Biology of Aging

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PART I

CHAPTER 1: INTRODUCTION TO HUMAN AGING

1. An Introduction to the Human Body

Introduction

Though you may approach a course in biology of aging strictly as a requirement for your field of study, the knowledge you gain in this course will serve you well in many aspects of your life. An understanding of aging is not only fundamental to any career in human services, but it can also benefit your own health. Familiarity with the human body can help you make healthful choices and prompt you to take appropriate action when signs of illness arise. Your knowledge in this field will help you understand changes to the human body through out your own and others life times. Additionally you will gain a knowledge base so that you can better understand future news about nutrition, medications, medical devices, and procedures. At some point, everyone will have a problem with some aspect of his or her body and your knowledge can help you to be a better parent, spouse, partner, friend, colleague, or caregiver.

This chapter begins with an overview of the human body and a preview of the body functions. It then covers the characteristics of life and how the body works to maintain stable conditions. Next the chapter will cover the standard methods used to study aging, rates of aging, and general changes to the body as it ages. It ends with standard terms related to aging that will serve as a foundation for more comprehensive information covered later in the text.

2. Structural Organization of the Human Body

Before you begin to study the aging of the human body, it is helpful to consider its basic architecture; that is, how its smallest parts are assembled into larger structures. It is convenient to consider the structures of the body in terms of fundamental levels of organization that increase in complexity: subatomic particles, atoms, molecules, organelles, cells, tissues, organs, organ systems, organisms and biosphere (Figure 1.3).

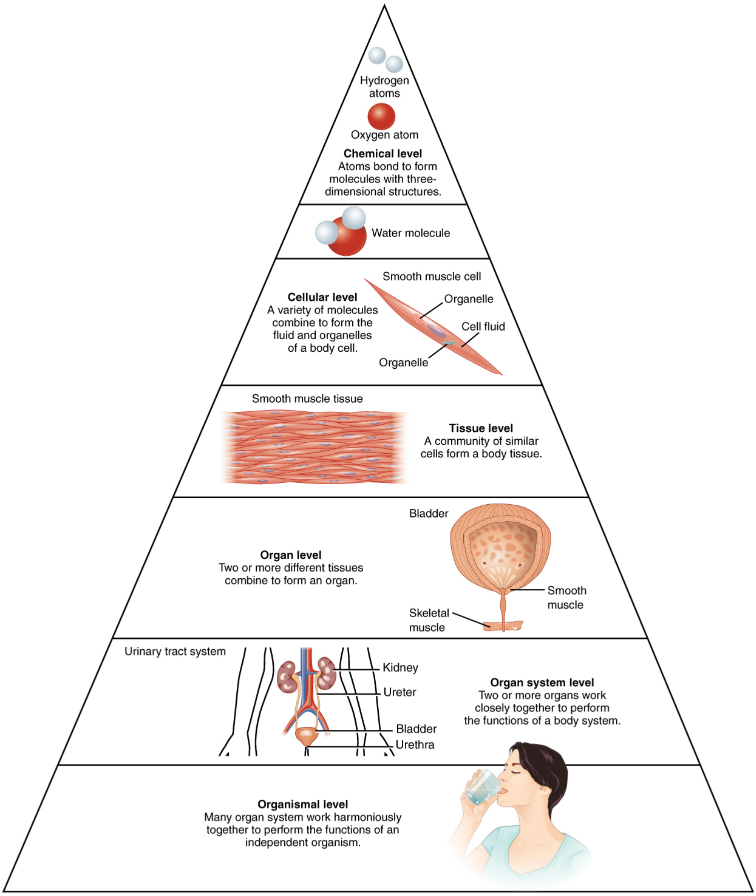


Figure 1.3. Levels of Structural Organization of the Human Body
The organization of the body often is discussed in terms of six distinct levels of increasing complexity, from the smallest chemical building blocks to a unique human organism.

The Levels of Organization

To study the chemical level of organization, scientists consider the simplest building blocks of matter: subatomic particles, atoms and molecules. All matter in the universe is composed of one or more unique pure substances called elements, familiar examples of which are hydrogen, oxygen, carbon, nitrogen, calcium, and iron. The smallest unit of any of these pure substances (elements) is an atom. Atoms are made up of subatomic particles such as the proton, electron and neutron. Two or more atoms combine to form a molecule, such as the water molecules, proteins, and sugars found in living things. Molecules are the chemical building blocks of all body structures.

A ***cell*** is the smallest independently functioning unit of a living organism. Even bacteria, which are extremely small, independently-living organisms, have a cellular structure. Each bacterium is a single cell. All living structures of human anatomy contain cells, and almost all functions of human physiology are performed in cells or are initiated by cells.

A human cell typically consists of flexible membranes that enclose cytoplasm, a water-based cellular fluid together with a variety of tiny functioning units called ***organelles***. In humans, as in all organisms, cells perform all functions of life. A ***tissue*** is a group of many similar cells (though sometimes composed of a few related types) that work together to perform a specific function. An ***organ*** is an anatomically distinct structure of the body composed of two or more tissue types. Each organ performs one or more specific physiological functions. **An *organ system*** is a group of organs that work together to perform major functions or meet physiological needs of the body.

This book covers eleven distinct organ systems in the human body (Figure 1.4 and Figure 1.5). Assigning organs to organ systems can be imprecise since organs that "belong" to one system can also have functions integral to another system. In fact, most organs contribute to more than one system.

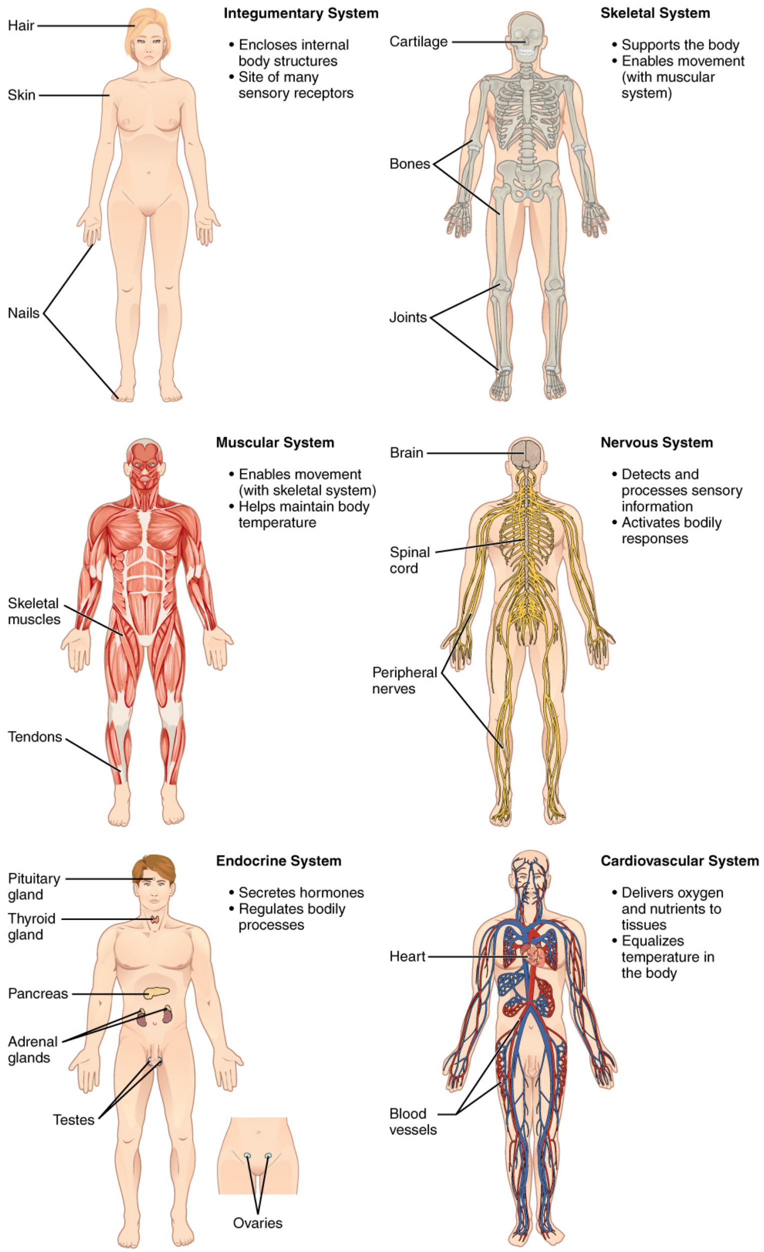

Integumentary System
• Encloses internal body structures
• Site of many sensory receptors
Hair
Skin
Nails
Skeletal System
• Supports the body
• Enables movement (with muscular system)
Cartilage
Bones
Joints
Muscular System
• Enables movement (with skeletal system)
• Helps maintain body temperature
Skeletal muscles
Tendons
Nervous System
• Detects and processes sensory information
• Activates bodily responses
Brain
Spinal cord
Peripheral nerves
Endocrine System
• Secretes hormones
• Regulates bodily processes
Pituitary gland
Thyroid gland
Pancreas
Adrenal glands
Testes
Ovaries
Cardiovascular System
• Delivers oxygen and nutrients to tissues
• Equalizes temperature in the body
Heart
Blood vessels

Figure 1.4. Organ Systems of the Human Body

Organs that work together are grouped into organ systems.

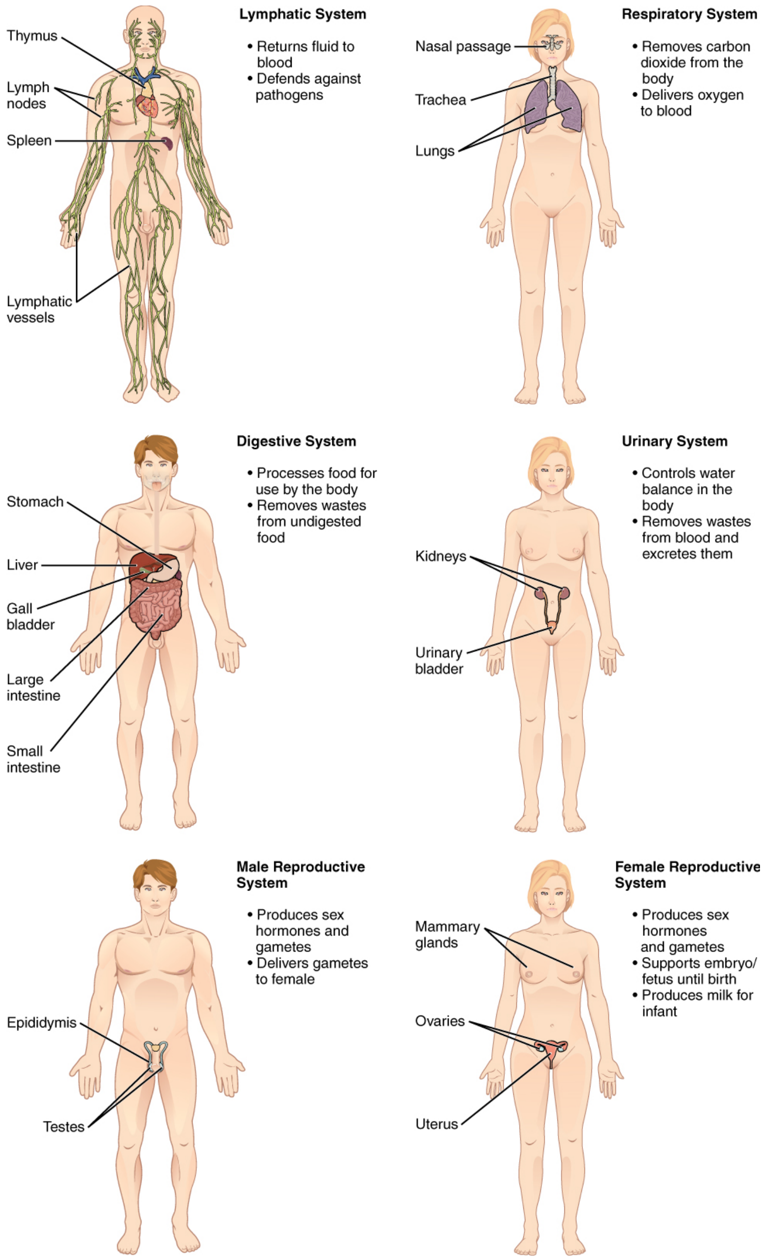


Figure 1.5. Organ Systems of the Human Body (continued)

Organs that work together are grouped into organ systems.

The organism level is the highest level of organization. An ***organism*** is a living being that has a cellular structure and that can independently perform all physiologic functions necessary for life. In multicellular organisms, including humans, all cells, tissues, organs, and organ systems of the body work together to maintain the life and health of the organism.

3. Functions of Human Life

The different organ systems each have different functions and therefore unique roles to perform in the human body. These many functions can be summarized in terms of a few that we might consider definitive of human life: organization, metabolism, responsiveness, movement, development, and reproduction.

Organization

A human body consists of trillions of cells organized in a way that maintains distinct internal compartments. These compartments keep body cells separated from external environmental threats and keep the cells moist and nourished. They also separate internal body fluids from the countless microorganisms that grow on body surfaces, including the lining of certain tracts, or passageways. The intestinal tract, for example, is home to even more bacteria cells than the total of all human cells in the body, yet these bacteria are outside the body and cannot be allowed to circulate freely inside the body.

Cells, for example, have a cell membrane (also referred to as the plasma membrane) that keeps the intracellular environment—the fluids and organelles—separate from the extracellular environment. Blood vessels keep blood inside a closed circulatory system, and nerves and muscles are wrapped in connective tissue sheaths that separate them from surrounding structures. In the chest and abdomen, a variety of internal membranes keep major organs such as the lungs, heart, and kidneys separate from others.

The body's largest organ system is the integumentary system, which includes the skin and its associated structures, such as hair and nails. The surface tissue of skin is a barrier that protects internal structures and fluids from potentially harmful microorganisms and other toxins.

Metabolism

The first law of thermodynamics holds that energy can neither be created nor destroyed—it can only change form. Your basic function as an organism is to consume (ingest) energy and molecules in the foods you eat, convert some of it into fuel for movement, sustain your body functions, and build and maintain your body structures. There are two types of reactions that accomplish this: ***anabolism*** and ***catabolism***.

- ***Anabolism*** is the process whereby smaller, simpler molecules are combined into larger, more complex substances. Your body can assemble, by utilizing energy, the complex chemicals it needs by combining small molecules derived from the foods you eat
- ***Catabolism*** is the process by which larger more complex substances are broken down into smaller simpler molecules. Catabolism releases energy. The complex molecules found in foods are broken down so the body can use their parts to assemble the structures and substances needed for life.

Taken together, these two processes are called metabolism. ***Metabolism*** is the sum of all anabolic and catabolic reactions that take place in the body (Figure 1.6). Both anabolism and catabolism occur simultaneously and continuously to keep you alive.

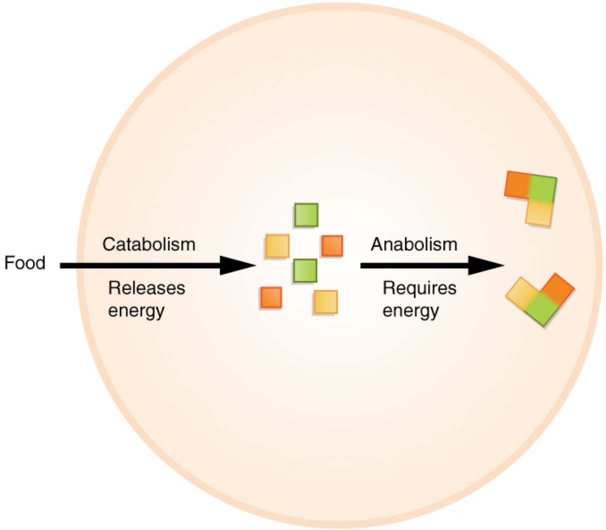


Figure 1.6. Metabolism
Anabolic reactions are building reactions, and they consume energy. Catabolic reactions break materials down and release energy. Metabolism includes both anabolic and catabolic reactions.

Every cell in your body makes use of a chemical compound, *adenosine triphosphate* (ATP), to store and release energy. The cell stores energy in the synthesis (anabolism) of ATP, then moves the ATP molecules to the location where energy is needed to fuel cellular activities. Then the ATP is broken down (catabolism) and a controlled amount of energy is released, which is used by the cell to perform a particular job.

View this animation to learn more about metabolic processes. What kind of catabolism occurs in the heart?

Responsiveness

Responsiveness is the ability of an organism to adjust to changes in its internal and external environments. An example of responsiveness to external stimuli could include moving toward sources of food and water and away from perceived dangers. Changes in an organism's internal environment, such as increased body temperature, can cause the responses of sweating and the dilation of blood vessels in the skin in order to decrease body temperature, as shown by the runners in Figure 1.7.

Movement

Human movement includes not only actions at the joints of the body, but also the motion of individual organs and even individual cells. As you read these words, red and white blood cells are moving throughout your body, muscle cells are contracting and relaxing to maintain your posture and to focus your vision, and glands are secreting chemicals to regulate body functions. Your body is coordinating the action of entire muscle groups to enable you to move air into and out of your lungs, to push blood throughout your body, and to propel the food you have eaten through your digestive tract. Consciously, of course, you contract your skeletal muscles to move the bones of your skeleton to get from one place to another (as the runners are doing in Figure 1.7), and to carry out all of the activities of your daily life.

Figure 1.7. Marathon Runners
Runners demonstrate two characteristics of living humans—responsiveness and movement. Anatomic structures and physiological processes allow runners to coordinate the action of muscle groups and sweat in response to rising internal body temperature. (credit: Phil Roeder/flickr)

Development, growth and reproduction

Development is all of the changes the body goes through in life. Development includes the processes of differentiation, growth, and renewal.

Growth is the increase in body size. Humans, like all multicellular organisms, grow by increasing the number of existing cells, increasing the amount of non-cellular material around cells (such as mineral deposits in bone), and, within very narrow limits, increasing the size of existing cells.

Reproduction is the formation of a new organism from parent organisms. In humans, reproduction is carried out by the male and female reproductive systems. Because death will come to all complex organisms, without reproduction, the line of organisms would end.

4. Methods Used to Study Aging

In this course of study we will be focusing on human aging, but of course all living things have a life time. In order to study aging scientists often look to other forms of life, both animals and plants. The reason for this is simple, humans along with most mammals live too long!

Imagine being a scientist who is studying the aging of individual people. If you start studying a person at his birth it is very likely your lifetime will end before his does. Of course groups of researchers have worked together to complete this type of research. An example of this is the Framingham Heart Study, which was begun in 1948 with 5209 men and women and continues today. This study has expanded to include the children and grandchildren of the original participants and also to include additional participants to create a more diverse study group. While the researchers have had to be patient the study has greatly increased our understanding of cardiovascular disease. This research method is referred to as *longitudinal study.*

Cross-sectional studies are more commonly used to study humans. These studies compare a measureable parameter across different groups of people. For example, a simple study could compare the average blood pressure of people between the ages of 20 and 30 to people between the ages of 40 and 50. This type of study can be done relative quickly and cheaply with large groups of people. This disadvantage is that is very difficult to differentiate age-related changes from the effects of numerous environmental and social factors.

Still another type of study involves lower animals. In studies which use lower animals researchers can more easily control genetic variability, environmental factors, and social factors. These are huge advantageous to the scientific process, but of course we are primarily interested in human aging. Scientists must be careful not to extrapolate findings which may or may not be applicable to humans.

5. Common Terms Related to Aging

The following terms are related to the study of aging. You should be come comfortable with meaning of each of these terms as they will be used throughout the text and class discussions.

- *Aging* is the process of growing old, regardless of chronological age.
- *Senescence* is a term used to describe the group of deleterious effects that lead to a decrease in the efficient functioning of an organism with increasing age and to an increased probability of death.
- *Senility* refers to the physical and mental deterioration often associated with old age.
- *Elderly* describes a person who is 60 to 75 years of age, as defined by the World Health Organization.
- *Old* describes a person who is 76 to 90 years of age, as defined by the World Health Organization.
- *Very old* describes a person who is over 90 years of age, as defined by the World Health Organization.
- *Gerontology* is the scientific study of the process of aging.
- *Geriatrics* refers to health care delivery for the elderly. It is the branch of medicine that treats the conditions and diseases associated with aging and old age.
- *Longevity* refers to the duration of life of an individual.
    - *Mean longevity* is the average longevity of a population. This often referred to as life expectancy.
    - *Maximum longevity* is the age at death of the longest-lived member of the population.
- *Demography* is the statistical study of human populations collectively, including geographic changes and trends in births,

marriages, diseases, and deaths.

6. Effects and Rates of Aging

Aging is process that begins at maturity and ends with death. While all adults are aging, the initial affects of aging for a person is their 20s are typically minimal. Culturally we have defined 40 years of age to be significant and in fact biologically speaking this is also when aging tend to become noticeable. By definition individuals above the age of 60 are elderly, but individual organs age at different rates and any specific organ does not age at the same rate in different individuals. Consequently individuals of the same chronological age may have vastly different physiological ages, which is a measure of functional capacity. An individual's aging process will be determined by a combination of his genetic makeup and environmental factors.

Each body system will be studied in depth throughout this course and in general each system's capacity to function is reduced as an individual ages. Additionally, while the decreased functionality of body systems is a normal part of the aging process and does not by itself cause disease the relationship between aging and disease is well known. The older one gets the more likely one is to die from a major disease. This is largely due to the fact that as the body ages it has a reduced capacity tolerate physiological stress and maintain homeostasis.

Maintaining homeostasis requires that the body continuously monitor its internal conditions. From body temperature to blood pressure to levels of certain nutrients, each physiological condition has a particular set point. A set point is the physiological value around which the normal range fluctuates. A normal range is the restricted set of values that is optimally healthful and stable. For example, the set point for normal human body temperature is approximately 37°C (98.6°F) Physiological parameters, such as body temperature and blood pressure, tend to fluctuate within a normal range a few degrees above and below that point. Control centers in the brain play roles in regulating physiological parameters and keeping them within the normal range. As the body works to maintain homeostasis, any significant deviation from the normal range will be resisted and homeostasis restored through a process called negative feedback. Negative feedback is a mechanism that prevents a physiological response from going beyond the normal range by reversing the action once the normal range is exceeded. The maintenance of homeostasis by negative feedback goes on throughout the body at all times.

7. Importance of Regular Health Examinations

The purpose of regular health examination is to evaluate health status, screen for risk factors and disease, and provide preventive counseling interventions. The major benefits of regular health examination is early detection of treatable disease. An important principal of clinical medicine is to "do no harm." In recent years there has been more awareness regarding the over treatment of nonlife threatening conditions.

PART II

CHAPTER 2: THEORIES OF AGING

8. Theories of Aging

In the past, maximum life span (the maximum biological limit of life in an ideal environment) was not thought to be subject to change with the process of aging considered non-adaptive, and subject to genetic traits. In the early 1900's, a series of flawed experiments by researcher Alexis Carrel demonstrated that in an optimal environment, cells of higher organisms (chickens) were able to divide continually, leading people to believe our cells to potentially possess immortal properties. In the 1960's Leonard Hayflick disproved this theory by identifying a maximal number of divisions a human cell could undergo in culture (known as the Hayflick limit), which set our maximal life span at around 115 years. Life span is the key to the intrinsic biological causes of aging, as these factors ensure an individual's survival to a certain point until biological ageing eventually causes death.

There are many theories about the mechanisms of age related changes. No one theory is sufficiently able to explain the process of aging, and they often contradict one another. All valid theories of aging must meet three broad criteria:

1. The aging changes that the theory addresses must occur commonly in all members of a humans.
2. The process must be progressive with time. That is, the changes that result from the proposed process must become more obvious as the person grows older.
3. The process must produce changes that cause organ dysfunctions and that ultimately cause a particular body organ or system to fail.

Modern biological theories of aging in humans currently fall into two main categories: programmed and damage or error theories. The programmed theories imply that aging follows a biological timetable (regulated by changes in gene expression that affect the systems responsible for maintenance, repair and defense responses), and the damage or error theories emphasize environmental assaults to living organisms that induce cumulative damage at various levels as the cause of ageing[1].

These two categories of theory[2] are also referred to as non-programmed aging theories based on evolutionary concepts (where aging is considered the result of an organism's inability to better combat natural deteriorative processes), and programmed ageing theories (which consider aging to ultimately be the result of a biological mechanism or program that purposely causes or allows deterioration and death in order to obtain a direct evolutionary benefit achieved by limiting lifespan beyond a species-specific optimum lifespan (Figure 1).

The programmed theory:

1. Aging by Program, where biological clocks act through hormones to control the pace of aging.
2. Gene Theory, which considers aging to be the result of a sequential switching on and off of certain genes, with senescence being defined as the time when age-associated deficits are manifested.
3. Autoimmune Theory, which states that the immune system is programmed to decline over time, leading to an increased vulnerability to infectious disease and thus ageing and death.

The damage or error theory:

1. Wear and tear theory, where vital parts in our cells and tissues wear out resulting in ageing.
2. Rate of living theory, that supports the theory that the greater

an organism's rate of oxygen basal, metabolism, the shorter its life span

3. Cross-linkage theory, according to which an accumulation of cross-linked proteins damages cells and tissues, slowing down bodily processes and thus result in ageing.
4. Free radicals theory, which proposes that superoxide and other free radicals cause damage to the macromolecular components of the cell, giving rise to accumulated damage causing cells, and eventually organs, to stop functioning.

9. Theory 1: Aging by Program

- There is strong evidence supporting the suggestion that aging is in some manner programmed into each species, including humans.
- This may be controlled neurologically or hormonally through the hypothalamus.
- Other studies suggest that aging is controlled by the thymus.
    - The gland atrophies at about the onset of adolescence. This implies that aging occurs more readily in the absence of the thymus gland.
- In studies cultured cells of a specific type divided a consistent number of times. This implies that the cell's life cycle is controlled within the cell, rather than externally by the hypothalamus or thymus.
    - Scientists agree that although normal cells may have a limited number of times they can divide this is only rarely, if ever, reached in the body.

10. Theory 2: Gene Theory

- The gene theory states that aging is programmed due to one or more harmful genes within each organism.
- The gene theory suggests that human life span is an inherited trait.
  - Studies show that identical twins die at similar ages, when compared to fraternal twins or siblings.

11. Theory 3: Autoimmune Theory

- The autoimmune theory proposes that the immune system is programmed so that it is no longer able to faultlessly distinguish foreign proteins from the body's own proteins.
    - If this happens the body's immune system will attack and destroy its own cells.
- It is well documented that the effectiveness of the immune system peaks at puberty and gradually declines thereafter with advance in age.

12. Theory 4: Wear-and-Tear Theory

- The wear and tear theory of aging was first introduced by Dr. August Weismann, a German biologist, in 1882.
    - It is very logical because it is what happens to the nonliving things that people observe around them (i.e. components of an aging car break due to repeated use).
- Cells and tissues have vital parts that wear out resulting in aging.
    - Parts of the body eventually wear out from repeated use killing the parts and then the body.

13. Theory 5: Rate of Living Theory

- The rate of living theory suggests that each animal, and perhaps each cell, has a specific amount of metabolic energy available to it and that the rate at which this energy is used determines the animal's length of life.
- Studies have demonstrated that rats kept on restricted diets and in cold environments live longer. Rats in these conditions have the appearance and behavior of younger animals.

14. Theory 6: Free Radical Theory

- This now very famous theory of aging was developed by Denham Harman MD at the University of Nebraska in 1956.
- The term free radical describes any molecule that has a free electron, and this property makes it react with healthy molecules in a destructive way.
- Because the free radical molecule has an extra electron it creates an extra negative charge. This unbalanced energy makes the free radical bind itself to another balanced molecule as it tries to steal electrons. In so doing, the balanced molecule becomes unbalanced and thus a free radical itself.
- It is known that diet, lifestyle, drugs (e.g. tobacco and alcohol) and radiation etc., are all accelerators of free radical production within the body.

15. Theory 7: Cross-linkage Theory

- The cross-linking theory, also referred to as the glycosylation theory of aging, was proposed by Johan Bjorksten in 1942.
- According to this theory, an accumulation of cross-linked proteins damages cells and tissues, slowing down bodily processes resulting in aging.
- Recent studies show that cross-linking reactions are involved in the age related changes in the studied proteins.
- In this theory it is the binding of glucose (simple sugars) to protein, (a process that occurs under the presence of oxygen) that causes various problems.
- Once this binding has occurred the protein becomes impaired and is unable to perform as efficiently.
- Living a longer life is going to lead to the increased possibility of oxygen meeting glucose and protein and known cross-linking disorders include senile cataract and the appearance of tough, leathery and yellow skin.

PART III

CHAPTER 3: CELLULAR AGING

16. The Cell

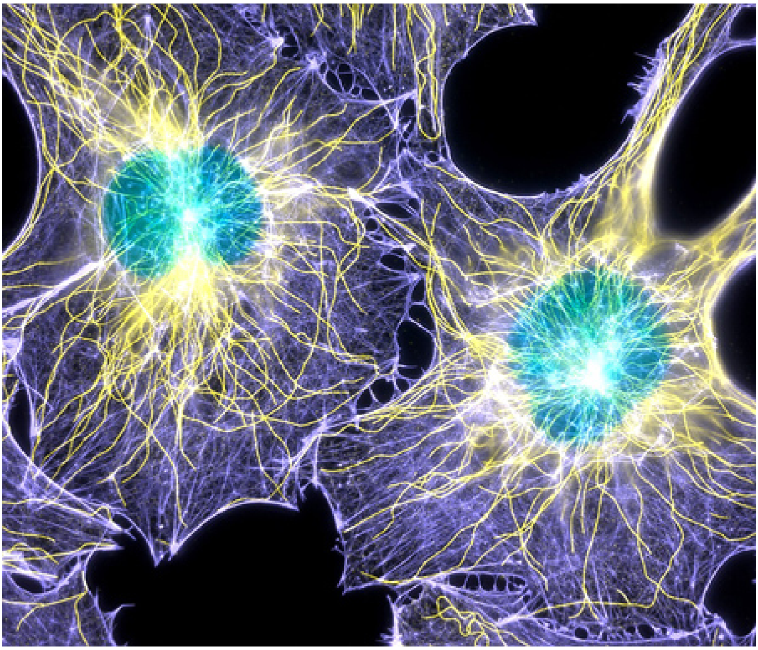
Cells are the basis of life—the basic structural unit of living things. Molecules such as water and amino acids are not alive but cells are! All life is comprised of cells of one type or another.

One of the hallmarks of living systems is the ability to maintain homeostasis, or a relatively constant internal state. The cell is the first level of complexity able to maintain homeostasis, and it is the unique structure of the cell that enables this critical function.

The current cell theory states that:

1. All known living things are composed of one or more cells.
2. All new cells are created by pre-existing cells dividing in two.
3. The cell is the most basic unit of structure and function in all living organisms.

Modern cell theorists assert that all functions essential to life occur within the cell; and that, during cell division, the cell contains and transmits to the next generation the information necessary to conduct and regulate cell functioning.



Let's begin our study of the cell by investigating the basic anatomy of an animal cell. Each cell consists of three components shown in the image above.

1. A cell membrane which surrounds and protects the cell
2. The cytoplasm which is the watery interior of the cell which contains ions, proteins, and organelles
3. Organelles which carry out all activities necessary for the cell to live, grow, and reproduce

Within the body, cells represent a level of organization between organelles and tissues. Organelles in turn are comprised of specialized macromolecules and tissues are collections of specialized cells. Brain, kidney, liver, muscle and lung tissues differ from each other because of the structure and function of their constituent cells. Thus, the cells comprising each tissue type vary in shape, size and interior structure to permit their specific physiological function within the tissue.

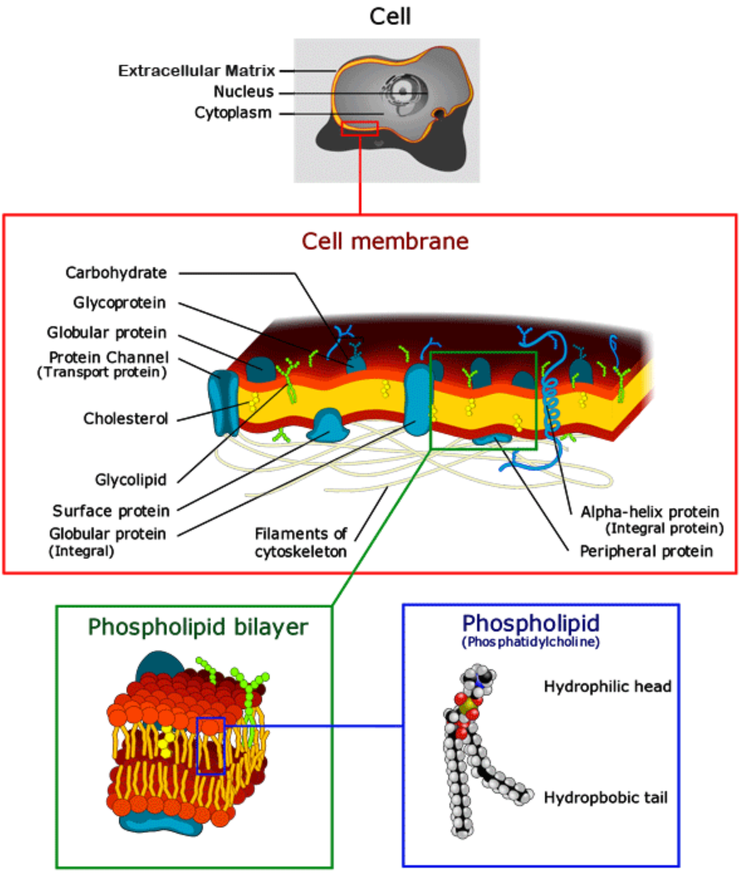
17. Membranes

Membrane Lipids

The cell membrane is a dynamic structure composed of lipids, proteins, and carbohydrates. It protects the cell by preventing materials from leaking out, controls what can enter or leave through the membrane, provides a binding site for hormones and other chemicals, and serves as an identification card for the immune system to distinguish between "self" and "non-self" cells. We will first investigate the anatomy of the cell membrane and then continue on to study the physiology of membrane transport.

The phospholipid bilayer is the main fabric of the membrane. The bilayer's structure causes the membrane to be semi-permeable. Remember that phospholipid molecules are amphiphilic, which means that they contain both a nonpolar and polar region. Phospholipids have a polar head (it contains a charged phosphate group) with two nonpolar hydrophobic fatty acid tails. The tails of the phospholipids face each other in the core of the membrane while each polar head lies on the outside and inside of the cell. Having the polar heads oriented toward the external and internal sides of the membrane attracts other polar molecules to the cell membrane. The hydrophobic core blocks the diffusion of hydrophilic ions and polar molecules. Small hydrophobic molecules and gases, which can dissolve in the membrane's core, cross it with ease.

Other molecules require proteins to transport them across the membrane. Proteins determine most of the membrane's specific functions. The plasma membrane and the membranes of the various organelles each have unique collections of proteins. For example, to date more than 50 kinds of proteins have been found in the plasma membrane of red blood cells.



Importance of Phospholipid Membrane Structure

What is important about the structure of a phospholipid membrane? First, it is fluid. This allows cells to change shape, permitting growth and movement. The fluidity of the membrane is regulated by the types of phospholipids and the presence of cholesterol. Second, the phospholipid membrane is selectively permeable.

The ability of a molecule to pass through the membrane depends on its polarity and to some extent its size. Many non-polar molecules such as oxygen, carbon dioxide, and small hydrocarbons can flow easily through cell membranes. This feature of membranes is very important because hemoglobin, the protein that carries oxygen in our blood, is contained within red blood cells. Oxygen must be able to freely cross the membrane so that hemoglobin can get fully loaded with oxygen in our lungs, and deliver it effectively to our tissues. Most polar substances are stopped by a cell membrane, except perhaps for small polar compounds like the one carbon alcohol, methanol. Glucose is too large to pass through the membrane unassisted and a special transporter protein ferries it across. One type of diabetes is caused by misregulation of the glucose transporter. This decreases the ability of glucose to enter the cell and results in high blood glucose levels. Charged ions, such as sodium (Na^+) or potassium (K^+) ions seldom go through a membrane, consequently they also need special transporter molecules to pass through the membrane. The inability of Na^+ and K^+ to pass through the membrane allows the cell to regulate the concentrations of these ions on the inside or outside of the cell. The conduction of electrical signals in your neurons is based on the ability of cells to control Na^+ and K^+ levels.

Selectively permeable membranes allow cells to keep the chemistry of the cytoplasm different from that of the external environment. It also allows them to maintain chemically unique conditions inside their organelles.

Fluidity of Cell Membranes

The cell membrane is not a static structure. It is a dynamic structure that allows the movement of phospholipids and proteins. Fluidity is a term used to describe the ease of movement of molecules in the membrane and is an important characteristic for cell function. Fluidity is dependent on the temperature (increased temperatures it more fluid and decreased temperatures make it more solid), saturated fatty acids and unsaturated fatty acids. Saturated fatty acids make the membrane less fluid while unsaturated fatty acids make it more fluid. The correct ratio of saturated to unsaturated fatty acids keeps the membrane fluid at any temperature conducive to life. For example, winter wheat responds to decreasing temperatures by increasing the amount of unsaturated fatty acids in cell membranes to prevent the cell membrane from becoming too solid in the cold. In animal cells, cholesterol helps to prevent the packing of fatty acid tails and thus lowers the requirement of unsaturated fatty acids. This helps maintain the fluid nature of the cell membrane without it becoming too liquid at body temperature.

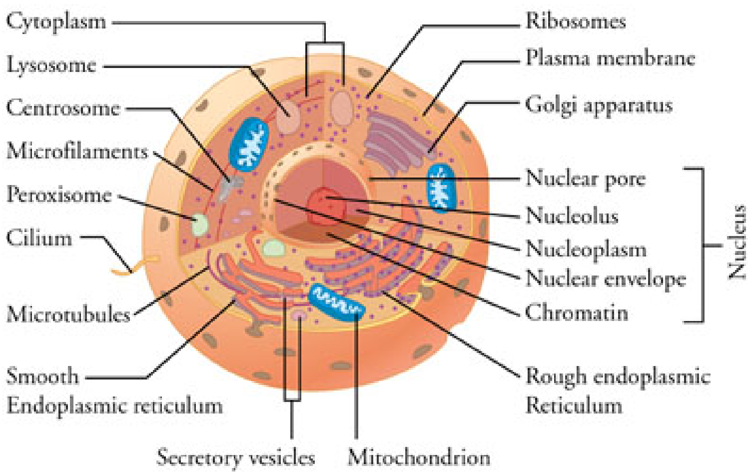
18. Organelles

Organelles

Each cell process is carried out in a specific location in the cell, often located in or around an **organelle**. Think of an organelle as a level of organization between macromolecules and the cell. Organelles carry out specialized tasks within the cell, localizing functions such as replication, energy production, protein synthesis, and processing of food and waste. The various cells differ in the arrangement and number of organelles, as well as structurally, giving rise to the hundreds of cell types found in the body.

The focus of this section is to understand the organelles of the cell, how they interact with each other, and how they function during transport, growth and division in the cell. You will learn about the controlled chemical environment a cell maintains and what restrictions this places on the types of chemical reactions it can perform. This background is vital to understanding key processes such as how a cell releases energy from glucose, makes and folds proteins, and goes through growth and cell division.

