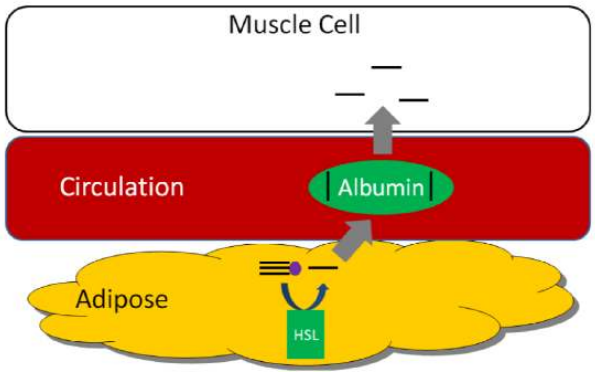


Figure 5.8.3.4: Hormone-sensitive lipase

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)

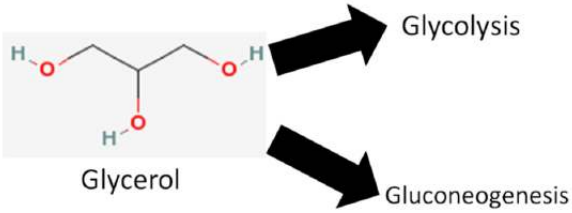


Figure 5.8.3.5: Metabolic fates of glycerol

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.

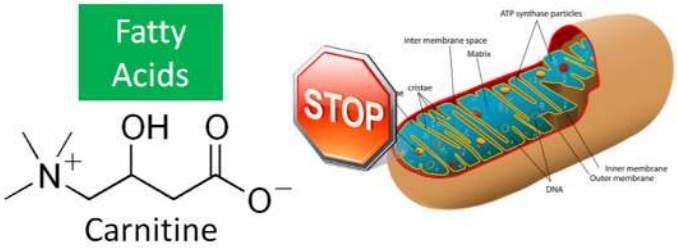


Figure 5.8.3.6: Carnitine shuttles fatty acids into the mitochondria[2,3]

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.

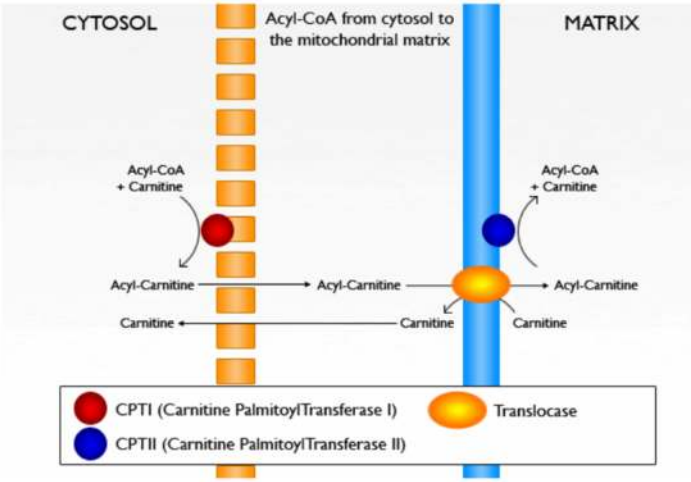


Figure 5.8.3.7: Transfer of fatty acids into the mitochondria[4]

Web Link

Fatty acid transfer from cytoplasm to mitochondria

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].

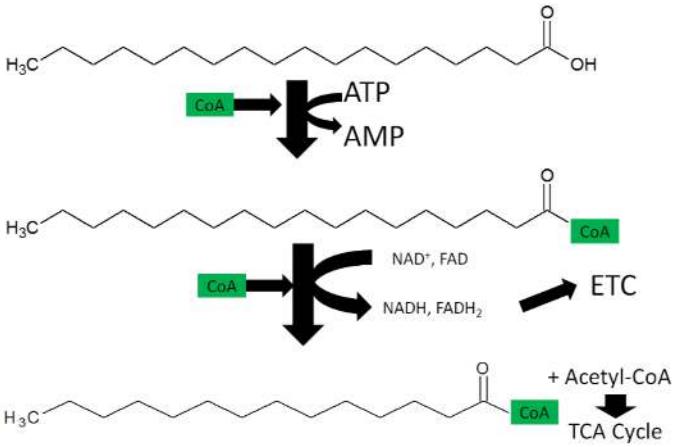


Figure 5.8.3.8: Fatty Acid Oxidation

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 $\mathbf{FADH_2}$.

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-**CoA**s, 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-**CoA**s

8 **NADH**

8 $\mathbf{FADH_2}$

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.

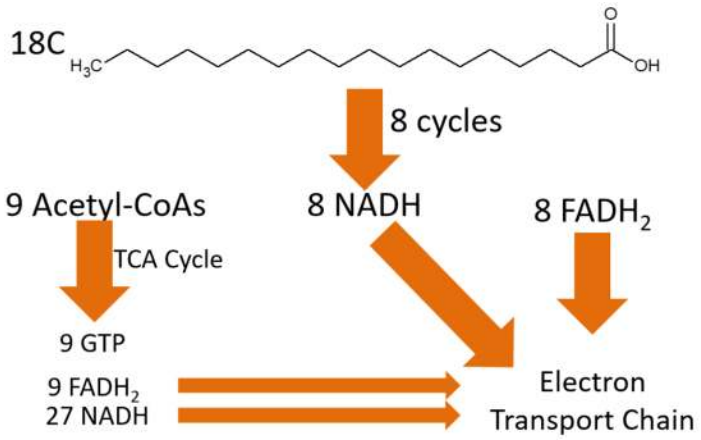


Figure 5.8.3.9: Complete oxidation of an 18 carbon (C) fatty acid

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

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.

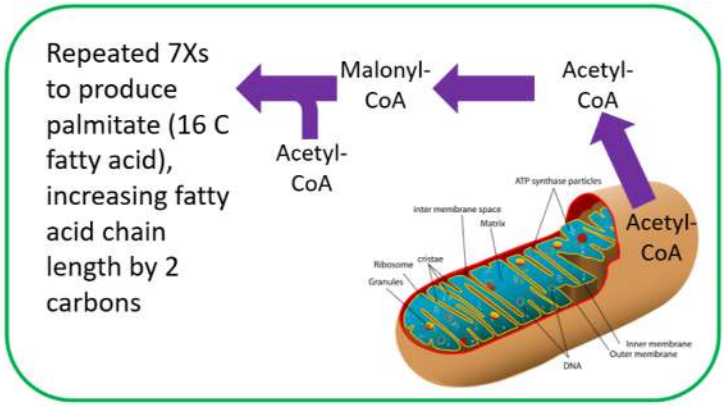


Figure 5.8.3.10: Fatty acid synthesis[7]

Most fatty acids synthesized will be esterified into triglycerides for storage.

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.

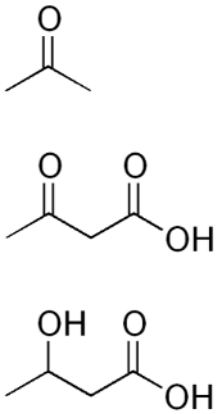


Figure 5.8.3.11: The three ketone bodies from top to bottom (acetone, acetoacetic acid, and beta-hydroxybutyric acid[8])

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.

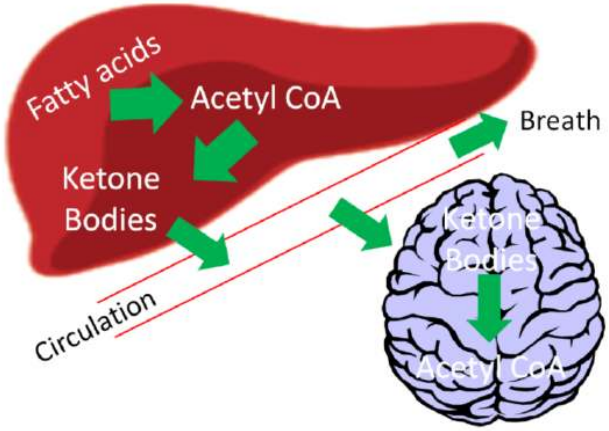


Figure 5.8.3.12: The production, release, use, or exhalation of ketone bodies[9]

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.

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.

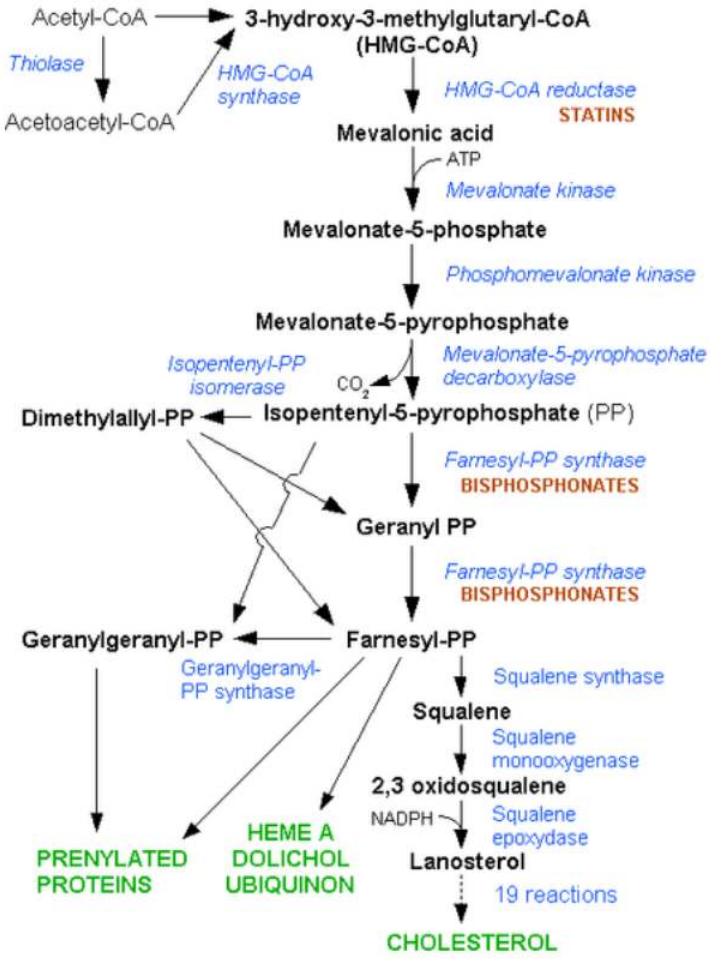


Figure 5.8.3.13: Cholesterol synthesis pathway10

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.

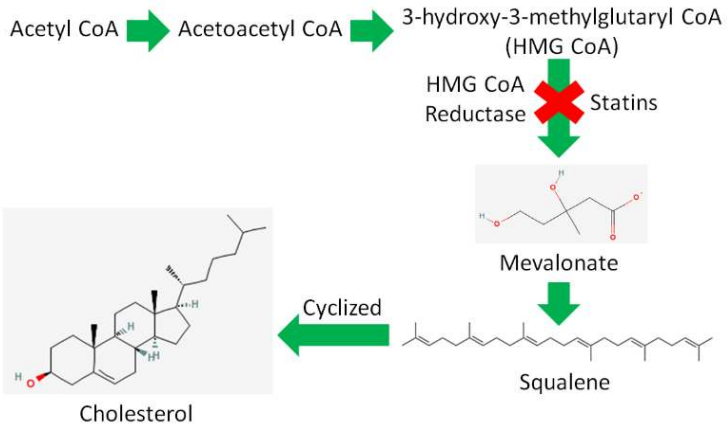


Figure 5.8.3.14: Cholesterol synthesis simplified11

A rate-limiting enzyme is like a bottleneck in a highway, as shown below, that determines the flow of traffic past it.

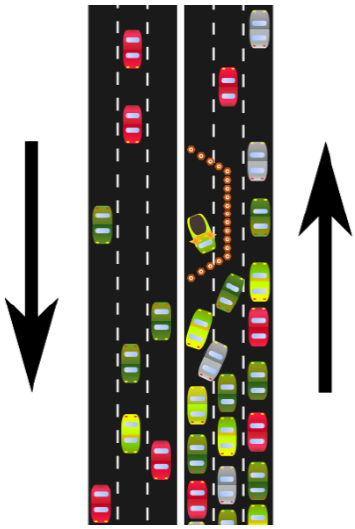


Figure 5.8.3.15: Bottleneck in traffic12

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.

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12. en.Wikipedia.org/wiki/File:Bottleneck.svg
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5.8.4: 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.

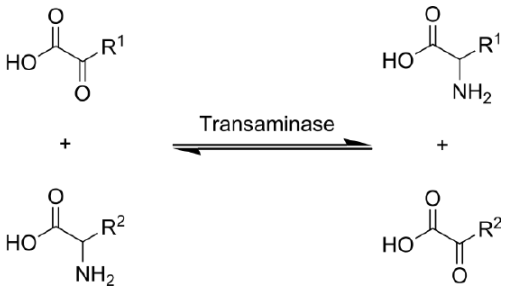


Figure 5.8.4.1: Generic transamination reaction where the top keto acid is converted to an amino acid, while the bottom amino acid is converted to a keto acid1

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.

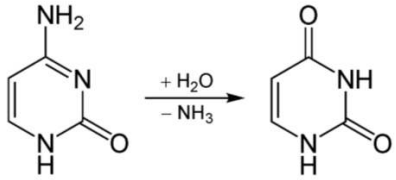


Figure 5.8.4.2: Deamination of cytosine to uracil (nucleotides, not amino acids)2

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.

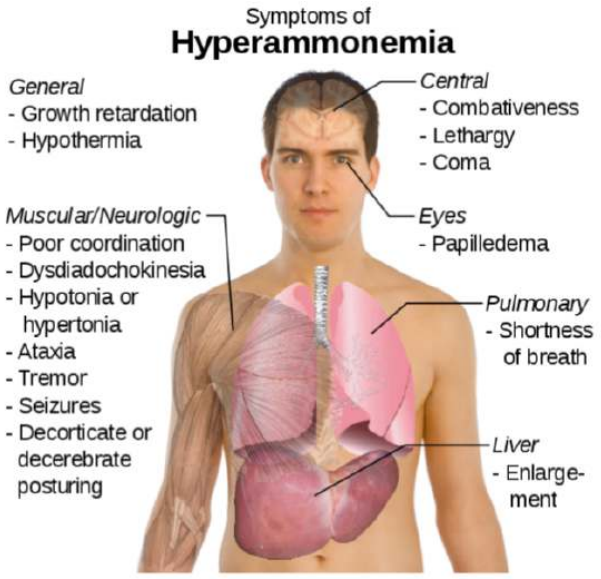


Figure **5.8.4.3**: Symptoms of Hyperammonemia[3]

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.

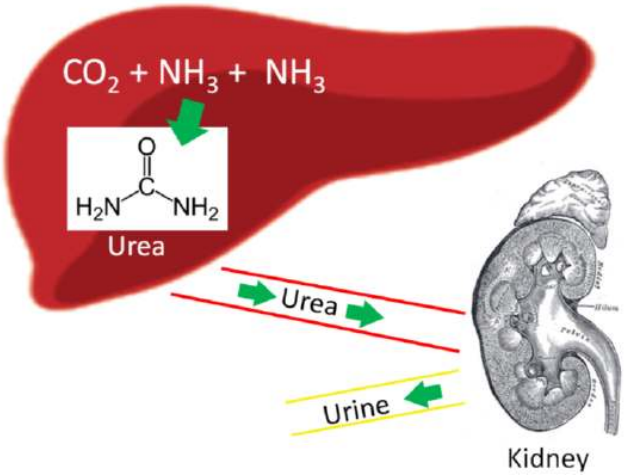


Figure **5.8.4.4**: Production of urea helps to safely remove ammonia from the body[4-6]

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.

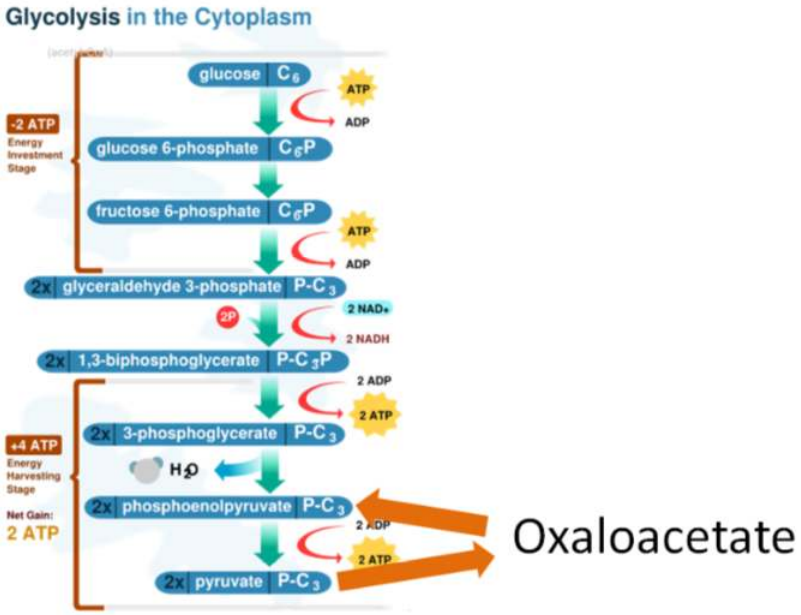


Figure 5.8.4.5: Gluconeogenesis is glycolysis in reverse with an oxaloacetate workaround7

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).

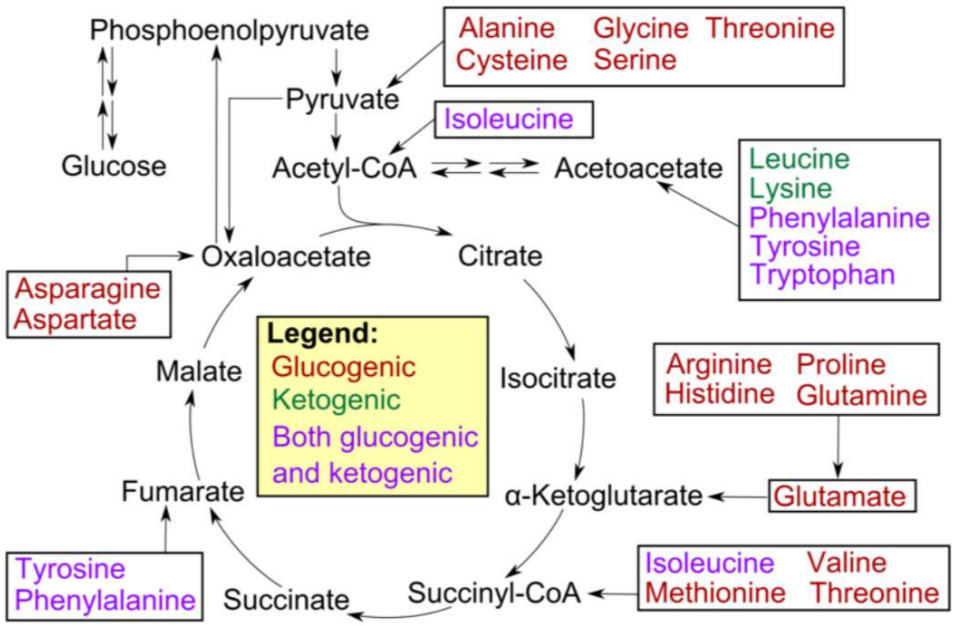


Figure 5.8.4.6: Glucogenic (red), ketogenic (green), and glucogenic and ketogenic amino acids8

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 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).

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.

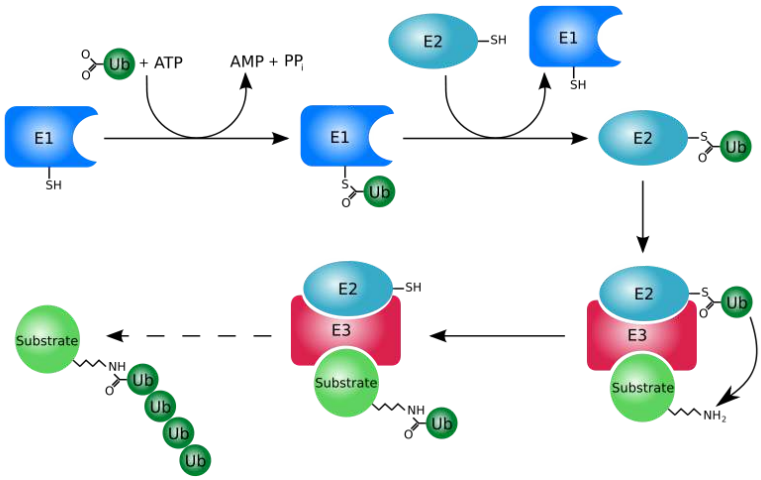


Figure 5.8.4.7: Ubiquitination of a protein (substrate)9

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.

https://med.libretexts.org/@go/page/146851



Video 5.8.4.1: 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.

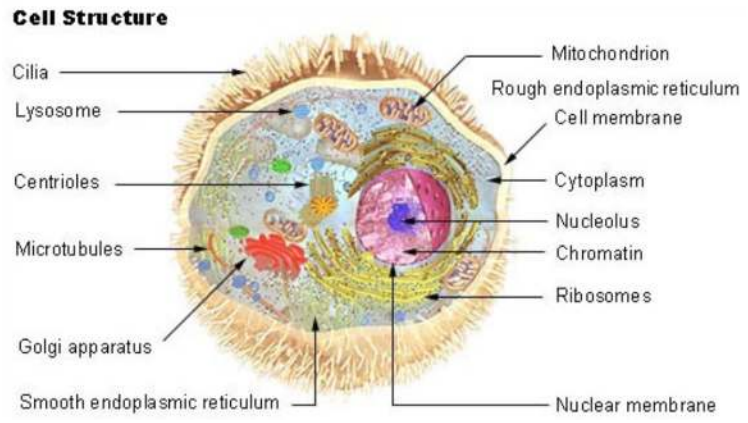


Figure 5.8.4.8: Lysosomes are organelles within the cell10

Calpain Degradation

The last degradation system is the calpain system, which is not as well understood, but does require calcium.

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1. en.Wikipedia.org/wiki/File:Transaminierung.svg
2. en.Wikipedia.org/wiki/File:De...ierungCtoU.png
3. en.Wikipedia.org/wiki/File:Sy...rammonemia.svg
4. commons.wikimedia.org/wiki/File:Liver.svg
5. upload.wikimedia.org/wikipedi...ey_section.jpg
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9. en.Wikipedia.org/wiki/File:Ubiquitylation.svg
10. en.Wikipedia.org/wiki/File:Il..._structure.jpg

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5.8.5: Alcohol Metabolism

The other energy source is alcohol. The alcohol we consume contains two carbons and is known as ethanol.

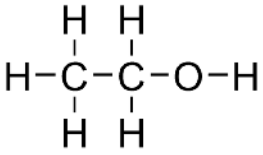


Figure **5.8.5.1**: Structure of ethanol[1]

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.

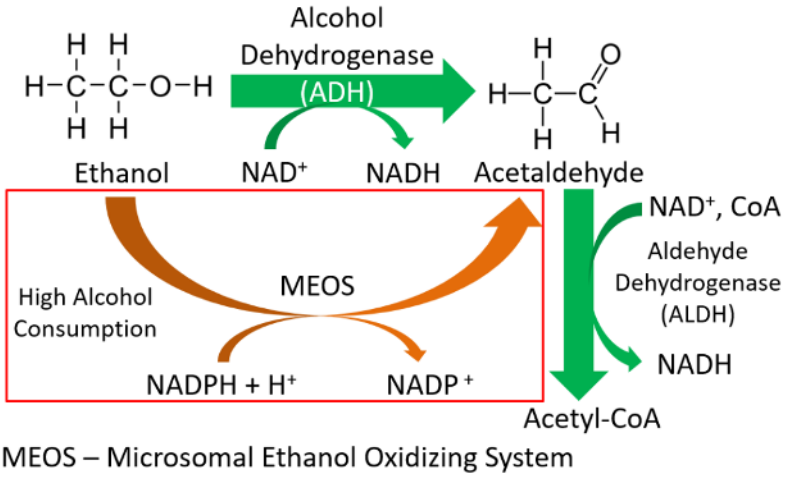


Figure **5.8.5.2**: Ethanol Metabolism[1,5]

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 ethanol[3], and it differs from **ADH** in that it uses ATP to convert reduced nicotinamide adenine dinucleotide phosphate (**$NADPH + H^+$**) 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 body[3].

Females have lower stomach **ADH** activity and body **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 activity[6]. This leads to acetaldehyde buildup and undesirable symptoms such as: flushing, dizziness, nausea, and headaches[2]. The following animation explains what happens when the MEOS system gets involved in alcohol metabolism.

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CHAPTER OVERVIEW

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.

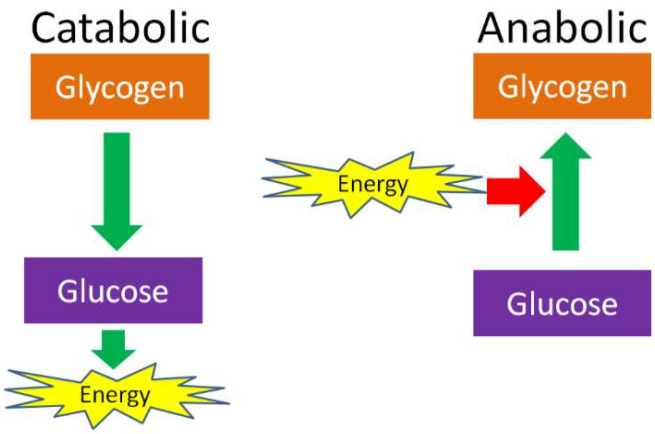


Figure **6.1.2**: The breakdown of glycogen to glucose is catabolic. The glucose can then be used to produce energy. The synthesis of glycogen from glucose is anabolic and requires energy.

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.

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.

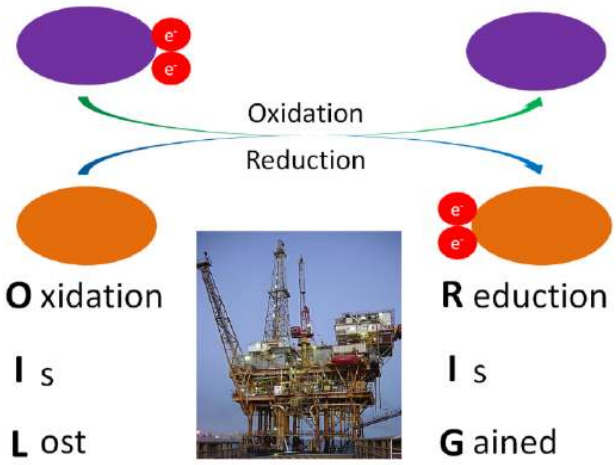


Figure **6.1.3**: The purple compound is being oxidized, the orange compound is being reduced[1]

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 ($\mathbf{Fe^{3+}}$ or $\mathbf{Fe^{2+}}$). It is constantly oxidized/reduced back and forth between the two states. The oxidation/reduction of iron is shown below.

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

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

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

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.

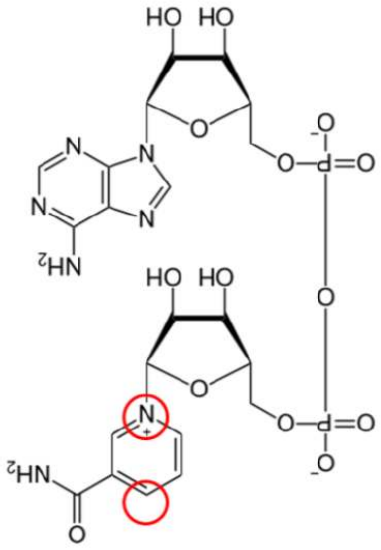


Figure **6.1.6**

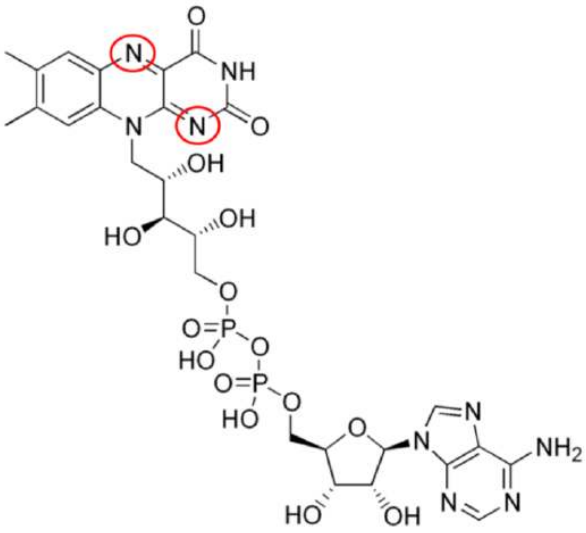


Figure **6.1.7**

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.

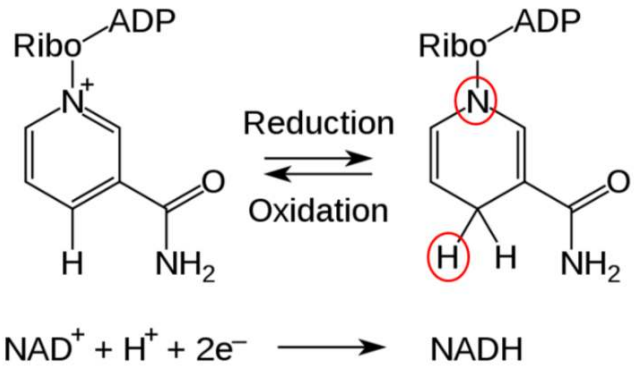


Figure **6.1.6**: The reduction of **NAD** to form **NADH**[4]

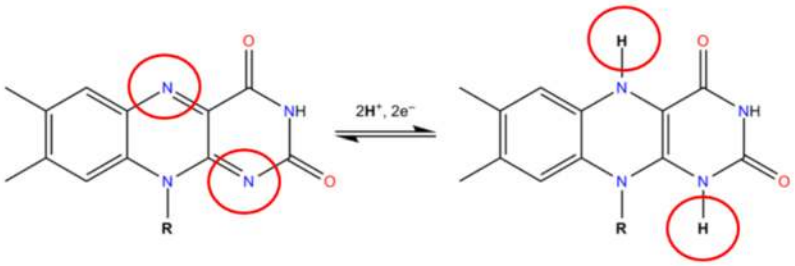


Figure 6.1.7: The reduction of FAD5 to $FADH_2$

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

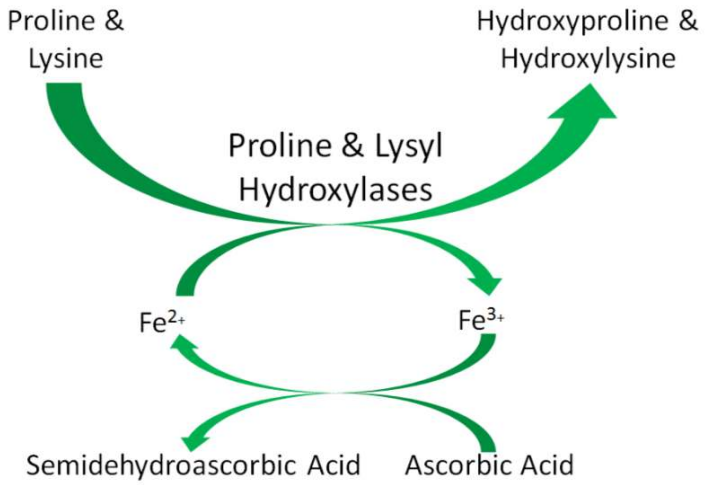


Figure 6.1.8: Iron (Fe^{2+}) is a cofactor for proline and lysyl hydroxylases

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 $\mathbf{FADH_2}$ are produced in the cycle
- **Electron Transport Chain:** oxidative phosphorylation, producing ATP from **NADH** and $\mathbf{FADH_2}$

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.

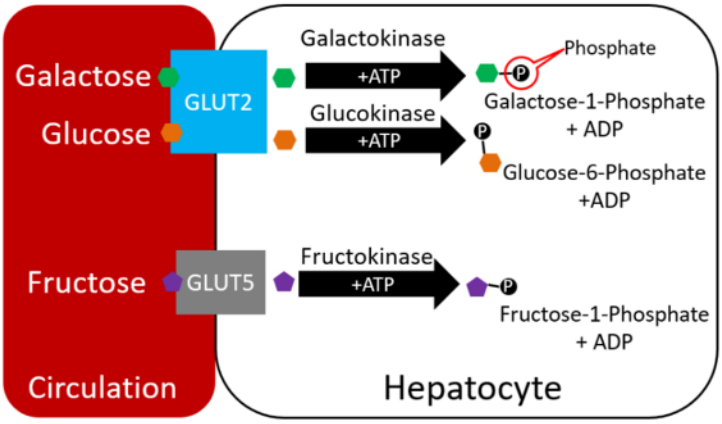


Figure 6.2.1: Uptake of monosaccharides into the hepatocyte

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.

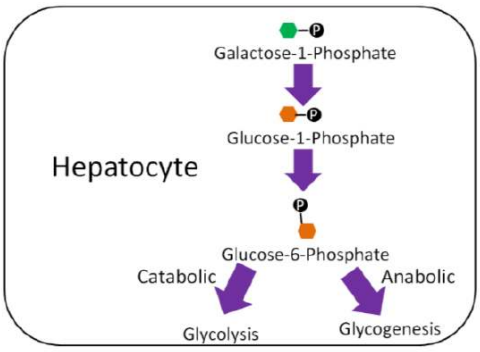


Figure **6.2.2**: Conversion of galactose-1-phosphate to glucose-6-phosphate

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.

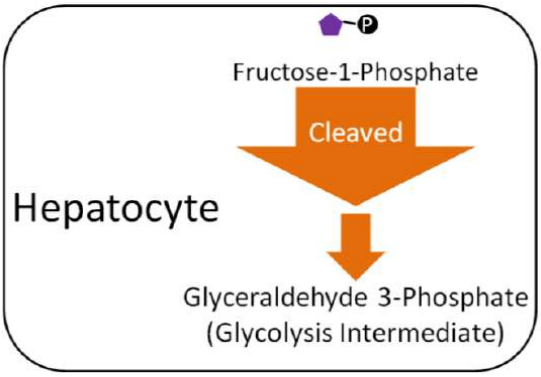


Figure **6.2.3**: Conversion of fructose-1-phosphate to glyceraldehyde 3-phosphate

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.

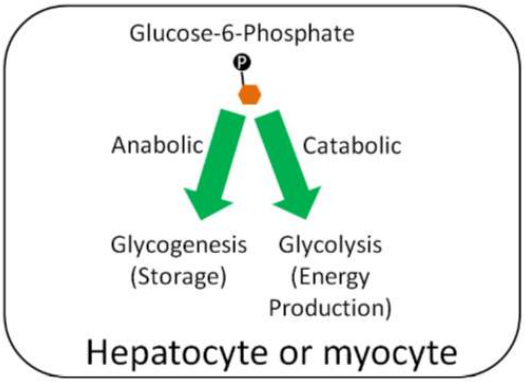


Figure **6.2.4**: The "fork in the road" for glucose-6-phosphate

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.

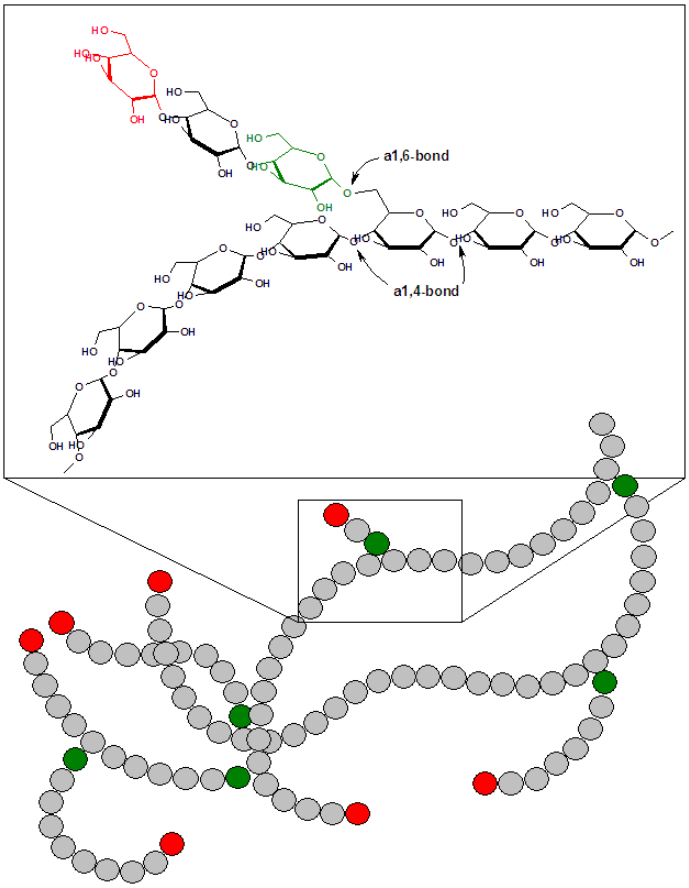


Figure **6.2.5**: Structure of glycogen[2]

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 liver[3]. 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.

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 points[1].

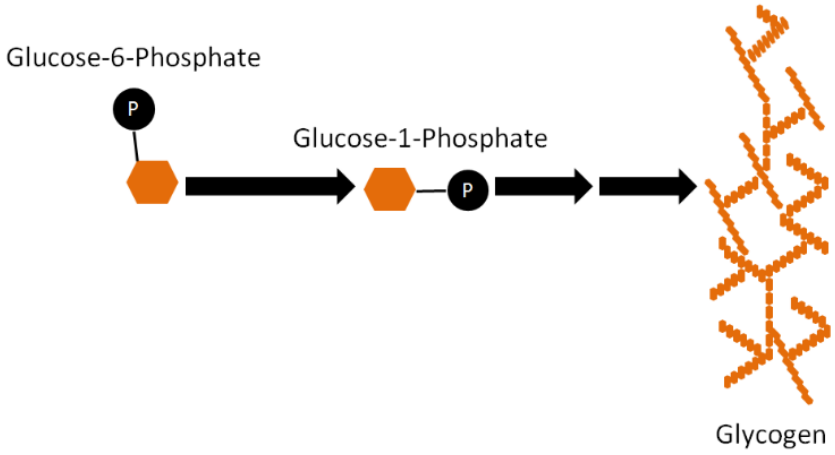


Figure **6.2.6**: Glycogenesis

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.

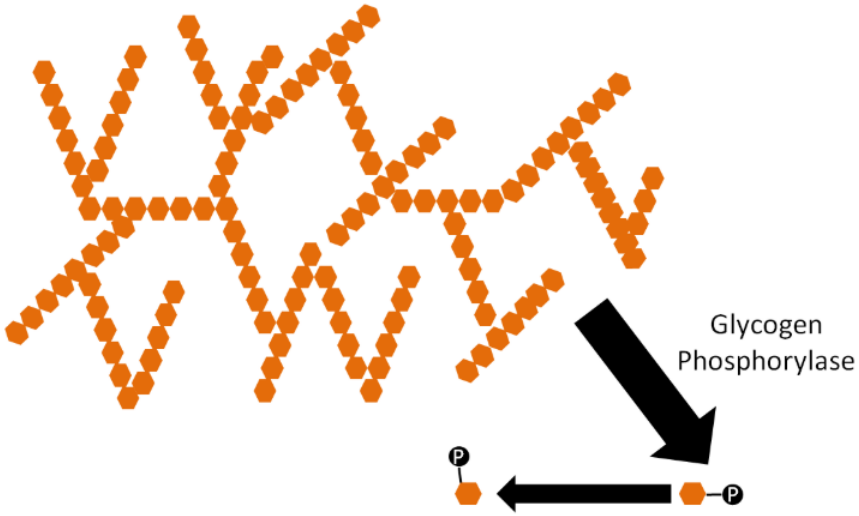


Figure **6.2.7**: Glycogenolysis

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 **NADH**s are also produced.

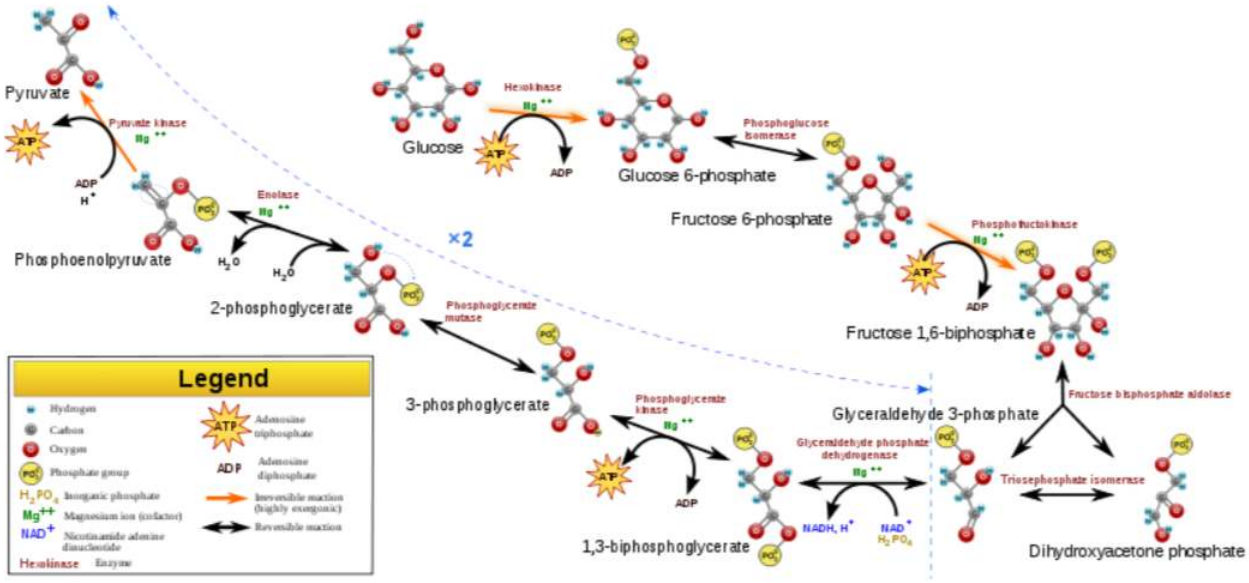


Figure **6.2.8**: Glycolysis[4]

3 steps of Glycolysis

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

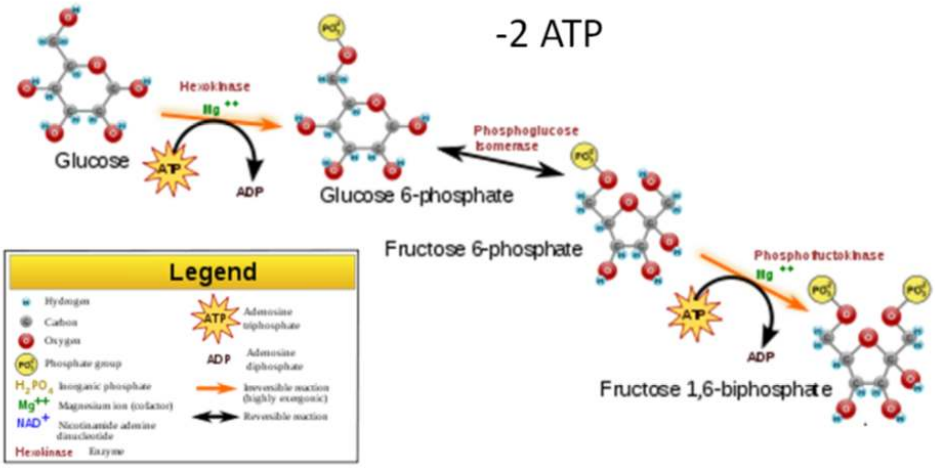


Figure **6.2.9**: Glycolysis step 1, energy investment[4]

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

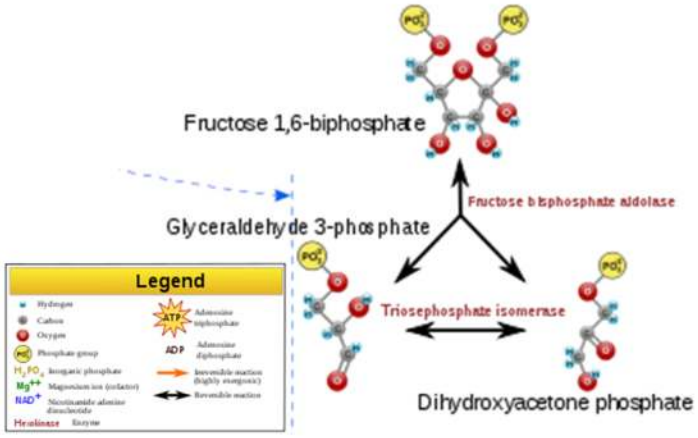


Figure **6.2.10**: Glycolysis step 2, glucose split[4]

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.

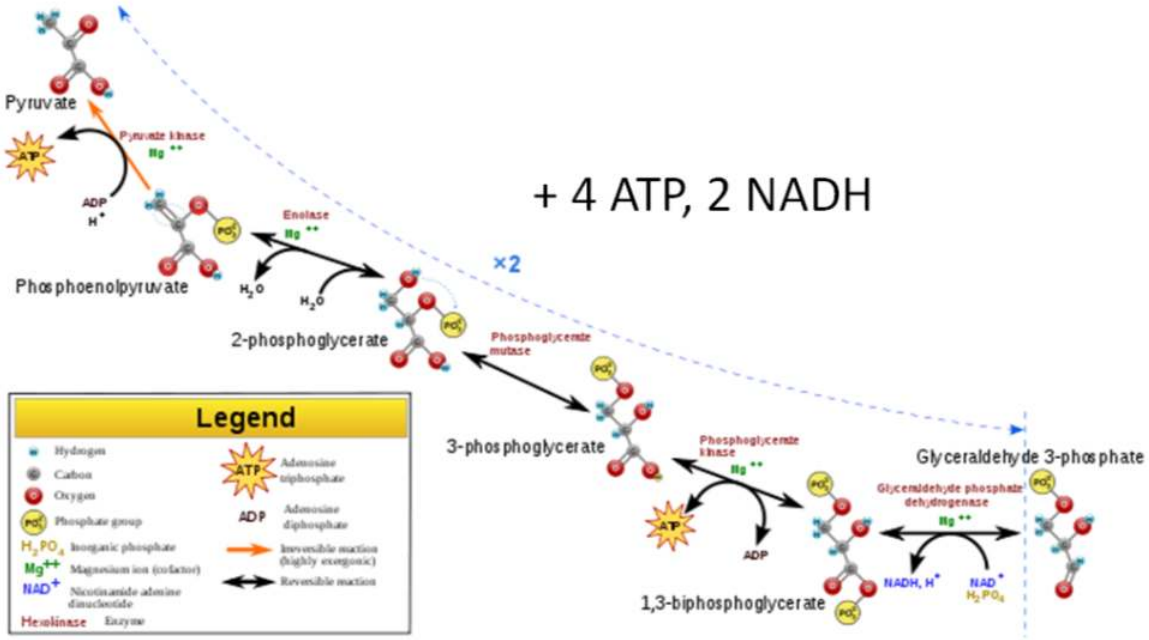


Figure **6.2.11**: Glycolysis step 3, energy harvesting[4]

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



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.

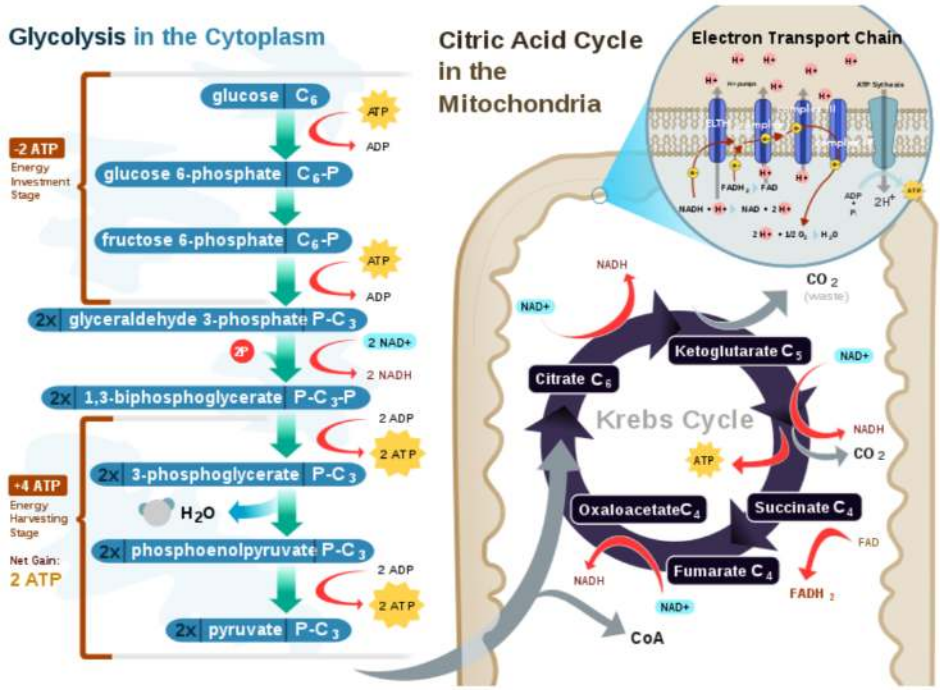


Figure **6.2.12**: Glycolysis, transition reaction, citric acid cycle, and the electron transport chain[5]

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.

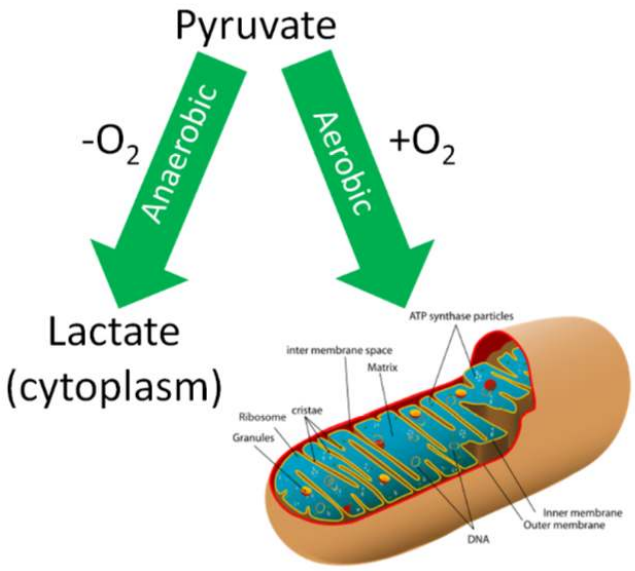


Figure **6.2.13**: Pyruvate fork in the road. What happens depends on whether it is aerobic or anaerobic respiration6

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.

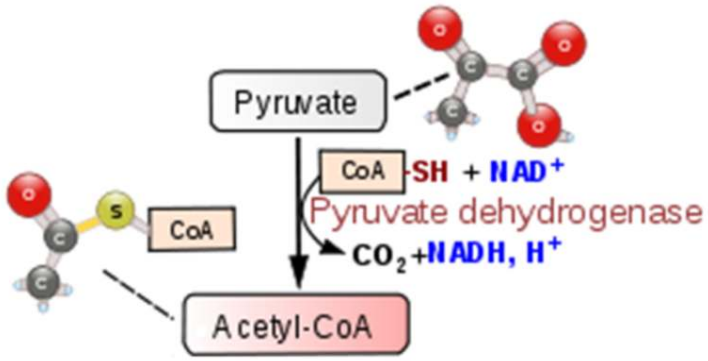


Figure **6.2.14**: Transition reaction7

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

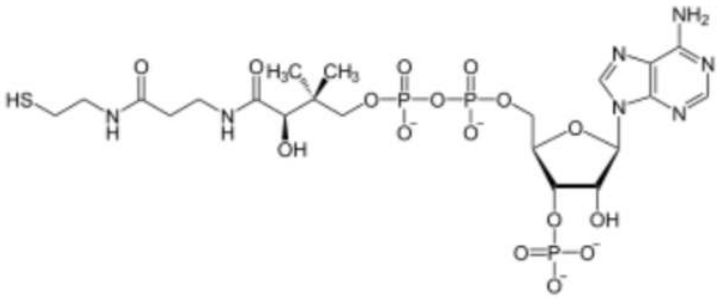


Figure **6.2.15**: Structure of coenzyme A8

Thus, for one molecule of glucose, the transition reaction produces 2 acetyl-**CoA**s, 2 molecules of CO_2, and 2 **NADH**s.

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.

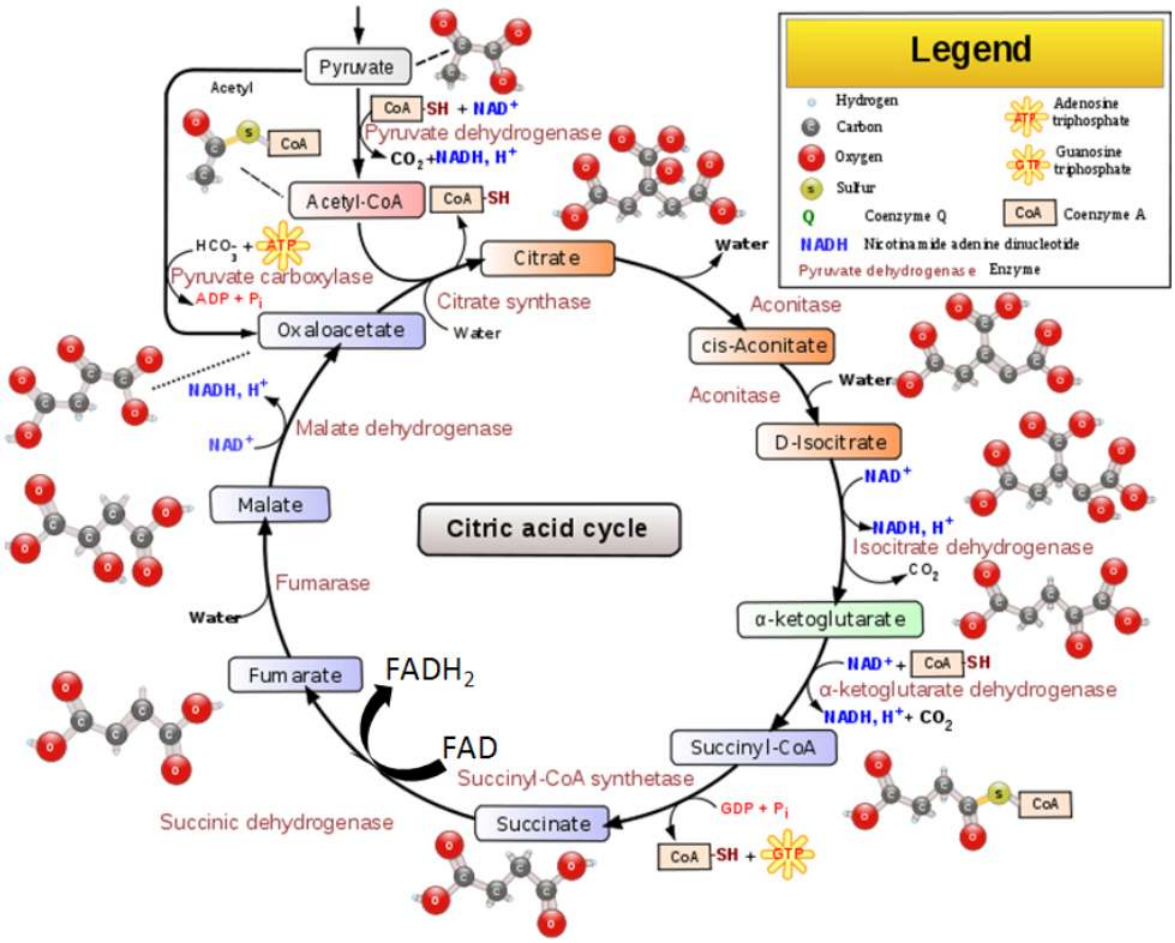


Figure **6.2.16**: The citric acid cycle[9]

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 $\mathbf{CO_2}$ 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 $\mathbf{FADH_2}$ 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 $\mathbf{CO_2}$
- 3 **NADH**
- 1 $\mathbf{FADH_2}$
- 1 GTP (converted to ATP)

The two carbons that are given off as $\mathbf{CO_2}$ 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.



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



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 CO_2
- 6 NADH
- 2 $FADH_2$
- 2 GTP (converted to ATP)

Through glycolysis, the transition reaction, and the citric acid cycle, multiple NADH and $FADH_2$ 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.

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 $FADH_2$, 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 $FADH_2$ to pump protons (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.

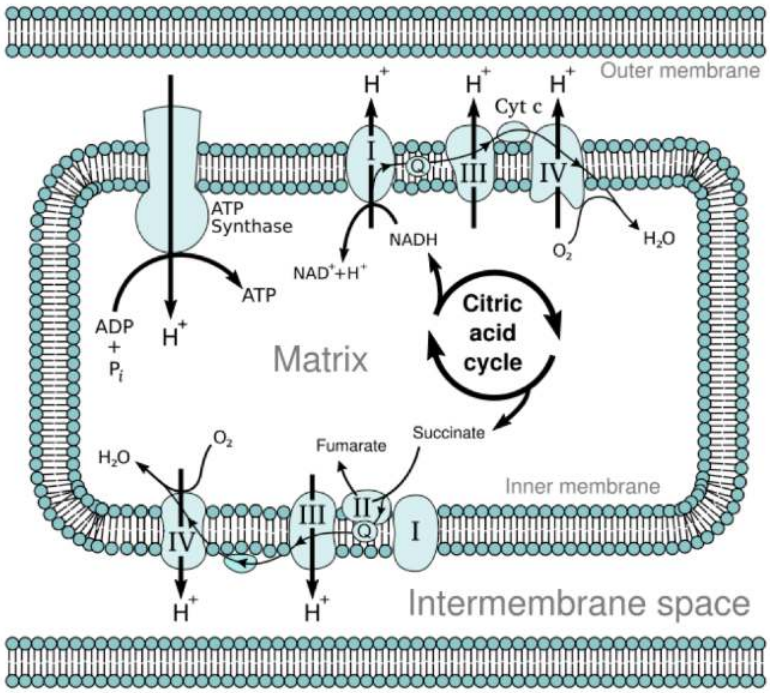


Figure **6.2.17**: Location of the electron transport chain in the mitochondria[10]

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

For one molecule of glucose, the preceding pathways produce:

Glycolysis:	**2NADH**
Transition Reaction:	**2NADH**
Citric Acid Cycle:	**6NADH, 2FADH$_2$**
Total:	**10NADH, 2FADH$_2$**

Multiply that by the amount of ATP per **NADH** or $\mathbf{FADH_2}$ to yield:

$$\frac{\mathbf{10NADH \times 2.5ATP}}{\mathbf{NADH}} = \mathbf{25ATP}$$

$$\frac{\mathbf{2FADH_2 \times 1.5ATP}}{\mathbf{FADH_2}} = \mathbf{3ATP}$$

$$\mathbf{Total = 28ATP}$$

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/$\mathbf{FADH_2}$ 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.



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



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

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/$\mathbf{FADH_2}$ are used instead of 2.5 ATP/**NADH** and 1.5 ATP/$\mathbf{FADH_2}$ 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.

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.

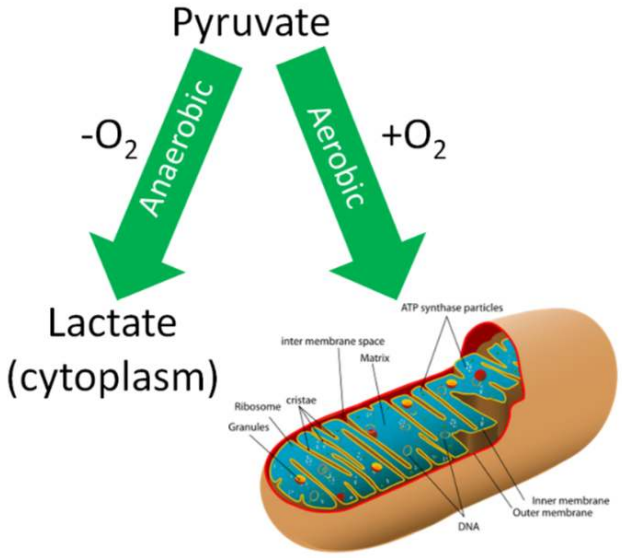


Figure **6.2.18**: Pyruvate fork in the road, what happens depends on whether it is aerobic or anaerobic respiration6

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 $\mathbf{FADH_2}$.



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

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

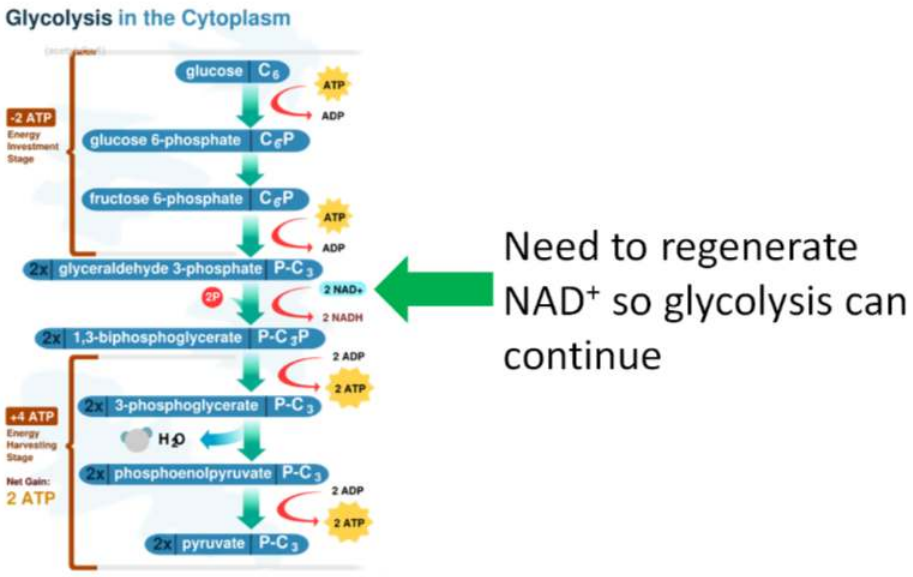


Figure **6.2.19**: Why **NAD** needs to be regenerated under anaerobic conditions[5]

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

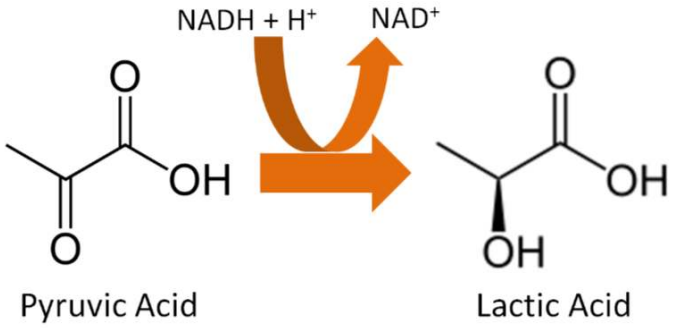


Figure **6.2.20**: The conversion of pyruvic acid to lactic acid regenerates NAD[12,13]

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.

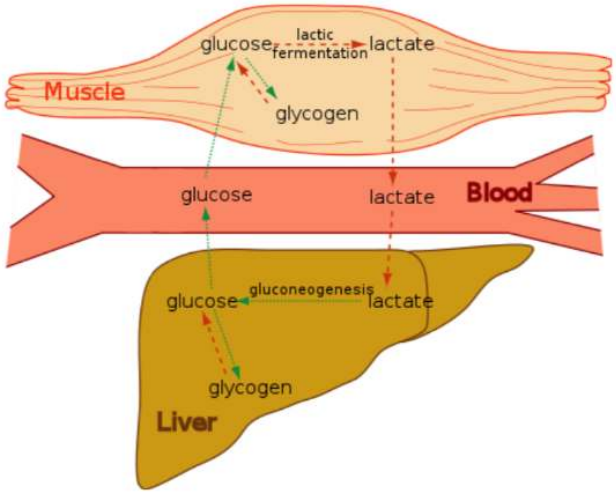


Figure **6.2.21**: The Cori cycle[14]

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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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.