Think of a city and the various jobs within a city. A cell is similar with each organelle serving a specific purpose. There are organelles whose job is to provide shape and structure to the cell, much like the city streets and bridges. These protein rich organelles include **intermediate filaments**, **microtubules**, and **microfilaments**. Some of these actually move other organelles around the cell or change the shape of the cell. When a muscle cell contracts or shortens it does so by the microfilaments made up of the proteins actin and myosin. One special organelle composed of microtubules is located in an area near the nucleus, the **centrosome**. The centrosome contains a pair called of microtubule bundles known as the **centrioles**. Centrioles are important because they move chromosomes to opposite ends of the cell during cell replication termed mitosis. Neurons do not have centrioles and cannot replicate.



Other organelles help synthesize the proteins needed by the cell. These protein factories are called **ribosomes**. They can be scattered within the cell or attached to a membrane channel system called the **endoplasmic reticulum** or ER. When the ER has ribosomes attached to it, it is termed the rough ER (the ribosomes give it a rough or grainy appearance). When the ER lacks ribosomes it is termed the smooth ER and functions for lipid synthesis and storage of toxins. When a protein is manufactured it must be folded into a specific shape to work. Often additional side chains of carbohydrates must be attached. The protein is processed in the rough ER. Once it is formed it enters the golgi apparatus which is the distributing plant for the cell. It completes any protein processing and then packages it into a **vesicle** for transport to its destination. Some proteins are needed in the cell membrane and the vesicles make sure they reach the membrane. The **golgi apparatus** also makes a special type of vesicle termed a **lysosome**. The lysosome is the garbage man of the cell. It takes in cell debris and waste and destroys it. The lysosome contains very powerful hydrolytic enzymes to accomplish this. It is very important that the enzymes remain in the lysosome or they would destroy the cell.

The power plant of the cell is the **mitochondria**. This organelle generates the ATP or energy for the cell. Mitochondria even have their own DNA termed mitochondrial DNA (mDNA) and can replicate.

Finally there is the controller of the cell. This is the **nucleus**. Not all cells have a nucleus and are termed anucleate. If you look at the image of the red blood cells you will see a white dot in the center of the cell – that is where the nucleus used to be. The nucleus is ejected when they mature. Some cells have more than one nucleus and are termed **multinucleate**. Skeletal muscle cells are very large cells and are multinucleate. The nucleus contains the DNA of the cell and the nucleolus. The **nucleolus** is an organelle that makes ribosomes. The DNA is your genetic code. It contains the genes that contain the instructions for making every protein in your body. The nucleus is surrounded by it's own membrane with tiny holes termed **nuclear pores**. The membrane is called the **nuclear membrane or nuclear envelope.**

19. The Nucleus and DNA Replication

Nucleus

The nucleus is the largest and most prominent of a cell's organelles (Figure 3.19). The nucleus is generally considered the control center of the cell because it stores all of the genetic instructions for manufacturing proteins. Interestingly, some cells in the body, such as muscle cells, contain more than one nucleus (Figure 3.20), which is known as multinucleated. Other cells, such as mammalian red blood cells (RBCs), do not contain nuclei at all. RBCs eject their nuclei as they mature, making space for the large numbers of hemoglobin molecules that carry oxygen throughout the body (Figure 3.21). Without nuclei, the life span of RBCs is short, and so the body must produce new ones constantly.

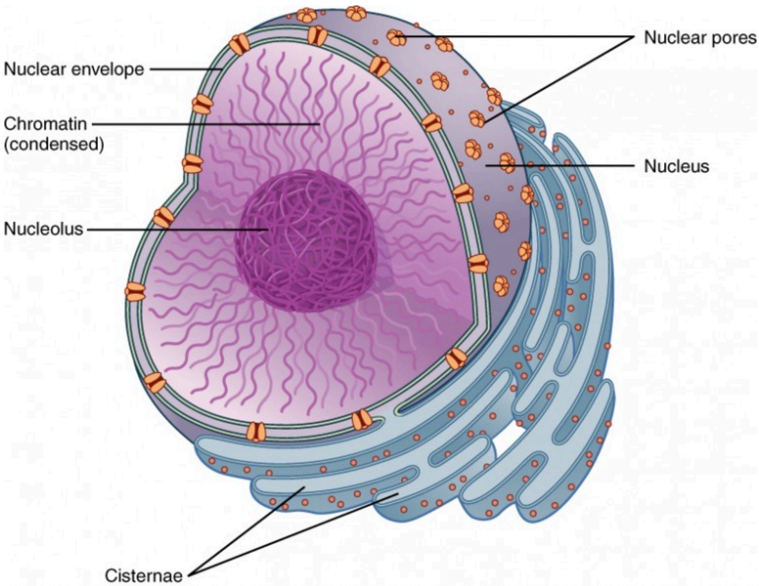


Figure 3.19. The Nucleus

The nucleus is the control center of the cell. The nucleus of living cells contains the genetic material that determines the entire structure and function of that cell.

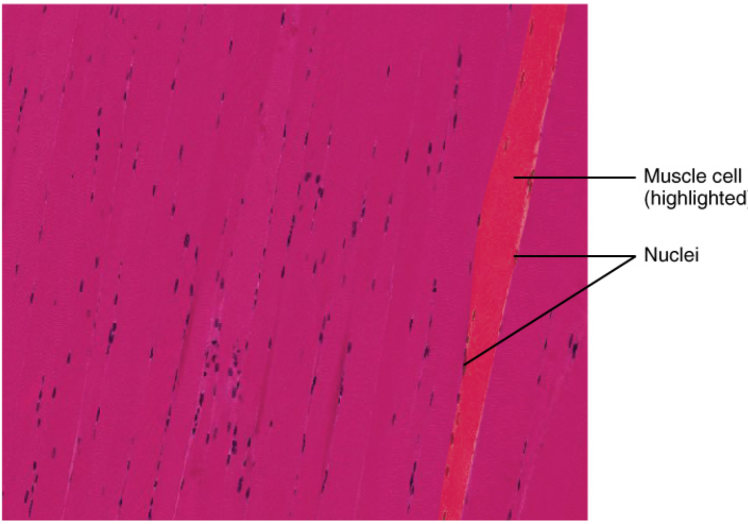


Figure 3.20. Multinucleate Muscle CellF
Unlike cardiac muscle cells and smooth muscle cells, which have a single nucleus, a skeletal muscle cell contains many nuclei, and is referred to as "multinucleated." These muscle cells are long and fibrous (often referred to as muscle fibers). During development, many smaller cells fuse to form a mature muscle fiber. The nuclei of the fused cells are conserved in the mature cell, thus imparting a multinucleate characteristic to mature muscle cells. LM × 104.3. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

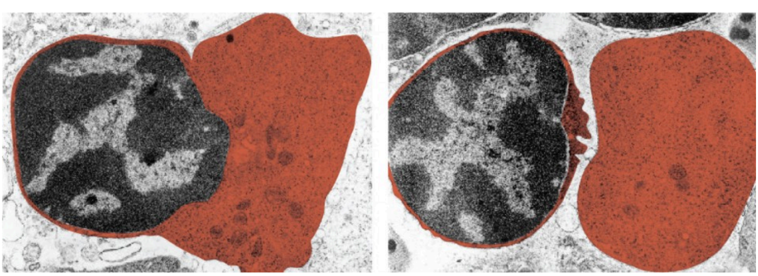


Figure 3.21. Red Blood Cell Extruding Its Nucleus
Mature red blood cells lack a nucleus. As they mature, erythroblasts extrude their nucleus, making room for more hemoglobin. The two

panels here show an erythroblast before and after ejecting its nucleus, respectively. (credit: modification of micrograph provided by the Regents of University of Michigan Medical School © 2012)

Inside the nucleus lies the blueprint that dictates everything a cell will do and all of the products it will make. This information is stored within DNA. The nucleus sends "commands" to the cell via molecular messengers that translate the information from DNA. Each cell in your body (with the exception of germ cells) contains the complete set of your DNA. When a cell divides, the DNA must be duplicated so that the each new cell receives a full complement of DNA. The following section will explore the structure of the nucleus and its contents, as well as the process of DNA replication.

Organization of the Nucleus and Its DNA

Like most other cellular organelles, the nucleus is surrounded by a membrane called the *nuclear envelope*. This membranous covering consists of two adjacent lipid bilayers with a thin fluid space in between them. Spanning these two bilayers are nuclear pores. A *nuclear pore* is a tiny passageway for the passage of proteins, RNA, and solutes between the nucleus and the cytoplasm. Proteins called pore complexes lining the nuclear pores regulate the passage of materials into and out of the nucleus. Inside the nuclear envelope is a gel-like nucleoplasm with solutes that include the building blocks of nucleic acids. There also can be a dark-staining mass often visible under a simple light microscope, called a*nucleolus* (plural = nucleoli). The nucleolus is a region of the nucleus that is responsible for manufacturing the RNA necessary for construction of ribosomes. Once synthesized, newly made ribosomal subunits exit the cell's nucleus through the nuclear pores. The genetic instructions that are used to build and maintain an organism are arranged in an orderly manner in strands of DNA. Within the nucleus are threads of *chromatin* composed of DNA and associated proteins (Figure 3.22). Along the chromatin threads, the DNA is wrapped around a set of *histone* proteins. A*nucleosome* is a single, wrapped DNA-histone complex. Multiple nucleosomes along the entire molecule of DNA appear like a beaded necklace, in which the string is the DNA and the beads are the associated histones. When a cell is in the process of division, the chromatin condenses into chromosomes, so that the DNA can be safely transported to the "daughter cells." The *chromosome* is composed of DNA and proteins; it is the condensed form of chromatin. It is estimated that humans have almost 22,000 genes distributed on 46 chromosomes.

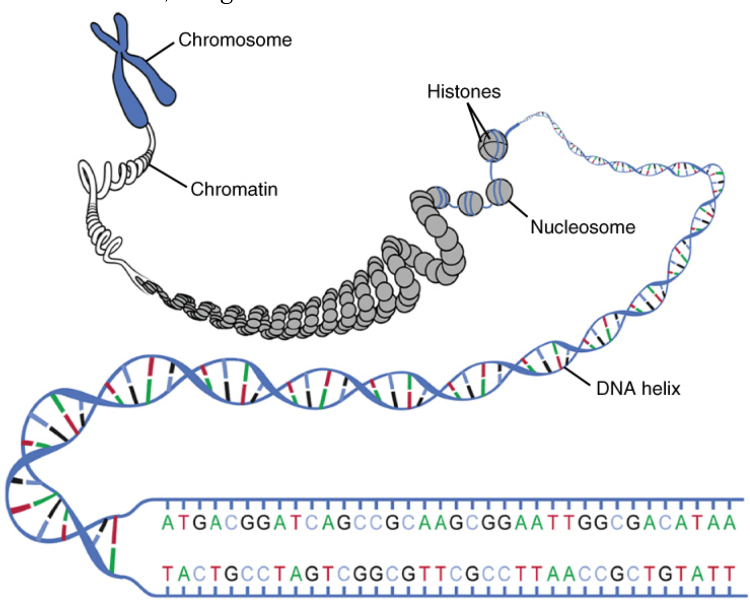


Figure 3.22. DNA Macrostructure
Strands of DNA are wrapped around supporting histones. These proteins are increasingly bundled and condensed into chromatin, which is packed tightly into chromosomes when the cell is ready to divide.

20. How Scientists Study Cells

Scientists observe that cells in the human body change and eventually die as part of the aging process. Studies that involve cells within a human body are referred to as in vivo. While human cells do not exist in isolation it is very difficult for scientists to study individual cells in the body because of the many variables affecting the individual cell's processes. These variables include both genetics and lifestyle.

As an alternative scientists often choose to study individual cells outside the human body. These studies take place in laboratories where scientists can control all lifestyle variables and manage genetic variables and are referred to as in vitro. In order to study cells in a culture, first they must be harvested from a human body, then they may be frozen in liquid nitrogen, before being thawed, and used in a study.

While it is much easier for scientists to study cells outside of the body, it is important for scientist to consider if in vitro studies produce valid results. Scientists have had to answer the question: do cells in cultures behave similarly to cells in the human body? In order to better understand how environment affects cells scientists utilized information they already understood regarding how cells behave in the body. Each cell type will only divide for a known quantity of time. Scientists found that these same cell types will only divide for the same quantity in a culture. This supports the conclusion that in vitro studies provide valid and valuable information regarding cells. Ongoing studies continue to support this conclusion.

21. Cellular Changes During Aging

Cellular Plasma Membrane Changes

- As the cell ages the plasma membrane has an increases amount fatty acids.
    - This structural change decreases the fluidity of the plasma membrane and reduces the transportation of ions, nutrients, amino acids, and proteins across the membrane.

Nuclear Changes

- As the cell ages cross-linkages form between the sulfur atoms on the DNA in the nucleus of the cells.
    - This structural change condenses the DNA which decreases the synthesis of RNA, reduced the cells ability to repair enzymes, and may reduce the cell's ability to divide.

Cytoplasmic Changes

- As the cell ages the volume of cytoplasm increases, enzymes that synthesize DNA move from the nucleus to the cytoplasm, and there is a gradual build up of lipofuscin.
    - While it is unclear how this directly affects the cell, it is known that once the DNA migrates from the nucleus it is

unable to synthesizes enzymes.

Ribosomal Changes

- As the cell ages the amount of ribosomal RNA and the number of ribosomes decreases.
    - This structural change results in a decreased level of protein synthesis.

Mitochondrial Changes

- As the cell ages the number of mitochondrial present in a cell decreases.
    - This structural change reduces the cell's ability to produce energy.

Lysosomal Changes

- As the cell ages the lysosomes become less able to break down waste proteins, nucleic acids, carbohydrates, and fats.
    - This results is a build up waste within the cell.

PART IV

CHAPTER 4: THE INTEGUMENTARY SYSTEM

22. The Integumentary System

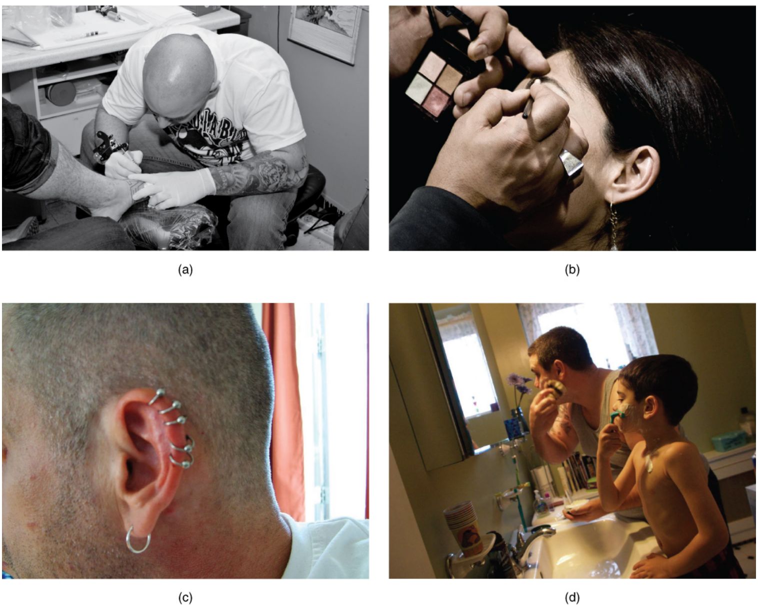


Figure 4.1.

Your skin is a vital part of your life and appearance (a–d). Some people choose to embellish it with tattoos (a), makeup (b), and even piercings (c). (credit a: Steve Teo; credit b: "spaceodissey"/flickr; credit c: Mark/flickr; credit d: Lisa Schaffer)

What do you think when you look at your skin in the mirror? Do you think about covering it with makeup, adding a tattoo, or maybe a body piercing? Or do you think about the fact that the skin belongs to one of the body's most essential and dynamic systems: the integumentary system? The integumentary system refers to the skin and its accessory structures, and it is responsible for much more than simply lending to your outward appearance. In the adult human body, the skin makes up about 16 percent of body weight and covers an area of 1.5 to 2 m^2. In fact, the skin and accessory structures are the largest organ system in the human body. As such, the skin protects your inner organs and it is in need of daily care and protection to maintain its health. This chapter will introduce the structure and functions of the integumentary system, as well as some of the diseases, disorders, and injuries that can affect this system.

Layers of the Skin

- The Epidermis
  - Stratum Basale
  - Stratum Spinosum
  - Stratum Granulosum
  - Stratum Lucidum
  - Stratum Corneum
- Dermis
  - Papillary Layer
  - Reticular Layer
- Hypodermis
- Pigmentation

Although you may not typically think of the skin as an organ, it is in fact made of tissues that work together as a single structure to perform unique and critical functions. The skin and its accessory structures make up the ***integumentary system***, which provides the body with overall protection. The skin is made of multiple layers of cells and tissues, which are held to underlying structures by connective tissue (Figure 4.2). The deeper layer of skin is well vascularized (has numerous blood vessels). It also has numerous sensory, and autonomic and sympathetic nerve fibers ensuring communication to and from the brain.

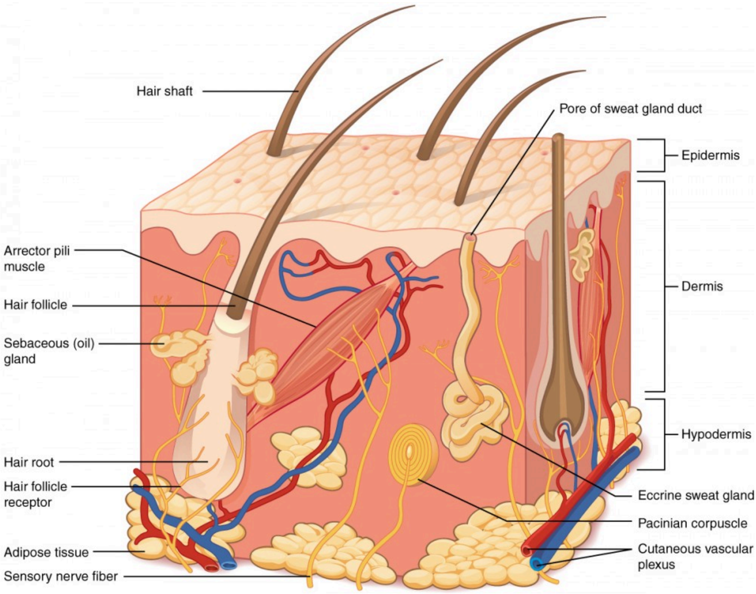


Figure 4.2. Layers of Skin
The skin is composed of two main layers: the epidermis, made of closely packed epithelial cells, and the dermis, made of dense, irregular connective tissue that houses blood vessels, hair follicles, sweat glands, and other structures. Beneath the dermis lies the hypodermis, which is composed mainly of loose connective and fatty tissues.

The skin consists of two main layers and a closely associated layer.

The Epidermis

The *epidermis* is composed of keratinized, stratified squamous epithelium. It is made of four or five layers of epithelial cells, depending on its location in the body. It does not have any blood vessels within it (i.e., it is avascular). Skin that has four layers of cells is referred to as “thin skin.” From deep to superficial, these layers are the stratum basale, stratum spinosum, stratum granulosum, and stratum corneum. Most of the skin can be classified as thin skin. “Thick skin” is found only on the palms of the hands and the soles of the feet. It has a fifth layer, called the stratum lucidum, located between the stratum corneum and the stratum granulosum (Figure 4.3).

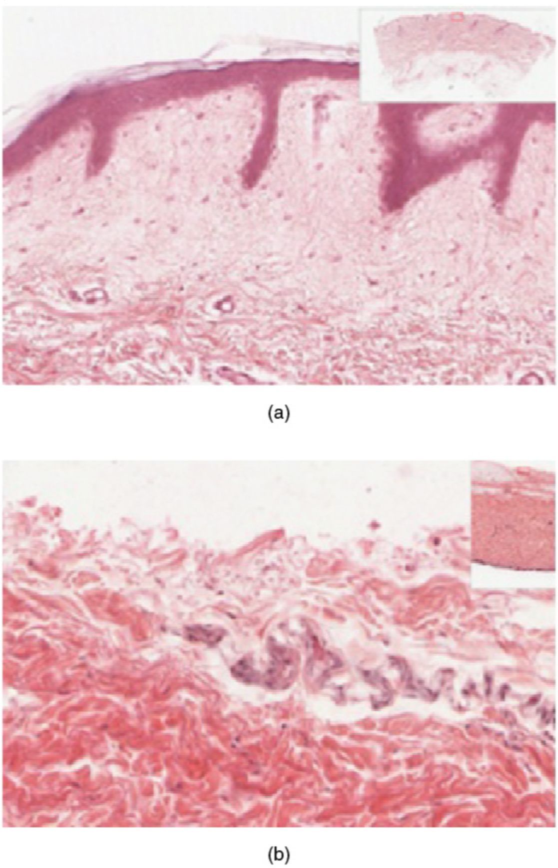


Figure 4.3. Thin Skin versus Thick Skin

These slides show cross-sections of the epidermis and dermis of (a) thin and (b) thick skin. Note the significant difference in the thickness *of the epithelial layer of the thick skin. From top, LM × 40, LM × 40. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)*

The cells in all of the layers except the stratum basale are called keratinocytes. A *keratinocyte* is a cell that manufactures and stores the protein keratin. *Keratin* is an intracellular fibrous protein that gives hair, nails, and skin their hardness and water-resistant properties. The keratinocytes in the stratum corneum are dead and regularly slough away, being replaced by cells from the deeper layers (Figure 4.4).

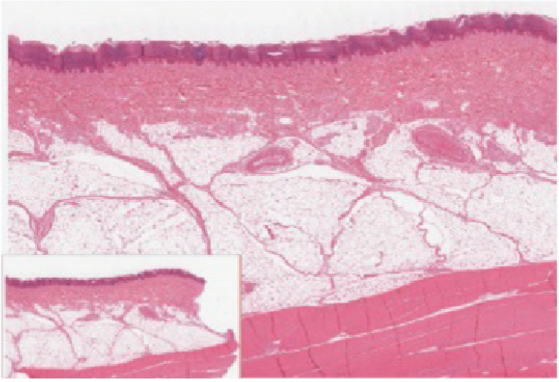


Figure 4.4. Epidermis
The epidermis is epithelium composed of multiple layers of cells. The basal layer consists of cuboidal cells, whereas the outer layers are squamous, keratinized cells, so the whole epithelium is often described as being keratinized stratified squamous epithelium. LM × 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Stratum Basale

The ***stratum basale*** (also called the stratum germinativum) is the deepest epidermal layer and attaches the epidermis to the basal lamina, below which lie the layers of the dermis. The cells in the stratum basale bond to the dermis via intertwining collagen fibers, referred to as the basement membrane. A finger-like projection, or fold, known as the ***dermal papilla*** (plural = dermal papillae) is found in the superficial portion of the dermis. Dermal papillae increase the strength of the connection between the epidermis and dermis; the greater the folding, the stronger the connections made (Figure 4.5).

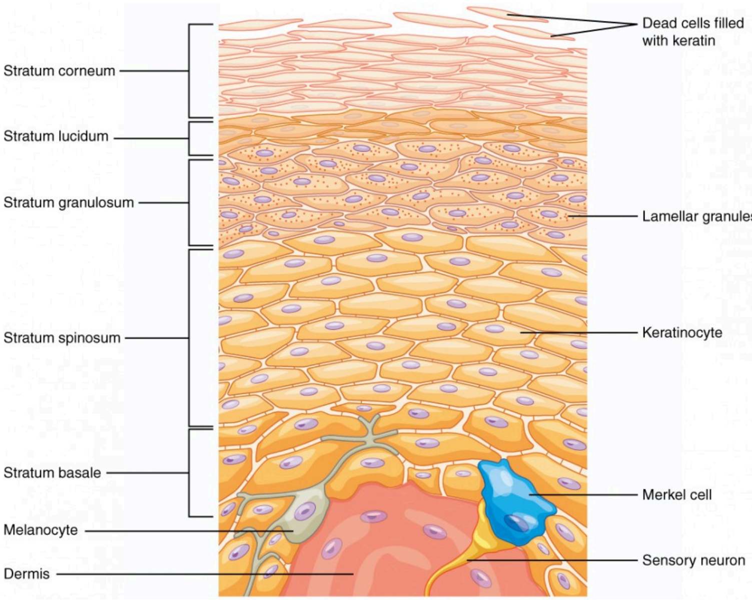


Figure 4.5. Layers of the Epidermis
The epidermis of thick skin has five layers: stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum.

The stratum basale is a single layer of cells primarily made of basal cells. A ***basal cell*** is a cuboidal-shaped stem cell that is a precursor of the keratinocytes of the epidermis. All of the keratinocytes are produced from this single layer of cells, which are constantly going through mitosis to produce new cells. As new cells are formed, the existing cells are pushed superficially away from the stratum basale. Two other cell types are found dispersed among the basal cells in the stratum basale. The first is a ***Merkel cell***, which functions as a receptor and is responsible for stimulating sensory nerves that the brain perceives as touch. These cells are especially abundant on the surfaces of the hands and feet. The second is a***melanocyte***, a cell that produces the pigment melanin. ***Melanin*** gives hair and skin its color, and also helps protect the living cells of the epidermis from ultraviolet (UV) radiation damage.

In a growing fetus, fingerprints form where the cells of the stratum basale meet the papillae of the underlying dermal layer (papillary layer), resulting in the formation of the ridges on your fingers that you recognize as fingerprints. Fingerprints are unique to each individual and are used for forensic analyses because the patterns do not change with the growth and aging processes.

Stratum Spinosum

As the name suggests, the ***stratum spinosum*** is spiny in appearance due to the protruding cell processes that join the cells via a structure called a ***desmosome***. The desmosomes interlock with each other and strengthen the bond between the cells. It is interesting to note that the "spiny" nature of this layer is an artifact of the staining process. Unstained epidermis samples do not exhibit this characteristic appearance. The stratum spinosum is composed of eight to 10 layers of keratinocytes, formed as a result of cell division in the stratum basale (Figure 4.6). Interspersed among the keratinocytes of this layer is a type of dendritic cell called the ***Langerhans cell***, which functions as a macrophage by engulfing bacteria, foreign particles, and damaged cells that occur in this layer.

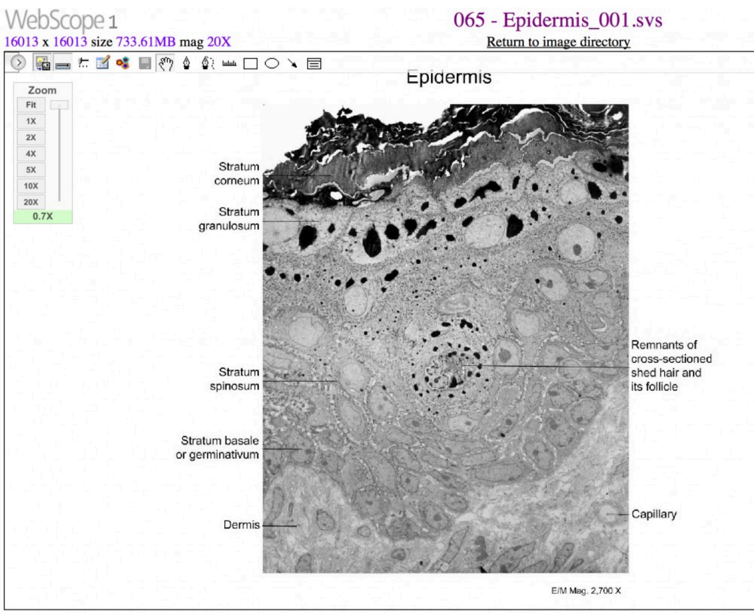


Figure 4.6. Cells of the Epidermis

The cells in the different layers of the epidermis originate from basal cells located in the stratum basale, yet the cells of each layer are distinctively different. EM × 2700. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Stratum Granulosum

The ***stratum granulosum*** has a grainy appearance due to further changes to the keratinocytes as they are pushed from the stratum spinosum. The cells (three to five layers deep) become flatter, their cell membranes thicken, and they generate large amounts of the proteins keratin, which is fibrous, and ***keratohyalin***, which accumulates as lamellar granules within the cells (see Figure 4.5). These two proteins make up the bulk of the keratinocyte mass in the stratum granulosum and give the layer its grainy appearance. The nuclei and other cell organelles disintegrate as the cells die, leaving behind the keratin, keratohyalin, and cell membranes that will form the stratum lucidum, the stratum corneum, and the accessory structures of hair and nails.

Stratum Lucidum

The ***stratum lucidum*** is a smooth, seemingly translucent layer of the epidermis located just above the stratum granulosum and below the stratum corneum. This thin layer of cells is found only in the thick skin of the palms, soles, and digits. The keratinocytes that compose the stratum lucidum are dead and flattened (see Figure 4.5). These cells are densely packed with ***eleiden***, a clear protein rich in lipids, derived from keratohyalin, which gives these cells their transparent (i.e., lucid) appearance and provides a barrier to water.

Stratum Corneum

The ***stratum corneum*** is the most superficial layer of the epidermis and is the layer exposed to the outside environment (see Figure 4.5). The increased keratinization (also called cornification) of the cells in this layer gives it its name. There are usually 15 to 30 layers of cells in the stratum corneum. This dry, dead layer helps prevent the penetration of microbes and the dehydration of underlying tissues, and provides a mechanical protection against abrasion for the more delicate, underlying layers. Cells in this layer are shed periodically and are replaced by cells pushed up from the stratum granulosum (or stratum lucidum in the case of the palms and soles of feet). The entire layer is replaced during a period of about 4 weeks. Cosmetic procedures, such as microdermabrasion, help remove some of the dry, upper layer and aim to keep the skin looking "fresh" and healthy.

Dermis

The ***dermis*** might be considered the "core" of the integumentary system (derma- = "skin"), as distinct from the epidermis (epi- = "upon" or "over") and hypodermis (hypo- = "below"). It contains blood and lymph vessels, nerves, and other structures, such as hair follicles and sweat glands. The dermis is made of two layers of connective tissue that compose an interconnected mesh of elastin and collagenous fibers, produced by fibroblasts (Figure 4.7).

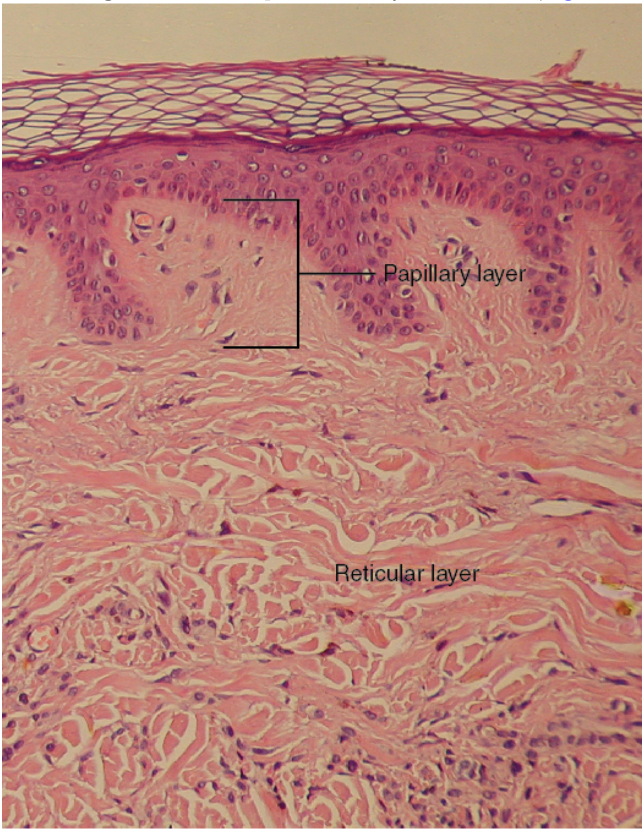


Figure 4.7. Layers of the Dermis
This stained slide shows the two components of the dermis—the papillary layer and the reticular layer. Both are made of connective

tissue with fibers of collagen extending from one to the other, making the border between the two somewhat indistinct. The dermal papillae extending into the epidermis belong to the papillary layer, whereas the dense collagen fiber bundles below belong to the reticular layer. LM × 10. (credit: modification of work by "kilbad"/Wikimedia Commons)

Papillary Layer

The ***papillary layer*** is made of loose, areolar connective tissue, which means the collagen and elastin fibers of this layer form a loose mesh. This superficial layer of the dermis projects into the stratum basale of the epidermis to form finger-like dermal papillae (see Figure 4.7). Within the papillary layer are fibroblasts, a small number of fat cells (adipocytes), and an abundance of small blood vessels. In addition, the papillary layer contains phagocytes, defensive cells that help fight bacteria or other infections that have breached the skin. This layer also contains lymphatic capillaries, nerve fibers, and touch receptors called the Meissner corpuscles.

Reticular Layer

Underlying the papillary layer is the much thicker ***reticular layer***, composed of dense, irregular connective tissue. This layer is well vascularized and has a rich sensory and sympathetic nerve supply. The reticular layer appears reticulated (net-like) due to a tight meshwork of fibers. ***Elastin fibers*** provide some elasticity to the skin, enabling movement. Collagen fibers provide structure and tensile strength, with strands of collagen extending into both the papillary layer and the hypodermis. In addition, collagen binds water to keep the skin hydrated. Collagen injections and Retin-A creams help restore skin turgor by either introducing collagen externally or stimulating blood flow and repair of the dermis, respectively.

Hypodermis

The ***hypodermis*** (also called the subcutaneous layer or superficial fascia) is a layer directly below the dermis and serves to connect the skin to the underlying fascia (fibrous tissue) of the bones and muscles. It is not strictly a part of the skin, although the border between the hypodermis and dermis can be difficult to distinguish. The hypodermis consists of well-vascularized, loose, areolar connective tissue and adipose tissue, which functions as a mode of fat storage and provides insulation and cushioning for the integument.

Everyday Connection: Lipid Storage

The hypodermis is home to most of the fat that concerns people when they are trying to keep their weight under control. Adipose tissue present in the hypodermis consists of fat-storing cells called adipocytes. This stored fat can serve as an energy reserve, insulate the body to prevent heat loss, and act as a cushion to protect underlying structures from trauma.

Where the fat is deposited and accumulates within the hypodermis depends on hormones (testosterone, estrogen, insulin, glucagon, leptin, and others), as well as genetic factors. Fat distribution changes as our bodies mature and age. Men tend to accumulate fat in different areas (neck, arms, lower back, and abdomen) than do women (breasts, hips, thighs, and buttocks). The body mass index (BMI) is often used as a measure of fat, although this measure is, in fact, derived from a mathematical formula that compares body weight (mass) to height. Therefore, its accuracy as a health indicator can be called into question in individuals who are extremely physically fit.

In many animals, there is a pattern of storing excess calories as fat to be used in times when food is not readily available. In much of the developed world, insufficient exercise coupled with the ready availability and consumption of high-calorie foods have resulted in unwanted accumulations of adipose tissue in many people. Although periodic accumulation of excess fat may have provided an evolutionary advantage to our ancestors, who experienced unpredictable bouts of famine, it is now becoming chronic and considered a major health threat. Recent studies indicate that a distressing percentage of our population is overweight and/or clinically obese. Not only is this a problem for the individuals affected, but it also has a severe impact on our healthcare system. Changes in lifestyle, specifically in diet and exercise, are the best ways to control body fat accumulation, especially when it reaches levels that increase the risk of heart disease and diabetes.

Pigmentation

The color of skin is influenced by a number of pigments, including melanin, carotene, and hemoglobin. Recall that melanin is produced by cells called melanocytes, which are found scattered throughout the stratum basale of the epidermis. The melanin is transferred into the keratinocytes via a cellular vesicle called a ***melanosome*** (Figure 4.8).

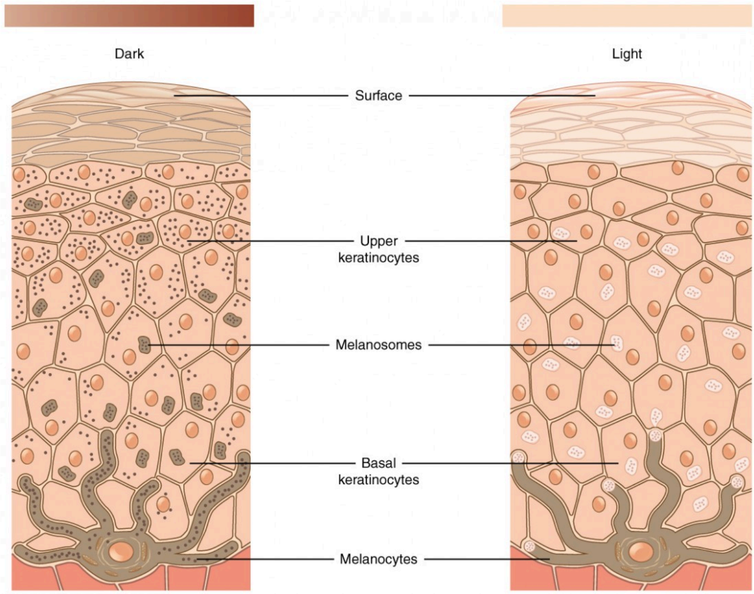


Figure 4.8. Skin Pigmentation

The relative coloration of the skin depends of the amount of melanin produced by melanocytes in the stratum basale and taken up by keratinocytes.

Melanin occurs in two primary forms. Eumelanin exists as black and brown, whereas pheomelanin provides a red color. Dark-skinned individuals produce more melanin than those with pale skin. Exposure to the UV rays of the sun or a tanning salon causes melanin to be manufactured and built up in keratinocytes, as sun exposure stimulates keratinocytes to secrete chemicals that stimulate melanocytes. The accumulation of melanin in keratinocytes results in the darkening of the skin, or a tan. This increased melanin accumulation protects the DNA of epidermal cells from UV ray damage and the breakdown of folic acid, a nutrient necessary for our health and well-being. In contrast, too much melanin can interfere with the production of vitamin D, an important nutrient involved in calcium absorption. Thus, the amount of melanin present in our skin is dependent on a balance between available sunlight and folic acid destruction, and protection from UV radiation and vitamin D production.

It requires about 10 days after initial sun exposure for melanin synthesis to peak, which is why pale-skinned individuals tend to suffer sunburns of the epidermis initially. Dark-skinned individuals can also get sunburns, but are more protected than are pale-skinned individuals. Melanosomes are temporary structures that are eventually destroyed by fusion with lysosomes; this fact, along with melanin-filled keratinocytes in the stratum corneum sloughing off, makes tanning impermanent.

Too much sun exposure can eventually lead to wrinkling due to the destruction of the cellular structure of the skin, and in severe cases, can cause sufficient DNA damage to result in skin cancer. When there is an irregular accumulation of melanocytes in the skin, freckles appear. Moles are larger masses of melanocytes, and although most are benign, they should be monitored for changes that might indicate the presence of cancer (Figure 4.9).

Figure 4.9. Moles

Moles range from benign accumulations of melanocytes to melanomas. These structures populate the landscape of our skin. (credit: the National Cancer Institute)

Disorders of the Integumentary System

The first thing a clinician sees is the skin, and so the examination of the skin should be part of any thorough physical examination. Most skin disorders are relatively benign, but a few, including melanomas, can be fatal if untreated. A couple of the more noticeable disorders, albinism and vitiligo, affect the appearance of the skin and its accessory organs. Although neither is fatal, it would be hard to claim that they are benign, at least to the individuals so afflicted.

Albinism is a genetic disorder that affects (completely or partially) the coloring of skin, hair, and eyes. The defect is primarily due to the inability of melanocytes to produce melanin. Individuals with albinism tend to appear white or very pale due to the lack of melanin in their skin and hair. Recall that melanin helps protect the skin from the harmful effects of UV radiation. Individuals with albinism tend to need more protection from UV radiation, as they are more prone to sunburns and skin cancer. They also tend to be more sensitive to light and have vision problems due to the lack of pigmentation on the retinal wall. Treatment of this disorder usually involves addressing the symptoms, such as limiting UV light exposure to the skin and eyes. In *vitiligo*, the melanocytes in certain areas lose their ability to produce melanin, possibly due to an autoimmune reaction. This leads to a loss of color in patches (Figure 4.10). Neither albinism nor vitiligo directly affects the lifespan of an individual.

Figure 4.10. Vitiligo
Individuals with vitiligo experience depigmentation that results in lighter colored patches of skin. The condition is especially noticeable on darker skin. (credit: Klaus D. Peter)

Other changes in the appearance of skin coloration can be indicative of diseases associated with other body systems. Liver disease or liver cancer can cause the accumulation of bile and the yellow pigment bilirubin, leading to the skin appearing yellow or jaundiced (*jaune* is the French word for "yellow"). Tumors of the pituitary gland can result in the secretion of large amounts of melanocyte-stimulating hormone (MSH), which results in a darkening of the skin. Similarly, Addison's disease can stimulate the release of excess amounts of adrenocorticotropic hormone (ACTH), which can give the skin a deep bronze color. A sudden drop in oxygenation can affect skin color, causing the skin to initially turn ashen (white). With a prolonged reduction in oxygen levels, dark red deoxyhemoglobin becomes dominant in the blood, making the skin appear blue, a condition referred to as cyanosis (*kyanos* is the Greek word for “blue”). This happens when the oxygen supply is restricted, as when someone is experiencing difficulty in breathing because of asthma or a heart attack. However, in these cases the effect on skin color has nothing do with the skin’s pigmentation.

23. Accessory Structures of the Skin

Accessory structures of the skin include hair, nails, sweat glands, and sebaceous glands. These structures embryologically originate from the epidermis and can extend down through the dermis into the hypodermis.

Hair

Hair is a keratinous filament growing out of the epidermis. It is primarily made of dead, keratinized cells. Strands of hair originate in an epidermal penetration of the dermis called the ***hair follicle***. The ***hair shaft*** is the part of the hair not anchored to the follicle, and much of this is exposed at the skin's surface. The rest of the hair, which is anchored in the follicle, lies below the surface of the skin and is referred to as the ***hair root***. The hair root ends deep in the dermis at the ***hair bulb***, and includes a layer of mitotically active basal cells called the ***hair matrix***. The hair bulb surrounds the ***hair papilla***, which is made of connective tissue and contains blood capillaries and nerve endings from the dermis (Figure 4.11).

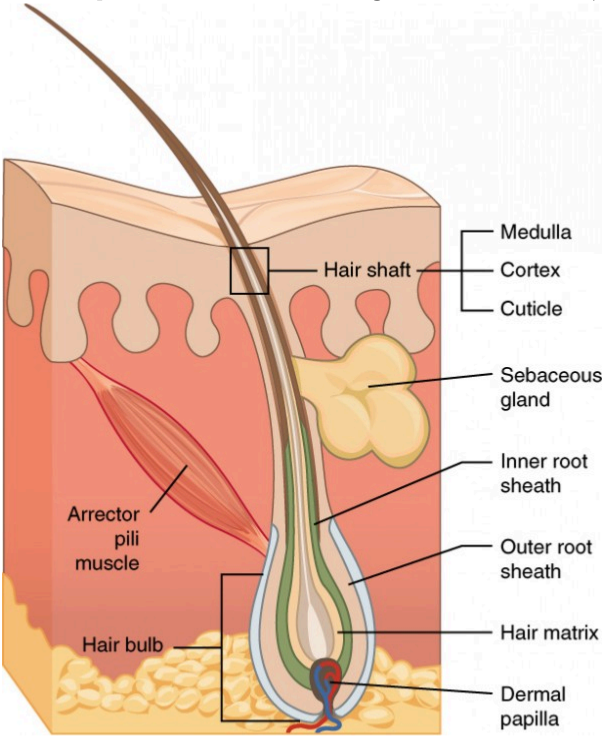


Figure 4.11. Hair
Hair follicles originate in the epidermis and have many different parts.

Just as the basal layer of the epidermis forms the layers of epidermis that get pushed to the surface as the dead skin on the surface sheds, the basal cells of the hair bulb divide and push cells outward in the hair root and shaft as the hair grows. The ***medulla*** forms the central core of the hair, which is surrounded by the ***cortex***, a layer of compressed, keratinized cells that is covered by an outer layer of very hard, keratinized cells known as the ***cuticle***. These layers are depicted in a longitudinal cross-section of the hair follicle

(Figure 4.12), although not all hair has a medullary layer. Hair texture (straight, curly) is determined by the shape and structure of the cortex, and to the extent that it is present, the medulla. The shape and structure of these layers are, in turn, determined by the shape of the hair follicle. Hair growth begins with the production of keratinocytes by the basal cells of the hair bulb. As new cells are deposited at the hair bulb, the hair shaft is pushed through the follicle toward the surface. Keratinization is completed as the cells are pushed to the skin surface to form the shaft of hair that is externally visible. The external hair is completely dead and composed entirely of keratin. For this reason, our hair does not have sensation. Furthermore, you can cut your hair or shave without damaging the hair structure because the cut is superficial. Most chemical hair removers also act superficially; however, electrolysis and yanking both attempt to destroy the hair bulb so hair cannot grow.

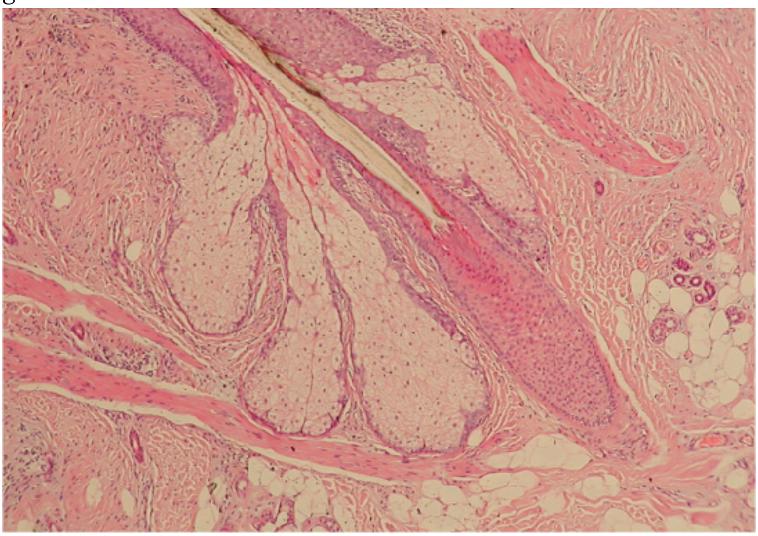


Figure 4.12. Hair Follicle

The slide shows a cross-section of a hair follicle. Basal cells of the hair matrix in the center differentiate into cells of the inner root sheath. Basal cells at the base of the hair root form the outer root sheath. LM × 4. *(credit: modification of work by "kilbad"/Wikimedia*

Commons)

The wall of the hair follicle is made of three concentric layers of cells. The cells of the ***internal root sheath*** surround the root of the growing hair and extend just up to the hair shaft. They are derived from the basal cells of the hair matrix. The ***external root sheath***, which is an extension of the epidermis, encloses the hair root. It is made of basal cells at the base of the hair root and tends to be more keratinous in the upper regions. The ***glassy membrane*** is a thick, clear connective tissue sheath covering the hair root, connecting it to the tissue of the dermis.

Hair serves a variety of functions, including protection, sensory input, thermoregulation, and communication. For example, hair on the head protects the skull from the sun. The hair in the nose and ears, and around the eyes (eyelashes) defends the body by trapping and excluding dust particles that may contain allergens and microbes. Hair of the eyebrows prevents sweat and other particles from dripping into and bothering the eyes. Hair also has a sensory function due to sensory innervation by a hair root plexus surrounding the base of each hair follicle. Hair is extremely sensitive to air movement or other disturbances in the environment, much more so than the skin surface. This feature is also useful for the detection of the presence of insects or other potentially damaging substances on the skin surface. Each hair root is connected to a smooth muscle called the ***arrector pili*** that contracts in response to nerve signals from the sympathetic nervous system, making the external hair shaft "stand up." The primary purpose for this is to trap a layer of air to add insulation. This is visible in humans as goose bumps and even more obvious in animals, such as when a frightened cat raises its fur. Of course, this is much more obvious in organisms with a heavier coat than most humans, such as dogs and cats.

Hair Growth

Hair grows and is eventually shed and replaced by new hair. This occurs in three phases. The first is the ***anagen*** phase, during which cells divide rapidly at the root of the hair, pushing the hair shaft up and out. The length of this phase is measured in years, typically from 2 to 7 years. The ***catagen*** phase lasts only 2 to 3 weeks, and marks a transition from the hair follicle's active growth. Finally, during the ***telogen*** phase, the hair follicle is at rest and no new growth occurs. At the end of this phase, which lasts about 2 to 4 months, another anagen phase begins. The basal cells in the hair matrix then produce a new hair follicle, which pushes the old hair out as the growth cycle repeats itself. Hair typically grows at the rate of 0.3 mm per day during the anagen phase. On average, 50 hairs are lost and replaced per day. Hair loss occurs if there is more hair shed than what is replaced and can happen due to hormonal or dietary changes. Hair loss can also result from the aging process, or the influence of hormones.

Hair Color

Similar to the skin, hair gets its color from the pigment melanin, produced by melanocytes in the hair papilla. Different hair color results from differences in the type of melanin, which is genetically determined. As a person ages, the melanin production decreases, and hair tends to lose its color and becomes gray and/or white.

Nails

The nail bed is a specialized structure of the epidermis that is found at the tips of our fingers and toes. The ***nail body*** is formed on the ***nail bed***, and protects the tips of our fingers and toes as they are the farthest extremities and the parts of the body that experience the maximum mechanical stress (Figure 4.13). In addition, the nail body forms a back-support for picking up small objects with the fingers. The nail body is composed of densely packed dead keratinocytes. The epidermis in this part of the body has evolved a specialized structure upon which nails can form. The nail body forms at the *nail* ***root***, which has a matrix of proliferating cells from the stratum basale that enables the nail to grow continuously. The lateral ***nail fold*** overlaps the nail on the sides, helping to anchor the nail body. The nail fold that meets the proximal end of the nail body forms the ***nail cuticle***, also called the ***eponychium***. The nail bed is rich in blood vessels, making it appear pink, except at the base, where a thick layer of epithelium over the nail matrix forms a crescent-shaped region called the ***lunula*** (the "little moon"). The area beneath the free edge of the nail, furthest from the cuticle, is called the ***hyponychium***. It consists of a thickened layer of stratum corneum.

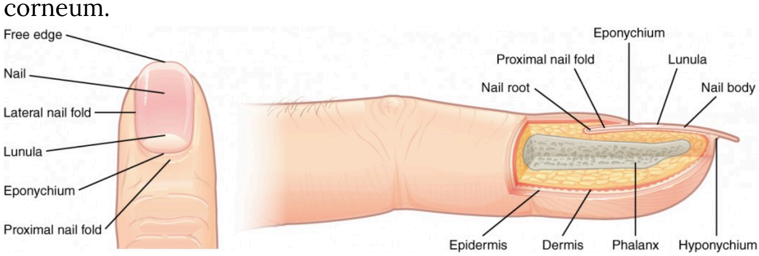


Figure 4.13. Nails
The nail is an accessory structure of the integumentary system.

Sweat Glands

When the body becomes warm, ***sudoriferous glands*** produce sweat to cool the body. Sweat glands develop from epidermal projections into the dermis and are classified as merocrine glands; that is, the secretions are excreted by exocytosis through a duct without affecting the cells of the gland. There are two types of sweat glands, each secreting slightly different products.

An ***eccrine sweat gland*** is type of gland that produces a hypotonic sweat for thermoregulation. These glands are found all over the skin's surface, but are especially abundant on the palms of the hand, the soles of the feet, and the forehead (Figure 4.14). They are coiled glands lying deep in the dermis, with the duct rising up to a pore on the skin surface, where the sweat is released. This type of sweat, released by exocytosis, is hypotonic and composed mostly of water, with some salt, antibodies, traces of metabolic waste, and dermicidin, an antimicrobial peptide. Eccrine glands are a primary component of thermoregulation in humans and thus help to maintain homeostasis.

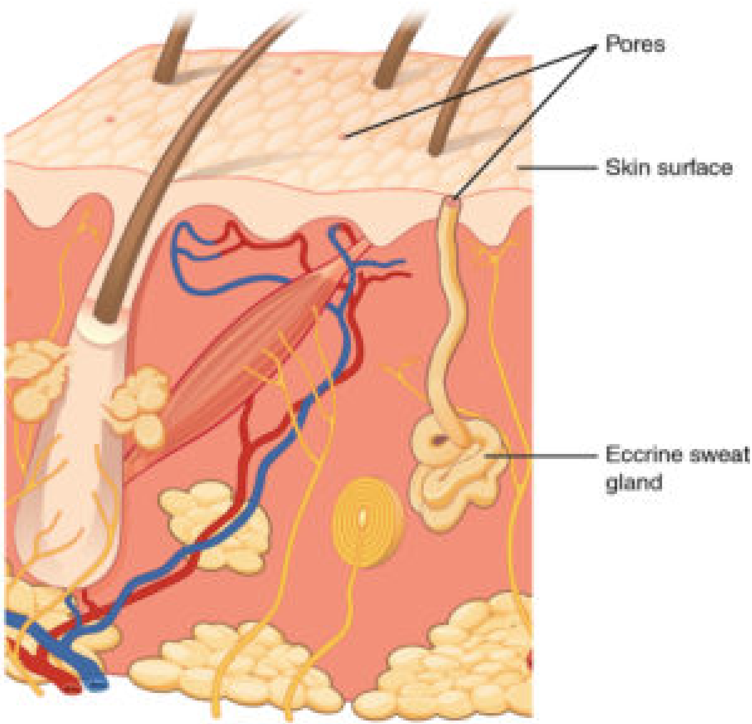


Figure 4.14. Eccrine Gland

Eccrine glands are coiled glands in the dermis that release sweat that is mostly water.

An ***apocrine sweat gland*** is usually associated with hair follicles in densely hairy areas, such as armpits and genital regions. Apocrine sweat glands are larger than eccrine sweat glands and lie deeper in the dermis, sometimes even reaching the hypodermis, with the duct normally emptying into the hair follicle. In addition to water and salts, apocrine sweat includes organic compounds that make the sweat thicker and subject to bacterial decomposition and subsequent smell. The release of this sweat is under both nervous and hormonal control, and plays a role in the poorly understood human pheromone response. Most commercial antiperspirants use an aluminum-based compound as their primary active ingredient to stop sweat. When the antiperspirant enters the sweat gland duct, the aluminum-based compounds precipitate due to a change in pH and form a physical block in the duct, which prevents sweat from coming out of the pore.

Sebaceous Glands

A ***sebaceous glan****d* is a type of oil gland that is found all over the body and helps to lubricate and waterproof the skin and hair. Most sebaceous glands are associated with hair follicles. They generate and excrete ***sebum***, a mixture of lipids, onto the skin surface, thereby naturally lubricating the dry and dead layer of keratinized cells of the stratum corneum, keeping it pliable. The fatty acids of sebum also have antibacterial properties, and prevent water loss from the skin in low-humidity environments. The secretion of sebum is stimulated by hormones, many of which do not become active until puberty. Thus, sebaceous glands are relatively inactive during childhood.

24. Functions of the Integumentary System

The skin and accessory structures perform a variety of essential functions, such as protecting the body from invasion by microorganisms, chemicals, and other environmental factors; preventing dehydration; acting as a sensory organ; modulating body temperature and electrolyte balance; and synthesizing vitamin D. The underlying hypodermis has important roles in storing fats, forming a "cushion" over underlying structures, and providing insulation from cold temperatures.

Protection

The skin protects the rest of the body from the basic elements of nature such as wind, water, and UV sunlight. It acts as a protective barrier against water loss, due to the presence of layers of keratin and glycolipids in the stratum corneum. It also is the first line of defense against abrasive activity due to contact with grit, microbes, or harmful chemicals. Sweat excreted from sweat glands deters microbes from over-colonizing the skin surface by generating dermicidin, which has antibiotic properties.

Everyday Connection: Tattoos and Piercings

The word "armor" evokes several images. You might think of a Roman centurion or a medieval knight in a suit of armor. The skin, in its own way, functions as a form of armor—body armor. It provides a barrier between your vital, life-sustaining organs and the influence of outside elements that could potentially damage them.

For any form of armor, a breach in the protective barrier poses a danger. The skin can be breached when a child skins a knee or an adult has blood drawn—one is accidental and the other medically necessary. However, you also breach this barrier when you choose to "accessorize" your skin with a tattoo or body piercing. Because the needles involved in producing body art and piercings must penetrate the skin, there are dangers associated with the practice. These include allergic reactions; skin infections; blood-borne diseases, such as tetanus, hepatitis C, and hepatitis D; and the growth of scar tissue. Despite the risk, the practice of piercing the skin for decorative purposes has become increasingly popular. According to the American Academy of Dermatology, 24 percent of people from ages 18 to 50 have a tattoo.

Tattooing has a long history, dating back thousands of years ago. The dyes used in tattooing typically derive from metals. A person with tattoos should be cautious when having a magnetic resonance imaging (MRI) scan because an MRI machine uses powerful magnets to create images of the soft tissues of the body, which could react with the metals contained in the tattoo dyes. Watch this video to learn more about tattooing.

Sensory Function

The fact that you can feel an ant crawling on your skin, allowing you to flick it off before it bites, is because the skin, and especially the hairs projecting from hair follicles in the skin, can sense changes in the environment. The hair root plexus surrounding the base of the hair follicle senses a disturbance, and then transmits the information to the central nervous system (brain and spinal cord), which can then respond by activating the skeletal muscles of your eyes to see the ant and the skeletal muscles of the body to act against the ant.

The skin acts as a sense organ because the epidermis, dermis, and the hypodermis contain specialized sensory nerve structures that detect touch, surface temperature, and pain. These receptors are more concentrated on the tips of the fingers, which are most sensitive to touch, especially the *Meissner corpuscle* (tactile corpuscle) (Figure 4.15), which responds to light touch, and the *Pacinian corpuscle* (lamellated corpuscle), which responds to vibration. Merkel cells, seen scattered in the stratum basale, are also touch receptors. In addition to these specialized receptors, there are sensory nerves connected to each hair follicle, pain and temperature receptors scattered throughout the skin, and motor nerves innervate the arrector pili muscles and glands. This rich innervation helps us sense our environment and react accordingly.

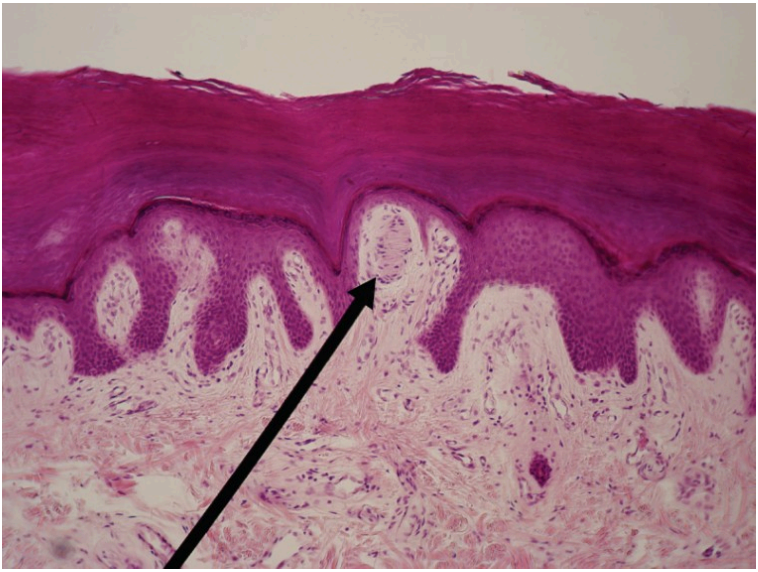


Figure 4.15. Light Micrograph of a Meissneer Corpuscle
In this micrograph of a skin cross-section, you can see a Meissner corpuscle (arrow), a type of touch receptor located in a dermal papilla adjacent to the basement membrane and stratum basale of the overlying epidermis. LM × 100. (credit: "Wbensmith"/Wikimedia Commons)

Thermoregulation

The integumentary system helps regulate body temperature through its tight association with the sympathetic nervous system, the division of the nervous system involved in our fight-or-flight responses. The sympathetic nervous system is continuously monitoring body temperature and initiating appropriate motor responses. Recall that sweat glands, accessory structures to the skin, secrete water, salt, and other substances to cool the body when it becomes warm. Even when the body does not appear to be noticeably sweating, approximately 500 mL of sweat (insensible perspiration) are secreted a day. If the body becomes excessively warm due to high temperatures, vigorous activity (Figure 4.16ac), or a combination of the two, sweat glands will be stimulated by the sympathetic nervous system to produce large amounts of sweat, as much as 0.7 to 1.5 L per hour for an active person. When the sweat evaporates from the skin surface, the body is cooled as body heat is dissipated.

In addition to sweating, arterioles in the dermis dilate so that excess heat carried by the blood can dissipate through the skin and into the surrounding environment (Figure 4.16b). This accounts for the skin redness that many people experience when exercising.

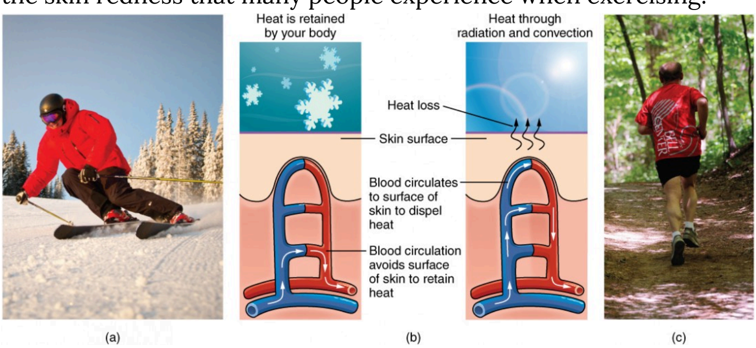


Figure 4.16. Thermoregulation

During strenuous physical activities, such as skiing (a) or running (c), the dermal blood vessels dilate and sweat secretion increases (b). These mechanisms prevent the body from overheating. In contrast, the dermal blood vessels constrict to minimize heat loss in response to low temperatures (b). (credit a: "Trysil"/flickr; credit c: Ralph Daily)

When body temperatures drop, the arterioles constrict to minimize heat loss, particularly in the ends of the digits and tip of the nose. This reduced circulation can result in the skin taking on a whitish hue. Although the temperature of the skin drops as a result, passive heat loss is prevented, and internal organs and structures remain warm. If the temperature of the skin drops too much (such as environmental temperatures below freezing), the conservation of body core heat can result in the skin actually freezing, a condition called frostbite.

Vitamin D Synthesis

The epidermal layer of human skin synthesizes *vitamin D* when exposed to UV radiation. In the presence of sunlight, a form of vitamin D_3 called cholecalciferol is synthesized from a derivative of the steroid cholesterol in the skin. The liver converts cholecalciferol to calcidiol, which is then converted to calcitriol (the active chemical form of the vitamin) in the kidneys. Vitamin D is essential for normal absorption of calcium and phosphorous, which are required for healthy bones. The absence of sun exposure can lead to a lack of vitamin D in the body, leading to a condition called *rickets*, a painful condition in children where the bones are misshapen due to a lack of calcium, causing bowleggedness. Elderly individuals who suffer from vitamin D deficiency can develop a condition called osteomalacia, a softening of the bones. In present day society, vitamin D is added as a supplement to many foods, including milk and orange juice, compensating for the need for sun exposure.

In addition to its essential role in bone health, vitamin D is essential for general immunity against bacterial, viral, and fungal infections. Recent studies are also finding a link between insufficient vitamin D and cancer.

25. Age Related Changes to the Integumentary System

Aging and the Integumentary System

All systems in the body accumulate subtle and some not-so-subtle changes as a person ages. Among these changes are reductions in cell division, metabolic activity, blood circulation, hormonal levels, and muscle strength (Figure 4.17). In the skin, these changes are reflected in decreased mitosis in the stratum basale, leading to a thinner epidermis. The dermis, which is responsible for the elasticity and resilience of the skin, exhibits a reduced ability to regenerate, which leads to slower wound healing. The hypodermis, with its fat stores, loses structure due to the reduction and redistribution of fat, which in turn contributes to the thinning and sagging of skin.

Figure 4.17. Aging

Generally, skin, especially on the face and hands, starts to display the first noticeable signs of aging, as it loses its elasticity over time. (credit: Janet Ramsden)

The accessory structures also have lowered activity, generating thinner hair and nails, and reduced amounts of sebum and sweat. A reduced sweating ability can cause some elderly to be intolerant to extreme heat. Other cells in the skin, such as melanocytes and dendritic cells, also become less active, leading to a paler skin tone and lowered immunity. Wrinkling of the skin occurs due to breakdown of its structure, which results from decreased collagen and elastin production in the dermis, weakening of muscles lying under the skin, and the inability of the skin to retain adequate moisture.

Many anti-aging products can be found in stores today. In general, these products try to rehydrate the skin and thereby fill out the wrinkles, and some stimulate skin growth using hormones and growth factors. Additionally, invasive techniques include collagen injections to plump the tissue and injections of BOTOX® (the name brand of the botulinum neurotoxin) that paralyze the muscles that crease the skin and cause wrinkling.

26. Diseases, Disorders, and Injuries

The integumentary system is susceptible to a variety of diseases, disorders, and injuries. These range from annoying but relatively benign bacterial or fungal infections that are categorized as disorders, to skin cancer and severe burns, which can be fatal. In this section, you will learn several of the most common skin conditions.

Diseases

One of the most talked about diseases is skin cancer. Cancer is a broad term that describes diseases caused by abnormal cells in the body dividing uncontrollably. Most cancers are identified by the organ or tissue in which the cancer originates. One common form of cancer is skin cancer. The Skin Cancer Foundation reports that one in five Americans will experience some type of skin cancer in their lifetime. The degradation of the ozone layer in the atmosphere and the resulting increase in exposure to UV radiation has contributed to its rise. Overexposure to UV radiation damages DNA, which can lead to the formation of cancerous lesions. Although melanin offers some protection against DNA damage from the sun, often it is not enough. The fact that cancers can also occur on areas of the body that are normally not exposed to UV radiation suggests that there are additional factors that can lead to cancerous lesions.

In general, cancers result from an accumulation of DNA mutations. These mutations can result in cell populations that do not die when they should and uncontrolled cell proliferation that leads to tumors. Although many tumors are benign (harmless), some produce cells that can mobilize and establish tumors in other organs of the body; this process is referred to as ***metastasis***. Cancers are characterized by their ability to metastasize.

Basal Cell Carcinoma

Basal cell carcinoma is a form of cancer that affects the mitotically active stem cells in the stratum basale of the epidermis. It is the most common of all cancers that occur in the United States and is frequently found on the head, neck, arms, and back, which are areas that are most susceptible to long-term sun exposure. Although UV rays are the main culprit, exposure to other agents, such as radiation and arsenic, can also lead to this type of cancer. Wounds on the skin due to open sores, tattoos, burns, etc. may be predisposing factors as well. Basal cell carcinomas start in the stratum basale and usually spread along this boundary. At some point, they begin to grow toward the surface and become an uneven patch, bump, growth, or scar on the skin surface (Figure 4.18). Like most cancers, basal cell carcinomas respond best to treatment when caught early. Treatment options include surgery, freezing (cryosurgery), and topical ointments (Mayo Clinic 2012).

Figure 4.18. Basal Cell Carcinoma

Basal cell carcinoma can take several different forms. Similar to other forms of skin cancer, it is readily cured if caught early and treated. (credit: John Hendrix, MD)

Squamous Cell Carcinoma

Squamous cell carcinoma is a cancer that affects the keratinocytes of the stratum spinosum and presents as lesions commonly found on the scalp, ears, and hands (Figure 4.19). It is the second most common skin cancer. The American Cancer Society reports that two of 10 skin cancers are squamous cell carcinomas, and it is more aggressive than basal cell carcinoma. If not removed, these carcinomas can metastasize. Surgery and radiation are used to cure squamous cell carcinoma.

Figure 4.19. Squamous Cell Carcinoma
Squamous cell carcinoma presents here as a lesion on an individual's nose. (credit: the National Cancer Institute)

Melanoma

A ***melanoma*** is a cancer characterized by the uncontrolled growth of melanocytes, the pigment-producing cells in the epidermis. Typically, a melanoma develops from a mole. It is the most fatal of all skin cancers, as it is highly metastatic and can be difficult to detect before it has spread to other organs. Melanomas usually appear as asymmetrical brown and black patches with uneven borders and a raised surface (Figure 4.20). Treatment typically involves surgical excision and immunotherapy.

Figure 4.20. Melanoma
Melanomas typically present as large brown or black patches with uneven borders and a raised surface. (credit: the National Cancer Institute)

Doctors often give their patients the following ABCDE mnemonic to help with the diagnosis of early-stage melanoma. If you observe a mole on your body displaying these signs, consult a doctor.

- **A**symmetry – the two sides are not symmetrical
- **B**orders – the edges are irregular in shape

- **C**olor – the color is varied shades of brown or black
- **D**iameter – it is larger than 6 mm (0.24 in)
- **E**volving – its shape has changed

Some specialists cite the following additional signs for the most serious form, nodular melanoma:

- **E**levated – it is raised on the skin surface
- **F**irm – it feels hard to the touch
- **G**rowing – it is getting larger

Skin Disorders

Two common skin disorders are eczema and acne. Eczema is an inflammatory condition and occurs in individuals of all ages. Acne involves the clogging of pores, which can lead to infection and inflammation, and is often seen in adolescents. Other disorders, not discussed here, include seborrheic dermatitis (on the scalp), psoriasis, cold sores, impetigo, scabies, hives, and warts.

Eczema

Eczema is an allergic reaction that manifests as dry, itchy patches of skin that resemble rashes (Figure 4.21). It may be accompanied by swelling of the skin, flaking, and in severe cases, bleeding. Many who suffer from eczema have antibodies against dust mites in their blood, but the link between eczema and allergy to dust mites has not been proven. Symptoms are usually managed with moisturizers, corticosteroid creams, and immunosuppressants.

Figure 4.21. Eczema

Eczema is a common skin disorder that presents as a red, flaky rash. (credit: "Jambula"/Wikimedia Commons)

Acne

Acne is a skin disturbance that typically occurs on areas of the skin that are rich in sebaceous glands (face and back). It is most common along with the onset of puberty due to associated hormonal changes, but can also occur in infants and continue into adulthood. Hormones, such as androgens, stimulate the release of sebum. An overproduction and accumulation of sebum along with keratin can block hair follicles. This plug is initially white. The sebum, when oxidized by exposure to air, turns black. Acne results from infection by acne-causing bacteria (*Propionibacterium* and *Staphylococcus*), which can lead to redness and potential scarring due to the natural wound healing process (Figure 4.22).

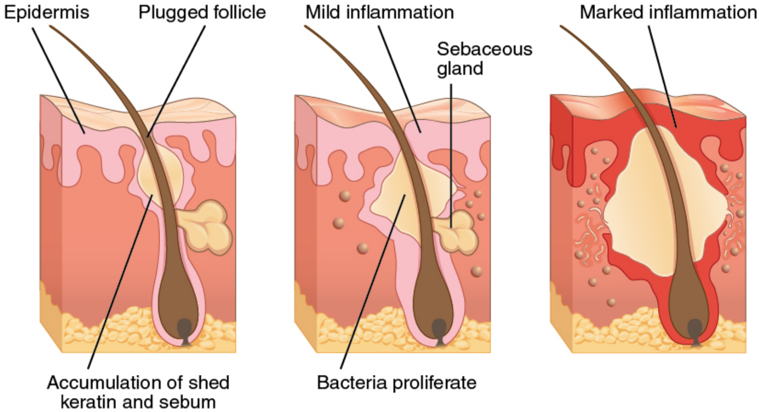


Figure 4.22. Acne

Acne is a result of over-productive sebaceous glands, which leads to formation of blackheads and inflammation of the skin.

Injuries

Because the skin is the part of our bodies that meets the world most directly, it is especially vulnerable to injury. Injuries include burns and wounds, as well as scars and calluses. They can be caused by sharp objects, heat, or excessive pressure or friction to the skin.

Skin injuries set off a healing process that occurs in several overlapping stages. The first step to repairing damaged skin is the formation of a blood clot that helps stop the flow of blood and scabs over with time. Many different types of cells are involved in wound repair, especially if the surface area that needs repair is extensive. Before the basal stem cells of the stratum basale can recreate the epidermis, fibroblasts mobilize and divide rapidly to repair the damaged tissue by collagen deposition, forming granulation tissue. Blood capillaries follow the fibroblasts and help increase blood circulation and oxygen supply to the area. Immune cells, such as macrophages, roam the area and engulf any foreign matter to reduce the chance of infection.

Burns

A burn results when the skin is damaged by intense heat, radiation, electricity, or chemicals. The damage results in the death of skin cells, which can lead to a massive loss of fluid. Dehydration, electrolyte imbalance, and renal and circulatory failure follow, which can be fatal. Burn patients are treated with intravenous fluids to offset dehydration, as well as intravenous nutrients that enable the body to repair tissues and replace lost proteins. Another serious threat to the lives of burn patients is infection. Burned skin is extremely susceptible to bacteria and other pathogens, due to the loss of protection by intact layers of skin.

Burns are sometimes measured in terms of the size of the total surface area affected. This is referred to as the "rule of nines," which associates specific anatomical areas with a percentage that is a factor of nine (Figure 4.23). Burns are also classified by the degree of their severity. A ***first-degree burn*** is a superficial burn that affects only the epidermis. Although the skin may be painful and swollen, these burns typically heal on their own within a few days. Mild sunburn fits into the category of a first-degree burn. A s***econd-degree burn*** goes deeper and affects both the epidermis and a portion of the dermis. These burns result in swelling and a painful blistering of the skin. It is important to keep the burn site clean and sterile to prevent infection. If this is done, the burn will heal within several weeks. A ***third-degree burn*** fully extends into the epidermis and dermis, destroying the tissue and affecting the nerve endings and sensory function. These are serious burns that may appear white, red, or black; they require medical attention and will heal slowly without it. A ***fourth-degree burn*** is even more severe, affecting the underlying muscle and bone. Oddly, third and fourth-degree burns are usually not as painful because the nerve endings themselves are damaged. Full-thickness burns cannot be repaired by the body, because the local tissues used for repair are damaged and require excision (debridement), or amputation in severe cases, followed by grafting of the skin from an unaffected part of the body, or from skin grown in tissue culture for grafting purposes.

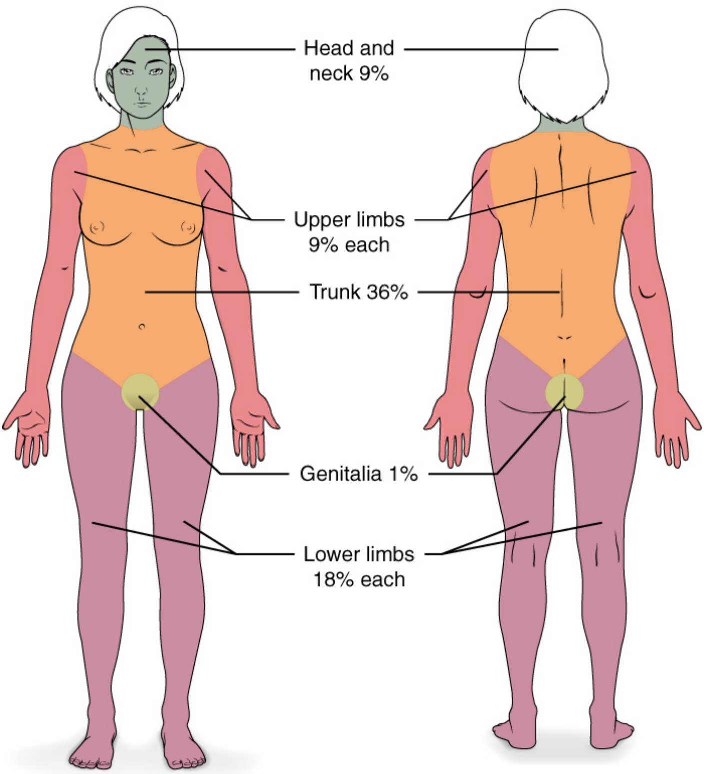


Figure 4.23. Calculating the Size of a Burn
The size of a burn will guide decisions made about the need for specialized treatment. Specific parts of the body are associated with a percentage of body area.

Scars and Keloids

Most cuts or wounds, with the exception of ones that only scratch the surface (the epidermis), lead to scar formation. A ***scar*** is collagen-rich skin formed after the process of wound healing that differs from normal skin. Scarring occurs in cases in which there is repair of skin damage, but the skin fails to regenerate the original skin structure. Fibroblasts generate scar tissue in the form of collagen, and the bulk of repair is due to the basket-weave pattern generated by collagen fibers and does not result in regeneration of the typical cellular structure of skin. Instead, the tissue is fibrous in nature and does not allow for the regeneration of accessory structures, such as hair follicles, sweat glands, or sebaceous glands.

Sometimes, there is an overproduction of scar tissue, because the process of collagen formation does not stop when the wound is healed; this results in the formation of a raised or hypertrophic scar called a ***keloid***. In contrast, scars that result from acne and chickenpox have a sunken appearance and are called atrophic scars.

Scarring of skin after wound healing is a natural process and does not need to be treated further. Application of mineral oil and lotions may reduce the formation of scar tissue. However, modern cosmetic procedures, such as dermabrasion, laser treatments, and filler injections have been invented as remedies for severe scarring. All of these procedures try to reorganize the structure of the epidermis and underlying collagen tissue to make it look more natural.

Bedsores and Stretch Marks

Skin and its underlying tissue can be affected by excessive pressure. One example of this is called a ***bedsore***. Bedsores, also called decubitis ulcers, are caused by constant, long-term, unrelieved pressure on certain body parts that are bony, reducing blood flow to the area and leading to necrosis (tissue death). Bedsores are most common in elderly patients who have debilitating conditions that cause them to be immobile. Most hospitals and long-term care facilities have the practice of turning the patients every few hours to prevent the incidence of bedsores. If left untreated by removal of necrotized tissue, bedsores can be fatal if they become infected.

The skin can also be affected by pressure associated with rapid growth. A ***stretch mark*** results when the dermis is stretched beyond its limits of elasticity, as the skin stretches to accommodate the excess pressure. Stretch marks usually accompany rapid weight gain during puberty and pregnancy. They initially have a reddish hue, but lighten over time. Other than for cosmetic reasons, treatment of stretch marks is not required. They occur most commonly over the hips and abdomen.

Calluses

When you wear shoes that do not fit well and are a constant source of abrasion on your toes, you tend to form a ***callus*** at the point of contact. This occurs because the basal stem cells in the stratum basale are triggered to divide more often to increase the thickness of the skin at the point of abrasion to protect the rest of the body from further damage. This is an example of a minor or local injury, and the skin manages to react and treat the problem independent of the rest of the body. Calluses can also form on your fingers if they are subject to constant mechanical stress, such as long periods of writing, playing string instruments, or video games. A ***corn*** is a specialized form of callus. Corns form from abrasions on the skin that result from an elliptical-type motion.

27. Age Related Dysfunctions to the Integumentary System

Acrochordon

Acrochordon is a condition which affects older women. Acrochordon is characterized by small pendulous growths on the skin, otherwise known as skin tags. The skin tags contain dermal connective tissues and blood vessels. They are thought to be associated with hormonal imbalances.