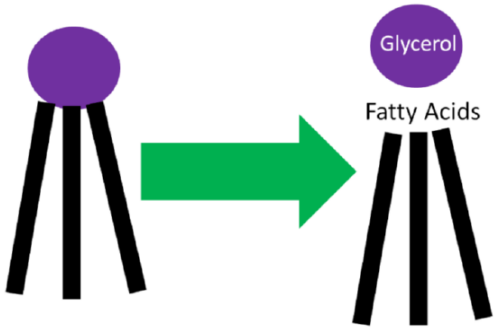


Figure **6.3.1**: Lipolysis

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.

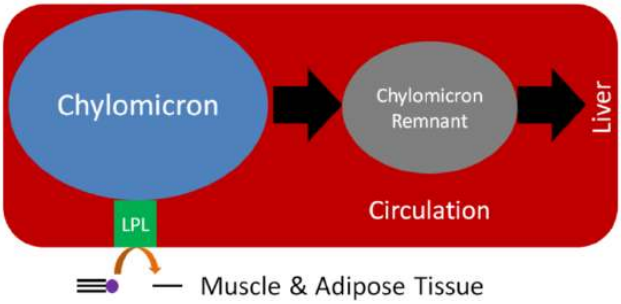


Figure **6.3.2**: Lipoprotein lipase cleaves fatty acids from the chylomicron, forming a chylomicron remnant.

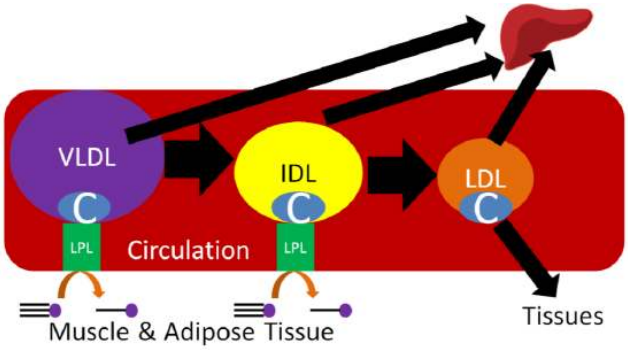


Figure **6.3.3**: Lipoprotein lipase cleaves triglycerides from VLDL and IDL, forming subsequent lipoproteins (IDL and LDL) that contain less triglyceride

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 production[1].

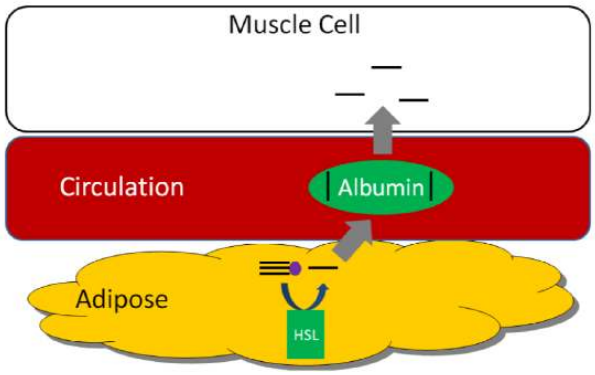


Figure **6.3.4**: Hormone-sensitive lipase

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)

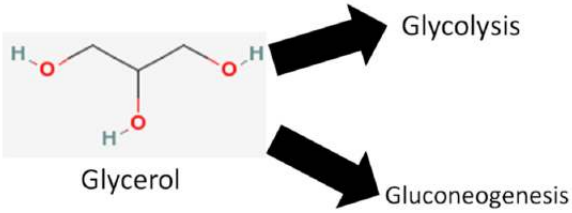


Figure **6.3.5**: Metabolic fates of glycerol

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.

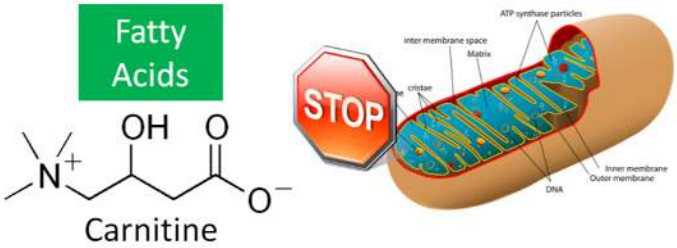


Figure **6.3.6**: Carnitine shuttles fatty acids into the mitochondria[2,3]

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.

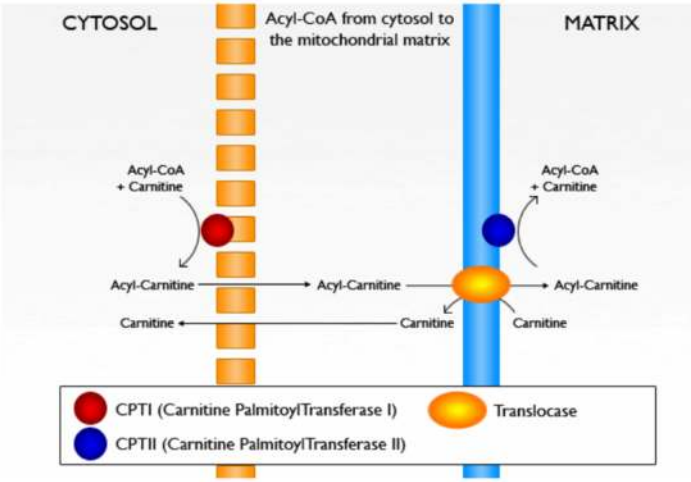


Figure **6.3.7**: Transfer of fatty acids into the mitochondria[4]

Web Link

Fatty acid transfer from cytoplasm to mitochondria

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].

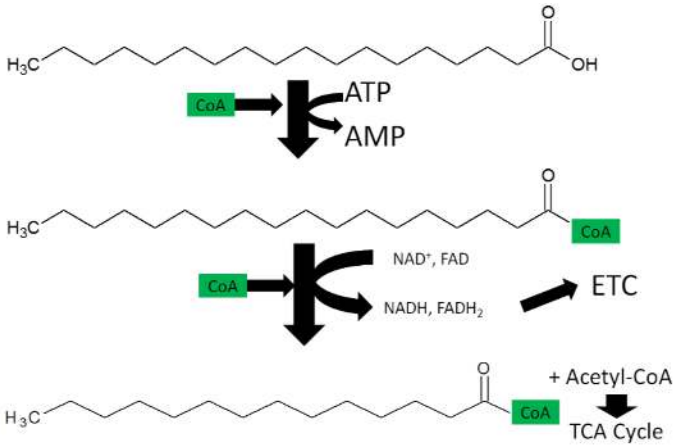


Figure **6.3.8**: Fatty Acid Oxidation

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 $\mathbf{FADH_2}$.

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-**CoA**s, 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-**CoA**s

8 **NADH**

8 $\mathbf{FADH_2}$

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.

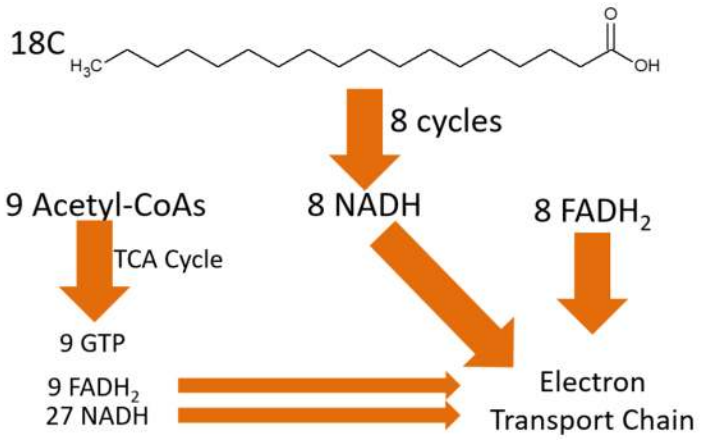


Figure **6.3.9**: Complete oxidation of an 18 carbon (C) fatty acid

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

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.

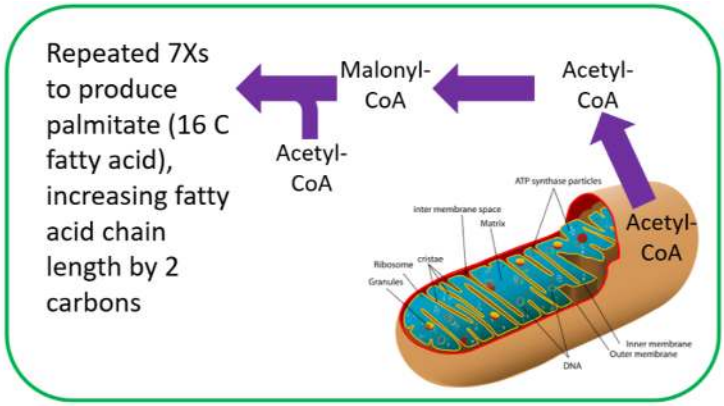


Figure **6.3.10**: Fatty acid synthesis[7]

Most fatty acids synthesized will be esterified into triglycerides for storage.

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.

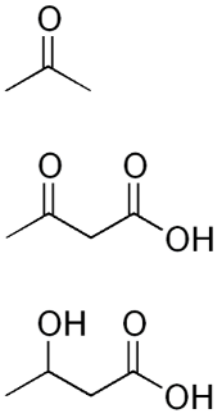


Figure **6.3.11**: The three ketone bodies from top to bottom (acetone, acetoacetic acid, and beta-hydroxybutyric acid[8])

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.

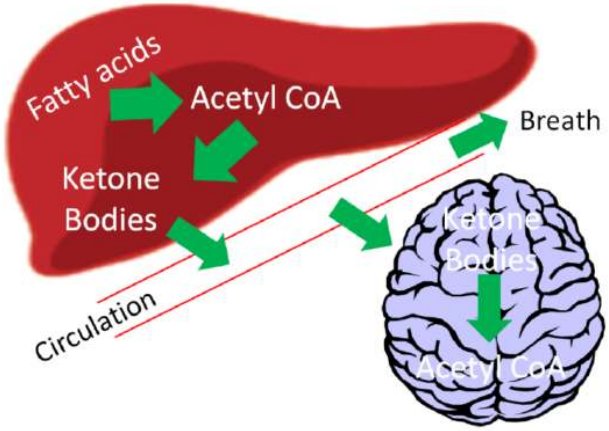


Figure **6.3.12**: The production, release, use, or exhalation of ketone bodies[9]

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.

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.

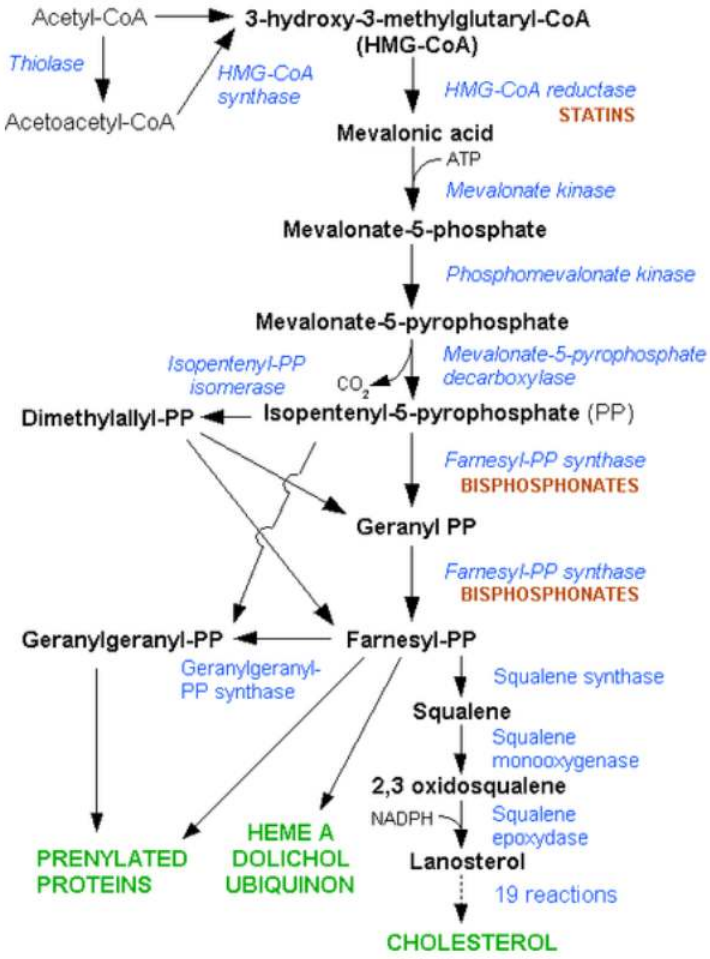


Figure **6.3.13**: Cholesterol synthesis pathway10

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.

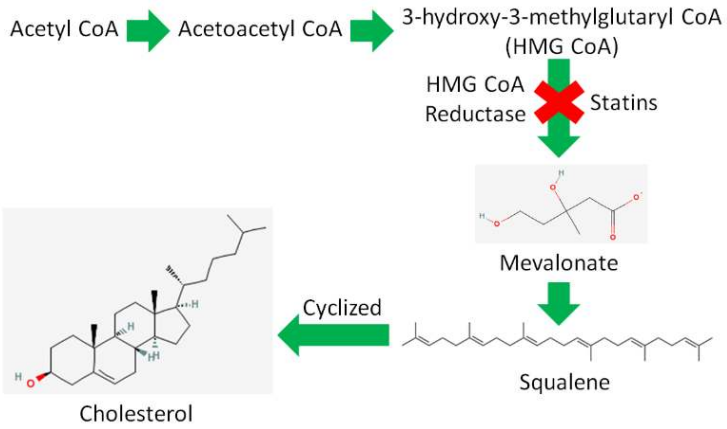


Figure **6.3.14**: Cholesterol synthesis simplified[11]

A rate-limiting enzyme is like a bottleneck in a highway, as shown below, that determines the flow of traffic past it.

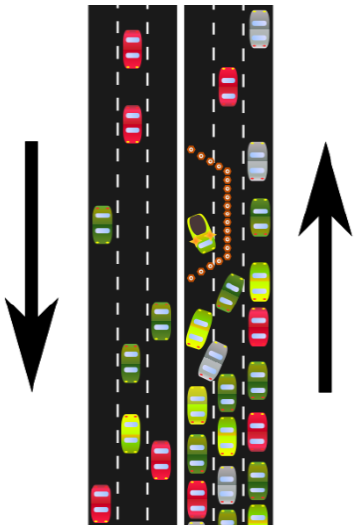


Figure **6.3.15**: Bottleneck in traffic[12]

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 are[13]:

- 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.

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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.

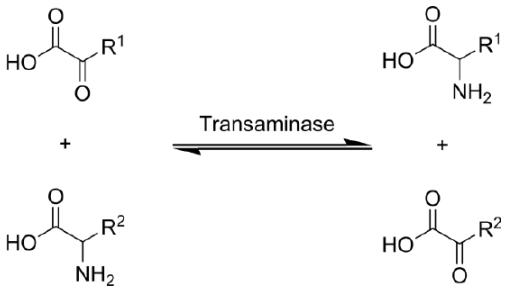


Figure 6.4.1: Generic transamination reaction where the top keto acid is converted to an amino acid, while the bottom amino acid is converted to a keto acid1

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.

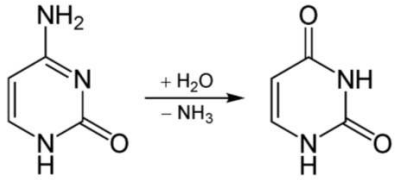


Figure 6.4.2: Deamination of cytosine to uracil (nucleotides, not amino acids)2

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.

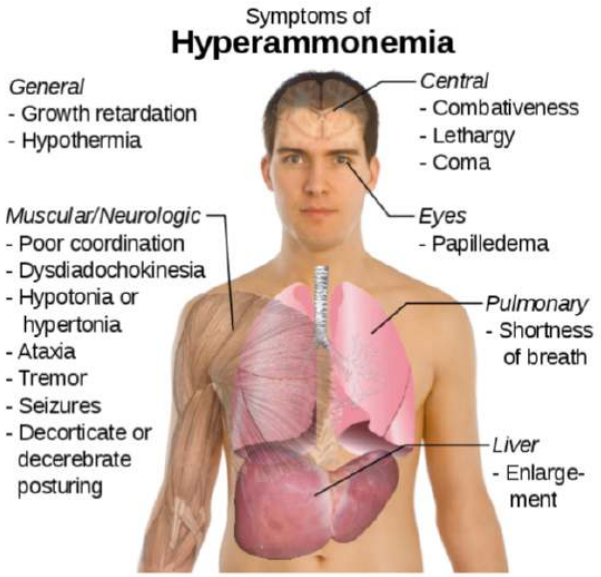


Figure **6.4.3**: Symptoms of Hyperammonemia[3]

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.

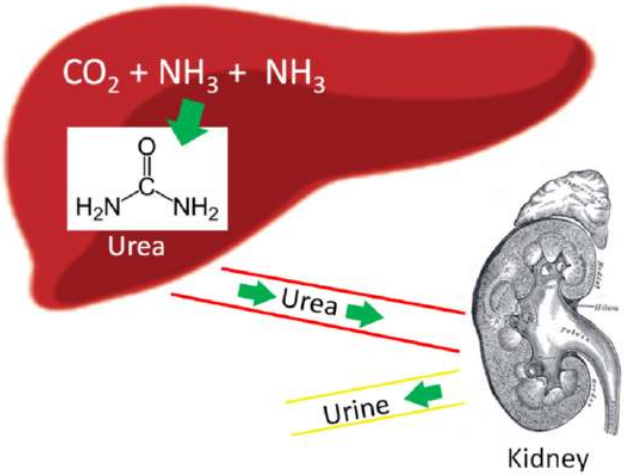


Figure **6.4.4**: Production of urea helps to safely remove ammonia from the body[4-6]

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.

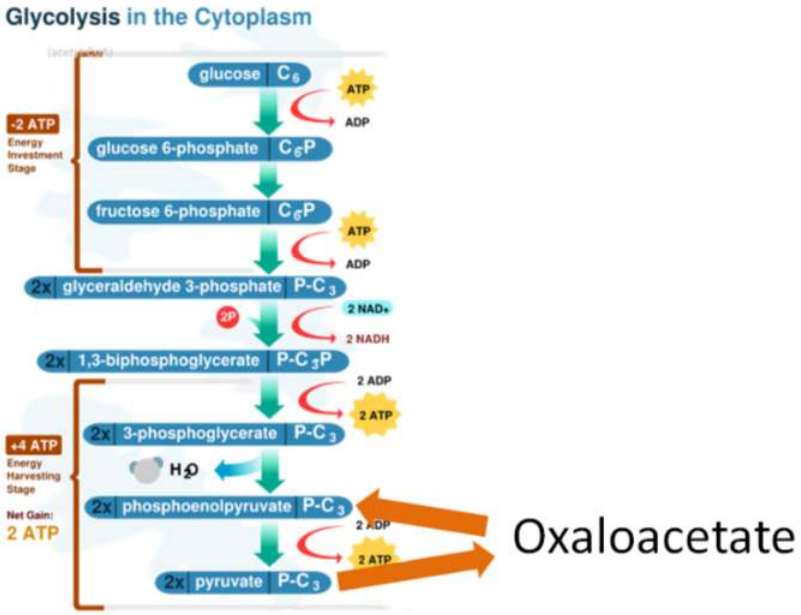


Figure 6.4.5: Gluconeogenesis is glycolysis in reverse with an oxaloacetate workaround7

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).

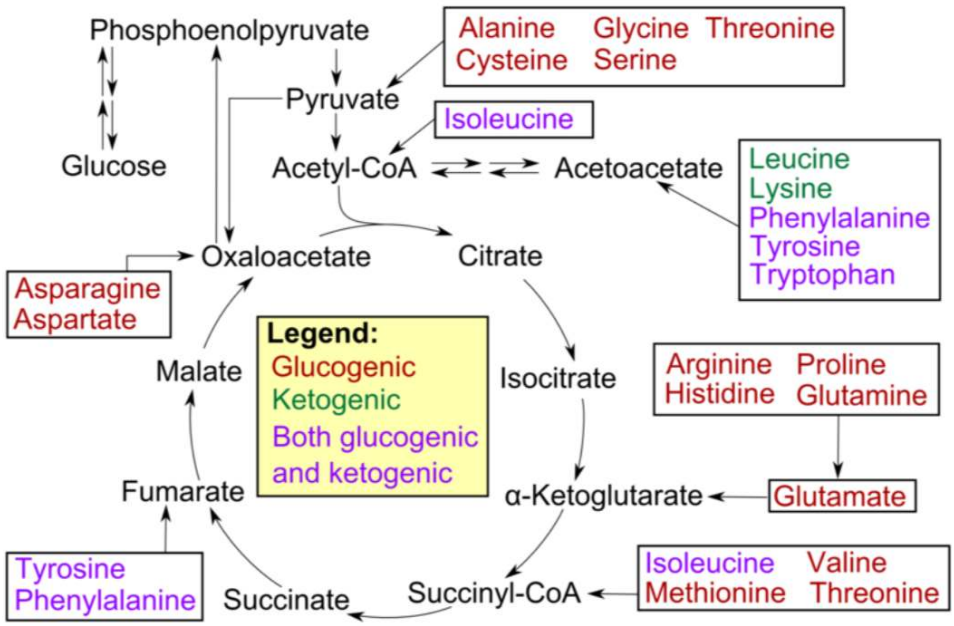


Figure 6.4.6: Glucogenic (red), ketogenic (green), and glucogenic and ketogenic amino acids8

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 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).

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.

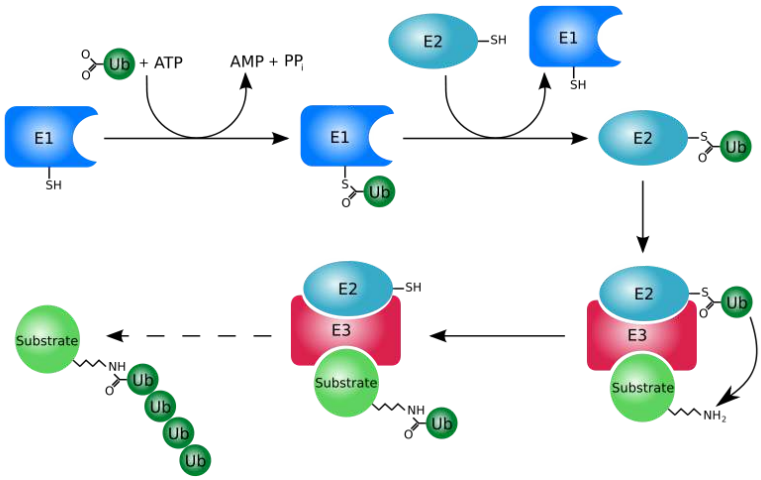


Figure 6.4.7: Ubiquitination of a protein (substrate)9

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.



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.

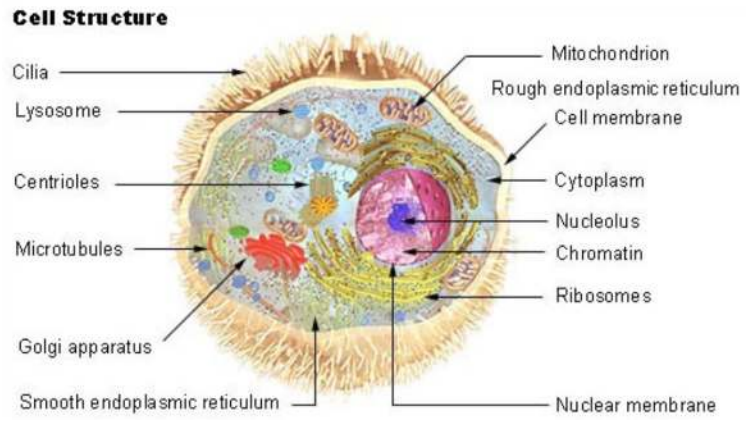


Figure 6.4.8: Lysosomes are organelles within the cell10

Calpain Degradation

The last degradation system is the calpain system, which is not as well understood, but does require calcium.

References

1. en.Wikipedia.org/wiki/File:Transaminierung.svg
2. en.Wikipedia.org/wiki/File:De...ierungCtoU.png
3. en.Wikipedia.org/wiki/File:Sy...rammonemia.svg
4. commons.wikimedia.org/wiki/File:Liver.svg
5. upload.wikimedia.org/wikipedi...ey_section.jpg
6. en.Wikipedia.org/wiki/File:Urea.png
7. en.Wikipedia.org/wiki/File:CellRespiration.svg
8. en.Wikipedia.org/wiki/File:Am...catabolism.png
9. en.Wikipedia.org/wiki/File:Ubiquitylation.svg
10. en.Wikipedia.org/wiki/File:Il..._structure.jpg

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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.

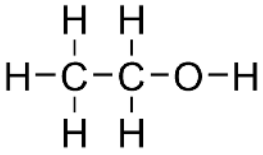


Figure **6.5.1**: Structure of ethanol[1]

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.

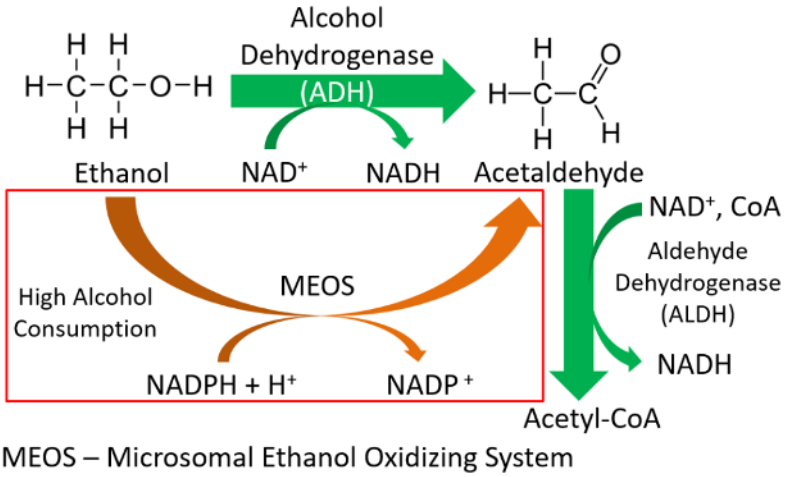


Figure **6.5.2**: Ethanol Metabolism[1,5]

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 ethanol[3], and it differs from **ADH** in that it uses ATP to convert reduced nicotinamide adenine dinucleotide phosphate (**NADPH + 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 body[3].

Females have lower stomach **ADH** activity and body **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 activity[6]. This leads to acetaldehyde buildup and undesirable symptoms such as: flushing, dizziness, nausea, and headaches[2]. The following animation explains what happens when the MEOS system gets involved in alcohol metabolism.

References

1. en.Wikipedia.org/wiki/File:Et..._structure.png
2. Byrd-Bredbenner C, Moe G, Beshgetoor D, Berning J. (2009) Wardlaw's perspectives in nutrition. New York, NY: McGraw-Hill.
3. Whitney E, Rolfes SR. (2008) Understanding nutrition. Belmont, CA: Thomson Wadsworth.
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5. en.Wikipedia.org/wiki/Acetal...de-2D-flat.svg
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CHAPTER OVERVIEW

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

7.5: Micronutrients Overview and Dietary Reference Intakes (DRIs)

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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

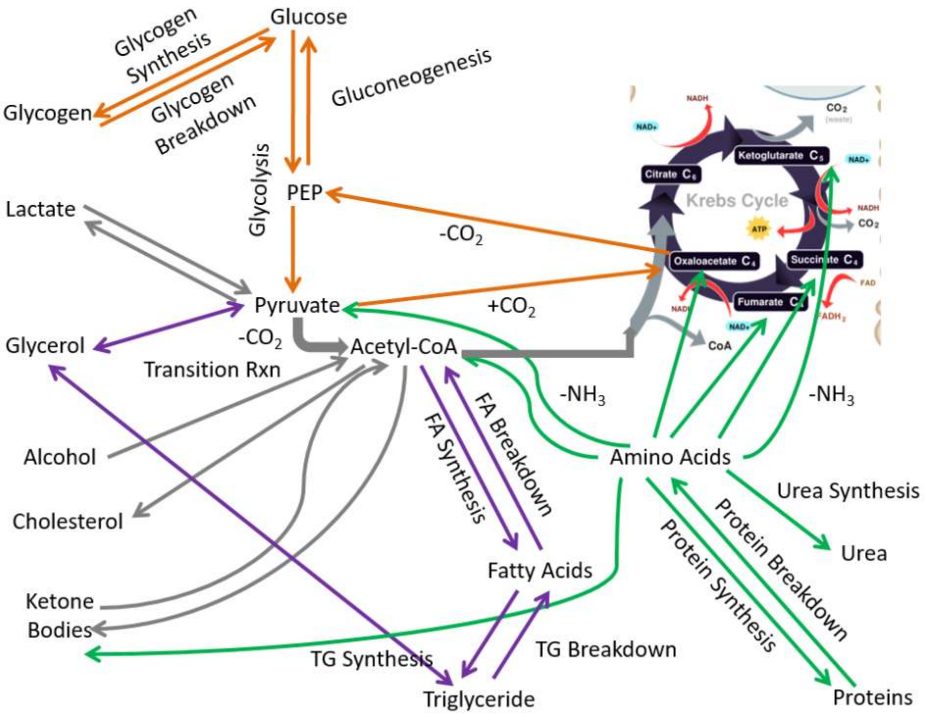


Figure **7.1.1**: Integrated macronutrient and alcohol metabolism

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.

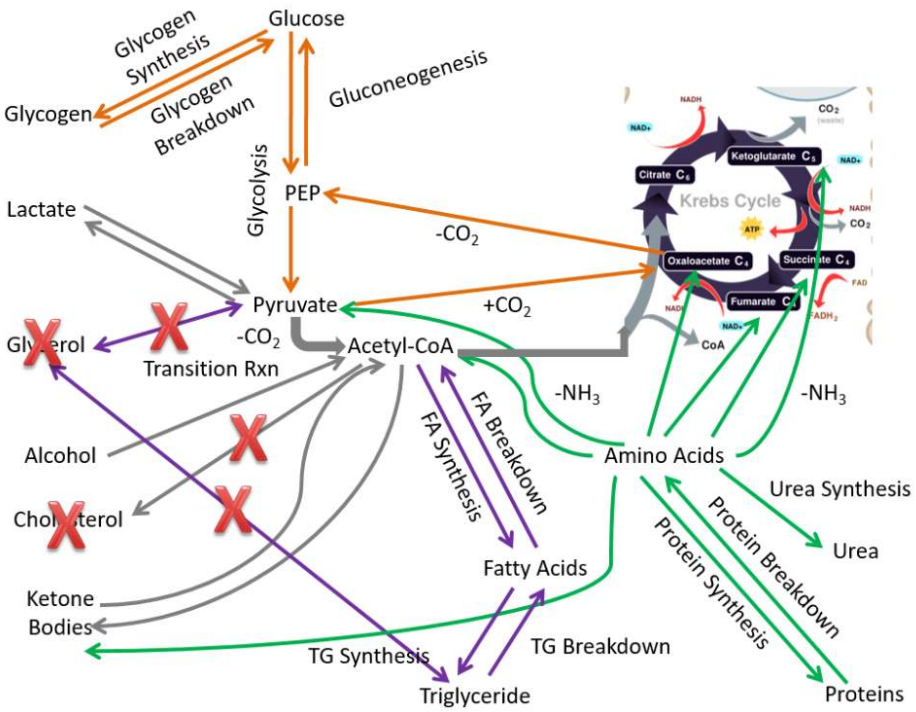


Figure 7.1.2: Removal of glycerol and cholesterol pathways[1]

Thus, we are left with the following simplified figure:

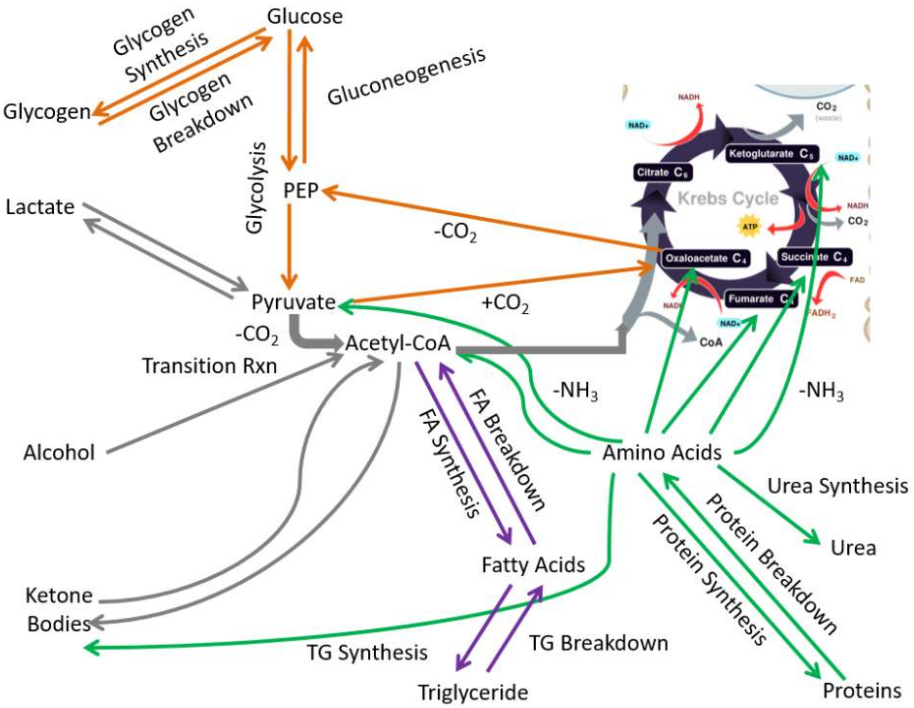


Figure 7.1.3: Simplified integrated macronutrient and alcohol metabolism[1]

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.

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.

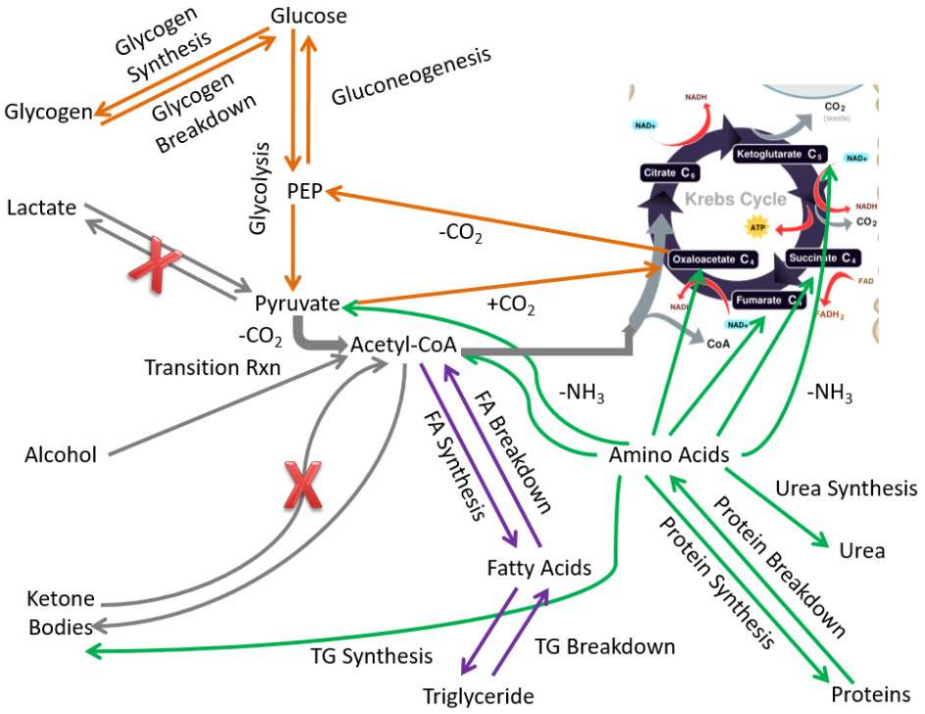


Figure **7.2.1**: Ketone body breakdown and lactate synthesis are major macronutrient metabolic pathways that the liver does not normally perform[1]

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

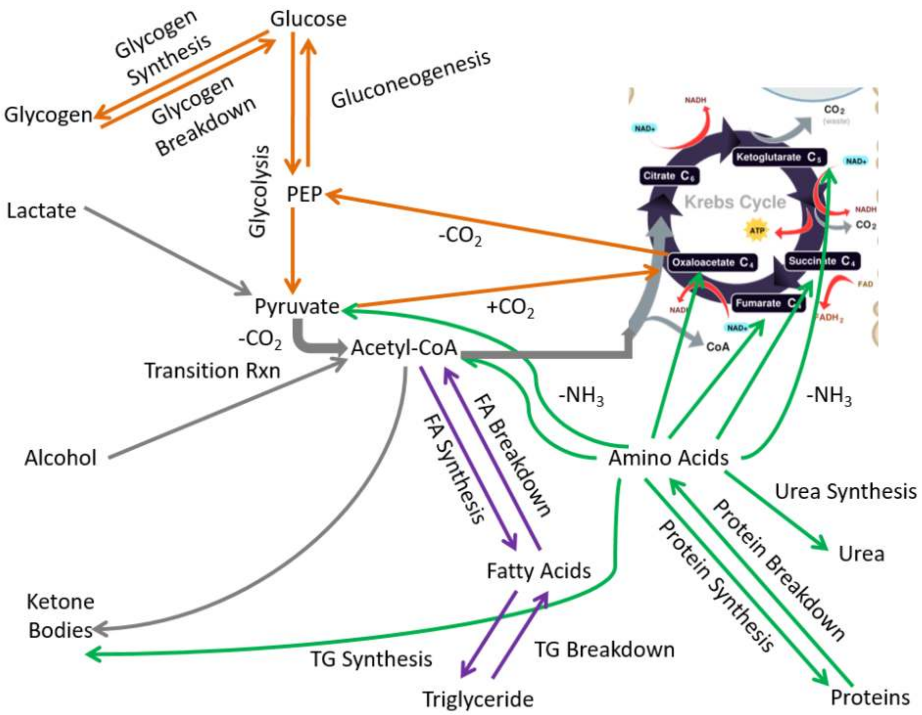


Figure 7.2.2: Metabolic capability of the liver[1]

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].

References

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.

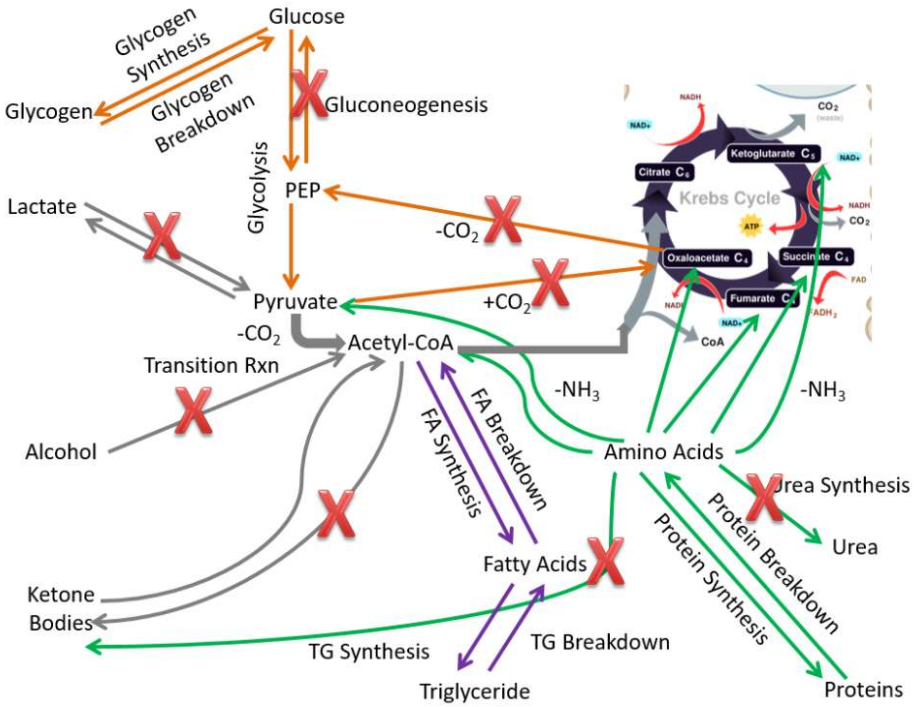


Figure **7.3.2**: Removing the pathways that only or mostly occur in the liver[3]

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

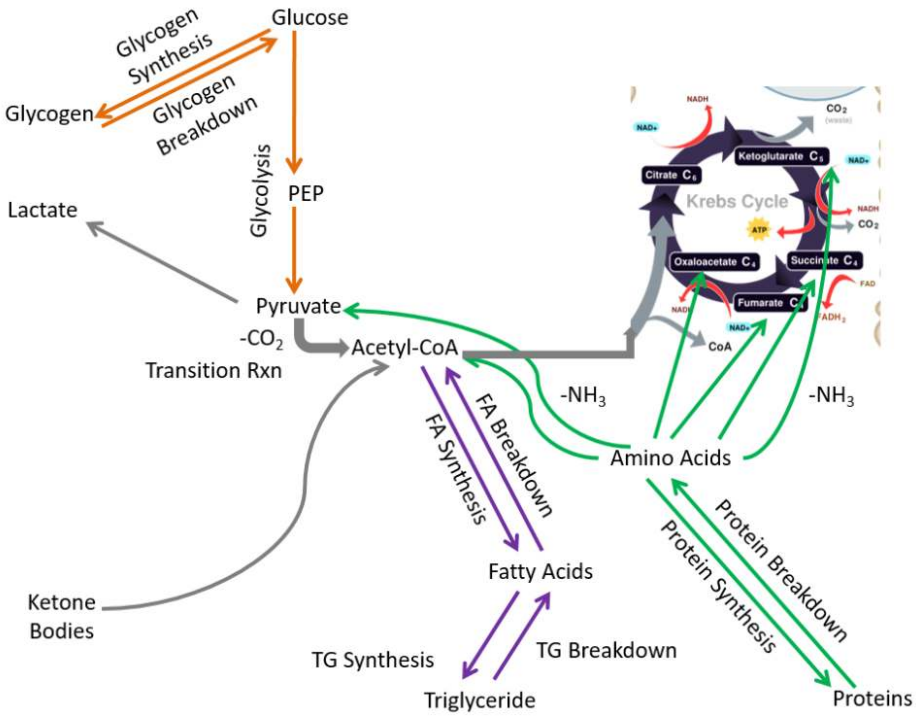


Figure **7.3.3**: The metabolic capability of the extrahepatic tissues[3]

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

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.

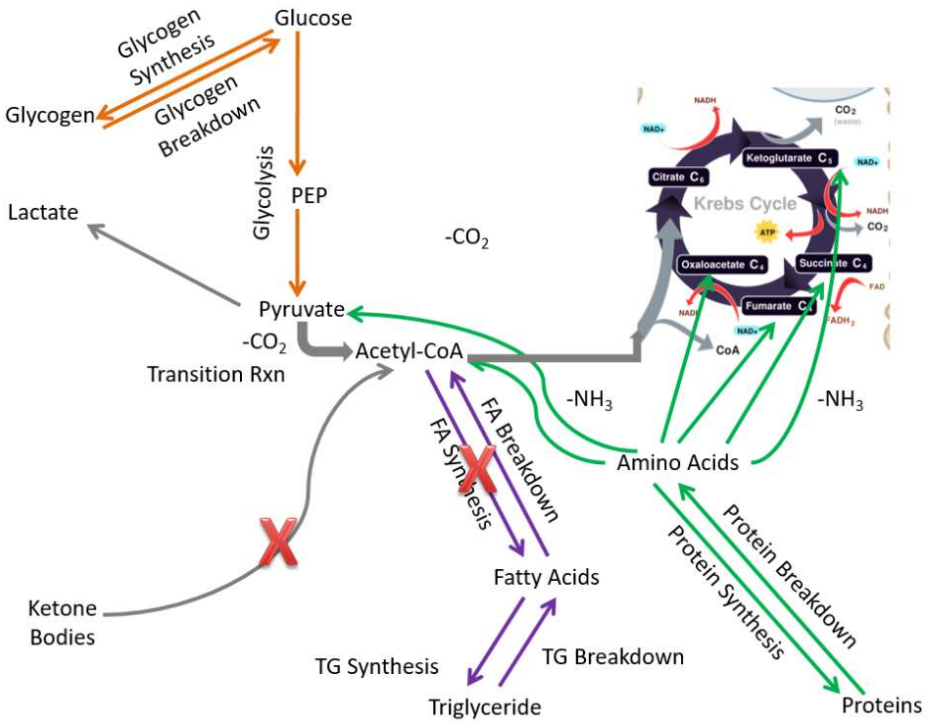


Figure **7.3.4**: The metabolic pathways that are not performed or important in the muscle, compared to extrahepatic tissues as a whole[3]

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

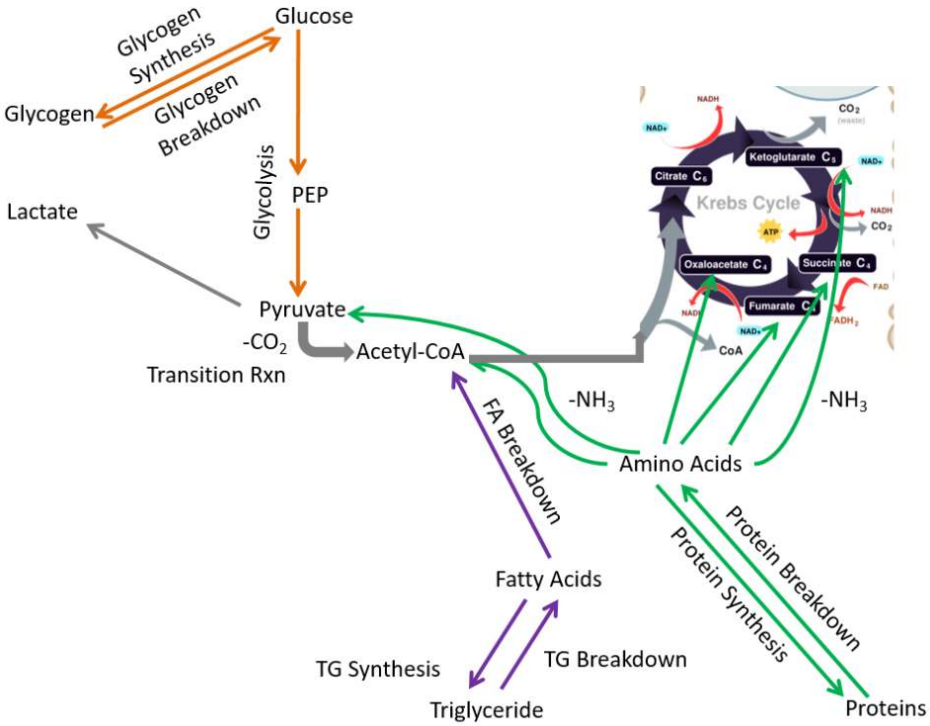


Figure **7.3.5**: Muscle metabolic capability[3]

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.

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.

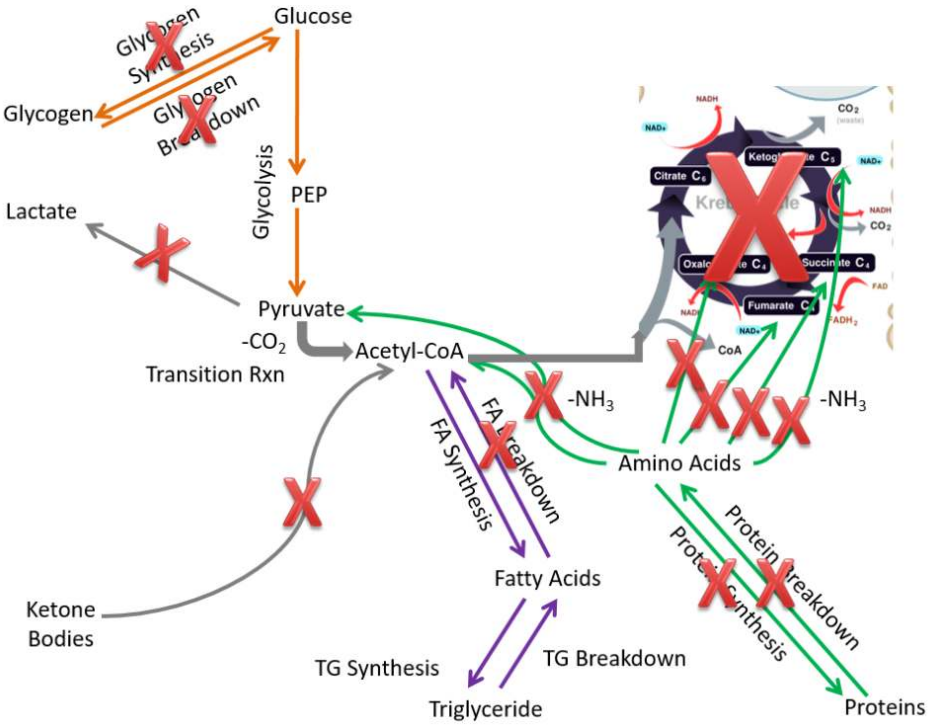


Figure **7.3.6**: The metabolic pathways that are not performed or important in the adipose, compared to extrahepatic tissues as a whole are crossed out[3]

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

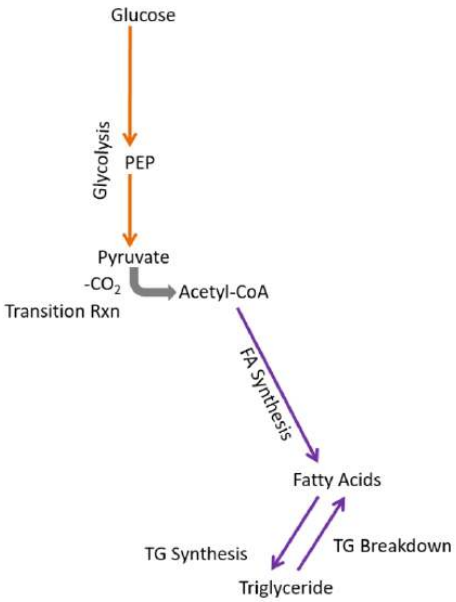


Figure **7.3.7**: Adipose metabolic capability

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.

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.

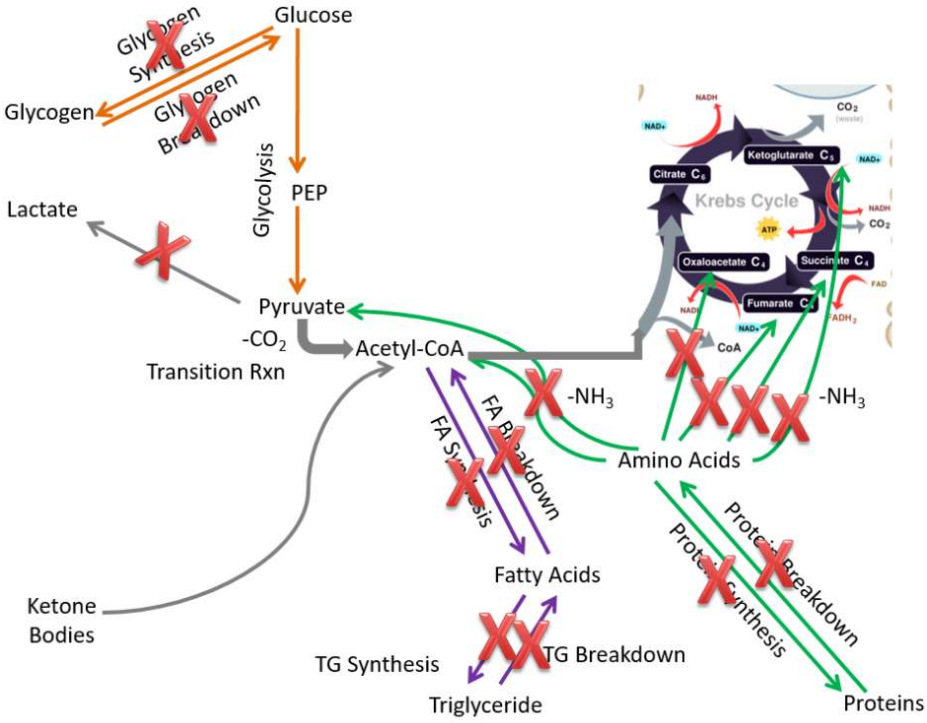


Figure **7.3.8**: The metabolic pathways that are not performed or important in the brain compared to extrahepatic tissues as a whole are crossed out3

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 pathway4.

By removing those pathways the only pathways left are:

- Glycolysis
- Ketone body breakdown

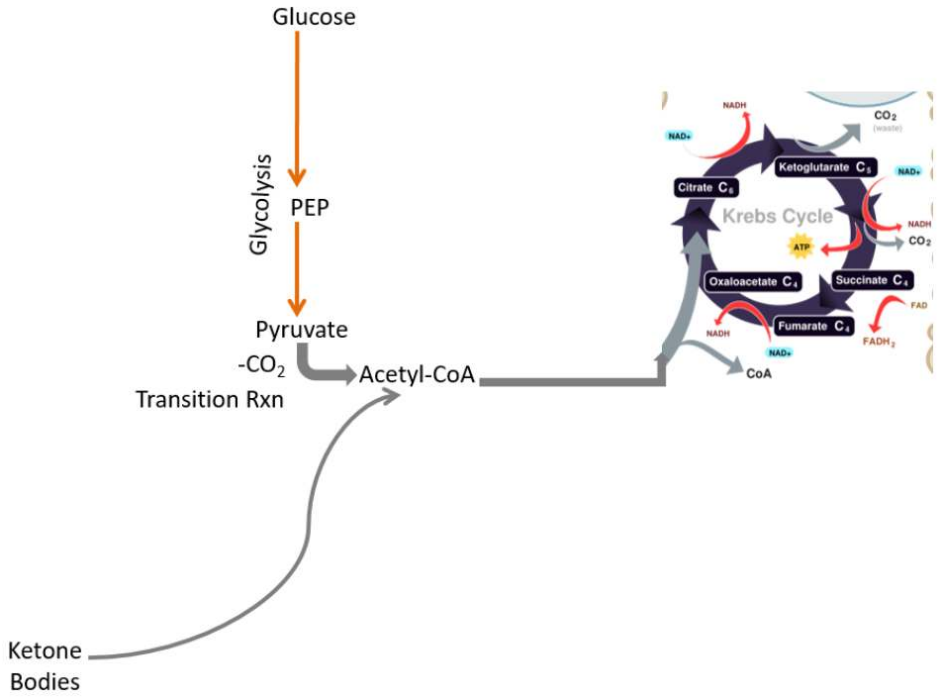


Figure **7.3.9**: Brain metabolic capability3

Thus, due to its limited metabolic capabilities, the brain needs to receive either glucose or ketone bodies to use as an energy source.

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.

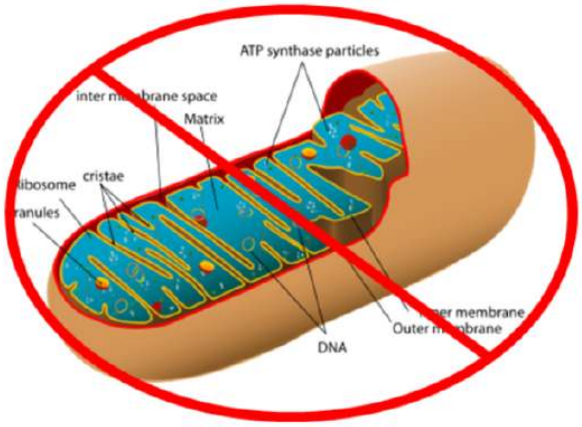


Figure **7.3.10**: Red blood cells do not contain mitochondria8

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.

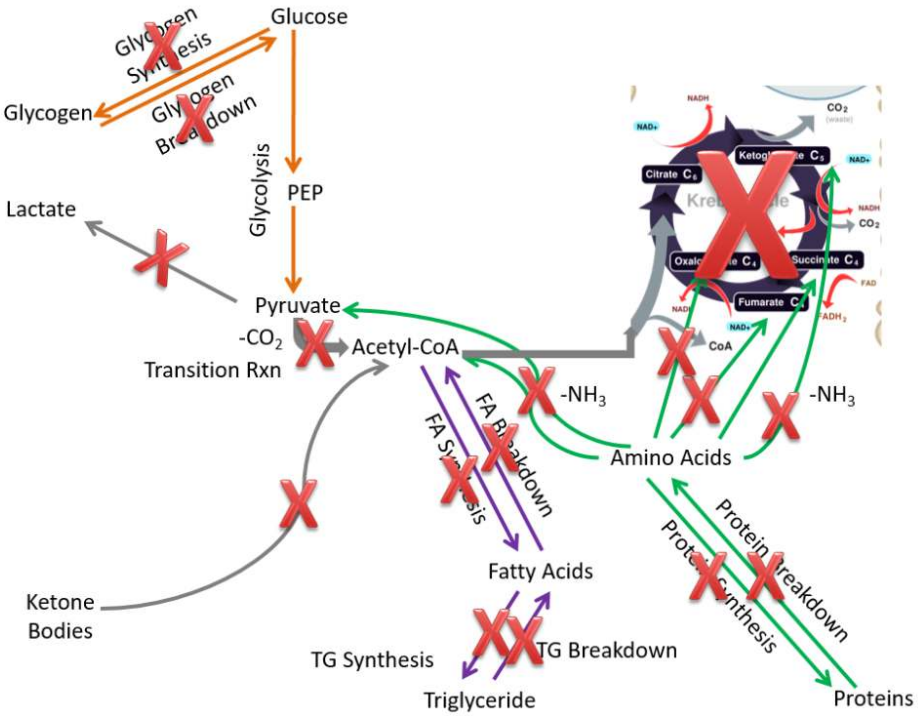


Figure **7.3.11**: The metabolic pathways that are not performed or important in the red blood cells, compared to extrahepatic tissues as a whole are crossed off[3]

If all those pathways are removed, only glycolysis is left, where pyruvate is converted to lactate.

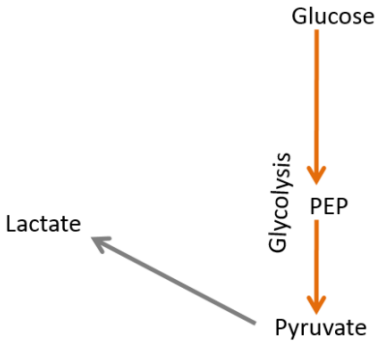


Figure **7.3.12**: Red blood cell metabolic capability

Thus, red blood cells are one-trick ponies, only being able to perform glycolysis and produce lactate.

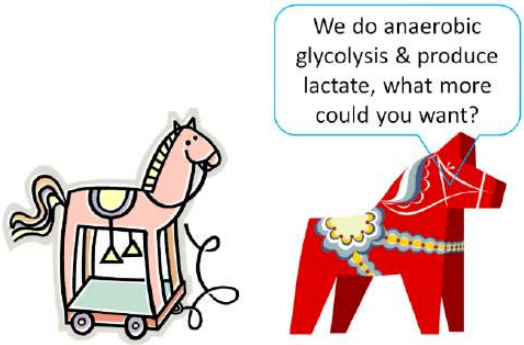


Figure **7.3.13**: Red blood cells are one-trick ponies

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3. en.Wikipedia.org/wiki/File:CellRespiration.svg
4. Yang SY, He XY, Schulz H (1987) Fatty acid oxidation in rat brain is limited by the low activity of 3-ketoacyl-coenzyme A thiolase. J BIol Chem 262 (27): 13027-13032.
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.

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 $FADH_2$ 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.

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.

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 $FADH_2$ 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.

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 $FADH_2$ 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.

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.

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 $\mathbf{FADH_2}$ 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 $\mathbf{FADH_2}$ 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).

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.

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.

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 $\mathbf{FADH_2}$ 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.

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.

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				
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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CHAPTER OVERVIEW

7.5: 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.

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CHAPTER OVERVIEW

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

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].

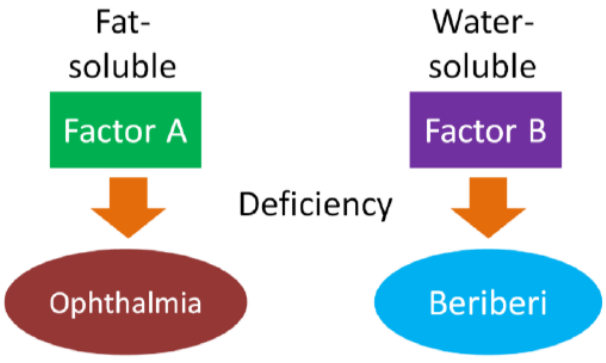


Figure **8.1.1**: Factor A deficiency led to ophthalmia, factor B deficiency led to beriberi

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 today[1].

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	-	-
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

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.

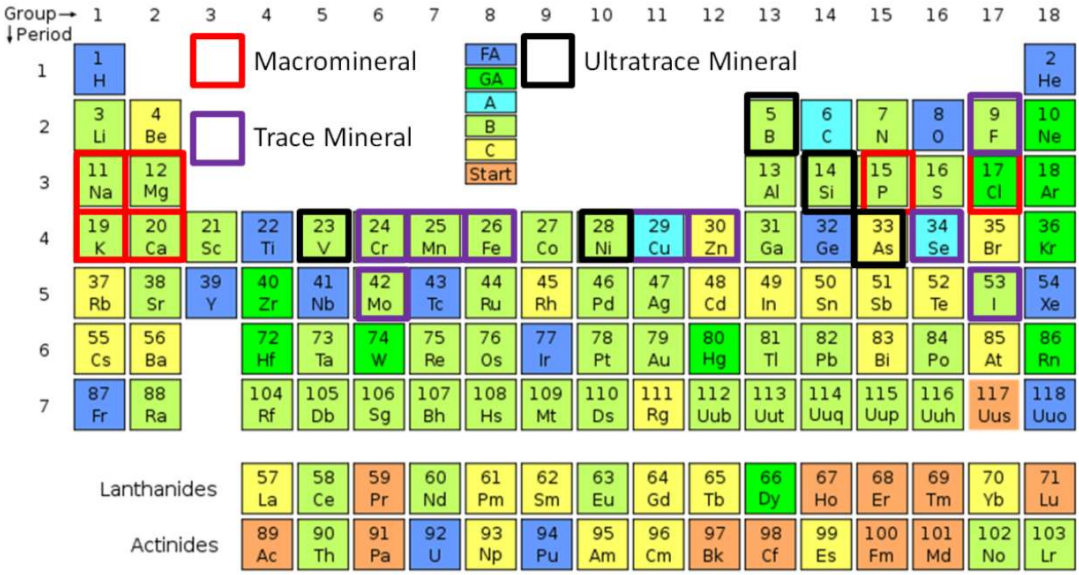


Figure **8.2.1**: Minerals are a subset of elements, this figure shows their position within the periodic table[2]

References

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 $\mathbf{B_{12}}$	Iron	Calcium	Potassium
Selenium	Niacin	Vitamin $\mathbf{B_6}$	Vitamin $\mathbf{B_6}$	Vitamin K	Chloride
Iron	Pantothenic Acid		Folate	Phosphorus	Phosphorus
Copper	Vitamin $\mathbf{B_6}$		Vitamin $\mathbf{B_{12}}$	Magnesium	Magnesium
Zinc	Biotin		Copper	Fluoride	
Manganese	Vitamin $\mathbf{B_{12}}$		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.

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”.

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%).

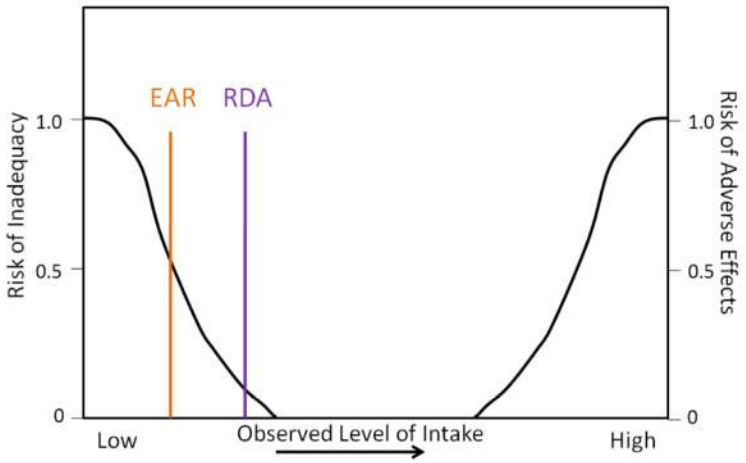


Figure 8.4.1: The EAR meets the needs of 50% of the population, RDA meets the needs of 97.5% of the population.

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.

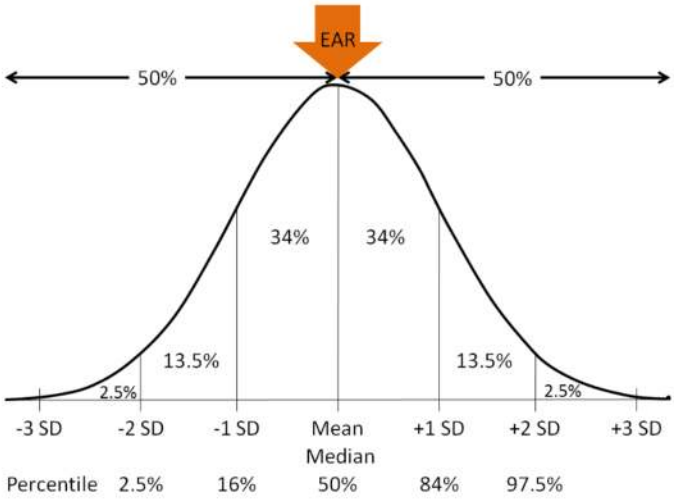


Figure **8.4.2**: The EAR meets the needs of 50% of the population as depicted in this normal distribution. SD - standard deviation

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.

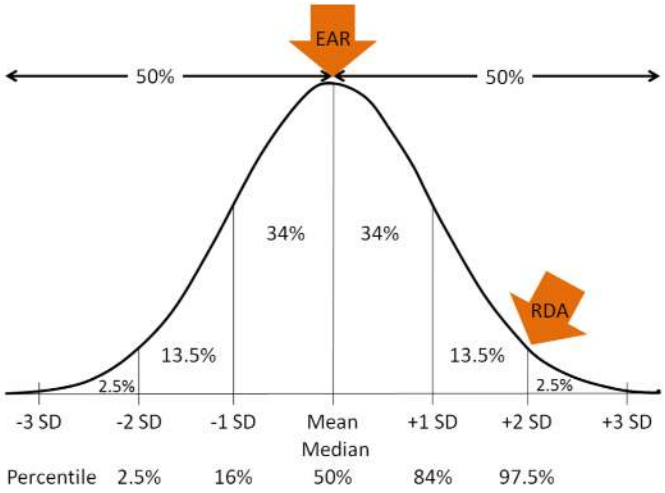


Figure **8.4.3**: The RDA meets the needs for 97.5% of the population

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.

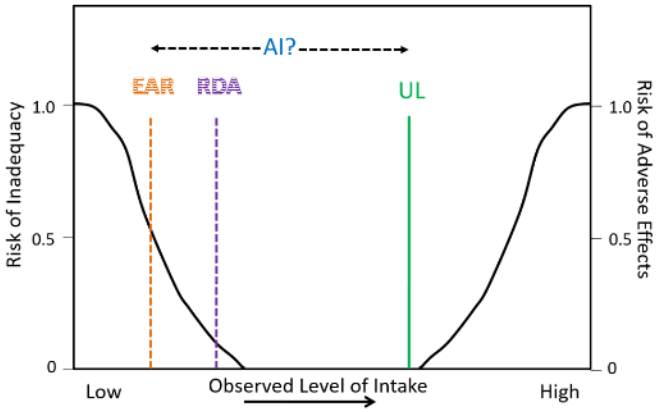


Figure 8.4.4: The AI compared to the other DRI components, the question mark and dotted line are meant to indicate that it is not known exactly where the AI would fall relative to and EAR/RDA if they were set. The dotted EAR/RDA is meant to indicate that these are not set when an AI is set.

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.

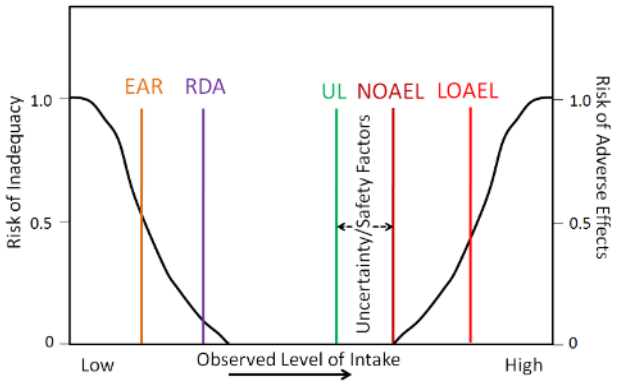


Figure 8.4.5: Setting of the UL

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.

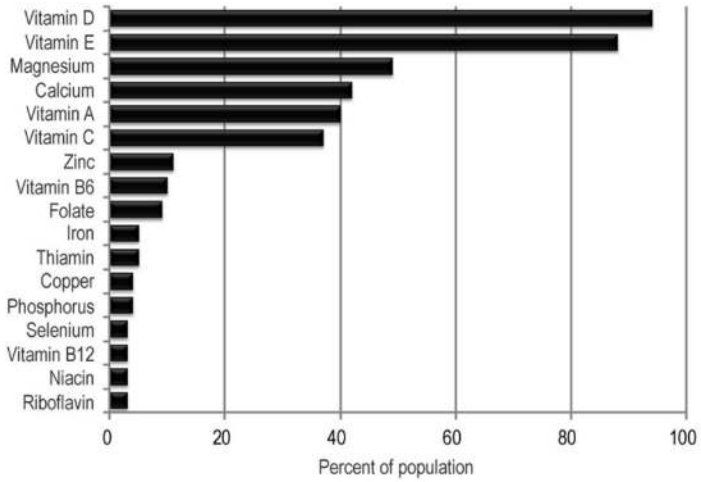


Figure **8.4.6**: Percent of Americans with usual intakes below the EAR[1]

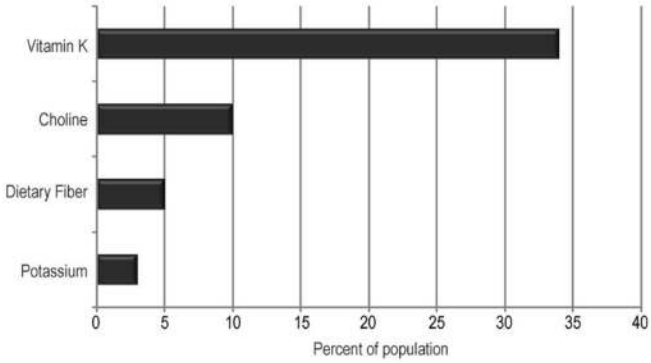


Figure **8.4.7**: Percent of Americans with usual intakes exceeding the AI[1]

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.

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].

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1. health.gov/dietaryguidelines/...er-1/d1-11.asp
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CHAPTER OVERVIEW

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.

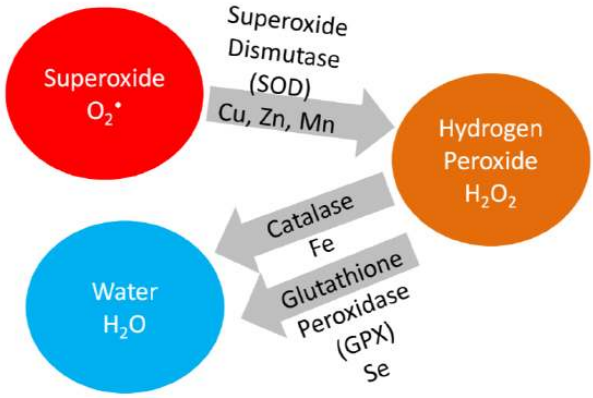


Figure **9.1.1**: Antioxidant enzymes that use minerals as cofactors

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).

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.

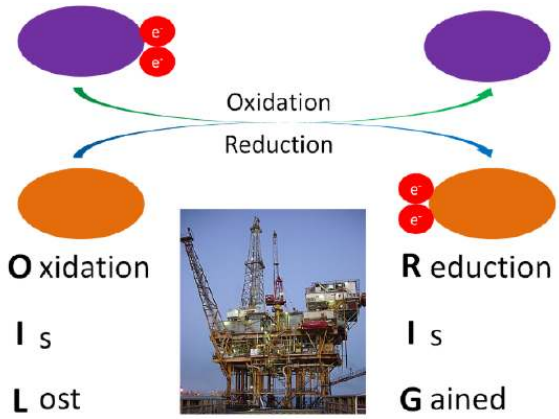


Figure **9.1.2**: The purple compound is oxidized; the orange compound is reduced[1]

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.

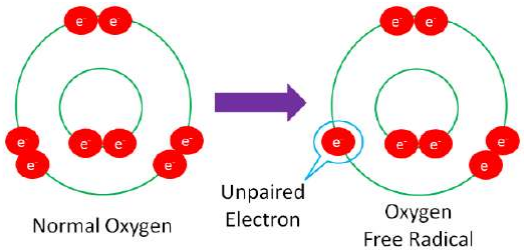


Figure **9.1.3**: Normal oxygen is converted to an oxygen free radical by losing one electron in its outer orbital, leaving one unpaired electron

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)

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.



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.

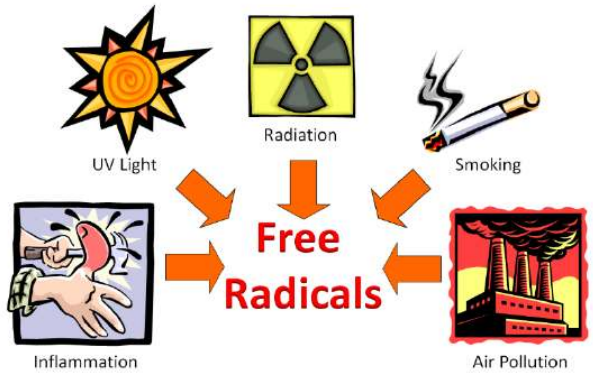


Figure **9.1.4**: Some sources of free radicals

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.

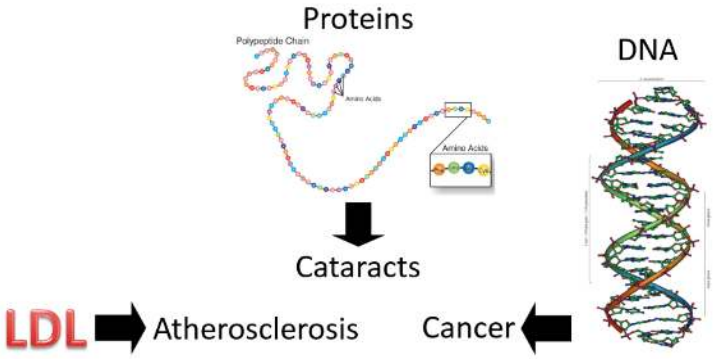


Figure **9.1.5**: Free radicals can attack LDL, proteins, and DNA[2,3]

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.

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.

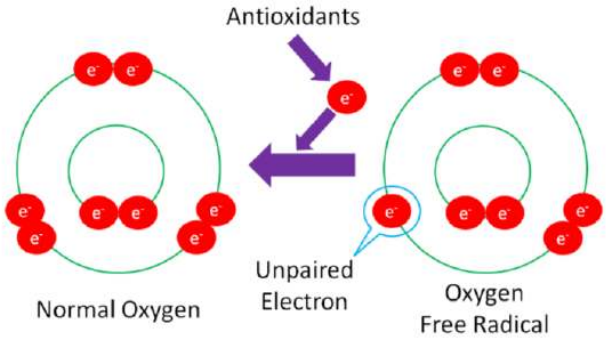


Figure **9.1.7**: Regeneration of normal oxygen from oxygen free radical by the donation of an electron from an antioxidant

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.

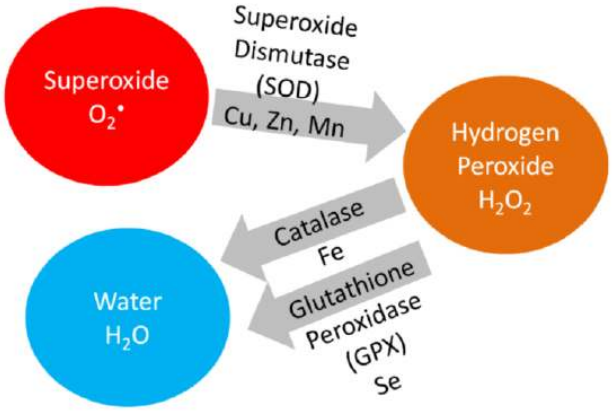


Figure **9.1.8**: Antioxidant enzymes that use minerals as cofactors

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.

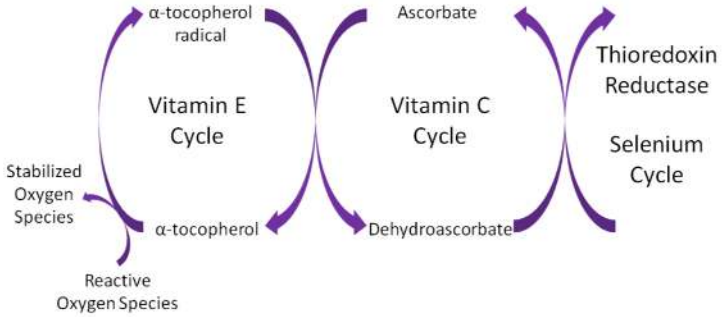


Figure **9.1.9**: The theorized antioxidant network[5]. This is to be read from left to right showing the transfer of an electron by oxidation to then be reduced as shown in the description above.

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 concentrations6

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.

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

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.

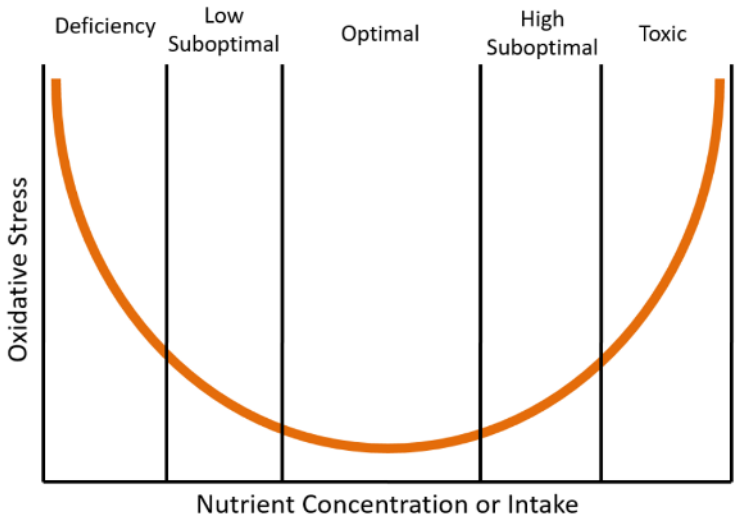


Figure **9.1.10**: How the levels of nutrient concentration or intake alters oxidative stress in the body. Going up the y-axis and to the right on the x-axis is higher (or increasing). Adapted from reference8

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.

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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.

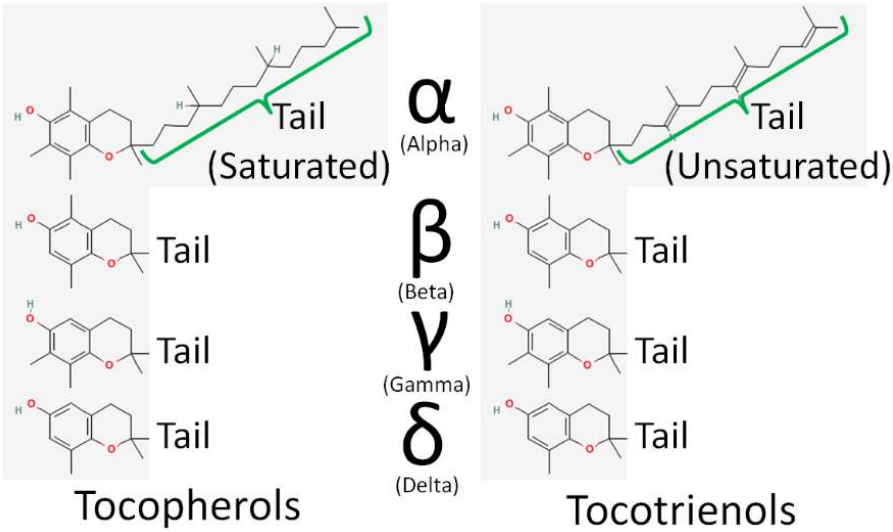


Figure 9.2.1: Structures of the different forms of vitamin E

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.

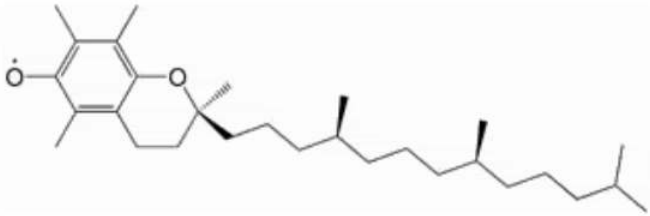


Figure 9.2.2: Alpha-tocopherol radical1

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.

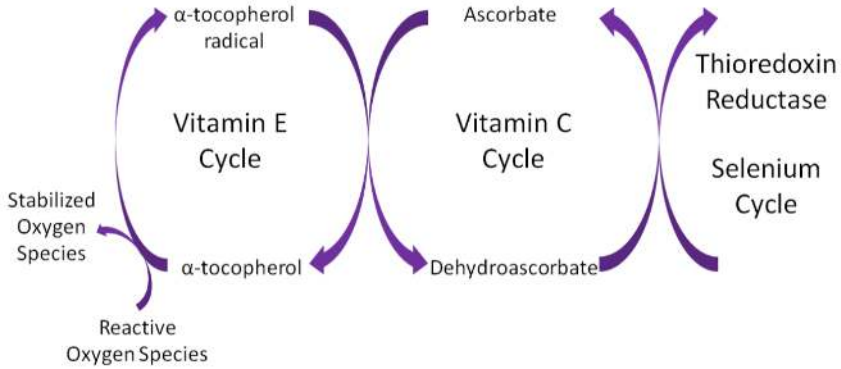


Figure 9.2.3: The theorized antioxidant network2

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.

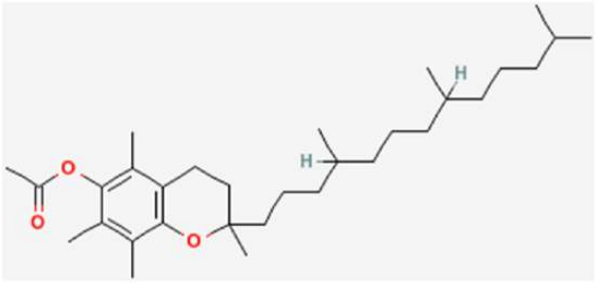


Figure **9.2.4**: Alpha-tocopherol acetate

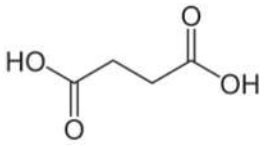


Figure **9.2.5**: Succinic acid[3]

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.

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.

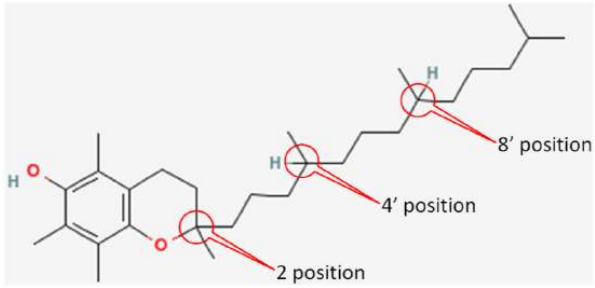


Figure **9.2.6**: The 2, 4', and 8' positions of alpha-tocopherol are chiral centers

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 below[4].

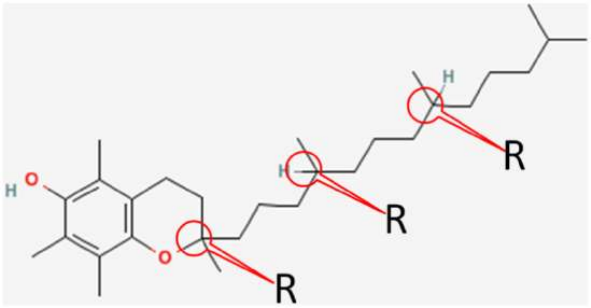


Figure **9.2.7**: Natural alpha-tocopherol 2, 4', and 8' positions are in the R conformation

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.

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.

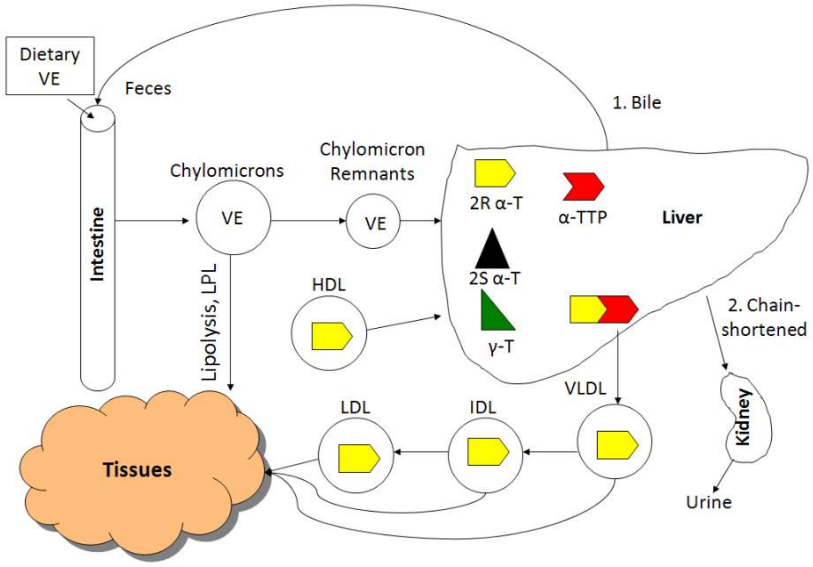


Figure **9.2.8**: The absorption, metabolism, and excretion of vitamin E

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

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].

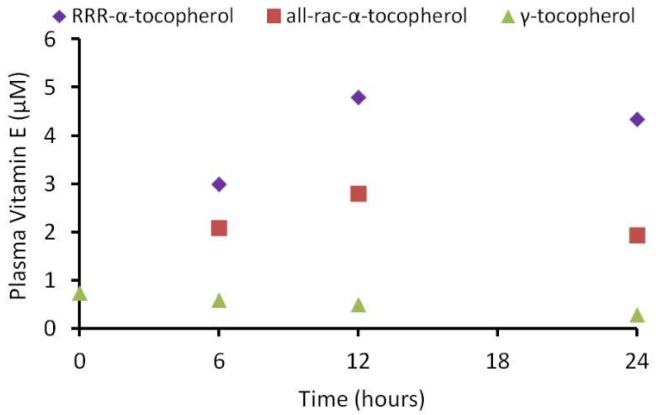


Figure **9.2.9**: Plasma vitamin E concentrations in response to a 150 mg dose of RRR-alpha-tocopherol, all-rac-alpha-tocopherol, or gamma-tocopherol. Adapted from reference[5]

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.

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.

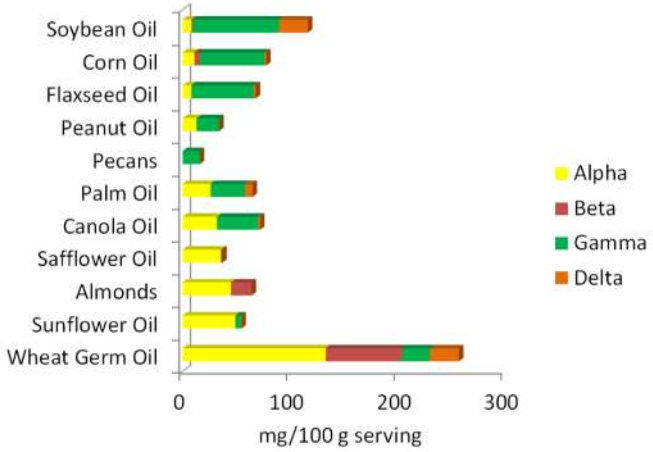


Figure **9.2.10**: Tocopherol distribution in plant products6

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
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

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.

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.

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.

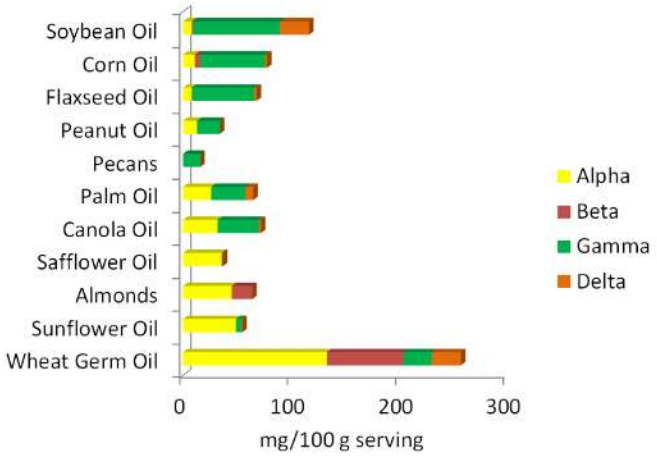


Figure 9.2.11: Only the yellow bars count toward the 2001 DRI requirement[6]

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 species[1]. 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.

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.

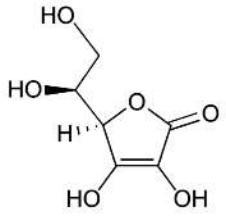


Figure **9.3.1**: Structure of ascorbic acid[2]

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.

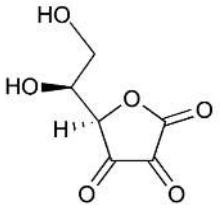


Figure **9.3.2**: Structure of dehydroascorbic acid[3]

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.

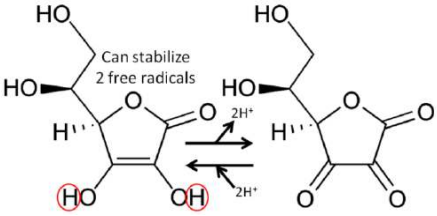


Figure **9.3.3**: The oxidation-reduction reaction between ascorbic acid (left) and dehydroascorbic acid (right)[2,3]

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.

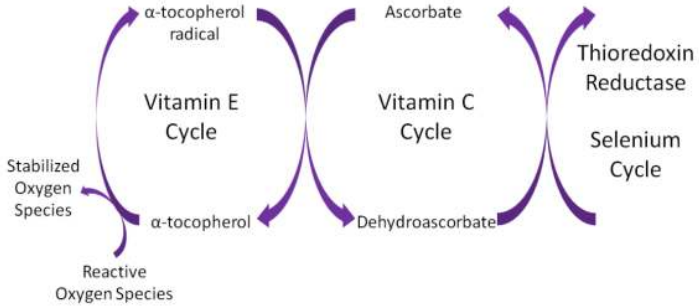


Figure **9.3.4**: The theorized antioxidant network[4]

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.

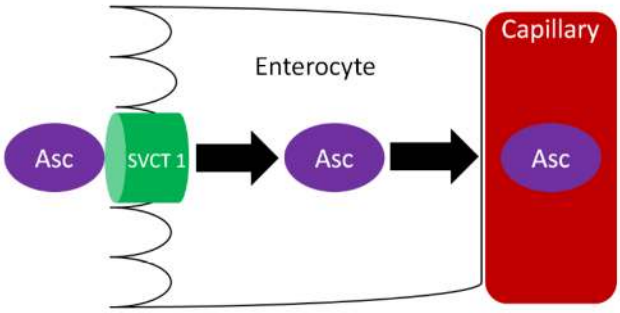


Figure **9.3.5**: Ascorbic acid (Asc) absorption

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 mechanism[7].

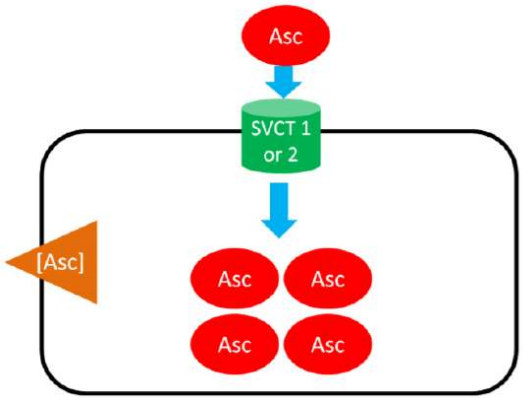


Figure **9.3.6**: Ascorbic acid (Asc) uptake using SVCT 1 and 2 against the ascorbic acid concentration gradient[7]

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 acid[6]. The figure below depicts ascorbic acid recycling.

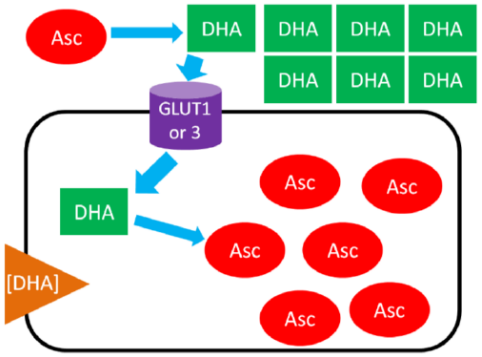


Figure **9.3.7**: Ascorbic acid (Asc) recycling[7]. Ascorbic acid is oxidized to dehydroascorbic acid (DHA) outside the cell. DHA concentration {DHA} is higher outside the cell than inside the cell as represented by the orange wedge, whose wide side is outside the cell and narrow point is inside the 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.

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, **–OH**) to the amino acids proline and lysine, as shown below.

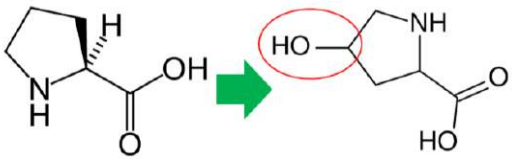


Figure **9.3.8**: Prolyl hydroxylase adds an alcohol group (circled) to proline forming hydroxyproline[7,8]

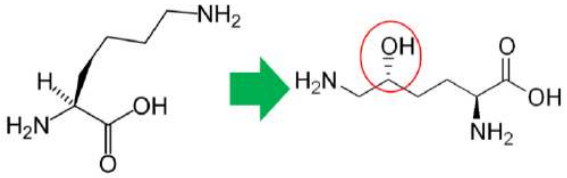


Figure **9.3.9**: Lysyl hydroxylase adds an alcohol group (circled) to lysine forming hydroxylysine9,10

As shown below, prolyl and lysyl hydroxylases require ferrous iron ($\mathbf{Fe^{2+}}$) to function. But in the course of the hydroxylating proline or lysine, ferrous iron ($\mathbf{Fe^{2+}}$) is oxidized to ferric iron ($\mathbf{Fe^{3+}}$). Ascorbic acid is required to reduce $\mathbf{Fe^{3+}}$ to $\mathbf{Fe^{2+}}$, forming semidehydroascorbic acid in the process. With $\mathbf{Fe^{2+}}$, the enzyme is then able to continue to hydroxylate proline and lysine.

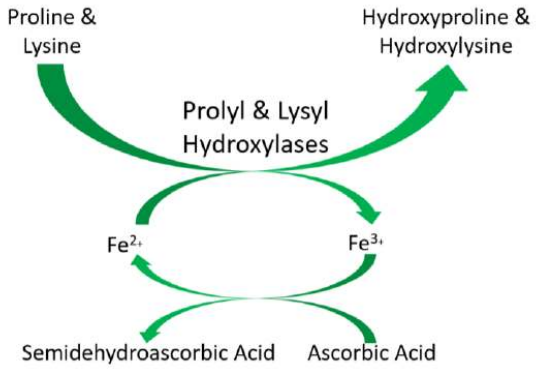


Figure **9.3.10**: Ascorbic acid reduces iron so that it can continue to serve as a cofactor for prolyl and lysyl hydroxylases

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.

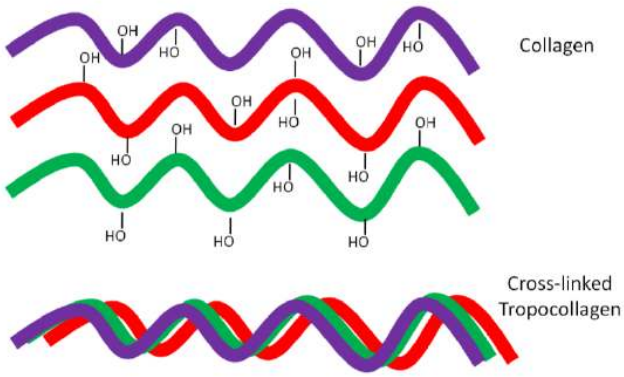


Figure **9.3.11**: Production of cross-linked tropocollagen in the presence of adequate vitamin C

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.

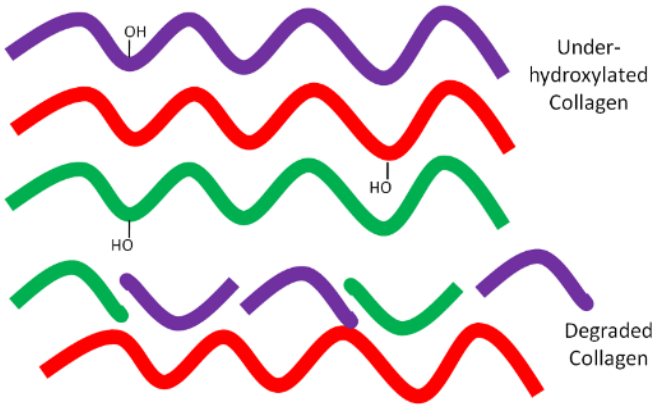


Figure 9.3.12: Production of underhydroxylated collagen

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 synthesis[12]

The figure below shows how ascorbic acid is needed for dopamine hydroxylase, which ultimately produces the hormone epinephrine.

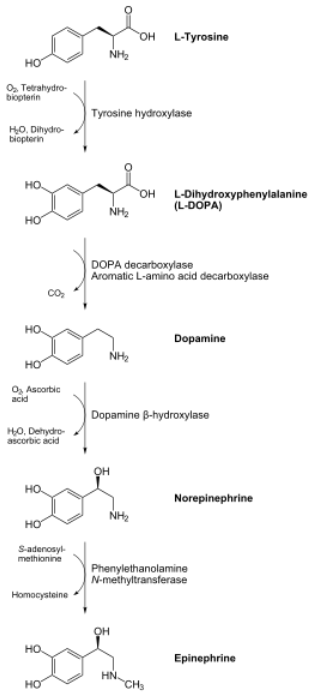


Figure 9.3.13: Dopamine beta-hydroxylase requires ascorbic acid to produce norepinephrine[13]

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

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

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.

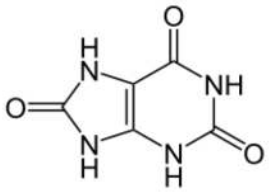


Figure **9.3.16**: Structure of uric acid17

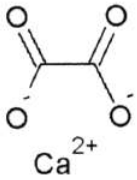


Figure **9.3.17**: Structure of calcium oxalate18

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.

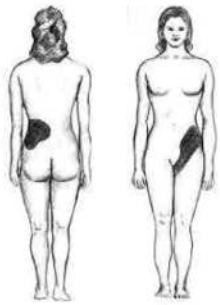


Figure **9.3.18**: Kidney stones normally cause pain in the shaded areas19

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.



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 rare20. 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 stones21.

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.

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.

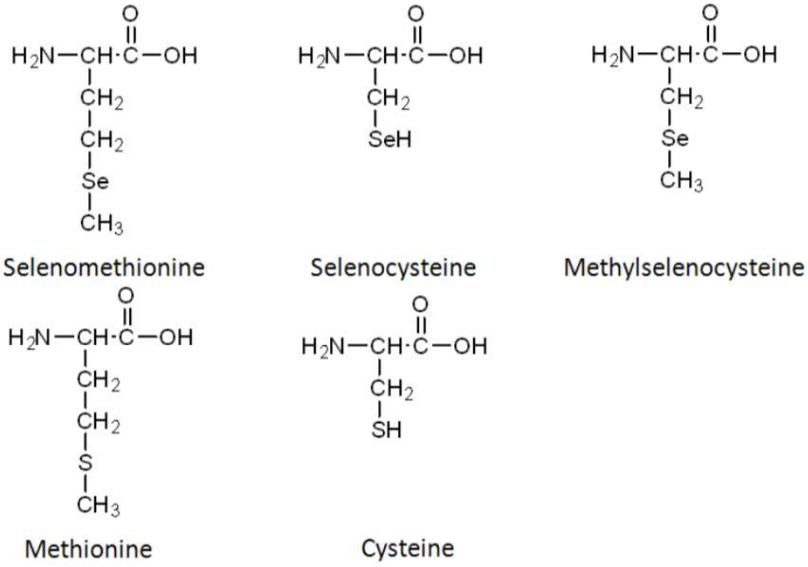


Figure 9.4.1: Structures of organic forms of selenium and similar sulfur-containing amino acids

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.

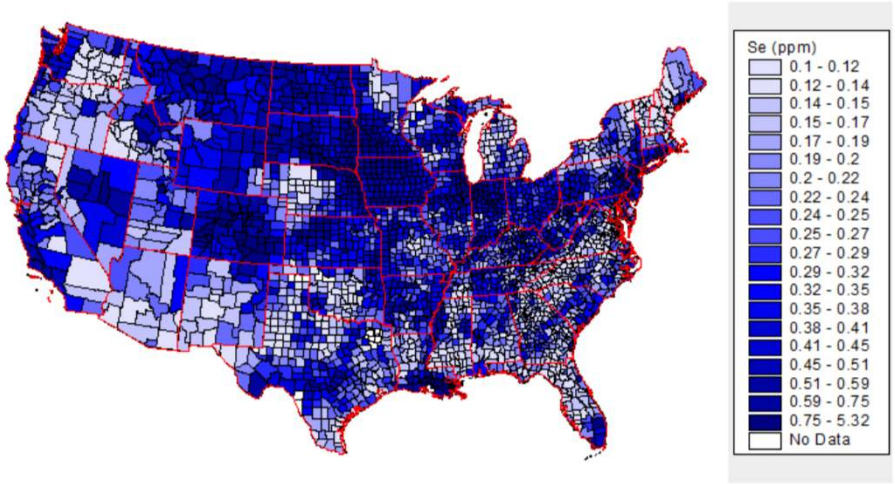


Figure 9.4.2: United States soil selenium levels2

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 models[3]. 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.

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.

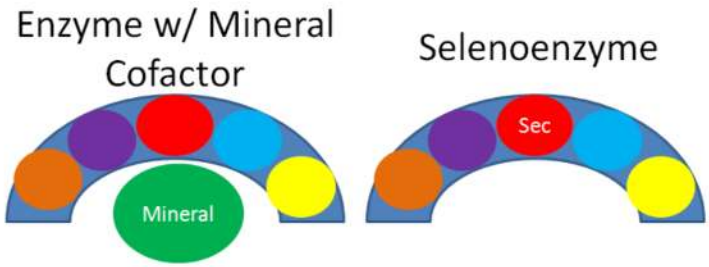


Figure **9.4.3**: Enzyme with a mineral cofactor versus a selenoenzyme with selenocysteine as an amino acid in its active site.

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 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.

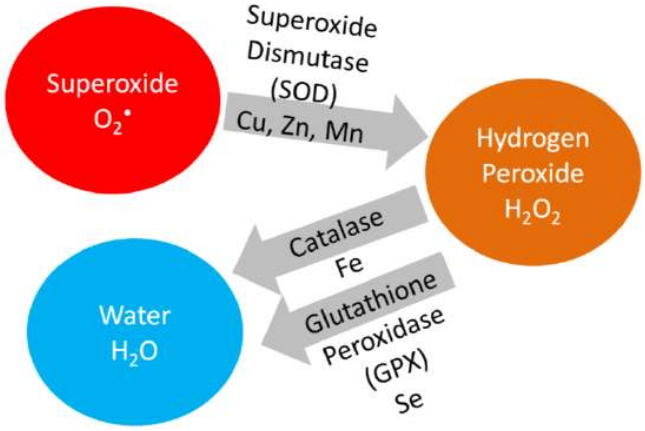


Figure 9.4.4: Antioxidant enzymes that use minerals as cofactors

Remember that thioredoxin reductase can regenerate ascorbate from dehydroascorbate in the theorized antioxidant network (shown below).

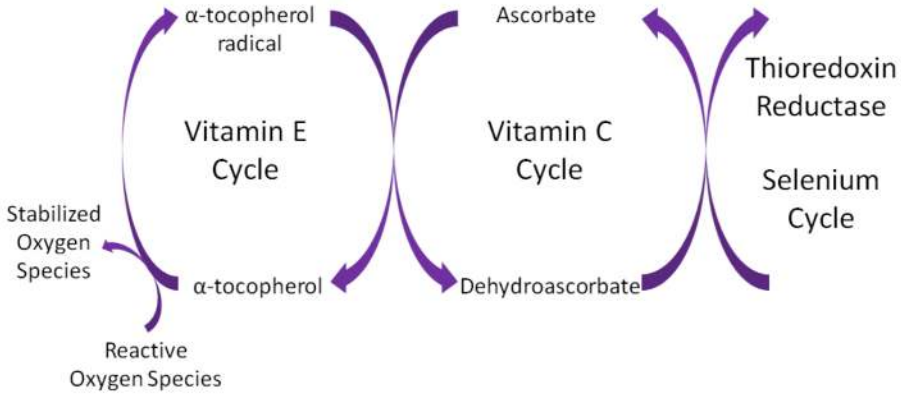


Figure 9.4.5: The theorized antioxidant network[5]

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 deficiency[6].

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.

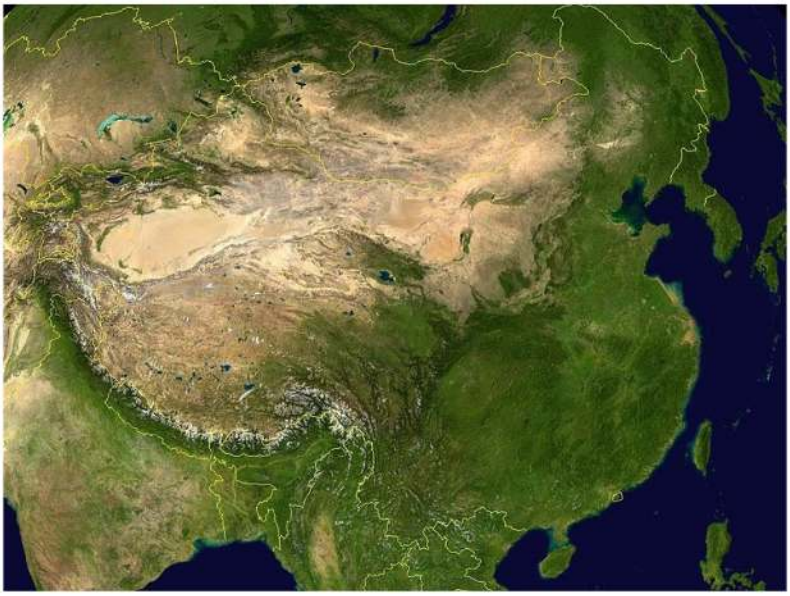


Figure **9.4.6**: Topographical map of China[7]

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.

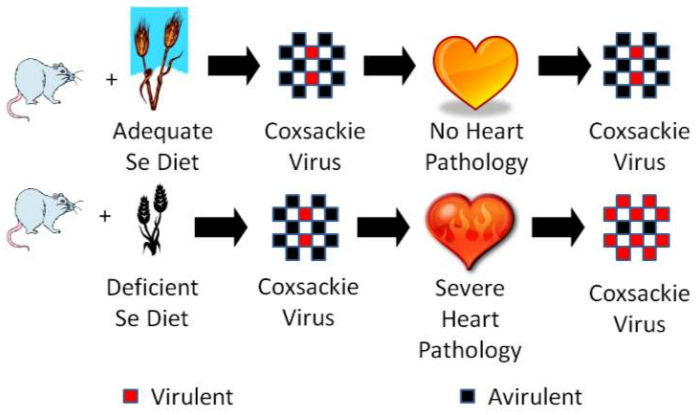


Figure **9.4.7**: Keshan disease experiment[8]

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 virulent[7]. They then took it one step further as shown in the figure below.

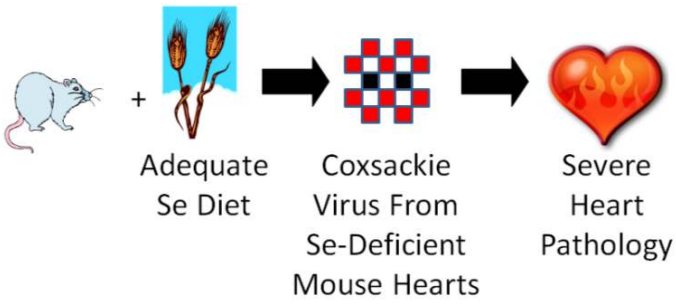


Figure **9.4.8**: Keshan disease experiment continued[8]

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 virulent[8].

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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CHAPTER OVERVIEW

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.

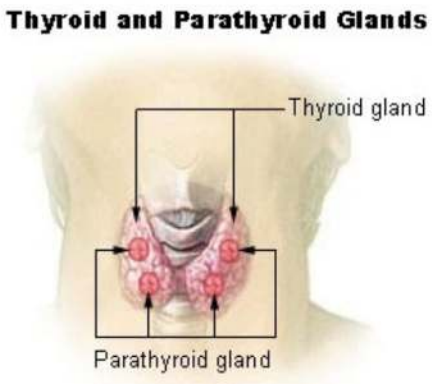


Figure **10.1.1**: Location of thyroid and parathyroid glands1

Iodine is found in foods primarily as iodide (I^-), some bread dough has iodate (IO_3^-) added to help with gluten cross-linking2. 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 facilities3,4.

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

Salt is iodized with either potassium iodide (**KI**) or potassium iodate (KIO_3). The positives of each are:

Potassium iodide

- Less expensive
- Higher iodine content (76% vs. 59% for 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 deficiency5.

Some examples of foods that contain goitrogens are3,4,6:

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 unprocessed7 (right) Peeled cassava roots8

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

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.



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).

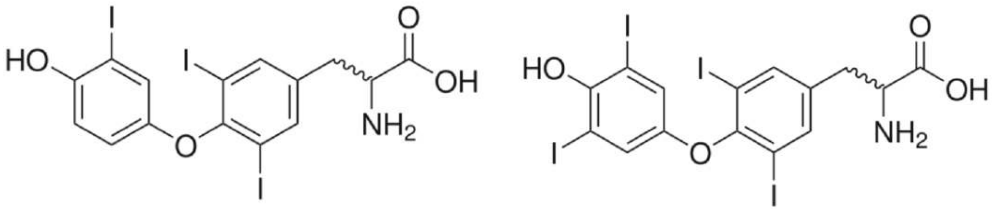


Figure **10.1.4**: (left) The structure of triiodothyronine (T3)11 and (right) The structure of thyroxine (T4)12

T4 is the primary circulating form, and is really a prohormone that is converted to the active T3 form.

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 development13.

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 diarrhea[2].

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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.

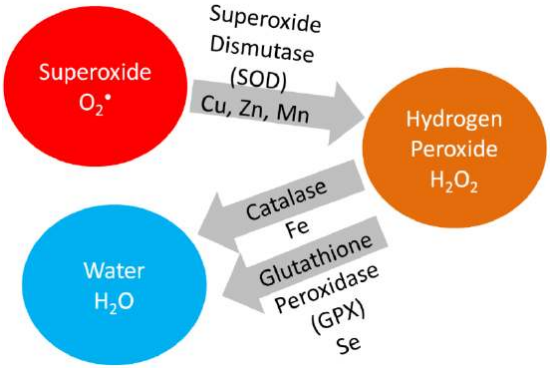


Figure **10.2.1**: Antioxidant enzymes that use minerals as cofactors

In addition, both the enzymes involved in the gluconeogenesis oxaloacetate workaround use manganese as cofactors as shown below.

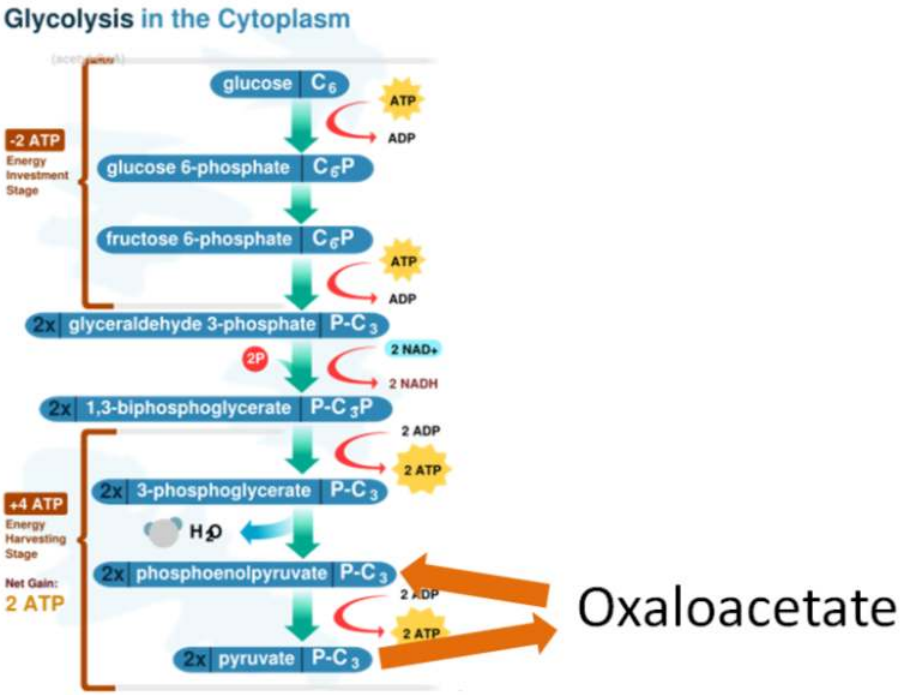


Figure **10.2.2**: Both enzymes of the oxaloacetate workaround in gluconeogenesis use manganese as cofactors (Cc BY-SA 3.0; via Wikipedia)

One enzyme in the urea cycle uses manganese as a cofactor.

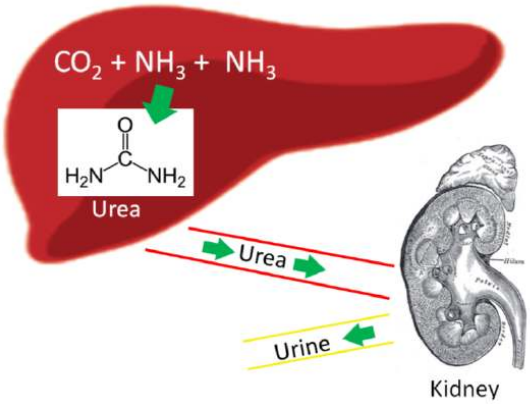


Figure **10.2.3**: Production of urea helps to safely remove ammonia from the body2-4

Enzymes critical to the production of proteoglycans, which are essential components of cartilage and bone, use manganese as a cofactor5.

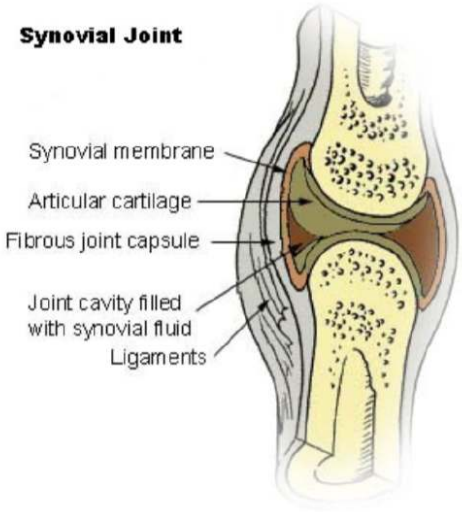


Figure **10.2.4**: Cartilage serves as a cushion between joints6

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.

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10.3: Thiamin

Thiamin (Vitamin B_1) structurally consists of 2 rings that are bridged together as shown below.

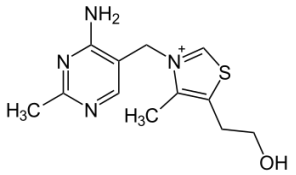


Figure **10.3.1**: Structure of thiamin1

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 activity2.

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.

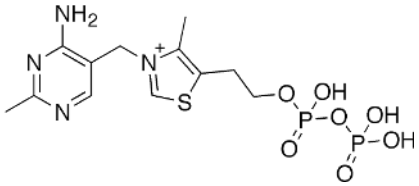


Figure **10.3.2**: Structure of thiamin pyrophosphate (aka thiamin diphosphate)3

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 enterocyte4.

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 low4. 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 below5.

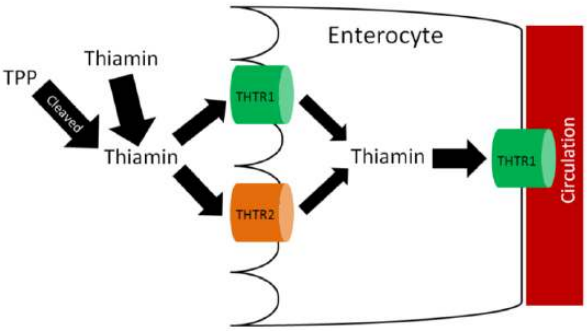


Figure **10.3.3**: Thiamin uptake and absorption

Like most water-soluble vitamins there is little storage of thiamin.

Thiamin Functions

There are three functions of thiamin4:

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 reaction6

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.

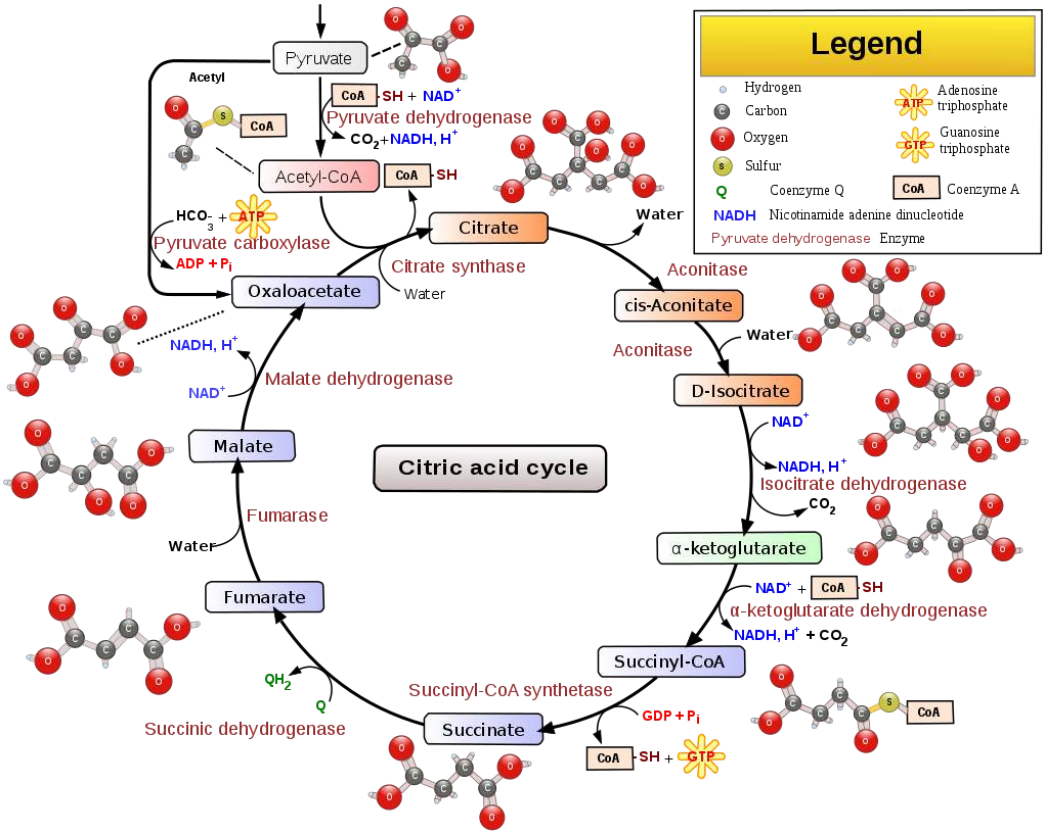


Figure 10.3.5: The transition reaction and citric acid cycle7

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.

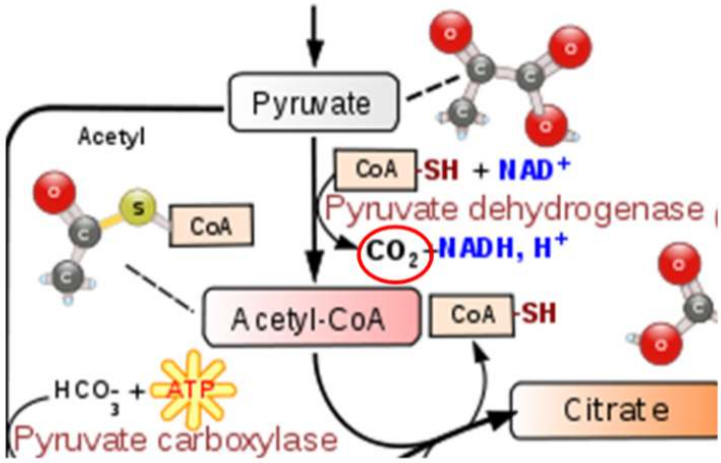


Figure **10.3.6**: The transition reaction requires TPP as a cofactor[7]

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.

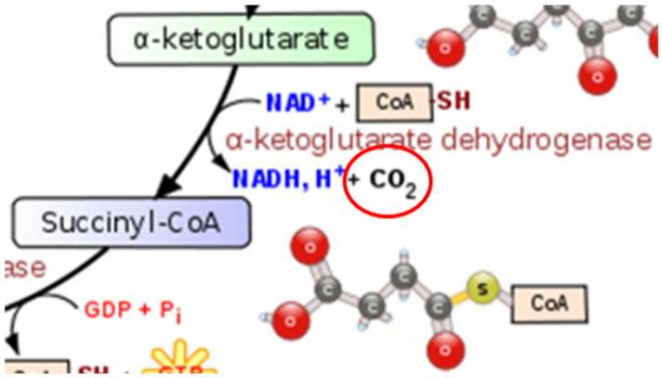


Figure **10.3.7**: Alpha-ketoglutarate dehydrogenase requires TPP as a cofactor[7]

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.

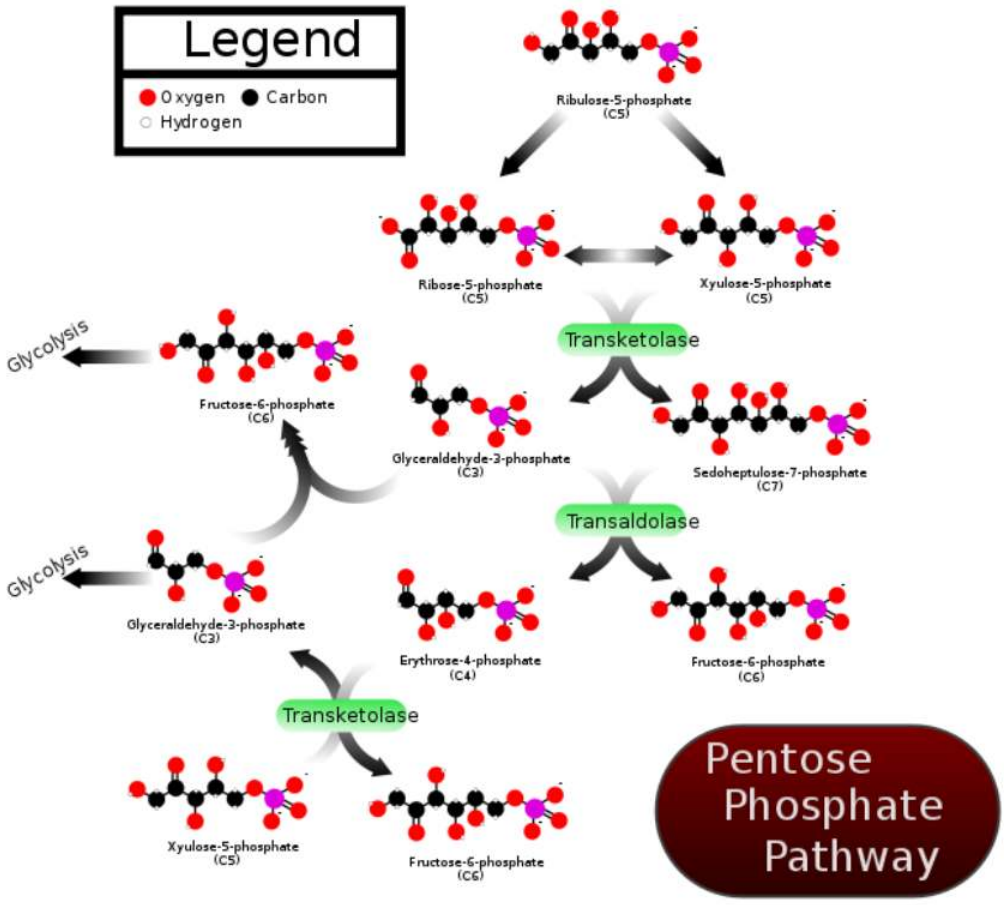


Figure **10.3.8**: Transketolase in the pentose phosphate pathway uses TPP as a cofactor[9]

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].

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.

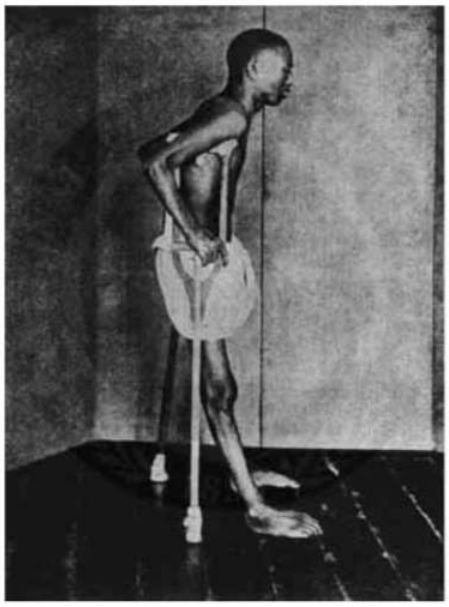


Figure **10.3.9**: A person suffering from beriberi[11]

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.



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 toxicity[13].