Decubitus Ulcers

Decubitus ulcers is a condition which affects people who are bedridden or otherwise immobilized, such as those confined to a wheelchair or who spend their days sitting rather than moving about. The decubitus ulcers are characterized by cavities of dead tissue that form in the skin. The constant pressure from being immobile reduces blood flow to skin and irritates the tissue. Bacteria can then attack the weakened tissue.

Herpes Zoster

Herpes zoster is a condition which can affects people of all ages, but is most common in people between the ages of 50 and 70. Also known as shingles, the disease is characterized by itching and aching pain which is followed by the appearance of small red papules on the skin. The papules are replaced by small fluid-filled vesicles which burst and can be quite painful. The disease is caused by the same virus that causes chickenpox. After entering the body and causing chickenpox, the virus lays dormant in the body for years only to reappear later in life.

Lentigo

Lentigo is a condition which affects people above the age of 50 years. Commonly known as liver spots or senile freckle, lentigo is characterized by blemishes on the skin associated with aging and exposure to ultraviolet radiation from the sun. They range in color from light brown to red or black and are located in areas most often exposed to the sun, particularly the hands, face, shoulders, arms and forehead, and the scalp if bald.

Seborrheic Keratosis

Seborrheic keratosis is a condition which affects middle-age and older adults. The condition is characterized by the formation of benign epidermal tumors. These flesh-colored, oval, raised plaques typically form on the face, scalp, chest, or back. Gradually these plaques thicken, enlarge, and darken. Seborrheic keratosis is an inherited condition.

Senile Angiomas

Senile angiomas is a condition which affects 75% of people over the age of seventy. The condition is characterized by red spots ranging from very tiny to over one-quarter inch in diameter. These spots are caused by clusters of dilated capillaries.

Senile Keratosis

Senile keratosis is a condition affecting middle-age and elderly adults. Senile keratosis is characterized by localized red areas on the skin. The areas are generally flat when they first appear but gradually thicken.

Senile Purpura

Senile purpura is a condition which affects older people and characterized by irregularly shaped purple patches. These are bruises resulting from minimal trauma, mostly commonly found on the forearms and hands. As one ages capillaries weakened and results in blood pools under the skin leaving a bruise.

Senile Pruritus

Senile pruritus is a condition which affects the elderly and characterized by drier and less pliant skin which leads to the development of tiny cracks in the skin. The condition develops as a result of the gradual loss of oil-secreting sebaceous glans and sweat glands, as well as a reduction in the water content of skin.

28. Glossary: The Integumentary System

acne
: skin condition due to infected sebaceous glands

albinism
: genetic disorder that affects the skin, in which there is no melanin production

anagen
: active phase of the hair growth cycle

apocrine sweat gland
: type of sweat gland that is associated with hair follicles in the armpits and genital regions

arrector pili
: smooth muscle that is activated in response to external stimuli that pull on hair follicles and make the hair "stand up"

basal cell carcinoma
: cancer that originates from basal cells in the epidermis of the skin

basal cell
: type of stem cell found in the stratum basale and in the hair matrix that continually undergoes cell division, producing the keratinocytes of the epidermis

bedsore
: sore on the skin that develops when regions of the body start necrotizing due to constant pressure and lack of blood supply; also called decubitis ulcers

callus
: thickened area of skin that arises due to constant abrasion

catagen
: transitional phase marking the end of the anagen phase of the hair growth cycle

corn
: type of callus that is named for its shape and the elliptical motion of the abrasive force

cortex
: in hair, the second or middle layer of keratinocytes originating from the hair matrix, as seen in a cross-section of the hair bulb

cuticle
: in hair, the outermost layer of keratinocytes originating from the hair matrix, as seen in a cross-section of the hair bulb

dermal papilla
: (plural = dermal papillae) extension of the papillary layer of the dermis that increases surface contact between the epidermis and dermis

dermis
: layer of skin between the epidermis and hypodermis, composed mainly of connective tissue and containing blood vessels, hair follicles, sweat glands, and other structures

desmosome
: structure that forms an impermeable junction between cells

eccrine sweat gland
: type of sweat gland that is common throughout the skin surface; it produces a hypotonic sweat for thermoregulation

eczema
: skin condition due to an allergic reaction, which resembles a

rash

elastin fibers
: fibers made of the protein elastin that increase the elasticity of the dermis

eleiden
: clear protein-bound lipid found in the stratum lucidum that is derived from keratohyalin and helps to prevent water loss

epidermis
: outermost tissue layer of the skin

eponychium
: nail fold that meets the proximal end of the nail body, also called the cuticle

external root sheath
: outer layer of the hair follicle that is an extension of the epidermis, which encloses the hair root

first-degree burn
: superficial burn that injures only the epidermis

fourth-degree burn
: burn in which full thickness of the skin and underlying muscle and bone is damaged

glassy membrane
: layer of connective tissue that surrounds the base of the hair follicle, connecting it to the dermis

hair bulb
: structure at the base of the hair root that surrounds the dermal papilla

hair follicle
: cavity or sac from which hair originates

hair matrix
: layer of basal cells from which a strand of hair grows

hair papilla
: mass of connective tissue, blood capillaries, and nerve endings at the base of the hair follicle

hair root
: part of hair that is below the epidermis anchored to the follicle

hair shaft
: part of hair that is above the epidermis but is not anchored to the follicle

hair
: keratinous filament growing out of the epidermis

hypodermis
: connective tissue connecting the integument to the underlying bone and muscle

hyponychium
: thickened layer of stratum corneum that lies below the free edge of the nail

integumentary system
: skin and its accessory structures

internal root sheath
: innermost layer of keratinocytes in the hair follicle that surround the hair root up to the hair shaft

keloid
: type of scar that has layers raised above the skin surface

keratin
: type of structural protein that gives skin, hair, and nails its hard, water-resistant properties

keratinocyte
: cell that produces keratin and is the most predominant type of cell found in the epidermis

keratohyalin
: granulated protein found in the stratum granulosum

Langerhans cell
: specialized dendritic cell found in the stratum spinosum that functions as a macrophage

lunula
: basal part of the nail body that consists of a crescent-shaped layer of thick epithelium

Meissner corpuscle
: (also, tactile corpuscle) receptor in the skin that responds to light touch

Merkel cell
: receptor cell in the stratum basale of the epidermis that responds to the sense of touch

medulla
: in hair, the innermost layer of keratinocytes originating from the hair matrix

melanin
: pigment that determines the color of hair and skin

melanocyte
: cell found in the stratum basale of the epidermis that produces the pigment melanin

melanoma
: type of skin cancer that originates from the melanocytes of the skin

melanosome
: intercellular vesicle that transfers melanin from melanocytes into keratinocytes of the epidermis

metastasis
: spread of cancer cells from a source to other parts of the body

nail bed
: layer of epidermis upon which the nail body forms

nail body
: main keratinous plate that forms the nail

nail cuticle
: fold of epithelium that extends over the nail bed, also called the eponychium

nail fold
: fold of epithelium at that extend over the sides of the nail body, holding it in place

nail root
: part of the nail that is lodged deep in the epidermis from which the nail grows

Pacinian corpuscle
: (also, lamellated corpuscle) receptor in the skin that responds to vibration

papillary layer
: superficial layer of the dermis, made of loose, areolar connective tissue

reticular layer
: deeper layer of the dermis; it has a reticulated appearance due to the presence of abundant collagen and elastin fibers

rickets
: disease in children caused by vitamin D deficiency, which leads

to the weakening of bones

scar
: collagen-rich skin formed after the process of wound healing that is different from normal skin

sebaceous gland
: type of oil gland found in the dermis all over the body and helps to lubricate and waterproof the skin and hair by secreting sebum

sebum
: oily substance that is composed of a mixture of lipids that lubricates the skin and hair

second-degree burn
: partial-thickness burn that injures the epidermis and a portion of the dermis

squamous cell carcinoma
: type of skin cancer that originates from the stratum spinosum of the epidermis

stratum basale
: deepest layer of the epidermis, made of epidermal stem cells

stratum corneum
: most superficial layer of the epidermis

stratum granulosum
: layer of the epidermis superficial to the stratum spinosum

stratum lucidum
: layer of the epidermis between the stratum granulosum and stratum corneum, found only in thick skin covering the palms, soles of the feet, and digits

stratum spinosum
: layer of the epidermis superficial to the stratum basale,

characterized by the presence of desmosomes

stretch mark
mark formed on the skin due to a sudden growth spurt and expansion of the dermis beyond its elastic limits

sudoriferous gland
sweat gland

telogen
resting phase of the hair growth cycle initiated with catagen and terminated by the beginning of a new anagen phase of hair growth

third-degree burn
burn that penetrates and destroys the full thickness of the skin (epidermis and dermis)

vitamin D
compound that aids absorption of calcium and phosphates in the intestine to improve bone health

vitiligo
skin condition in which melanocytes in certain areas lose the ability to produce melanin, possibly due an autoimmune reaction that leads to loss of color in patches

PART V

CHAPTER 5: BONE TISSUE AND THE SKELETAL SYSTEM

29. Bone Tissue and the Skeletal System

Figure 5.1. Child Looking at Bones
Bone is a living tissue. Unlike the bones of a fossil made inert by a process of mineralization, a child's bones will continue to grow and develop while contributing to the support and function of other body systems. (credit: James Emery)

Introduction

Bones make good fossils. While the soft tissue of a once living organism will decay and fall away over time, bone tissue will, under the right conditions, undergo a process of mineralization, effectively turning the bone to stone. A well-preserved fossil skeleton can give us a good sense of the size and shape of an organism, just as your skeleton helps to define your size and shape. Unlike a fossil skeleton, however, your skeleton is a structure of living tissue that grows, repairs, and renews itself. The bones within it are dynamic and complex organs that serve a number of important functions, including some necessary to maintain homeostasis.

The Functions of the Skeletal System

Bone, or ***osseous tissue***, is a hard, dense connective tissue that forms most of the adult skeleton, the support structure of the body. In the areas of the skeleton where bones move (for example, the ribcage and joints), ***cartilage***, a semi-rigid form of connective tissue, provides flexibility and smooth surfaces for movement. The ***skeletal system*** is the body system composed of bones and cartilage and performs the following critical functions for the human body:

- supports the body
- facilitates movement
- protects internal organs
- produces blood cells
- stores and releases minerals and fat

Support, Movement, and Protection

The most apparent functions of the skeletal system are the gross functions—those visible by observation. Simply by looking at a person, you can see how the bones support, facilitate movement, and protect the human body.

Just as the steel beams of a building provide a scaffold to support its weight, the bones and cartilage of your skeletal system compose the scaffold that supports the rest of your body. Without the skeletal system, you would be a limp mass of organs, muscle, and skin.

Bones also facilitate movement by serving as points of attachment for your muscles. While some bones only serve as a support for the muscles, others also transmit the forces produced when your muscles contract. From a mechanical point of view, bones act as levers and joints serve as fulcrums (Figure 5.2). Unless a muscle spans a joint and contracts, a bone is not going to move. For information on the interaction of the skeletal and muscular systems, that is, the musculoskeletal system, seek additional content.

Figure 5.2. Bones Support Movement
Bones act as levers when muscles span a joint and contract. (credit: Benjamin J. DeLong)

Bones also protect internal organs from injury by covering or surrounding them. For example, your ribs protect your lungs and heart, the bones of your vertebral column (spine) protect your spinal cord, and the bones of your cranium (skull) protect your brain (Figure 5.3).

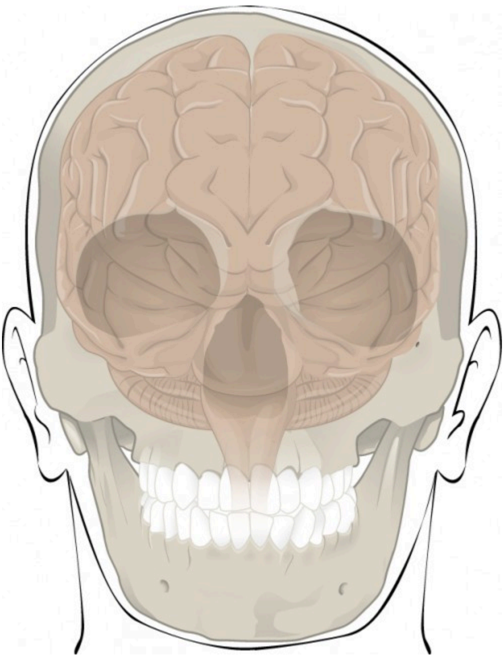


Figure 5.3. Bones Protect Brain
The cranium completely surrounds and protects the brain from non-traumatic injury.

Mineral Storage, Energy Storage, and Hematopoiesis

On a metabolic level, bone tissue performs several critical functions. For one, the bone matrix acts as a reservoir for a number of minerals important to the functioning of the body, especially calcium, and potassium. These minerals, incorporated into bone tissue, can be released back into the bloodstream to maintain levels needed to support physiological processes. Calcium ions, for example, are essential for muscle contractions and controlling the flow of other ions involved in the transmission of nerve impulses.

Bone also serves as a site for fat storage and blood cell production. The softer connective tissue that fills the interior of most bone is referred to as bone marrow (Figure 5.5). There are two types of bone marrow: yellow marrow and red marrow. ***Yellow marrow*** contains adipose tissue; the triglycerides stored in the adipocytes of the tissue can serve as a source of energy. ***Red marrow*** is where ***hematopoiesis***—the production of blood cells—takes place. Red blood cells, white blood cells, and platelets are all produced in the red marrow.

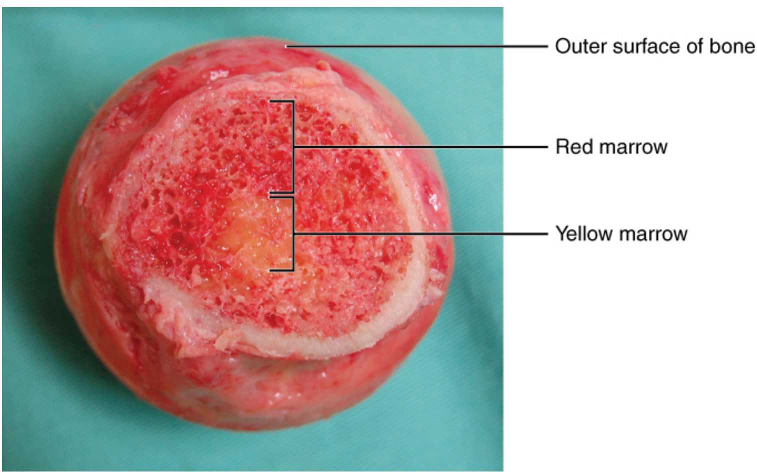


Figure 5.5. Head of Femur Showing Red and Yellow Marrow
The head of the femur contains both yellow and red marrow. Yellow marrow stores fat. Red marrow is responsible for hematopoiesis. (credit: modification of work by "stevenfruitsmaak"/Wikimedia Commons)

30. Bone Formation and Development

In the early stages of embryonic development, the embryo's skeleton consists of fibrous membranes and hyaline cartilage. By the sixth or seventh week of embryonic life, the actual process of bone development, *ossification* (osteogenesis), begins. There are two osteogenic pathways—intramembranous ossification and endochondral ossification—but bone is the same regardless of the pathway that produces it.

Cartilage Templates

Bone is a replacement tissue; that is, it uses a model tissue on which to lay down its mineral matrix. For skeletal development, the most common template is cartilage. During fetal development, a framework is laid down that determines where bones will form. This framework is a flexible, semi-solid matrix produced by chondroblasts and consists of hyaluronic acid, chondroitin sulfate, collagen fibers, and water. As the matrix surrounds and isolates chondroblasts, they are called chondrocytes. Unlike most connective tissues, cartilage is avascular, meaning that it has no blood vessels supplying nutrients and removing metabolic wastes. All of these functions are carried on by diffusion through the matrix. This is why damaged cartilage does not repair itself as readily as most tissues do.

Throughout fetal development and into childhood growth and development, bone forms on the cartilaginous matrix. By the time a fetus is born, most of the cartilage has been replaced with bone. Some additional cartilage will be replaced throughout childhood, and some cartilage remains in the adult skeleton.

Intramembranous Ossification

During ***intramembranous ossification***, compact and spongy bone develops directly from sheets of mesenchymal (undifferentiated) connective tissue. The flat bones of the face, most of the cranial bones, and the clavicles (collarbones) are formed via intramembranous ossification.

The process begins when mesenchymal cells in the embryonic skeleton gather together and begin to differentiate into specialized cells (Figure 6.16a). Some of these cells will differentiate into capillaries, while others will become osteogenic cells and then osteoblasts. Although they will ultimately be spread out by the formation of bone tissue, early osteoblasts appear in a cluster called an ***ossification center***.

The osteoblasts secrete ***osteoid***, uncalcified matrix, which calcifies (hardens) within a few days as mineral salts are deposited on it, thereby entrapping the osteoblasts within. Once entrapped, the osteoblasts become osteocytes (Figure 6.16b). As osteoblasts transform into osteocytes, osteogenic cells in the surrounding connective tissue differentiate into new osteoblasts.

Osteoid (unmineralized bone matrix) secreted around the capillaries results in a trabecular matrix, while osteoblasts on the surface of the spongy bone become the periosteum (Figure 6.16**c**). The periosteum then creates a protective layer of compact bone superficial to the trabecular bone. The trabecular bone crowds nearby blood vessels, which eventually condense into red marrow (Figure 6.16**d**).

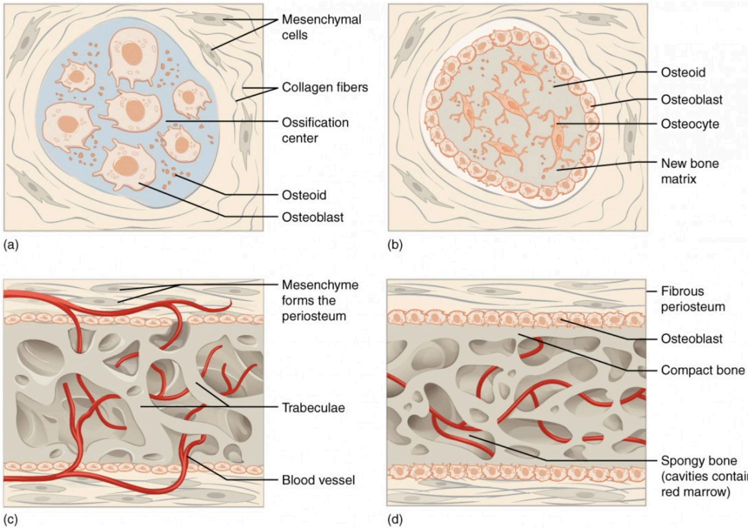


Figure 6.16. Intramembranous Ossification
Intramembranous ossification follows four steps. (a) Mesenchymal cells group into clusters, and ossification centers form. (b) Secreted osteoid traps osteoblasts, which then become osteocytes. (c) Trabecular matrix and periosteum form. (d) Compact bone develops superficial to the trabecular bone, and crowded blood vessels condense into red marrow.

Intramembranous ossification begins *in utero* during fetal development and continues on into adolescence. At birth, the skull and clavicles are not fully ossified nor are the sutures of the skull closed. This allows the skull and shoulders to deform during passage through the birth canal. The last bones to ossify via intramembranous ossification are the flat bones of the face, which reach their adult size at the end of the adolescent growth spurt.

Endochondral Ossification

In ***endochondral ossification***, bone develops by *replacing* hyaline cartilage. Cartilage does not become bone. Instead, cartilage serves as a template to be completely replaced by new bone. Endochondral ossification takes much longer than intramembranous ossification. Bones at the base of the skull and long bones form via endochondral ossification.

In a long bone, for example, at about 6 to 8 weeks after conception, some of the mesenchymal cells differentiate into chondrocytes (cartilage cells) that form the cartilaginous skeletal precursor of the bones (Figure 6.17a). Soon after, the ***perichondrium***, a membrane that covers the cartilage, appears Figure 6.17b).

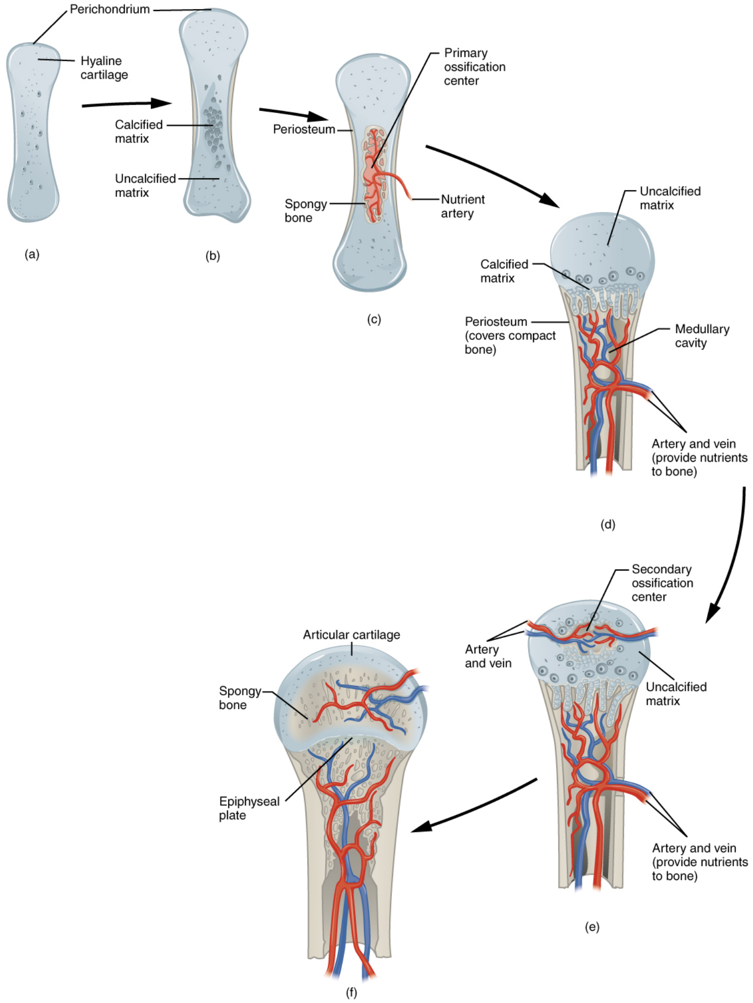


Figure 6.17. Endochondral Ossification

Endochondral ossification follows five steps. (a) Mesenchymal cells differentiate into chondrocytes. (b) The cartilage model of the future bony skeleton and the perichondrium form. (c) Capillaries penetrate cartilage. Perichondrium transforms into periosteum. Periosteal collar develops. Primary ossification center develops. (d) Cartilage and chondrocytes continue to grow at ends of the bone. (e) Secondary ossification centers develop. (f) Cartilage remains at epiphyseal *(growth) plate and at joint surface as articular cartilage.*

As more matrix is produced, the chondrocytes in the center of the cartilaginous model grow in size. As the matrix calcifies, nutrients can no longer reach the chondrocytes. This results in their death and the disintegration of the surrounding cartilage. Blood vessels invade the resulting spaces, not only enlarging the cavities but also carrying osteogenic cells with them, many of which will become osteoblasts. These enlarging spaces eventually combine to become the medullary cavity.

As the cartilage grows, capillaries penetrate it. This penetration initiates the transformation of the perichondrium into the bone-producing periosteum. Here, the osteoblasts form a periosteal collar of compact bone around the cartilage of the diaphysis. By the second or third month of fetal life, bone cell development and ossification ramps up and creates the *primary ossification center*, a region deep in the periosteal collar where ossification begins (Figure 6.17**c**).

While these deep changes are occurring, chondrocytes and cartilage continue to grow at the ends of the bone (the future epiphyses), which increases the bone's length at the same time bone is replacing cartilage in the diaphyses. By the time the fetal skeleton is fully formed, cartilage only remains at the joint surface as articular cartilage and between the diaphysis and epiphysis as the epiphyseal plate, the latter of which is responsible for the longitudinal growth of bones. After birth, this same sequence of events (matrix mineralization, death of chondrocytes, invasion of blood vessels from the periosteum, and seeding with osteogenic cells that become osteoblasts) occurs in the epiphyseal regions, and each of these centers of activity is referred to as a *secondary ossification center* (Figure 6.17**e**).

How Bones Grow in Length

The epiphyseal plate is the area of growth in a long bone. It is a layer of hyaline cartilage where ossification occurs in immature bones. On the epiphyseal side of the epiphyseal plate, cartilage is formed. On the diaphyseal side, cartilage is ossified, and the diaphysis grows in length. The epiphyseal plate is composed of four zones of cells and activity (Figure 6.18). The *reserve zone* is the region closest to the epiphyseal end of the plate and contains small chondrocytes within the matrix. These chondrocytes do not participate in bone growth but secure the epiphyseal plate to the osseous tissue of the epiphysis.

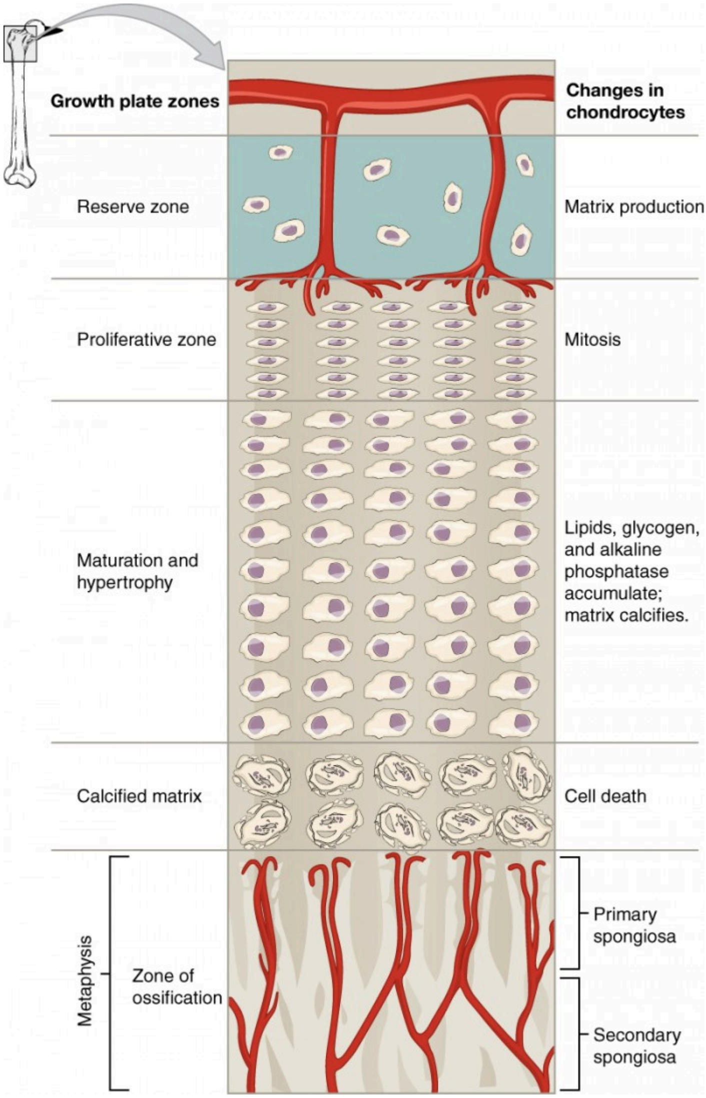


Figure 6.18. Longitudinal Bone Growth
The epiphyseal plate is responsible for longitudinal bone growth.

The ***proliferative zone*** is the next layer toward the diaphysis and contains stacks of slightly larger chondrocytes. It makes new chondrocytes (via mitosis) to replace those that die at the diaphyseal end of the plate. Chondrocytes in the next layer, the ***zone of maturation and hypertrophy***, are older and larger than those in the proliferative zone. The more mature cells are situated closer to the diaphyseal end of the plate. The longitudinal growth of bone is a result of cellular division in the proliferative zone and the maturation of cells in the zone of maturation and hypertrophy.

Most of the chondrocytes in the ***zone of calcified matrix***, the zone closest to the diaphysis, are dead because the matrix around them has calcified. Capillaries and osteoblasts from the diaphysis penetrate this zone, and the osteoblasts secrete bone tissue on the remaining calcified cartilage. Thus, the zone of calcified matrix connects the epiphyseal plate to the diaphysis. A bone grows in length when osseous tissue is added to the diaphysis.

Bones continue to grow in length until early adulthood. The rate of growth is controlled by hormones, which will be discussed later. When the chondrocytes in the epiphyseal plate cease their proliferation and bone replaces the cartilage, longitudinal growth stops. All that remains of the epiphyseal plate is the ***epiphyseal line*** (Figure 6.19).

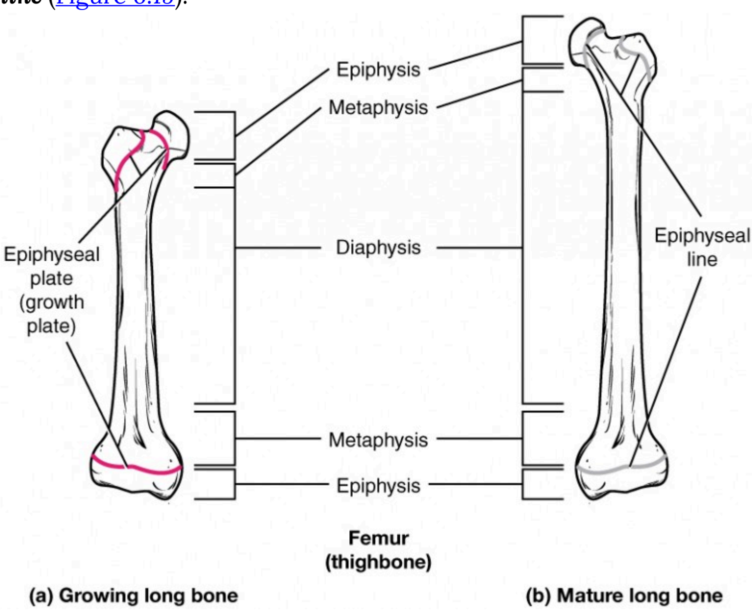


Figure 6.19. Progression from Epiphyseal Plate to Epiphyseal Line
As a bone matures, the epiphyseal plate progresses to an epiphyseal line. (a) Epiphyseal plates are visible in a growing bone. (b) Epiphyseal lines are the remnants of epiphyseal plates in a mature bone.

How Bones Grow in Diameter

While bones are increasing in length, they are also increasing in diameter; growth in diameter can continue even after longitudinal growth ceases. This is called appositional growth. Osteoclasts resorb old bone that lines the medullary cavity, while osteoblasts, via intramembranous ossification, produce new bone tissue beneath the periosteum. The erosion of old bone along the medullary cavity and the deposition of new bone beneath the periosteum not only increase the diameter of the diaphysis but also increase the diameter of the medullary cavity. This process is called ***modeling***.

Bone Remodeling

The process in which matrix is resorbed on one surface of a bone and deposited on another is known as bone modeling. Modeling primarily takes place during a bone's growth. However, in adult life, bone undergoes ***remodeling***, in which resorption of old or damaged bone takes place on the same surface where osteoblasts lay new bone to replace that which is resorbed. Injury, exercise, and other activities lead to remodeling. Those influences are discussed later in the chapter, but even without injury or exercise, about 5 to 10 percent of the skeleton is remodeled annually just by destroying old bone and renewing it with fresh bone.

Diseases of the Skeletal System

Osteogenesis imperfecta (OI) is a genetic disease in which bones do not form properly and therefore are fragile and break easily. It is also called brittle bone disease. The disease is present from birth and affects a person throughout life.

The genetic mutation that causes OI affects the body's production of collagen, one of the critical components of bone matrix. The severity of the disease can range from mild to severe. Those with the most severe forms of the disease sustain many more fractures than those with a mild form. Frequent and multiple fractures typically lead to bone deformities and short stature. Bowing of the long bones and curvature of the spine are also common in people afflicted with OI. Curvature of the spine makes breathing difficult because the lungs are compressed.

Because collagen is such an important structural protein in many parts of the body, people with OI may also experience fragile skin, weak muscles, loose joints, easy bruising, frequent nosebleeds, brittle teeth, blue sclera, and hearing loss. There is no known cure for OI. Treatment focuses on helping the person retain as much independence as possible while minimizing fractures and maximizing mobility. Toward that end, safe exercises, like swimming, in which the body is less likely to experience collisions or compressive forces, are recommended. Braces to support legs, ankles, knees, and wrists are used as needed. Canes, walkers, or wheelchairs can also help compensate for weaknesses.

When bones do break, casts, splints, or wraps are used. In some cases, metal rods may be surgically implanted into the long bones of the arms and legs. Research is currently being conducted on using bisphosphonates to treat OI. Smoking and being overweight are especially risky in people with OI, since smoking is known to weaken bones, and extra body weight puts additional stress on the bones.

Watch this video to see how a bone grows.

31. Fractures: Bone Repair

A ***fracture*** is a broken bone. It will heal whether or not a physician resets it in its anatomical position. If the bone is not reset correctly, the healing process will keep the bone in its deformed position.

When a broken bone is manipulated and set into its natural position without surgery, the procedure is called a ***closed reduction***. ***Open reduction*** requires surgery to expose the fracture and reset the bone. While some fractures can be minor, others are quite severe and result in grave complications. For example, a fractured diaphysis of the femur has the potential to release fat globules into the bloodstream. These can become lodged in the capillary beds of the lungs, leading to respiratory distress and if not treated quickly, death.

Types of Fractures

Fractures are classified by their complexity, location, and other features (Figure 5.20). Table 5.4 outlines common types of fractures. Some fractures may be described using more than one term because it may have the features of more than one type (e.g., an open transverse fracture).

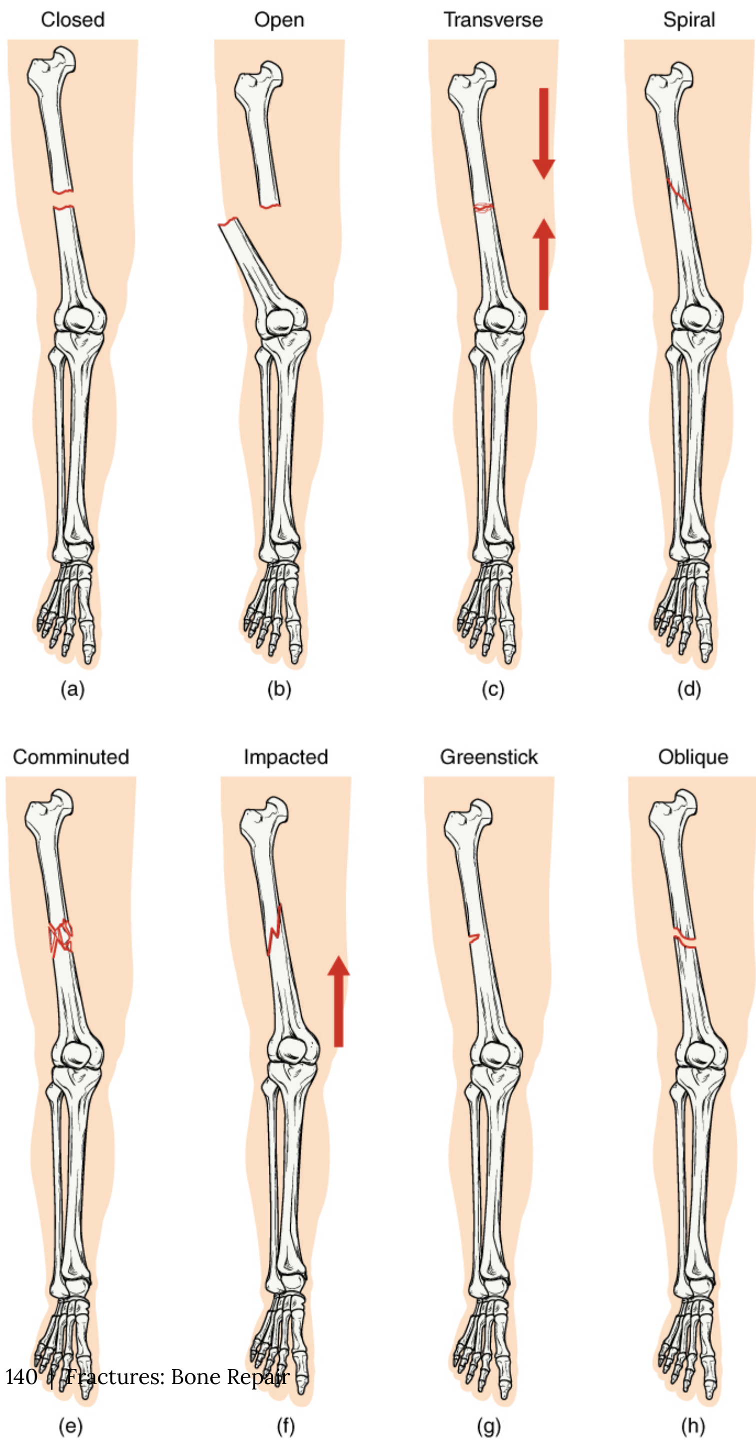

Closed
Open
Transverse
Spiral
(a)
(b)
(c)
(d)
Comminuted
Impacted
Greenstick
Oblique
(e)
(f)
(g)
(h)

Figure 5.20. Types of Fractures

Compare healthy bone with different types of fractures: (a) closed fracture, (b) open fracture, (c) transverse fracture, (d) spiral fracture, (e) comminuted fracture, (f) impacted fracture, (g) greenstick fracture, and (h) oblique fracture.

Table 5.4.

Types of Fractures

Type of fracture	**Description**
Transverse	Occurs straight across the long axis of the bone
Oblique	Occurs at an angle that is not 90 degrees
Spiral	Bone segments are pulled apart as a result of a twisting motion
Comminuted	Several breaks result in many small pieces between two large segments
Impacted	One fragment is driven into the other, usually as a result of compression
Greenstick	A partial fracture in which only one side of the bone is broken
Open (or compound)	A fracture in which at least one end of the broken bone tears through the skin; carries a high risk of infection
Closed (or simple)	A fracture in which the skin remains intact

Bone Repair

When a bone breaks, blood flows from any vessel torn by the fracture. These vessels could be in the periosteum, osteons, and/or medullary cavity. The blood begins to clot, and about six to eight hours after the fracture, the clotting blood has formed a ***fracture hematoma*** (Figure 5.21**a**). The disruption of blood flow to the bone results in the death of bone cells around the fracture.

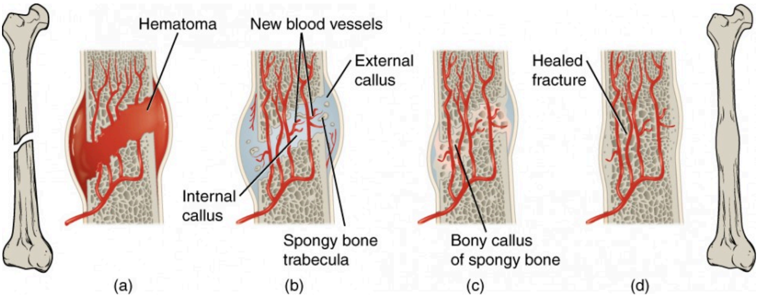


Figure 5.21. Stages in Fracture Repair
The healing of a bone fracture follows a series of progressive steps: (a) A fracture hematoma forms. (b) Internal and external calli form. (c) Cartilage of the calli is replaced by trabecular bone. (d) Remodeling occurs.