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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]

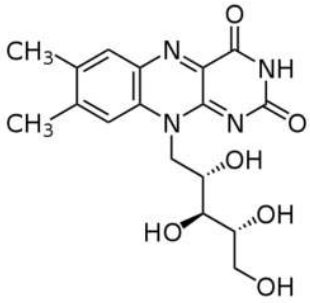


Figure **10.4.2**: Structure of riboflavin[2]

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.

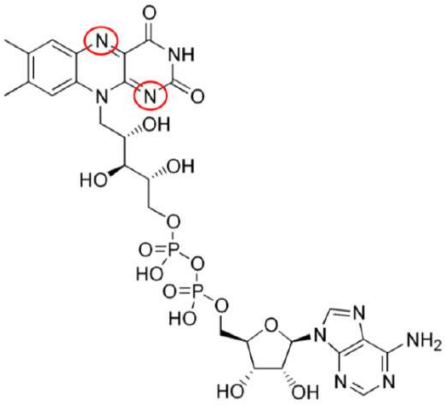


Figure **10.4.3**: Structure of **FAD**[3]

The 2 circled nitrogens are the sites that accept hydrogen to become **$FADH_2$** as illustrated below.

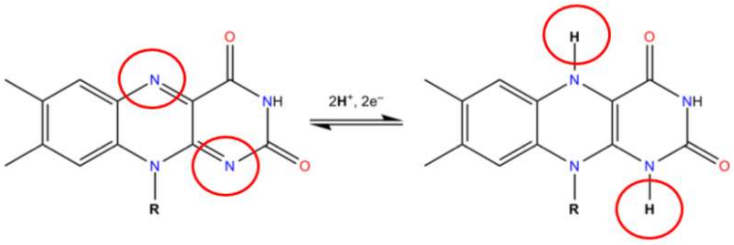


Figure **10.4.4**: Addition of two hydrogens to the rings of FAD to form **$FADH_2$**[4]

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**.

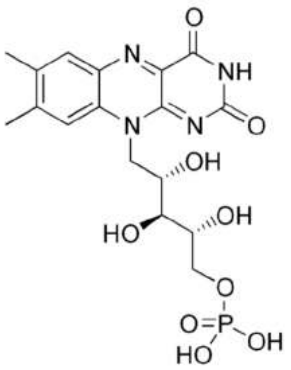


Figure 10.4.5: The structure of FMN[5]

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.

Riboflavin Functions

Riboflavin is required for the production of FAD and FMN. Below are some of the functions of FAD and FMN[6]:

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.

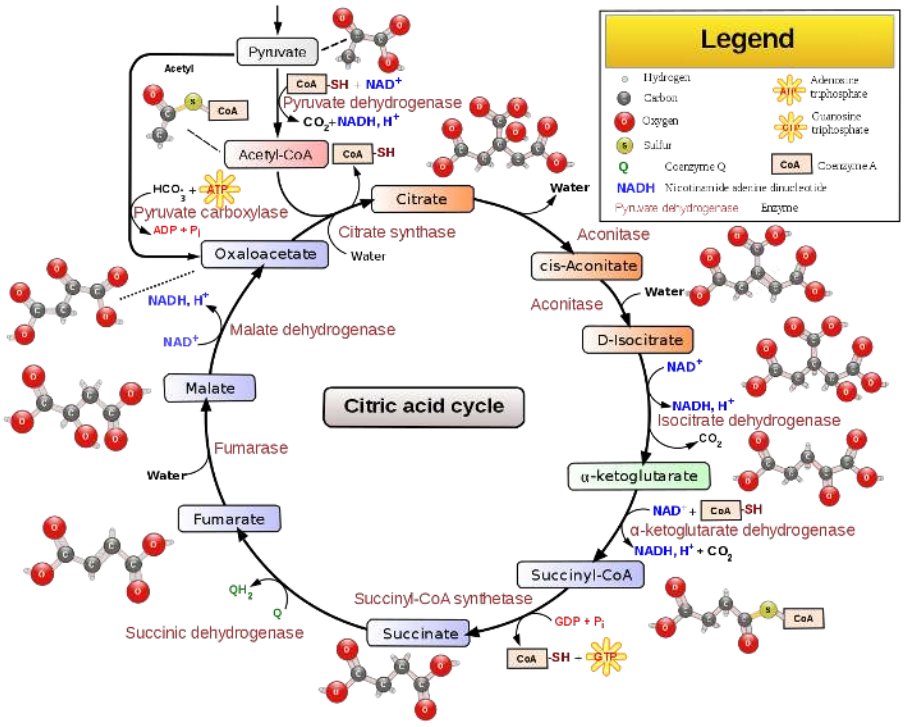


Figure **10.4.7**: The citric acid cycle requires **FAD**[8]

Electron Transport Chain

Under aerobic conditions, the electron transport chain is where the $\mathbf{FADH_2}$ is used to produce ATP. Complex I of the electron transport chain includes an **FMN** molecule. The electron transport chain is shown below.

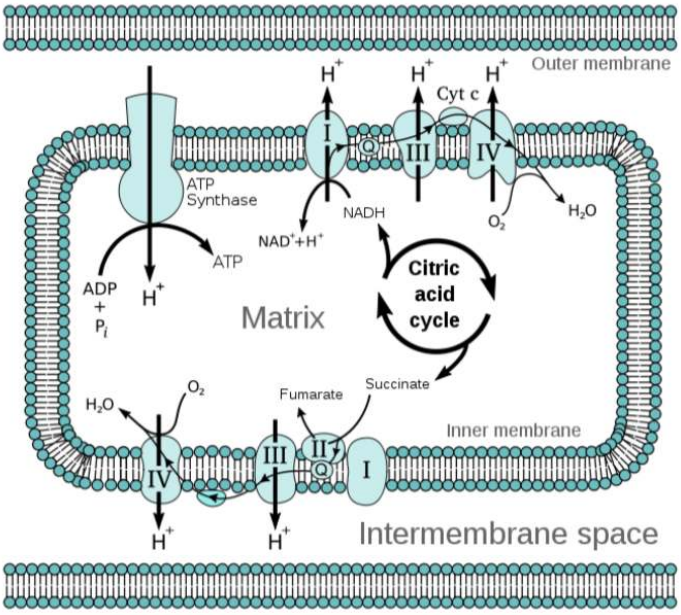


Figure **10.4.8**: Complex I in the electron transport chain contains **FMN**[9]

Fatty Acid oxidation

During fatty acid oxidation **FAD** is converted to $\mathbf{FADH_2}$ as shown below.

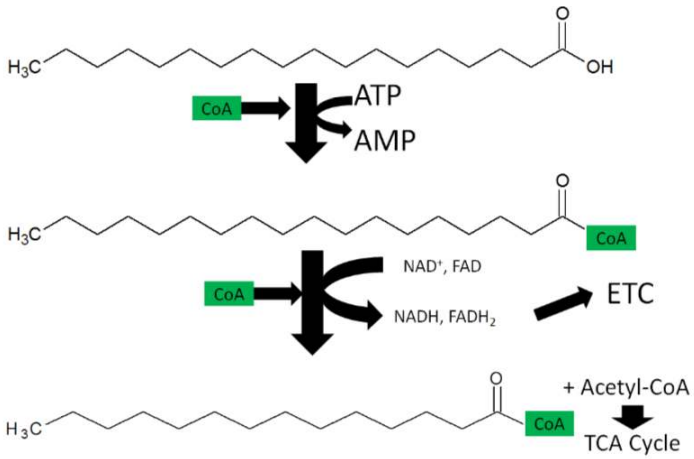


Figure 10.4.9: Fatty acid oxidation requires **FAD**

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**.

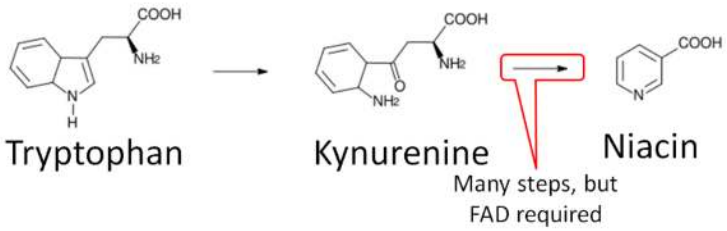


Figure 10.4.10: Niacin synthesis from tryptophan requires **FAD**[10]

Vitamin B_6 Activation

The enzyme that creates the active form of vitamin B_6 (pyridoxal phosphate) requires **FMN**.

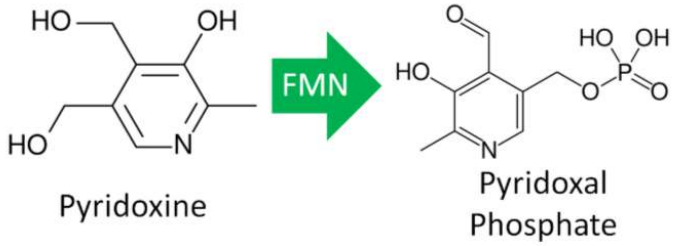


Figure 10.4.11: Vitamin B_6 activation requires **FMN**[11,12]

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.

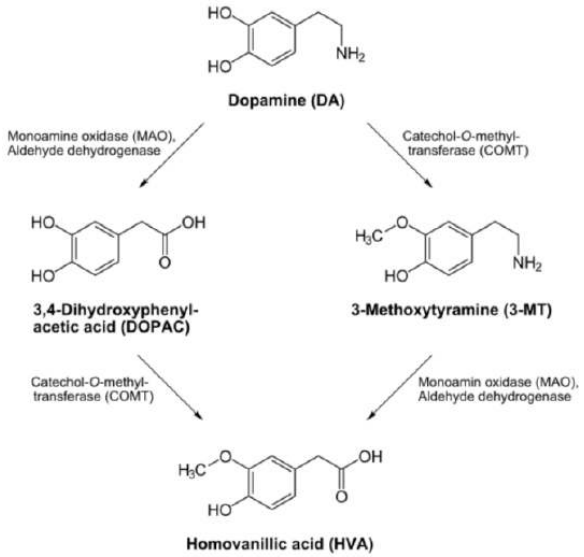


Figure **10.4.12**: Catabolism of dopamine involves monoamine oxidase, an enzyme that requires **FAD**13

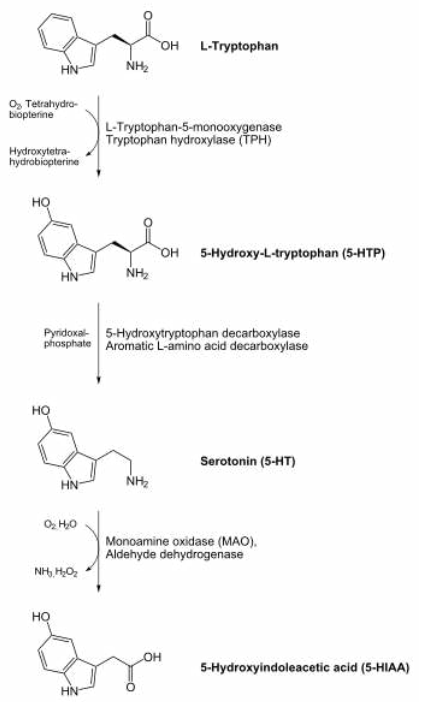


Figure **10.4.13**: Catabolism of serotonin involves monoamine oxidase, an enzyme that requires **FAD**14

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.

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.

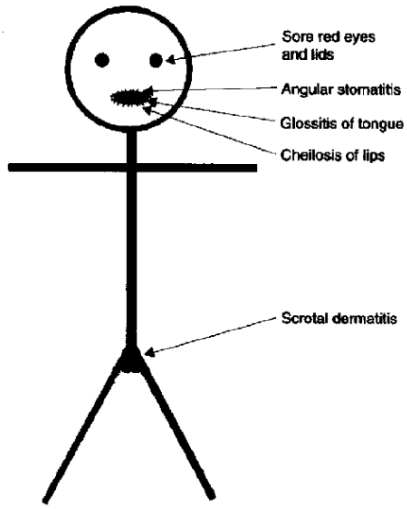


Figure **10.4.14**: The symptoms of riboflavin deficiency[15]

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.

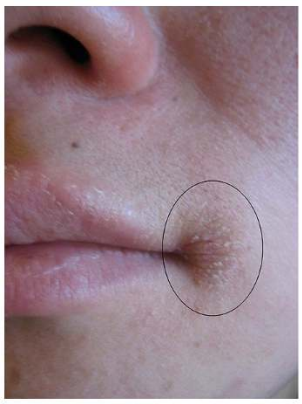


Figure **10.4.15**: Angular Cheilitis[16]

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].

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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.

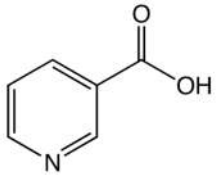


Figure **10.5.1**: Structure of nicotinic acid[1]

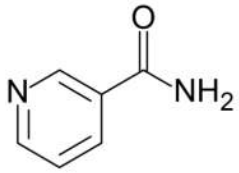


Figure **10.5.2**: Structure of nicotinamide[2]

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.

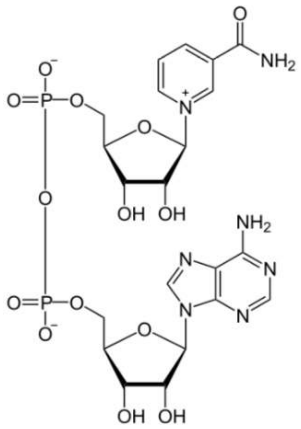


Figure **10.5.3**: Structure of **NAD**[3]

NAD is reduced to form **NADH**, as shown below.

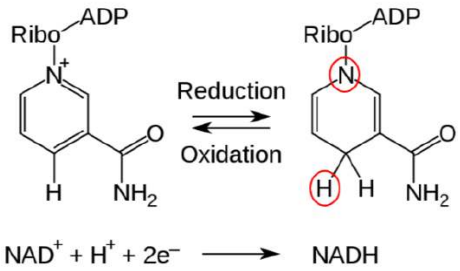


Figure **10.5.4**: Reduction of **NAD** to **NADH**[4]

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.

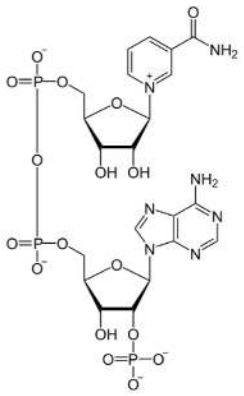


Figure 10.5.5: Structure of $\mathbf{NADP^+}$[5]

Like **NAD**, $\mathbf{NADP^+}$ can be reduced to **NADPH**.

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

$$13.403\,NE\,(\text{from niacin}) + 4.182\,(\text{from tryptophan}) = 17.585\,NE$$

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].

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**$^+$.

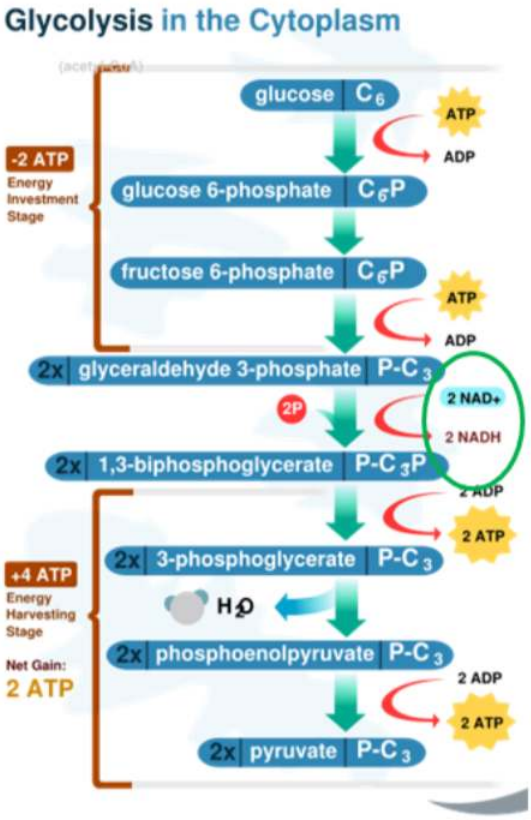


Figure **10.5.7**: **NAD** is required for glycolysis[11]

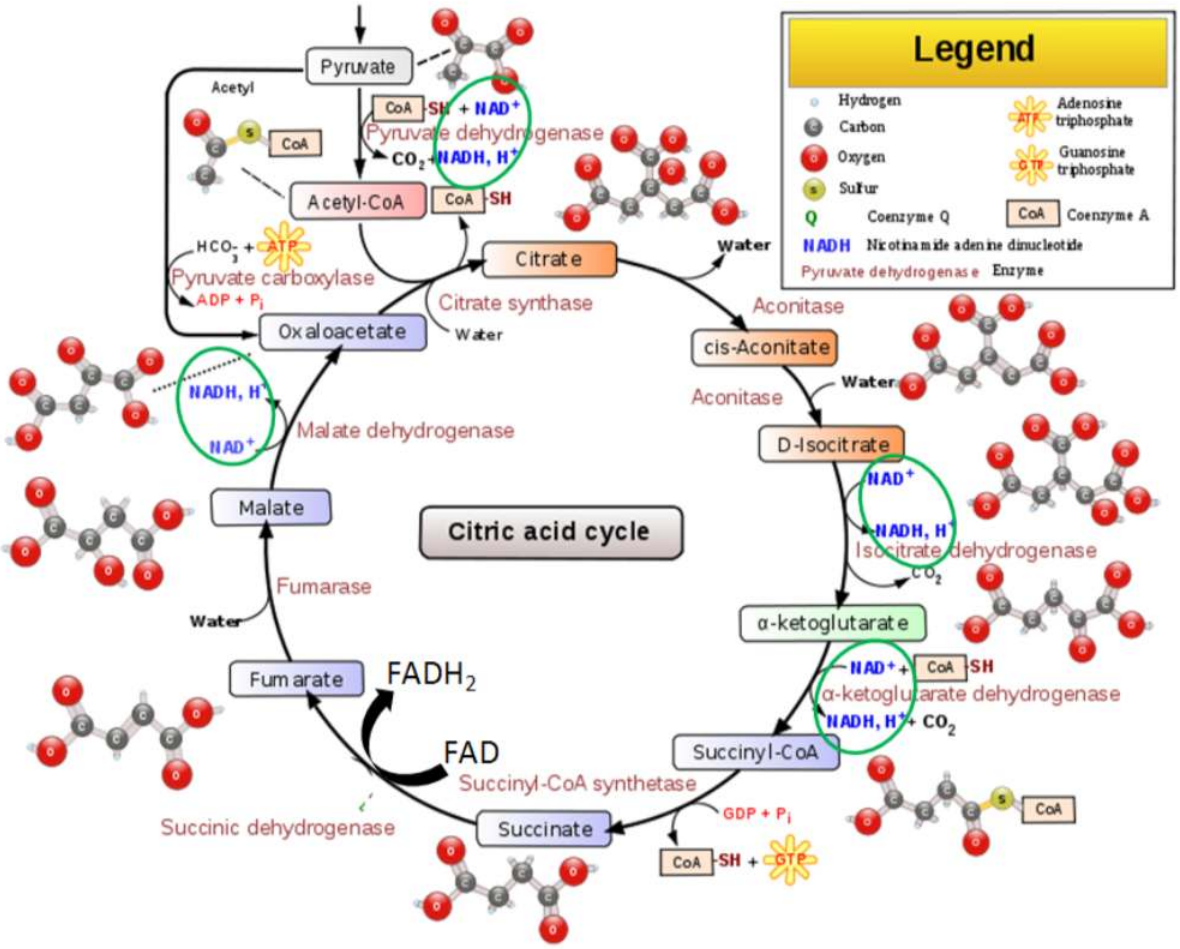


Figure 10.5.8: NAD is required for the transition reaction and at three different points in the citric acid cycle12

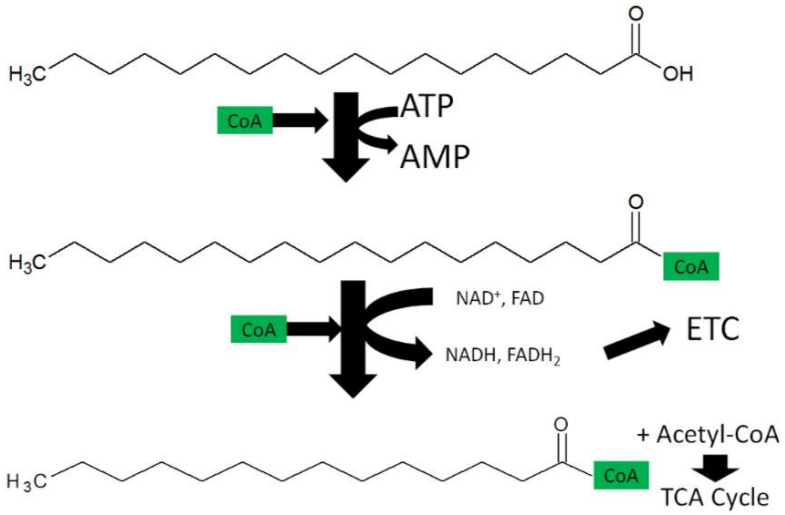


Figure 10.5.9: NAD is required for fatty acid oxidation

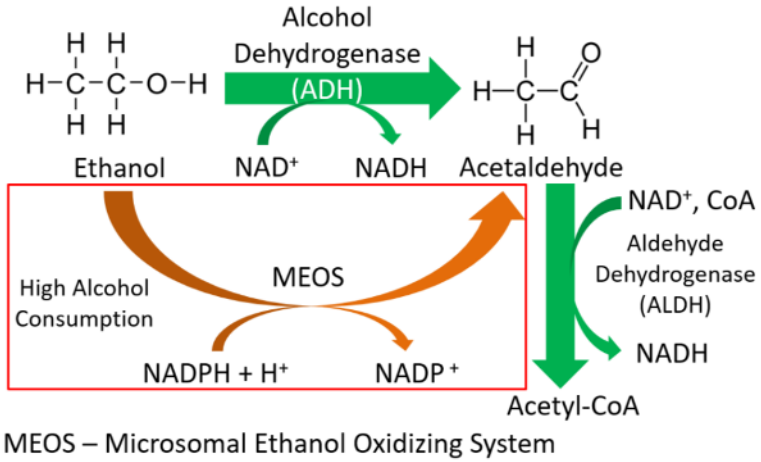


Figure 10.5.10: Alcohol oxidation; **NAD** is required by alcohol dehydrogenase, and the MEOS uses **NADPH**13,14

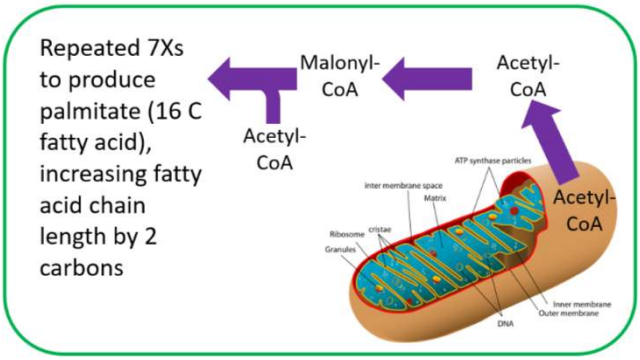


Figure 10.5.11: Fatty acid synthesis uses **NADPH**15

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 below9.

Web Link

The Glutathione Oxidation Reduction (Redox) Cycle

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.

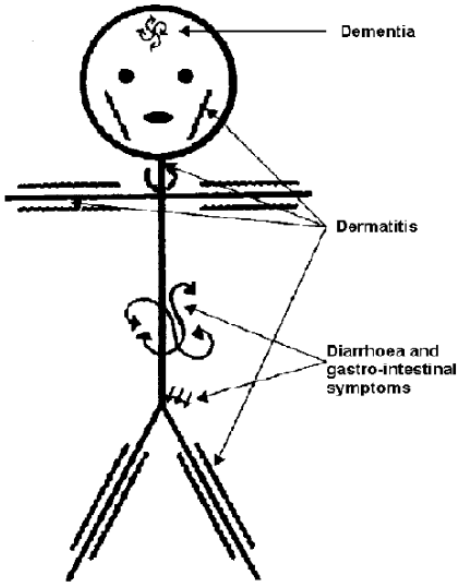


Figure **10.5.12**: The 3 D's of pellagra[16]



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

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 symptoms19. 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 it20,21. It is not clear at this time the mechanism of action for the improvements in lipid profiles20. 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 lipids22. 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 patients23.

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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.

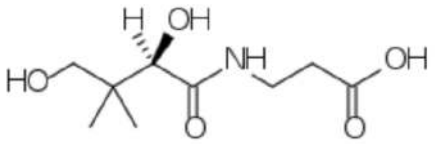


Figure 10.6.1: The structure of pantothenic acid[1]

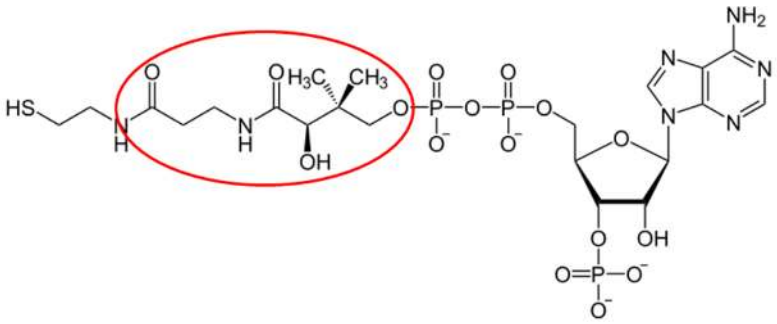


Figure 10.6.2: The structure of coenzyme A (CoA) with pantothenic acid circled[2]

The functions of CoA are shown and described below[3].

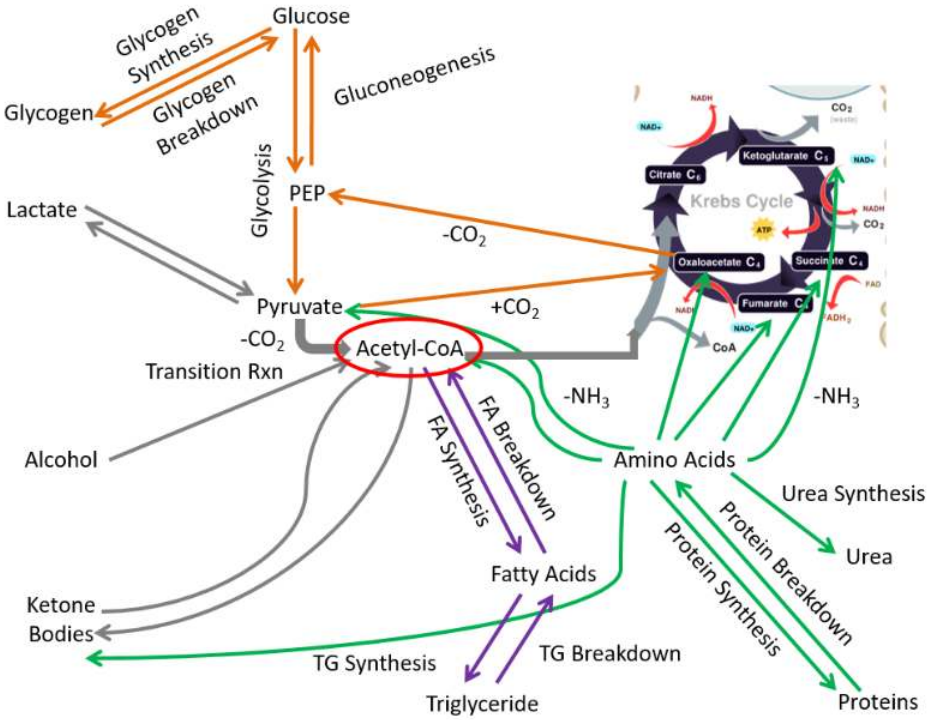


Figure 10.6.3: Acetyl-CoA is a central point in metabolism, and contains CoA[4]

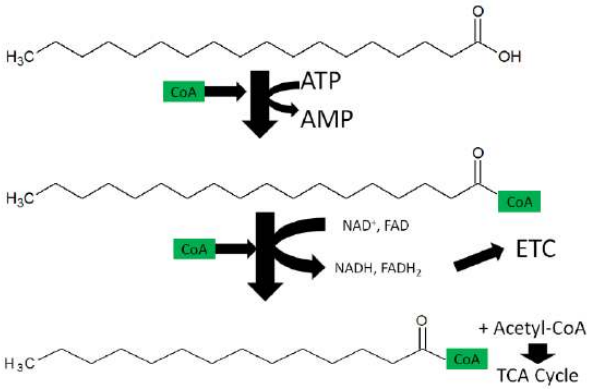


Figure 10.6.4: CoA is used in fatty acid oxidation. The fatty acid is activated by adding CoA, forming acyl-CoA.

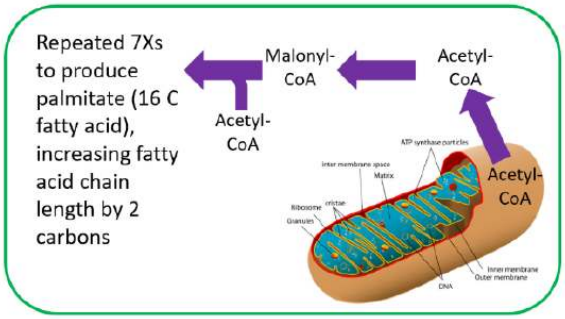


Figure 10.6.5: Fatty acid synthesis uses CoA5

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.

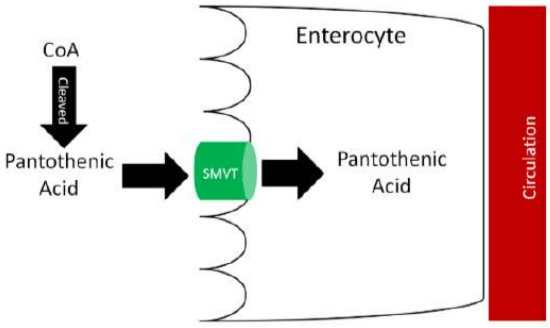


Figure 10.6.6: The absorption of pantothenic acid

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.

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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 ($-CH_3OH$), pyridoxal an aldehyde ($-CHO$), and pyridoxamine an aminomethyl group ($-CH_3NH_2$), as shown below.

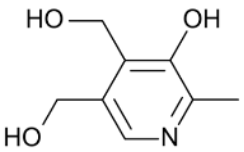


Figure 10.7.1: Structure of pyridoxine[1]

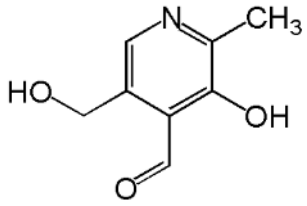


Figure 10.7.2: Structure of pyridoxal[2]

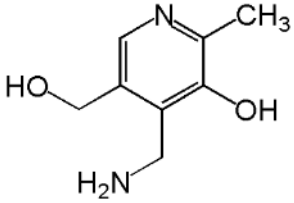


Figure 10.7.3: Structure of pyridoxamine[3]

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.

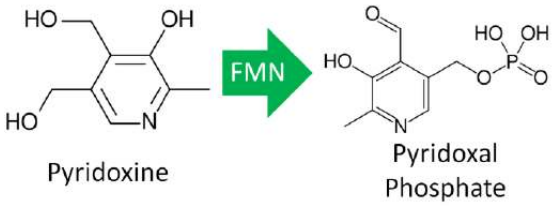


Figure 10.7.4: Vitamin B_6 activation[1,4]

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 form[6]. Pyridoxine glucoside has a glucose added to pyridoxine as shown below.

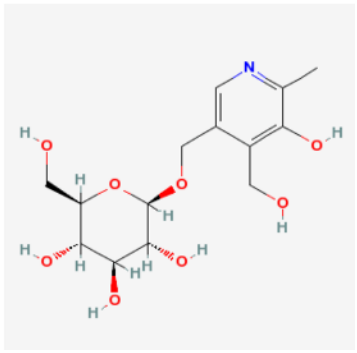


Figure 10.7.5: Structure of pyridoxine glucoside[5]

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].

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]

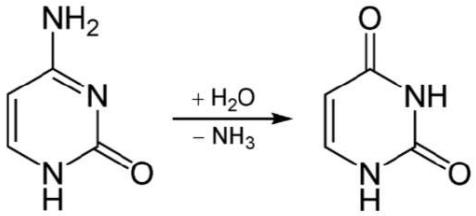


Figure 10.7.7: Some deaminases require **PLP**[9]

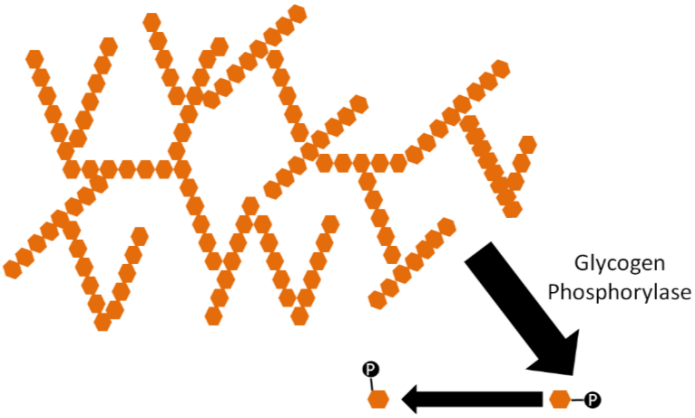


Figure 10.7.8: Glycogen phosphorylase (glycogenolysis) requires **PLP**

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 below[7].

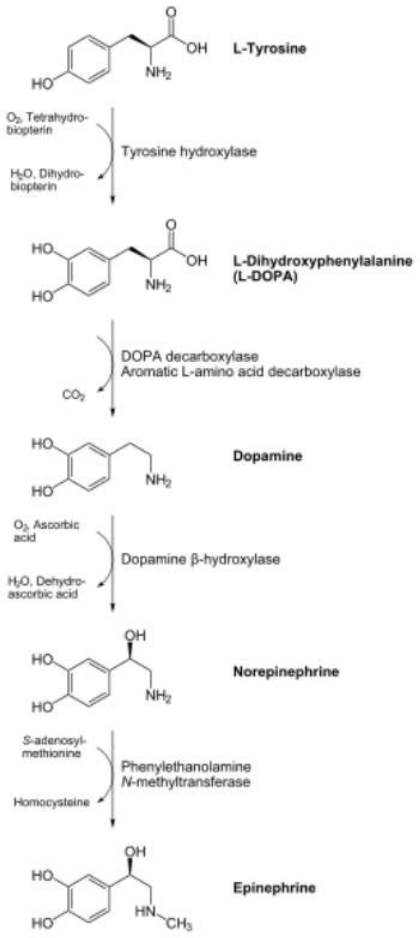


Figure **10.7.9**: DOPA decarboxylase uses **PLP** to synthesize dopamine[10]

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.

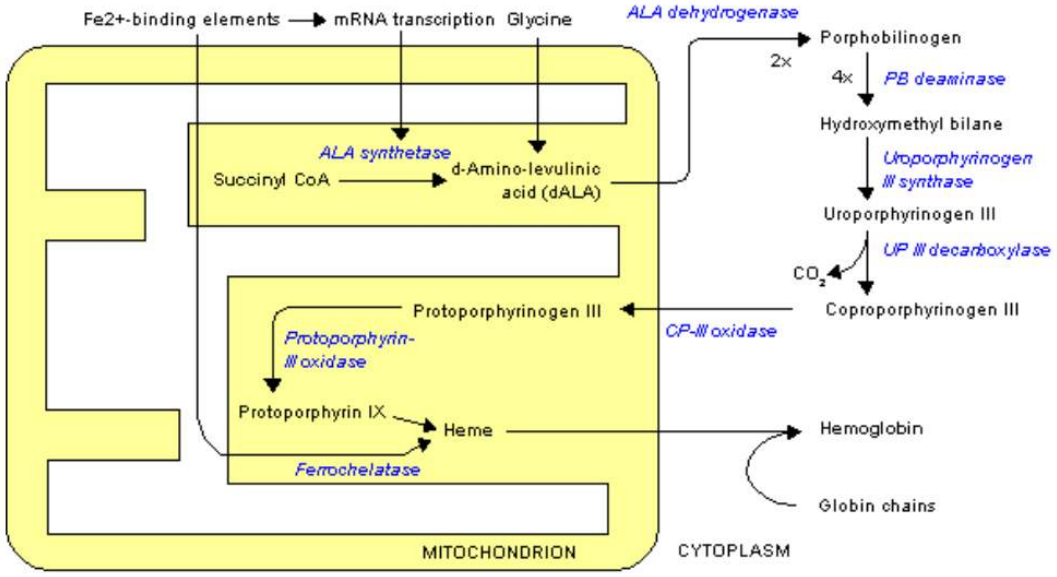


Figure **10.7.10**: ALA synthetase uses **PLP** in the heme synthesis pathway[11]

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 tryptophan12

In addition, **PLP** is also involved in:

- Carnitine Synthesis
- 1-Carbon Metabolism

Vitamin B_6 Deficiency & Toxicity

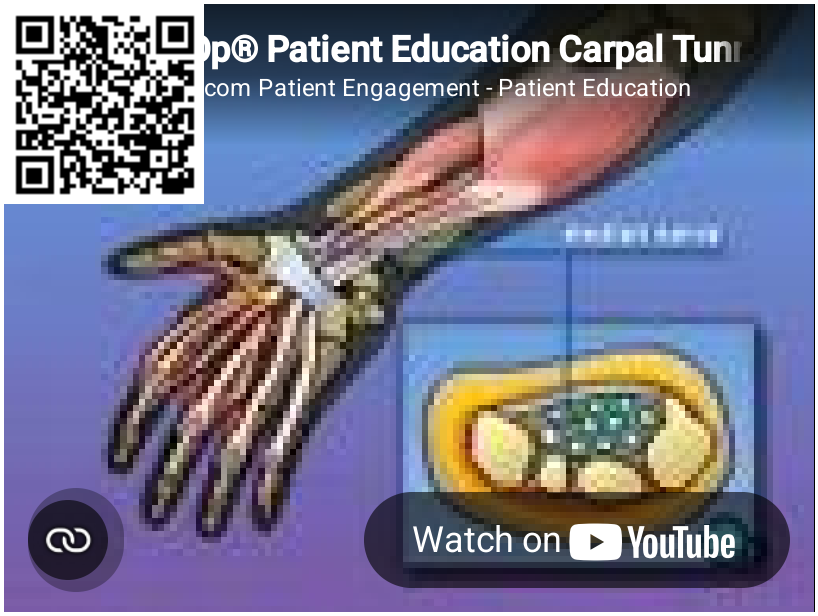
Vitamin B_6 deficiency is rare, but symptoms include:

- 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 neurotransmitters13.

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 damage13. 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.



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.

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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.

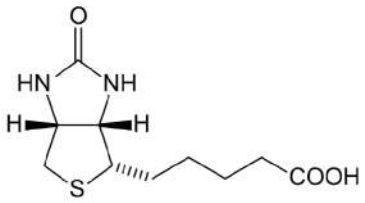


Figure **10.8.1**: Structure of biotin[2]

Biocytin is biotin bound to the amino acid lysine as seen in its structure below.

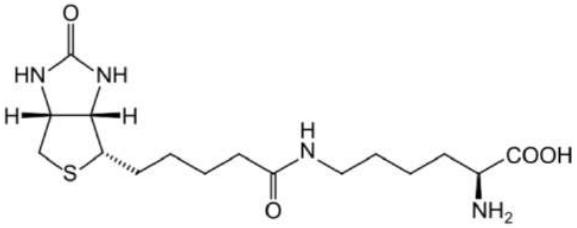


Figure **10.8.2**: Structure of biocytin[3]

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 below[1,4,5].

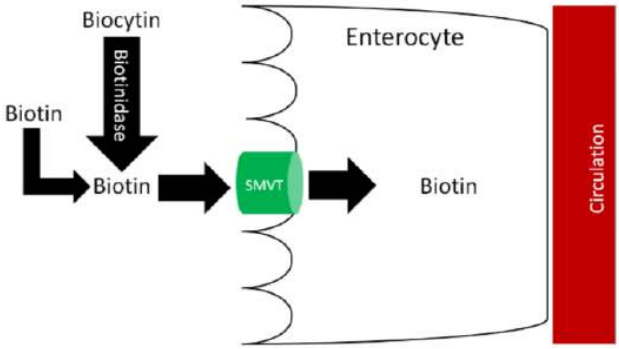


Figure **10.8.3**: Free biotin is taken up into the enterocyte by the SMVT.

Most biotin is excreted in the urine.

Biotin Functions

Biotin is an important cofactor for carboxylase enzymes. As the name sounds, these enzymes add carboxylic acid groups (**–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 below[1].

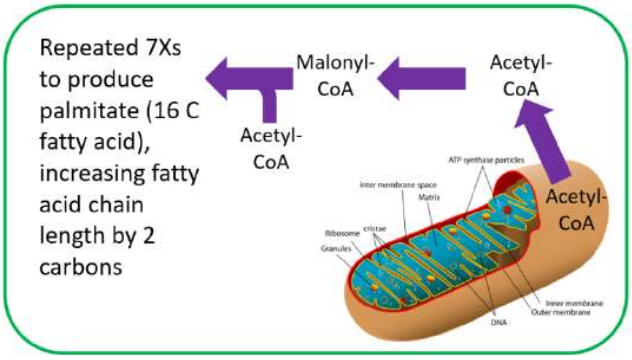


Figure 10.8.4: The conversion of acetyl CoA to malonyl CoA in fatty acid synthesis requires biotin[6]

Another biotin-requiring carboxylase is one that converts pyruvate to oxaloacetate in gluconeogenesis as shown below[1].

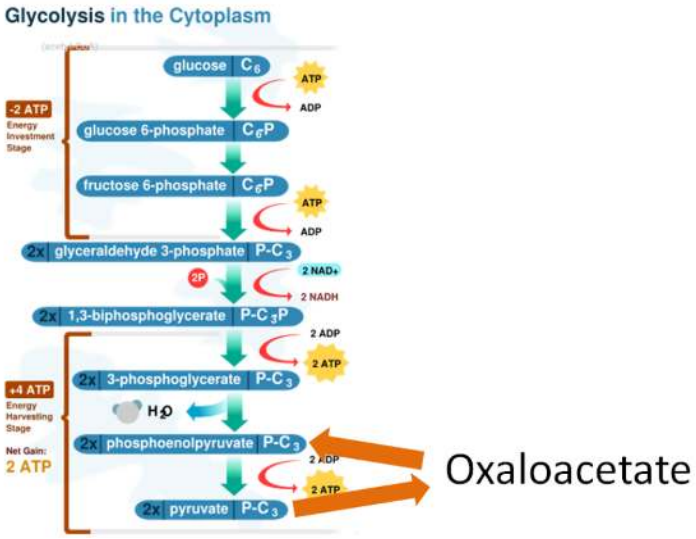


Figure 10.8.5: Biotin is required for conversion of pyruvate to oxaloacetate in the oxaloacetate workaround of gluconeogenesis (like glycolysis in reverse with oxaloacetate workaround)[7]

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].

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.

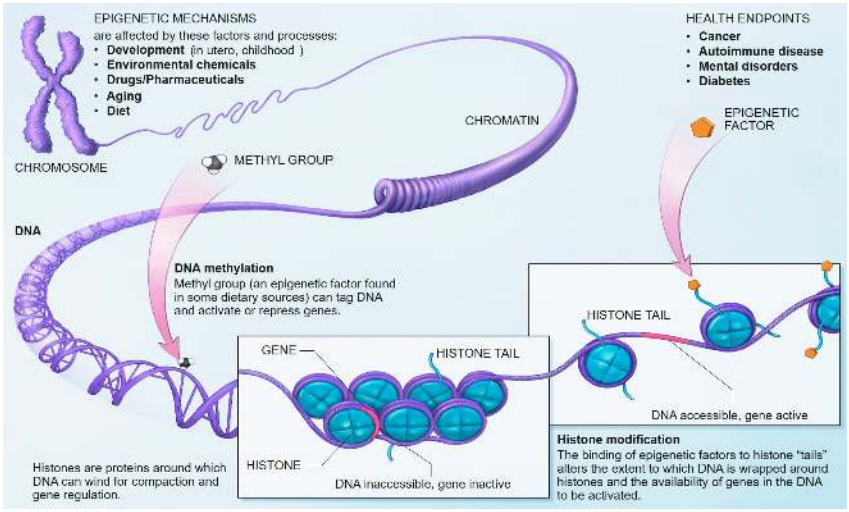


Figure **10.8.6**: DNA methylation and histon modification epigenetic modification10

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.

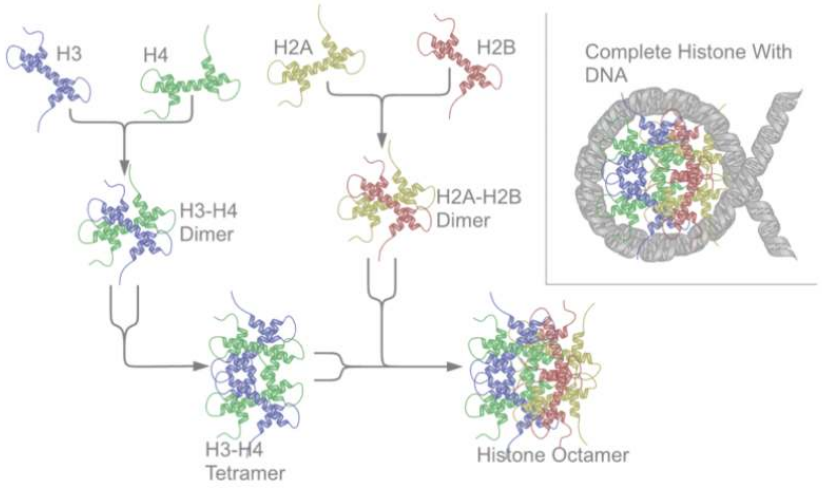


Figure **10.8.7**: DNA is wrapped around histones11

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.

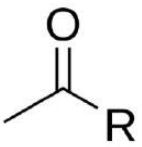


Figure **10.8.8**: Structure of acetyl12

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.



Video 10.8.1: A Tale of Two Mice. https://www.youtube.com/watch?v=OOiCu5kzGxg



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.

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.



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.

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CHAPTER OVERVIEW

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.

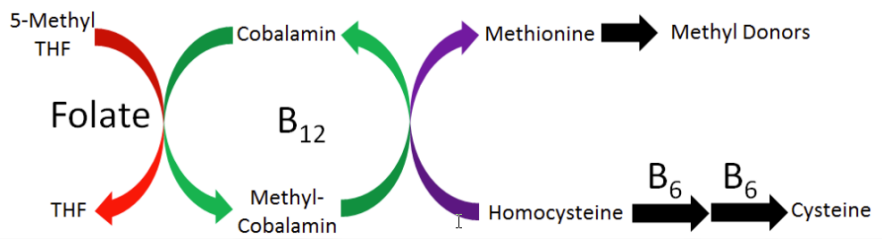


Figure 11.1: One-carbon metabolism depiction. 5-methyltetrahydrofolate (THF) donates a methyl group to cobalamin forming methylcobalamin. Methylcobalamin donates a methyl group to homocysteine, forming methionine (an amino acid). Alternatively, vitamin B_6 can be utilized to convert homocysteine into 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.

11.1: Folate and Folic Acid

11.2: Vitamin B12

11.3: B Vitamins, Homocysteine and Cardiovascular Disease

11.4: Blood, Bones and Teeth Micronutrients

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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.

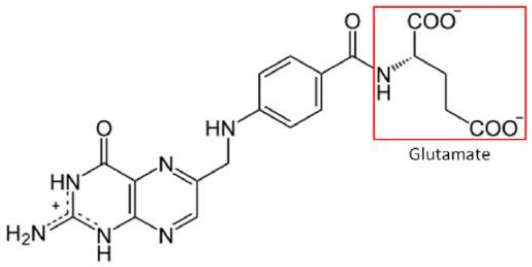


Figure **11.1.1**: Structure of Folic Acid[1]

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

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 DRIs[4]. 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 believed[3]. 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 source[5].

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 carrier[5]. This series of events is depicted in the figure below.

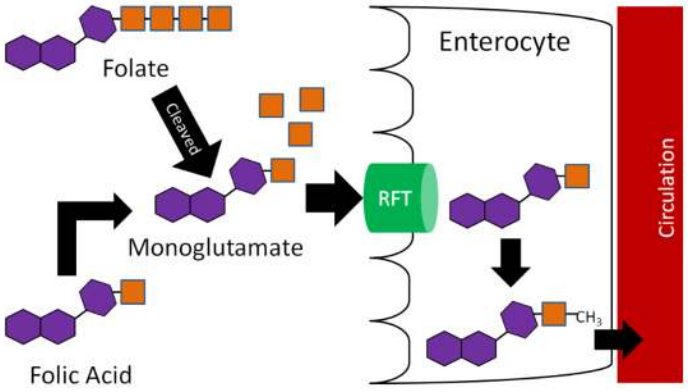


Figure **11.1.2**: The uptake and absorption of folate and folic acid (orange boxes represent glutamate)

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.

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.

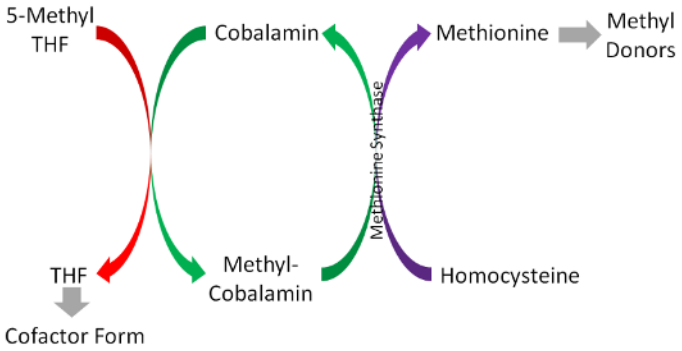


Figure **11.1.3**: One-carbon metabolism

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 methionine7. The following link shows that **THF** is a cofactor for serine hydroxymethyltransferase, the enzyme that converts serine to glycine.

Web Link

Serine to Glycine

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 properly2. As a result, fewer and poorer functioning red blood cells are produced that cannot carry oxygen as efficiently as normal red blood cells9.

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 defects8. 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 below10,11. 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 development12.

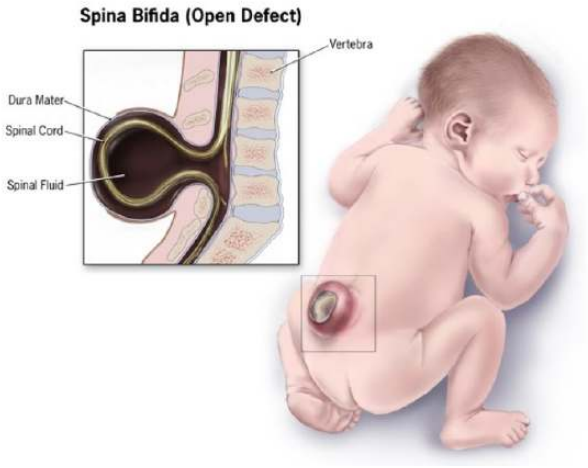


Figure **11.1.4**: Spina bifida13

The following video illustrates and describes spina bifida.



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.

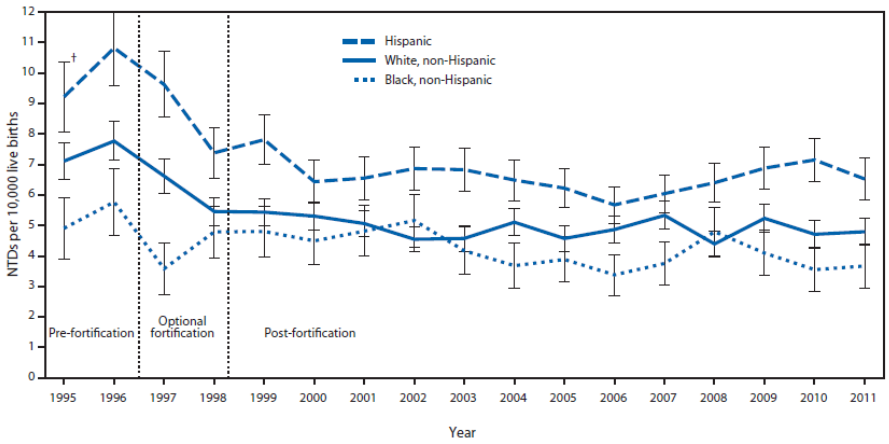


Figure **11.1.5**: Neural tube defect prevalence 1995-201114

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.

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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 absorbed[1]. 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} source[2] and spirulina contains a pseudovitamin B_{12} compound that is not bioavailable[3]. For vegans, supplements, nutritional yeast, and fortified products like fortified soy milk can help them meet their vitamin B_{12} needs[4].

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.

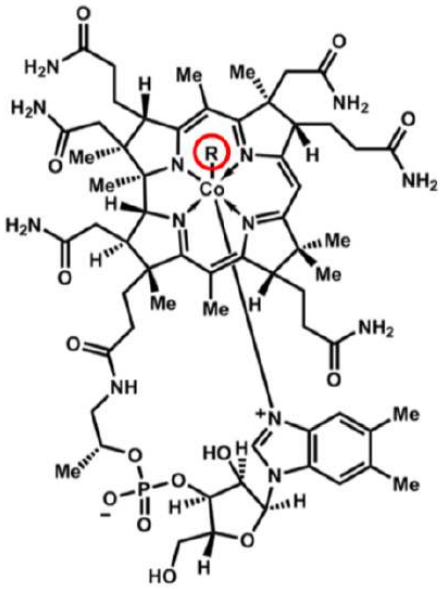


Figure **11.2.1**: Structure of vitamin B_{12} (cobalamin)[5]

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
NO_2	Nitritocobalamin
5'-deoxyadenosyl	Adenosylcobalamin*
CH_3	Methylcobalamin*

*Cofactor Forms

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 bioavailabilities7. Sublingual supplements of vitamin B_{12} have been found to be equally efficacious as oral supplements7. Excretion occurs mostly through bile, with little loss in urine6. 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 cells1,8.

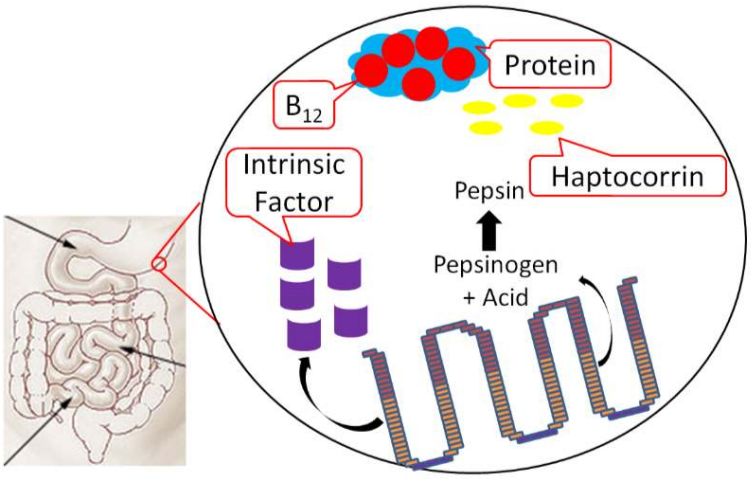


Figure **11.2.2**: Vitamin B_{12} in the stomach part 18,9

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 duodenum1,8.

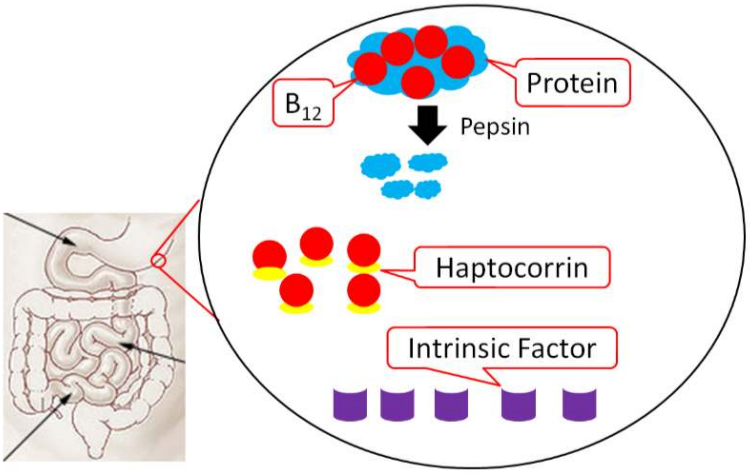


Figure **11.2.3**: Vitamin B_{12} in the stomach part 28,9

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 absorption1,8.

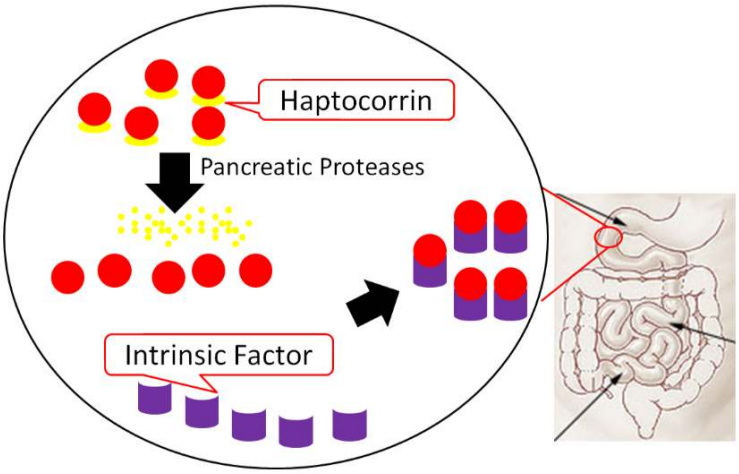


Figure **11.2.4**: Vitamin B_{12} in the duodenum8,9

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 circulation8.

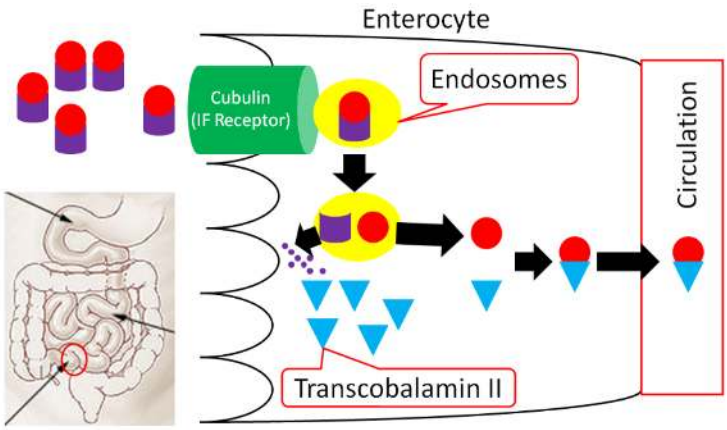


Figure **11.2.5**: Vitamin B_{12} absorption8,9

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.

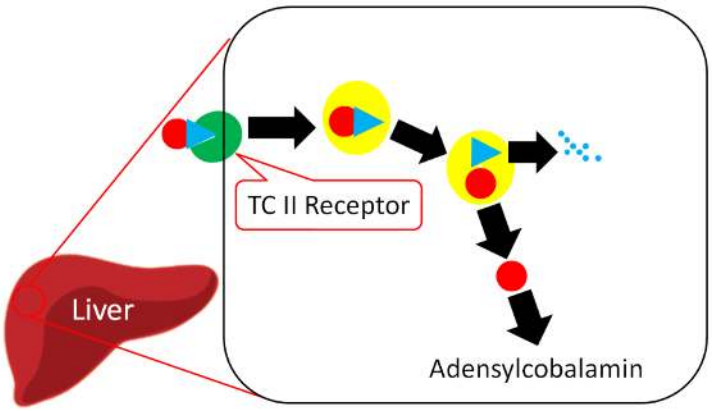


Figure **11.2.6**: Hepatic uptake and storage of vitamin B_{12}9

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 below[1].

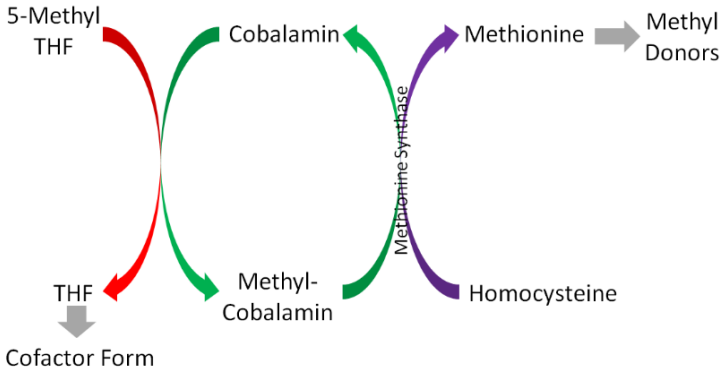


Figure 11.2.7: One-carbon metabolism

These methyl donors can donate methyl groups for methylating DNA, an epigenetic modification[1].

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 acids[1].

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.

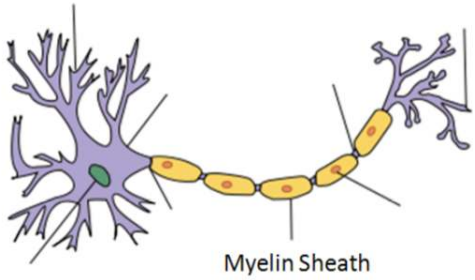


Figure 11.2.8: Vitamin B_{12} is needed to maintain the myelin sheath that surrounds neurons[10]

The mechanism by which vitamin B_{12} prevents demyelination is not known[11].

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.

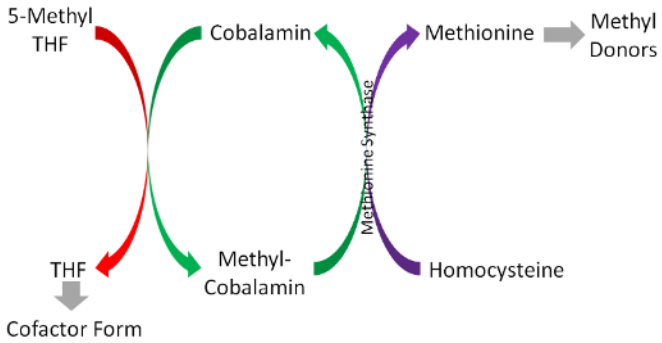


Figure 11.2.9: One-carbon metabolism

Thus, THF is not available for normal DNA synthesis and the red blood cells do not divide correctly.

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.

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.

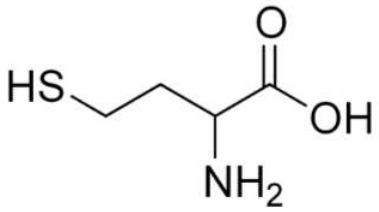


Figure **11.3.1**: Structure of homocysteine[1]

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.

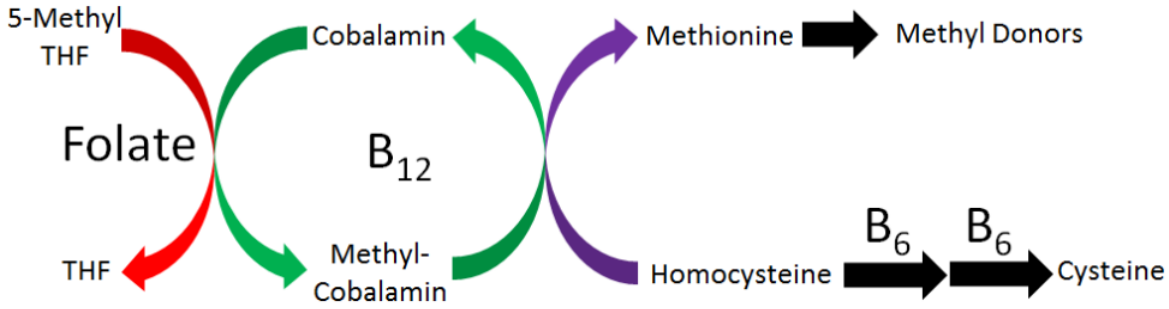


Figure **11.3.2**: One-carbon metabolism

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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CHAPTER OVERVIEW

11.4: 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.