Within about 48 hours after the fracture, chondrocytes from the endosteum have created an ***internal callus*** (plural = calli) by secreting a fibrocartilaginous matrix between the two ends of the broken bone, while the periosteal chondrocytes and osteoblasts create an ***external callus*** of hyaline cartilage and bone, respectively, around the outside of the break (Figure 5.21**b**). This stabilizes the fracture.

Over the next several weeks, osteoclasts resorb the dead bone; osteogenic cells become active, divide, and differentiate into osteoblasts. The cartilage in the calli is replaced by trabecular bone via endochondral ossification (Figure 5.21**c**).

Eventually, the internal and external calli unite, compact bone replaces spongy bone at the outer margins of the fracture, and healing is complete. A slight swelling may remain on the outer surface of the bone, but quite often, that region undergoes remodeling (Figure 5.21**d**), and no external evidence of the fracture remains.

32. Exercise, Nutrition, Hormones, and Bone Tissue

All of the organ systems of your body are interdependent, and the skeletal system is no exception. The food you take in via your digestive system and the hormones secreted by your endocrine system affect your bones. Even using your muscles to engage in exercise has an impact on your bones.

Exercise and Bone Tissue

During long space missions, astronauts can lose approximately 1 to 2 percent of their bone mass per month. This loss of bone mass is thought to be caused by the lack of mechanical stress on astronauts' bones due to the low gravitational forces in space. Lack of mechanical stress causes bones to lose mineral salts and collagen fibers, and thus strength. Similarly, mechanical stress stimulates the deposition of mineral salts and collagen fibers. The internal and external structure of a bone will change as stress increases or decreases so that the bone is an ideal size and weight for the amount of activity it endures. That is why people who exercise regularly have thicker bones than people who are more sedentary. It is also why a broken bone in a cast atrophies while its contralateral mate maintains its concentration of mineral salts and collagen fibers. The bones undergo remodeling as a result of forces (or lack of forces) placed on them.

Numerous, controlled studies have demonstrated that people who exercise regularly have greater bone density than those who are more sedentary. Any type of exercise will stimulate the deposition of more bone tissue, but resistance training has a greater effect than cardiovascular activities. Resistance training is especially important to slow down the eventual bone loss due to aging and for preventing osteoporosis.

Nutrition and Bone Tissue

The vitamins and minerals contained in all of the food we consume are important for all of our organ systems. However, there are certain nutrients that affect bone health.

Calcium and Vitamin D

You already know that calcium is a critical component of bone, especially in the form of calcium phosphate and calcium carbonate. Since the body cannot make calcium, it must be obtained from the diet. However, calcium cannot be absorbed from the small intestine without vitamin D. Therefore, intake of vitamin D is also critical to bone health. In addition to vitamin D's role in calcium absorption, it also plays a role, though not as clearly understood, in bone remodeling.

Milk and other dairy foods are not the only sources of calcium. This important nutrient is also found in green leafy vegetables, broccoli, and intact salmon and canned sardines with their soft bones. Nuts, beans, seeds, and shellfish provide calcium in smaller quantities.

Except for fatty fish like salmon and tuna, or fortified milk or cereal, vitamin D is not found naturally in many foods. The action of sunlight on the skin triggers the body to produce its own vitamin D (Figure 5.22), but many people, especially those of darker complexion and those living in northern latitudes where the sun's rays are not as strong, are deficient in vitamin D. In cases of deficiency, a doctor can prescribe a vitamin D supplement.

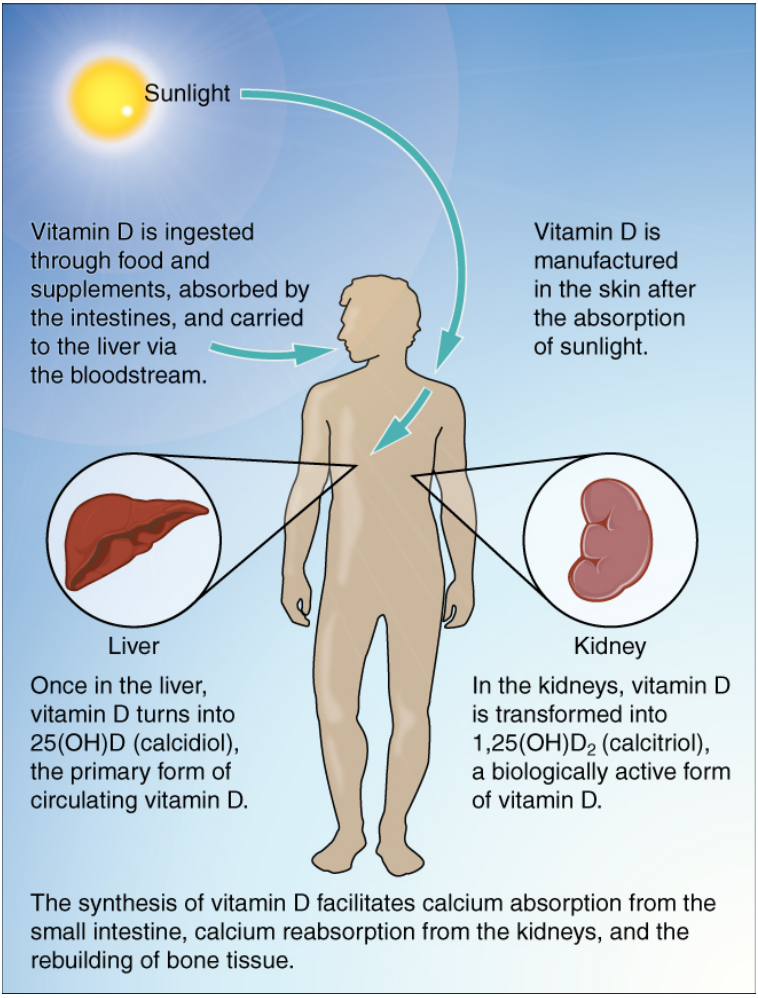


Figure 5.22. Synthesis of Vitamin D
Sunlight is one source of vitamin D.

Other Nutrients

Vitamin K also supports bone mineralization and may have a synergistic role with vitamin D in the regulation of bone growth. Green leafy vegetables are a good source of vitamin K.

The minerals magnesium and fluoride may also play a role in supporting bone health. While magnesium is only found in trace amounts in the human body, more than 60 percent of it is in the skeleton, suggesting it plays a role in the structure of bone. Fluoride can displace the hydroxyl group in bone's hydroxyapatite crystals and form fluorapatite. Similar to its effect on dental enamel, fluorapatite helps stabilize and strengthen bone mineral. Fluoride can also enter spaces within hydroxyapatite crystals, thus increasing their density.

Omega-3 fatty acids have long been known to reduce inflammation in various parts of the body. Inflammation can interfere with the function of osteoblasts, so consuming omega-3 fatty acids, in the diet or in supplements, may also help enhance production of new osseous tissue. Table 5.5 summarizes the role of nutrients in bone health.

Table 5.5.

Nutrients and Bone Health

Nutrient	**Role in bone health**
Calcium	Needed to make calcium phosphate and calcium carbonate, which form the hydroxyapatite crystals that give bone its hardness
Vitamin D	Needed for calcium absorption
Vitamin K	Supports bone mineralization; may have synergistic effect with vitamin D
Magnesium	Structural component of bone
Fluoride	Structural component of bone
Omega-3 fatty acids	Reduces inflammation that may interfere with osteoblast function

Hormones and Bone Tissue

The endocrine system produces and secretes hormones, many of which interact with the skeletal system. These hormones are involved in controlling bone growth, maintaining bone once it is formed, and remodeling it.

Hormones That Influence Osteoblasts and/or Maintain the Matrix

Several hormones are necessary for controlling bone growth and maintaining the bone matrix. The pituitary gland secretes growth hormone (GH), which, as its name implies, controls bone growth in several ways. It triggers chondrocyte proliferation in epiphyseal plates, resulting in the increasing length of long bones. GH also increases calcium retention, which enhances mineralization, and stimulates osteoblastic activity, which improves bone density.

GH is not alone in stimulating bone growth and maintaining osseous tissue. Thyroxine, a hormone secreted by the thyroid gland promotes osteoblastic activity and the synthesis of bone matrix. During puberty, the sex hormones (estrogen in girls, testosterone in boys) also come into play. They too promote osteoblastic activity and production of bone matrix, and in addition, are responsible for the growth spurt that often occurs during adolescence. They also promote the conversion of the epiphyseal plate to the epiphyseal line (i.e., cartilage to its bony remnant), thus bringing an end to the longitudinal growth of bones. Additionally, calcitriol, the active form of vitamin D, is produced by the kidneys and stimulates the absorption of calcium and phosphate from the digestive tract.

Aging and the Skeletal System

Osteoporosis is a disease characterized by a decrease in bone mass that occurs when the rate of bone resorption exceeds the rate of bone formation, a common occurrence as the body ages. Notice how this is different from Paget's disease. In Paget's disease, new bone is formed in an attempt to keep up with the resorption by the overactive osteoclasts, but that new bone is produced haphazardly. In fact, when a physician is evaluating a patient with thinning bone, he or she will test for osteoporosis and Paget's disease (as well as other diseases). Osteoporosis does not have the elevated blood levels of alkaline phosphatase found in Paget's disease.

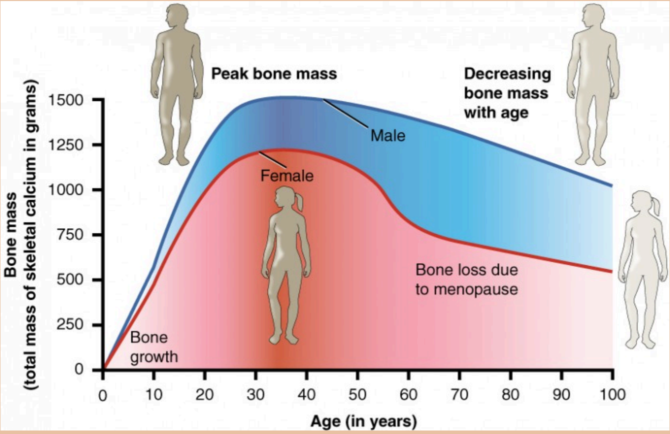


Figure 5.23. Graph Showing Relationship Between Age and Bone Mass

Bone density peaks at about 30 years of age. Women lose bone mass more rapidly than men.

While osteoporosis can involve any bone, it most commonly affects the proximal ends of the femur, vertebrae, and wrist. As a result of the loss of bone density, the osseous tissue may not provide adequate support for everyday functions, and something as simple as a sneeze can cause a vertebral fracture. When an elderly person falls and breaks a hip (really, the femur), it is very likely the femur that broke first, which resulted in the fall. Histologically, osteoporosis is characterized by a reduction in the thickness of compact bone and the number and size of trabeculae in cancellous bone.

Figure 5.23 shows that women lose bone mass more quickly than men starting at about 50 years of age. This occurs because 50 is the approximate age at which women go through menopause. Not only do their menstrual periods lessen and eventually cease, but their ovaries reduce in size and then cease the production of estrogen, a hormone that promotes osteoblastic activity and production of bone matrix. Thus, osteoporosis is more common in women than in men, but men can develop it, too. Anyone with a family history of osteoporosis has a greater risk of developing the disease, so the best treatment is prevention, which should start with a childhood diet that includes adequate intake of calcium and vitamin D and a lifestyle that includes weight-bearing exercise. These actions, as discussed above, are important in building bone mass. Promoting proper nutrition and weight-bearing exercise early in life can maximize bone mass before the age of 30, thus reducing the risk of osteoporosis.

For many elderly people, a hip fracture can be life threatening. The fracture itself may not be serious, but the immobility that comes during the healing process can lead to the formation of blood clots that can lodge in the capillaries of the lungs, resulting in respiratory failure; pneumonia due to the lack of poor air exchange that accompanies immobility; pressure sores (bed sores) that allow pathogens to enter the body and cause infections; and urinary tract infections from catheterization.

Current treatments for managing osteoporosis include bisphosphonates (the same medications often used in Paget's disease), calcitonin, and estrogen (for women only). Minimizing the risk of falls, for example, by removing tripping hazards, is also an important step in managing the potential outcomes from the disease.

Hormones That Influence Osteoclasts

Bone modeling and remodeling require osteoclasts to resorb unneeded, damaged, or old bone, and osteoblasts to lay down new bone. Two hormones that affect the osteoclasts are parathyroid hormone (PTH) and calcitonin.

PTH stimulates osteoclast proliferation and activity. As a result, calcium is released from the bones into the circulation, thus increasing the calcium ion concentration in the blood. PTH also promotes the reabsorption of calcium by the kidney tubules, which can affect calcium homeostasis (see below).

The small intestine is also affected by PTH, albeit indirectly. Because another function of PTH is to stimulate the synthesis of vitamin D, and because vitamin D promotes intestinal absorption of calcium, PTH indirectly increases calcium uptake by the small intestine. Calcitonin, a hormone secreted by the thyroid gland, has some effects that counteract those of PTH. Calcitonin inhibits osteoclast activity and stimulates calcium uptake by the bones, thus reducing the concentration of calcium ions in the blood. As evidenced by their opposing functions in maintaining calcium homeostasis, PTH and calcitonin are generally *not* secreted at the same time. Table 5.6 summarizes the hormones that influence the skeletal system.

Table 5.6.

Hormones That Affect the Skeletal System	
Hormone	**Role**
Growth hormone	Increases length of long bones, enhances mineralization, and improves bone density
Thyroxine	Stimulates bone growth and promotes synthesis of bone matrix
Sex hormones	Promote osteoblastic activity and production of bone matrix; responsible for adolescent growth spurt; promote conversion of epiphyseal plate to epiphyseal line
Calcitriol	Stimulates absorption of calcium and phosphate from digestive tract
Parathyroid hormone	Stimulates osteoclast proliferation and resorption of bone by osteoclasts; promotes reabsorption of calcium by kidney tubules; indirectly increases calcium absorption by small intestine
Calcitonin	Inhibits osteoclast activity and stimulates calcium uptake by bones

33. Calcium Homeostasis: Interactions of the Skeletal System and Other Organ Systems

Calcium is not only the most abundant mineral in bone, it is also the most abundant mineral in the human body. Calcium ions are needed not only for bone mineralization but for tooth health, regulation of the heart rate and strength of contraction, blood coagulation, contraction of smooth and skeletal muscle cells, and regulation of nerve impulse conduction. The normal level of calcium in the blood is about 10 mg/dL. When the body cannot maintain this level, a person will experience hypo- or hypercalcemia.

Hypocalcemia, a condition characterized by abnormally low levels of calcium, can have an adverse effect on a number of different body systems including circulation, muscles, nerves, and bone. Without adequate calcium, blood has difficulty coagulating, the heart may skip beats or stop beating altogether, muscles may have difficulty contracting, nerves may have difficulty functioning, and bones may become brittle. The causes of hypocalcemia can range from hormonal imbalances to an improper diet. Treatments vary according to the cause, but prognoses are generally good.

Conversely, in ***hypercalcemia***, a condition characterized by abnormally high levels of calcium, the nervous system is underactive, which results in lethargy, sluggish reflexes, constipation and loss of appetite, confusion, and in severe cases, coma.

Obviously, calcium homeostasis is critical. The skeletal, endocrine, and digestive systems play a role in this, but the kidneys do, too. These body systems work together to maintain a normal calcium level in the blood (Figure 5.24).

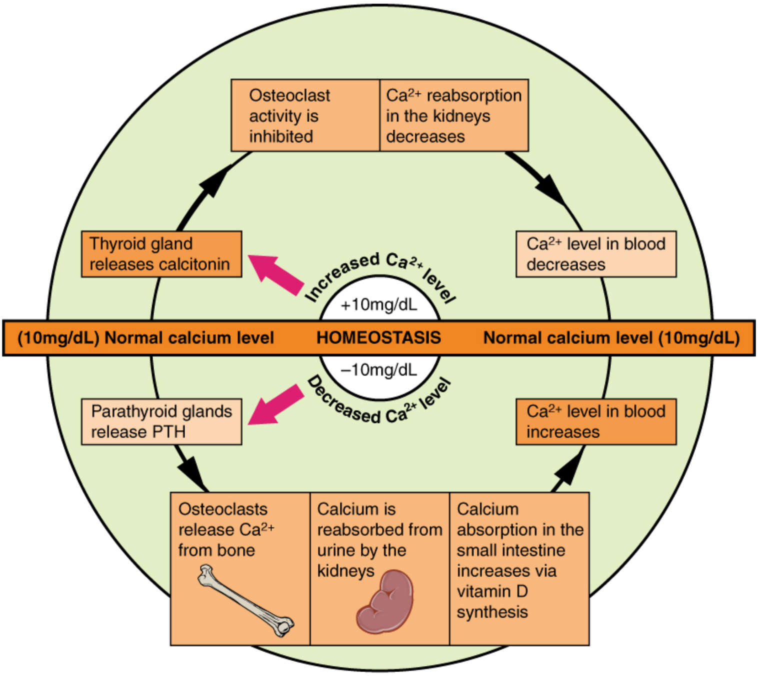


Figure 5.24. Pathways in Calcium Homeostasis

The body regulates calcium homeostasis with two pathways; one is signaled to turn on when blood calcium levels drop below normal and one is the pathway that is signaled to turn on when blood calcium levels are elevated.

Calcium is a chemical element that cannot be produced by any biological processes. The only way it can enter the body is through the diet. The bones act as a storage site for calcium: The body deposits calcium in the bones when blood levels get too high, and it releases calcium when blood levels drop too low. This process is regulated by PTH, vitamin D, and calcitonin.

Cells of the parathyroid gland have plasma membrane receptors for calcium. When calcium is not binding to these receptors, the cells release PTH, which stimulates osteoclast proliferation and resorption of bone by osteoclasts. This demineralization process releases calcium into the blood. PTH promotes reabsorption of calcium from the urine by the kidneys, so that the calcium returns to the blood. Finally, PTH stimulates the synthesis of vitamin D, which in turn, stimulates calcium absorption from any digested food in the small intestine.

When all these processes return blood calcium levels to normal, there is enough calcium to bind with the receptors on the surface of the cells of the parathyroid glands, and this cycle of events is turned off (Figure 5.24).

When blood levels of calcium get too high, the thyroid gland is stimulated to release calcitonin (Figure 5.24), which inhibits osteoclast activity and stimulates calcium uptake by the bones, but also decreases reabsorption of calcium by the kidneys. All of these actions lower blood levels of calcium. When blood calcium levels return to normal, the thyroid gland stops secreting calcitonin.

34. Age Related Changes to the Skeletal System

Age Related Changes to Bone

The major age related change in the skeletal system is the loss of calcium in the bone. As previously discussed calcium homeostasis is critical to maintaining bone structure. As one ages this homeostasis is disrupted, which results in a weakening of the bones. While the exact causes of the disruption are not fully understood it has been observed that bone loss is more severe in women that men. In women bones begin to lose calcium around the age of 30. By the age of 70 women may have lose 30% or more of their bone calcium. Most men don't begin to the lose calcium until they reach the age of 60.

In addition to the lose of calcium as one ages protein synthesis also slows. As a result there is little to no new formation of collagen fibers. These fibers are what give the bones strength and flexibility. Without them bones become brittle resulting in a higher rate of fracture.

Finally bone reabsorption continues without the continued formation of new bone. This results in larger centrally located medullary cavities of the long bones and thinner walls of compact bone.

All of these changes result in a decrease of bone mass. While the causes of these changes are not well understood, it is thought that hormonal imbalances and changes in activity level may be factors.

Age Related Changes to Cartilage

One of the main roles of the skeletal system is the smooth functioning of the various movable joints of the body. Articular cartilage covers the ends of bone involved in a joint. As the joint moves articular cartilage rubs against articular cartilage, as opposed to bone on bone contact. This cartilage reduces friction and produces smooth movements in the joints. As you age this cartilage becomes thinner and deteriorates. The resulting bone on bone contact makes movement of the joint painful.

Costal cartilage has the specific function of connecting the ribs to the sternum. This cartilage make it possible for the rib cage to expand and contract with respiration. As one ages the cartilage calcifies resulting in a loss of flexibility. This restricts breathing.

Fibrocartilage makes up the intervertebral discs which specifically provides cushioning between the vertebrae which make up the spinal column. After the age of about 40 years of age, the cartilage experiences a gradual loss of cells and water. This results in a decreased level of cushioning provided by these discs.

35. Age Related Dysfunctions of the Skeletal System

Bursitis

Bursitis is a condition in which bursea become inflamed due injury, exercise, bacterial infection, or the deposition of crystals in the bursa. Bursae are small sacs of synovial fluid located in the synovial joints of the body. Normally they create cushion and reduce friction between tendons and bone. Bursitis is characterized by pain when the joint is moved or when it is lain upon in bed. Treatment is dependent on the cause of inflammation. It may include antibiotics, aspiration of the inflamed bursa, or the injection of anti-inflammatory drugs.

Arthritis

Arthritis is one of the most common conditions affecting older people. It is a general term referring to various types of inflammation or degenerative changes that occur in joints.

Osteoarthritis is the most common form of arthritis, but the specific causes of osteoarthritis are not well understood. Osteoarthritis is a chronic inflammation that causes the articular cartilages covering the ends of the bones in the affected joint to degenerate gradually. Osteoarthritis is characterized by pain in the joints. This is due to bone spurs which form on the exposed ends of the bone after the articular cartilage degrades.

Rheumatoid Arthritis is an auto immune disorder that is not strictly a disease of old people. It can begin at any age, but rheumatoid arthritis is progressive and becomes more debilitating with age. Rheumatoid arthritis begins with the inflammation of the synovial membrane causing pain. Prolonged inflammation causes scare tissue to form which destroys the articular cartilage of the joint and bone beneath it. Rheumatoid arthritis can become so severe that surgery may be necessary to repair the affected joints, and in some cases the diseased bone of the joint is removed and replaced with a prosthetic device.

Gouty Arthritis is an inherited condition most commonly affecting men beginning between the ages of 40 and 55. Gouty arthritis is caused by excessive levels if uric acid in the blood. The uric acid then crystalized in joints of the body. The crystals often begin in the great toe but may also affect other joints. As the crystals accumulate in the synovial joint they cause pain and swelling. Attacks often subside after a few days but often chronically reappear every few weeks or months. This chronic condition may eventually erode the cartilage and bone of the affected joint. Individuals suffering from this condition are advised to reduce consumption of proteins and increase the consumption of carbohydrates.

Osteoporosis

Osteoporosis is a condition which affects many elderly people, particularly post-menopausal women. The disease is car by the gradual increase in the resorption of bone while the rate of new bone formation remains normal. External signs of the disease include diminished height and curvature of the spine.

36. Glossary: Bone Tissue

articular cartilage
: thin layer of cartilage covering an epiphysis; reduces friction and acts as a shock absorber

articulation
: where two bone surfaces meet

bone
: hard, dense connective tissue that forms the structural elements of the skeleton

canaliculi
: (singular = canaliculus) channels within the bone matrix that house one of an osteocyte's many cytoplasmic extensions that it uses to communicate and receive nutrients

cartilage
: semi-rigid connective tissue found on the skeleton in areas where flexibility and smooth surfaces support movement

central canal
: longitudinal channel in the center of each osteon; contains blood vessels, nerves, and lymphatic vessels; also known as the Haversian canal

closed reduction
: manual manipulation of a broken bone to set it into its natural position without surgery

compact bone
: dense osseous tissue that can withstand compressive forces

diaphysis
: tubular shaft that runs between the proximal and distal ends of

a long bone

diploë
: layer of spongy bone, that is sandwiched between two the layers of compact bone found in flat bones

endochondral ossification
: process in which bone forms by replacing hyaline cartilage

endosteum
: delicate membranous lining of a bone's medullary cavity

epiphyseal line
: completely ossified remnant of the epiphyseal plate

epiphyseal plate
: (also, growth plate) sheet of hyaline cartilage in the metaphysis of an immature bone; replaced by bone tissue as the organ grows in length

epiphysis
: wide section at each end of a long bone; filled with spongy bone and red marrow

external callus
: collar of hyaline cartilage and bone that forms around the outside of a fracture

flat bone
: thin and curved bone; serves as a point of attachment for muscles and protects internal organs

fracture hematoma
: blood clot that forms at the site of a broken bone

fracture
: broken bone

hematopoiesis
: production of blood cells, which occurs in the red marrow of the bones

hole
: opening or depression in a bone

hypercalcemia
: condition characterized by abnormally high levels of calcium

hypocalcemia
: condition characterized by abnormally low levels of calcium

internal callus
: fibrocartilaginous matrix, in the endosteal region, between the two ends of a broken bone

intramembranous ossification
: process by which bone forms directly from mesenchymal tissue

irregular bone
: bone of complex shape; protects internal organs from compressive forces

lacunae
: (singular = lacuna) spaces in a bone that house an osteocyte

long bone
: cylinder-shaped bone that is longer than it is wide; functions as a lever

medullary cavity
: hollow region of the diaphysis; filled with yellow marrow

modeling
: process, during bone growth, by which bone is resorbed on one surface of a bone and deposited on another

nutrient foramen
: small opening in the middle of the external surface of the diaphysis, through which an artery enters the bone to provide nourishment

open reduction
: surgical exposure of a bone to reset a fracture

orthopedist
: doctor who specializes in diagnosing and treating musculoskeletal disorders and injuries

osseous tissue
: bone tissue; a hard, dense connective tissue that forms the structural elements of the skeleton

ossification center
: cluster of osteoblasts found in the early stages of intramembranous ossification

ossification
: (also, osteogenesis) bone formation

osteoblast
: cell responsible for forming new bone

osteoclast
: cell responsible for resorbing bone

osteocyte
: primary cell in mature bone; responsible for maintaining the matrix

osteogenic cell
: undifferentiated cell with high mitotic activity; the only bone cells that divide; they differentiate and develop into osteoblasts

osteoid
: uncalcified bone matrix secreted by osteoblasts

osteon

(also, Haversian system) basic structural unit of compact bone; made of concentric layers of calcified matrix

osteoporosis

disease characterized by a decrease in bone mass; occurs when the rate of bone resorption exceeds the rate of bone formation, a common occurrence as the body ages

perforating canal

(also, Volkmann's canal) channel that branches off from the central canal and houses vessels and nerves that extend to the periosteum and endosteum

perichondrium

membrane that covers cartilage

periosteum

fibrous membrane covering the outer surface of bone and continuous with ligaments

primary ossification center

region, deep in the periosteal collar, where bone development starts during endochondral ossification

projection

bone markings where part of the surface sticks out above the rest of the surface, where tendons and ligaments attach

proliferative zone

region of the epiphyseal plate that makes new chondrocytes to replace those that die at the diaphyseal end of the plate and contributes to longitudinal growth of the epiphyseal plate

red marrow

connective tissue in the interior cavity of a bone where hematopoiesis takes place

remodeling
: process by which osteoclasts resorb old or damaged bone at the same time as and on the same surface where osteoblasts form new bone to replace that which is resorbed

reserve zone
: region of the epiphyseal plate that anchors the plate to the osseous tissue of the epiphysis

secondary ossification center
: region of bone development in the epiphyses

sesamoid bone
: small, round bone embedded in a tendon; protects the tendon from compressive forces

short bone
: cube-shaped bone that is approximately equal in length, width, and thickness; provides limited motion

skeletal system
: organ system composed of bones and cartilage that provides for movement, support, and protection

spongy bone
: (also, cancellous bone) trabeculated osseous tissue that supports shifts in weight distribution

trabeculae
: (singular = trabecula) spikes or sections of the lattice-like matrix in spongy bone

yellow marrow
: connective tissue in the interior cavity of a bone where fat is stored

zone of calcified matrix
: region of the epiphyseal plate closest to the diaphyseal end;

functions to connect the epiphyseal plate to the diaphysis

zone of maturation and hypertrophy
region of the epiphyseal plate where chondrocytes from the proliferative zone grow and mature and contribute to the longitudinal growth of the epiphyseal plate

PART VI

CHAPTER 6: THE SKELETAL MUSCLE SYSTEM

37. Interactions of Skeletal Muscles

Figure 6.1. A Body in Motion
The muscular system allows us to move, flex and contort our bodies. Practicing yoga, as pictured here, is a good example of the voluntary use of the muscular system. (credit: Dmitry Yanchylenko)

Introduction

Think about the things that you do each day—talking, walking, sitting, standing, and running—all of these activities require movement of particular skeletal muscles. Skeletal muscles are even used during sleep. The diaphragm is a sheet of skeletal muscle that has to contract and relax for you to breathe day and night. If you recall from your study of the skeletal system and joints, body movement occurs around the joints in the body. The focus of this chapter is on skeletal muscle organization. The system to name skeletal muscles will be explained; in some cases, the muscle is named by its shape, and in other cases it is named by its location or attachments to the skeleton. If you understand the meaning of the name of the muscle, often it will help you remember its location and/or what it does. This chapter also will describe how skeletal muscles are arranged to accomplish movement, and how other muscles may assist, or be arranged on the skeleton to resist or carry out the opposite movement. The actions of the skeletal muscles will be covered in a regional manner, working from the head down to the toes.

Interactions of Skeletal Muscles, Their Fascicle Arrangement, and Their Lever Systems

To move the skeleton, the tension created by the contraction of the fibers in most skeletal muscles is transferred to the tendons. The tendons are strong bands of dense, regular connective tissue that connect muscles to bones. The bone connection is why this muscle tissue is called skeletal muscle.

Interactions of Skeletal Muscles in the Body

To pull on a bone, that is, to change the angle at its synovial joint, which essentially moves the skeleton, a skeletal muscle must also be attached to a fixed part of the skeleton. The moveable end of the muscle that attaches to the bone being pulled is called the muscle's ***insertion***, and the end of the muscle attached to a fixed (stabilized) bone is called the ***origin***. During forearm ***flexion***—bending the elbow—the brachioradialis assists the brachialis.

Although a number of muscles may be involved in an action, the principal muscle involved is called the ***prime mover***, or ***agonist***. To lift a cup, a muscle called the biceps brachii is actually the prime mover; however, because it can be assisted by the brachialis, the brachialis is called a ***synergist*** in this action (Figure 6.2). A synergist can also be a ***fixator*** that stabilizes the bone that is the attachment for the prime mover's origin.

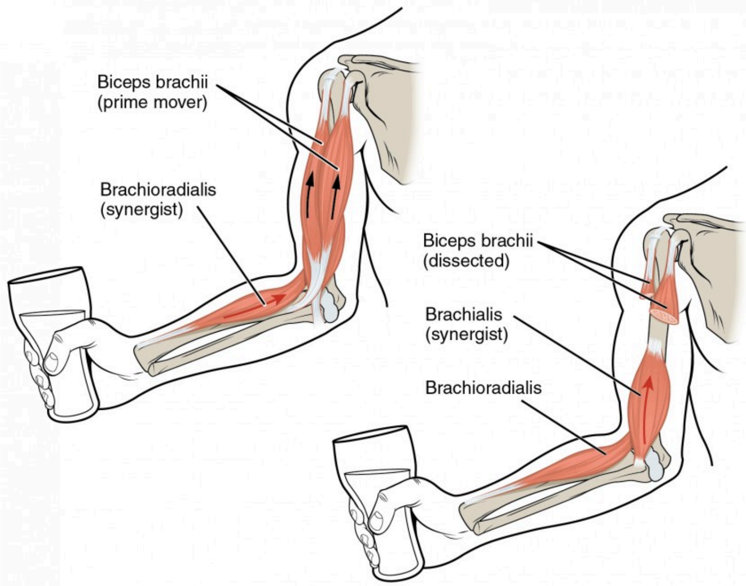


Figure 6.2. Prime Movers and Synergists

The biceps brachii flex the lower arm. The brachoradialis, in the forearm, and brachialis, located deep to the biceps in the upper arm, are both synergists that aid in this motion.

A muscle with the opposite action of the prime mover is called an ***antagonist***. Antagonists play two important roles in muscle function: (1) they maintain body or limb position, such as holding the arm out or standing erect; and (2) they control rapid movement, as in shadow boxing without landing a punch or the ability to check the motion of a limb.

For example, to extend the knee, a group of four muscles called the quadriceps femoris in the anterior compartment of the thigh are activated (and would be called the agonists of knee extension). However, to flex the knee joint, an opposite or antagonistic set of muscles called the hamstrings is activated.

As you can see, these terms would also be reversed for the opposing action. If you consider the first action as the knee bending, the hamstrings would be called the agonists and the quadriceps femoris would then be called the antagonists. See Table 6.1 for a list of some agonists and antagonists.

Table 6.1.

Agonist and Antagonist Skeletal Muscle Pairs

Agonist	**Antagonist**	**Movement**
Biceps brachii: in the anterior compartment of the arm	Triceps brachii: in the posterior compartment of the arm	The biceps brachii flexes the forearm, whereas the triceps brachii extends it.
Hamstrings: group of three muscles in the posterior compartment of the thigh	Quadriceps femoris: group of four muscles in the anterior compartment of the thigh	The hamstrings flex the leg, whereas the quadriceps femoris extend it.
Flexor digitorum superficialis and flexor digitorum profundus: in the anterior compartment of the forearm	Extensor digitorum: in the posterior compartment of the forearm	The flexor digitorum superficialis and flexor digitorum profundus flex the fingers and the hand at the wrist, whereas the extensor digitorum extends the fingers and the hand at the wrist.

There are also skeletal muscles that do not pull against the skeleton for movements. For example, there are the muscles that produce facial expressions. The insertions and origins of facial muscles are in the skin, so that certain individual muscles contract to form a smile or frown, form sounds or words, and raise the eyebrows. There also are skeletal muscles in the tongue, and the external urinary and anal sphincters that allow for voluntary regulation of urination and defecation, respectively. In addition, the diaphragm contracts and relaxes to change the volume of the pleural cavities but it does not move the skeleton to do this.

Everyday Connections: Exercise and Stretching

When exercising, it is important to first warm up the muscles. Stretching pulls on the muscle fibers and it also results in an increased blood flow to the muscles being worked. Without a proper warm-up, it is possible that you may either damage some of the muscle fibers or pull a tendon. A pulled tendon, regardless of location, results in pain, swelling, and diminished function; if it is moderate to severe, the injury could immobilize you for an extended period.

Recall the discussion about muscles crossing joints to create movement. Most of the joints you use during exercise are synovial joints, which have synovial fluid in the joint space between two bones. Exercise and stretching may also have a beneficial effect on synovial joints. Synovial fluid is a thin, but viscous film with the consistency of egg whites. When you first get up and start moving, your joints feel stiff for a number of reasons. After proper stretching and warm-up, the synovial fluid may become less viscous, allowing for better joint function.

The Lever System of Muscle and Bone Interactions

Skeletal muscles do not work by themselves. Muscles are arranged in pairs based on their functions. For muscles attached to the bones of the skeleton, the connection determines the force, speed, and range of movement. These characteristics depend on each other and can explain the general organization of the muscular and skeletal systems.

The skeleton and muscles act together to move the body. Have you ever used the back of a hammer to remove a nail from wood? The handle acts as a lever and the head of the hammer acts as a fulcrum, the fixed point that the force is applied to when you pull back or push down on the handle. The effort applied to this system is the pulling or pushing on the handle to remove the nail, which is the load, or "resistance" to the movement of the handle in the system. Our musculoskeletal system works in a similar manner, with bones being stiff levers and the articular endings of the bones—encased in synovial joints—acting as fulcrums. The load would be an object being lifted or any resistance to a movement (your head is a load when you are lifting it), and the effort, or applied force, comes from contracting skeletal muscle.

38. Age Related Changes to the Skeletal Muscle System

As one ages the mass of skeletal muscle decreases throughout the body. The muscles atrophy resulting in a decreased number of muscle fibers and decrease in the size of the remaining fibers. As skeletal muscles are postmitotic they can not reproduce to produce new fibers. As a result the fibers are replaced with fat tissue. The muscle fiber loss has been reported to be as high as 30% between the ages of 30 and 80. Proper nutrition and exercise can slow the loss muscle cells, but heredity also seems to be a factor.

Along with the loss of skeletal muscle mass comes the loss of skeletal muscle strength. For most individuals there is only a ten to twenty percent reduction in strength up to the age of seventy. After the age of seventy the reduction in strength may increase to fifty percent.

39. Age Related Dysfunctions of the Skeletal Muscle System

Parkinson's Disease

Parkinson's disease primarily affects people over 50 years of age. It is characterized by uncontrollable contractions of skeletal muscles, producing tremors and rigidity of the muscles. There is often a decrease in normal muscular activities that are usually related to other movements. For example, a person with Parkinson's Disease may not swing their arms while walking. The changes in the muscular system are only symptoms of this condition. The true causes lie in the central nervous system.

Myasthenia Gravis

Myasthenia gravis can occur at any age, but it is more prevalent in older persons. The condition is an autoimmune disease which disrupts the normal contraction of muscles by interfering with the neurotransmitter acetylocholine. As a result, the muscles do not contract as they normally would in response to stimulation. The condition is characterized by drooping of the upper eyelid, difficulty swallowing and speaking, chronic generalized muscular weakness, and fatigue.

Muscle Cramps

Muscle cramps are not unique to older persons, but are more common in them. Causes of muscle cramps include low oxygen supply to the muscle, over stimulation from then nervous system, and low blood sugar, sodium, and/or calcium. The sever, sustained contraction of a muscle may last from a few seconds to several hours.

Polymyositis

Polymyositis most commonly affects adults in their 30s, 40s, and 50s. It is an autoimmune that causes inflammation of muscles resulting in weakness of the muscles of the hips, thighs, and extensor muscles of the neck. The condition is characterized by difficulty in rising from squatting, in kneeling, or in climbing and descending stairs.

Polymyalgia Rhumatica

Polymyalgia rhumatica is ten times more common in those over 80 years of age as in those aged 50 to 59 and twice as common in woman as in men. The condition is characterized by bilateral pain and stiffness of the shoulders and thighs. The discomfort my be so severe that it causes immobility, depression, weight loss, and fever. Fortunately, the condition responds dramatically to treatment with corticosteroids.