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CHAPTER OVERVIEW

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
12.10: Electrolyte Micronutrients

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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.

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.

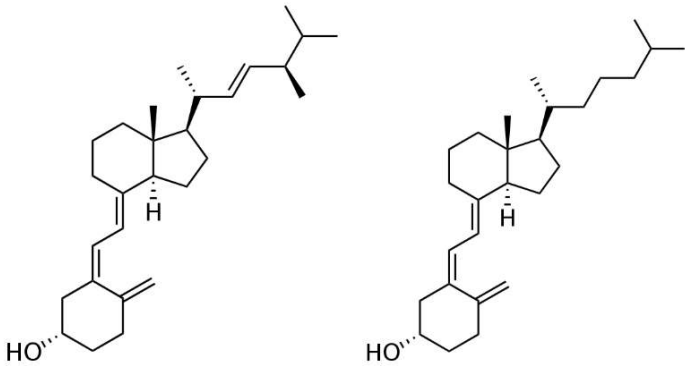


Figure **12.1.1**: Structure of vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol)[1,2]

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 ($-\mathbf{OH}$) 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.

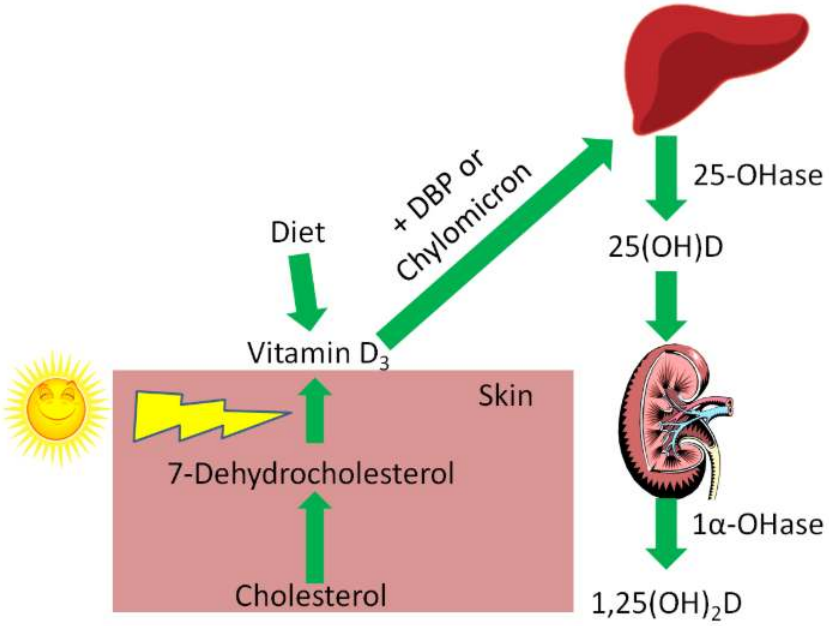


Figure **12.1.2**: Vitamin D synthesis and activation[3,4]

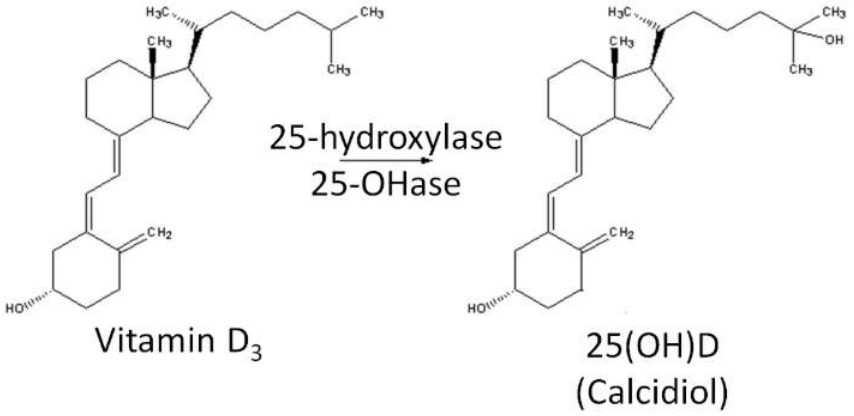


Figure **12.1.3**: Synthesis of 25(**OH**)D (calcidiol) from vitamin D_3 by 25-hydroxylase[5,6]

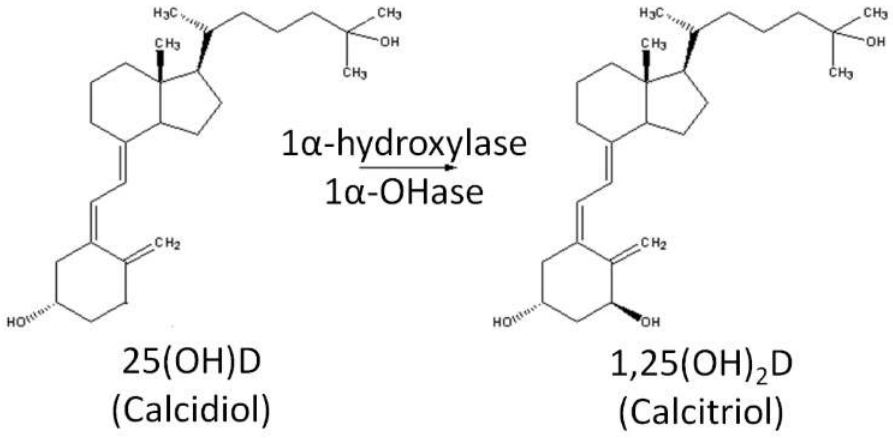


Figure **12.1.4**: Synthesis of 1,25(**OH**)2D (calcitriol) from 25(**OH**)D by 1alpha-hydroxylase[6]

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 supplementation[7,8].

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 round[10]. 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 surface[9].



Figure **12.1.5**: Seasons are also an important factor affecting vitamin D_3 synthesis

Time

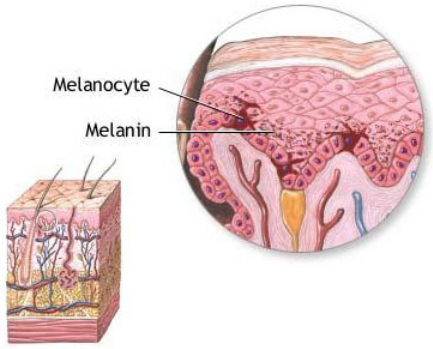
Time of day is also an important factor in affecting vitamin D_3 synthesis. Vitamin D_3 synthesis increases in the morning before peaking at noon, then declines the rest of the day[9].



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 burn2. 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 7011.



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.

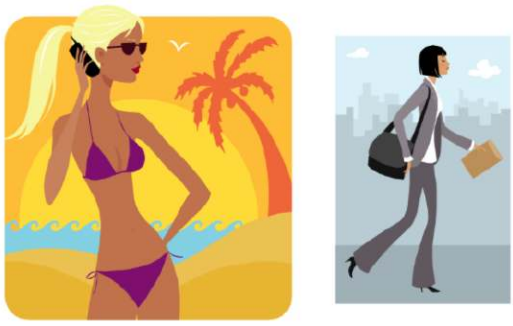


Figure **12.1.8**: Which of these 2 do you think is synthesizing less vitamin D?

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 synthesis[12]. 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 PM[10,13]. 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 supplementation[11].

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 case[14]. Virtually every health organization advises against using tanning beds, because the risks are far greater than the potential benefits[14,15].

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 salmon[16]. 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 fish[16]

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.

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.

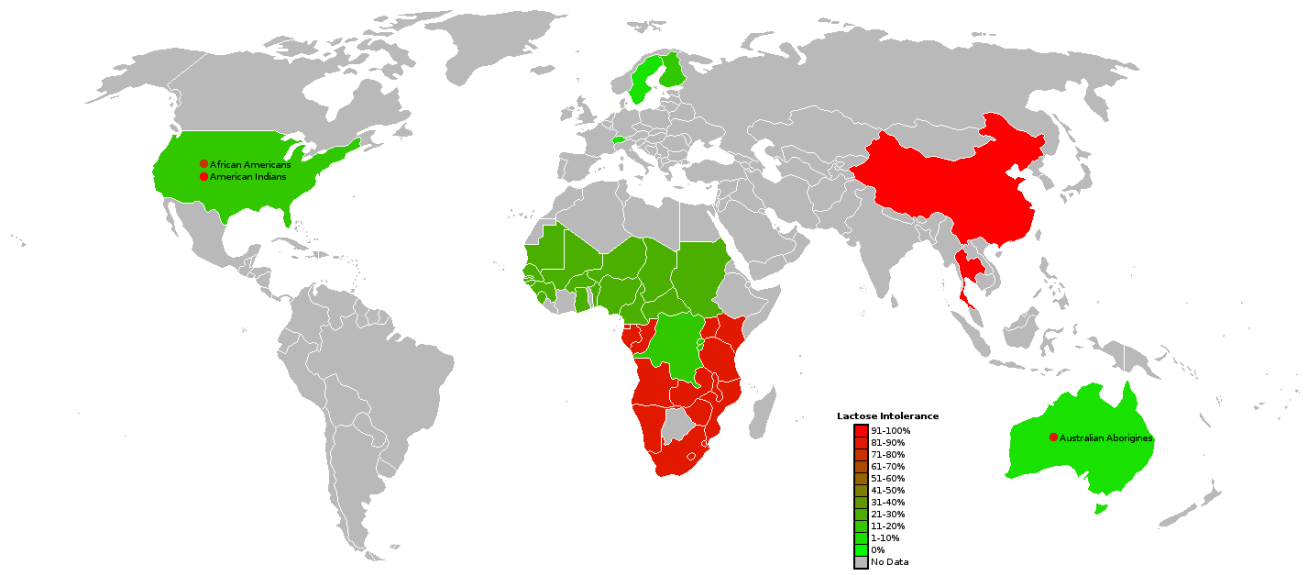


Figure **12.1.9**: Lactose intolerance worldwide (red high, green low). (Public Domain; Stevenfruitsmaak via Wikipedia)

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 juice24.

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.

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 $Ca_{10}(PO_4)_6(OH)_2$.

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.

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.

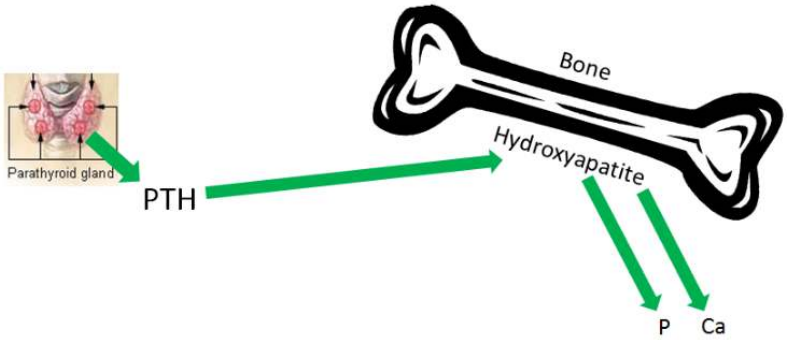


Figure 12.1.10: PTH effect 1: increased bone resorption26

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.

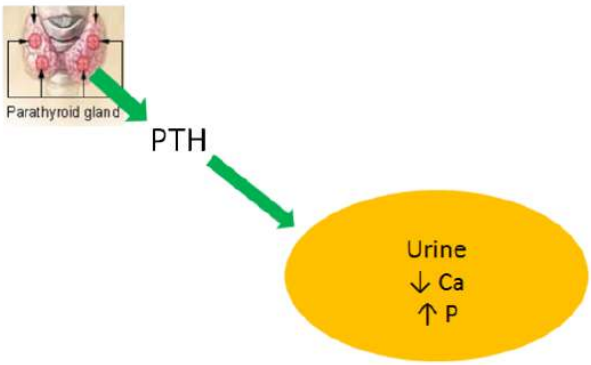


Figure 12.1.11: PTH effect 2: decreased calcium, increased phosphorus excretion26

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.

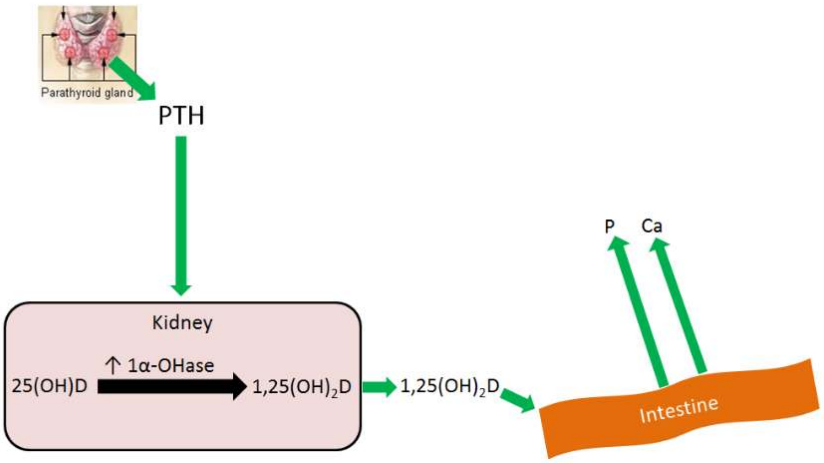


Figure **12.1.12**: PTH effect 3: increased 1,25(**OH**)2D activation26

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.

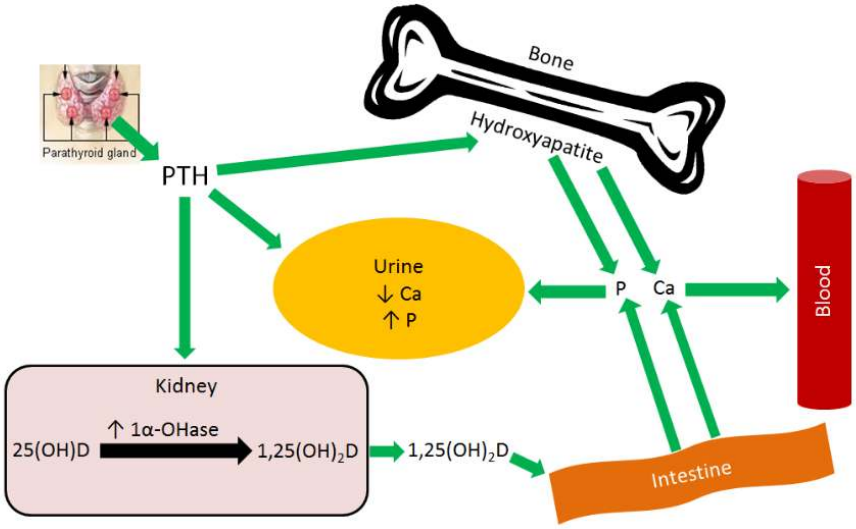


Figure **12.1.13**: 1,25(**OH**)2D increased calcium and phosphorus absorption26

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 high3.

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 effects3,14:

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.

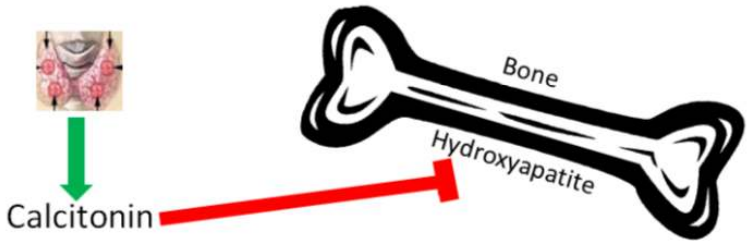


Figure 12.1.14: Calcitonin effect 1: increased bone deposition26

The second effect of calcitonin is to increase calcium and phosphorus excretion in urine.

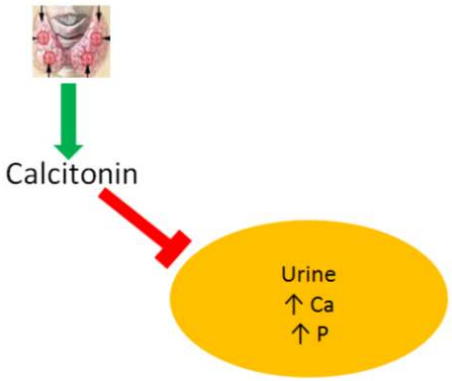


Figure 12.1.15: Calcitonin effect 2: increased calcium and phosphorus excretion26

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.

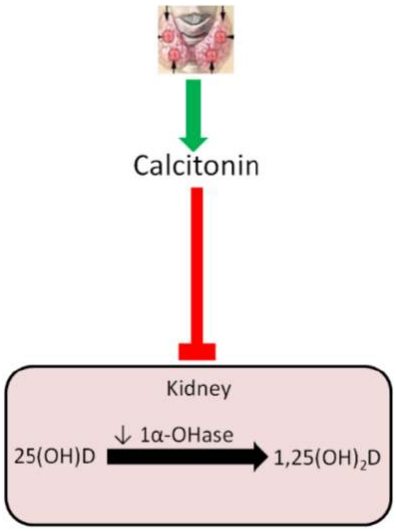


Figure 12.1.16: Calcitonin effect 3: decreased 1,25(OH)2D activation26

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.

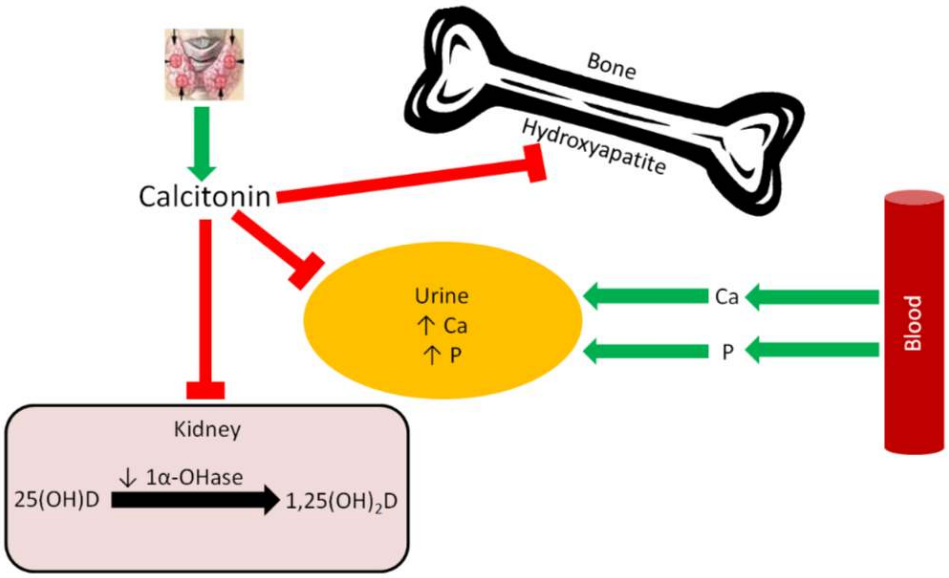


Figure 12.1.17: Response to high blood calcium26

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.

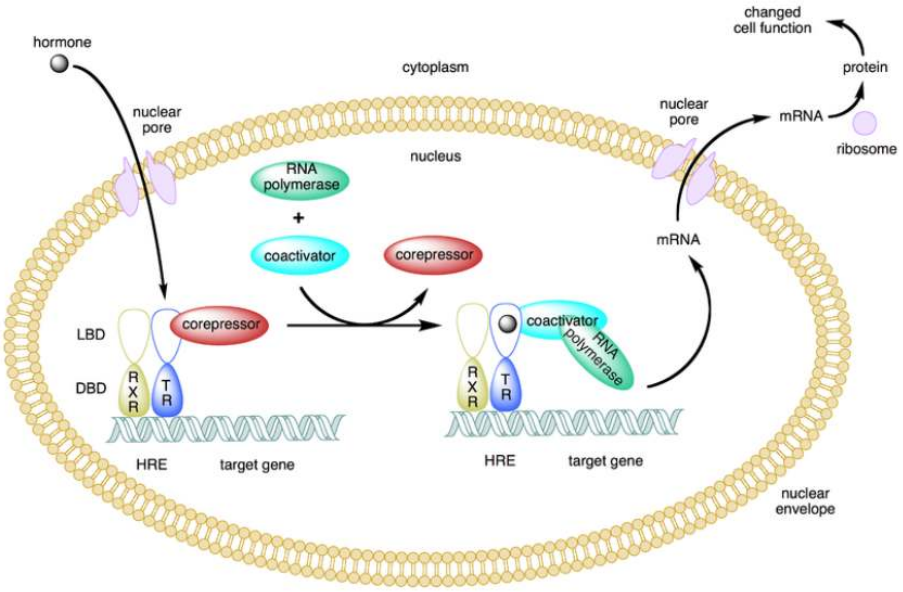


Figure 12.1.18: Nuclear hormone receptors action27

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.



Video **12.1.1**: Steroid hormone receptors. https://www.youtube.com/watch?v=Dxyq8GAWbpo

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.

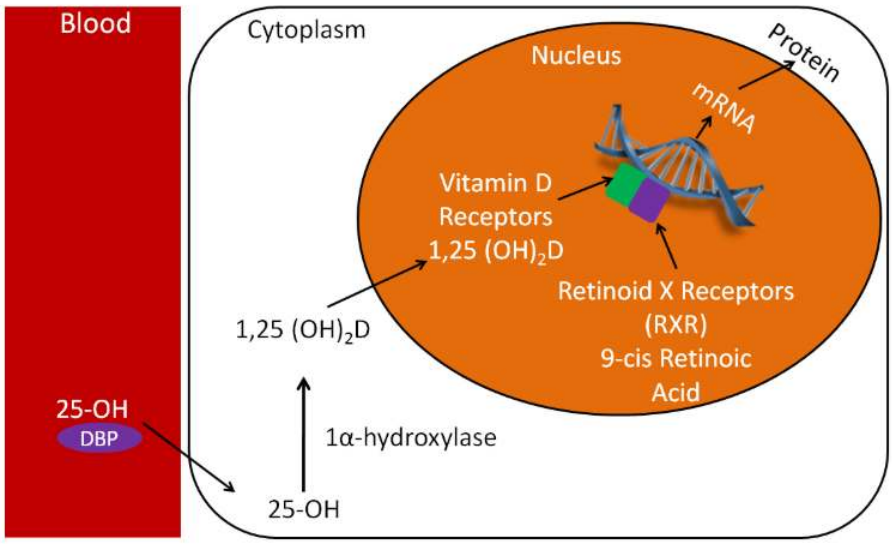


Figure **12.1.19**: Vitamin D receptor and a generic target gene

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.

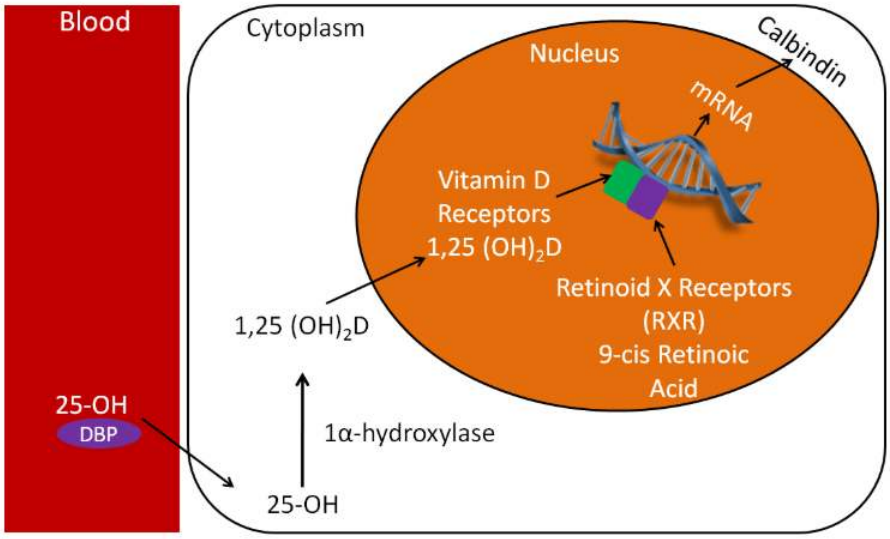


Figure **12.1.20**: Vitamin D receptor and calbindin

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.

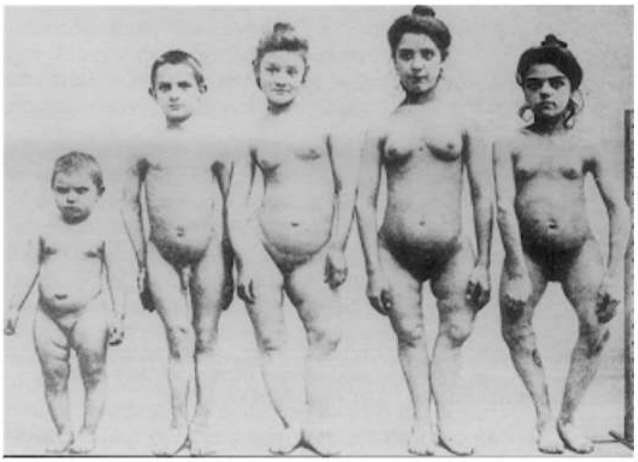


Figure **12.1.21**: Children suffering from rickets[28]

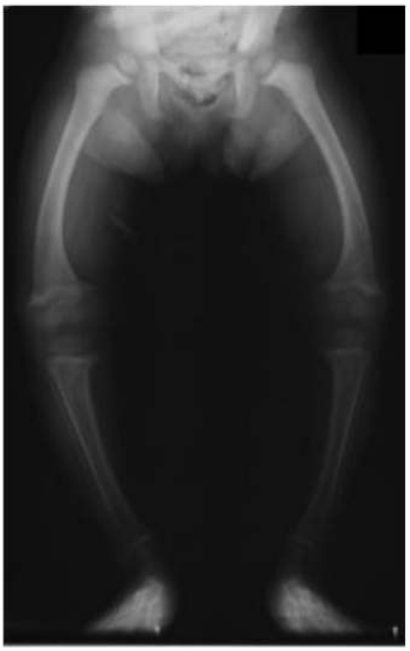


Figure **12.1.22**: X-ray from child suffering from rickets29

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.

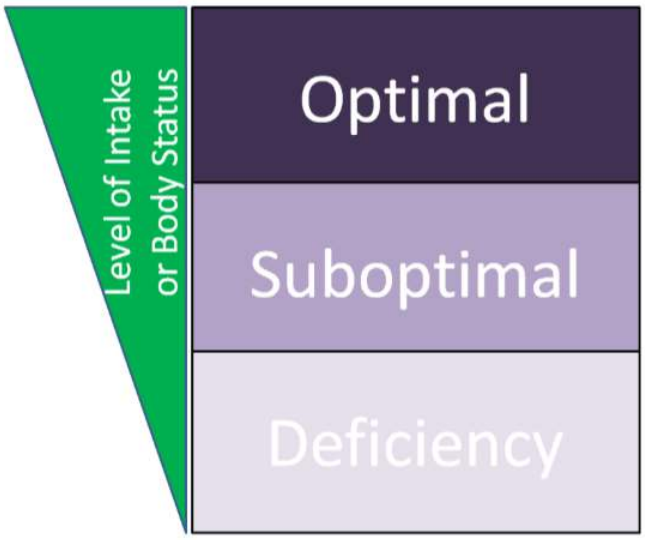


Figure **12.1.23**: Illustration of insufficient or suboptimal levels

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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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. $Ca^{2+} - Mg^{2+}$ ATPase functions to pump calcium out of the enterocyte and into circulation and to pump magnesium into the enterocyte, as shown below1.

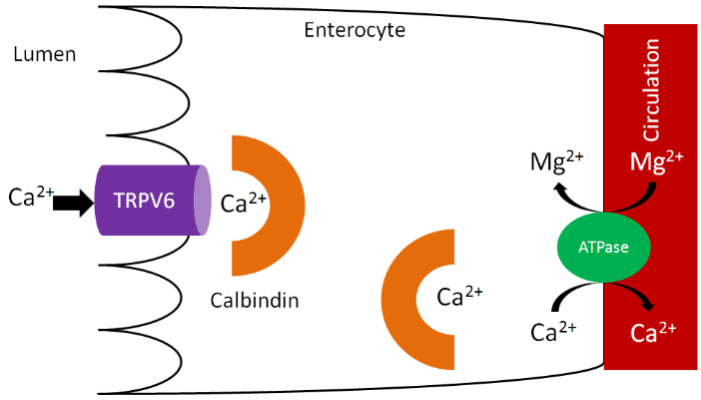


Figure 12.2.1: Calcium uptake and absorption

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.

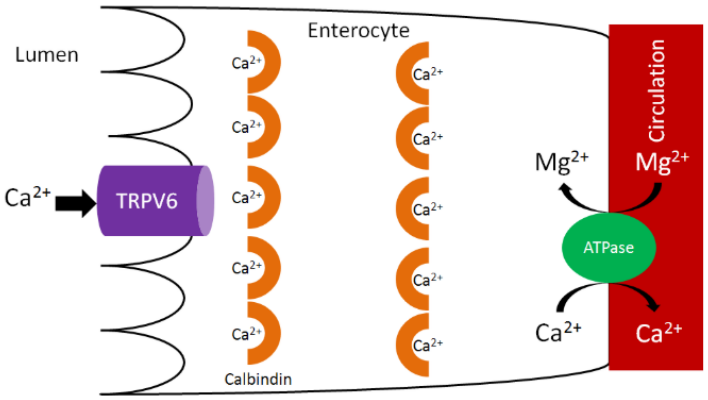


Figure 12.2.2: Increased calbindin increases calcium absorption

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.

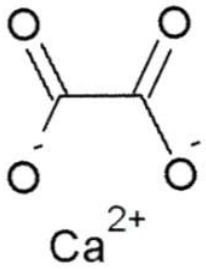


Figure 12.2.3: Structure of calcium oxalate3

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.

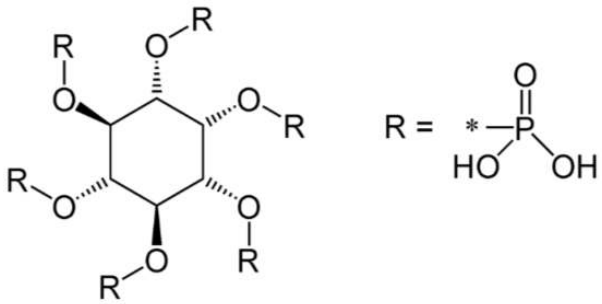


Figure 12.2.4: Structure of phytate4

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 sources5-7

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
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

Food	Serving Size (g)	Calcium content (mg)	Absorption (%)	Estimated Calcium Absorbed	Servings needed to equal 240 mL cow's milk
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.

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.

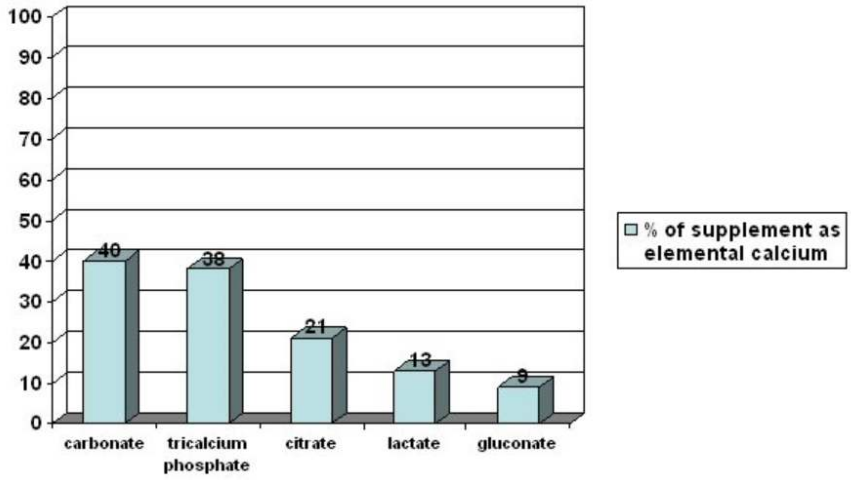


Figure **12.2.5**: Percent of calcium supplements that is elemental calcium[8]

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].

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].

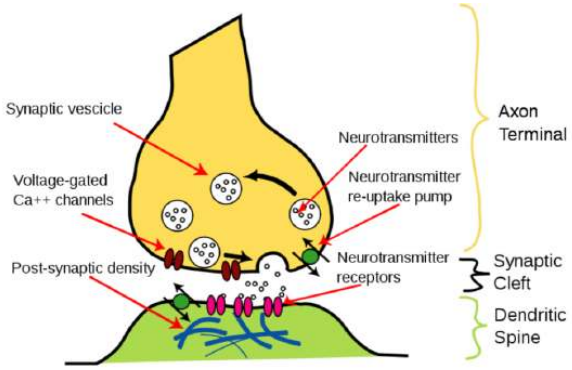


Figure 12.2.6: Calcium regulates neurotransmitter release12

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 occur13. This can be seen in the following figure and video.

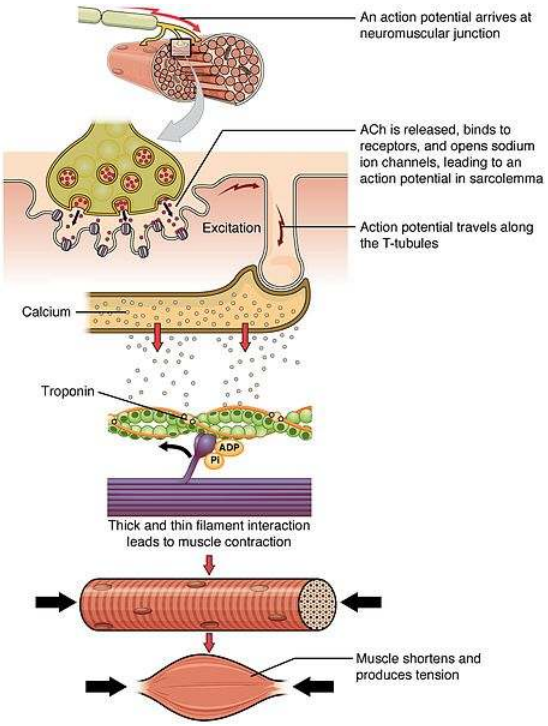


Figure 12.2.7: The role of calcium in muscle contraction14

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.

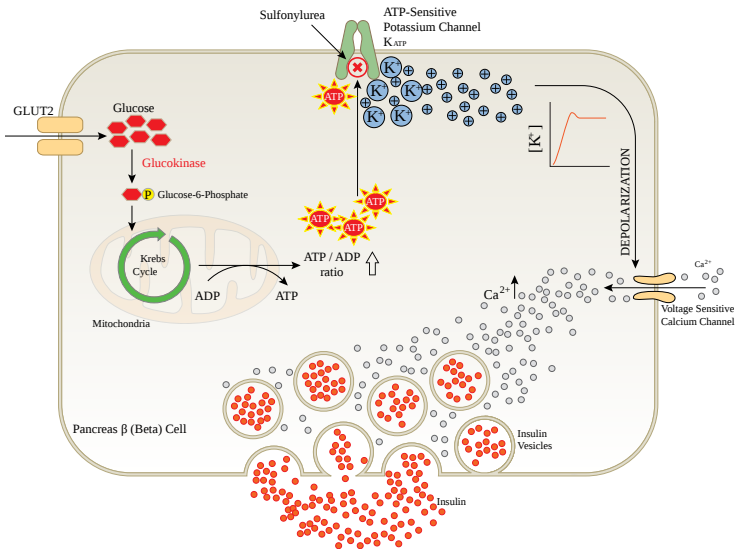


Figure **12.2.8**: Calcium signalling insulin release15

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.

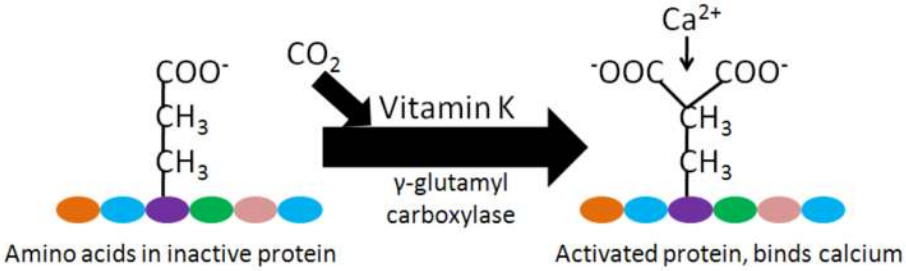


Figure **12.2.9**: Calcium bind to Gla proteins. Adapted from reference 1.

Enzyme regulation

The binding of calcium to calcium-binding proteins also regulates the action of a number of enzymes17.

Calcium Deficiency & Toxicity

Because of the large amount of calcium in bones (which can be mobilized), deficiency is rare2. 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.

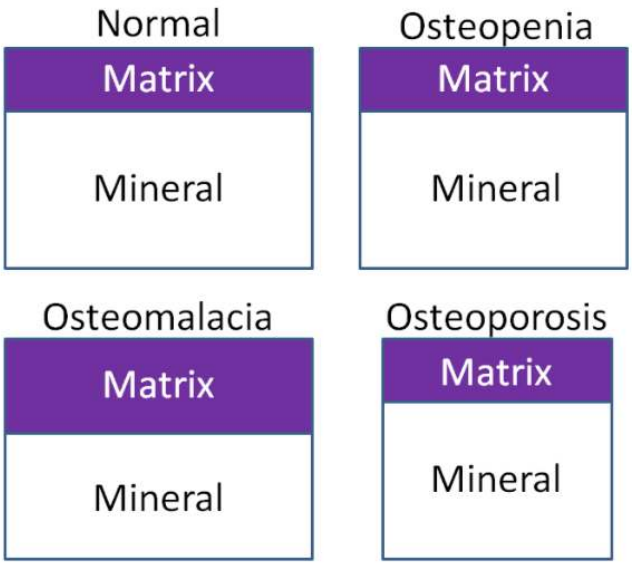


Figure **12.2.10**: Bone states; the width of each figure represents the bone mass. The height of the matrix and mineral boxes represents the relative proportion for matrix to mineral in the bone. Adapted from reference 16.

- **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 bone16.

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 below17.

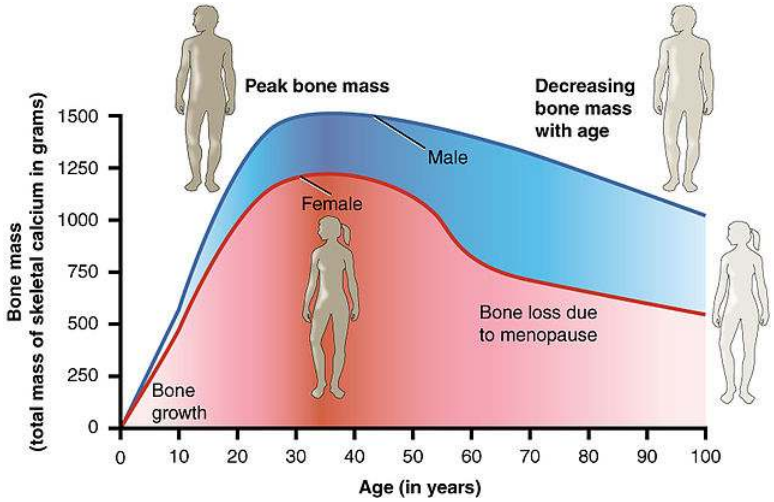


Figure **12.2.11**: Age and bone mass18

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 scanner19

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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19. en.Wikipedia.org/wiki/File:Bo...ty_scanner.jpg
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 below1.

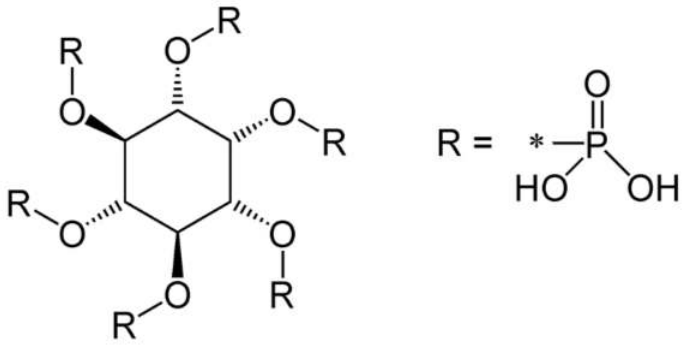


Figure 12.3.1: Structure of phytic acid2

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 up3. 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 absorbed1. 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 females4,5. 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 pain6. Toxicity is also rare, but it causes low blood calcium concentrations and tetany1.

Phosphorus Functions

Phosphorus has a number of functions in the body1.

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.

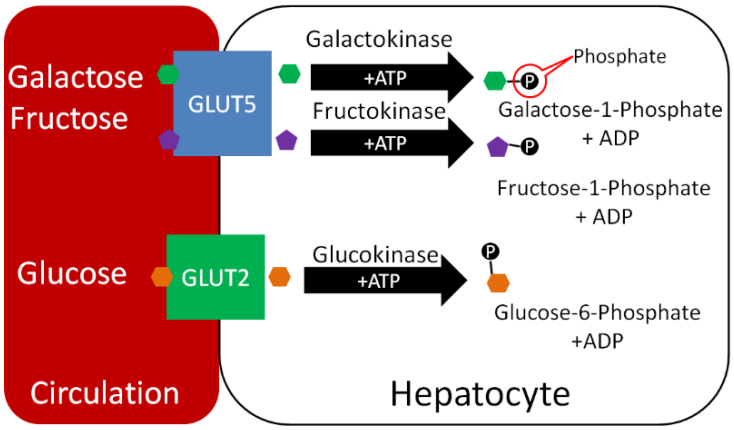


Figure **12.3.2**: Uptake of monosaccharides into the hepatocyte

Phospholipids

Phosphates are a component of phospholipids, as shown below.

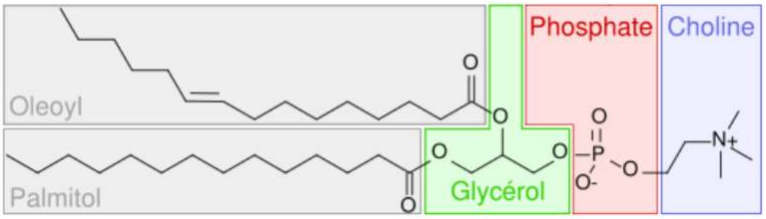


Figure **12.3.3**: Structure of phosphatidylcholine (lecithin)[7]

DNA/RNA

DNA/RNA have a phosphate backbone as shown below.

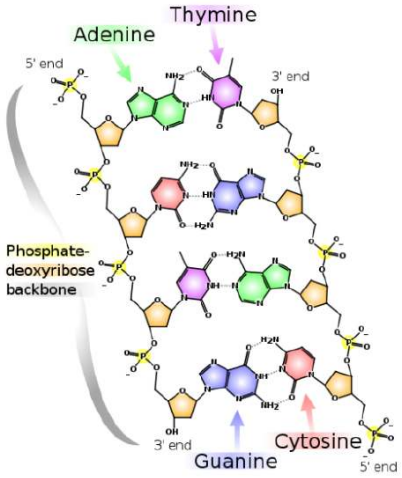


Figure **12.3.4**: Structure of DNA[8]

ATP

The major energy currency, ATP, stores energy in its phosphate bonds.

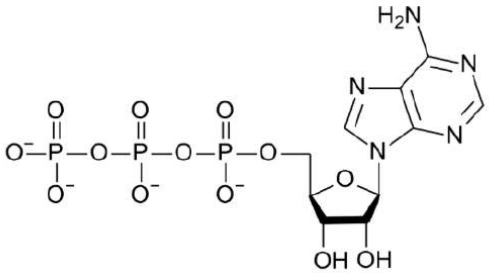


Figure 12.3.5: Structure of ATP9

Other functions of phosphate include:

- Intracellular secondary messengers cyclic AMP (cAMP) and inositol triphosphate (IP_3) both contain phosphate
- Acid/Base Balance
- Intracellular Anion

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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 ($Ca_{10}(PO_4)_6(OH)_2$), 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.

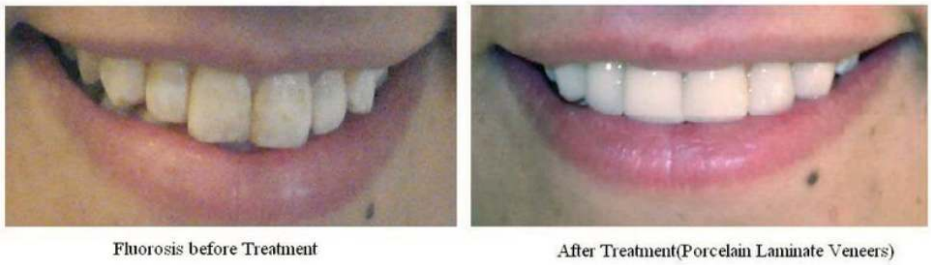


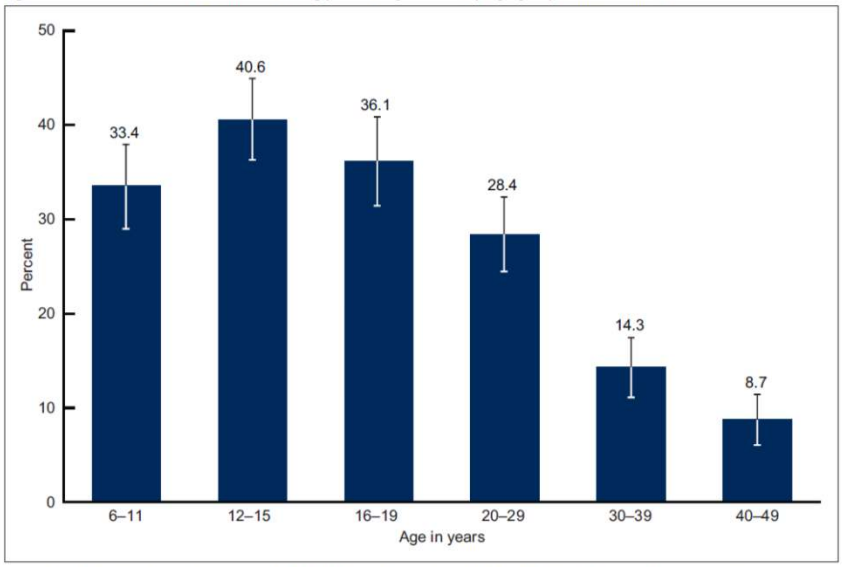
Figure **12.4.1**: Fluorosis[3]



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 2. Prevalence of dental fluorosis among persons aged 6–49, by age group: United States, 1999–2004

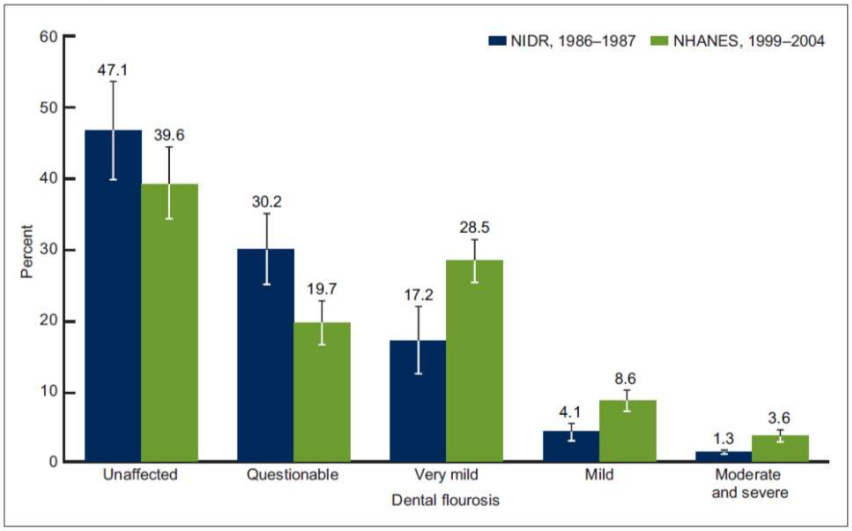


NOTES: Dental fluorosis is defined as having very mild, mild, moderate, or severe forms and is based on Dean's Fluorosis Index. Error bars represent 95% confidence intervals.
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 1999–2004.

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

References

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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.

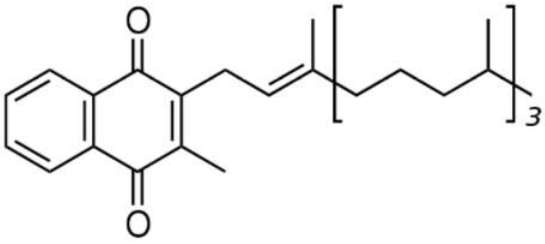


Figure **12.5.1**: Structure of phylloquinone (K1), the 3 outside of the brackets indicates that the structural unit inside the brackets is repeated 3 times[1]

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].

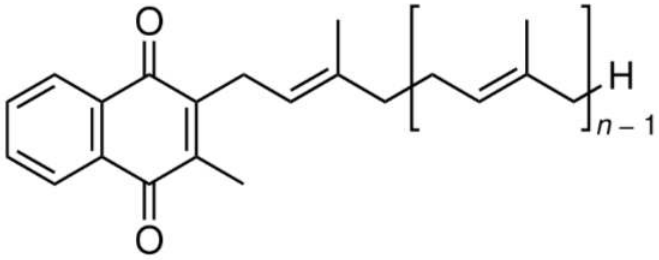


Figure **12.5.2**: Structure of menaquinone (K2). Menaquinones have side chains of varying length[4]

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.

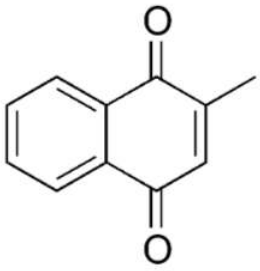


Figure **12.5.3**: Structure of menadione (K3)[5]

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].

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.

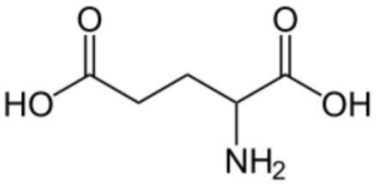


Figure 12.5.4: Glutamic acid structure7

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).

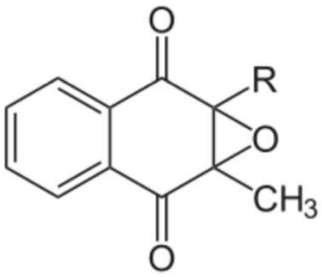


Figure 12.5.5: Vitamin K epoxide structure8

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.

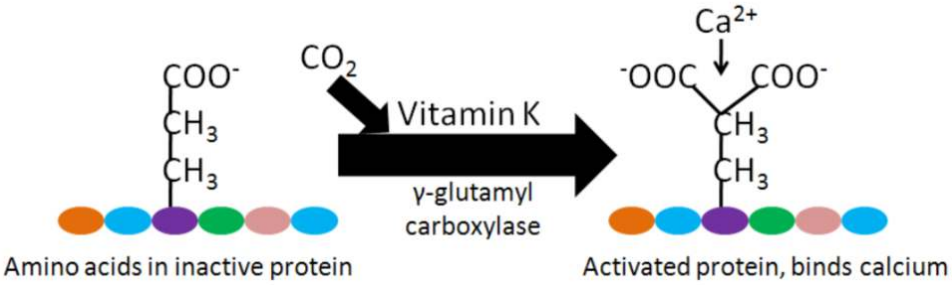


Figure 12.5.6: Gamma-glutamyl carboxylase converts glutamic acid (left) to gamma-carboxyglutamic acid (Gla, right). Proteins containing gamma-carboxyglutamic acid are known as Gla proteins. Binding of calcium activates Gla proteins. Adapted from reference 6.

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.



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



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.

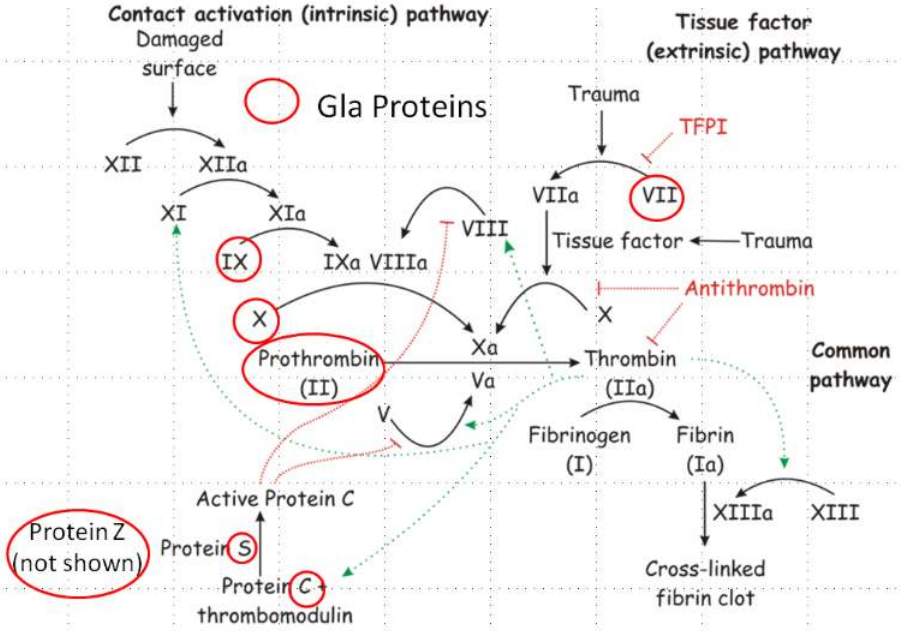


Figure **12.5.7**: Blood clotting cascade with potential Gla proteins circled[9]

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.

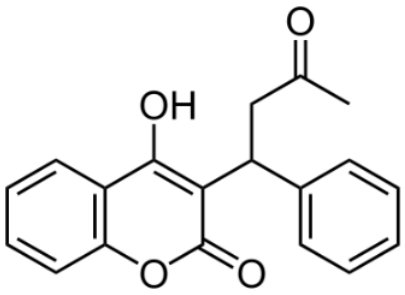


Figure **12.5.8**: Structure of warfarin[11]

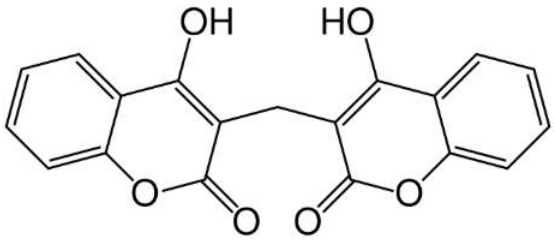


Figure **12.5.9**: Structure of dicumarol[12]

The following coumadin rap song video gives further information on warfarin.



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 S10. 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 known3,6. 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 health13.

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).

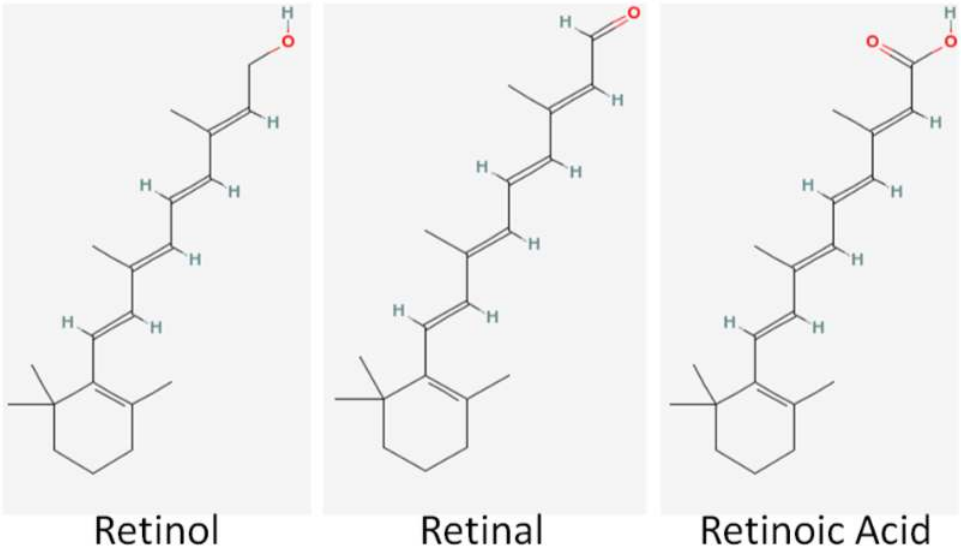


Figure **12.6.1**: Structure of the retinoids[1]

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.

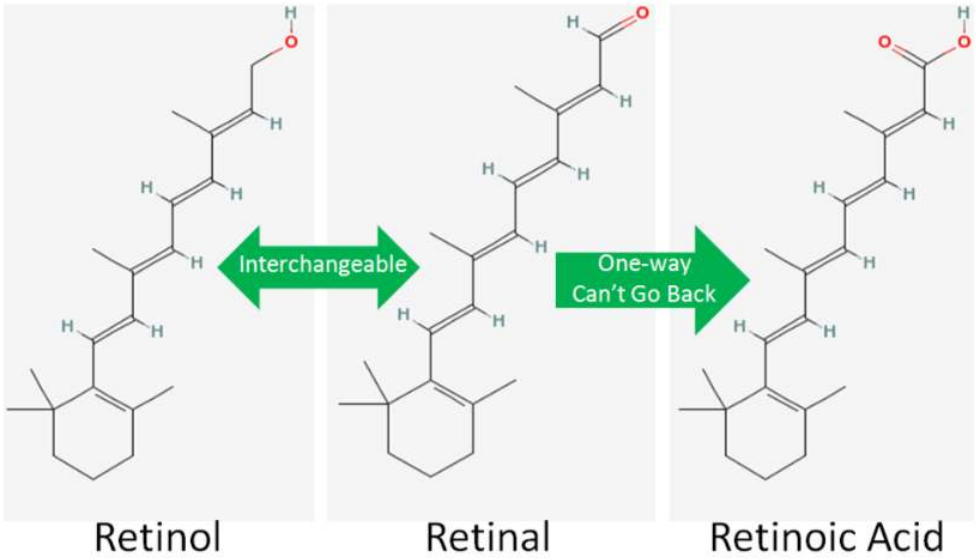


Figure **12.6.2**: Metabolism of retinoids[1]

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.

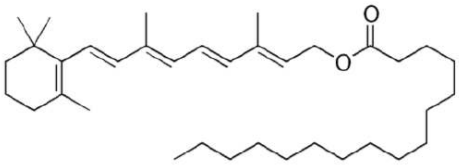


Figure **12.6.3**: Retinyl palmitate[2]

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

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

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.

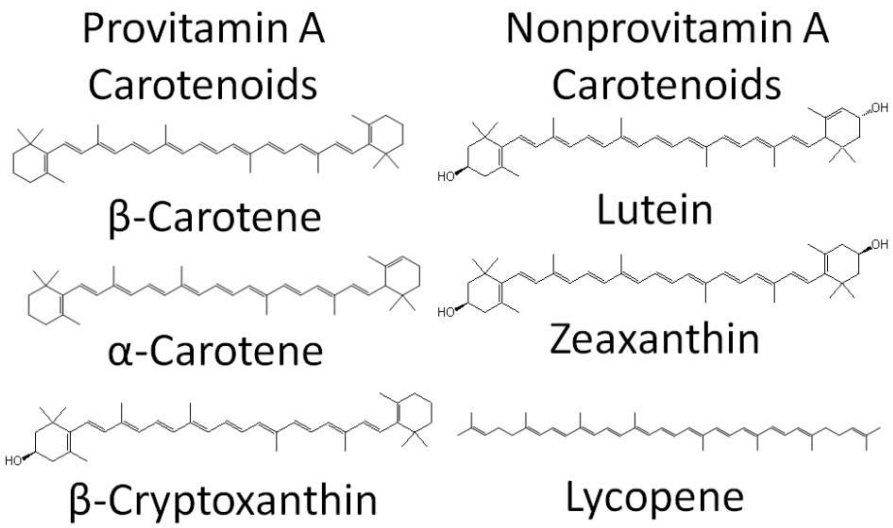


Figure **12.6.4**: Structure and classification of the 6 major carotenoids

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.

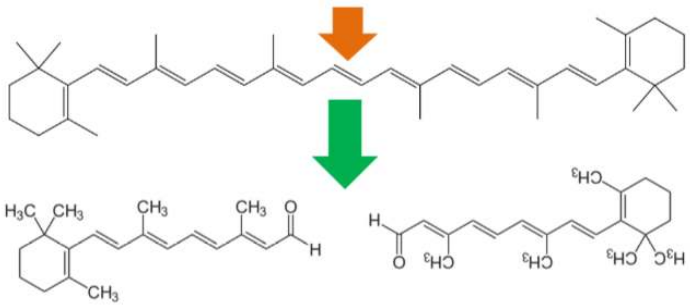


Figure **12.6.5**: Cleavage of beta-carotene 2 to retinal molecules[4]

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-cryptoxanthin[5]

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.

Vitamin A Uptake, Absorption, Transport & Storage

The uptake, absorption, transport, and storage of vitamin A and carotenoids are summarized in the figure below.

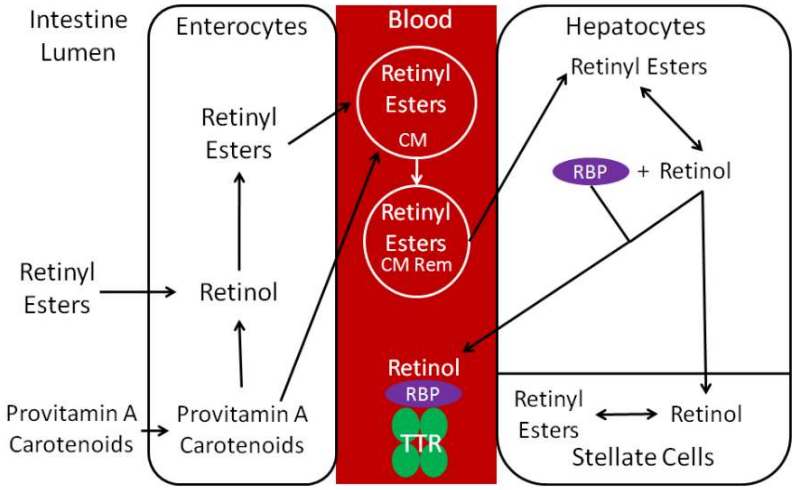


Figure **12.6.6**: Vitamin A uptake, absorption, transport, and storage. Adapted from reference6

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.

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.

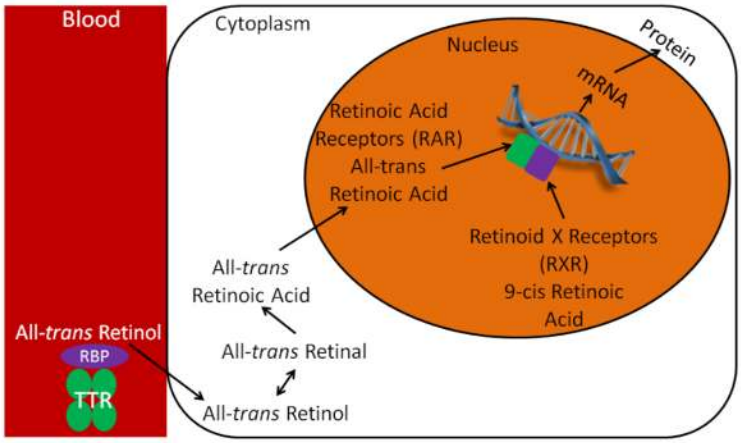


Figure 12.6.7: All-trans retinoic acid and retinoid X receptors

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.

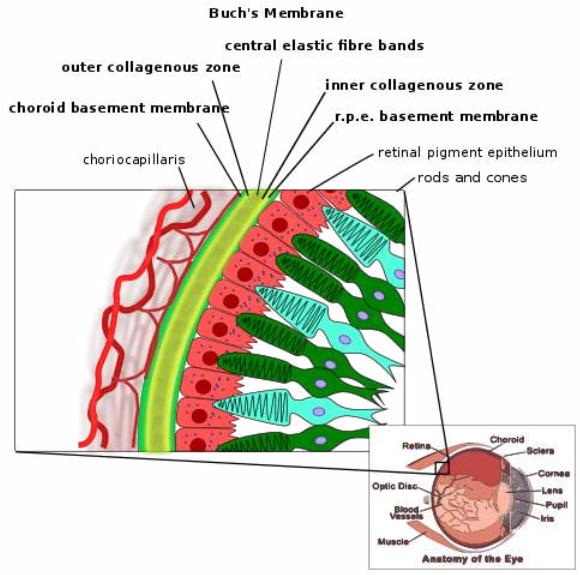


Figure 12.6.8: Retina, rods and cones8.

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.

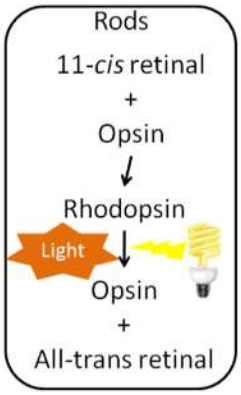


Figure **12.6.8**: Vitamin A in the rod

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 see10.

Cell Differentiation

Vitamin A, in particular retinoic acid, is important for cell differentiation, or the ability of stem cells to develop into specialized cells.

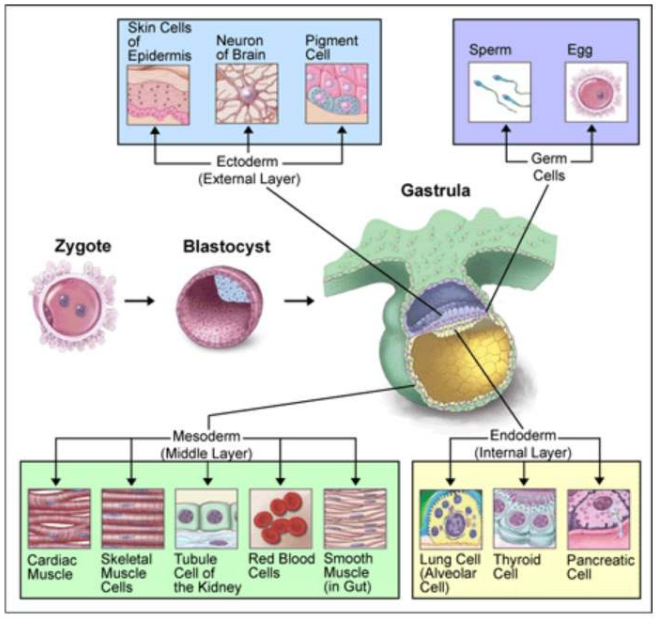


Figure **12.6.10**: Cellular differentiation11

Other functions that vitamin A is important for include:

- Growth and development
- Reproduction
- Immune function

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.

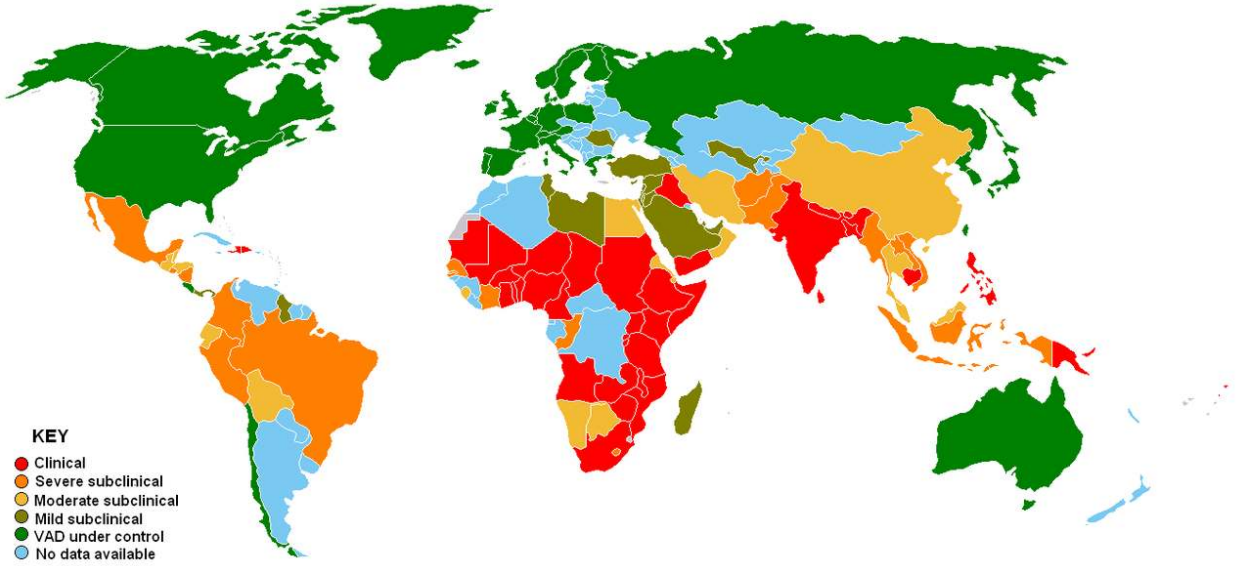


Figure **12.6.11**: Prevalence of vitamin A deficiency worldwide. (Public Domain; Petaholmes via Wikipedia)

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 world12.

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

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.



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 200913. 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 pregnant9. People should not consume huge doses of vitamin A expecting to get the same effects seen from these 2 medications14.

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

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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.

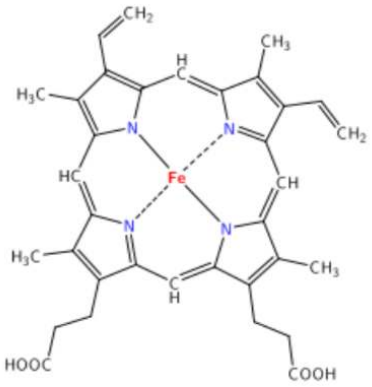


Figure 12.7.1: Structure of heme iron1

Approximately 40% of iron in meat, fish, and poultry is heme-iron, and the other 60% is non-heme iron2.

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 absorbed2. Approximately 85-90% of the iron we consume is non-heme iron2,3.

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.



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 absorbed4.

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.

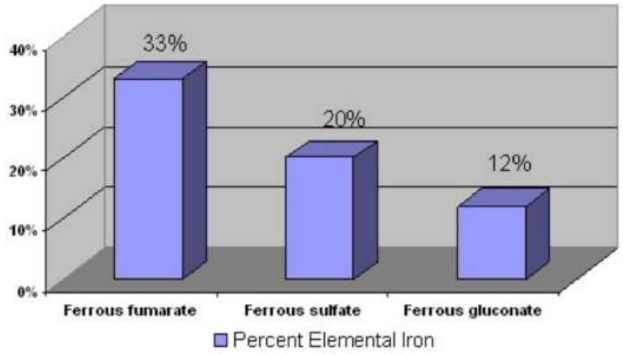


Figure **12.7.2**: Elemental iron in different iron supplements[3]

Iron chelates are marketed as being better absorbed than other forms of iron supplements, but this has not been proven[5]. It is recommended that supplements are not taken with meals, because they are better absorbed when not consumed with food[2].

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 $\mathbf{Fe^{2+}}$ into the enterocyte. Heme iron is taken up through heme carrier protein 1 (HCP-1), and then metabolized to $\mathbf{Fe^{2+}}$. $\mathbf{Fe^{2+}}$ 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 ferroportin[5,6]. This process is summarized in the figure below.

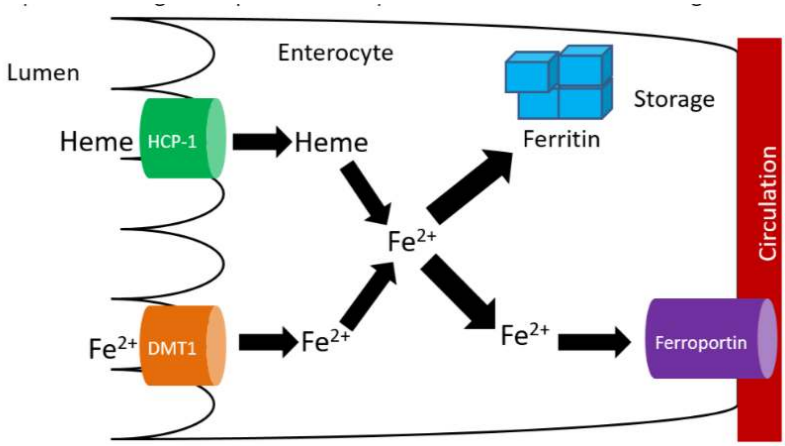


Figure **12.7.3**: Iron uptake into the enterocyte

Since only the reduced form of non-heme iron ($\mathbf{Fe^{2+}}$) is taken up, $\mathbf{Fe^{3+}}$ must be reduced. There is a reductase enzyme on the brush border, duodenal cytochrome b (Dcytb), that catalyzes the reduction of $\mathbf{Fe^{3+}}$ to $\mathbf{Fe^{2+}}$, 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 $\mathbf{Fe^{2+}}$ 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.

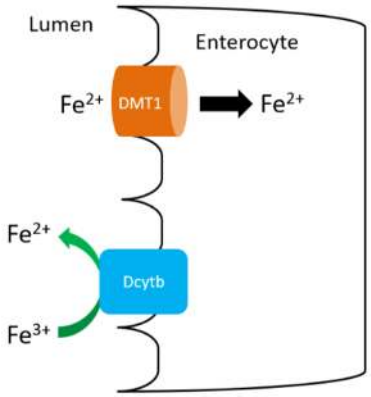


Figure **12.7.4**: Reduction of non-heme iron by Dcytb

In addition to vitamin C, there is an unidentified factor in muscle that enhances non-heme iron absorption if consumed at the same meal[7]. 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 fraction[7]

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 albumin[7].

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.

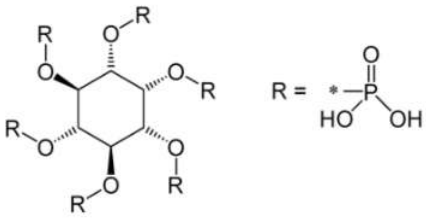


Figure **12.7.5**: Structure of phytic acid[8]

Other compounds that inhibit absorption are:

Polyphenols (coffee, tea)[6]

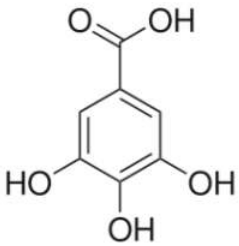


Figure **12.7.6**: Structure of gallic acid, a polyphenol[9]

Oxalate (spinach, rhubarb, sweet potatoes, and dried beans)[7]

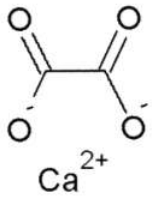


Figure **12.7.7**: Structure of calcium oxalate[10]

Calcium is also believed to inhibit iron uptake.

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].

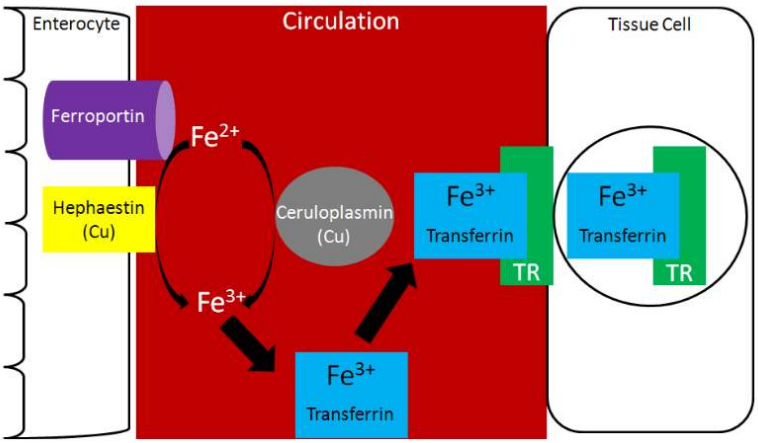


Figure **12.7.8**: Transport and uptake of iron

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 hemosiderin[5].

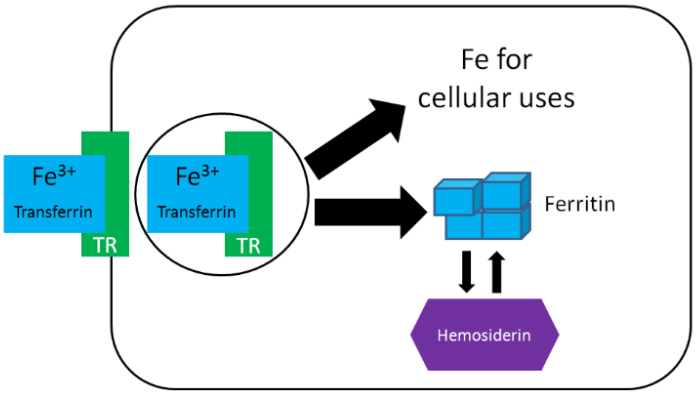


Figure **12.7.9**: Fates of iron within cells

There are 3 major compartments of iron in the body[12]:

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).

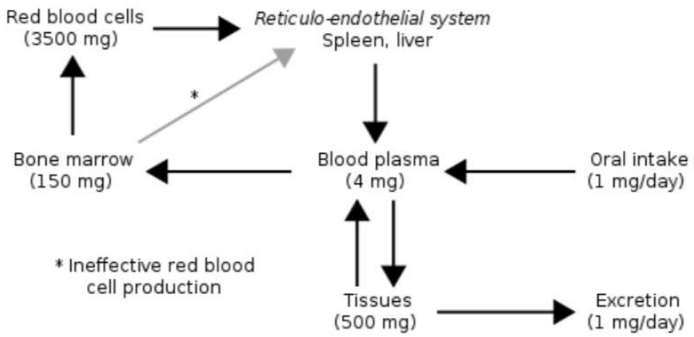


Figure **12.7.10**: Iron distribution in different compartments13

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.

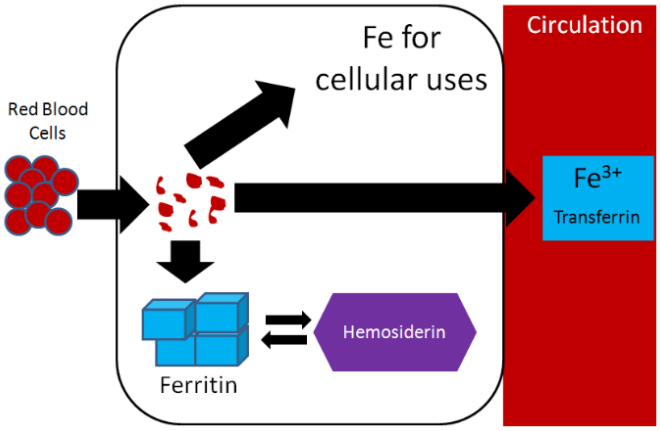


Figure **12.7.11**: Iron recycling from red blood cells

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.

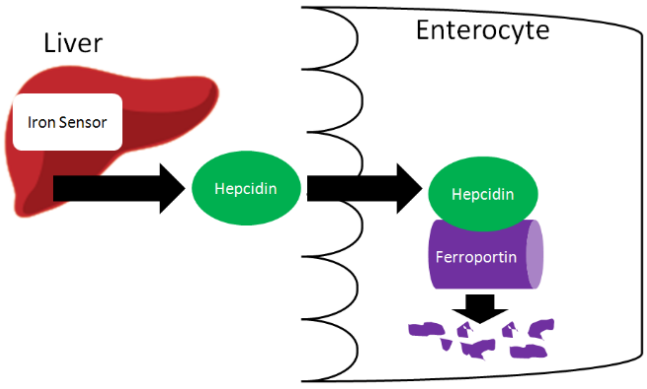


Figure **12.7.12**: Action of hepcidin14

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.

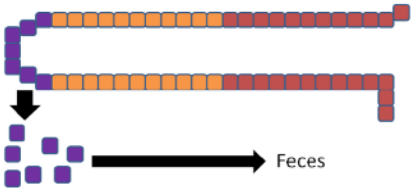


Figure **12.7.13**: Enterocytes are sloughed off the villus and unless digested and their components reabsorbed, they will be excreted in feces

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.

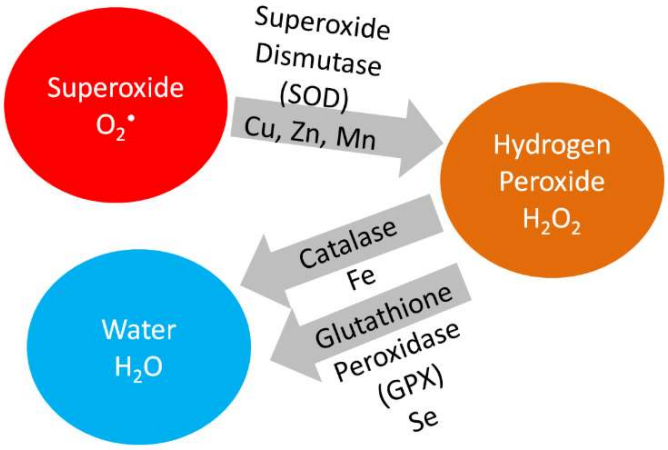


Figure **12.7.14**: Catalase uses iron as a cofactor

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.

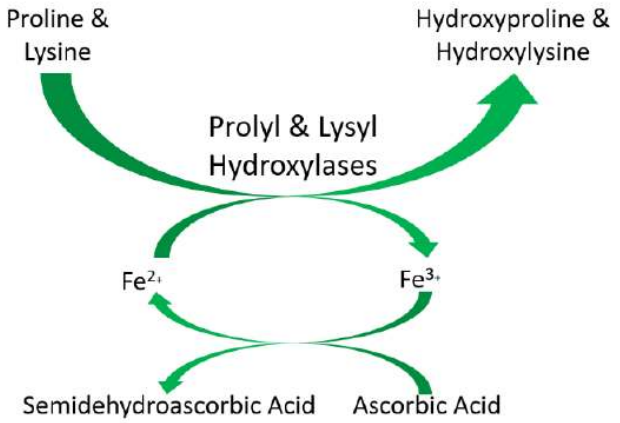


Figure **12.7.15**: Importance of ascorbic acid and iron to proline and lysyl hydroxylases

Heme iron is also found in cytochromes, like cytochrome c in the electron transport chain as shown below5.

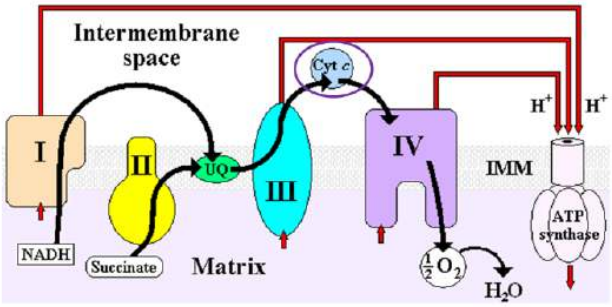


Figure **12.7.16**: Cytochrome c in the electron transport chain contains iron15

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

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.

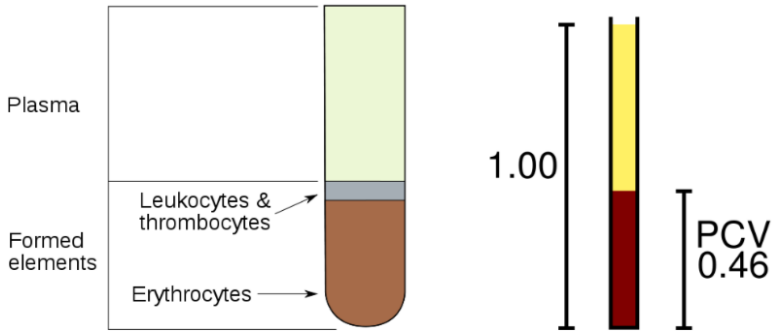


Figure 12.7.18: Hematocrit figures17,18

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 plasma19.

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 headaches19. Other side effects include decreased immune function and delayed cognitive development in children20.

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.

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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' consume1. An estimated 15-40% of consumed zinc is absorbed2. 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 albumin3.

These functions are represented in the figure below.

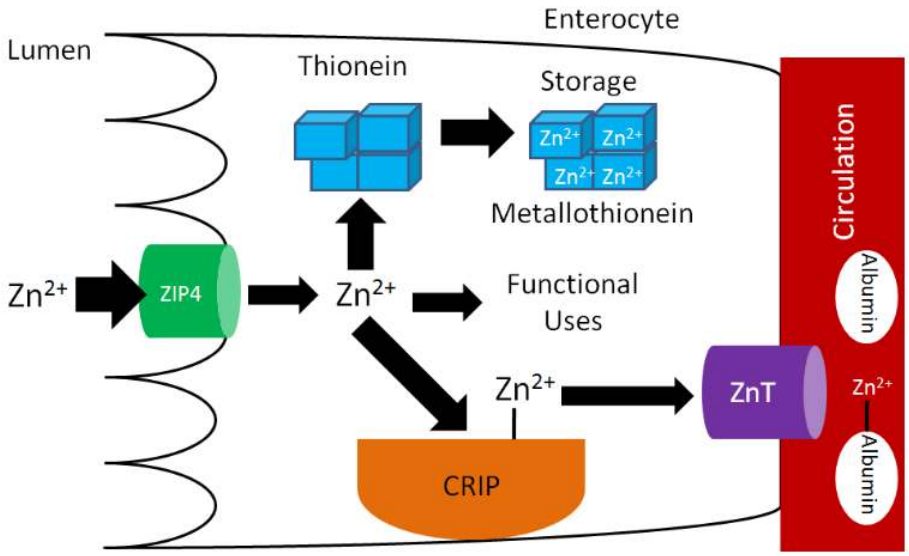


Figure **12.8.1**: Fates of zinc once it is taken up into the enterocyte

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 kidney1. 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.

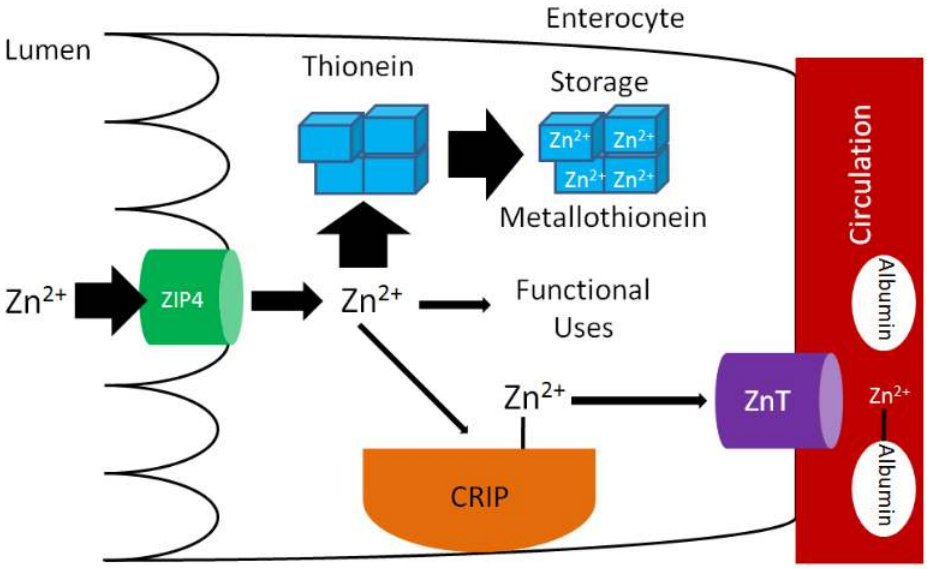


Figure **12.8.2**: Fate of zinc under high zinc status

The enterocytes are then sloughed off preventing the bound zinc from being absorbed.

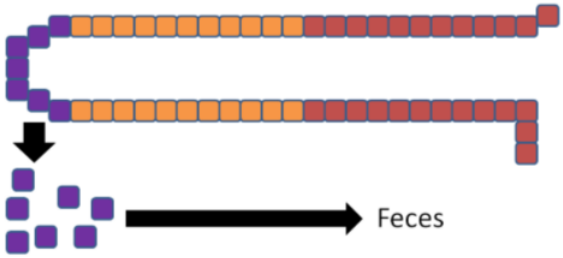


Figure **12.8.3**: Enterocytes are sloughed off and excreted in feces.

There are a 3 inhibitors of zinc absorption (same inhibitors you learned about of iron absorption)3:

Phytate (phytic acid)

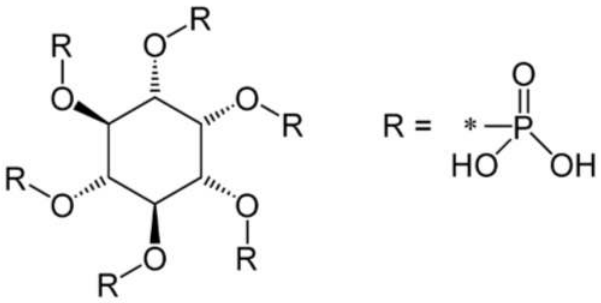


Figure **12.8.4**: Phytic acid structure4

Polyphenols (coffee, tea)3

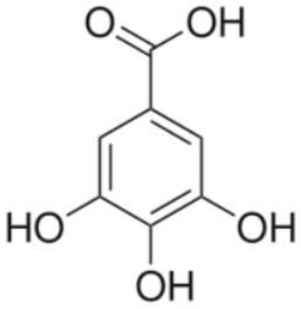


Figure **12.8.5**: Structure of the polyphenol gallic acid5

Oxalate (spinach, rhubarb, sweet potatoes, and dried beans)3

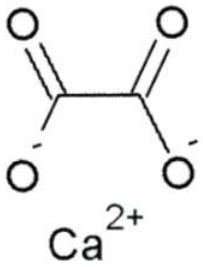


Figure **12.8.6**: Structure of calcium oxalate6

Non-heme iron also inhibits zinc absorption.

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.

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.

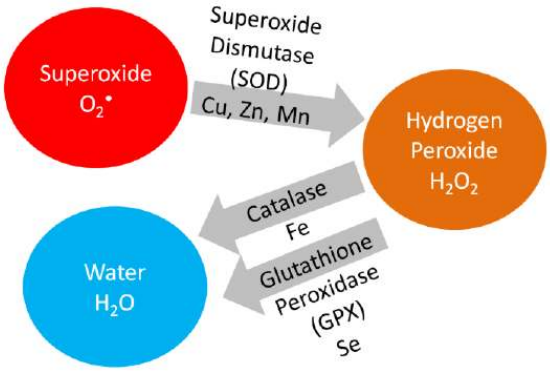


Figure **12.8.7**: Superoxide dismutase uses zinc as a cofactor

Alcohol dehydrogenase uses 4 zincs per enzyme. Its role in ethanol metabolism is shown below3.

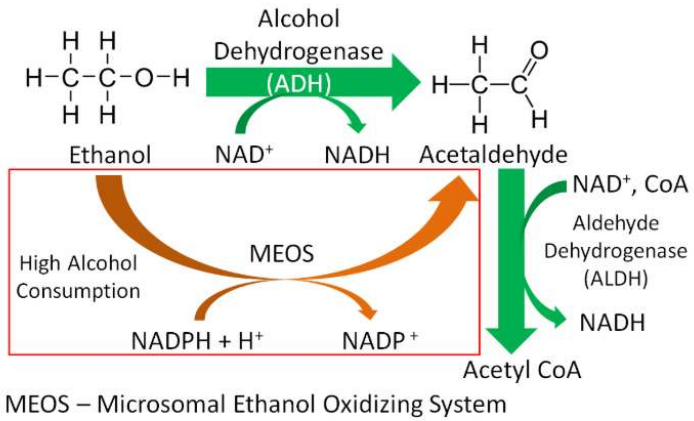


Figure 12.8.8: Ethanol metabolism[8,9]

Delta-aminolevulinic acid dehydratase (ALA dehydrogenase), which is involved in heme synthesis, uses 8 zincs/enzyme to form porphobilinogen, as shown below[3].

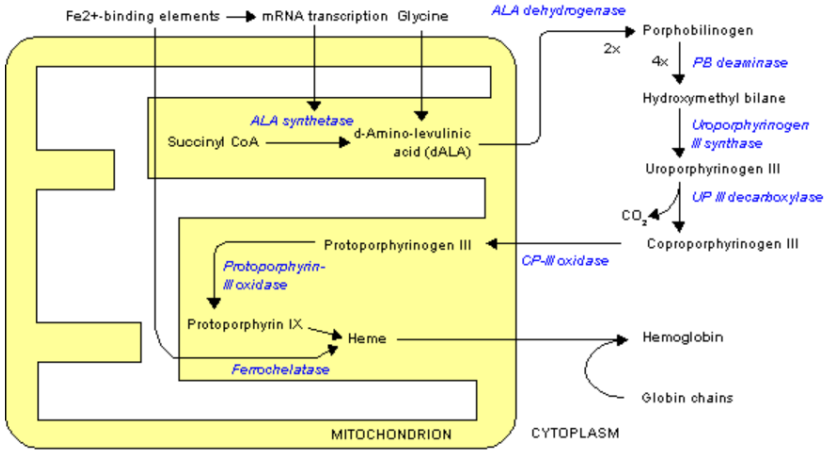


Figure 12.8.9: ALA dehydrogenase requires zinc in the heme synthesis pathway[10]

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.

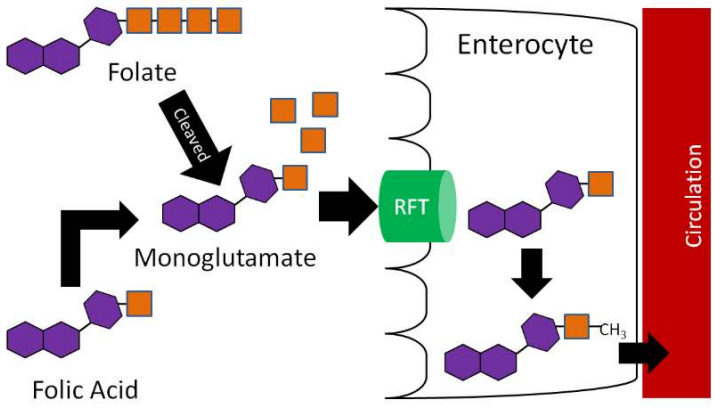


Figure 12.8.10: The absorption of folate and folic acid

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].

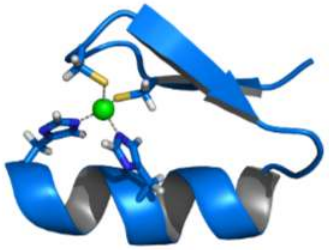


Figure **12.8.11**: Structure of a zinc finger, zinc is the green atom bound in the center[11]

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.

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.

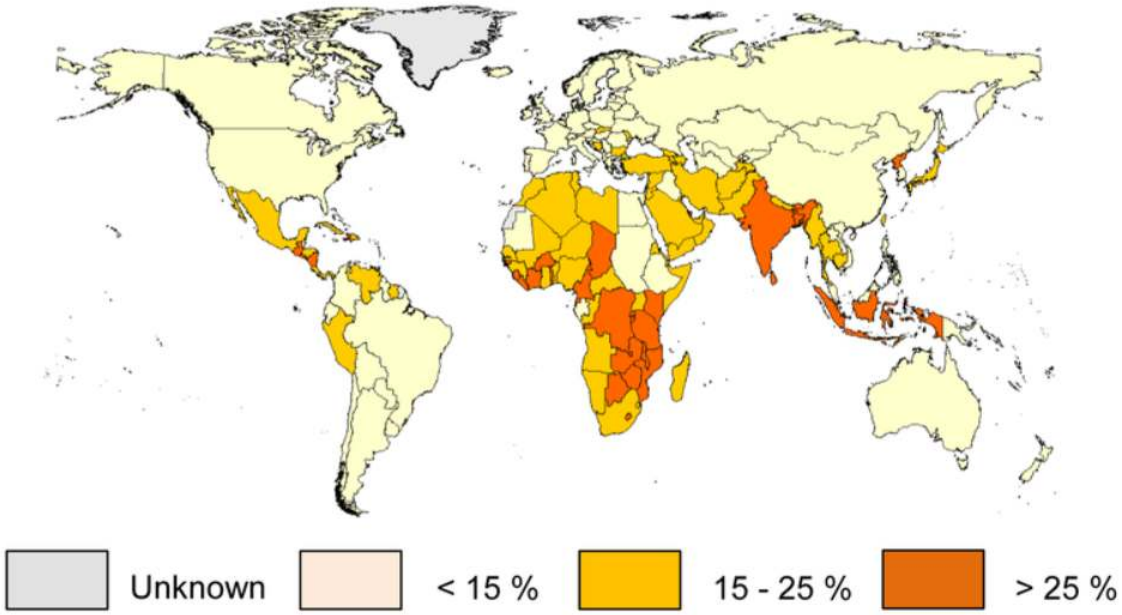


Figure **12.8.12**: Worldwide prevalence of zinc deficiency[12]

At particular risk are children, pregnant women, elderly and the poor[13]. Symptoms of zinc deficiency include[1,3]:

- 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.

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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.

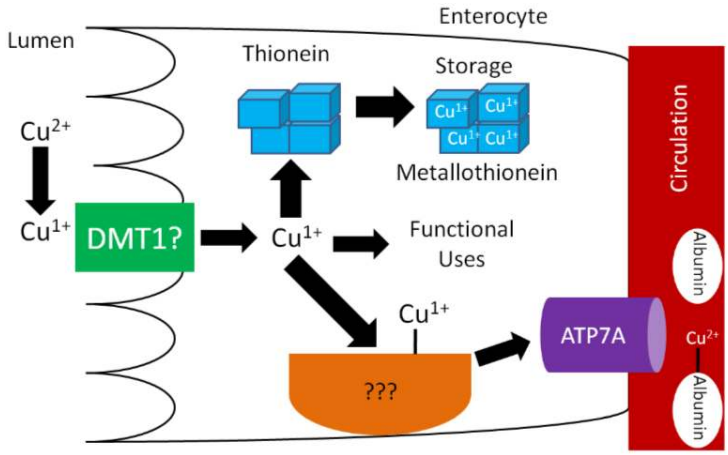


Figure 12.9.1: Copper absorption

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.

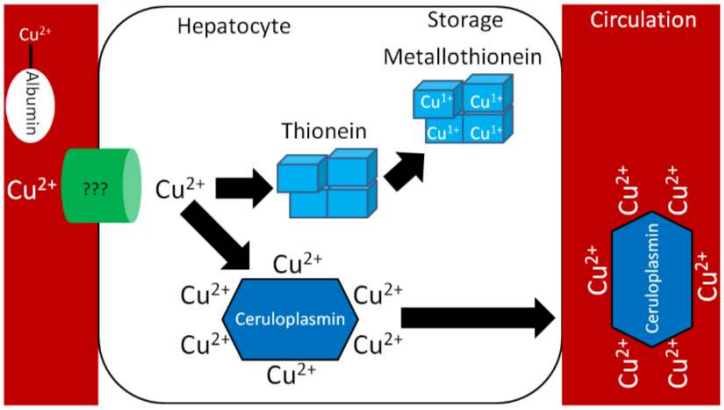


Figure 12.9.2: Copper in the hepatocyte

Legumes, whole grains, nuts, shellfish, and seeds are good sources of copper2. It is estimated that over 50% of copper consumed is absorbed1. 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 (17% 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].

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 below[1].

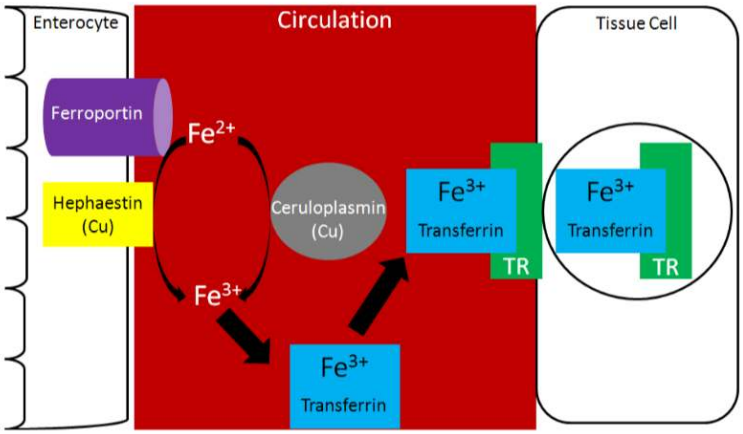


Figure 12.9.3: Transport and uptake of iron

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.

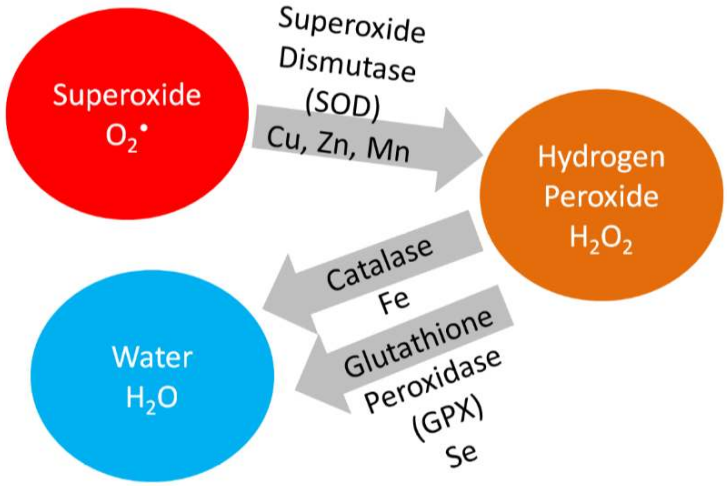


Figure 12.9.4: Superoxide dismutase uses zinc as a cofactor

Copper is also needed for hormone synthesis. For example, it is a cofactor for dopamine beta-hydroxylase, which converts dopamine to norepinephrine, as shown below[1].

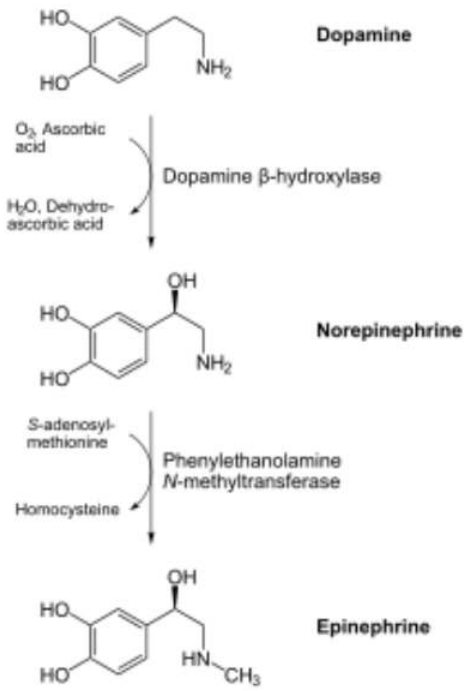


Figure **12.9.5**: Dopamine beta-hydroxylase requires copper[4]

Hopefully the following example looks vaguely familiar because we talked about this pathway in the vitamin C functions subsection. Ascorbic acid reduces $\mathbf{Cu^{2+}}$ back to $\mathbf{Cu^{1+}}$ so that this enzyme can continue to function, as shown below[1]. This is analogous to how ascorbic acid reduces $\mathbf{Fe^{3+}}$ back to $\mathbf{Fe^{2+}}$ so proline and lysyl hydroxylases can continue to function.

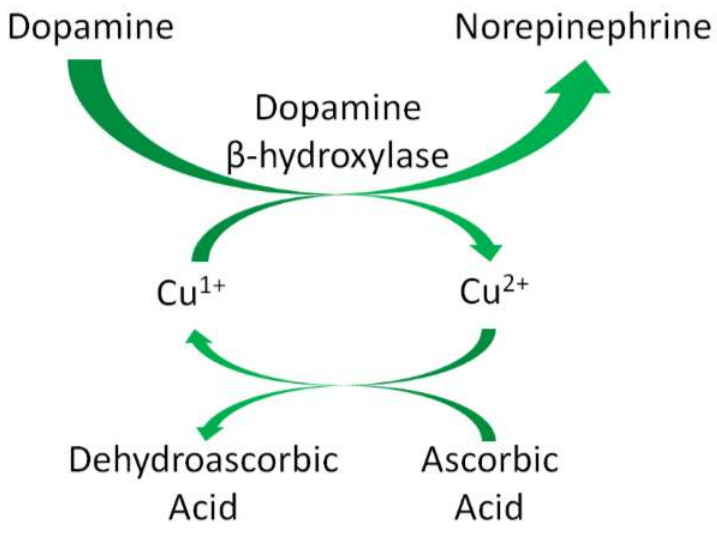


Figure **12.9.6**: Dopamine beta-hydroxylase

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].

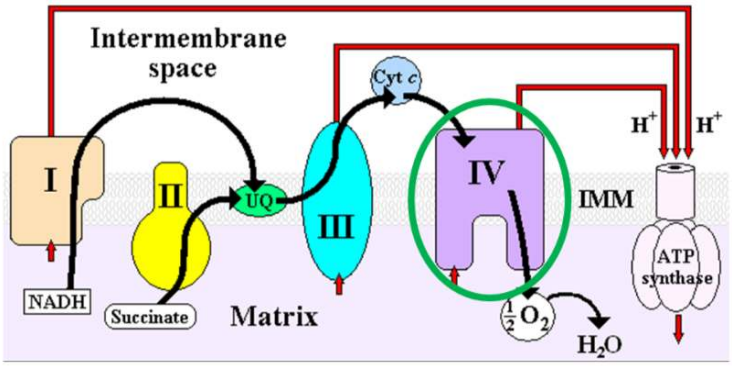


Figure **12.9.7**: Cytochrome c oxidase (complex IV)[5]

Lysyl oxidase, an enzyme that is important for cross-linking between structural proteins (collagen and elastin), requires copper as a cofactor[1].

Copper Deficiency & Toxicity

Copper deficiency is rare in humans, but results in the following symptoms[1,6]:

- Hypochromic anemia
- Decreased white blood cell counts leading to decreased immune function
- Bone abnormalities

Copper deficiency can result in a secondary iron deficiency, since $\mathbf{Fe^{2+}}$ cannot be oxidized to $\mathbf{Fe^{3+}}$ 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 absorption[7].

Copper toxicity is also rare in humans, but acute toxicity results in the following symptoms[1,6]:

- Nausea, vomiting, diarrhea, abdominal pain

Chronic symptoms include[1,6]:

- 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]

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.

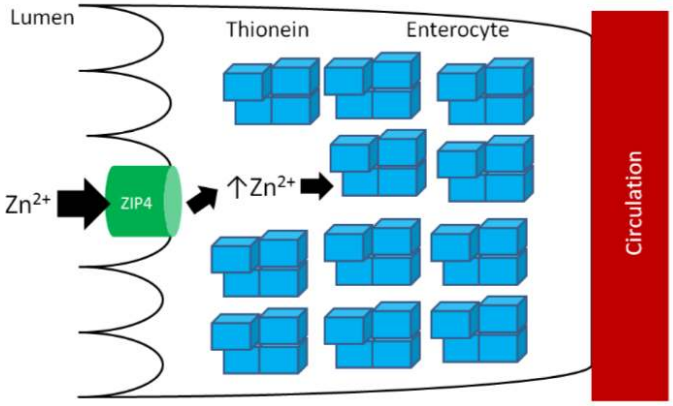


Figure 12.9.9: Zinc increases thionein production

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.

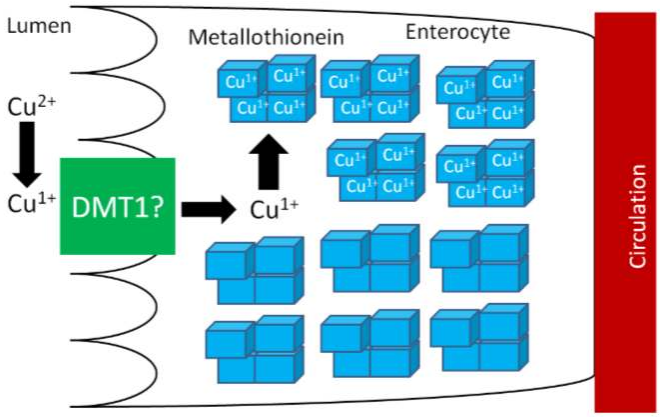


Figure 12.9.10: Copper taken up into the enterocyte is bound to thionein forming metallothionein.

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.

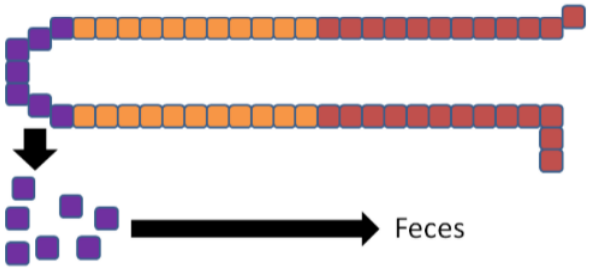


Figure 12.9.11: Enterocytes are sloughed off and excreted in feces

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 Fe^{2+} to Fe^{3+} so that iron can bind to transferrin.

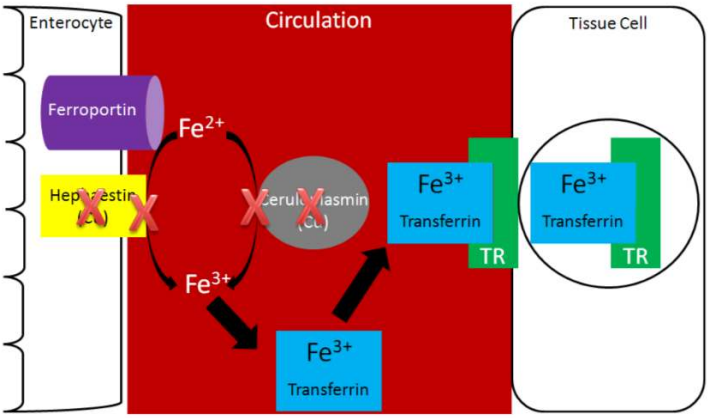


Figure 12.9.12: Lack of copper means that hephaestin and ceruloplasmin aren't available to oxidize Fe^{2+} to Fe^{3+}

Without hephaestin and ceruloplasmin, Fe^{3+} is not formed from Fe^{2+}. As a result Fe^{2+} is "trapped" in the enterocyte because it can't bind to transferrin as shown below.

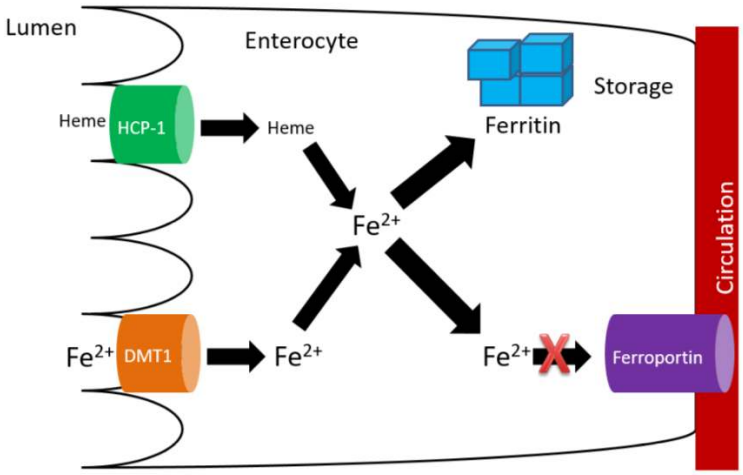


Figure 12.9.13: Fe^{2+} is trapped in the enterocyte

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.

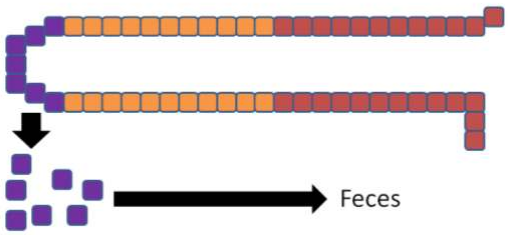


Figure 12.9.14: Enterocytes are sloughed off and excreted in feces

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.

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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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CHAPTER OVERVIEW

12.10: 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.

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CHAPTER OVERVIEW

13: Food Politics and Perspectives

In this chapter, food politics, sustainability, the food industry, food security, and diets from around the world are explored.

13.1: Prelude to Food Politics and Perspectives
13.2: Historical Perspectives on Food
13.3: The Food Industry
13.4: The Politics of Food
13.5: Food Cost and Inflation
13.6: The Issue of Food Security
13.7: Nutrition and Your Health
13.8: Diets around the World
13.E: Food Politics and Perspectives (Exercise)

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13.1: Prelude to Food Politics and Perspectives

Big Ideas

- Sustainability promotes nutrition today and protects natural resources for tomorrow.

As discussed in previous chapters, sustainability is a word that's often talked about in the realm of food and nutrition. The term relates to the goal of achieving a world that meets the needs of its present inhabitants while preserving resources for future generations. As awareness about sustainability has increased among the media and the public, both agricultural producers and consumers have made more of an effort to consider how the choices they make today will impact the planet tomorrow.



Figure **13.1.1**: Raising free-range chickens that feed out in the open is one example of a sustainable agricultural practice. Free Range Hens The eggs these hens produce will be pretty tasty. from Adam Ward (via Wikipedia).

However, defining sustainability can be difficult because the term means different things to different groups. For most, sustainable agriculture can best be described as an umbrella term that encompasses food production and consumption practices that do not harm the environment, that do support agricultural communities, and that are healthy for the consumer.Sustainable Table. "Introduction to Sustainability." Accessed October 10, 2011. www.sustainabletable.org/intro/. From factory farms to smaller-scale ranches and granges, sustainable farming practices are being implemented more and more as the long-term viability of the current production system has been called into question.

Yet, the concept of sustainability is not new to agricultural science, practice, or even policy. It has evolved throughout modern history as a way to achieve self-reliance. It is also a vehicle for maintaining rural communities and supporting the concept of conservation and protection of the land.Ecological Agriculture Projects. "A History of Sustainable Agriculture." © 1990 Rod MacRae. http://eap.mcgill.ca/AASA_1.htm. In 1990, the US federal government defined sustainable agriculture in a piece of legislation known as the Farm Bill. The practice was described as an integrated system of plant and animal production that satisfies human needs for food, along with fiber for fabric and other uses. The Farm Bill further defines sustainable agriculture as a practice that enhances environmental quality and also the natural resource base upon which the agricultural economy depends. Sustainable agriculture also makes the most efficient use of nonrenewable resources, sustains the economic viability of farm operations, and supports the quality of life for farmers and society as a whole.Gold, M.V. "Sustainable Agriculture: Definitions and Terms." US Department of Agriculture, National Agricultural Library. *Special Reference Briefs Series* no. SRB 99-02 (September 1999, August 2007). http://www.nal.usda.gov/afsic/pubs/t...902.shtml#toc1.

In other words, the practice of sustainable agriculture strives to eschew conventional farming methods, including the cultivation of single crops and row crops continuously over many seasons, the dependency on agribusiness, and the rearing of livestock in concentrated, confined systems.Gold, M.V. "Sustainable Agriculture: Definitions and Terms." US Department of Agriculture, National Agricultural Library. *Special Reference Briefs Series* no. SRB 99-02 (September 1999, August 2007). http://www.nal.usda.gov/afsic/pubs/t...902.shtml#toc1. Instead, sustainability includes a focus on biodiversity among both crops and livestock; conservation and preservation to replenish the soil, air, and water; animal welfare; and fair treatment and wages for

farm workers.Sustainable Table. “What Is Sustainable Agriculture?” Accessed October 10, 2011. www.sustainabletable.org/intro/whatis/. Sustainable agriculture also encourages the health of consumers by rejecting extensive use of pesticides and fertilizers and promoting the consumption of organic, locally produced food. Although many farmers and food companies work to implement these practices, some use the idea of sustainability to attract consumers without completely committing to the concept. “Greenwashing” is a derisive term (similar to “whitewashing”) for a corporation or industry falsely utilizing a proenvironmental image or message to expand its market base.

Sustainability depends not only on agricultural producers, but also on consumers. The average person can do a number of things to consume a more sustainable diet, from eating less meat to purchasing fruits and vegetables grown on nearby farms. For example, produce sold in the Midwest typically travels an average of more than fifteen hundred miles from farm to supermarket. However, increasing the consumption of more locally-grown produce by 10 percent would save thousands of gallons in fossil fuel each year.Heller, M. C., G. A. Keoleian. “US Food System Factsheet.” Center for Sustainable Systems, University of Michigan. *CSS Factsheets*, no. CSS01-06 (2001). http://www.css.snre.umich.edu/public...us-food-system.

You Decide

How will you adapt your lifestyle and dietary choices to help promote sustainable agricultural practices?

Some consumers are choosing to make smarter nutritional choices, eat healthier foods, and enjoy fresh, locally grown products. They read the labels on products in their local stores, make more home-cooked meals using whole-food ingredients, and pay attention to the decisions that legislators and other officials make regarding food production and consumption. Will you be one of them? How you can adjust your dietary selections to benefit not only your body and mind but also to help sustain the planet for future generations?



Video **13.1.1**: Green Careers: Sustainable Agriculture. This video focuses on the role of a farm manager on a small farm that follows sustainable agricultural practices.

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13.2: Historical Perspectives on Food

Learning Objectives

- Contrast ancient perspectives on food and nutrition with more modern explanatory systems

Throughout history, our relationship with food has been influenced by changing practices and perspectives. From the invention of agriculture to the birth of refrigeration, technological advances have also affected what we eat and how we feel about our food. Therefore, it can be helpful to examine theories and customs related to diet and nutrition across different civilizations and time periods.

Civilizations and Time Periods

Diet and cuisine have undergone enormous changes from ancient times to today. The basic diet of the ancient era consisted of cereals, legumes, oil, and wine. These staples were supplemented by vegetables and meat or fish, along with other items, such as honey and salt. During the Middle Ages, poor people consumed meager diets that consisted of small game supplemented with either barley, oat, or rye, while the wealthy had regular access to meat and fish, along with wheat.Our Food Recipes. “European Medieval Food.” © 2011–2012. www.our-food-recipes.com/medieval-food.html. During the Industrial Revolution, diets became more varied, partly because of the development of refrigeration and other forms of food preservation. In the contemporary era, many people have access to a wide variety of food that is grown locally or shipped from far-off places.



Figure 13.2.1: Flatbread made from barley or wheat was a staple in the traditional diet during the ancient era. Image used with permissin (CC -BY-SA 3.0; Jonathunder).

Hunters and Gatherers

Human beings lived as hunters and gatherers until the invention of agriculture. Following a nomadic lifestyle, early people hunted, fished, and gathered fruit and wild berries, depending on their location and the availability of wild plants and wild game. To aid their constant quest for food, humans developed weapons and tools, including spears, nets, traps, fishing tackle, and the bow and arrow.Our Food Recipes. “Pre Historic Food.” © 2011–2012. www.our-food-recipes.com/pre-...oric-food.html.

The Beginning of Agriculture

About ten thousand years ago, people began to cultivate crops and domesticate livestock in Mesopotamia, an area of the world that is known today as the Middle East. Agriculture flourished in this region due to the fertile floodplain between the Euphrates and Tigris Rivers, and early crops included wheat, barley, and dates. The development of agriculture not only enriched the diet of these early people, it also led to the birth of civilization as farmers began to settle into sizable, stable communities.Bioworld. “History of Agriculture.” Accessed October 10, 2011. www.bioworldusa.com/agricultu...ry-agriculture.

One of the most fertile regions of the ancient world was located along the Nile River Valley in ancient Egypt. The rich soil yielded several harvests per year. Common crops were barley, wheat, lentils, peas, and cabbage, along with grapes, which were used to make wine. Even poor Egyptians ate a reasonably healthy diet that included fish, vegetables, and fruit. However, meat was primarily a privilege of the rich. Popular seasonings of this era included salt, pepper, cumin, coriander, sesame, fennel, and dill.Experience Ancient Egypt. “Ancient Egyptian Food: The Pharaonic Diet.” © 2009–2011. http://www.experience-ancient-egypt....tian-food.html.

The “Three Sisters”

Thousands of years ago, across an area that encompasses Mexico and Central America today,Foundation for the Advancement of Mesoamerican Studies. “Mesoamerica.” Accessed October 10, 2011. http://www.famsi.org/. Mesoamerican farmers cultivated three major plants—squash, beans, and maize (also known as corn). Known as the “three sisters,” these crops proved to be both complementary and sustainable. Corn provides a pole for bean vines to climb. The roots of bean vines provide nitrogen that helps corn grow. These vines also stabilize corn stalks by making them less vulnerable to the wind. Shallow-rooted squash vines prevent the evaporation of soil moisture, while their spiny plants discourage predators. Both of these attributes aid the cultivation of all three crops.Renee’s Garden. “Celebrate the Three Sisters,” During the post-Columbian era, Native American groups adopted the practice of interplanting squash, beans, and maize, and now thousands of years later, many small farmers continue to cultivate the “three sisters.”

Meals Determined Social Status

In ancient Rome, differences in social standing affected the diet. For people of all socioeconomic classes, breakfast and lunch were typically light meals that were often consumed in taverns and cafes. However, dinners were eaten at home and were taken much more seriously. Wealthy senators and landowners ate meals with multiple courses, including appetizers, entrees, and desserts. Rich Romans also held extravagant dinner parties, where guests dined on exotic foods, such as roasted ostrich or pheasant. In contrast, people of the lower classes ate mostly bread and cereals.PBS. “Home Life.” *The Roman Empire in the First Century*. © 2006 Devillier Donegan Enterprises. http://www.pbs.org/empires/romans/empire/home.html. The average person ate out of clay dishes, while wealthy people used bronze, gold, or silver.

Social status determined the kinds of food that people consumed in many other parts of the world as well. In ancient China, emperors used their wealth and power to hire the best chefs and acquire delicacies, such as honey, to sweeten food. Dishes of the ancient era included steamed Mandarin fish, rice and wheat noodles, and fried prawns. Imperial cuisine also included improved versions of dishes that were consumed by the common people, such as soups and cereals.China.org. “The History of Chinese Imperial Cuisines.” © China Information Center. Accessed December 5, 2011. http://www.china.org.cn/english/imperial/25995.htm.

The Medieval Era

The eating habits of most people during the Medieval Era depended mainly on location and financial status. In the feudal system of Europe, the majority of the population could not afford to flavor their food with extravagant spices or sugar. In addition, transporting food was either outrageously expensive or out of the question due to the inability to preserve food for a long period of time. As a result, the common diet consisted of either wheat, meat, or fish, depending on location. The typical diet of the lower classes was based on cereals and grains, porridge, and gruel. These staples were supplemented with seasonal fruits, vegetables, and herbs. Wine, beer, and cider were also common, and were often safer to drink than the unsanitized, untreated water.

The Crusades

During the Medieval Era, soldiers from Europe waged war over religion in the Middle East in military campaigns that came to be known as the Crusades. Upon their return, the crusaders brought back new foods and spices, exposing Europeans of the Middle Ages to unusual flavors. Cooking with exotic spices, such as black pepper, saffron, and ginger, became associated with wealth because they were expensive and had to be imported.

Food Preservation in the Past

During the Medieval and Renaissance eras, most meals consisted of locally grown crops because it was extremely difficult to transport food over long distances. This was mostly due to an inability to preserve food for long periods. At that time, food preservation consisted mostly of drying, salting, and smoking. Pickling, which is also known as brining or corning, was another common practice and involved the use of fermentation to preserve food.

The Modern Era

The modern era began in North America and Europe with the dawn of the Industrial Age. Before that period, people predominantly lived in agrarian communities. Farming played an important role in the development of the United States and Canada. Almost all areas of the country had agrarian economies dictated by the harvesting seasons.

In the 1800s, society began to change as new machines made it easier to cultivate crops, and to package, ship, and store food. The invention of the seed drill, the steel plow, and the reaper helped to speed up planting and harvesting. Also, food could be transported more economically as a result of developments in rail and refrigeration. These and other changes ushered in the modern era and affected the production and consumption of food.

Food Preservation in Modern Times

Technological innovations during the 1800s and 1900s also changed the way we cultivate, prepare, and think about food. The invention and refinement of the refrigerator and freezer made it possible for people to store food for much longer periods. This, in turn, allowed for the transportation of food over greater distances. For example, oranges grown in Florida would still be fresh when they arrived in Seattle.

Prior to refrigeration, people relied on a number of different methods to store and preserve food, such as pickling. Other preservation techniques included using sugar or honey, canning, and preparing a confit, which is one of the oldest ways to preserve food and involves salting meat and cooking it in its own fat. To store foods for long periods, people used iceboxes or kept vegetables, such as potatoes, onions, and winter squash, in cellars during the winter months.

The Great Depression

During the Great Depression of the 1930s, the United States faced incredible food shortages and many people went hungry. This was partly because extreme droughts turned parts of the Midwest into a Dust Bowl, where farmers struggled to raise crops. Millions of Americans were unemployed or underemployed and were forced to wait in long breadlines for free food. This was also a period of incredible reforms, as the government worked to provide for and protect the people. Some important changes included subsidies and support for suffering farmers.

World War II

Food shortages also occurred during World War II in the 1940s. At that time, people voluntarily made due with less to ensure that soldiers training and fighting overseas had the supplies they needed. To focus on saving at home, government programs included rationing food (particularly meat, butter, and sugar), while the media encouraged families to plant their own fruits and vegetables in “victory” (backyard) gardens.

Contemporary Life

Today, agriculture remains a large part of the economy in many developing nations. In fact, nearly 50 percent of the world’s labor is employed in agriculture.Bioworld. “History of Agriculture.” Accessed October 10, 2011. www.bioworldusa.com/agricultu...ry-agriculture. In the United States however, less than 2 percent of Americans produce food for the rest of the population.Gold, M.V. “Sustainable Agriculture: Definitions and Terms.” US Department of Agriculture, National Agricultural Library. *Special Reference Briefs Series* no. SRB 99-02 (September 1999, August 2007). http://www.nal.usda.gov/afsic/pubs/t...902.shtml#toc1. Also, most farms are no longer small-scale or family-owned. Large-scale agribusiness is typical for both crop cultivation and livestock rearing, including concentrated animal feeding operations. Conventional farming practices can include abuses to animals and the land. Therefore, more and more consumers have begun to seek out organic and locally grown foods from smaller-scale farms that are less harmful to the environment.

Other changes also affect food production and consumption in the modern era. The invention of the microwave in the 1950s spurred the growth of frozen foods and TV dinners. Appliances such as blenders and food processors, toasters, coffee and espresso machines, deep fryers, and indoor grills have all contributed to the convenience of food preparation and the kinds of meals that people enjoy cooking and eating.

Diet Trends Over Time

Today, consumers can choose from a huge variety of dietary choices that were not available in the past. For example, strawberries can be purchased in New York City in wintertime, because they are quickly and easily transported from places where the crop is in season, such as California, Mexico, or South America. In the western world, especially in North America, food products are also relatively cheap. As a result, there is much less disparity between the diets of the lower and upper classes than in the past. It would not be unusual to find the same kind of meat or poultry served for dinner in a wealthy neighborhood as in a poorer community.

Key Takeaways

Perspectives and practices related to food and nutrition have greatly changed from the ancient era to today. In the ancient world, location and economic status had a profound effect on what people ate. Also, societies often were based on crop cultivation and livestock rearing, which influenced how people ate, worked, and lived. During the Medieval Era, people became more exposed to food from other parts of the world because of the growing ability to ship goods and because of the Crusades, among other factors. Technological advances, such as refrigeration and the microwave, have had huge effects on the way food is produced and consumed.