40. Glossary: The Muscular System

abduct
: move away from midline in the sagittal plane

abductor digiti minimi
: muscle that abducts the little finger

abductor pollicis brevis
: muscle that abducts the thumb

abductor pollicis longus
: muscle that inserts into the first metacarpal

abductor
: moves the bone away from the midline

adductor brevis
: muscle that adducts and medially rotates the thigh

adductor longus
: muscle that adducts, medially rotates, and flexes the thigh

adductor magnus
: muscle with an anterior fascicle that adducts, medially rotates and flexes the thigh, and a posterior fascicle that assists in thigh extension

adductor pollicis
: muscle that adducts the thumb

adductor
: moves the bone toward the midline

agonist
(also, prime mover) muscle whose contraction is responsible for producing a particular motion

anal triangle
posterior triangle of the perineum that includes the anus

anconeus
small muscle on the lateral posterior elbow that extends the forearm

antagonist
muscle that opposes the action of an agonist

anterior compartment of the arm
(anterior flexor compartment of the arm) the biceps brachii, brachialis, brachioradialis, and their associated blood vessels and nerves

anterior compartment of the forearm
(anterior flexor compartment of the forearm) deep and superficial muscles that originate on the humerus and insert into the hand

anterior compartment of the leg
region that includes muscles that dorsiflex the foot

anterior compartment of the thigh
region that includes muscles that flex the thigh and extend the leg

anterior scalene
a muscle anterior to the middle scalene

appendicular
of the arms and legs

axial
of the trunk and head

belly
: bulky central body of a muscle

bi
: two

biceps brachii
: two-headed muscle that crosses the shoulder and elbow joints to flex the forearm while assisting in supinating it and flexing the arm at the shoulder

biceps femoris
: hamstring muscle

bipennate
: pennate muscle that has fascicles that are located on both sides of the tendon

brachialis
: muscle deep to the biceps brachii that provides power in flexing the forearm.

brachioradialis
: muscle that can flex the forearm quickly or help lift a load slowly

brevis
: short

buccinator
: muscle that compresses the cheek

calcaneal tendon
: (also, Achilles tendon) strong tendon that inserts into the calcaneal bone of the ankle

caval opening
: opening in the diaphragm that allows the inferior vena cava to pass through; foramen for the vena cava

circular
: (also, sphincter) fascicles that are concentrically arranged around an opening

compressor urethrae
: deep perineal muscle in women

convergent
: fascicles that extend over a broad area and converge on a common attachment site

coracobrachialis
: muscle that flexes and adducts the arm

corrugator supercilii
: prime mover of the eyebrows

deep anterior compartment
: flexor pollicis longus, flexor digitorum profundus, and their associated blood vessels and nerves

deep posterior compartment of the forearm
: (deep posterior extensor compartment of the forearm) the abductor pollicis longus, extensor pollicis brevis, extensor pollicis longus, extensor indicis, and their associated blood vessels and nerves

deep transverse perineal
: deep perineal muscle in men

deglutition
: swallowing

deltoid
: shoulder muscle that abducts the arm as well as flexes and medially rotates it, and extends and laterally rotates it

diaphragm
: skeletal muscle that separates the thoracic and abdominal

cavities and is dome-shaped at rest

digastric
muscle that has anterior and posterior bellies and elevates the hyoid bone and larynx when one swallows; it also depresses the mandible

dorsal group
region that includes the extensor digitorum brevis

dorsal interossei
muscles that abduct and flex the three middle fingers at the metacarpophalangeal joints and extend them at the interphalangeal joints

epicranial aponeurosis
(also, galea aponeurosis) flat broad tendon that connects the frontalis and occipitalis

erector spinae group
large muscle mass of the back; primary extensor of the vertebral column

extensor carpi radialis brevis
muscle that extends and abducts the hand at the wrist

extensor carpi ulnaris
muscle that extends and adducts the hand

extensor digiti minimi
muscle that extends the little finger

extensor digitorum brevis
muscle that extends the toes

extensor digitorum longus
muscle that is lateral to the tibialis anterior

extensor digitorum
muscle that extends the hand at the wrist and the phalanges

extensor hallucis longus
muscle that is partly deep to the tibialis anterior and extensor digitorum longus

extensor indicis
muscle that inserts onto the tendon of the extensor digitorum of the index finger

extensor pollicis brevis
muscle that inserts onto the base of the proximal phalanx of the thumb

extensor pollicis longus
muscle that inserts onto the base of the distal phalanx of the thumb

extensor radialis longus
muscle that extends and abducts the hand at the wrist

extensor retinaculum
band of connective tissue that extends over the dorsal surface of the hand

extensor
muscle that increases the angle at the joint

external intercostal
superficial intercostal muscles that raise the rib cage

external oblique
superficial abdominal muscle with fascicles that extend inferiorly and medially

extrinsic eye muscles
originate outside the eye and insert onto the outer surface of the white of the eye, and create eyeball movement

extrinsic muscles of the hand
: muscles that move the wrists, hands, and fingers and originate on the arm

fascicle
: muscle fibers bundled by perimysium into a unit

femoral triangle
: region formed at the junction between the hip and the leg and includes the pectineus, femoral nerve, femoral artery, femoral vein, and deep inguinal lymph nodes

fibularis brevis
: (also, peroneus brevis) muscle that plantar flexes the foot at the ankle and everts it at the intertarsal joints

fibularis longus
: (also, peroneus longus) muscle that plantar flexes the foot at the ankle and everts it at the intertarsal joints

fibularis tertius
: small muscle that is associated with the extensor digitorum longus

fixator
: synergist that assists an agonist by preventing or reducing movement at another joint, thereby stabilizing the origin of the agonist

flexion
: movement that decreases the angle of a joint

flexor carpi radialis
: muscle that flexes and abducts the hand at the wrist

flexor carpi ulnaris
: muscle that flexes and adducts the hand at the wrist

flexor digiti minimi brevis
: muscle that flexes the little finger

flexor digitorum longus
: muscle that flexes the four small toes

flexor digitorum profundus
: muscle that flexes the phalanges of the fingers and the hand at the wrist

flexor digitorum superficialis
: muscle that flexes the hand and the digits

flexor hallucis longus
: muscle that flexes the big toe

flexor pollicis brevis
: muscle that flexes the thumb

flexor pollicis longus
: muscle that flexes the distal phalanx of the thumb

flexor retinaculum
: band of connective tissue that extends over the palmar surface of the hand

flexor
: muscle that decreases the angle at the joint

frontalis
: front part of the occipitofrontalis muscle

fusiform
: muscle that has fascicles that are spindle-shaped to create large bellies

gastrocnemius
: most superficial muscle of the calf

genioglossus
: muscle that originates on the mandible and allows the tongue to move downward and forward

geniohyoid
: muscle that depresses the mandible, and raises and pulls the hyoid bone anteriorly

gluteal group
: muscle group that extends, flexes, rotates, adducts, and abducts the femur

gluteus maximus
: largest of the gluteus muscles that extends the femur

gluteus medius
: muscle deep to the gluteus maximus that abducts the femur at the hip

gluteus minimus
: smallest of the gluteal muscles and deep to the gluteus medius

gracilis
: muscle that adducts the thigh and flexes the leg at the knee

hamstring group
: three long muscles on the back of the leg

hyoglossus
: muscle that originates on the hyoid bone to move the tongue downward and flatten it

hypothenar eminence
: rounded contour of muscle at the base of the little finger

hypothenar
: group of muscles on the medial aspect of the palm

iliacus
: muscle that, along with the psoas major, makes up the iliopsoas

iliococcygeus
: muscle that makes up the levator ani along with the pubococcygeus

iliocostalis cervicis
: muscle of the iliocostalis group associated with the cervical region

iliocostalis group
: laterally placed muscles of the erector spinae

iliocostalis lumborum
: muscle of the iliocostalis group associated with the lumbar region

iliocostalis thoracis
: muscle of the iliocostalis group associated with the thoracic region

iliopsoas group
: muscle group consisting of iliacus and psoas major muscles, that flexes the thigh at the hip, rotates it laterally, and flexes the trunk of the body onto the hip

iliotibial tract
: muscle that inserts onto the tibia; made up of the gluteus maximus and connective tissues of the tensor fasciae latae

inferior extensor retinaculum
: cruciate ligament of the ankle

inferior gemellus
: muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip

infrahyoid muscles
: anterior neck muscles that are attached to, and inferior to the hyoid bone

infraspinatus
: muscle that laterally rotates the arm

innermost intercostal
: the deepest intercostal muscles that draw the ribs together

insertion
: end of a skeletal muscle that is attached to the structure (usually a bone) that is moved when the muscle contracts

intercostal muscles
: muscles that span the spaces between the ribs

intermediate
: group of midpalmar muscles

internal intercostal
: muscles the intermediate intercostal muscles that draw the ribs together

internal oblique
: flat, intermediate abdominal muscle with fascicles that run perpendicular to those of the external oblique

intrinsic muscles of the hand
: muscles that move the wrists, hands, and fingers and originate in the palm

ischiococcygeus
: muscle that assists the levator ani and pulls the coccyx anteriorly

lateral compartment of the leg
: region that includes the fibularis (peroneus) longus and the fibularis (peroneus) brevis and their associated blood vessels

and nerves

lateral pterygoid
muscle that moves the mandible from side to side

lateralis
to the outside

latissimus dorsi
broad, triangular axial muscle located on the inferior part of the back

levator ani
pelvic muscle that resists intra-abdominal pressure and supports the pelvic viscera

linea alba
white, fibrous band that runs along the midline of the trunk

longissimus capitis
muscle of the longissimus group associated with the head region

longissimus cervicis
muscle of the longissimus group associated with the cervical region

longissimus group
intermediately placed muscles of the erector spinae

longissimus thoracis
muscle of the longissimus group associated with the thoracic region

longus
long

lumbrical
muscle that flexes each finger at the metacarpophalangeal

joints and extend each finger at the interphalangeal joints

masseter
main muscle for chewing that elevates the mandible to close the mouth

mastication
chewing

maximus
largest

medial compartment of the thigh
a region that includes the adductor longus, adductor brevis, adductor magnus, pectineus, gracilis, and their associated blood vessels and nerves

medial pterygoid
muscle that moves the mandible from side to side

medialis
to the inside

medius
medium

middle scalene
longest scalene muscle, located between the anterior and posterior scalenes

minimus
smallest

multifidus
muscle of the lumbar region that helps extend and laterally flex the vertebral column

multipennate
pennate muscle that has a tendon branching within it

mylohyoid
: muscle that lifts the hyoid bone and helps press the tongue to the top of the mouth

oblique
: at an angle

obturator externus
: muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip

obturator internus
: muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip

occipitalis
: posterior part of the occipitofrontalis muscle

occipitofrontalis
: muscle that makes up the scalp with a frontal belly and an occipital belly

omohyoid
: muscle that has superior and inferior bellies and depresses the hyoid bone

opponens digiti minimi
: muscle that brings the little finger across the palm to meet the thumb

opponens pollicis
: muscle that moves the thumb across the palm to meet another finger

orbicularis oculi
: circular muscle that closes the eye

orbicularis oris
: circular muscle that moves the lips

origin
: end of a skeletal muscle that is attached to another structure (usually a bone) in a fixed position

palatoglossus
: muscle that originates on the soft palate to elevate the back of the tongue

palmar interossei
: muscles that abduct and flex each finger at the metacarpophalangeal joints and extend each finger at the interphalangeal joints

palmaris longus
: muscle that provides weak flexion of the hand at the wrist

parallel
: fascicles that extend in the same direction as the long axis of the muscle

patellar ligament
: extension of the quadriceps tendon below the patella

pectineus
: muscle that abducts and flexes the femur at the hip

pectoral girdle
: shoulder girdle, made up of the clavicle and scapula

pectoralis major
: thick, fan-shaped axial muscle that covers much of the superior thorax

pectoralis minor
: muscle that moves the scapula and assists in inhalation

pelvic diaphragm
: muscular sheet that comprises the levator ani and the ischiococcygeus

pelvic girdle
: hips, a foundation for the lower limb

pennate
: fascicles that are arranged differently based on their angles to the tendon

perineum
: diamond-shaped region between the pubic symphysis, coccyx, and ischial tuberosities

piriformis
: muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip

plantar aponeurosis
: muscle that supports the longitudinal arch of the foot

plantar group
: four-layered group of intrinsic foot muscles

plantaris
: muscle that runs obliquely between the gastrocnemius and the soleus

popliteal fossa
: diamond-shaped space at the back of the knee

popliteus
: muscle that flexes the leg at the knee and creates the floor of the popliteal fossa

posterior compartment of the leg
: region that includes the superficial gastrocnemius, soleus, and plantaris, and the deep popliteus, flexor digitorum longus, flexor hallucis longus, and tibialis posterior

posterior compartment of the thigh
: region that includes muscles that flex the leg and extend the

thigh

posterior scalene
smallest scalene muscle, located posterior to the middle scalene

prime mover
(also, agonist) principle muscle involved in an action

pronator quadratus
pronator that originates on the ulna and inserts on the radius

pronator teres
pronator that originates on the humerus and inserts on the radius

psoas major
muscle that, along with the iliacus, makes up the iliopsoas

pubococcygeus
muscle that makes up the levator ani along with the iliococcygeus

quadratus femoris
muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip

quadratus lumborum
posterior part of the abdominal wall that helps with posture and stabilization of the body

quadriceps femoris group
four muscles, that extend and stabilize the knee

quadriceps tendon
(also, patellar tendon) tendon common to all four quadriceps muscles, inserts into the patella

rectus abdominis
: long, linear muscle that extends along the middle of the trunk

rectus femoris
: quadricep muscle on the anterior aspect of the thigh

rectus sheaths
: tissue that makes up the linea alba

rectus
: straight

retinacula
: fibrous bands that sheath the tendons at the wrist

rhomboid major
: muscle that attaches the vertebral border of the scapula to the spinous process of the thoracic vertebrae

rhomboid minor
: muscle that attaches the vertebral border of the scapula to the spinous process of the thoracic vertebrae

rotator cuff
: (also, musculotendinous cuff) the circle of tendons around the shoulder joint

sartorius
: band-like muscle that flexes, abducts, and laterally rotates the leg at the hip

scalene muscles
: flex, laterally flex, and rotate the head; contribute to deep inhalation

segmental muscle group
: interspinales and intertransversarii muscles that bring together the spinous and transverse processes of each consecutive vertebra

semimembranosus
hamstring muscle

semispinalis capitis
transversospinales muscle associated with the head region

semispinalis cervicis
transversospinales muscle associated with the cervical region

semispinalis thoracis
transversospinales muscle associated with the thoracic region

semitendinosus
hamstring muscle

serratus anterior
large and flat muscle that originates on the ribs and inserts onto the scapula

soleus
wide, flat muscle deep to the gastrocnemius

sphincter urethrovaginalis
deep perineal muscle in women

spinalis capitis
muscle of the spinalis group associated with the head region

spinalis cervicis
muscle of the spinalis group associated with the cervical region

spinalis group
medially placed muscles of the erector spinae

spinalis thoracis
muscle of the spinalis group associated with the thoracic region

splenius capitis
neck muscle that inserts into the head region

splenius cervicis
neck muscle that inserts into the cervical region

splenius
posterior neck muscles; includes the splenius capitis and splenius cervicis

sternocleidomastoid
major muscle that laterally flexes and rotates the head

sternohyoid
muscle that depresses the hyoid bone

sternothyroid
muscle that depresses the larynx’s thyroid cartilage

styloglossus
muscle that originates on the styloid bone, and allows upward and backward motion of the tongue

stylohyoid
muscle that elevates the hyoid bone posteriorly

subclavius
muscle that stabilizes the clavicle during movement

subscapularis
muscle that originates on the anterior scapula and medially rotates the arm

superficial anterior compartment of the forearm
flexor carpi radialis, palmaris longus, flexor carpi ulnaris, flexor digitorum superficialis, and their associated blood vessels and nerves

superficial posterior compartment of the forearm
: extensor radialis longus, extensor carpi radialis brevis, extensor digitorum, extensor digiti minimi, extensor carpi ulnaris, and their associated blood vessels and nerves

superior extensor retinaculum
: transverse ligament of the ankle

superior gemellus
: muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip

supinator
: muscle that moves the palm and forearm anteriorly

suprahyoid muscles
: neck muscles that are superior to the hyoid bone

supraspinatus
: muscle that abducts the arm

synergist
: muscle whose contraction helps a prime mover in an action

temporalis
: muscle that retracts the mandible

tendinous intersections
: three transverse bands of collagen fibers that divide the rectus abdominis into segments

tensor fascia lata
: muscle that flexes and abducts the thigh

teres major
: muscle that extends the arm and assists in adduction and medial rotation of it

teres minor
: muscle that laterally rotates and extends the arm

thenar eminence
: rounded contour of muscle at the base of the thumb

thenar
: group of muscles on the lateral aspect of the palm

thyrohyoid
: muscle that depresses the hyoid bone and elevates the larynx's thyroid cartilage

tibialis anterior
: muscle located on the lateral surface of the tibia

tibialis posterior
: muscle that plantar flexes and inverts the foot

transversospinales
: muscles that originate at the transverse processes and insert at the spinous processes of the vertebrae

transversus abdominis
: deep layer of the abdomen that has fascicles arranged transversely around the abdomen

trapezius
: muscle that stabilizes the upper part of the back

triceps brachii
: three-headed muscle that extends the forearm

tri
: three

unipennate
: pennate muscle that has fascicles located on one side of the tendon

urogenital triangle
anterior triangle of the perineum that includes the external genitals

vastus intermedius
quadricep muscle that is between the vastus lateralis and vastus medialis and is deep to the rectus femoris

vastus lateralis
quadricep muscle on the lateral aspect of the thigh

vastus medialis
quadricep muscle on the medial aspect of the thigh

PART VII

CHAPTER 7: THE NERVOUS SYSTEM

41. Anatomy of the Nervous System

Figure 7.1. Human Nervous System
The ability to balance like an acrobat combines functions throughout the nervous system. The central and peripheral divisions coordinate control of the body using the senses of balance, body position, and touch on the soles of the feet. (credit: Rhett Sutphin)

Introduction

The nervous system is responsible for controlling much of the body, both through somatic (voluntary) and autonomic (involuntary) functions. The structures of the nervous system must be described in detail to understand how many of these functions are possible. There is a physiological concept known as localization of function that states that certain structures are specifically responsible for prescribed functions. It is an underlying concept in all of anatomy and physiology, but the nervous system illustrates the concept very well. Fresh, unstained nervous tissue can be described as gray or white matter, and within those two types of tissue it can be very hard to see any detail. However, as specific regions and structures have been described, they were related to specific functions. Understanding these structures and the functions they perform requires a detailed description of the anatomy of the nervous system, delving deep into what the central and peripheral structures are. The place to start this study of the nervous system is the beginning of the individual human life, within the womb. The embryonic development of the nervous system allows for a simple framework on which progressively more complicated structures can be built. With this framework in place, a thorough investigation of the nervous system is possible.

The Embryologic Perspective

The brain is a complex organ composed of gray parts and white matter, which can be hard to distinguish. Starting from an embryologic perspective allows you to understand more easily how the parts relate to each other. The embryonic nervous system begins as a very simple structure—essentially just a straight line, which then gets increasingly complex. Looking at the development of the nervous system with a couple of early snapshots makes it easier to understand the whole complex system. Many structures that appear to be adjacent in the adult brain are not connected, and the connections that exist may seem arbitrary. But there is an underlying order to the system that comes from how different parts develop. By following the developmental pattern, it is possible to learn what the major regions of the nervous system are.

The Neural Tube

To begin, a sperm cell and an egg cell fuse to become a fertilized egg. The fertilized egg cell, or zygote, starts dividing to generate the cells that make up an entire organism. Sixteen days after fertilization, the developing embryo's cells belong to one of three germ layers that give rise to the different tissues in the body. The endoderm, or inner tissue, is responsible for generating the lining tissues of various spaces within the body, such as the mucosae of the digestive and respiratory systems. The mesoderm, or middle tissue, gives rise to most of the muscle and connective tissues. Finally the ectoderm, or outer tissue, develops into the integumentary system (the skin) and the nervous system. It is probably not difficult to see that the outer tissue of the embryo becomes the outer covering of the body. But how is it responsible for the nervous system? As the embryo develops, a portion of the ectoderm differentiates into a specialized region of neuroectoderm, which is the precursor for the tissue of the nervous system. Molecular signals induce cells in this region to differentiate into the neuroepithelium, forming a ***neural plate***. The cells then begin to change shape, causing the tissue to buckle and fold inward (Figure 7.2). A ***neural groove*** forms, visible as a line along the dorsal surface of the embryo. The ridge-like edge on either side of the neural groove is referred as the ***neural fold***. As the neural folds come together and converge, the underlying structure forms into a tube just beneath the ectoderm called the ***neural tube***. Cells from the neural folds then separate from the ectoderm to form a cluster of cells referred to as the ***neural crest***, which runs lateral to the neural tube. The neural crest migrates away from the nascent, or embryonic, central nervous system (CNS) that will form along the neural groove and develops into several parts of the peripheral nervous system (PNS), including the enteric nervous tissue. Many tissues that are not part of the nervous system also arise from the neural crest, such as craniofacial cartilage and bone, and melanocytes.

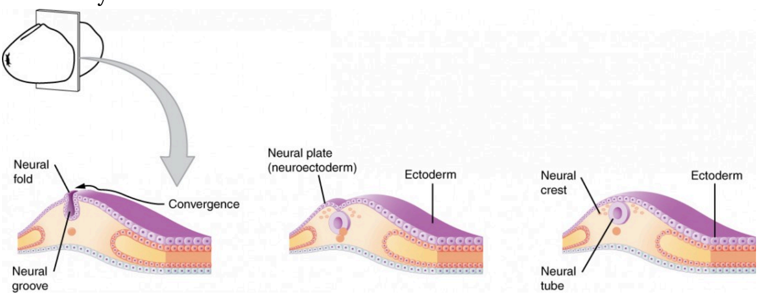


Figure 7.2. Early Embryonic Development of Nervous System
The neuroectoderm begins to fold inward to form the neural groove. As the two sides of the neural groove converge, they form the neural tube, which lies beneath the ectoderm. The anterior end of the neural tube will develop into the brain, and the posterior portion will become the spinal cord. The neural crest develops into peripheral structures.

At this point, the early nervous system is a simple, hollow tube. It runs from the anterior end of the embryo to the posterior end. Beginning at 25 days, the anterior end develops into the brain, and the posterior portion becomes the spinal cord. This is the most basic arrangement of tissue in the nervous system, and it gives rise to the more complex structures by the fourth week of development.

Primary Vesicles

As the anterior end of the neural tube starts to develop into the brain, it undergoes a couple of enlargements; the result is the production of sac-like vesicles. Similar to a child's balloon animal, the long, straight neural tube begins to take on a new shape. Three vesicles form at the first stage, which are called ***primary vesicles***. These vesicles are given names that are based on Greek words, the main root word being *enkephalon*, which means "brain" (en- = "inside"; kephalon = "head"). The prefix to each generally corresponds to its position along the length of the developing nervous system. The ***prosencephalon*** (pros- = "in front") is the forward-most vesicle, and the term can be loosely translated to mean ***forebrain***. The ***mesencephalon*** (mes- = "middle") is the next vesicle, which can be called the ***midbrain***. The third vesicle at this stage is the ***rhombencephalon***. The first part of this word is also the root of the word rhombus, which is a geometrical figure with four sides of equal length (a square is a rhombus with 90° angles). Whereas prosencephalon and mesencephalon translate into the English words forebrain and midbrain, there is not a word for "four-sided-figure-brain." However, the third vesicle can be called the ***hindbrain***. One way of thinking about how the brain is arranged is to use these three regions—forebrain, midbrain, and hindbrain—which are based on the primary vesicle stage of development (Figure 7.3**a**).

Secondary Vesicles

The brain continues to develop, and the vesicles differentiate further (see Figure 7.3b). The three primary vesicles become five ***secondary vesicles***. The prosencephalon enlarges into two new vesicles called the ***telencephalon*** and the ***diencephalon***. The telecephalon will become the cerebrum. The diencephalon gives rise to several adult structures; two that will be important are the thalamus and the hypothalamus. In the embryonic diencephalon, a structure known as the eye cup develops, which will eventually become the retina, the nervous tissue of the eye called the retina.

This is a rare example of nervous tissue developing as part of the CNS structures in the embryo, but becoming a peripheral structure in the fully formed nervous system. The mesencephalon does not differentiate into any finer divisions. The midbrain is an established region of the brain at the primary vesicle stage of development and remains that way. The rest of the brain develops around it and constitutes a large percentage of the mass of the brain. Dividing the brain into forebrain, midbrain, and hindbrain is useful in considering its developmental pattern, but the midbrain is a small proportion of the entire brain, relatively speaking. The rhombencephalon develops into the ***metencephalon*** and ***myelencephalon***. The metencephalon corresponds to the adult structure known as the pons and also gives rise to the cerebellum. The cerebellum (from the Latin meaning "little brain") accounts for about 10 percent of the mass of the brain and is an important structure in itself. The most significant connection between the cerebellum and the rest of the brain is at the pons, because the pons and cerebellum develop out of the same vesicle. The myelencephalon corresponds to the adult structure known as the medulla oblongata. The structures that come from the mesencephalon and rhombencephalon, except for the cerebellum, are collectively considered the ***brain stem***, which specifically includes the midbrain, pons, and medulla.

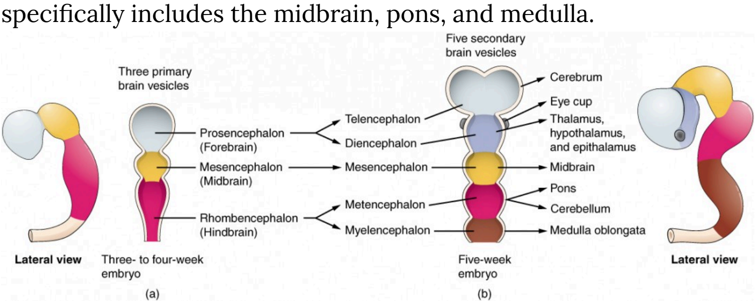


Figure 7.3. Primary and Secondary Vesicle Stages of Development
The embryonic brain develops complexity through enlargements of the neural tube called vesicles; (a) The primary vesicle stage has three regions, and (b) the secondary vesicle stage has five regions.

Spinal Cord Development

While the brain is developing from the anterior neural tube, the spinal cord is developing from the posterior neural tube. However, its structure does not differ from the basic layout of the neural tube. It is a long, straight cord with a small, hollow space down the center. The neural tube is defined in terms of its anterior versus posterior portions, but it also has a dorsal–ventral dimension. As the neural tube separates from the rest of the ectoderm, the side closest to the surface is dorsal, and the deeper side is ventral. As the spinal cord develops, the cells making up the wall of the neural tube proliferate and differentiate into the neurons and glia of the spinal cord. The dorsal tissues will be associated with sensory functions, and the ventral tissues will be associated with motor functions.

Relating Embryonic Development to the Adult Brain

Embryonic development can help in understanding the structure of the adult brain because it establishes a framework on which more complex structures can be built. First, the neural tube establishes the anterior–posterior dimension of the nervous system, which is called the ***neuraxis***. The embryonic nervous system in mammals can be said to have a standard arrangement. Humans (and other primates, to some degree) make this complicated by standing up and walking on two legs. The anterior–posterior dimension of the neuraxis overlays the superior–inferior dimension of the body. However, there is a major curve between the brain stem and forebrain, which is called the ***cephalic flexure***. Because of this, the neuraxis starts in an inferior position—the end of the spinal cord—and ends in an anterior position, the front of the cerebrum. If this is confusing, just imagine a four-legged animal standing up on two legs. Without the flexure in the brain stem, and at the top of the neck, that animal would be looking straight up instead of straight in front (Figure 7.4).

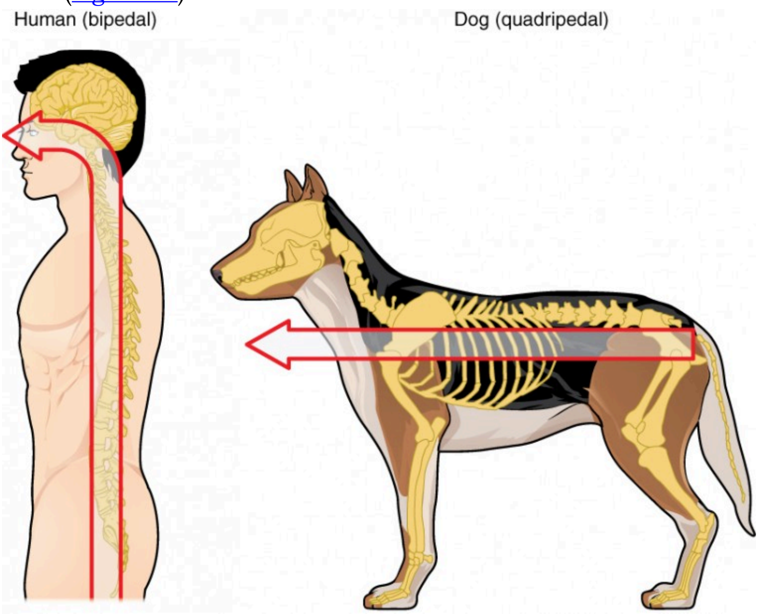


Figure 7.4. Human Neuraxis
The mammalian nervous system is arranged with the neural tube running along an anterior to posterior axis, from nose to tail for a four-legged animal like a dog. Humans, as two-legged animals, have a bend in the neuraxis between the brain stem and the diencephalon, along with a bend in the neck, so that the eyes and the face are oriented forward.

In summary, the primary vesicles help to establish the basic regions of the nervous system: forebrain, midbrain, and hindbrain. These divisions are useful in certain situations, but they are not equivalent regions. The midbrain is small compared with the hindbrain and particularly the forebrain. The secondary vesicles go on to establish the major regions of the adult nervous system that will be followed in this text. The telencephalon is the cerebrum, which is the major portion of the human brain. The diencephalon continues to be referred to by this Greek name, because there is no better term for it (dia- = “through”). The diencephalon is between the cerebrum and the rest of the nervous system and can be described as the region through which all projections have to pass between the cerebrum and everything else. The brain stem includes the midbrain, pons, and medulla, which correspond to the mesencephalon, metencephalon, and myelencephalon. The cerebellum, being a large portion of the brain, is considered a separate region. Table 7.1 connects the different stages of development to the adult structures of the CNS. One other benefit of considering embryonic development is that certain connections are more obvious because of how these adult structures are related. The retina, which began as part of the diencephalon, is primarily connected to the diencephalon. The eyes are just inferior to the anterior-most part of the cerebrum, but the optic nerve extends back to the thalamus as the optic tract, with branches into a region of the hypothalamus. There is also a connection of the optic tract to the midbrain, but the mesencephalon is adjacent to the diencephalon, so that is not difficult to imagine. The cerebellum originates out of the metencephalon, and its largest white matter connection is to the pons, also from the metencephalon. There are connections between the cerebellum and both the medulla and midbrain, which are adjacent structures in the secondary vesicle stage of development. In the adult brain, the cerebellum seems close to the cerebrum, but there is no direct connection between them. Another aspect of the adult CNS structures that relates to embryonic development is the ventricles—open spaces within the CNS where cerebrospinal fluid circulates. They are the remnant of the hollow center of the neural tube. The four ventricles and the tubular spaces associated with them can be linked back to the hollow center of the embryonic brain (see Table 7.1).

Table 7.1.

Stages of Embryonic Development				
Neural tube	**Primary vesicle stage**	**Secondary vesicle stage**	**Adult structures**	**Ventricles**
Anterior neural tube	Prosencephalon	Telencephalon	Cerebrum	Lateral ventricles
Anterior neural tube	Prosencephalon	Diencephalon	Diencephalon	Third ventricle
Anterior neural tube	Mesencephalon	Mesencephalon	Midbrain	Cerebral aqueduct
Anterior neural tube	Rhombencephalon	Metencephalon	Pons cerebellum	Fourth ventricle
Anterior neural tube	Rhombencephalon	Myelencephalon	Medulla	Fourth ventricle
Posterior neural tube			Spinal cord	Central canal

42. The Central Nervous System

The brain and the spinal cord are the central nervous system, and they represent the main organs of the nervous system. The spinal cord is a single structure, whereas the adult brain is described in terms of four major regions: the cerebrum, the diencephalon, the brain stem, and the cerebellum. A person's conscious experiences are based on neural activity in the brain. The regulation of homeostasis is governed by a specialized region in the brain. The coordination of reflexes depends on the integration of sensory and motor pathways in the spinal cord.

The Cerebrum

The iconic gray mantle of the human brain, which appears to make up most of the mass of the brain, is the*cerebrum* (Figure 7.5). The wrinkled portion is the ***cerebral cortex***, and the rest of the structure is beneath that outer covering. There is a large separation between the two sides of the cerebrum called the ***longitudinal fissure***. It separates the cerebrum into two distinct halves, a right and left ***cerebral hemisphere***. Deep within the cerebrum, the white matter of the ***corpus callosum*** provides the major pathway for communication between the two hemispheres of the cerebral cortex.

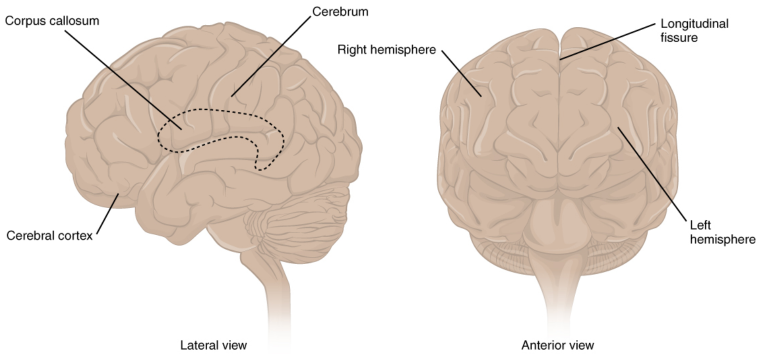


Figure 7.5. The Cerebrum
The cerebrum is a large component of the CNS in humans, and the most obvious aspect of it is the folded surface called the cerebral cortex.

Many of the higher neurological functions, such as memory, emotion, and consciousness, are the result of cerebral function. The complexity of the cerebrum is different across vertebrate species. The cerebrum of the most primitive vertebrates is not much more than the connection for the sense of smell. In mammals, the cerebrum comprises the outer gray matter that is the cortex (from the Latin word meaning "bark of a tree") and several deep nuclei that belong to three important functional groups. The ***basal nuclei*** are responsible for cognitive processing, the most important function being that associated with planning movements. The ***basal forebrain*** contains nuclei that are important in learning and memory. The ***limbic cortex*** is the region of the cerebral cortex that is part of the ***limbic system***, a collection of structures involved in emotion, memory, and behavior.

Cerebral Cortex

The cerebrum is covered by a continuous layer of gray matter that wraps around either side of the forebrain—the cerebral cortex. This thin, extensive region of wrinkled gray matter is responsible for the higher functions of the nervous system. A ***gyrus*** (plural = gyri) is the ridge of one of those wrinkles, and a ***sulcus*** (plural = sulci) is the groove between two gyri. The pattern of these folds of tissue indicates specific regions of the cerebral cortex. The head is limited by the size of the birth canal, and the brain must fit inside the cranial cavity of the skull. Extensive folding in the cerebral cortex enables more gray matter to fit into this limited space. If the gray matter of the cortex were peeled off of the cerebrum and laid out flat, its surface area would be roughly equal to one square meter. The folding of the cortex maximizes the amount of gray matter in the cranial cavity. During embryonic development, as the telencephalon expands within the skull, the brain goes through a regular course of growth that results in everyone's brain having a similar pattern of folds. The surface of the brain can be mapped on the basis of the locations of large gyri and sulci. Using these landmarks, the cortex can be separated into four major regions, or lobes (Figure 7.6). The ***lateral sulcus*** that separates the ***temporal lobe*** from the other regions is one such landmark. Superior to the lateral sulcus are the ***parietal lobe*** and ***frontal lobe***, which are separated from each other by the ***central sulcus***. The posterior region of the cortex is the ***occipital lobe***, which has no obvious anatomical border between it and the parietal or temporal lobes on the lateral surface of the brain. From the medial surface, an obvious landmark separating the parietal and occipital lobes is called the ***parieto-occipital sulcus***. The fact that there is no obvious anatomical border between these lobes is consistent with the functions of these regions being interrelated.

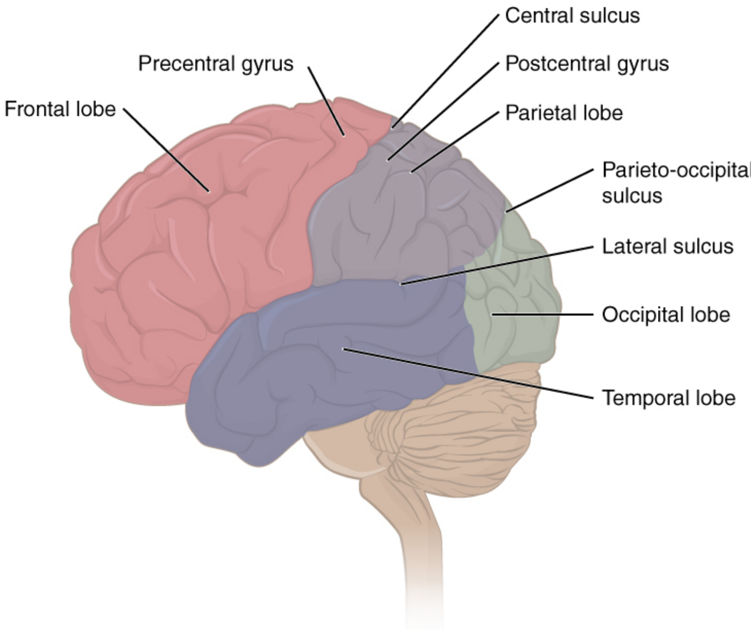


Figure 7.6. Lobes of the Cerebral Cortex
The cerebral cortex is divided into four lobes. Extensive folding increases the surface area available for cerebral functions.

Different regions of the cerebral cortex can be associated with particular functions, a concept known as localization of function. In the early 1900s, a German neuroscientist named Korbinian Brodmann performed an extensive study of the microscopic anatomy—the cytoarchitecture—of the cerebral cortex and divided the cortex into 52 separate regions on the basis of the histology of the cortex. His work resulted in a system of classification known as ***Brodmann's areas***, which is still used today to describe the anatomical distinctions within the cortex (Figure 7.7). The results from Brodmann's work on the anatomy align very well with the functional differences within the cortex. Areas 17 and 18 in the occipital lobe are responsible for primary visual perception. That visual information is complex, so it is processed in the temporal and parietal lobes as well. The temporal lobe is associated with primary auditory sensation, known as Brodmann's areas 41 and 42 in the superior temporal lobe. Because regions of the temporal lobe are part of the limbic system, memory is an important function associated with that lobe. Memory is essentially a sensory function; memories are recalled sensations such as the smell of Mom's baking or the sound of a barking dog. Even memories of movement are really the memory of sensory feedback from those movements, such as stretching muscles or the movement of the skin around a joint. Structures in the temporal lobe are responsible for establishing long-term memory, but the ultimate location of those memories is usually in the region in which the sensory perception was processed. The main sensation associated with the parietal lobe is ***somatosensation***, meaning the general sensations associated with the body. Posterior to the central sulcus is the ***postcentral gyrus***, the primary somatosensory cortex, which is identified as Brodmann's areas 1, 2, and 3. All of the tactile senses are processed in this area, including touch, pressure, tickle, pain, itch, and vibration, as well as more general senses of the body such as ***proprioception*** and ***kinesthesia***, which are the senses of body position and movement, respectively. Anterior to the central sulcus is the frontal lobe, which is primarily associated with motor functions. The ***precentral gyrus*** is the primary motor cortex. Cells from this region of the cerebral cortex are the upper motor neurons that instruct cells in the spinal cord to move skeletal muscles. Anterior to this region are a few areas that are associated with planned movements. The ***premotor area*** is responsible for thinking of a movement to be made. The ***frontal eye fields*** are important in eliciting eye movements and in attending to visual stimuli. ***Broca's area*** is responsible for the production of language, or controlling movements responsible for speech; in the vast majority of people, it is located only on the left side. Anterior to these regions is the ***prefrontal lobe***, which serves cognitive functions that can be the basis of personality, short-term memory, and consciousness. The prefrontal lobotomy is an outdated mode of treatment for personality disorders (psychiatric conditions) that profoundly affected the personality of the patient.

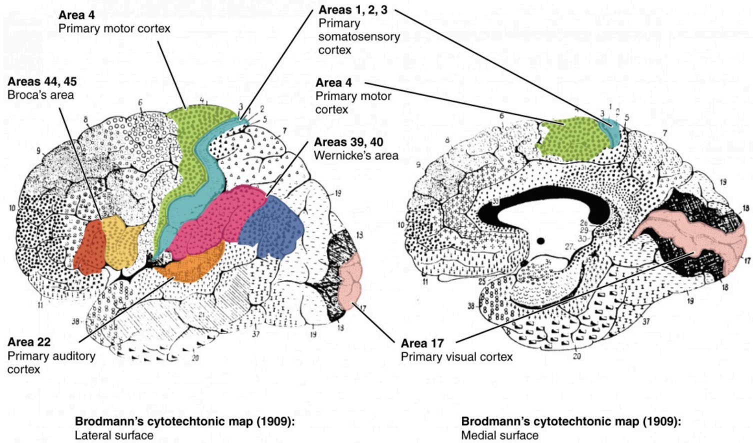


Figure 7.7. Brodmann's Areas of the Cerebral Cortex
Brodmann mapping of functionally distinct regions of the cortex was based on its cytoarchitecture at a microscopic level.

Subcortical structures

Beneath the cerebral cortex are sets of nuclei known as ***subcortical nuclei*** that augment cortical processes. The nuclei of the basal forebrain serve as the primary location for acetylcholine production, which modulates the overall activity of the cortex, possibly leading to greater attention to sensory stimuli. Alzheimer's disease is associated with a loss of neurons in the basal forebrain. The ***hippocampus*** and ***amygdala*** are medial-lobe structures that, along with the adjacent cortex, are involved in long-term memory formation and emotional responses. The basal nuclei are a set of nuclei in the cerebrum responsible for comparing cortical processing with the general state of activity in the nervous system to influence the likelihood of movement taking place. For example, while a student is sitting in a classroom listening to a lecture, the basal nuclei will keep the urge to jump up and scream from actually happening. (The basal nuclei are also referred to as the basal ganglia, although that is potentially confusing because the term ganglia is typically used for peripheral structures.) The major structures of the basal nuclei that control movement are the ***caudate***, ***putamen***, and ***globus pallidus***, which are located deep in the cerebrum. The caudate is a long nucleus that follows the basic C-shape of the cerebrum from the frontal lobe, through the parietal and occipital lobes, into the temporal lobe. The putamen is mostly deep in the anterior regions of the frontal and parietal lobes. Together, the caudate and putamen are called the ***striatum***. The globus pallidus is a layered nucleus that lies just medial to the putamen; they are called the lenticular nuclei because they look like curved pieces fitting together like lenses. The globus pallidus has two subdivisions, the external and internal segments, which are lateral and medial, respectively. These nuclei are depicted in a frontal section of the brain in Figure 7.8.

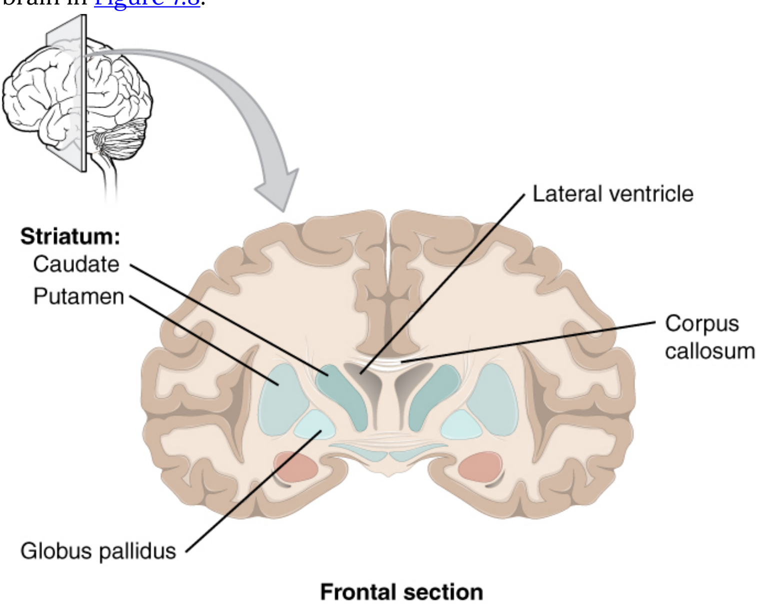


Figure 7.8. Frontal Section of Cerebral Cortex and Basal Nuclei
The major components of the basal nuclei, shown in a frontal section

of the brain, are the caudate (just lateral to the lateral ventricle), the putamen (inferior to the caudate and separated by the large white-matter structure called the internal capsule), and the globus pallidus (medial to the putamen).

The basal nuclei in the cerebrum are connected with a few more nuclei in the brain stem that together act as a functional group that forms a motor pathway. Two streams of information processing take place in the basal nuclei. All input to the basal nuclei is from the cortex into the striatum (Figure 7.9). The ***direct pathway*** is the projection of axons from the striatum to the globus pallidus internal segment (GPi) and the ***substantia nigra pars reticulata*** (SNr). The GPi/SNr then projects to the thalamus, which projects back to the cortex. The ***indirect pathway*** is the projection of axons from the striatum to the globus pallidus external segment (GPe), then to the subthalamic nucleus (STN), and finally to GPi/SNr. The two streams both target the GPi/SNr, but one has a direct projection and the other goes through a few intervening nuclei. The direct pathway causes the ***disinhibition*** of the thalamus (inhibition of one cell on a target cell that then inhibits the first cell), whereas the indirect pathway causes, or reinforces, the normal inhibition of the thalamus. The thalamus then can either excite the cortex (as a result of the direct pathway) or fail to excite the cortex (as a result of the indirect pathway).

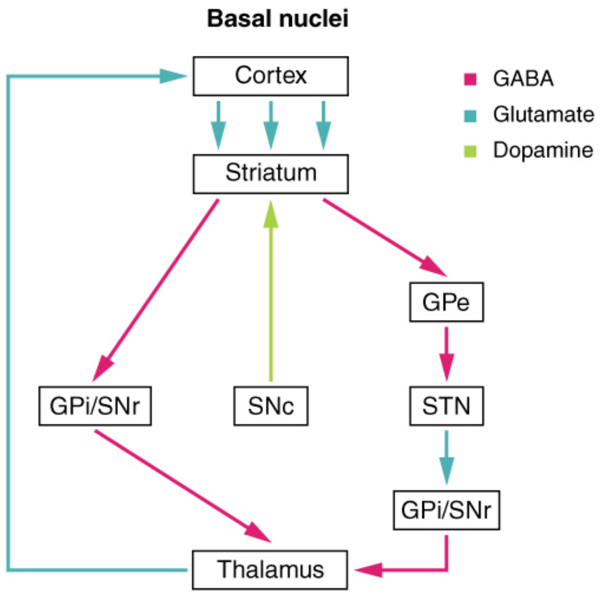


Figure 7.9. Connections of Basal Nuclei
Input to the basal nuclei is from the cerebral cortex, which is an excitatory connection releasing glutamate as a neurotransmitter. This input is to the striatum, or the caudate and putamen. In the direct pathway, the striatum projects to the internal segment of the globus pallidus and the substantia nigra pars reticulata (GPi/SNr). This is an inhibitory pathway, in which GABA is released at the synapse, and the target cells are hyperpolarized and less likely to fire. The output from the basal nuclei is to the thalamus, which is an inhibitory projection using GABA.

The switch between the two pathways is the ***substantia nigra pars compacta***, which projects to the striatum and releases the neurotransmitter dopamine. Dopamine receptors are either excitatory (D1-type receptors) or inhibitory (D2-type receptors). The direct pathway is activated by dopamine, and the indirect pathway is inhibited by dopamine. When the substantia nigra pars compacta is firing, it signals to the basal nuclei that the body is in an active state, and movement will be more likely. When the substantia nigra pars compacta is silent, the body is in a passive state, and movement is inhibited. To illustrate this situation, while a student is sitting listening to a lecture, the substantia nigra pars compacta would be silent and the student less likely to get up and walk around. Likewise, while the professor is lecturing, and walking around at the front of the classroom, the professor's substantia nigra pars compacta would be active, in keeping with his or her activity level.

Everyday Connections: ***The Myth of Left Brain/Right Brain***

There is a persistent myth that people are "right-brained" or "left-brained," which is an oversimplification of an important concept about the cerebral hemispheres. There is some lateralization of function, in which the left side of the brain is devoted to language function and the right side is devoted to spatial and nonverbal reasoning. Whereas these functions are predominantly associated with those sides of the brain, there is no monopoly by either side on these functions. Many pervasive functions, such as language, are distributed globally around the cerebrum. Some of the support for this misconception has come from studies of split brains. A drastic way to deal with a rare and devastating neurological condition (intractable epilepsy) is to separate the two hemispheres of the brain. After sectioning the corpus callosum, a split-brained patient will have trouble producing verbal responses on the basis of sensory information processed on the right side of the cerebrum, leading to the idea that the left side is responsible for language function. However, there are well-documented cases of language functions lost from damage to the right side of the brain. The deficits seen in damage to the left side of the brain are classified as aphasia, a loss of speech function; damage on the right side can affect the use of language. Right-side damage can result in a loss of ability to understand figurative aspects of speech, such as jokes, irony, or metaphors. Nonverbal aspects of speech can be affected by damage to the right side, such as facial expression or body language, and right-side damage can lead to a "flat affect" in speech, or a loss of emotional expression in speech—sounding like a robot when talking.

The Diencephalon

The diencephalon is the one region of the adult brain that retains its name from embryologic development. The etymology of the word diencephalon translates to "through brain." It is the connection between the cerebrum and the rest of the nervous system, with one exception. The rest of the brain, the spinal cord, and the PNS all send information to the cerebrum through the diencephalon. Output from the cerebrum passes through the diencephalon. The single exception is the system associated with ***olfaction***, or the sense of smell, which connects directly with the cerebrum. In the earliest vertebrate species, the cerebrum was not much more than olfactory bulbs that received peripheral information about the chemical environment (to call it smell in these organisms is imprecise because they lived in the ocean). The diencephalon is deep beneath the cerebrum and constitutes the walls of the third ventricle. The diencephalon can be described as any region of the brain with "thalamus" in its name. The two major regions of the diencephalon are the thalamus itself and the hypothalamus (Figure 7.10). There are other structures, such as the ***epithalamus***, which contains the pineal gland, or the ***subthalamus***, which includes the subthalamic nucleus that is part of the basal nuclei.

Thalamus

The ***thalamus*** is a collection of nuclei that relay information between the cerebral cortex and the periphery, spinal cord, or brain stem. All sensory information, except for the sense of smell, passes through the thalamus before processing by the cortex. Axons from the peripheral sensory organs, or intermediate nuclei, synapse in the thalamus, and thalamic neurons project directly to the cerebrum. It is a requisite synapse in any sensory pathway, except for olfaction. The thalamus does not just pass the information on, it also processes that information. For example, the portion of the thalamus that receives visual information will influence what visual stimuli are important, or what receives attention. The cerebrum also sends information down to the thalamus, which usually communicates motor commands. This involves interactions with the cerebellum and other nuclei in the brain stem. The cerebrum interacts with the basal nuclei, which involves connections with the thalamus. The primary output of the basal nuclei is to the thalamus, which relays that output to the cerebral cortex. The cortex also sends information to the thalamus that will then influence the effects of the basal nuclei.

Hypothalamus

Inferior and slightly anterior to the thalamus is the ***hypothalamus***, the other major region of the diencephalon. The hypothalamus is a collection of nuclei that are largely involved in regulating homeostasis. The hypothalamus is the executive region in charge of the autonomic nervous system and the endocrine system through its regulation of the anterior pituitary gland. Other parts of the hypothalamus are involved in memory and emotion as part of the limbic system.

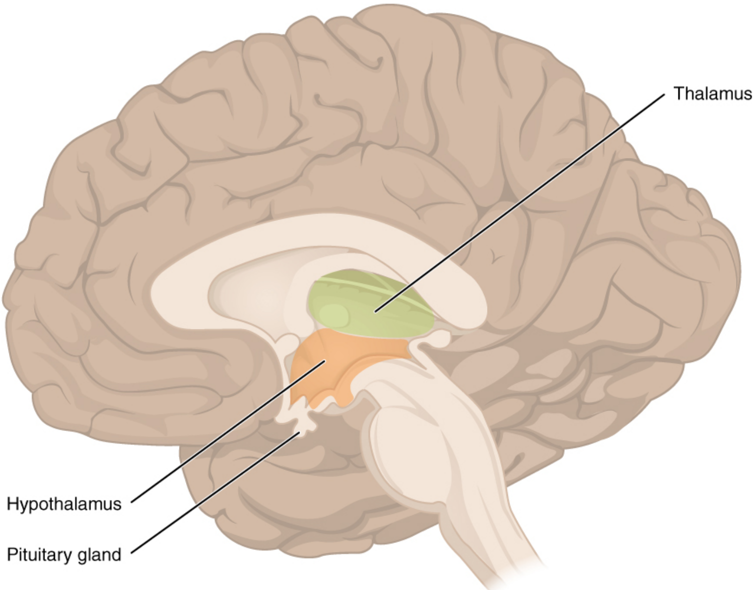


Figure 7.10. The Diencephalon
The diencephalon is composed primarily of the thalamus and hypothalamus, which together define the walls of the third ventricle. The thalami are two elongated, ovoid structures on either side of the midline that make contact in the middle. The hypothalamus is inferior and anterior to the thalamus, culminating in a sharp angle to which the pituitary gland is attached.

Brain Stem

The midbrain and hindbrain (composed of the pons and the medulla) are collectively referred to as the brain stem (Figure 7.11). The structure emerges from the ventral surface of the forebrain as a tapering cone that connects the brain to the spinal cord. Attached to the brain stem, but considered a separate region of the adult brain, is the cerebellum. The midbrain coordinates sensory representations of the visual, auditory, and somatosensory perceptual spaces. The pons is the main connection with the cerebellum. The pons and the medulla regulate several crucial functions, including the cardiovascular and respiratory systems and rates. The cranial nerves connect through the brain stem and provide the brain with the sensory input and motor output associated with the head and neck, including most of the special senses. The major ascending and descending pathways between the spinal cord and brain, specifically the cerebrum, pass through the brain stem.

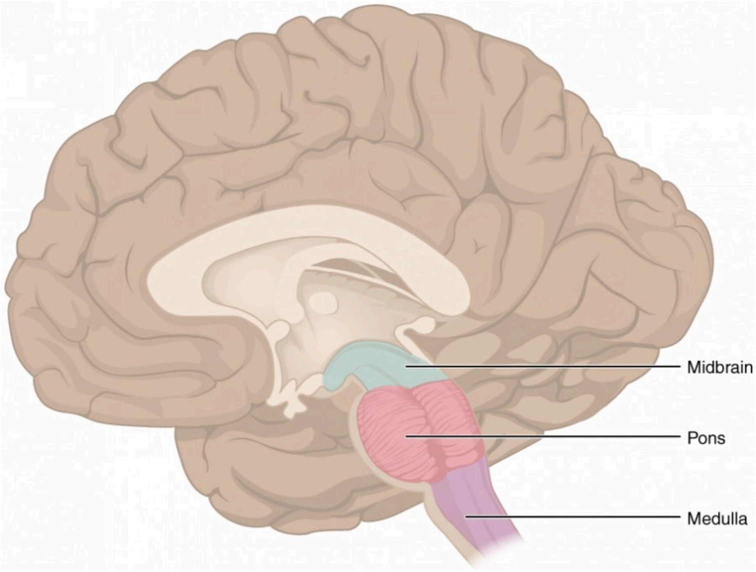


Figure 7.11. The Brain Stem

The brain stem comprises three regions: the midbrain, the pons, and the medulla.

Midbrain

One of the original regions of the embryonic brain, the midbrain is a small region between the thalamus and pons. It is separated into the ***tectum*** and ***tegmentum***, from the Latin words for roof and floor, respectively. The cerebral aqueduct passes through the center of the midbrain, such that these regions are the roof and floor of that canal. The tectum is composed of four bumps known as the colliculi (singular = colliculus), which means “little hill” in Latin. The ***inferior colliculus*** is the inferior pair of these enlargements and is part of the auditory brain stem pathway. Neurons of the inferior colliculus project to the thalamus, which then sends auditory information to the cerebrum for the conscious perception of sound. The ***superior colliculus*** is the superior pair and combines sensory information about visual space, auditory space, and somatosensory space. Activity in the superior colliculus is related to orienting the eyes to a sound or touch stimulus. If you are walking along the sidewalk on campus and you hear chirping, the superior colliculus coordinates that information with your awareness of the visual location of the tree right above you. That is the correlation of auditory and visual maps. If you suddenly feel something wet fall on your head, your superior colliculus integrates that with the auditory and visual maps and you know that the chirping bird just relieved itself on you. You want to look up to see the culprit, but do not. The tegmentum is continuous with the gray matter of the rest of the brain stem. Throughout the midbrain, pons, and medulla, the tegmentum contains the nuclei that receive and send information through the cranial nerves, as well as regions that regulate important functions such as those of the cardiovascular and respiratory systems.

Pons

The word pons comes from the Latin word for bridge. It is visible on the anterior surface of the brain stem as the thick bundle of white matter attached to the cerebellum. The pons is the main connection between the cerebellum and the brain stem. The bridge-like white matter is only the anterior surface of the pons; the gray matter beneath that is a continuation of the tegmentum from the midbrain. Gray matter in the tegmentum region of the pons contains neurons receiving descending input from the forebrain that is sent to the cerebellum.

Medulla

The medulla is the region known as the myelencephalon in the embryonic brain. The initial portion of the name, "myel," refers to the significant white matter found in this region—especially on its exterior, which is continuous with the white matter of the spinal cord. The tegmentum of the midbrain and pons continues into the medulla because this gray matter is responsible for processing cranial nerve information. A diffuse region of gray matter throughout the brain stem, known as the ***reticular formation***, is related to sleep and wakefulness, such as general brain activity and attention.

The Cerebellum

The ***cerebellum***, as the name suggests, is the "little brain." It is covered in gyri and sulci like the cerebrum, and looks like a miniature version of that part of the brain (Figure 7.12). The cerebellum is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord. It accounts for approximately 10 percent of the mass of the brain.

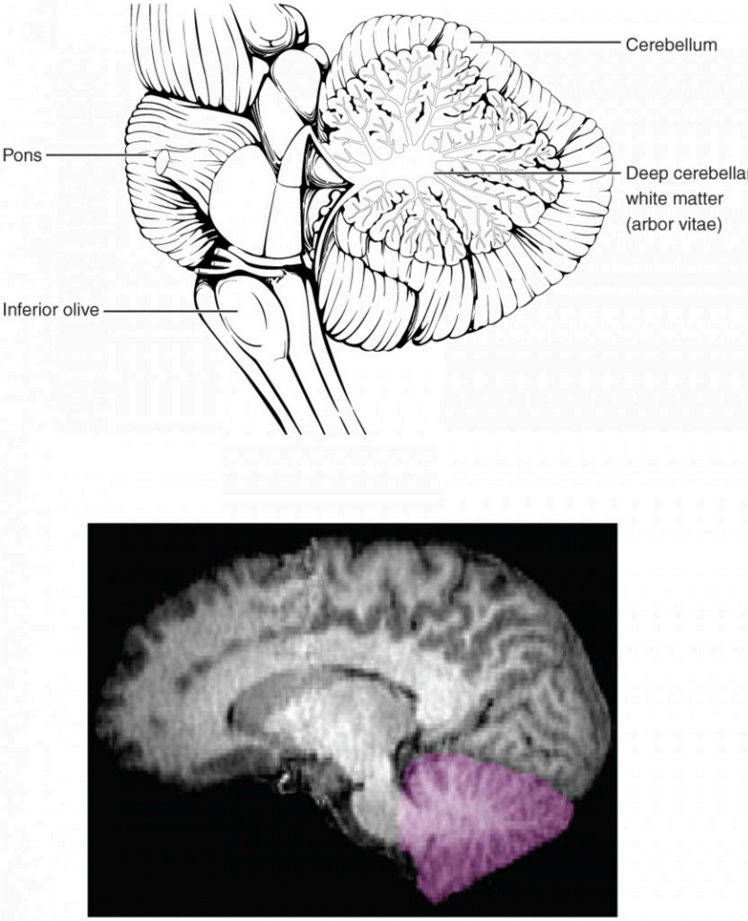


Figure 7.12. The Cerebellum
The cerebellum is situated on the posterior surface of the brain stem. Descending input from the cerebellum enters through the large white matter structure of the pons. Ascending input from the periphery and spinal cord enters through the fibers of the inferior olive. Output goes to the midbrain, which sends a descending signal to the spinal cord.

Descending fibers from the cerebrum have branches that connect to neurons in the pons. Those neurons project into the cerebellum, providing a copy of motor commands sent to the spinal cord. Sensory information from the periphery, which enters through spinal or cranial nerves, is copied to a nucleus in the medulla known as the ***inferior olive***. Fibers from this nucleus enter the cerebellum and are compared with the descending commands from the cerebrum. If the primary motor cortex of the frontal lobe sends a command down to the spinal cord to initiate walking, a copy of that instruction is sent to the cerebellum. Sensory feedback from the muscles and joints, proprioceptive information about the movements of walking, and sensations of balance are sent to the cerebellum through the inferior olive and the cerebellum compares them. If walking is not coordinated, perhaps because the ground is uneven or a strong wind is blowing, then the cerebellum sends out a corrective command to compensate for the difference between the original cortical command and the sensory feedback. The output of the cerebellum is into the midbrain, which then sends a descending input to the spinal cord to correct the messages going to skeletal muscles.

The Spinal Cord

The description of the CNS is concentrated on the structures of the brain, but the spinal cord is another major organ of the system. Whereas the brain develops out of expansions of the neural tube into primary and then secondary vesicles, the spinal cord maintains the tube structure and is only specialized into certain regions. As the spinal cord continues to develop in the newborn, anatomical features mark its surface. The anterior midline is marked by the ***anterior median fissure***, and the posterior midline is marked by the ***posterior median sulcus***. Axons enter the posterior side through the ***dorsal (posterior) nerve root***, which marks the ***posterolateral sulcus*** on either side. The axons emerging from the anterior side do so through the ***ventral (anterior) nerve root***. Note that it is common to see the terms dorsal (dorsal = “back”) and ventral (ventral = “belly”) used interchangeably with posterior and anterior, particularly in reference to nerves and the structures of the spinal cord. You should learn to be comfortable with both. On the whole, the posterior regions are responsible for sensory functions and the anterior regions are associated with motor functions. This comes from the initial development of the spinal cord, which is divided into the ***basal plate*** and the ***alar plate***. The basal plate is closest to the ventral midline of the neural tube, which will become the anterior face of the spinal cord and gives rise to motor neurons. The alar plate is on the dorsal side of the neural tube and gives rise to neurons that will receive sensory input from the periphery. The length of the spinal cord is divided into regions that correspond to the regions of the vertebral column. The name of a spinal cord region corresponds to the level at which spinal nerves pass through the intervertebral foramina. Immediately adjacent to the brain stem is the cervical region, followed by the thoracic, then the lumbar, and finally the sacral region. The spinal cord is not the full length of the vertebral column because the spinal cord does not grow significantly longer after the first or second year, but the skeleton continues to grow. The nerves that emerge from the spinal cord pass through the intervertebral formina at the respective levels. As the vertebral column grows, these nerves grow with it and result in a long bundle of nerves that resembles a horse’s tail and is named the ***cauda equina***. The sacral spinal cord is at the level of the upper lumbar vertebral bones. The spinal nerves extend from their various levels to the proper level of the vertebral column.

Gray Horns

In cross-section, the gray matter of the spinal cord has the appearance of an ink-blot test, with the spread of the gray matter on one side replicated on the other—a shape reminiscent of a bulbous capital “H.” As shown in Figure 7.13, the gray matter is subdivided into regions that are referred to as horns. The ***posterior horn*** is responsible for sensory processing. The ***anterior horn*** sends out motor signals to the skeletal muscles. The ***lateral horn***, which is only found in the thoracic, upper lumbar, and sacral regions, is the central component of the sympathetic division of the autonomic nervous system. Some of the largest neurons of the spinal cord are the multipolar motor neurons in the anterior horn. The fibers that cause contraction of skeletal muscles are the axons of these neurons. The motor neuron that causes contraction of the big toe, for example, is located in the sacral spinal cord. The axon that has to reach all the way to the belly of that muscle may be a meter in length. The neuronal cell body that maintains that long fiber must be quite large, possibly several hundred micrometers in diameter, making it one of the largest cells in the body.

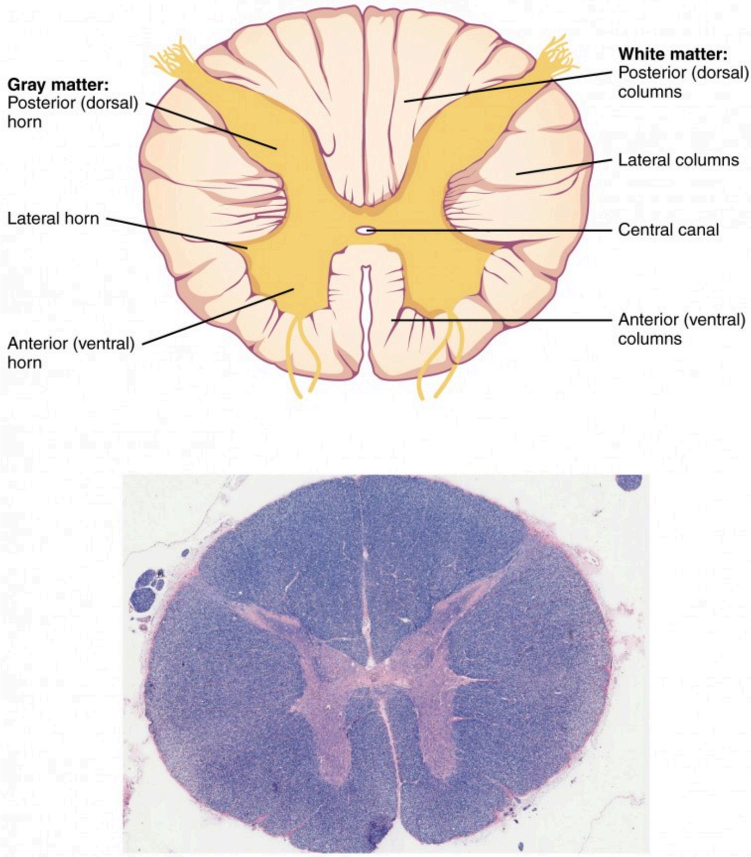


Figure 7.13. Cross-section of Spinal Cord

The cross-section of a thoracic spinal cord segment shows the posterior, anterior, and lateral horns of gray matter, as well as the posterior, anterior, and lateral columns of white matter. LM × 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

White Columns

Just as the gray matter is separated into horns, the white matter of the spinal cord is separated into columns. ***Ascending tracts*** of nervous system fibers in these columns carry sensory information up to the brain, whereas ***descending tracts*** carry motor commands from the brain. Looking at the spinal cord longitudinally, the columns extend along its length as continuous bands of white matter. Between the two posterior horns of gray matter are the ***posterior columns***. Between the two anterior horns, and bounded by the axons of motor neurons emerging from that gray matter area, are the ***anterior columns***. The white matter on either side of the spinal cord, between the posterior horn and the axons of the anterior horn neurons, are the ***lateral columns***. The posterior columns are composed of axons of ascending tracts. The anterior and lateral columns are composed of many different groups of axons of both ascending and descending tracts—the latter carrying motor commands down from the brain to the spinal cord to control output to the periphery.

43. The Peripheral Nervous System

The PNS is not as contained as the CNS because it is defined as everything that is not the CNS. Some peripheral structures are incorporated into the other organs of the body. In describing the anatomy of the PNS, it is necessary to describe the common structures, the nerves and the ganglia, as they are found in various parts of the body. Many of the neural structures that are incorporated into other organs are features of the digestive system; these structures are known as the ***enteric nervous system*** and are a special subset of the PNS.

Ganglia

A ganglion is a group of neuron cell bodies in the periphery. Ganglia can be categorized, for the most part, as either sensory ganglia or autonomic ganglia, referring to their primary functions. The most common type of sensory ganglion is a ***dorsal (posterior) root ganglion***. These ganglia are the cell bodies of neurons with axons that are sensory endings in the periphery, such as in the skin, and that extend into the CNS through the dorsal nerve root. The ganglion is an enlargement of the nerve root. Under microscopic inspection, it can be seen to include the cell bodies of the neurons, as well as bundles of fibers that are the posterior nerve root (Figure 7.14). The cells of the dorsal root ganglion are unipolar cells, classifying them by shape. Also, the small round nuclei of satellite cells can be seen surrounding—as if they were orbiting—the neuron cell bodies.

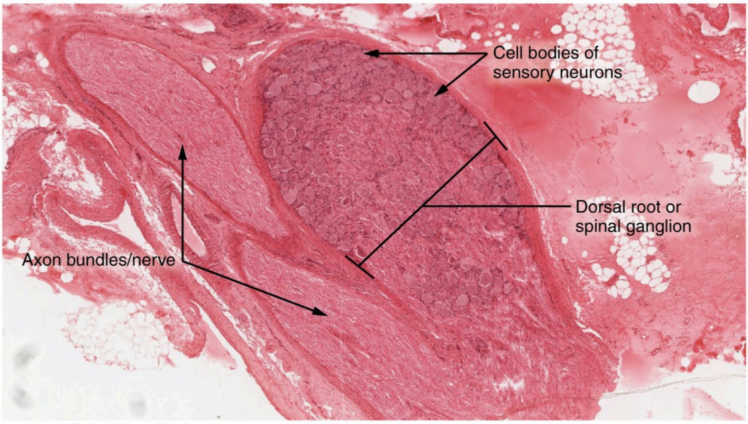


Figure 7.14. Dorsal Root Ganglion
The cell bodies of sensory neurons, which are unipolar neurons by shape, are seen in this photomicrograph. Also, the fibrous region is composed of the axons of these neurons that are passing through the ganglion to be part of the dorsal nerve root (tissue source: canine). LM × 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Figure 7.15. Spinal Cord and Root Ganglion

The slide includes both a cross-section of the lumbar spinal cord and a section of the dorsal root ganglion (see also [Figure 7.14](#)) (tissue source: canine). LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Another type of sensory ganglion is a ***cranial nerve ganglion***. This is analogous to the dorsal root ganglion, except that it is associated with a ***cranial nerve*** instead of a ***spinal nerve***. The roots of cranial nerves are within the cranium, whereas the ganglia are outside the skull. For example, the ***trigeminal ganglion*** is superficial to the temporal bone whereas its associated nerve is attached to the mid-pons region of the brain stem. The neurons of cranial nerve ganglia are also unipolar in shape with associated satellite cells. The other major category of ganglia are those of the autonomic nervous system, which is divided into the sympathetic and parasympathetic nervous systems. The ***sympathetic chain ganglia*** constitute a row of ganglia along the vertebral column that receive central input from the lateral horn of the thoracic and upper lumbar spinal cord. Superior to the chain ganglia are three ***paravertebral ganglia*** in the cervical region. Three other autonomic ganglia that are related to the sympathetic chain are the ***prevertebral ganglia***, which are located outside of the chain but have similar functions. They are referred to as prevertebral because they are anterior to the vertebral column. The neurons of these autonomic ganglia are multipolar in shape, with dendrites radiating out around the cell body where synapses from the spinal cord neurons are made. The neurons of the chain, paravertebral, and prevertebral ganglia then project to organs in the head and neck, thoracic, abdominal, and pelvic cavities to regulate the sympathetic aspect of homeostatic mechanisms. Another group of autonomic ganglia are the ***terminal ganglia*** that receive input from cranial nerves or sacral spinal nerves and are responsible for regulating the parasympathetic aspect of homeostatic mechanisms. These two sets of ganglia, sympathetic and parasympathetic, often project to the same organs—one input from the chain ganglia and one input from a terminal ganglion—to regulate the overall function of an organ. For example, the heart receives two inputs such as these; one increases heart rate, and the other decreases it. The terminal ganglia that receive input from cranial nerves are found in the head and neck, as well as the thoracic and upper abdominal cavities, whereas the terminal ganglia that receive sacral input are in the lower abdominal and pelvic cavities. Terminal ganglia below the head and neck are often incorporated into the wall of the target organ as a ***plexus***. A plexus, in a general sense, is a network of fibers or vessels. This can apply to nervous tissue (as in this instance) or structures containing blood vessels (such as a choroid plexus). For example, the ***enteric plexus*** is the extensive network of axons and neurons in the wall of the small and large intestines. The enteric plexus is actually part of the enteric nervous system, along with the ***gastric plexuses*** and the ***esophageal plexus***. Though the enteric nervous system receives input originating from central neurons of the autonomic nervous system, it does not require CNS input to function. In fact, it operates independently to regulate the digestive system.

Nerves

Bundles of axons in the PNS are referred to as nerves. These structures in the periphery are different than the central counterpart, called a tract. Nerves are composed of more than just nervous tissue. They have connective tissues invested in their structure, as well as blood vessels supplying the tissues with nourishment. The outer surface of a nerve is a surrounding layer of fibrous connective tissue called the ***epineurium***. Within the nerve, axons are further bundled into ***fascicles***, which are each surrounded by their own layer of fibrous connective tissue called ***perineurium***. Finally, individual axons are surrounded by loose connective tissue called the ***endoneurium*** (Figure 7.16). These three layers are similar to the connective tissue sheaths for muscles. Nerves are associated with the region of the CNS to which they are connected, either as cranial nerves connected to the brain or spinal nerves connected to the spinal cord.

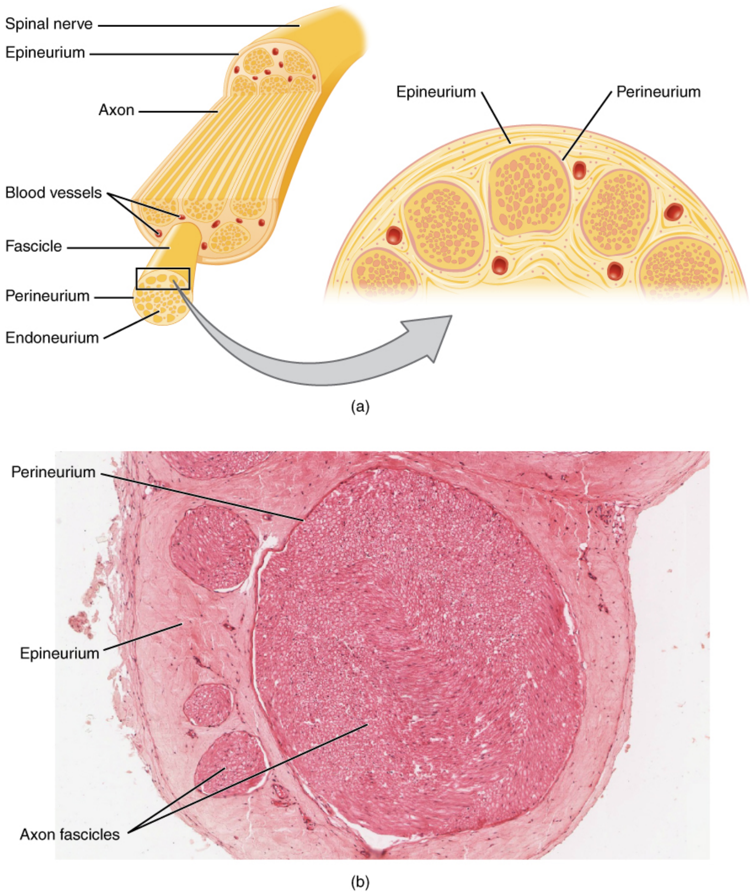


Figure 7.16. Nerve Structure

The structure of a nerve is organized by the layers of connective tissue on the outside, around each fascicle, and surrounding the individual nerve fibers (tissue source: simian). LM × 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Figure 7.17. Close-Up of Nerve Trunk
Zoom in on this slide of a nerve trunk to examine the endoneurium, perineurium, and epineurium in greater detail (tissue source: simian). LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Cranial Nerves

The nerves attached to the brain are the cranial nerves, which are primarily responsible for the sensory and motor functions of the head and neck (one of these nerves targets organs in the thoracic and abdominal cavities as part of the parasympathetic nervous system). There are twelve cranial nerves, which are designated CNI through CNXII for “Cranial Nerve,” using Roman numerals for 1 through 12. They can be classified as sensory nerves, motor nerves, or a combination of both, meaning that the axons in these nerves originate out of sensory ganglia external to the cranium or motor nuclei within the brain stem. Sensory axons enter the brain to synapse in a nucleus. Motor axons connect to skeletal muscles of the head or neck. Three of the nerves are solely composed of sensory fibers; five are strictly motor; and the remaining four are mixed nerves. Learning the cranial nerves is a tradition in anatomy courses, and students have always used mnemonic devices to remember the nerve names. A traditional mnemonic is the rhyming couplet, “On Old Olympus’ Towering Tops/A Finn And German Viewed Some Hops,” in which the initial letter of each word corresponds to the initial letter in the name of each nerve. The names of the nerves have changed over the years to reflect current usage and more accurate naming. An exercise to help learn this sort of information is to generate a mnemonic using words that have personal significance. The names of the cranial nerves are listed in Table 7.2 along with a brief description of their function, their source (sensory ganglion or motor nucleus), and their target (sensory nucleus or skeletal muscle). They are listed here with a brief explanation of each nerve (Figure 7.18). The ***olfactory nerve*** and ***optic nerve*** are responsible for the sense of smell and vision, respectively. The ***oculomotor nerve*** is responsible for eye movements by controlling four of the ***extraocular muscles***. It is also responsible for lifting the upper eyelid when the eyes point up, and for pupillary constriction. The ***trochlear nerve*** and the ***abducens nerve*** are both responsible for eye movement, but do so by controlling different extraocular muscles. The ***trigeminal nerve*** is responsible for cutaneous sensations of the face and controlling the muscles of mastication. The ***facial nerve*** is responsible for the muscles involved in facial expressions, as well as part of the sense of taste and the production of saliva. The ***vestibulocochlear nerve*** is responsible for the senses of hearing and balance. The ***glossopharyngeal nerve*** is responsible for controlling muscles in the oral cavity and upper throat, as well as part of the sense of taste and the production of saliva. The ***vagus nerve*** is responsible for contributing to homeostatic control of the organs of the thoracic and upper abdominal cavities. The ***spinal accessory nerve*** is responsible for controlling the muscles of the neck, along with cervical spinal nerves. The ***hypoglossal nerve*** is responsible for controlling the muscles of the lower throat and tongue.

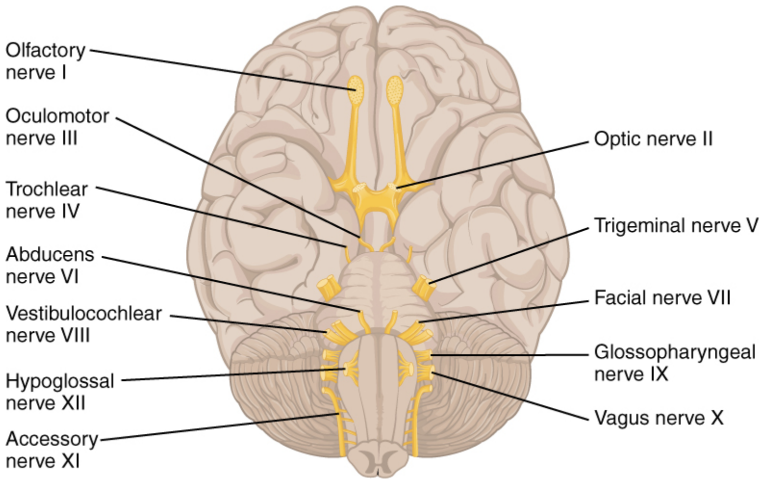


Figure 7.18. The Cranial Nerves

The anatomical arrangement of the roots of the cranial nerves observed from an inferior view of the brain.