Discussion Starter

1. Compare and contrast the diet of a civilization from the ancient world or the Medieval Era to the food choices of today. In what ways has our diet changed? In what ways has it remained the same?

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13.3: The Food Industry

Learning Objectives

- Explain what is meant by the term “the food industry” and identify the food technologies and innovations that have shaped the current food system

Agriculture is one of the world’s largest industries. It encompasses trillions of dollars and employs billions of people. In the United States alone, customers spent about $500 billion annually on food products at grocery stores and supermarkets.Plunkett Research, Ltd. “US Food Industry Overview.” Accessed December 5, 2011, http://www.plunkettresearch.com/food...ocery%20market%20research/industry%20statistics. The food industry includes a complex collective of businesses that touches on everything from crop cultivation to manufacturing and processing, from marketing and advertising to distribution and shipment, to food regulation.

The Food System

The food system is a network of farmers and related operations, including food processing, wholesale and distribution, retail, industry technology, and marketing. The milk industry, for example, includes everything from the farm that raises livestock, to the milking facility that extracts the product, to the processing company that pasteurizes milk and packages it into cartons, to the shipping company that delivers the product to stores, to the markets and groceries that stock and sell the product, to the advertising agency that touts the product to consumers. All of these components play a part in a very large system.

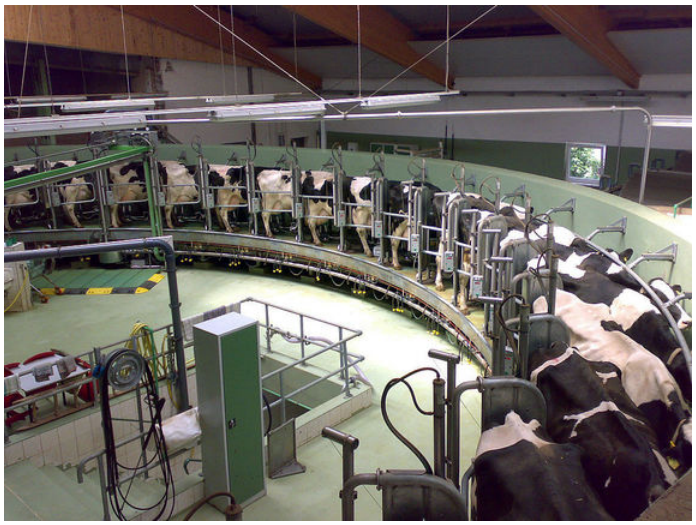


Figure **13.3.1**: These cows are lined up at a Rotary milking parlor. (CC BY-SA 3.0; Gunnar Richter Namenlos.net).

Food Preservation and Processing

Two important aspects of a food system are preservation and processing. Each provides for or protects consumers in different ways. Food preservation includes the handling or treating of food to prevent or slow down spoilage. Food processing involves transforming raw ingredients into packaged food, from fresh-baked goods to frozen dinners. Although there are numerous benefits to both, preservation and processing also pose some concerns, in terms of both nutrition and sustainability.

Food Preservation

Food preservation protects consumers from harmful or toxic food. There are different ways to preserve food. Some are ancient methods that have been practiced for generations, such as curing, smoking, pickling, salting, fermenting, canning, and preserving fruit in the form of jam. Others include the use of modern techinques and technology, including drying, vacuum packing, pasteurization, and freezing and refrigeration. Preservation guards against food-bourne illnesses, and also protects the flavor, color, moisture content, or nutritive value of food.

Irradiation

Another method of preservation is irradiation, which reduces potential pathogens to enhance food safety. This process involves treating food with ionizing radiation, which kills the bacteria and parasites that cause toxicity and disease. Similar technology is used to sterilize surgical instruments to avoid infection.Centers for Disease Control and Prevention. “Food Irradiation.” Accessed October 11, 2005. www.cdc.gov/ncidod/dbmd/disea...rradiation.htm. Foods currently approved for irradiation by the FDA include flour, fruits and vegetables, juices, herbs, spices, eggs, and meat and poultry.

Most forms of preservation can affect the quality of food. For example, freezing slightly affects the nutritional content, curing and smoking can introduce carcinogens, and salting greatly increases the sodium. There are also concerns about the effects of using irradiation to preserve food. Studies have shown that this process can change the flavor, texture, color, odor, and nutritional content of food. For example, the yolks of irradiated eggs have less color than nonirradiated eggs.

Food Processing

Food processing includes the methods and techniques used to transform raw ingredients into packaged food. Workers in this industry use harvested crops or slaughtered and butchered livestock to create products that are marketed to the public. There are different ways in which food can be processed, from a one-off product, such as a wedding cake, to a mass-produced product, such as a line of cupcakes packaged and sold in stores.

The Pros and Cons of Food Processing

Food processing has a number of important benefits, such as creating products that have a much longer shelf life than raw foods. Also, food processing protects the health of the consumer and allows for easier shipment and the marketing of foods by corporations. However, there are certain drawbacks. Food processing can reduce the nutritional content of raw ingredients. For example, canning involves the use of heat, which destroys the vitamin C in canned fruit. Also, certain food additives that are included during processing, such as high fructose corn syrup, can affect the health of a consumer. However, the level of added sugar can make a major difference. Small amounts of added sugar and other sweeteners, about 6 to 9 teaspoons a day or less, are not considered harmful.American Heart Association. “Sugar and Carbohydrates.” Last updated October 12, 2010. www.heart.org/HEARTORG/Gettin...6_Article.jsp#.



Figure **13.3.2**: Industrial cheese production. 10,000 l milk in the left tank, the milk was mixed with rennet and is now broken for the production of Emmentaler.. (CC BY-SA 3.0; MatthiasKabel).

Food Regulation and Control

Food regulatory agencies work to protect the consumer and ensure the safety of our food. Food and drug regulation in the United States began in the late nineteenth century when state and local governments began to enact regulatory policies. In 1906, Congress passed the Pure Food and Drugs Act, which led to the creation of the US Food and Drug Administration (FDA). Today, a number of agencies are in charge of monitoring how food is produced, processed, and packaged.EH.Net Encyclopedia. “History of Food and Drug Regulation in the United States.” February 4, 2010. eh.net/encyclopedia/article/L...rug.Regulation.

Regulatory Agencies

Food regulation is divided among different agencies, primarily the FDA and the US Department of Agriculture (USDA). Regulatory agencies in Canada include the Canadian Food Inspection Agency and Health Canada. The North American public

depends on these and other agencies to ensure that the food they purchase and consume from supermarkets, restaurants, and other sources is safe and healthy to eat. It can be confusing to know which agency monitors and manages which regulatory practice. For example, the FDA oversees the safety of eggs when they're in the shells, while the USDA is in charge of the eggs once they are out of their shells.

The Food and Drug Administration

The FDA enforces the safety of domestic and imported foods. It also monitors supplements, food labels, claims that corporations make about the benefits of products, and pharmaceutical drugs. Sometimes, the FDA must recall contaminated foods and remove them from the market to protect public health. For example, in 2011 contaminated peanut butter led to the recall of thousands of jars of a few popular brands.US Food and Drug Administration. "FDA 101: Product Recalls—From First Alert to Effectiveness Checks." Last updated September 9, 2011. http://www.fda.gov/ForConsumers/Cons.../ucm049070.htm. Recalls are almost always voluntary and often are requested by companies after a problem has been discovered. In rare cases, the FDA will request a recall. But no matter what triggers the removal of a product, the FDA's role is to oversee the strategy and assess the adequacy and effectiveness of the recall.



Video **13.3.1**: FDA 101: Product Recalls. This video explains how the FDA recalls contaminated products to protect consumers.

The US Department of Agriculture

Headed by the Secretary of Agriculture, the USDA develops and executes federal policy on farming and food. This agency supports farmers and ranchers, protects natural resources, promotes trade, and seeks to end hunger in the United States and abroad. The USDA also assures food safety, and in particular oversees the regulation of meat, poultry, and processed egg products.

The Environmental Protection Agency

A third federal government agency, the Environmental Protection Agency (EPA), also plays a role in the regulation of food. The EPA works to protect human health and the environment. Founded in 1970, the agency conducts environmental assessment, education, research, and regulation. The EPA also works to prevent pollution and protect natural resources. Two of its many regulatory practices in the area of agriculture include overseeing water quality and the use of pesticides.

Food Safety and Hazard Analysis

Government regulatory agencies utilize HACCP programs to ensure food safety. HACCP, or hazard analysis and critical control points, is a system used to identify potential hazards and prevent foodbourne illnesses. Some of the seven aspects of an HACCP program include identifying the points in a manufacturing process during which potential hazards could be introduced, establishing corrective actions, and maintaining record-keeping procedures. The USDA uses HACCP to regulate meat, while the FDA uses the seven-point system to monitor seafood and juice. In these industries, HACCP systems are used in all stages of production, processing, packaging, and distribution.US Food and Drug Administration. "Hazard Analysis & Critical Control Points (HACCP)." Last updated April 27, 2011. www.fda.gov/food/foodsafety/h...cp/default.htm. Currently, the use of HACCP is voluntary for all other food products.

Food Additives

If you examine the label for a processed food product, it is not unusual to see a long list of added materials. These natural or synthetic substances are food additives and there are more than three hundred used during food processing today. The most popular additives are benzoates, nitrites, sulfites, and sorbates, which prevent molds and yeast from growing on food.How Stuff Works. "The Dangers of Food Additives." Accessed October 5, 2011. http://health.howstuffworks.com/wellness/food-nutrition/facts/dangers-of-food -additives.htm.

Food additives are introduced in the processing stage for a variety of reasons. Some control acidity and alkalinity, while others enhance the color or flavor of food. Some additives stabilize food and keep it from breaking down, while others add body or texture. Table **13.3.1** lists some common food additives and their uses:

Table **13.3.1**: Food Additives

Additive	Reason for Adding
Beta-carotene	Adds artificial coloring to food
Caffeine	Acts as a stimulant
Citric acid	Increases tartness to prevent food from becoming rancid
Dextrin	Thickens gravies, sauces, and baking mixes
Gelatin	Stabilizes, thickens, or texturizes food
Modified food starch	Keeps ingredients from separating and prevents lumps
MSG	Enhances flavor in a variety of foods
Pectin	Gives candies and jams a gel-like texture
Polysorbates	Blends oil and water and keep them from separating
Soy lecithin	Emulsifies and stabilizes chocolate, margarine, and other items
Sulfites	Prevent discoloration in dried fruits
Xanthan gum	Thickens, emulsifies, and stabilizes dairy products and dressings

Source: Center for Science in the Public Interest. "Chemical Cuisine: Learn about Food Additives." ©2012. Center for Science in the Public Interest. http://www.cspinet.org/reports/chemcuisine.htm.

The Pros and Cons of Food Additives

The FDA works to protect the public from potentially dangerous additives. Passed in 1958, the Food Additives Amendment states that a manufacturer is responsible for demonstrating the safety of an additive before it can be approved. The Delaney Clause that was added to this legislation prohibits the approval of any additive found to cause cancer in animals or humans. However, most additives are considered to be "generally recognized as safe," a status that is determined by the FDA and referred to as GRAS.

Food additives are typically included in the processing stage to improve the quality and consistency of a product. Many additives also make items more "shelf stable," meaning they will last a lot longer on store shelves and can generate more profit for store owners. Additives can also help to prevent spoilage that results from changes in temperature, damage during distribution, and other adverse conditions. In addition, food additives can protect consumers from exposure to rancid products and food-bourne illnesses.

Food additives aren't always beneficial, however. Some substances have been associated with certain diseases if consumed in large amounts. For example, the FDA estimates that sulfites can cause allergic reactions in 1 percent of the general population and in 5 percent of asthmatics. Similarly, the additive monosodium glutamate, which is commonly known as MSG, may cause headaches, nausea, weakness, difficulty breathing, rapid heartbeat, and chest pain in some individuals.Sustainable Table. "The Issues: Additives." Accessed October 10, 2011. www.sustainabletable.org/issu...dditives/#fn14.

The Effect of New Technologies

As mentioned earlier, new technology has had a tremendous effect on the food we eat and the customs and culture related to food consumption. For example, microwaves are used to reduce cooking time or to heat up leftover food. Refrigerators and freezers allow produce to travel great distances and last longer. On the extreme end of making food last longer, there is special food for astronauts that is appropriate for consumption in space. It is safe to store, easy to prepare in the low-gravity environment of a spacecraft, and contains balanced nutrition to promote the health of people working in space. In the military, soldiers consume Meals Ready-to-Eat (MREs), which contain an entire meal in a single pouch.

Genetically Modified Foods

Genetically modified foods (also known as GM or GMO foods), are plants or animals that have undergone some form of genetic engineering. In the United States, much of the soybean, corn, and canola crop is genetically modified. The process involves the alteration of an organism's DNA, which allows farmers to cultivate plants with desirable characteristics.Genomics.Energy.gov. "What Are Genetically Modified Foods?" Last modified November 5, 2008. http://www.ornl.gov/sci/techresource...i/gmfood.shtml. For example, scientists could extract a gene that produces a chemical with antifreeze properties from a fish that lives in an arctic region (such as a flounder). They could then splice that gene into a completely different species, such as a tomato, to make it resistant to frost, which would enable farms to grow that crop year-round.Whitman, D. B. "Genetically Modified Foods: Harmful or Helpful?" *ProQuest Discovery Guides* (April 2000). www.csa.com/discoveryguides/g...d/overview.php.

Certain modifications can be beneficial in resisting pests or pesticides, improving the ripening process, increasing the nutritional content of food, or providing resistance to common viruses. Although genetic engineering has improved productivity for farmers, it has also stirred up debate about consumer safety and environmental protection. Possible side effects related to the consumption of GM foods include an increase in allergenicity, or tendencies to provoke allergic reactions. There is also some concern related to the possible transfer of the genes used to create genetically engineered foods from plants to people. This could influence human health if antibiotic-resistant genes are transferred to the consumer. Therefore, the World Health Organization (WHO) and other groups have encouraged the use of genetic engineering without antibiotic-resistance genes. Genetically modified plants may adversely affect the environment as well and could lead to the contamination of nongenetically engineered organisms.World Health Organization. "Food Safety: 20 Questions on Genetically Modified Foods." © 2011. http://www.who.int/foodsafety/public...0questions/en/.

Genetically modified foods fall under the purview of the EPA, the USDA, and the FDA. Each agency has different responsibilities and concerns in the regulation of GM crops. The EPA ensures that pesticides used for GM plants are safe for the environment. The USDA makes sure genetically engineered seeds are safe for cultivation prior to planting. The FDA determines if foods made from GM plants are safe to eat. Although these agencies act independently, they work closely together and many products are reviewed by all three.Whitman, D. B. "Genetically Modified Foods: Harmful or Helpful?" *ProQuest Discovery Guides* (April 2000).



Video **13.3.2**: Too Much Controversy Over Genetically Modified Foods?

Food Enrichment and Fortification

Many foods are enriched or fortified to boost their nutritional value. Enrichment involves adding nutrients to restore those that were lost during processing. For example, iron and certain B vitamins are added to white flour to replace the nutrients that are removed in the process of milling wheat. Fortification is slightly different than enrichment and involves adding new nutrients to enhance a food's nutritive value. For example, folic acid is typically added to cereals and grain products, while calcium is added to some orange juice.

The Health of the Population

Certain enrichment and fortification processes have been instrumental in protecting public health. For example, adding iodine to salt has virtually eliminated iodine deficiencies, which protects against thyroid problems. Adding folic acid to wheat helps increase intake for pregnant women, which decreases the risk of neural tube defects in their children. Also, vegans or other people who do not consume many dairy products are able to drink orange juice or soy milk that has been fortified with calcium to meet the daily recommendations. However, there is some concern that foods of little nutritive value will be fortified in an effort to improve their allure, such as soft drinks with added vitamins.

Key Takeaways

The food industry encompasses all aspects of food production: manufacturing, distribution, marketing, retail, regulation, and consumption. Food preservation and processing have a number of benefits including improving the quality of food products, making them more shelf-stable, and aiding the marketing and advertising of food. There are more than three hundred additives used during food processing today. Food preservation and processing also have some drawbacks, including potentially damaging the nutritive value of food. The cultivation and consumption of genetically modified foods are also highly controversial, with many people opposed to the genetic modification of crops. There are three key government agencies that regulate food in the United States: the US Department of Agriculture, the US Food and Drug Administration, and the US Environmental Protection Agency.

Discussion Starter

1. Discuss the debate about the use of food additives, such as beta-carotene and citric acid. What are the benefits to using them? What are the drawbacks? Do you believe that food additives are more helpful or more harmful, and why?

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13.4: The Politics of Food

Learning Objectives

- Discuss how food has become politicized, and give specific examples of how food choices are related to food politics

Some people have begun to view their choices regarding diet and nutrition in light of their political views. More and more, consumers weigh their thoughts on the environment and the world, while making decisions about what to purchase in the grocery store. For example, many people choose to eat free-range chickens due to concerns about animal welfare. Others worry about the higher cost of organically produced food or find that those products are not available in their communities. As a result, feelings about food have become a political mine field.

Food Politics

The production and sale of food is an extremely big business and touches people in all industries and walks of life. Food is not only crucial for day-to-day survival, but also strongly affects overall health and well-being, as well as the economy and culture of a region or a country. So, it is no wonder that more and more producers and consumers alike are speaking out about food to ensure that their interests are protected. Food politics can influence many stakeholders and interests, but always involve the production, regulation, inspection, distribution, and/or retail of food.

Stakeholders

Stakeholders in food politics include large and small farmers, along with large and small food companies. Other important stakeholders include restaurants and other food-service providers, food distributors, grocery stores and other retail outlets, consumers, and trade associations. Antihunger advocates, nutrition advocates, and food-industry lobbyists also have important roles to play. Nongovernmental organizations, such as the American Cancer Society and the WHO, also work to promote good health and nutrition. Each group has its own perspective and its own agenda in disputes related to food.

Disputes

Food politics can be influenced by ethical, cultural, medical, and environmental disputes over agricultural methods and regulatory policies. They are also greatly influenced by manufacturing processes, marketing practices, and the pursuit of the highest possible profit margin by food manufacturers and distributers. Common disputes and controversies include the genetic modification of plants, the potential dangers of food additives, chemical run-off from large-scale farms, and the reliance on factory-farming practices, such as the use of pesticides in crop cultivation and antibiotics in livestock feed. Additional issues and concerns include the use of sugar, salt, and other potentially unhealthy ingredients, the promotion of fast food and junk food to children, and sanitary standards related to livestock.

The Nitrate Dispute

One current dispute relates to the use of nitrates in agriculture. At the dawn of the twentieth century, German chemists Fritz Haber and Carl Bosch invented a system that synthesizes ammonia to produce nitrates on an industrial scale. The compound could then be used to make fertilizers, which along with pesticides and herbicides, made large-scale, modern agriculture possible. However, when nitrates are used in excess, they can create runoff that pollutes surface- and groundwater. For example, chemical runoff has had a profound effect on the Aral Sea and the surrounding area in Kazakhstan and Uzbekistan. The Aral Sea, which was once one of the four largest lakes in the world, was crucial to irrigation projects in the former Soviet Union. But when the lake became contaminated by farm runoff, salinity increased and the lake dramatically shrank, crippling the area's fishing industry. Also, as the lakebed became exposed, dust storms spread contaminated soil, and thousands of people were forced out of the region.Grant, L. "Nitrates: Dangerous Necessity." Environmentalism @ Suite 101.com. May 7, 2011. larry-grant.suite101.com/nitr...essity-a369949. Contaminated runoff from the use of nitrates not only leads to serious consequences for the environment, but also to human health. Nitrate poisoning reduces the oxygen-carrying capacity of the blood and can be fatal to infants.US Environmental Protection Agency. "Ag 101: Nitrate." Last updated September 10, 2009. http://www.epa.gov/agriculture/ag101...ctnitrate.html. Therefore, significant efforts are being made to use nitrates and other agricultural chemicals in more environmentally friendly ways and to monitor drinking water for dangerous levels of contamination.

The Role of Government

Federal and state policy plays a major role in the politics of food production and distribution. As previously discussed, government agencies regulate the proper processing and preparation of foods, as well as overseeing shipping and storage. They pay particular attention to concerns related to public health. As a result, the enforcement of regulations has been strongly influenced by public concern over food-related events, such as outbreaks of food-bourne illnesses.

Food Production, Distribution, and Safety

Many consumers have concerns about safety practices during the production and distribution of food. This is especially critical given recent outbreaks of food-borne illnesses. For example, during fall 2011 in the United States, there was an eruption of the bacteria *Listeria monocytogenes* in cantaloupe. It was one of the deadliest outbreaks in over a decade and resulted in a number of deaths and hospitalizations.Centers for Disease Control and Prevention. "Multistate Outbreak of Listeriosis Associated with Jensen Farms Cantaloupe—United States." August–September, 2011. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6039a5.htm?s_cid= mm6039a5_w.



Figure **13.4.1**: Whole chickens are suspended in a public market. (CC-BY-SA; 3.0; Tomás Castelazo)

In January 2011, the Food Safety Modernization Act was passed to grant more authority to the FDA to improve food safety. The FDA and other agencies also address consumer-related concerns about protecting the nation's food supply in the event of a terrorist attack.

Addressing Hunger

Government agencies also play an important role in addressing hunger via federal food-assistance programs. The agencies provide debit cards (formerly distributed in the form of food vouchers or food stamps) to consumers to help them purchase food and they also provide other forms of aid to low-income adults and families who face hunger and nutritional deficits. This topic will be discussed in greater detail later in this chapter.

The Dual Role of the USDA

The USDA has a dual role in the advancement of American agribusiness and the promotion of health and nutrition among the public. This can create conflicts of interest, and some question whether the USDA values the interests of the agriculture and food industries over consumer health.

However, there is no question that the USDA makes a great deal of effort to educate the public about diet and nutrition. Working with the US Department of Health and Human Services, the agency codeveloped the *Dietary Guidelines for Americans* to inform consumers about the ways their dietary habits affect their health. The USDA also implements all federal nutrition programs.

The Farm Bill

The Farm Bill (introduced in 1990) is a massive piece of legislation that determines the farm and food policy of the federal government. It addresses policy related to federal food programs and other responsibilities of the USDA. The Farm Bill also covers a wide range of agricultural programs and provisions, including farm subsidies and rural development. And, it influences international trade, commodity prices, environmental preservation, and food safety.

The massive Farm Bill is updated and renewed every five years. Over the decades, it has expanded to incorporate new issues, such as conservation and bioenergy. The Farm Bill passed in 2008, known as the Food, Conservation, and Energy Act, included new policy on horticulture and livestock provisions. The 2008 bill also differed from previous legislation in terms of the large number and scope of proposals that were raised.Johnson, R. and J. Monke, "What Is the 'Farm Bill'?" Congressional Research Service. *CRS Report for Congress*, no. RS22131 (January 3, 2011). www.nationalaglawcenter.org/a...rs/RS22131.pdf.

Tools for Change

Start paying attention to the news when you hear about the next upcoming Farm Bill to learn about proposals that could affect the food that arrives in your local supermarket or that is served in your favorite restaurant. To learn more about the upcoming legislation, visit http://www.usda.gov/farmbill. You may also wish to "vote with your fork" and make choices about what you eat based on practices you approve of, such as choosing a vegetarian, vegan, organic, locavore, sustainable, slow-food movement or other type of diet.

Agricultural Subsidies

The Farm Bill can directly and indirectly have wide-ranging effects. For example, the bill dictates subsidies and other forms of agricultural funding or support. Farmers rely on this kind of support to offset varying crop yields and unfavorable weather conditions. The agricultural industry also depends on the federal government to provide some form of price control to guard against flooding the market and dragging down prices. As an example, major changes in the policy of agricultural subsidies were implemented in the 1970s to increase farm incomes and produce cheaper food. As a result of these policies and subsidies, much more corn was grown, giving rise to high fructose corn syrup as a primary sweetener in a number of products today, since corn syrup is cheaper to produce. It is also sweeter than cane sugar, which encouraged its widespread use.

Historically, Congress has pursued farm support programs to ensure that the US population has continued access to abundant and affordable food. However, some leaders worry about the effectiveness of government programs as well as the cost to taxpayers and consumers. Others question if continued farm support is even needed and wonder if it remains compatible with current economic objectives, domestic policy, trade policy, and regulatory restrictions.Johnson, R. and J. Monke, "What Is the 'Farm Bill'?" Congressional Research Service. *CRS Report for Congress*, no. RS22131 (January 3, 2011). www.nationalaglawcenter.org/a...rs/RS22131.pdf. For example, federal dairy policies can raise the price of milk and other dairy products, which can detrimentally affect school lunch and food stamp programs. Regarding all of these issues, Congress must heed the demands of its constituents. In the end, it is inevitable that consumers' growing interest in food issues will affect not only the choices they make in the grocery store, but also the decisions they make in the voting booth.

Key Takeaways

Food politics reflect changing perspectives and policies in the areas of production, distribution, marketing, regulation, and consumption. Over the years, there have been a number of controversies and disputes over food, including concerns about additives and GM foods, the push for sustainable agriculture, and the need to alleviate hunger. In the United States, a massive piece of legislation known as the Farm Bill determines the agricultural and food policy of the federal government.

Discussion Starter

1. Debate a controversial issue related to food politics, such as sustainable agriculture, farm subsidies, or the Farm Bill. Identify the stakeholders involved with the issue and discuss the pros and cons of the differing sides.

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13.5: Food Cost and Inflation

Learning Objectives

- Cite a recent event that has had a profound effect on how consumers feel about the food supply.
- Give a historical overview of the era of cheap food.

Statistics show that Americans spend more than $1.5 trillion on food each year at supermarkets, in restaurants, and from other food providers.Plunkett Research, Ltd. “US Food Industry Overview.” 2011. http://www.plunkettresearch.com/food...ocery%20market%20research/industry%20statistics. According to the USDA, a thrifty family of four spends about $540-$620 per month on groceries.US Department of Agriculture. “Official USDA Food Plans: Cost of Food at Home at Four Levels, US Average, August 2011.” Issued September 2011. www.cnpp.usda.gov/Publication...oodAug2011.pdf. A number of factors affect the rising cost of food. They include agricultural production, processing and manufacturing, wholesale distribution, retail distribution, and consumption.

Around the world, commodity prices rose sharply in 2010 as crop production shortfalls led to reduced supplies and a higher volatility in agricultural markets. Other factors that played a role in increasing food prices include a population boom that has drastically increased demand, droughts and other natural disasters that have crippled farmers, and trade policies and practices that are unfair to developing nations.

Rising agricultural commodity prices have led to concerns about food insecurity and hunger. In an agricultural outlook report for 2010–2020, the Secretary-General of the Organisation for Economic Co-operation and Development states, “While higher prices are generally good news for farmers, the effect on the poor in developing countries who spend a high proportion of their income on food can be devastating. That is why we are calling on governments to improve information and transparency of both physical and financial markets, encourage investments that increase productivity in developing countries, remove production and trade distorting policies, and assist the vulnerable to better manage risk and uncertainty.”Organisation for Economic Co-operation and Development. “OECD-FAO Agricultural Outlook 2010–2020.” June 17, 2011. www.oecd.org/document/31/0,37..._1_1_1,00.html.

Who Bears the Cost?

The cost of our food is influenced by the policies and practices of farms, food and beverage companies, food wholesalers, food retailers, and food service companies. These costs include the energy required to produce and distribute food products from farm field to supermarket to table. Rising prices also reflect the marketing and advertising of food. All of these factors affect all participants in a food system, but some participants are more affected than others. A 2011 report by the Economic Research Service of the USDA shows the division of the consumer food dollar among various aspects of the American food system. A far greater amount of the money you spend to buy a product goes toward the marketing components than toward the actual farmer.US Department of Agriculture, Economic Research Service. “Overview.” Last updated November 19, 2012. http://www.ers.usda.gov/data-product...enditures.aspx.

The Consumer Price Index

The Consumer Price Index (CPI) measures changes in the price level paid for goods and services. This economic indicator is based on the expenditures of the residents of urban areas, including working professionals, the self-employed, the poor, the unemployed, and retired workers, as well as urban wage earners and clerical workers. The CPI has subindices for many different types of products, including food and beverages. It is a closely-watched statistic that is used in a variety of ways, including measuring inflation and regulating prices.

Implications Around the World

Food prices and inflation disproportionately affect people at lower income levels. For the poorest people of the world, increasing prices can raise levels of hunger and starvation. In many developing countries where the cost for staple crops steadily rises, consumers have faced shortages or even the fear of shortages, which can result in hoarding and rioting. This happened in 2007 and 2008 during rice shortages in India and other parts of Asia. Rioters burned hundreds of food ration stores in the Indian region West Bengal. In the West African nation Burkina Faso, food rioters looted stores and burned government buildings as a result of rising

prices for food and other necessities.Vivienne Walt, “The World’s Growing Food-Price Crisis,” *Time* Magazine, 27 February 2008. www.time.com/time/world/artic...7572-1,00.html. In some poor countries, protests also have been fueled by concerns over corruption, because officials earned fortunes from oil and minerals, while locals struggled to put food on their tables. Bringing down prices would quell protests, but could take a decade or more to accomplish.

The End of the Era of Cheap Food

Concerns about food shortages and rising prices reflect the end of the era of cheap food. Following World War II, grain prices fell steadily around the world for decades. As farms grew in scale, factory-farm practices, such as the use of synthetic and mined fertilizers and pesticides, increased. Agribusinesses also invested in massive planting and harvesting machines. These practices pushed crop yields up and crop prices down. Food became so inexpensive that we entered what came to be called the “era of cheap food.”

However, by 2008, economic experts had declared that the era of cheap food was over. The rapid growth in farm output had slowed to the point that it failed to keep pace with population increases and rising affluence in once-developing nations. Consumption of four staples—wheat, rice, corn, and soybeans—outstripped production and resulted in dramatic stockpile decreases. The consequence of this imbalance has been huge spikes felt moderately in the West and to a much greater degree in the developing world. As a result, hunger has worsened for tens of millions of poor people around the world.Justin Gillis, “A Warming Planet Struggles to Feed Itself,” *The New York Times*, 4 June 2011. http://www.nytimes.com/2011/06/05/sc...t.html?_r=2&hp.

Two major trends played a part in this shift. First, prosperity in India and China led to increased food consumption in general, but more specifically to increased meat consumption. Increased meat consumption has led to an increased demand for livestock feed, which has contributed to an overall rise in prices. The second trend relates to biofuels, which are made from a wide variety of crops (such as corn and palm nuts), which increasingly are used to make fuel instead of to feed people.

The world population in 2010 was 6.9 billion.United Nations. “World Population Prospects, the 2010 Revision.” http://esa.un.org/wpp/Analytical-Fig.../htm/fig_1.htm. It is projected to grow to 9.4 billion by 2050.Food and Agricultural Organization of the United Nations. “Executive Summary.” www.fao.org/docrep/004/y3557e/y3557e03.htm. The rate of increase is particularly high in the developing world, and the increased population, along with poverty and political instability, are helping to foster long-term food insecurity. In the coming decades, farmers will need to greatly increase their output to meet the rising demand, while adapting to any future trends.Christian Science Monitor. “Why the Era of Cheap Food Is Over.” December 31, 2007. http://www.csmonitor.com/2007/1231/p13s01-wogi.html.

Key Takeaways

Food prices are rising in the United States and around the world, which has greatly affected both agricultural producers and consumers. A number of factors have contributed to rising costs, including population booms, natural disasters, and the production of biofuels, among others. Economic experts have declared that the era of cheap food, which began after World War II, has ended due to rising population rates and decreased agricultural production worldwide. As a result, hunger has worsened for tens of millions of poor people globally.

Discussion Starter

1. Examine the graphics from http://www.ers.usda.gov/data-product...mentation.aspx. What does each image indicate about agriculture and the American economy?

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13.6: The Issue of Food Security

Learning Objectives

- Share an example of a food and nutrition program that seeks to mitigate hunger in the United States and/or Canada.

Physiologically, hunger relates to appetite and is the body's response to a need for nourishment. Through stomach discomfort or intestinal rumbling, the body alerts the brain that it requires food. This uneasy sensation is easily addressed with a snack or a full meal. However, the term "hunger" also relates to a weakened condition that is a consequence of a prolonged lack of food. People who suffer from this form of hunger typically experience malnourishment, along with poor growth and development.

Hunger

Adequate food intake that meets nutritional requirements is essential to achieve a healthy, productive lifestyle. However, millions of people in North America, not to mention globally, go hungry and are malnourished each year due to a recurring and involuntary lack of food. The economic crisis of 2008 caused a dramatic increase in hunger across the United States.World Hunger.org. "Hunger in America: 2011 United States Hunger and Poverty Facts." Accessed October 10, 2011. www.worldhunger.org/articles/...nger_facts.htm.

Key Hunger Statistics

In 2010, 925 million people around the world were classified as hungry. Although this was a decrease from a historic high of more than one billion people from the previous year, it is still an unbearable number. Every night, millions and millions of people go to sleep hungry due to a lack of the money or resources needed to acquire an adequate amount of food. This graph shows the division of hungry people around the globe.

Key Hunger Terms

A number of terms are used to categorize and classify hunger. Two key terms, food security and food insecurity, focus on status and affect hunger statistics. Another term, malnutrition, refers to the deficiencies that a hungry person experiences.

Food Security

Most American households are considered to be food secure, which means they have adequate access to food and consume enough nutrients to achieve a healthy lifestyle. However, a minority of US households experiences food insecurity at certain points during the year, which means their access to food is limited due to a lack of money or other resources. This graphic shows the percentage of food-secure and food-insecure households in the United States during the year 2010.

Food Insecurity

Food insecurity is defined as not having adequate access to food that meets nutritional needs. According to the USDA, about 48.8 million people live in food-insecure households and have reported multiple indications of food access problems. About sixteen million of those have "very low food security," which means one or more people in the household were hungry at some point over the course of a year due to the inability to afford enough food. The difference between low and very low food security is that members of low insecurity households have reported problems of food access, but have reported only a few instances of reduced food intake, if any.Coleman-Jensen, A. et al. "Household Food Security in the United States in 2010." US Department of Agriculture, *Economic Research Report*, no. ERR-125 (September 2011). African American and Hispanic households experience food insecurity at much higher rates than the national average.Coleman-Jensen, A. et al. "Household Food Security in the United States in 2010." US Department of Agriculture, *Economic Research Report*, no. ERR-125 (September 2011).

Households with limited resources employ a variety of methods to increase their access to adequate food. Some families purchase junk food and fast food—cheaper options that are also very unhealthy. Other families who struggle with food security supplement the groceries they purchase by participating in government assistance programs. They may also obtain food from emergency providers, such as food banks and soup kitchens in their communities.

Malnutrition

A person living in a food-insecure household may suffer from malnutrition, which results from a failure to meet nutrient requirements. This can occur as a result of consuming too little food or not enough key nutrients. There are two basic types of malnutrition. The first is macronutrient deficiency and relates to the lack of adequate protein, which is required for cell growth, maintenance, and repair. The second type of malnutrition is micronutrient deficiency and relates to inadequate vitamin and mineral intake.World Hunger. “2011 World Hunger and Poverty Facts and Statistics.” Accessed October 10, 2011. http://www.worldhunger.org/articles/...cts%202002.htm. Even people who are overweight or obese can suffer from this kind of malnutrition if they eat foods that do not meet all of their nutritional needs.

At-Risk Groups

Worldwide, three main groups are most at risk of hunger: the rural poor in developing nations who also lack access to electricity and safe drinking water, the urban poor who live in expanding cities and lack the means to buy food, and victims of earthquakes, hurricanes, and other natural and man-made catastrophes.Food and Agriculture Organization of the United Nations. “Hunger: Frequently Asked Questions.” Accessed October 10, 2011. www.fao.org/hunger/en/ In the United States, there are additional subgroups that are at risk and are more likely than others to face hunger and malnutrition. They include low-income families and the working poor, who are employed but have incomes below the federal poverty level.

Senior citizens are also a major at-risk group. Many elderly people are frail and isolated, which affects their ability to meet their dietary requirements. In addition, many also have low incomes, limited resources, and difficulty purchasing or preparing food due to health issues or poor mobility. As a result, more than six million senior citizens in the United States face the threat of hunger. Meals on Wheels. “Our Vision and Mission.” Accessed October 10, 2011. www.mowaa.org/page.aspx?pid=299

The Homeless

One of the groups that struggles with hunger are the millions of homeless people across North America. According to a recent study by the US Conference of Mayors, the majority of reporting cities saw an increase in the number of homeless families.The United States Conference of Mayors. “Hunger and Homelessness Survey: A Status Report on Hunger and Homelessness in America’s Cities, a 27-City Survey.” December 2009. usmayors.org/pressreleases/up...eteWEB2009.pdf. Hunger and homelessness often go hand-in-hand as homeless families and adults turn to soup kitchens or food pantries or resort to begging for food.

Children

Rising hunger rates in the United States particularly affect children. Nearly one out of four children, or 21.6 percent of all American children, lives in a food-insecure household and spends at least part of the year hungry.Coleman-Jensen, A. et al. “Household Food Security in the United States in 2010.” US Department of Agriculture, *Economic Research Report*, no. ERR-125 (September 2011). Hunger delays their growth and development and affects their educational progress because it is more difficult for hungry or malnourished students to concentrate in school. In addition, children who are undernourished are more susceptible to contracting diseases, such as measles and pneumonia.World Hunger. “2011 World Hunger and Poverty Facts and Statistics.” Accessed October 10, 2011.



Video **13.6.1**: Going Hungry in America. This video examines the effect of hunger on many American children.

Government Programs

The federal government has established a number of programs that work to alleviate hunger and ensure that many low-income families receive the nutrition they require to live a healthy life. A number of programs were strengthened by the passage of the Healthy, Hunger-Free Kids Act of 2010. This legislation authorized funding and set the policy for several key core programs that provide a safety net for food-insecure children across the United States.

The Federal Poverty Level

The federal poverty level (FPL) is used to determine eligibility for food-assistance programs. This monetary figure is the minimum amount that a family would need to acquire shelter, food, clothing, and other necessities. It is calculated based on family size and is adjusted for annual inflation. Although many people who fall below the FPL are unemployed, the working poor can qualify for food programs and other forms of public assistance if their income is less than a certain percentage of the federal poverty level, along with other qualifications.

USDA Food Assistance Programs

Government food and nutrition assistance programs that are organized and operated by the USDA work to increase food security. They provide low-income households with access to food, the tools for consuming a healthy diet, and education about nutrition. The USDA monitors the extent and severity of food insecurity via an annual survey. This contributes to the efficiency of food assistance programs as well as the effectiveness of private charities and other initiatives aimed at reducing food insecurity.Coleman-Jensen, A. et al. “Household Food Security in the United States in 2010.” US Department of Agriculture, *Economic Research Report*, no. ERR-125 (September 2011).

The Supplemental Nutrition Assistance Program

Formerly known as the Food Stamp Program, the Supplemental Nutrition Assistance Program (SNAP) provides monthly benefits for low-income households to purchase approved food items at authorized stores. Clients qualify for the program based on available household income, assets, and certain basic expenses. In an average month, SNAP provides benefits to more than forty million people in the United States.Coleman-Jensen, A. et al. “Household Food Security in the United States in 2010.” US Department of Agriculture, *Economic Research Report*, no. ERR-125 (September 2011).

The program provides Electronic Benefit Transfers (EBT) which work similarly to a debit card. Clients receive a card with a certain allocation of money for each month that can be used only for food. In 2010, the average benefit was about $134 per person, per month and total federal expenditures for the program were $68.2 billion.Coleman-Jensen, A. et al. “Household Food Security in the United States in 2010.” US Department of Agriculture, *Economic Research Report*, no. ERR-125 (September 2011).

The Special, Supplemental Program for Women, Infants, and Children

The Special, Supplemental Program for Women, Infants and Children (WIC) provides food packages to pregnant and breastfeeding women, as well as to infants and children up to age five, to promote adequate intake for healthy growth and development. Most state WIC programs provide vouchers that participants use to acquire supplemental packages at authorized stores. In 2010, WIC served approximately 9.2 million participants per month at an average monthly cost of about forty-two dollars per person.Coleman-Jensen, A. et al. "Household Food Security in the United States in 2010." US Department of Agriculture, *Economic Research Report*, no. ERR-125 (September 2011).

The National School Lunch Program

The National School Lunch Program (NSLP) and School Breakfast Program (SBP) ensure that children in elementary and middle schools receive at least one healthy meal each school day, or two if both the NSLP and SBP are provided. According to the USDA, these programs operate in over 101,000 public and nonprofit private schools and residential child-care institutions.US Department of Agriculture. "National School Lunch Program." October 2011. www.fns.usda.gov/cnd/Lunch/Ab...PFactSheet.pdf. In 2010, the programs provided meals to an average of 31.6 million children each school day. Fifty-six percent of the lunches served were free, and an additional 10 percent were provided at reduced prices.

Other Food-Assistance Programs for Children

Other government programs provide meals for children after school hours and during summer breaks. The Child and Adult Care Food Program (CACFP) offers meals and snacks at child-care centers, daycare homes, and after-school programs. Through CACFP, more than 3.2 million children and 112,000 adults receive nutritious meals and snacks each day.US Department of Agriculture. "Child & Adult Care Food Program." Last modified June 10, 2011. www.fns.usda.gov/cnd/care/. The Summer Food Service Program provides meals to children during summer break. Sponsors include day camps and other recreation programs where at least half of the attendees live in households with incomes below the federal poverty level.US Department of Agriculture. "Summer Food Service Program." st.TER 14 2011r Congressbrary. Last modified July 20, 2011. http://www.summerfood.usda.gov/default.htm. These and other programs help to fill in the gaps during the typical day of a food-insecure child.

The Head Start Program

Head Start is a health and development program for children ages three to five, from low-income families. The philosophy behind the organization is that early intervention can help address the educational, social, and nutritional deficiencies that children from lower-income families often experience. Launched in 1965, it is one of the longest-running, poverty-related programs in the United States. Today, Head Start programs include education, meals, snacks, and access to other social services and health guidance.US Department of Health and Human Services. "About the Office of Head Start." Last reviewed February 23, 2011. www.acf.hhs.gov/programs/ohs/about/index.html.

Other Forms of Assistance

Other forms of assistance include locally-operated charitable organizations, such as food banks and food pantries, which acquire food from local manufacturers, retailers, farmers, and community members to give to low-income families. Neighborhood soup kitchens provide meals to the homeless and other people in need. These and other organizations are run by nonprofit groups, as well as religious institutions, to provide an additional safety net for those in need of food.

Meals on Wheels

An organization known as Meals on Wheels delivers meals to elderly people who have difficulty buying or making their own food because of poor health or limited mobility. It is the oldest and largest program dedicated to addressing the nutritional needs of senior citizens. Each day, Meals on Wheels volunteers deliver more than one million meals across the United States. The first Meals on Wheels program began in Philadelphia in the 1950s. In the decades since, the organization has expanded into a vast network that serves the elderly in all fifty states and several US territories. Today, Meals on Wheels remains committed to ending hunger among the senior citizen community.Meals on Wheels. "The Meals on Wheels Association of America." Accessed October 10, 2011. www.mowaa.org/page.aspx?pid=212.



Figure 13.6.1: Delivery of Thanksgiving dinner to a Meals on Wheels recipient. Clara Donney, (right), a Meals on Wheels recipient of a Thanksgiving dinner sponsored by the Great Falls Community Food Bank, is all smiles as Airman 1st Class Courtney Taylor, customer service technician with the 341st Comptroller Squadron, delivers her meal. (Public Domain; US Air Force).

Key Takeaways

Around the world, nearly one billion people suffer the effects of constant hunger. Key terms related to hunger include food security, which means having continual access to safe, sufficient, nutritious food, and food insecurity, which means not having continual access to safe, sufficient, nutritious food. There are two types of malnutrition. The first is macronutrient deficiency and relates to the lack of adequate protein, which is required for cell growth, maintenance, and repair. The second type of malnutrition is micronutrient deficiency and relates to inadequate vitamin and mineral intake. There are a number of groups at risk for hunger, including the unemployed and underemployed, poor families, the elderly, and the homeless. The United States has a number of federal and state programs, as well as local charities, which provide assistance and education for people who fall into the category of food insecurity.

Discussion Starter

1. Do you believe there are enough government programs currently in place to address the problem of hunger? Why or why not? If not, what additional solutions would you recommend?

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13.7: Nutrition and Your Health

Learning Objectives

- Relate the research on home-cooked family meals to comprehensive health and wellness, taste, sustainability, and the strengthening of family bonds

The adage, “you are what you eat,” seems to be more true today than ever. In recent years, consumers have become more conscientious about the decisions they make in the supermarket. Organically grown food is the fastest growing segment of the food industry. Also, farmers’ markets and chains that are health-food-oriented are thriving in many parts of North America. Shoppers have begun to pay more attention to the effect of food on their health and well-being. That includes not only the kinds of foods that they purchase, but also the manner in which meals are cooked and consumed. The preparation of food can greatly affect its nutritional value. Also, studies have shown that eating at a table with family members or friends can promote both health and happiness.

Family Meals

In the past, families routinely sat down together to eat dinner. But in recent decades, that comfortable tradition has fallen by the wayside. In 1900, 2 percent of meals were eaten outside of the home. By 2010, that figure had risen to 50 percent. Mark Hyman, MD, “How Eating at Home Can Save Your Life,” Huffington Post.com, 9 January 2011. http://www.huffingtonpost.com/dr-mar...ily-dinner-how _b_806114.html? Today, family members often go their own way at mealtimes and when they do sit down together, about three times a week, the meal often lasts less than twenty minutes and is spent eating a microwaved meal in front of a television.

However, recent studies have shown that home-cooked, family meals really matter. Family meals usually lead to the consumption of healthy food packed with nutrition, rather than an intake of empty calories. Other benefits include strengthening familial bonds, improving family communication, and helping young children learn table manners. Increased frequency of family meals has also been associated with certain developmental assets, such as support, boundaries and expectations, commitment to learning, positive values, and social competency.Rochford, M. “Do Family Meals Still Matter?” *Visions: Family and Community Health Sciences* (Rutgers University) 21, no. 3 (2009).

Home-prepared meals provide an opportunity for more balanced and better-portioned meals with fewer calories, sodium, and less saturated fat. When families prepare food together, parents or caregivers can also use the time to teach children about the ways their dietary selections can affect their health.

The Adolescent Diet

Teenagers’ dietary choices are influenced by their family’s economic status, the availability of food inside and outside the home, and established traditions. Studies have found links between the prevalence of family meals during adolescence and the establishment of healthy dietary behaviors by young adulthood. Yet, many of today’s teenagers make food selections on their own, which often means eating junk food or fast food on the go.

However, adolescents who regularly consume family meals or have done so in the past are more likely to eat breakfast and to eat more fruits and vegetables. Research has shown that adolescents who have regular meals with their parents are 42 percent less likely to drink alcohol, 50 percent less likely to smoke cigarettes, and 66 percent less likely to use marijuana. Regular family dinners also help protect teens from bulimia, anorexia, and diet pills. In addition, the frequency of family meals was inversely related to lower academic scores and incidents of depression or suicide.Mark Hyman, MD, “How Eating at Home Can Save Your Life,” Huffington Post.com, 9 January 2011. http://www.huffingtonpost.com/dr-mar...ily-dinner-how _b_806114.html?

Sustainable Eating

As discussed at the beginning of this chapter, sustainable agricultural practices provide healthy, nutritious food for the consumers of today, while preserving natural resources for the consumers of tomorrow. Sustainability not only has economic and environmental benefits, but also personal benefits, including reduced exposure to pesticides, antibiotics, and growth hormones. Sustainable eaters do all of the following:

- **Consume less processed food.** People who eat sustainably focus on whole foods that are high in nutritive value, rather than heavily processed foods with lots of additives.
- **Eat more home-cooked meals.** Sustainable eaters go out to restaurants less often, and when they do, they dine at establishments that provide dishes made from whole-food ingredients.
- **Consume a plant-based diet.** Research has shown that a plant-based diet, focused on whole grains, vegetables, fruits, and legumes, greatly reduces the risk of heart disease.
- **Buy organic food products.** Organically produced foods have been cultivated or raised without synthetic pesticides, antibiotics, or genetic engineering. Certified organic foods can be identified by the USDA's stamp.
- **Buy locally grown foods.** Buying locally benefits the environment by reducing the fossil fuels needed to transport food from faraway places. Also, farmers keep eighty to ninety cents for every dollar spent at a farmer's market.

Disease Prevention and Management

Eating fresh, healthy foods not only stimulates your taste buds, but also can improve your quality of life and help you to live longer. As discussed, food fuels your body and helps you to maintain a healthy weight. Nutrition also contributes to longevity and plays an important role in preventing a number of diseases and disorders, from obesity to cardiovascular disease. Some dietary changes can also help to manage certain chronic conditions, including high blood pressure and diabetes. A doctor or a nutritionist can provide guidance to determine the dietary changes needed to ensure and maintain your health.

Heart Health

According to the WHO, cardiovascular disease is the leading cause of death on the planet.World Health Organization. "The Top 10 Causes of Death." Accessed http://www.who.int/mediacentre/factsheets/fs310/en/. However, a healthy diet can go a long way toward preventing a number of conditions that contribute to cardiovascular malfunction, including high levels of blood cholesterol and narrowed arteries. As discussed in this text, it is extremely helpful to reduce the intake of trans fat, saturated fat, and sodium. This can considerably lower the risk of cardiovascular disease, or manage further incidents and artery blockages in current heart patients. It is also beneficial to eat a diet high in fiber and to include more omega-3 fatty acids, such as the kind found in mackerel, salmon, and other oily fish.

High Blood Pressure

Blood pressure is the force of blood pumping through the arteries. When pressure levels become too high, it results in a condition known as hypertension, which is asymptomatic but can lead to a number of other problems, including heart attacks, heart failure, kidney failure, and strokes. For people with high blood pressure, it can be beneficial to follow the same recommendations as those for heart patients. First of all, it is crucial to reduce the intake of sodium to prevent pressure levels from continuing to rise. It can also be helpful to increase potassium intake. However, patients should check with a doctor or dietitian first, especially if there are kidney disease concerns.

Tools for Change

The Dietary Approaches to Stop Hypertension, or DASH diet, is highly recommended to lower blood pressure. This program promotes an increased intake of potassium and calcium by emphasizing fruits, vegetables, whole grains, low-fat dairy products, and limited amounts of lean meat. The DASH diet also decreases the intake of saturated fat and sugar. Studies have shown that blood-pressure patients on the DASH diet were able to reduce their diastolic pressure levels (the lower measurement, which is taken between beats when the heart is relaxed) by up to 5 mmHg regardless of age, gender, or ethnicity. You can learn more about the DASH diet at http://dashdiet.org/.

Diabetes

The rising rates of diabetes have triggered a health crisis in the United States and around the world. In diabetics, the levels of blood glucose, or blood sugar, are too high because of the body's inability to produce insulin or to use it effectively. There are two types of this disease. Although the causes of Type 1 diabetes are not completely understood, it is known that obesity and genetics are major factors for Type 2.

Nutrition plays a role in lowering the risk of Type 2 diabetes or managing either form of the disease. However, it is a myth that there is one diabetes diet that every patient should follow. Instead, diabetics should keep track of the foods they consume that contain carbohydrates to manage and control blood-glucose levels. Also, a dietitian can help patients create a specific meal plan that fits their preferences, lifestyle, and health goals.

The Crisis of Obesity

Excessive weight gain has become an epidemic. According to the National Institutes of Health, over two-thirds of American adults are overweight, and one in three is obese. Obesity in particular puts people at risk for a host of complications, including Type 2 diabetes, heart disease, high cholesterol, hypertension, osteoarthritis, and some forms of cancer. The more overweight a person is, the greater his or her risk of developing life-threatening complications. There is no single cause of obesity and no single way to treat it. However, a healthy, nutritious diet is generally the first step, including consuming more fruits and vegetables, whole grains, and lean meats and dairy products.National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. "Overweight and Obesity Statistics." *NIH Publication No. 04-4158*. Updated February 2010. win.niddk.nih.gov/publication...s/stat904z.pdf.

Kidney Disease

Chronic kidney failure is the gradual loss of kidney function and can cause dangerous levels of fluid and waste to build up in the body. Nutrition is very important in managing end-stage renal disease, and a patient with this condition should discuss a meal plan with a dietitian and physician. Certain macro- and micronutrients will need to be monitored closely, including protein, potassium, sodium, and phosphorus. Kidney patients must also keep track of their caloric intake and dietitians may recommend consuming more fast-releasing carbohydrates and low-saturated fats to boost the number of calories consumed each day.

Cancer

Certain cancers are linked to being overweight or obese. Additionally, some foods are related to either an increased or decreased risk for certain cancers. Foods linked to decreased cancer risk include whole grains, high-fiber foods, fruits, and vegetables. Foods linked to increased cancer risk include processed meats and excess alcohol.

Digestive Disorders

Digestive disorders can include constipation, heartburn or gastroesophageal reflux disease, inflammatory bowel disease, including Crohn's and ulcerative colitis, and irritable bowel syndrome. These disorders should be addressed with a physician. However, for many of them, diet can play an important role in prevention and management. For example, getting enough fiber and fluids in your diet and being active can help to alleviate constipation.

Key Takeaways

More and more consumers are weighing nutritional considerations as they choose which foods to purchase and prepare for their families. Studies have shown that family meals and home-cooked food not only benefit a person's health, but also their overall well-being. Family meals lead to the consumption of healthy food, tighter familial bonds, improved communication, and the teaching of table manners to young children. Diet plays a key role in the prevention and management of many chronic conditions or diseases, such as hypertension and diabetes.

Discussion Starter

1. What would you recommend to help people who are struggling with diabetes? What tips would you provide? What lifestyle changes might help? Use the dietary guidelines at the Mayo Clinic's website to help provide specific suggestions. www.mayoclinic.com/health/dia...s-diet/DA00027.

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13.8: Diets around the World

Learning Objectives

- Give examples of how local taste preferences and availability influence food choices in different regions of the globe.
- Explain what is meant by Alice Waters' statement: "Food is precious."

In the past, people's culture and location determined the foods they ate and the manner in which they prepared their meals. For example, in the Middle East, wheat was a staple grain and was used to make flatbread and porridge, while halfway around the world in Mesoamerica, maize was the staple crop and was used to make tortillas and tamales. Today, most people have access to a wide variety of food and can prepare them any way they choose. However, customs and traditions still strongly influence diet and cuisine in most areas of the world.

Comparing Diets

There are a multitude of diets across the globe, in all regions and cultures. Each is influenced by the traditions of the past, along with the produce and livestock available. Local tastes, agricultural economics, and incomes still have a profound effect on what many people eat around the world. In this section, you will read a few examples of cuisines in different countries and regions, demonstrating differences in preferences. We will also compare common dietary choices in each region for a key meal—breakfast.

North America

The people of the United States and Canada consume a wide variety of food. Throughout both countries, people enjoy eating all kinds of cuisine from barbecue, pizza, peanut butter sandwiches, and pie to sushi, tacos, chow mein, and roti (an Indian flatbread). This is partly due to the influence of immigration. As people emmigrated to North America, they brought their dietary differences with them. In the 1800s, for example, Italian immigrants continued to cook spaghetti, pesto, and other cultural dishes after arriving in the United States. Today, Italian cuisine is enjoyed by many Americans from all backgrounds.

The variety of North American cuisine has also been impacted by regional variations. For example, fried chicken, cornbread, and sweet tea are popular in the southern states, while clam chowder, lobster rolls, and apple cider are enjoyed in New England. Also, as more people seek to support sustainable agriculture, locally grown crops and whole-food cooking practices often factor into what Americans eat and how they eat it.

Breakfast in North America

Meals can vary widely from one region of the world to another. Therefore, it can be interesting and informative to compare the choices made for a particular meal around the globe. Throughout this section, we will explore the kinds of foods that people consume as they begin their day. Breakfast is a vital meal in any part of the world because it breaks the long overnight fast. An adequate breakfast also provides fuel for the first part of the day and helps improve concentration and energy levels.

Let's begin with breakfast in North America. On weekdays, North Americans often eat breakfast in a hurry or on the go. Therefore, many people choose breakfast foods that are quick and easy to prepare or can be eaten during the trip to school or the office. As a result, breakfast cereals with milk are extremely popular, and also oatmeal, toast, or bagels. However, on the weekends, some people spend a longer time enjoying a hearty breakfast or going out for brunch. Typical choices emphasize hot foods and include egg dishes, such as omelettes and scrambled or fried eggs, along with pancakes, waffles, french toast, bacon or sausage, and orange juice, coffee, or tea to drink.

Central and South America

Both Central America and South America feature cuisines with rich Latin flavors. In addition, rice and corn are staples in both and form the basis for many dishes. Both regions are also affected by the mixture of influences from the native populations and the cultural traditions brought by Spanish and Portuguese immigrants during the 1600s and beyond.

South America has a diverse population, which is reflected in dietary choices across the continent. The northwestern region boasts some of the most exotic food in Latin America. In northeastern South America, many dishes feature a contrast of sweet and salty tastes, including raisins, prunes, capers, and olives. Also, rice grown in the area and seafood off the coast are key ingredients in

South American-style paella. The north central part of the continent reflects a Spanish influence. Many of the dominant spices—cumin, oregano, cinnamon, and anise—came from Spain, along with orange and lime juices, wine, and olive oil. The south is cattle country and the locals enjoy grass-fed beef cooked in the form of asados, which are large cuts roasted in a campfire. Another popular meat dish is parrilladas, which are thick steaks grilled over oak.Cooking Light. “South American Cuisine.” © 2012 Time Inc. Lifestyle Group. http://www.cookinglight.com/food/wor...erican-cuisine -00400000001391/.

From Mexico in the North to Panama in the South, Central American cuisine features some of the world’s favorite foods, including rice, beans, corn, peppers, and tropical fruits. This area combines a variety of culinary traditions derived from the native Maya and Aztec populations, arrivals from Spain, and African and Latin-influenced neighbors along the Caribbean. In this region of the world, tamales are common. Spicy seasonings, including hot chili peppers, are also very popular.

Typical Southern and Central American Foods

Typical foods in South and Central America include quinoa, which is a grain-like crop that is cultivated for its edible seeds. Quinoa has a high protein and fiber content, is gluten-free, and is particulary tasty cooked in pilafs. Another popular grain product is the tortilla, which is a flatbread made from wheat or corn. Tortillas are used to make a number of dishes, including burritos, enchiladas, and tacos. Fruits and vegetables that are common in Mexico, Central America, and South America include corn, avocados, yucca, peppers, potatoes, mangoes, and papayas. Rice, beans, and a soft cheese known as queso fresco are common to the cuisine in this area of the world as well.



Figure **13.8.1**: Tamales, which are popular in Mexico and parts of Central and South America, are made from a shell called a masa that is stuffed with meat or vegetables and steamed or boiled in a wrapper of dried corn leaves. The wrapping is discarded prior to eating. Salvadorean tamales shown above are made in banana or plantain leaves, and the masa (corn meal) is often seasoned with chicken stock. (Public Domain; Ll1324).

Breakfast in Central America

In this region, the first meal of the day commonly includes huevos rancheros (fried eggs served over a tortilla and topped with tomato sauce). Other popular breakfast dishes include pan dulce (a sweetened bread), along with fried plantains, and a spicy sausage called chorizo. The typical beverage is coffee, which is available in many forms, including café con leche (which is sweetened with lots of milk) and café de olla (with cinnamon and brown sugar). Hot chocolate is also popular and tends to be thick, rich, and flavored with spices such as cinnamon or achiote. In the Yucatan region, huevos motulenos are prepared by spreading refried beans onto fresh tortillas with fried eggs, peas, chopped ham, and cheese.

Europe

European cuisine is extremely diverse. The diet in Great Britain is different from what people typically consume in Germany, for example. However, across the continent, meat dishes are prominent, along with an emphasis on sauces. Potatoes, wheat, and dairy products are also staples of the European diet.

The nations along the Mediterranean Sea are particularly renowned for their flavorful food. This part of the world boasts a number of famous dishes associated with their countries of origin. They include Italy’s pasta, France’s coq au vin, and Spain’s paella.

Italy

Although Italy is a relatively small nation, the difference in cuisine from one region to another can be great. For example, the people of northern Italy tend to rely on dairy products such as butter, cream, and cheeses made from cow's milk, because the land is flatter and better suited to raising cattle. In southern Italy, there is greater reliance on olive oil than butter, and cheeses are more likely to be made from sheep's milk.Cooking Light. "Regional Italian Cuisine." © 2012 Time Inc. Lifestyle Group. http://www.cookinglight.com/food/wor...talian-cuisine -00400000001340/.

However, there are a number of common ingredients and dishes across the country. Italian cuisine includes a variety of pasta, such as spaghetti, linguine, penne, and ravioli. Other well-known dishes are pizza, risotto, and polenta. Italians are also known for cooking with certain spices, including garlic, oregano, and basil.

France

For centuries, the French have been famous for their rich, extravagant cuisine. Butter, olive oil, pork fat, goose fat, and duck fat are all key ingredients. Common French dishes include quiche, fondue, baguettes, and also creams and tarts. Frites, or French fries, are cut in different shapes and fried in different fats, depending on the region. Fresh-baked bread is also found across the nation from the skinny baguettes of Paris to the sourdough breads in other parts of the country.

Every region of France seems to have its version of coq au vin (braised chicken most often cooked with garlic, mushrooms, and pork fat in wine). For instance, in the northeast, the dish is prepared a la biere (in beer). In Normandy in the northwest, coq au vin is cooked au cidre (in apple cider).Cooking Light. "France's Regional Cuisine." © 2012 Time Inc. Lifestyle Group. http://www.cookinglight.com/food/wor...gional-cuisine -00400000001365/.

Spain

One of the most popular Spanish dishes is paella, a gumbo of rice, seafood, green vegetables, beans, and various meats. The ingredients can vary wildly from one region to another, but rice is always the staple of the dish. Spain is also renowned for its tapas, which are appetizers or snacks. In restaurants that specialize in preparing and serving tapas, diners often order a number of different dishes from a lengthy menu and combine them to make a full meal.

Cooks in Spain rely on a variety of olive oils known for their flavors, ranging from smooth and subtle to fruity and robust. Spanish cuisine combines Roman, Moorish, and New World flavors. Key ingredients include rice, paprika, saffron, chorizo, and citrus fruits.Cooking Light. "Spanish Flavor." © 2012 Time Inc. Lifestyle Group. http://www.cookinglight.com/food/wor...alties-spanish -00400000001203/.



Video **13.8.1**: The Mediterranean Diet. This video shows the cultural history of the cuisine enjoyed by many people who live in the Mediterranean region of Europe.

Breakfast in Europe

In some countries, such as France, Italy, and Belgium, coffee and bread are common breakfast foods. However, the people of Great Britain and Ireland tend to enjoy a bigger breakfast with oatmeal or cold cereal, along with meats like bacon and sausage, plus eggs

and toast. Tea is also popular in this area, not only for breakfast, but throughout the day. The continental-style breakfast is most commonly associated with France and includes fresh-baked croissants, toast, or a rich French pastry called brioche, along with a hot cup of tea, coffee, or café au lait.

Africa

The continent of Africa is home to many different countries and cultural groups. This diversity is reflected in the cuisine and dietary choices of the African people. Traditionally, various African cusines combine locally grown cereals and grains, with fruits and vegetables. In some regions, dairy products dominate, while in others meat and poultry form the basis of many dishes.

Ethiopia

Ethiopia, located along the Horn of Africa, is one of the few African countries never colonized by a foreign nation prior to the modern era. So, outside influences on the culture were limited. Religious influences from Jewish, Islamic, and Catholic traditions played a larger role on the shaping of Ethiopian cuisine, because of the need to adhere to different dietary restrictions. For example, approximately half of Ethiopians are Muslim and must abstain from eating pork or using spices and nuts to flavor dishes. Ethiopia is also known for dishes that use local herbs and spices, including fenugreek, cumin, cardamom, coriander, saffron, and mustard. Many dishes also reflect a history of vegetarian cooking since meat was not always readily available.Cooking Light. “Ethiopian Tastes.” © 2012 Time Inc. Lifestyle Group. http://www.cookinglight.com/food/veg...0400000037116/.

In addition, Ethiopians use their hands to eat. First, diners tear off pieces of injera, a spongy, tangy flatbread made from teff flour. Then, they use the pieces as utensils to scoop up vegetables, legumes, and meats from a communal plate.Ethiopian Restaurant.com. “Injera.” © 2004–2012. http://www.ethiopianrestaurant.com/injera.html Teff is a grass that grows in the highlands of Ethiopia and is a staple of the diet.

Central and West Africa

Stretching from mountains in the north to the Congo River, Central Africa primarily features traditional cuisine. Meals are focused on certain staples, including cassava, which is a mashed root vegetable, and also plantains, peanuts, and chili peppers. In West Africa, which includes the Sahara Desert and Atlantic coast, the cuisine features dishes made from tomatoes, onions, chili peppers, and palm nut oil. Popular dishes in both regions include stews and porridges, such as ground nut stew made from peanuts, and also fufu, a paste made from cassava or maize.

Breakfast in Africa

African breakfast choices are strongly influenced by the colonial heritage of a region. The people of West Africa typically enjoy the French continental-style breakfast. However, in the eastern and southern parts of the continent, the traditional English breakfast is more common. In North Africa, breakfast is likely to include tea or coffee, with breads made from sorghum or millet. In East and West Africa, a common breakfast dish is uji, a thick porridge made from cassava, millet, rice, or corn. Kitoza is a delicacy made from dried strips of beef that are eaten with porridge in Madagascar. In Algeria, French bread, jam, and coffee is a typical breakfast. The people of Cameroon eat beignets, which is a doughnut eaten with beans or dipped in a sticky, sugary liquid called bouilli.

Asia

Asia is a massive continent that encompasses the countries of the Middle East, parts of Russia, and the island nations of the southeast. Due to this diversity, Asian cuisine can be broken down into several regional styles, including South Asia, which is represented for our purposes here by India, and East Asia which is represented for our purposes by China, Korea, and Japan. Even with this variety, the Asian nations have some dietary choices in common. For example, rice is a staple used in many dishes across the continent.

India

In India, there is much variety between the different provinces. The nation’s many kinds of regional cuisines can date back thousands of years and are influenced by geography, food availability, economics, and local customs. However, vegetarian diets are common across the nation for religious reasons, among others. As a result, Indian dishes are often based on rice, lentils, and vegetables, rather than meat or poultry. Indian cooking also features spicy seasonings, including curries, mustard oil, cumin, chili

pepper, garlic, ginger, and garam masala, which is a blend of several spices.Curry Dishes.com. “Guide to Easy Indian Recipes, Curry Recipes and Curry Spices.” © 2009. www.currydishes.com/. India is also known for its breads, including the flatbreads roti and chapati. Dishes that are popular not only in India but around the world include samosa, a potato-stuffed pastry; shahi paneer, a creamy curry dish made out of soft cheese and tomato sauce; and chana masala, chickpeas in curry sauce.Food-India.com. “Your Guide to Indian Food.” © 2003–2011. http://www.food-india.com/.

China

China has the world’s most sizable population. As a result, there are many different culinary traditions across this vast country, which is usually divided into eight distinct cuisine regions. For example, Cantonese cuisine, which is also known as Guangdong, features light, mellow dishes that are often made with sauces, including sweet-and-sour sauce and oyster sauce. Cantonese-style cuisine has been popularized in Chinese restaurants around the world. Another cuisine is known as Zhejiang, which is often shortened to Zhe, and originates from a province in southern China. It features dishes made from seafood, freshwater fish, and bamboo shoots.eChinacities.com. “China’s Eight Cuisines Revealed and How to Identify Them.” ©2008–2011 www.echinacities.com/expat-co...sines-revealed -and-how-to-indentify-them.html Key ingredients that are used in several, but not all, of the different regions include rice, tofu, ginger, and garlic. Tea is also a popular choice in most parts of the country.

Chinese use chopsticks as utensils. These small tapered sticks can be made from a variety of materials, including wood, plastic, bamboo, metal, bone, and ivory. Both chopsticks are held in one hand, between the thumb and fingers, and are used to pick up food.

Korea

Korean cuisine is primarily centered around rice, vegetables, and meat. Commonly-used ingredients include sesame oil, soy sauce, bean paste, garlic, ginger, and red pepper. Most meals feature a number of side dishes, along with a bowl of steam-cooked, short grain rice. Kimchi, a fermented cabbage dish, is the most common side dish served in Korea and is consumed at almost every meal. Another signature dish, bibimbap, is a bowl of white rice topped with sautéed vegetables and chili pepper paste and can include egg or sliced meat. Bulgogi consists of marinated, barbecued beef.Korea Tourism Organization. “Food in Korea.” Accessed October 10, 2011. visitkorea.or.kr/enu/1051_Food.jsp.

Japan

As in other parts of Asia, rice is a staple in Japan, along with seafood, which is plentiful on this island nation. Other commonly-used ingredients include noodles, teriyaki sauce, dried seaweed, mushrooms and other vegetables, meat, and miso, which is soybean paste. Some favorite foods include the raw fish dishes sashimi and sushi, which are not only popular in Japan, but are also around the world. Typical beverages include green tea and also sake, which is a wine made of fermented rice.Web MD. “Diets of the World: The Japanese Diet.” © 2005–2011. http://www.webmd.com/diet/features/d...-japanese-diet.

The traditional table setting in Japan includes placing a bowl of rice on the left and a bowl of miso soup on the right side. Behind the rice and the soup are three flat plates which hold the accompanying side dishes. Similar to China, chopsticks are used in Japan and are generally placed at the front of the table setting. At school or work, many Japanese people eat out of a bento lunch box, which is a single-portion takeout or home-cooked meal. Bento boxes typically include rice, fish or meat, and cooked or pickled vegetables.

The Middle East

Middle Eastern cuisine encompasses a number of different cooking styles from Asian countries along the Mediterranean, as well as from North African nations, such as Egypt and Libya. In this part of the world, lamb is the most commonly consumed meat and is prepared in a number of ways, including as a shish kebab, in a stew, or spit-roasted. However, kosher beef, kosher poultry, and fish are eaten as well. Other staples include the fruits and vegetables that grow in the hills of many Middle Eastern countries, such as dates, olives, figs, apricots, cucumber, cabbage, potatoes, and eggplant. Common grains include couscous, millet, rice, and bulghur. Popular dishes include Syrian baba ganoush, which is pureed eggplant, and kibbeh, or lamb with bulghur wheat, from Lebanon.Saveur. “Middle Eastern Recipes.” Accessed December 5, 2011. www.saveur.com/solrSearchResu...le\%20Eastern& sitesection=recipes. A flatbread called pita served with hummus, or pureed chickpeas, is another popular dish in this region of the world.

Most people who reside in the Arab countries of the Middle East are Muslim, which can affect their diet. Many Muslims do not consume alcohol or pork. They also observe certain diet-related religious traditions, such as a daytime fast during the month of Ramadan. Other residents of the Middle East include Jews and Christians, and their traditions also affect what foods they eat and how they prepare it. For example, many Jews in Israel keep kosher and follow a set of dietary laws that impact food choices, storage, and preparation.

Breakfast in Asia

To continue the comparison of breakfast around the world, let's examine the first meal of the day in many parts of Asia. In India, the first meal of the day commonly includes eggs scrambled with spices, potatoes, and onions, as well as fresh fruit and yogurt. Breakfast in China often consists of rice complemented by vegetables, meat, or fish. In Korea, a traditional breakfast would include soup made of either beef ribs or pork intestines, a selection of bread and pastries, rice, and kimchi, which is believed to promote intestinal health. Breakfast in Japan does not greatly differ from any other meal. It typically consists of a bowl of steamed white rice, a small piece of fish, a bowl of miso soup with tofu, vegetables, green tea, and occasionally pickled plums called umeboshi. Hot bowls of noodles in broth topped with pork slices, scallions, and bamboo shoots are also common.



Figure **13.8.2**: In the different regions of China, congee is prepared with various types of rice, which results in different consistencies. In Japan, Nanakusa-gayu (七草粥), seven-herb porridge. (CC BY-SA 3.0; Blue Lotus).

Congee is a common breakfast food across Asia. This dish is a porridge made of rice that is consumed in a number of Asian countries, including Vietnam, Thailand, Burma, and Bangladesh. Congee can be prepared both savory and sweet and contain a variety of ingredients, usually meats, vegetables, and herbs. It can be eaten alone or served as a side dish.

The Diversity of Palates and Habits

Around the globe, people enjoy different foods and different flavors. In some cultures, the main dishes are meat-based, while others focus on plant-based meals. You can also find different staples in different regions of the world, including rice, potatoes, pasta, corn, beans, root vegetables, and many kinds of grains. Different flavors are also popular on different parts of the planet, from sweet to salty to sour to spicy.

Food Availability

People tend to eat what grows or lives nearby. For example, people in coastal areas tend to consume more seafood, while those in inland areas tend to structure their diet around locally-grown crops, such as potatoes or wheat. In many developing countries, a large part of the diet is composed of cereal grains, starchy roots, and legumes. However, a number of common staples are consumed worldwide, including rice, corn, wheat, potatoes, cassava, and beans.

Income and Consumption

In addition to regional dissimilarities in diets, income also plays a major role in what foods people eat and how they prepare them. The average global calorie consumption has increased to record levels in recent years. This is a consequence of rising incomes, which have allowed consumers in many regions to expand both the variety and the quantity of food they eat. Among developing countries, the daily intake of calories per person rose by nearly 25 percent from the early 1970s to the mid-1990s.US Department of Agriculture, Foreign Agricultural Service. “Diets Around the World: How the Menu Varies.” Last modified October 14, 2004. www.fas.usda.gov/info/agexpor.../Apr/diets.htm.’ Centers for Disease Control and Prevention. “Caloric Consumption on the Rise in the United States, Particularly Among Women.” NCHS Press Room, February 5, 2004. http://www.cdc.gov/nchs/pressroom/04news/calorie.htm. People in the western world were able to increase their consumption of meat and poultry, fruits and vegetables, and fats and oils. However, those gains were minimal in the poorest countries, where many continue to struggle with hunger and a limited diet.US Department of Agriculture, Foreign Agricultural Service. “Diets Around the World: How the Menu Varies.” Last modified October 14, 2004. www.fas.usda.gov/info/agexpor.../Apr/diets.htm.

Different Ways of Eating

People from different parts of the world consume their food in different ways and what is common in one country may be considered impolite in another. For example, in some areas people eat with their fingers, while in others using a fork is much more acceptable. In some regions of the world, people slurp their soup, while in others they quietly sip it. In some places, diners eat off of individual plates, while in others people sit at a table with a large communal plate from which everyone eats.

No matter where you travel, you will find that food production, purchase, and preparation affect all facets of life, from health and economics to religion and culture. Therefore, it is vital for people from all walks of life to consider the choices they make regarding food, and how those decisions affect not only their bodies, but also their world. Alice Waters, an influential chef and founder of the nonprofit program Edible Schoolyard, as well as an advocate for sustainable production and consumption, has said, “Remember food is precious. Good food can only come from good ingredients. Its proper price includes the cost of preserving the environment and paying fairly for the labor of the people who produce it. Food should never be taken for granted.”Waters, A. “The Art of Eating.” PlanetGreen.com. March 31, 2009. http://planetgreen.discovery.com/fea...eat-green.html.



***Figure* 13.8.2**: *Alice Waters: Edible Education. In this video, Edible Schoolyard founder Alice Waters talks about the value of growing a garden and learning about food.*

Key Takeaways

Many people around the world have access to a wide variety of food and can prepare it any way they choose. However, cuisine remains strongly influenced by location, culture, tradition, and economics. People from all cultures and all walks of life should consider the choices they make regarding food, and how those decisions affect not only their bodies, but also the world.

Discussion Starter

1. Compare and contrast breakfast in different parts of the world. What are common attitudes about the first meal of the day? How are the choices that people make the same? How are they different? Are there any breakfast dishes in common?

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13.E: Food Politics and Perspectives (Exercise)

It's Your Turn

1. Visit a store and study the labels for one kind of processed food. List all of the additives it contains and research them at the library or on the Internet. Why was each substance included during the processing stage?
2. Create a brochure for tourists to explain the kinds of foods they can expect to encounter in one region of the world. Reference a few popular dishes and a few considerations they might need to keep in mind during their travels.
3. How can you move toward a more sustainable diet? Make a list of the kinds of changes you could make to the foods you choose and the ways you prepare them.

Apply It

1. Create a short newsletter for parents explaining the value of home-cooked, family meals. Describe how sitting down together for a few meals each week can benefit different members of the family. You may also wish to include one or two tips that parents can use to encourage their children to make mealtimes a priority.
2. Plan a website that addresses the rising price of food around the world. Describe the look and focus of the main page, along with subsections that you will include. Also provide links to related material already available online.
3. Research one of the different cuisines described in this chapter, such as the Indian or Ethiopian diet. Explore the history of the diet, along with the climate, soil, and other factors that affect the foods that farmers grow and how consumers prepare them. Then create a report to explain your findings.

Expand Your Knowledge

1. Write a short script for a public service announcement that explains the benefits and risks of food additives. What do you believe the public should know about the natural and synthetic substances that are introduced to foods during the processing stage?
2. Summarize in a written discussion why economic experts believe the era of cheap food is over. What factors have contributed to rising food prices around the globe?
3. Draw a comic strip that shows the different facets of a food system for a particular crop, from production to consumption.

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CHAPTER OVERVIEW

14.1: Immigrants as Transformers- The Case for Immigrant Food Enterprises and Community Revitalization

14.1.1: Introduction

14.1.2: Buffalo, New York- The Role of Immigrant- Run Grocery Stores in Shaping Urban Food Environments

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14.1.1: Introduction

> *In the 20th century, the Rust Belt housed industrial powerhouses like the U.S. steel, coal, and auto industries, but today it is entrepreneurial partnerships between immigrants and local communities that are fueling the region's economies. … The WE Global Network recognizes that if we're to remain competitive in the global economy, we must support and maximize the efforts of local initiatives that welcome, retain, integrate, and empower immigrant communities.*
>
> *—David Lubell, executive director of Welcoming America*

David Lubell's words at the launch of "The Welcoming America Global Network"—a regional initiative that promotes the economic contribution of immigrants in the Midwest—represents the core of numerous government programs that have been established in recent years to attract immigrant communities and tap into their potential for economic development (McDaniel 2014). Some initiatives, such as "Welcoming Pittsburgh," aim to provide an immigrant-friendly environment for the newcomers, while others, such as Chicago's "New Americans Plan," focus on promoting immigrant entrepreneurship. Scholarly works, for the most part, echo these initiatives in regard to the impact of immigrants on communities by showing how newcomers have revitalized commercial corridors, occupied vacant housing, and stimulated real estate markets, especially in areas that have experienced disinvestment (Vigdor 2017; Schuch and Wang 2015).

While these studies and initiatives provide a promising case to support immigrant revitalization, the complex and sometimes contested mechanisms and processes through which immigrants reshape their communities are less understood. This is because the contribution of immigrants to community revitalizations is viewed largely through an economic lens, which leaves out the multifaceted ways that immigrants build their communities. The most visible, yet underappreciated, way that immigrants define the boundaries of their environment is by establishing businesses that offer cultural (food) products. The visibility of immigrant food businesses not only (re)shapes the physical environment, but also restructures social and racial processes embedded within the built environment. This chapter explores the contribution of immigrant food entrepreneurs to community development in two neighborhoods, one in Buffalo, New York, and the other in Philadelphia, Pennsylvania. In this chapter, community development encompasses a broader definition to include the ways that immigrants impact the health and well-being of residents by providing increased access to affordable, healthful, and cultural foods. The conditions under which these food enterprises operate (Buffalo) and the interaction between the newcomers and the established residents (Philadelphia) provide an opportunity to unpack some of the complexities that exist in the relationship between immigrants and their environments.

Public health and food-related scholarship has paid a great deal of attention to understanding how the predominant food environment of the host country impacts the health of newcomers. These studies largely focus on the impact of dietary acculturation on health outcomes of immigrants (Zhang et al. 2019). The health and living conditions of immigrants who work on farms, in processing plants, and in the food service industry have also been subjects of many inquiries that illuminate how labor regulations—or the lack thereof—impact some of the most marginalized, yet crucial, actors in the food system (Moyce and Schenker 2018; Mucci et al. 2019). While these studies are important in making visible the cruelty of the food industry, they often present immigrants in the US food system as victims of abuse and discrimination. This narrative focuses on how immigrants are shaped by their new physical environment and does less to argue how newcomers are active agents in reshaping the food systems of their new communities.

Similarly, literature on immigration's effects on receiving communities tends to view immigrants as those in need of assistance and not as agents of change. More often than not, immigrants are understood through a bifurcated cost-benefit framework of analysis (Brettell and Hollifield 2014). This narrative, which runs strong in political debates and public perception of immigrants, centers on the fiscal implication of immigrants and provides a static understanding of the ways immigrants could shape their new communities. In reality, the relationship between immigrants and their new environment is dynamic and interactive. Through pathways such as entrepreneurship, immigrants play an active role in (re)shaping their new environments. The decisions made by immigrant entrepreneurs on where to locate, what products and services to offer, and who to serve have definite impacts on the well-being of communities.

Some local governments celebrate immigrant entrepreneurs as heroic actors who build up communities (Waters 2018). However, they fail to incorporate immigrant businesses in the overall economic development strategies. As a result, the particular needs and challenges faced by immigrant entrepreneurs are off the radar of officials charged with the promotion of small business ownership, such as local chambers of commerce (Center for an Urban Future 2007). To most local governments and scholars, the appreciation for immigrant-run businesses ends with their contribution to generating revenue and increasing the local tax base, and is less concerned with the nature of services and products they provide. All the while, immigrant food entrepreneurs are shaping community food systems around their own needs, culture, and social relations.

The latest wave of immigrants from Asian and Latin American countries has had a significant role in transforming the US food system at both national and community scales. On the national level, these entrepreneurs have introduced new seeds and agricultural practices, formed alternative food supply chains, and shaped the pattern of food production in the United States (Imbruce 2015). On the community level, immigrant entrepreneurs impact the quality and quantity of foods available in a neighborhood by operating food-related enterprises (Emond, Madanat, and Ayala 2012). This is especially important since many immigrant-run businesses are located in places often underserved by the general market, where access to healthy and affordable food is scarce (Kim 2010).

Most public health scholarship that informs public policy and interventions undermines the value of small-scale food stores in healthy food provision, largely because of an overemphasis on supermarkets as the prime outlet for healthy foods (Zhang et al. 2016; Gordon et al. 2011). However, the mixed results of recent supermarket interventions to promote positive diet-related health outcomes have pushed public health scholars to consider the diverse ways that individuals procure food besides shopping at national chain supermarkets (Dubowitz et al. 2015; Cummins, Flint, and Matthews 2014). A handful of studies have examined the potential of immigrant-run food businesses to increase food access and contribute to food security (Emond, Madanat, and Ayala 2012; Short, Guthman, and Raskin 2007). These businesses, despite their small size, often carry a diverse range of products, from meat to fresh produce. A study of Latino grocery stores (tiendas) in San Diego, California, compared the availability, quality, and cost of fresh produce at tiendas with supermarkets and concluded there is no significant difference between the two food markets in terms of access to fresh produce. In fact, the cost of meeting the USDA's recommended weekly produce serving was three dollars lower in tiendas compared with supermarkets (Emond, Madanat, and Ayala 2012). Research shows that particular ethnic diets are beneficial to health, as they are largely based on plant-based dishes (Ooraikul, Sirichote, and Siripongvutikorn 2008). A study of food shopping venues in a diverse community supports this claim by demonstrating an association between shopping at ethnic markets and a lower body mass index among Guyanese participants, arguing that ethnic markets offer access to a diet that protects against obesity (Hosler, Michaels, and Buckenmeyer 2016).

Immigrant food businesses in urban environments increase access to culturally appropriate, affordable, and healthy foods, and rebuild communities while doing so. For example, these businesses provide access to jobs and income, and transform communities by turning once abandoned properties into places for business transactions and social interactions. Immigrant merchants play a critical role in community building by supporting ethnic-based organizations and using their power to influence planning and political decisions that may impact their communities. The success stories of immigrants revitalizing disinvested communities have been embraced and celebrated by local governments and planners (Center for an Urban Future 2007). However, this narrative of immigrant revitalization reflects an incomplete understanding of the dynamic, and sometimes contentious, relationships between immigrants, their new environments, and the established residents.

The remainder of this chapter sheds light on some of the existing challenges that immigrant food entrepreneurs face in creating healthier food environments (Buffalo) and contributing to community and economic revitalization in urban neighborhoods (Philadelphia). The Buffalo case study is a qualitative examination of two Middle Eastern grocers located in a "food desert" who manage to carry healthy and affordable foods in a low-resource environment. The promising examples from Buffalo argue for inclusion of ethnic groceries in healthy food initiatives and financing to leverage these existing community assets in creating healthier urban food environments. The Philadelphia case study uses historical literature, business inventories, field observations, and interviews with storeowners to demonstrate how recent Mexican entrepreneurs successfully revitalized a run-down public food market that used to be owned and managed by Italian immigrants.

My status as a university-affiliated immigrant from the Middle East both helped and hindered my access to these immigrant communities. In Buffalo, I had relatively easy access to Arab business owners. However, my identity did only so much in gaining their trust; the participants were hesitant to speak freely about their perception of the local government. In Philadelphia, my

university-affiliated status was more important than my immigrant status, since to many (undocumented) workers it was not clear "who I am working for." I am grateful to my translator, who not only aided with conducting the interview but also helped to gain the trust of the Mexican community.

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14.1.2: Buffalo, New York- The Role of Immigrant- Run Grocery Stores in Shaping Urban Food Environments

> *Fruits and vegetables are good items for everyone. Everyone wants fresh produce, even American[s]. … If they know I have fresh produce, everyone will come.*
>
> *–Ali,[1] a new Buffalonian grocer of Iraqi heritage*

Realizing the unmet demand for fresh produce in his neighborhood, Ali established a small-scale grocery store in Buffalo, New York, that provides cultural products for customers from Iraq, Turkey, India, and Pakistan and brings access to fresh produce for a broader range of customers who may not have walkable access to healthy food retailers. Ali and his fellow immigrant food entrepreneurs who have settled in Buffalo in recent years are shaping the city's food environment one block at a time.

Buffalo, a Rust Belt city characterized by abandoned and vacant properties, outmigration, and departure of businesses, has seen a slow resurgence in recent years, with the population increasing by 5% from 2005 to 2009 (US Census Bureau 2009). These recent changes can be partially attributed to the arrival of new immigrants and refugees who have diversified their traditional destinations and now settle across the United States. The foreign-born population of Buffalo increased by 40% from 2005 to 2009, a growth rate eight times higher than that of the city overall. These newcomers have changed their neighborhoods in small and incremental ways, by starting businesses and offering newly available products to serve community needs. Despite their role in rebuilding communities, these actors are often invisible in the local government's economic development strategies, which often focus on physical improvement projects to attract large companies and businesses, such as the downtown and waterfront revitalization projects (Shibley, Hovey, and Teaman 2016).

Buffalo's recent economic growth has had little translation into actual development for low-income communities. Today, only a few supermarkets serve the city, and they are often out of the physical reach of low-income residents who don't have access to a private vehicle (Widener, Metcalf, and Bar-Yam 2011). Despite the lack of access to large-scale food outlets, immigrant neighborhoods are home to many small-scale grocery stores that offer fresh produce and culturally appropriate foods. The increasing population of immigrants and refugees begets a growth in demand for cultural products unmet by the general market. As a result, Buffalo has witnessed visible growth in immigrant-run eateries and food businesses throughout the city. As of 2013, the most recent year for which statistics are available, there were 56 ethnic food places, a significant enough number to draw the attention of news outlets and magazines about the growing diversity of Buffalo's food landscape (Kelly 2013).

Using a private business vendor, store audits, and consultation with a community partner, two full-service Middle Eastern grocery stores were chosen from the northern neighborhoods of Buffalo with a foreign-born population share similar to that of the city (7% vs. 9%). The nearest super-market is located outside the neighborhood, in an adjacent suburb with limited pedestrian and public transportation access. While it is classified by the USDA Food Atlas as a "food desert," the neighborhood is anything but "deserted"; it is home to a vibrant commercial corridor of ethnic eateries and grocery stores.

The stores provide a wide variety of dairy products, dry goods, fresh and frozen meat, poultry, and seafood, beans, grains, herbs, spices, and fruits and vegetables. The diverse array of fresh produce sets these stores apart from other small-scale urban food stores. While the quantity of fresh produce may be less than at larger food markets, its availability is critical to the success of these businesses. Both storeowners showed an acute understanding of the market conditions and unmet demands of the residents for fresh produce. They shared the fact that fresh produce attracts customers to their stores, shaping about 10% of their total sale, and increases the overall sale, as those who come for the fresh produce often end up purchasing multiple items.

The variety of foods mimics the line of products available at supermarkets but with lesser-known brands and names. The store audits show that besides a few specialized food items, the main inventory is staple food products found in many cuisines. Thus, it is not surprising that both stores reported that nonethnic customers represent 5%– 10% of their customer base. The immigrant food entrepreneurs, aware of a need to diversify their clientele and services, allocate parts of their stores to catering services. This strategy helps them survive as a small business with low profit margins and to advertise their name to a wider population. The catering divisions also provide face-to-face interaction among community members, which builds social connections and facilitates information sharing among the immigrant communities (Liu, Miller, and Wang 2014).

To evaluate how conventional metrics would assess these stores' provision of "healthy" food, I used a modified version of a previously validated tool known as the Nutritional Environmental Measure Survey (Glanz et al. 2005). Both stores scored relatively high (38 and 24) on a scale of 0 (no healthy foods) to 54 (no unhealthy food), mainly because of the availability of fresh produce and absence of tobacco and alcoholic beverages. However, the limits of this type of metric are significant. For example, the tool does not consider a store's capacity to enable customers to prepare a homemade meal. To Zahra, an Iraqi storeowner with 25 years of business experience, providing convenience for residents where they can meet most of their needs with a one-stop shopping trip is an intentional goal when she selects products for her store. She explains, "Because I am a cook and I am a mom, I know what people will need to prepare meals and I bring them … my customers even ask me to give them recipes."

To provide this breadth of ingredients, these businesses need to navigate multiple challenges to offer culturally appropriate fresh produce at their stores. Ali reported how the absence of ethnic wholesalers in this region impacts his business: "It confuses our customers. They need produce on [a] daily basis, but if they come and they don't find it and they don't know when we will get it again, they may go and never come back again." Since these stores are small, it is not profitable for distributors to provide them with direct delivery. The immigrant storeowners overcome this challenge by making multiple trips to the nearest city with an established network of ethnic wholesalers; both storeowners travel twice a month to Detroit, Michigan, to access suppliers. Making these trips comes with additional costs and challenges for the entrepreneurs, such as arranging truck rentals, incorporating long--distance and time-consuming procurement trips into their schedules, and delegating work responsibilities. Despite the personal efforts that the storeowners make to meet this demand, other factors, such as weather or truck availability, could affect their commitment to offer fresh produce on a fixed schedule.

The immigrant entrepreneurs also need to overcome the challenge of navigating the regulatory environment and establishing relationships with local government agencies. Ali noted that the challenge is to "stick to [the regulations]. The laws are changing every now and then so we have to keep up with changes." To Zahra, the bigger challenge is establishing a relationship with government agencies: "If you are new and nobody knows you, you are gonna get people to trust you … [running the business] used to be harder 'cause they didn't know what we are gonna sell. So we had to explain it to them. We get a lot of stuff in bulk, and we have to package it and label them; it is required by law. They send inspectors to check if we do." Local agencies, such as the County Health Department, may be unfamiliar with ethnic products and their handling, which could delay the licensing process, hence restraining the entrepreneurs' ability to sell and generate revenue in a timely manner.

While not-for-profit organizations, such as the Small Business Development Center, help immigrant entrepreneurs with the start-up process, a staff member from the Office of Licenses shared that local government does not have any formal program or strategy to attenuate their particular challenges. This is especially important since local governments have the capacity to offer financial support to foster healthy food retailing. For example, the FRESH program in New York City offers a combination of tax reductions, sales tax exemptions, and grants for infrastructure changes to operators who meet particular health guidelines. Importantly, the local government could play a central role in connecting local and regional growers with ethnic grocers and distributors/wholesalers. Such a strategy could promote the operation of small-scale grocery stores throughout the city and provide a viable commercial strategy to support the new refugee farmers and growers, currently supported by grant-based nonprofits, with limited capacity to scale up their food production. Finally, the local government could improve their understanding of the needs and challenges of immigrant entrepreneurs by establishing partnerships with ethnic community organizations (see chapter 11 of this volume for Ostenso, Dring, and Wittman's analysis of food policy councils' successes and failures toward this goal in Vancouver). Through such relationships, the local government could better connect entrepreneurs to existing resources, share information about federal and state funding opportunities, and notify entrepreneurs about changes in regulations and laws.

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14.1.3: Philadelphia, Pennsylvania- Continuous Wave of Immigrant Food Entrepreneurs and Community Revitalization

South Philadelphia, a reemerging immigrant neighborhood, is a prime example of how interactions between the new wave of immigrants and the children of the earlier European immigrants have created a vibrant, yet contentious, urban food landscape. This study focuses on two food stores, a Mexican-owned fish market and an Italian American butchery, in the South 9th Street Food Market (hereafter the Market) that provide staple food products and represent enterprises owned by the new wave of immigrants (hereafter new immigrant entrepreneurs) and by the descendants of the earlier immigrants (hereafter old immigrant entrepreneurs).

Noticing the largely African American clientele and diverse array of seafood in a small fish market, one may not immediately assume that a Mexican family owns and runs this store. Jose—a Mexican immigrant who arrived in the United States in 1998—is no stranger to managing his own business. He had years of experience producing and selling garden products prior to his migration to the United States. Describing his experience entering the US food industry, he explains, “I had to shift my business because of need … the need to survive when you arrive to this country. In my first [work] opportunity here I was introduced to the fish market.” That fish market is still owned by an Italian American entrepreneur located not too far away from Jose’s own business today. Working at the fish market not only met Jose’s “need to survive” but also gave him an opportunity to learn new skills and gain necessary market information to establish his own business 20 years later.

The relationship between the old Italian food entrepreneurs and the new immigrant entrepreneurs, largely from Mexico, is a dynamic that has shaped and rebuilt the Market. In the late nineteenth and early twentieth centuries, South Philadelphia was the second-largest Italian enclave on the East Coast, becoming a gateway neighborhood for European immigrants. Upon their arrival, Italian immigrants formed a food market along South 9th Street. The Market was a major employment center for the incoming Italians, often single men, who worked at the Market and lived in nearby boardinghouses. The prosperous years of the Market were short lived; it faced a persistent and gradual decline following World War II, with outmigration of Italian immigrants and their children to the surrounding suburbs. However, the post-1965 wave of new immigrants and refugees from Asian and Latin American countries provided a renewed source of population, labor, and entrepreneurial activity for the Market. There were few Italian American businesses left at the Market when the new immigrants started to open businesses. The contribution of the newcomers to the Market and the real estate in the area flipped the predominant narrative from one that was formally identified as “blighted” by the Philadelphia Redevelopment Agency to one centered on community-led revitalization.

These community changes, however, did not happen in a vacuum. The community-led development occurred in the midst of racial controversies. Jose, in fact, cited his experience of abuse and discrimination at work as a motivation for him to seek self--employment: “I was bad treated because of my look and I am thankful for that because it motivated me to do more things and move forward. I had to go to school to educate myself because of Geno my neighbor. He said that if in his store they speak English then I should learn it too. He was saying the truth and instead of being mad I did the opposite and learned the language with a positive attitude.”

Exemplifying this racist sentiment, nearby business owner Joe Vento attracted national attention to the Market over the years with his anti-immigration rhetoric. A third-generation Italian American himself, who held his own grandparents as the frame of reference for “doing it the right way,” Joe Vento took issue with the undocumented immigrants and their lack of “assimilation,” threatening those who hired undocumented workers and supporting multiple anti-immigration legislative actions locally and nationally. Joe’s tactics were particularly loud and aggressive, but he was not alone in his stance. Many Italian American merchants threatened by the influx of new immigrants used a variety of tactics (e.g., unified awnings showing the business establishment’s years in operation) to remind visitors of the Italian identity of the market and ultimately of its ownership (Vitiello 2014). Geno, son and heir of Joe Vento, did not take the “Speak English or Press 2 for Deportation” sign off his (in)famous steak shop until 2016, against the dying wish of his deceased father.

While these narratives center on tensions over ethnic identity, a closer look into the reciprocal relationship between the old and new immigrant food entrepreneurs provides a detailed picture of the processes that enabled the Market’s revitalization. Many Italian American property owners rent their vacant business spaces to the new immigrant entrepreneurs. The already established physical commercial infrastructure—such as storefronts and warehouses— helps new immigrants acquire spaces for commercial purposes. In return, new businesses have revitalized this once run-down commercial corridor, stimulating growth and bringing vitality back to the Market. This vitality is a result of the diverse products now found at the Market. Once entirely a food market, the Market now

provides access to other essential products and services, such as clothing, sporting goods, and entertainment, that serve the growing immigrant community. The combination of these businesses with the Italian food vendors— which often offer specialty food items such as cheese, olive oils, and handmade pastas—attracts both regular and loyal customers as well as clientele seeking a "cosmopolitan" experience.

The increased diversity of customers has worked in favor of the Italian American entrepreneurs. Francesco, a fourth-generation Italian American butcher, takes pride in serving a racially and economically diverse clientele: "We have a diverse group … we have a large black following … a lot of welfare … we have a large yuppie following now. We have whites, blacks and not as many Asians as we used to have, they now shop at their own supermarket around the corner. We have a mixed Jamaican clientele … they go for their own traditional stuff. You go from a person on welfare to an executive of a company and everybody gets along here. The store on Saturdays is a big melting pot." Francesco has responded to this increased diversity by expanding his business to tap into the growing demand of his customers. Francesco expanded his great-grandfather's small butchery into a large store with two new divisions (catering and poultry) that are managed by his wife and son. Similarly, many Italian businesses have benefited from the increased diversity, as it has forced them to keep expanding their businesses to stay competitive in the market. For example, a small Italian cheese store across the street that opened in 1939 has now evolved into a multidepartment company with its own importing division supporting more than 300 employees.

Instead of following most Mexican food vendors in providing cultural products, Jose chose the fish market based on his personal experience and the profitability of this sector. He explains, "People ask me do you know what color the business is? … I said business is neither black nor white. While the black people say it is black, the white people will say it's white, [I say] it is green, whoever has the money can buy the product." He points to the opportunity he found in the fish market by adding that "African Americans consume a lot of fish. As Mexicans, because of our geographic zone [at home] we don't have it a lot on our daily menu … but African Americans, Africans and Jamaicans have it. I have some products that come from Jamaica. If they ask for a product I will find it for them."

Successful new Mexican food entrepreneurs have managed to open additional stores in the surrounding neighborhoods. Upward mobility centered around individuals' successes has a special appeal in the American narrative of immigration, but the benefit of these success stories goes beyond an individual or a household to influence the community at large. For example, Jose has already helped two of his relatives establish their own fresh produce businesses by providing them with market information, financial support, and access to facilities such as refrigerators. Jose also contributes by shortening and facilitating the self-employment pathway of other community members and by creating additional businesses at the Market, which function as a continuous source of income and taxes. Italian American entrepreneurs have a similar trajectory in sustaining and expanding their businesses, but with a distinct difference: instead of helping their families and relatives to have their own businesses and spread horizontally across the market, they train, employ, and retain them within the same family business. This often results in a vertical and consolidated growth of Italian businesses, providing them with access to increased prosperity and subsequently more power and leverage over the market.

To Francesco and his fellow Italian American entrepreneurs, the Market functions as a "melting pot," which provides them with greater opportunities to grow their businesses. To these businesses, the increasing popularity of the Market among "yuppies" is not a concern but rather a business opportunity. However, beneath the surface of this "melting pot," there exists a complex range of challenges to the success and growth of the Mexican entrepreneurs. To many Mexican businesses, continuous growth of the Market, combined with the fast pace of gentrification in the area, makes them unable to keep up with the increasing rents. Consequently, the very same people who contributed to the growth of the Market may be forced out of their businesses if they do not compete in this "prosperous" market. To be sure, the Market still provides opportunities for Mexican entrepreneurs, as new Mexican businesses have opened in the Market since this study was initiated. However, the growth of businesses does not seem to go hand in hand with their increased power: of the 12 seats on the board of directors at the South 9th Street Business Association, all are allocated to entrepreneurs with Italian heritage. The embedded racial conflicts in the Market and the unequal distribution of power could ultimately cost the Market its newly regained vitality and its "cosmopolitan" status.

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14.1.4: Conclusion

The case studies presented showcase how immigrant food entrepreneurs are increasing access to healthy foods, contributing to community wealth, and rebuilding social and economic dimensions of their receiving communities. These examples demonstrate the multifaceted impact of immigrants on community revitalization and that the process through which the newcomers interact and reshape their new environments is filled with physical challenges (e.g., lack of access to infrastructure) and racial conflicts (e.g., lack of power and control over their environment).

The Buffalo case study shows how small-scale immigrant-run grocery stores are improving food access in urban environments. These ethnic grocery stores are offering healthy produce while navigating multiple systemic barriers, such as lack of access to ethnic distributors and the need to gain the trust and approval of government agencies. Both issues highlight how Buffalo, unlike traditional gateways such as New York City, is relatively new to hosting a diverse group of entrepreneurs. In traditional gateways, immigrants benefit from already established networks and civil societies that play a great role in incorporating immigrants. In Buffalo, such a connection between multiple actors—whether that be government agencies, ethnic community centers, or refugee settlement institutions—needs to be established. Local government—particularly planning, economic development, and public health departments—can play a significant role in initiating such a network by taking a proactive and comprehensive approach toward strengthening the community food system. In the absence of local government support, nonprofit organizations fill this gap. In 2018, United Way of Buffalo and Erie County allocated funding to 13 organizations to strengthen the community's food system, of which two work directly with refugee farmers (Somali Bantu Community Organization) and immigrant food businesses (West Side Bazaar). However, the degree to which these organizations work and speak to one another is unclear (Niagara Frontier 2018). Connecting ethnic grocers to refugee producers and regional farmers, supporting the establishment of a food hub, training health and licensing staff about ethnic food products, and effectively disseminating information are among the many ways that local government could play an active role in promoting the businesses of these community actors.

The Philadelphia case study provides an example of how immigrant food entrepreneurship is playing a central role in market revitalization. In fact, the interaction between the old and new immigrant food entrepreneurs accomplished the same goals sought by many community economic development professionals who focus on both people and place- based strategies, such as training a new generation of entrepreneurs and stimulating development in a previously run-down area.

The city government in Philadelphia acknowledges the contribution of immigrants to the city's growth and strives to provide a welcoming environment to protect the well-being of the immigrant communities, whether through mandating language access to all city services or declaring Philadelphia a sanctuary city. However, the local government tends to focus more on the outcome (i.e., revitalization) rather than the process that could enable or hinder the incorporation of the newcomers. Scholars argue that a promising outcome of immigrant revitalization is conditioned on the social, political, and economic context of their receiving communities, where a hostile and anti-immigration attitude could hamper immigrants' incorporation (Reitz 2002). This has been observed to some degree in the case of the South 9th Street Market. On the surface, the Mexican entrepreneurs have become economically incorporated by joining the Market and establishing businesses. However, the existing racial conflicts have prevented the newcomers from becoming fully integrated within the Market, as they are often excluded from decision-making processes that could ultimately impact their businesses. In this case, the overall pro-immigration approach of the city government could only do so much to protect immigrants, leaving the newcomers to navigate ethnic conflict and tensions with the established residents on their own. A prime example of individual-level effort is the owner of South Philly Barbacoa, a Mexican restaurant in the Market that has gained national recognition after being featured on multiple cooking shows and documentaries. The owner uses her own undocumented status and newly gained platform to advocate for the rights of undocumented workers in the food industry, even if that means being more visible to the Immigration and Customs Enforcement agents who have been actively present in South Philadelphia since 2017.

This chapter demonstrates the opportunities that immigrant food entrepreneurs create in their new environments while giving a reminder that urban food environments are extremely diverse, complex, and contentious places. Until the day that these community actors' successes, needs, and challenges are formally incorporated into cities' plans and policies, local policymakers will continue to create policy for urban food environments that remains ignorant of some of those environments' most transformative actors.

Note

1. All names are changed to protect the identities of the study participants.

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CHAPTER OVERVIEW

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14.2.1: Introduction

Sitting at an English-language school in Anchorage, Alaska, a middle-aged Angolan woman called Nattat[1] distinguished the multifaceted meanings of "local food." Local food in Angola is "food from home," whereas local food in Anchorage is "food from here." Her definitions contrasted the mainstream understanding of "local"[2] that I came to query in Anchorage, where the Alaskan government has mobilized to increase in-state food production in order to address the state's food security challenges. For Nattat, her foodscape is constructed through these distinctions of familiarity and unfamiliarity. She practices these distinctions through her desire to try local foods in Alaska and by interchanging traditional Angolan flavors for more commonly found ingredients to make fufu. Fufu, a pastelike corn flour dish widespread in Africa, is her favorite dish from home. In one sense, Nattat's fufu utilizes ingredients that evoke a familiarity with her home in Angola. She associates local food with the connection between fufu and Angola and her home. However, when describing how she makes fufu in the United States, she said, "You can find the corn flour here. It's actually the Spanish version, which is the maize flour that the Spanish people use and that's what I use." When I asked if the taste compares to eating it at home in Angola, she said, "No, not really. But it's edible," identifying unfamiliarity in the ingredients disassociated from home.

Nattat's retelling of making fufu demonstrates her distinction of food from here and food from home. While she can't find all the ingredients to make fufu in Alaska, she reassembles the recipe with food from here in order to try and make a dish that is comforting and familiar in an unfamiliar place. These re-creations of familiarity are reassembled through the global movement of foods and recipes from her home country to Anchorage. Komarnisky (2009) terms this a foodscape, where food plays the dual role of being connected to a place and connecting places. This dual role of food is important in understanding how "local foods" create an invisible barrier to participation and comfort in the daily food practices of a growing population of immigrants and refugees residing in Anchorage, Alaska.

Conversations about "local food" within race, class, and nutrition inequalities suggest that food systems require understanding the experiences and categories of belonging that can inadvertently exclude immigrant and refugee communities. Since the rise of the term "local food" in the first decade of this century, in movies like Robert Kenner's Food, Inc. (2009), popular books like Michael Pollan's The Omnivore's Dilemma (2006), and quick industry usage in marketing, it has been dominated by imagery of food sourcing within state borders or predefined spatial or geographic boundaries. "Local food" has come to be associated with increased traceability, quality of food, and trust in exchanges between producer and consumer (Hinrichs 2015). While these values benefit overall environmental health and community health, the rhetoric of "local" as a specific distance mobilizes notions of food locality that perpetuate a specific white imaginary around food systems (Guthman 2008a). The alternative food discourses that are supported in farmers markets and "local food" systems disregard subjects and communities that utilize practices not yet recognized by dominant narratives within local food movements. Purchasing and cooking practices are further marginalized through race and class inequalities in health and nutritional access (Slocum 2006; Drewnowski and Specter 2004; Pothukuchi and Kaufman 1999) and land resource access in urban food systems (White 2011a, 2011b) and urban food justice movements (Loo 2014; Gottlieb and Joshi 2010). While outside the legal legitimation that occurs in "agricultural racial formations" or the everyday experiences of racial exclusions and "othering" (Minkoff-Zern et al. 2011), I argue that a local food movement similarly constitutes an acceptable type of local food that makes visible subjects of those who participate in purchasing and consuming local foods grown within a specific geographical distance.

Nattat's dual meaning of "local food" shows what is lost when neglecting diverse understandings and practices of local food. The established use of the term creates a binary of acceptable and unacceptable food consumers, segregating those who do not or cannot support local food (DuPuis and Goodman 2005; Valiente-Neighbours 2012). I use ethnographic cases of immigrants' and refugees' experiences to show the limits of local food movements mobilized in the popularity of farmers markets, community-supported agriculture programs, the US Department of Agriculture's defining of local and regional food systems, and the sourcing of local foods by large food retailers in Alaska (Hinrichs 2015). Immigrants and refugees challenge the concept of "local" in the food movement and push sustainable and local food systems3 to better consider the migration of foods and peoples. Excluding how foods and peoples move becomes especially harmful when discourses of cultural foodways are minimized in sociopolitical decision making regarding what counts as local food and what it means to participate in growing local food.

To complicate the local food concept (Hinrichs 2015, 2003; Ostrom 2006) within the reality of the local-global interplay of cultural identity and the creation of local diets (Ohnuki-Tierney 1994; Watson and Caldwell 2005), scholars offer solutions for a deeper

cross-cultural understanding of the unique needs and contributions of immigrant communities. These solutions take into account how food is utilized in “longing for home” and the “painful struggle to accommodate to new ways of being in the world” when placed within the context of Michael Pollan’s “food rules” (Pollan 2008; Mares 2012, 335). Nattat’s description at the start of this chapter of local food as food from home and food from here encapsulates how these shifts in purchasing and cooking practices to accommodate unfamiliar ingredients requires that localness not be static or monolithic but move beyond spatial boundedness toward relationality, contextuality, and translocalism (Appadurai 1996; Komarnisky 2009). I utilize the definition of translocality, building from the work of Holtzman (2006), Choo (2007), and Conradson and McKay (2007), to describe the relationship between food and people in the process of ongoing emplacement, commitments to families and communities, and emotional and material affiliations. Nattat’s story is only one example of how food can express familiarity and unfamiliarity, where “the absence of familiar material culture, and its subtle evocations of home, is surely one of the most profound dislocations of transnational migration” (Law 2001, 277). This ethnographic project details how unfamiliarity exists in different modes for immigrants and refugees navigating the multiple layers of nonbelonging created through “local food” systems.

Food becomes the material object for reflection on the arrangements of power that allow for the inclusion and exclusion of peoples. It acts as a symbol of belonging to a food movement or recognition of how cultures establish a local food system not represented by the dominant food movements (Alkon and Vang 2016; Mintz 1985; Law 2001). This chapter aims to create greater understanding of how immigrant and refugee communities understand their roles in local food production while adapting familiarities of foodscapes from their home countries to Anchorage, Alaska.

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14.2.2: Researching Transnationalities in Anchorage, Alaska

This chapter is based on ethnographic research conducted with immigrants representing 19 countries and refugee farmers from Bhutan residing in Anchorage, Alaska, in summer 2015. Given its geographic location, Alaska is not widely recognized for its immigrant and refugee communities, but it has recently gained press coverage in state and national newscasters' and academic scholars' reporting of Anchorage's diversity (Saleeby 2010; Jessen 2011; O'Malley 2015; Allen-Young 2014). Among Alaska's growing immigrant population, Native Hawaiians and Pacific Islanders made up the fastest-growing communities, increasing by 73% between 1990 and 2000. And the Latino/a community saw substantial growth of 45.2% in that same time frame (Bibbs 2006). In addition, refugees began arriving in Alaska in the early 1980s and have been supported by Catholic Social Services' Refugee Assistance and Immigration Service, a state and federally funded resettlement program in Alaska (Saleeby 2010; Tsong 2004).

Since the 1970s, Alaska has been addressing food security through sustainable agricultural systems given Alaska's precarious geographic and political location, caught between government protection of resource extraction, subsistence hunting shortages, and environmental uncertainties resulting from record high temperatures in both summer and winter (Hodges Snyder and Meter 2015; Stevenson et al. 2014). Alaska's food security is addressed through programs and research conducted by community food organizations, government agencies, academics, cooperative extension agents, and the Alaska Food Policy Council (Stevenson et al. 2014). These models for addressing food security would benefit from an understanding of how diverse peoples participate within these parts of Alaska's food system.

To explore these questions about inclusion of a growing immigrant and refugee community in Anchorage's local food movement, I utilized participant observation and semistructured interviews at various sites across Anchorage in summer 2015, including community gardens, farmers markets, English-language centers, and refugee assistance program sites. To recruit participants, I relied on connections with local organizations, including a farm-to-market program and an English-language center. These two sites were essential in connecting with participants and providing sites at which to conduct participant observation in spaces directly related to the area's local food scene. Through semistructured interviews, my goal was to better understand the nuances of lived experiences as an immigrant or refugee in gaining access to food needs and desires, participation in local food practices, and understanding of how local food differs between their home countries and Anchorage. I asked questions to compare experiences between their home country and Anchorage regarding access to foods, food practices, "good foods," and "local foods." I interviewed 20 people, 14 women and 6 men, who have lived in the United States between three months and 38 years. Of these participants, seven people work in food-related jobs at farmers markets, grocery stores, or restaurants.

In this chapter, I first situate Anchorage, Alaska, as an important site for exploring current trends in urban food systems. I then examine how refugee farmers from the Growing Community Gardens (GCG) program and other immigrant residents understand what it means to be part of a "local food" system. I close with the challenges and opportunities through which food scholars, food movement participants, and policymakers can better connect meanings of locality, as food from here and food from home, to create a local food system accessible to immigrants and refugees living in urban spaces.

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14.2.3: Constructing Food Landscapes and Connecting Alaska

Alaska's long histories of a locally producing agricultural sector (Davies 2007; Francis 1967; Lewis and Pearson 1990) and subsistence-based Alaska Native cultures (Loring and Gerlach 2009; Lee 2003, 2002; Kancewick and Smith 1991) set the context for Alaska's diverse food system guided by state laws, federal laws, and food development programs. After the US government purchased Alaska from Russia in 1867, Congress passed the Homestead Act of 1898 to set up experimental agricultural stations throughout the state, build agricultural infrastructure, and move a workforce of 202 families from the Lower 48 states to generate Alaska's agricultural industry (Davies 2007; Haycox 2002). With the economic downturn leading into the Great Depression, providing food for the state's population became a priority. Federal policymakers provided moving costs and supplies to families transplanted from the Midwest into preconstructed barns and houses to farm north of Anchorage-Matanuska Valley (Meter and Phillips Goldenberg 2014). This access to farmland and agricultural development from the government started a history of family farms, homesteaders, and land-use practices that later influenced today's food system meant to sustain the state's food sufficiency and supply Anchorage markets.

Food security in Alaska, as defined by Loring and Gerlach (2009, involves a food system that supports biophysical, social, and ecological health, yet continues to be strained by fluctuations in oil prices and global costs of food (Meter and Phillips Goldenberg 2014). In order to address these strains, Meter and Phillips Goldenberg (2014) suggest that Alaska's future food system must be fueled through local resources and a renewed interest and investment in local capacity building or residents' food access may suffer from the scarcity and rising costs of fossil fuels. However, Alaska's food system is currently reliant on energy-intensive imported food and climatic changes that have the potential to strain 95% of the food that Alaskans purchase from out of state (Alaska Cooperative Extension Service 2006; Meter and Phillips Goldenberg 2014). The state's strategy to localize Alaska's food system, defined as in-state production, is to reduce the amount of food imported from the Lower 48 states by developing small-farm, greenhouse, and aquaculture production.

The Alaska Department of Natural Resources (2013) developed the Alaska Grown labeling campaign to promote the production and consumption of food grown within the state. This project stems from the US Department of Agriculture's definition of "local food" as "marketing of food to consumers produced and distributed in a limited geographic area" (USDA 2016). This model does not explicitly assign a specific distance to the term "local" but still aligns with dominant definitions of locality, effectively limiting perceptions of the local to a confined space within Alaska and belonging to Alaska. As this research investigates how Alaska's residents take part in local food system programming where food is grown within the state, it becomes clear that this limited perception of "local food" ostracizes the cultural histories and traditions that Alaska's residents participate in and actively construct.

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14.2.4: Navigating the Familiar and Unfamiliar

Fatima fumbled with the large bundle of keys in her hand as she sat across from me in the lobby on the University of Alaska—Anchorage's campus. "In America, for me, I have to shop like either twice a week or once a week 'cause of the work schedule, my three children, and the stores are bigger. I have to jump from store to store to find what I want to cook. [In Jordan], we don't have to worry about it, even if you work, you just walk by the store and pick up what you're gonna cook" (interview, August 7, 2015). Her discomfort is visible in her body language, and the keys still shifting in her hand amplify her discomfort in having to shop for food in a food system unfamiliar to her. Here, she is describing two places. One place is home, a foodscape that was built for the types of foods that she recognizes and can easily find. Another place is here, a foodscape that is not recognizable to her and results in the invisible discomforts that marginalize her food decision making.

Fatima describes how to make beef and rice stews or couscous and grilled chicken down to the spices in each dish. Her description of these processes builds a menu of foods that she describes as local food in Jordan. Locality, as Fatima distinguishes it, is defined as the dishes frequently served in homes in Jordan, dishes that she knows well enough to be able to provide me with a step-by-step process for preparing them. But when asked to define "local" in Alaska, she stuttered and searchingly said, "I don't think there is anything local. Mmmm local I think … when you say local I think the things that grow up in Anchorage, or Alaska" (interview, August 8, 2015). In her unfamiliarity with Alaska, she assumes that local foods are those that are produced within the state, disassociated from the foods cooked in people's houses or the relationality of food sharing she associates with Jordan's local foods. While her definition of local food aligns with the Alaska Grown definition, she points to an important distinction: that local food is food from a place that evokes a sense of familiarity and home. Fatima embodies these distinctions of local food through her discomfort in talking about grocery shopping in Alaska and her ease in talking about shopping in Jordan. She describes shopping at a halal store on Mountain View Drive in Anchorage:

"Even though it's like an African store, [the storeowners] have items that have Arabic writing. If it has English and Arabic writing, I know what it is. But some of them have their own language or [the storeowners] tell you, 'I don't know what this is, how do you guys use this?'" (interview, August 7, 2015). She is able to navigate different shops to find familiar foods to create the local Jordanian dishes in her home in Alaska. But more importantly, her desire to be able to find familiarity through local foods, as food from home, showcases the type of exclusion that creates discomfort in a place or emphasizes an inability to perform certain food purchasing or consumption practices (Slocum 2007). By seeking the familiar through various ingredients found in stores throughout Anchorage, Fatima must navigate barriers of unfamiliarity that exclude her from Anchorage's food system and the types of foods that count as local in Alaska and in Jordan.

These landscapes of invisible barriers to access are expressed in locations of large-box grocery stores like Fred Meyer or Carr's. Carlos, a middle-aged Colombian man, describes how these stores differ in accessibility of foods based on the neighborhood where they are located. He gave the example of the Penland Park Carr's, which although considered a large-box grocery store sells nopanelles and yucca, produce that he says you cannot find in other Carr's stores or other large-box grocery stores:

Then if you go three miles into Midtown and shop at the Midtown Carr's, like in the very center of the Sears mall, that one will have almost nothing compared to the Penland Park one. It won't even seem like the same store. You'll have like your apples, your oranges, but you're not going to find that much of a variety in the ethnic foods. And it gets even weirder when you go down Northern Lights heading west maybe another 1.4 mile[s] away to Carr's Aurora Village, where that one is really, it's like maybe a yuppie food store. They have lots of produce, then they have a big organic section, but they're definitely thin on sort of the ethnic foods like foods that are specific from certain regions or where people will recognize specific labels. (interview, August 9, 2015)

Understanding where ingredients from home are located in Anchorage can better serve immigrants and refugees in food access (Taylor and Ard 2015). However, this funneling of food access into particular neighborhoods creates borders of inclusion and exclusion in food systems. This form of exclusion, such as the racial makeup of neighborhoods and familiarity with stores and types of food, can obscure avenues of access to "local foods" and familiarity. When these neighborhood particularities are couched within histories of whiteness in the food system (Guthman 2008b), then exclusions by ethnicity and race and food create perceptions of what foods and food resources are recognized as part of Anchorage's local food movement. Fatima shows how familiarity with stores and certain types of stores allows her access to her local foods in Jordan that she cooks at home. But traveling between stores like the halal market or large-box grocery stores showcases the ethnic and racial boundaries of Anchorage's urban landscape. Places like the halal market or a Korean grocery store, frequently visited by GCG farmers, are not

given the same recognition in local food movements as the Alaska Grown products found in some large-box grocery stores, nor are they equally accessible on public transportation routes or main roads. The distinctions between these large-box grocery stores of carrying either organic foods or "ethnic foods" further pushes categorizations of places of belonging within the "food rules" of purchasing organic or "local" foods. Aside from these large-box grocery stores in Anchorage, farmers markets became important sites for the marketing of Alaska Grown products and engagements of refugee farmers in Anchorage's local food movement.

While refugee farmers rely on purchasing networks within an immigrant and pan-Asian community in Anchorage to acquire foods from home, these differ from the foods from here, or the vegetables that they sell at three farmers markets in Anchorage. These differences between foods from home and foods from here are based on how the refugee farmers understand what is considered local food based on the dynamics they see at the markets. I frequented three farmers markets in Anchorage based on where GCG farmers sold their produce. These examples showcase the most visible forms of exclusion in the creation of a "local food system."

Puja, a Bhutanese farmer at GCG, believes that "local food" is grown in Alaska, much like the kale he was selling at the market. After the market, Puja hands me a plastic grocery bag filled with leftover kale, suggesting I take it home. The program coordinator at GCG said, "After we decided to grow kale at the garden, because I knew that it would sell well at the farmers markets, they wanted to take it home to eat. They replaced it for a green in a Bhutanese dish, but came back the next day saying, 'Anne, why do you like this? It's not good.'" The gardeners at GCG continue to grow kale because it is one of their best-selling products at the markets. Individual gardeners like Puja and Suba now grow kale in their own gardens to sell at the markets. Suba said, "Puja and I sell this one (pointing to sesame leaves on the market table) instead of [sesame leaf] seeds because no one eats [sesame leaf seeds]." Puja and Suba's affinity for vegetables that they perceive as nonpreferable by white customers at the farmers markets is supported by a normalness of cultural practices that go unacknowledged within community food movements, such as local food movements (Slocum 2006). Hegemonic discourses of "local" perpetuate normal behaviors, such as those performed at farmers markets, by overlooking how refugee farmers are excluded in the consumption of local foods despite being involved in their production. Puja and Suba navigate the unfamiliarity of local foods by trying to eat kale, but, similar to Nattat and Fatima, resort to finding ways to make familiar foods in the confines of their homes while engaging in a food system unfamiliar to them. Thus, Puja and Suba point to a disconnect of local food systems: while farmers markets bring consumer and producer closer, they only do so for particular types of consumers and producers who can access the local food movement. Suba started gardening with other Bhutanese refugee farmers in 2012 and has continued to farm with GCG while also growing produce for her own consumption at other community gardens. Her understanding of access to farmers markets is determined by what she sees as common behaviors of vendors at the three farmers markets that I visited with her. The GCG program coordinator, Anne, told me that when Suba started selling her own produce, she was adamant about selling underneath the same tent as GCG because she was not able to purchase a tent on her own and she wanted to look like all the other farmers. Anne said, "I've been trying to get Puja and Suba to sell at [the other market] because they live over there, but Suba doesn't want to because they don't have a tent. She thinks that she doesn't look official [Anne's emphasis] unless she has a tent. I told them I wouldn't mind buying them a $30 tent so that they could sell their stuff separately at the market, but they declined" (conversation from August 5, 2015). For Suba, the unspoken rules of farmers market displays act as a barrier to feeling like she could be a legitimate vendor at the farmers markets.

At a Thursday market, Suba nudged me to the front of the table as an older white woman approached the GCG market stand. The woman looked directly at me and asked me about Suba's sesame leaves that were neatly bundled with a rubber band at the stem. I encouraged Suba to tell the woman about how she cooks them at home. Suba nervously looked at me and then began talking to the woman about eating sesame leaves with rice. Suba nodded me over to where she was standing and leaned close to my

ear, whispering, "Sarah, I need you to speak with [the customers]. You know English better than me and can sell." She was afraid that if she couldn't speak English well enough, then she wouldn't be able to sell her sesame leaves. Suba's idea of belonging at the farmers market developed from her perceptions of white farmers who speak to customers in a native-English accent and display their produce under tents. In these cases, Suba and Puja's experiences show how the outward appearance of their participation in the local food scene of Anchorage hides the barriers that they, as immigrants and refugees, are facing from truly feeling like agents within this scene. The inclusion of refugees and immigrants as producers of local food falls into the "local trap," defined as an inherently good quality of the "local" (Born and Purcell 2006). Without attention to the weaknesses or complexities of what it means for these immigrants and refugees to produce local food, the local trap makes it easier to see only the benefits of producing local food while ignoring how the participation of immigrants and refugees in mostly white farmers markets puts them on the peripheries of local food movements.

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14.2.5: Conclusion

While the immigrants and refugees I met while selling at farmers markets, growing vegetables in community gardens, and working in Anchorage's restaurant industry have carved out a niche for themselves in Anchorage, they remain on the peripheries of dominant definitions of the "local food" movement. For them, "local food" is not just something that is grown in Alaska, or "of Alaska" as Nattat described. Rather, it is transformed as it moves between places called home or here, where immigrants and refugees find opportunities to bring familiar flavors, produce, and practices from their home countries to Alaska. However, these familiar and unfamiliar practices further illuminate the invisible barriers by which the "local food" movement further ostracizes the translocal nature of how these immigrants and refugees create their own local food systems. Despite providing the labor that grows these local foods, immigrants and refugee farmers continue to exist just outside the borders of alternative food practices by providing labor and vegetables to fill a whiter and wealthier demographic's table. These local food spaces do not resonate with their food needs and result in their having to obtain multiple garden plots to grow "food from here" for white customers at the market and "food from home" for their own families. These farmers earn an income from farmers markets but are doubly burdened with expending labor in local food spaces while facing barriers to inclusion in a local food system. These limiting factors of spatial proximity disproportionately favor family farms, which own the majority of agricultural land, and exclude refugee and immigrant farmers expending their energies and land resources to feed a local food movement that does not accept their own practices and vegetables as part of that system.

This chapter has offered insight into the lives of a few immigrants and refugees living in Anchorage, Alaska, and their understandings of the dynamic definition of "local food." These narratives are personal and relatable in that they describe the complexities of how immigrants and refugees make sense of their new places of settlement through food practices and food choices. Thus, they reveal the importance of access to culturally important foods. By rooting my analysis of local foods in these narratives, I show the importance of understanding the multiple layers of local foods that are applied in home countries, in Anchorage, Alaska, in farmers markets, and in homes. I call for greater attention to those who remain at the peripheries of these dominant food movements in the United States and how these movements continue to foster exclusions regarding what it means to be "local." Alongside many of my fellow chapter authors in this volume, my recommendation is not for a new definition of "local" but rather for more attention to how immigrants and refugees are carving out spaces of familiarity by connecting home countries and countries of settlement through the multiple meanings of food that can extend translocal foodscapes into "local food" systems. Through a more attentive perspective of what "local food" means, policymakers, scholars, and food movement participants may be able to foster greater opportunities for these populations that recognize that "local foods" can exist as "food from home" and "food from here."

Notes

1. The names of all persons and organizations have been changed.
2. I utilize "local" in opposition to the mainstream definition of local foods as foods within a specific geographic distance.
3. As illustrated by Pollan (2008), Nestle (2013), Berry (2010), and Lappe (2010).

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