Three of the cranial nerves also contain autonomic fibers, and a fourth is almost purely a component of the autonomic system. The oculomotor, facial, and glossopharyngeal nerves contain fibers that contact autonomic ganglia. The oculomotor fibers initiate pupillary constriction, whereas the facial and glossopharyngeal fibers both initiate salivation. The vagus nerve primarily targets autonomic ganglia in the thoracic and upper abdominal cavities.

Another important aspect of the cranial nerves that lends itself to a mnemonic is the functional role each nerve plays. The nerves fall into one of three basic groups. They are sensory, motor, or both (see Table 7.2). The sentence, “Some Say Marry Money But My Brother Says Brains Beauty Matter More,” corresponds to the basic function of each nerve. The first, second, and eighth nerves are purely sensory: the olfactory (CNI), optic (CNII), and vestibulocochlear (CNVIII) nerves. The three eye-movement nerves are all motor: the oculomotor (CNIII), trochlear (CNIV), and abducens (CNVI). The spinal accessory (CNXI) and hypoglossal (CNXII) nerves are also strictly motor. The remainder of the nerves contain both sensory and motor fibers. They are the trigeminal (CNV), facial (CNVII), glossopharyngeal (CNIX), and vagus (CNX) nerves. The nerves that convey both are often related to each other. The trigeminal and facial nerves both concern the face; one concerns the sensations and the other concerns the muscle movements. The facial and glossopharyngeal nerves are both responsible for conveying gustatory, or taste, sensations as well as controlling salivary glands. The vagus nerve is involved in visceral responses to taste, namely the gag reflex. This is not an exhaustive list of what these combination nerves do, but there is a thread of relation between them.

Cranial Nerves

Mnemonic	#	Name	Function (S/M/B)	Central connection (nuclei)	Peripheral connection (ganglion or muscle)
On	I	Olfactory	Smell (S)	Olfactory bulb	Olfactory epithelium
Old	II	Optic	Vision (S)	Hypothalamus/ thalamus/midbrain	Retina (retinal ganglion cells)
Olympus'	III	Oculomotor	Eye movements (M)	Oculomotor nucleus	Extraocular muscles (other 4), levator palpebrae superioris, ciliary ganglion (autonomic)
Towering	IV	Trochlear	Eye movements (M)	Trochlear nucleus	Superior oblique muscle
Tops	V	Trigeminal	Sensory/ motor – face (B)	Trigeminal nuclei in the midbrain, pons, and medulla	Trigeminal
A	VI	Abducens	Eye movements (M)	Abducens nucleus	Lateral rectus muscle
Finn	VII	Facial	Motor – face, Taste (B)	Facial nucleus, solitary nucleus, superior salivatory nucleus	Facial muscles, Geniculate ganglion, Pterygopalatine ganglion (autonomic)
And	VIII	Auditory (Vestibulocochlear)	Hearing/ balance (S)	Cochlear nucleus, Vestibular nucleus/ cerebellum	Spiral ganglion (hearing), Vestibular ganglion (balance)
German	IX	Glossopharyngeal	Motor – throat Taste (B)	Solitary nucleus, inferior salivatory nucleus, nucleus ambiguus	Pharyngeal muscles, Geniculate ganglion, Otic ganglion (autonomic)
Viewed	X	Vagus	Motor/ sensory – viscera (autonomic) (B)	Medulla	Terminal ganglia serving thoracic and upper abdominal organs (heart and small intestines)
Some	XI	Spinal Accessory	Motor – head and neck (M)	Spinal accessory nucleus	Neck muscles
Hops	XII	Hypoglossal	Motor – lower throat (M)	Hypoglossal nucleus	Muscles of the larynx and lower pharynx

Table 13.3

Spinal Nerves

The nerves connected to the spinal cord are the spinal nerves. The arrangement of these nerves is much more regular than that of the cranial nerves. All of the spinal nerves are combined sensory and motor axons that separate into two nerve roots. The sensory axons enter the spinal cord as the dorsal nerve root. The motor fibers, both somatic and autonomic, emerge as the ventral nerve root. The dorsal root ganglion for each nerve is an enlargement of the spinal nerve. There are 31 spinal nerves, named for the level of the spinal cord at which each one emerges. There are eight pairs of cervical nerves designated C1 to C8, twelve thoracic nerves designated T1 to T12, five pairs of lumbar nerves designated L1 to L5, five pairs of sacral nerves designated S1 to S5, and one pair of coccygeal nerves. The nerves are numbered from the superior to inferior positions, and each emerges from the vertebral column through the intervertebral foramen at its level. The first nerve, C1, emerges between the first cervical vertebra and the occipital bone. The second nerve, C2, emerges between the first and second cervical vertebrae. The same occurs for C3 to C7, but C8 emerges between the seventh cervical vertebra and the first thoracic vertebra. For the thoracic and lumbar nerves, each one emerges between the vertebra that has the same designation and the next vertebra in the column. The sacral nerves emerge from the sacral foramina along the length of that unique vertebra. Spinal nerves extend outward from the vertebral column to enervate the periphery. The nerves in the periphery are not straight continuations of the spinal nerves, but rather the reorganization of the axons in those nerves to follow different courses. Axons from different spinal nerves will come together into a ***systemic nerve***. This occurs at four places along the length of the vertebral column, each identified as a ***nerve plexus***, whereas the other spinal nerves directly correspond to nerves at their respective levels. In this instance, the word plexus is used to describe networks of nerve fibers with no associated cell bodies. Of the four nerve plexuses, two are found at the cervical level, one at the lumbar level, and one at the sacral level (Figure 7.19).

The ***cervical plexus*** is composed of axons from spinal nerves C1 through C5 and branches into nerves in the posterior neck and head, as well as the ***phrenic nerve***, which connects to the diaphragm at the base of the thoracic cavity. The other plexus from the cervical level is the ***brachial plexus***. Spinal nerves C4 through T1 reorganize through this plexus to give rise to the nerves of the arms, as the name brachial suggests. A large nerve from this plexus is the ***radial***

nerve from which the ***axillary nerve*** branches to go to the armpit region. The radial nerve continues through the arm and is paralleled by the ***ulnar nerve*** and the ***median nerve***. The ***lumbar plexus*** arises from all the lumbar spinal nerves and gives rise to nerves enervating the pelvic region and the anterior leg. The ***femoral nerve*** is one of the major nerves from this plexus, which gives rise to the ***saphenous nerve*** as a branch that extends through the anterior lower leg. The ***sacral plexus*** comes from the lower lumbar nerves L4 and L5 and the sacral nerves S1 to S4. The most significant systemic nerve to come from this plexus is the ***sciatic nerve***, which is a combination of the ***tibial nerve*** and the ***fibular nerve***. The sciatic nerve extends across the hip joint and is most commonly associated with the condition ***sciatica***, which is the result of compression or irritation of the nerve or any of the spinal nerves giving rise to it. These plexuses are described as arising from spinal nerves and giving rise to certain systemic nerves, but they contain fibers that serve sensory functions or fibers that serve motor functions. This means that some fibers extend from cutaneous or other peripheral sensory surfaces and send action potentials into the CNS. Those are axons of sensory neurons in the dorsal root ganglia that enter the spinal cord through the dorsal nerve root. Other fibers are the axons of motor neurons of the anterior horn of the spinal cord, which emerge in the ventral nerve root and send action potentials to cause skeletal muscles to contract in their target regions. For example, the radial nerve contains fibers of cutaneous sensation in the arm, as well as motor fibers that move muscles in the arm. Spinal nerves of the thoracic region, T2 through T11, are not part of the plexuses but rather emerge and give rise to the ***intercostal nerves*** found between the ribs, which articulate with the vertebrae surrounding the spinal nerve.

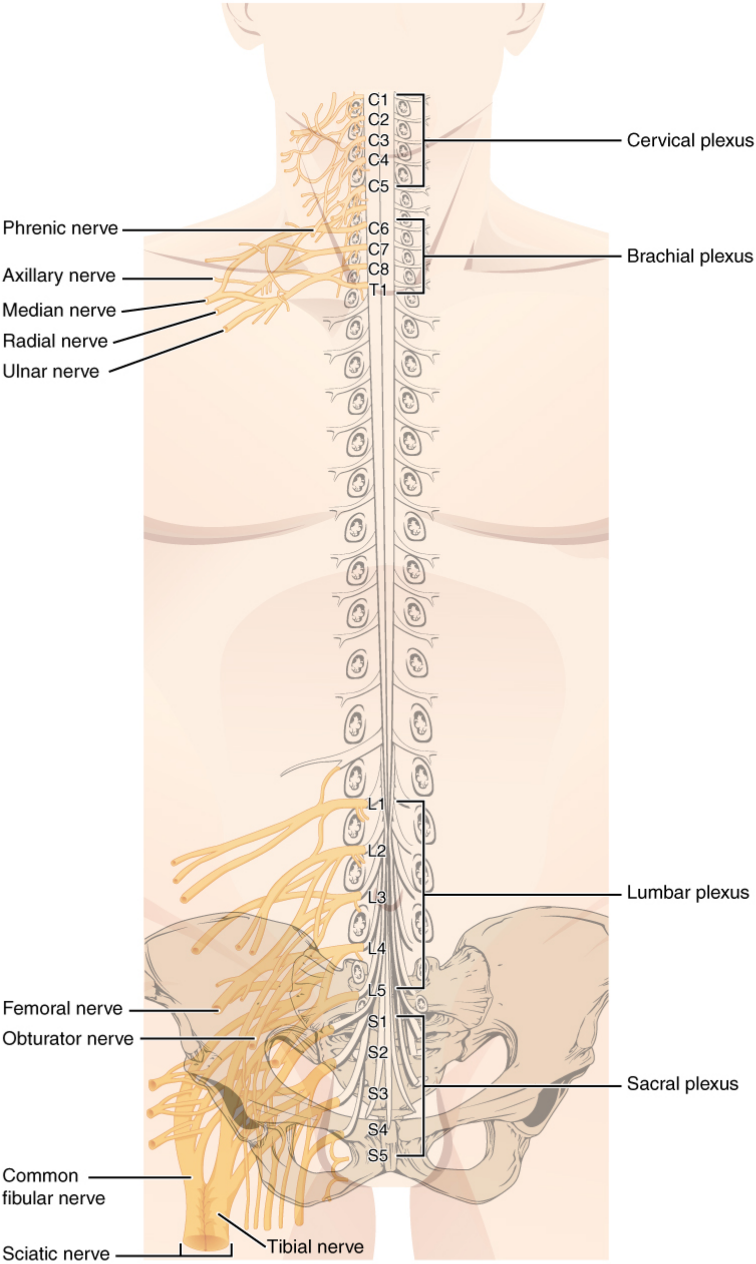


Figure 7.19. Nerve Plexuses of the Body

There are four main nerve plexuses in the human body. The cervical plexus supplies nerves to the posterior head and neck, as well as to the diaphragm. The brachial plexus supplies nerves to the arm. The lumbar plexus supplies nerves to the anterior leg. The sacral plexus supplies nerves to the posterior leg.

44. Age Related Changes to the Nervous System

As one ages there is a loss of up to 10,000 nerve cells a day. While there is a loss of all cell types in the body as part of the aging process, nerve cells do not reproduce so the lost cells are not replaced. The loss of nerve cells results in a decreases in the function of the nervous system. The exact function lost is depended on the individual and the exact cells lost. As there are many more nerve cells than are necessary for the proper functioning of the nervous system, it is unlikely that routine loss of nerve cells causes any apparent problems until advanced old age.

Some apparent decreases in functioning include decline in speed of response and ability to integrate what is observed than there is in verbal ability or memory. There is also an age-related decline in intelligence, as measured with standard intelligence tests. Memory is also affected by age.

45. Age Related Dysfunctions to the Nervous System

Decreased Reflex Responses

A decrease in reflex responses begins around the age of 60 and continues to decline as part of the aging process. This includes the absence of jerk reflexes of the ankle, knee, bicep muscles, and tricep muscles.

Declining Autonomic Responses

The autonomic nervous system is responsible for regulating body temperature, pulse rate, and the control of anal and urethral sphincters. As humans age maintaining normal body temperature during periods of extreme hot or cold, returning to a normal pulse rate after exercise, and maintaining control of urine and fecal matter due to a declining autonomic response.

Insomnia

There are two types of sleep: rapid-sys-movement (REM) sleep and slow-wave (non-REM) sleep. Throughout the sleep cycle REM and non-REM sleep cycle. It is thought that physiological recuperation occurs during non-REM sleep. Although the time spent sleeping changes little with age, the ratio between REM and non-REM sleep changes, resulting in fewer periods of restorative non-REM. Older people also complain of difficulty failing asleep and staying asleep.

Dementia

Dementia is a general term for a group of brain disorders that increase with age and cause memory changes, intellectual defects, behavioral disturbances, and other signs of mental deterioration.

Alzheimer's disease, otherwise known as senile dementia of the Alzheimer type, is the most common form of dementia. 10% of people over the age 65 are afflicted with this disease while 40% of people over the age of 85 are afflicted with this disease. The symptoms of Alzheimer's disease are progressive, and at least three stages of this disease have been defined.

Stage one symptoms include impairments of recent memory, spatial disorientation, and a lessening of spontaneous emotional responses. By stage two the patient loses higher learning functions, such as the abilities to read, write, and calculate. The person will become confused, lose track of time, and eventually the person is unable to recognize his or her family. In the final stage of the disease the person experiences seizures and becomes unable to speak appropriately. While the exact cause of Alzheimer's disease is unknown it is know that all people suffering from Alzheimer's experience an accumulation of proteins in the brain. It is thought that these proteins, also known as plaques, interfere with normal brain functioning.

Non-Alzheimer dementias the cognitive and behavioral changes resemble Alzheimer's disease, but differ in that they are not progressive.

Multi-infarction dementia is characterized by multiple mini-strokes which cause damage to many small regions of the brain. The person suffering from the mini-strokes may not be aware of the strokes or the progressive damage they are causing. Over time if the strokes are left untreated the person may exhibit Alzheimer's like symptoms.

Parkinson's disease is a disorder of the basal nuclei, specifically of the substantia nigra, that demonstrates the effects of the direct and indirect pathways. Parkinson's disease is the result of neurons in the substantia nigra pars compacta dying. These neurons release dopamine into the striatum. Without that modulatory influence, the basal nuclei are stuck in the indirect pathway, without the direct pathway being activated. The direct pathway is responsible for increasing cortical movement commands. The increased activity of the indirect pathway results in the hypokinetic disorder of Parkinson's disease. Parkinson's disease is neurodegenerative, meaning that neurons die that cannot be replaced, so there is no cure for the disorder. Treatments for Parkinson's disease are aimed at increasing dopamine levels in the striatum. Currently, the most common way of doing that is by providing the amino acid L-DOPA, which is a precursor to the neurotransmitter dopamine and can cross the blood-brain barrier. With levels of the precursor elevated, the remaining cells of the substantia nigra pars compacta can make more neurotransmitter and have a greater effect. Unfortunately, the patient will become less responsive to L-DOPA treatment as time progresses, and it can cause increased dopamine levels elsewhere in the brain, which are associated with psychosis or schizophrenia.

Cerebrovascular accident, or stroke, is a common aging dysfunction that is often considered to be a dementia because it affects the brain. The disease originates in the cardiovascular system when a blood vessel to the brain is obstructed or ruptures. This cuts off blood flow to a region of the brain, causing the area to deteriorate and possibly producing permanent brain damage. Large strokes may cause paralysis, dementia, or even death. The death rates increase dramatically in individuals 65 years of age or older.

46. Glossary: The Nervous System

abducens nerve
: sixth cranial nerve; responsible for contraction of one of the extraocular muscles

alar plate
: developmental region of the spinal cord that gives rise to the posterior horn of the gray matter

amygdala
: nucleus deep in the temporal lobe of the cerebrum that is related to memory and emotional behavior

anterior column
: white matter between the anterior horns of the spinal cord composed of many different groups of axons of both ascending and descending tracts

anterior horn
: gray matter of the spinal cord containing multipolar motor neurons, sometimes referred to as the ventral horn

anterior median fissure
: deep midline feature of the anterior spinal cord, marking the separation between the right and left sides of the cord

anterior spinal artery
: blood vessel from the merged branches of the vertebral arteries that runs along the anterior surface of the spinal cord

arachnoid granulation
: outpocket of the arachnoid membrane into the dural sinuses

that allows for reabsorption of CSF into the blood

arachnoid mater
middle layer of the meninges named for the spider-web–like trabeculae that extend between it and the pia mater

arachnoid trabeculae
filaments between the arachnoid and pia mater within the subarachnoid space

ascending tract
central nervous system fibers carrying sensory information from the spinal cord or periphery to the brain

axillary nerve
systemic nerve of the arm that arises from the brachial plexus

Broca's area
region of the frontal lobe associated with the motor commands necessary for speech production and located only in the cerebral hemisphere responsible for language production, which is the left side in approximately 95 percent of the population

Brodmann's areas
mapping of regions of the cerebral cortex based on microscopic anatomy that relates specific areas to functional differences, as described by Brodmann in the early 1900s

basal forebrain
nuclei of the cerebrum related to modulation of sensory stimuli and attention through broad projections to the cerebral cortex, loss of which is related to Alzheimer's disease

basal nuclei
nuclei of the cerebrum (with a few components in the upper brain stem and diencephalon) that are responsible for assessing cortical movement commands and comparing them

with the general state of the individual through broad modulatory activity of dopamine neurons; largely related to motor functions, as evidenced through the symptoms of Parkinson's and Huntington's diseases

basal plate
: developmental region of the spinal cord that gives rise to the lateral and anterior horns of gray matter

basilar artery
: blood vessel from the merged vertebral arteries that runs along the dorsal surface of the brain stem

brachial plexus
: nerve plexus associated with the lower cervical spinal nerves and first thoracic spinal nerve

brain stem
: region of the adult brain that includes the midbrain, pons, and medulla oblongata and develops from the mesencephalon, metencephalon, and myelencephalon of the embryonic brain

carotid canal
: opening in the temporal bone through which the internal carotid artery enters the cranium

cauda equina
: bundle of spinal nerve roots that descend from the lower spinal cord below the first lumbar vertebra and lie within the vertebral cavity; has the appearance of a horse's tail

caudate
: nucleus deep in the cerebrum that is part of the basal nuclei; along with the putamen, it is part of the striatum

central canal
: hollow space within the spinal cord that is the remnant of the center of the neural tube

central sulcus
surface landmark of the cerebral cortex that marks the boundary between the frontal and parietal lobes

cephalic flexure
curve in midbrain of the embryo that positions the forebrain ventrally

cerebellum
region of the adult brain connected primarily to the pons that developed from the metencephalon (along with the pons) and is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord

cerebral aqueduct
connection of the ventricular system between the third and fourth ventricles located in the midbrain

cerebral cortex
outer gray matter covering the forebrain, marked by wrinkles and folds known as gyri and sulci

cerebral hemisphere
one half of the bilaterally symmetrical cerebrum

cerebrum
region of the adult brain that develops from the telencephalon and is responsible for higher neurological functions such as memory, emotion, and consciousness

cervical plexus
nerve plexus associated with the upper cervical spinal nerves

choroid plexus
specialized structures containing ependymal cells lining blood capillaries that filter blood to produce CSF in the four ventricles of the brain

circle of Willis
: unique anatomical arrangement of blood vessels around the base of the brain that maintains perfusion of blood into the brain even if one component of the structure is blocked or narrowed

common carotid artery
: blood vessel that branches off the aorta (or the brachiocephalic artery on the right) and supplies blood to the head and neck

corpus callosum
: large white matter structure that connects the right and left cerebral hemispheres

cranial nerve ganglion
: sensory ganglion of cranial nerves

cranial nerve
: one of twelve nerves connected to the brain that are responsible for sensory or motor functions of the head and neck

descending tract
: central nervous system fibers carrying motor commands from the brain to the spinal cord or periphery

diencephalon
: region of the adult brain that retains its name from embryonic development and includes the thalamus and hypothalamus

direct pathway
: connections within the basal nuclei from the striatum to the globus pallidus internal segment and substantia nigra pars reticulata that disinhibit the thalamus to increase cortical control of movement

disinhibition
: disynaptic connection in which the first synapse inhibits the

second cell, which then stops inhibiting the final target

dorsal (posterior) nerve root
axons entering the posterior horn of the spinal cord

dorsal (posterior) root ganglion
sensory ganglion attached to the posterior nerve root of a spinal nerve

dura mater
tough, fibrous, outer layer of the meninges that is attached to the inner surface of the cranium and vertebral column and surrounds the entire CNS

dural sinus
any of the venous structures surrounding the brain, enclosed within the dura mater, which drain blood from the CNS to the common venous return of the jugular veins

endoneurium
innermost layer of connective tissue that surrounds individual axons within a nerve

enteric nervous system
peripheral structures, namely ganglia and nerves, that are incorporated into the digestive system organs

enteric plexus
neuronal plexus in the wall of the intestines, which is part of the enteric nervous system

epineurium
outermost layer of connective tissue that surrounds an entire nerve

epithalamus
region of the diecephalon containing the pineal gland

esophageal plexus
: neuronal plexus in the wall of the esophagus that is part of the enteric nervous system

extraocular muscles
: six skeletal muscles that control eye movement within the orbit

facial nerve
: seventh cranial nerve; responsible for contraction of the facial muscles and for part of the sense of taste, as well as causing saliva production

fascicle
: small bundles of nerve or muscle fibers enclosed by connective tissue

femoral nerve
: systemic nerve of the anterior leg that arises from the lumbar plexus

fibular nerve
: systemic nerve of the posterior leg that begins as part of the sciatic nerve

foramen magnum
: large opening in the occipital bone of the skull through which the spinal cord emerges and the vertebral arteries enter the cranium

forebrain
: anterior region of the adult brain that develops from the prosencephalon and includes the cerebrum and diencephalon

fourth ventricle
: the portion of the ventricular system that is in the region of the brain stem and opens into the subarachnoid space through the median and lateral apertures

frontal eye field
: region of the frontal lobe associated with motor commands to orient the eyes toward an object of visual attention

frontal lobe
: region of the cerebral cortex directly beneath the frontal bone of the cranium

gastric plexuses
: neuronal networks in the wall of the stomach that are part of the enteric nervous system

globus pallidus
: nuclei deep in the cerebrum that are part of the basal nuclei and can be divided into the internal and external segments

glossopharyngeal nerve
: ninth cranial nerve; responsible for contraction of muscles in the tongue and throat and for part of the sense of taste, as well as causing saliva production

gyrus
: ridge formed by convolutions on the surface of the cerebrum or cerebellum

hindbrain
: posterior region of the adult brain that develops from the rhombencephalon and includes the pons, medulla oblongata, and cerebellum

hippocampus
: gray matter deep in the temporal lobe that is very important for long-term memory formation

hypoglossal nerve
: twelfth cranial nerve; responsible for contraction of muscles of the tongue

hypothalamus
: major region of the diencephalon that is responsible for coordinating autonomic and endocrine control of homeostasis

indirect pathway
: connections within the basal nuclei from the striatum through the globus pallidus external segment and subthalamic nucleus to the globus pallidus internal segment/substantia nigra pars compacta that result in inhibition of the thalamus to decrease cortical control of movement

inferior colliculus
: half of the midbrain tectum that is part of the brain stem auditory pathway

inferior olive
: nucleus in the medulla that is involved in processing information related to motor control

intercostal nerve
: systemic nerve in the thoracic cavity that is found between two ribs

internal carotid artery
: branch from the common carotid artery that enters the cranium and supplies blood to the brain

interventricular foramina
: openings between the lateral ventricles and third ventricle allowing for the passage of CSF

jugular veins
: blood vessels that return “used” blood from the head and neck

kinesthesia
: general sensory perception of movement of the body

lateral apertures
pair of openings from the fourth ventricle to the subarachnoid space on either side and between the medulla and cerebellum

lateral column
white matter of the spinal cord between the posterior horn on one side and the axons from the anterior horn on the same side; composed of many different groups of axons, of both ascending and descending tracts, carrying motor commands to and from the brain

lateral horn
region of the spinal cord gray matter in the thoracic, upper lumbar, and sacral regions that is the central component of the sympathetic division of the autonomic nervous system

lateral sulcus
surface landmark of the cerebral cortex that marks the boundary between the temporal lobe and the frontal and parietal lobes

lateral ventricles
portions of the ventricular system that are in the region of the cerebrum

limbic cortex
collection of structures of the cerebral cortex that are involved in emotion, memory, and behavior and are part of the larger limbic system

limbic system
structures at the edge (limit) of the boundary between the forebrain and hindbrain that are most associated with emotional behavior and memory formation

longitudinal fissure
large separation along the midline between the two cerebral hemispheres

lumbar plexus
nerve plexus associated with the lumbar spinal nerves

lumbar puncture
procedure used to withdraw CSF from the lower lumbar region of the vertebral column that avoids the risk of damaging CNS tissue because the spinal cord ends at the upper lumbar vertebrae

median aperture
singular opening from the fourth ventricle into the subarachnoid space at the midline between the medulla and cerebellum

median nerve
systemic nerve of the arm, located between the ulnar and radial nerves

meninges
protective outer coverings of the CNS composed of connective tissue

mesencephalon
primary vesicle of the embryonic brain that does not significantly change through the rest of embryonic development and becomes the midbrain

metencephalon
secondary vesicle of the embryonic brain that develops into the pons and the cerebellum

midbrain
middle region of the adult brain that develops from the mesencephalon

myelencephalon
secondary vesicle of the embryonic brain that develops into the medulla

nerve plexus
network of nerves without neuronal cell bodies included

neural crest
tissue that detaches from the edges of the neural groove and migrates through the embryo to develop into peripheral structures of both nervous and non-nervous tissues

neural fold
elevated edge of the neural groove

neural groove
region of the neural plate that folds into the dorsal surface of the embryo and closes off to become the neural tube

neural plate
thickened layer of neuroepithelium that runs longitudinally along the dorsal surface of an embryo and gives rise to nervous system tissue

neural tube
precursor to structures of the central nervous system, formed by the invagination and separation of neuroepithelium

neuraxis
central axis to the nervous system, from the posterior to anterior ends of the neural tube; the inferior tip of the spinal cord to the anterior surface of the cerebrum

occipital lobe
region of the cerebral cortex directly beneath the occipital bone of the cranium

occipital sinuses
dural sinuses along the edge of the occipital lobes of the cerebrum

oculomotor nerve
: third cranial nerve; responsible for contraction of four of the extraocular muscles, the muscle in the upper eyelid, and pupillary constriction

olfaction
: special sense responsible for smell, which has a unique, direct connection to the cerebrum

olfactory nerve
: first cranial nerve; responsible for the sense of smell

optic nerve
: second cranial nerve; responsible for visual sensation

orthostatic reflex
: sympathetic function that maintains blood pressure when standing to offset the increased effect of gravity

paravertebral ganglia
: autonomic ganglia superior to the sympathetic chain ganglia

parietal lobe
: region of the cerebral cortex directly beneath the parietal bone of the cranium

parieto-occipital sulcus
: groove in the cerebral cortex representing the border between the parietal and occipital cortices

perineurium
: layer of connective tissue surrounding fascicles within a nerve

phrenic nerve
: systemic nerve from the cervical plexus that enervates the diaphragm

pia mater
: thin, innermost membrane of the meninges that directly

covers the surface of the CNS

plexus
network of nerves or nervous tissue

postcentral gyrus
ridge just posterior to the central sulcus, in the parietal lobe, where somatosensory processing initially takes place in the cerebrum

posterior columns
white matter of the spinal cord that lies between the posterior horns of the gray matter, sometimes referred to as the dorsal column; composed of axons of ascending tracts that carry sensory information up to the brain

posterior horn
gray matter region of the spinal cord in which sensory input arrives, sometimes referred to as the dorsal horn

posterior median sulcus
midline feature of the posterior spinal cord, marking the separation between right and left sides of the cord

posterolateral sulcus
feature of the posterior spinal cord marking the entry of posterior nerve roots and the separation between the posterior and lateral columns of the white matter

precentral gyrus
primary motor cortex located in the frontal lobe of the cerebral cortex

prefrontal lobe
specific region of the frontal lobe anterior to the more specific motor function areas, which can be related to the early planning of movements and intentions to the point of being personality-type functions

premotor area
: region of the frontal lobe responsible for planning movements that will be executed through the primary motor cortex

prevertebral ganglia
: autonomic ganglia that are anterior to the vertebral column and functionally related to the sympathetic chain ganglia

primary vesicle
: initial enlargements of the anterior neural tube during embryonic development that develop into the forebrain, midbrain, and hindbrain

proprioception
: general sensory perceptions providing information about location and movement of body parts; the "sense of the self"

prosencephalon
: primary vesicle of the embryonic brain that develops into the forebrain, which includes the cerebrum and diencephalon

putamen
: nucleus deep in the cerebrum that is part of the basal nuclei; along with the caudate, it is part of the striatum

radial nerve
: systemic nerve of the arm, the distal component of which is located near the radial bone

reticular formation
: diffuse region of gray matter throughout the brain stem that regulates sleep, wakefulness, and states of consciousness

rhombencephalon
: primary vesicle of the embryonic brain that develops into the hindbrain, which includes the pons, cerebellum, and medulla

sacral plexus
nerve plexus associated with the lower lumbar and sacral spinal nerves

saphenous nerve
systemic nerve of the lower anterior leg that is a branch from the femoral nerve

sciatic nerve
systemic nerve from the sacral plexus that is a combination of the tibial and fibular nerves and extends across the hip joint and gluteal region into the upper posterior leg

sciatica
painful condition resulting from inflammation or compression of the sciatic nerve or any of the spinal nerves that contribute to it

secondary vesicle
five vesicles that develop from primary vesicles, continuing the process of differentiation of the embryonic brain

sigmoid sinuses
dural sinuses that drain directly into the jugular veins

somatosensation
general senses related to the body, usually thought of as the senses of touch, which would include pain, temperature, and proprioception

spinal accessory nerve
eleventh cranial nerve; responsible for contraction of neck muscles

spinal nerve
one of 31 nerves connected to the spinal cord

straight sinus
dural sinus that drains blood from the deep center of the brain to collect with the other sinuses

striatum
the caudate and putamen collectively, as part of the basal nuclei, which receive input from the cerebral cortex

subarachnoid space
space between the arachnoid mater and pia mater that contains CSF and the fibrous connections of the arachnoid trabeculae

subcortical nucleus
all the nuclei beneath the cerebral cortex, including the basal nuclei and the basal forebrain

substantia nigra pars compacta
nuclei within the basal nuclei that release dopamine to modulate the function of the striatum; part of the motor pathway

substantia nigra pars reticulata
nuclei within the basal nuclei that serve as an output center of the nuclei; part of the motor pathway

subthalamus
nucleus within the basal nuclei that is part of the indirect pathway

sulcus
groove formed by convolutions in the surface of the cerebral cortex

superior colliculus
half of the midbrain tectum that is responsible for aligning visual, auditory, and somatosensory spatial perceptions

superior sagittal sinus
: dural sinus that runs along the top of the longitudinal fissure and drains blood from the majority of the outer cerebrum

sympathetic chain ganglia
: autonomic ganglia in a chain along the anterolateral aspect of the vertebral column that are responsible for contributing to homeostatic mechanisms of the autonomic nervous system

systemic nerve
: nerve in the periphery distal to a nerve plexus or spinal nerve

tectum
: region of the midbrain, thought of as the roof of the cerebral aqueduct, which is subdivided into the inferior and superior colliculi

tegmentum
: region of the midbrain, thought of as the floor of the cerebral aqueduct, which continues into the pons and medulla as the floor of the fourth ventricle

telencephalon
: secondary vesicle of the embryonic brain that develops into the cerebrum

temporal lobe
: region of the cerebral cortex directly beneath the temporal bone of the cranium

terminal ganglion
: autonomic ganglia that are near or within the walls of organs that are responsible for contributing to homeostatic mechanisms of the autonomic nervous system

thalamus
: major region of the diencephalon that is responsible for relaying information between the cerebrum and the hindbrain,

spinal cord, and periphery

third ventricle
portion of the ventricular system that is in the region of the diencephalon

tibial nerve
systemic nerve of the posterior leg that begins as part of the sciatic nerve

transverse sinuses
dural sinuses that drain along either side of the occipital–cerebellar space

trigeminal ganglion
sensory ganglion that contributes sensory fibers to the trigeminal nerve

trigeminal nerve
fifth cranial nerve; responsible for cutaneous sensation of the face and contraction of the muscles of mastication

trochlear nerve
fourth cranial nerve; responsible for contraction of one of the extraocular muscles

ulnar nerve
systemic nerve of the arm located close to the ulna, a bone of the forearm

vagus nerve
tenth cranial nerve; responsible for the autonomic control of organs in the thoracic and upper abdominal cavities

ventral (anterior) nerve root
axons emerging from the anterior or lateral horns of the spinal cord

ventricles
remnants of the hollow center of the neural tube that are spaces for cerebrospinal fluid to circulate through the brain

vertebral arteries
arteries that ascend along either side of the vertebral column through the transverse foramina of the cervical vertebrae and enter the cranium through the foramen magnum

vestibulocochlear nerve
eighth cranial nerve; responsible for the sensations of hearing and balance

PART VIII

CHAPTER 8: THE SPECIAL SENSES

47. The Brain and Cranial Nerves

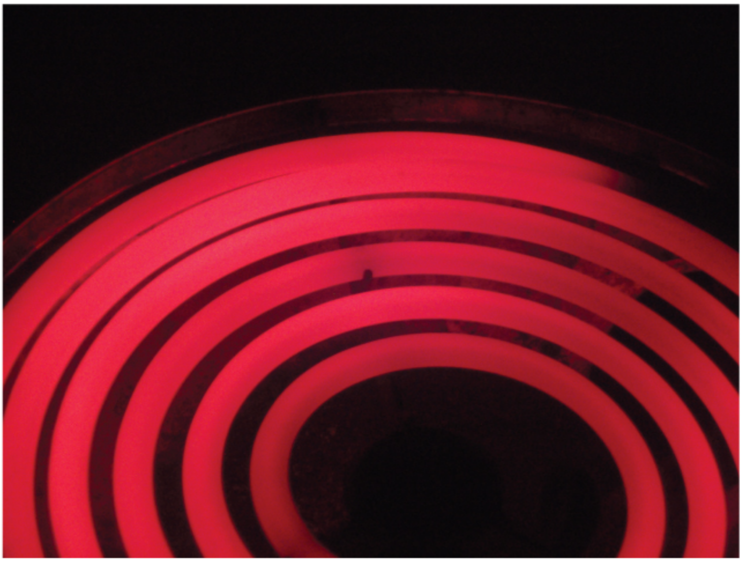


Figure 8.1. Too Hot to Touch
When high temperature is sensed in the skin, a reflexive withdrawal is initiated by the muscles of the arm. Sensory neurons are activated by a stimulus, which is sent to the central nervous system, and a motor response is sent out to the skeletal muscles that control this movement.

Introduction

The somatic nervous system is traditionally considered a division within the peripheral nervous system. However, this misses an important point: somatic refers to a functional division, whereas peripheral refers to an anatomic division. The somatic nervous system is responsible for our conscious perception of the environment and for our voluntary responses to that perception by means of skeletal muscles. Peripheral sensory neurons receive input from environmental stimuli, but the neurons that produce motor responses originate in the central nervous system. The distinction between the structures (i.e., anatomy) of the peripheral and central nervous systems and functions (i.e., physiology) of the somatic and autonomic systems can most easily be demonstrated through a simple reflex action. When you touch a hot stove, you pull your hand away. Sensory receptors in the skin sense extreme temperature and the early signs of tissue damage. This triggers an action potential, which travels along the sensory fiber from the skin, through the dorsal spinal root to the spinal cord, and directly activates a ventral horn motor neuron. That neuron sends a signal along its axon to excite the biceps brachii, causing contraction of the muscle and flexion of the forearm at the elbow to withdraw the hand from the hot stove. The withdrawal reflex has more components, such as inhibiting the opposing muscle and balancing posture while the arm is forcefully withdrawn, which will be further explored at the end of this chapter.

The basic withdrawal reflex explained above includes sensory input (the painful stimulus), central processing (the synapse in the spinal cord), and motor output (activation of a ventral motor neuron that causes contraction of the biceps brachii). Expanding the explanation of the withdrawal reflex can include inhibition of the opposing muscle, or cross extension, either of which increase the complexity of the example by involving more central neurons. A collateral branch of the sensory axon would inhibit another ventral horn motor neuron so that the triceps brachii do not contract and slow the withdrawal down. The cross extensor reflex provides a counterbalancing movement on the other side of the body, which requires another collateral of the sensory axon to activate contraction of the extensor muscles in the contralateral limb.

A more complex example of somatic function is conscious muscle movement. For example, reading of this text starts with visual sensory input to the retina, which then projects to the thalamus, and on to the cerebral cortex. A sequence of regions of the cerebral cortex process the visual information, starting in the primary visual cortex of the occipital lobe, and resulting in the conscious perception of these letters. Subsequent cognitive processing results in understanding of the content. As you continue reading, regions of the cerebral cortex in the frontal lobe plan how to move the eyes to follow the lines of text. The output from the cortex causes activity in motor neurons in the brain stem that cause movement of the extraocular muscles through the third, fourth, and sixth cranial nerves. This example also includes sensory input (the retinal projection to the thalamus), central processing (the thalamus and subsequent cortical activity), and motor output (activation of neurons in the brain stem that lead to coordinated contraction of extraocular muscles).

A major role of sensory receptors is to help us learn about the environment around us, or about the state of our internal environment. Stimuli from varying sources, and of different types, are received and changed into the electrochemical signals of the nervous system. This occurs when a stimulus changes the cell membrane potential of a sensory neuron. The stimulus causes the sensory cell to produce an action potential that is relayed into the central nervous system (CNS), where it is integrated with other sensory information—or sometimes higher cognitive functions—to become a conscious perception of that stimulus. The central integration may then lead to a motor response. Describing sensory function with the term sensation or perception is a deliberate distinction. Sensation is the activation of sensory receptor cells at the level of the stimulus. Perception is the central processing of sensory stimuli into a meaningful pattern. Perception is dependent on sensation, but not all sensations are perceived. Receptors are the cells or structures that detect sensations. A receptor cell is changed directly by a stimulus. A transmembrane protein receptor is a protein in the cell membrane that mediates a physiological change in a neuron, most often through the opening of ion channels or changes in the cell signaling processes. Transmembrane receptors are activated by chemicals called ligands. For example, a molecule in food can serve as a ligand for taste receptors. Other transmembrane proteins, which are not accurately called receptors, are sensitive to mechanical or thermal changes. Physical changes in these proteins increase ion flow across the membrane, and can generate an action potential or a graded potential in the sensory neurons.

Sensory Receptors

Stimuli in the environment activate specialized receptor cells in the peripheral nervous system. Different types of stimuli are sensed by different types of receptor cells. Receptor cells can be classified into types on the basis of three different criteria: cell type, position, and function. Receptors can be classified structurally on the basis of cell type and their position in relation to stimuli they sense. They can also be classified functionally on the basis of the ***transduction*** of stimuli, or how the mechanical stimulus, light, or chemical changed the cell membrane potential.

Structural Receptor Types

The cells that interpret information about the environment can be either (1) a neuron that has a ***free nerve ending***, with dendrites embedded in tissue that would receive a sensation; (2) a neuron that has an ***encapsulated ending*** in which the sensory nerve endings are encapsulated in connective tissue that enhances their sensitivity; or (3) a specialized ***receptor cell***, which has distinct structural components that interpret a specific type of stimulus (Figure 8.2). The pain and temperature receptors in the dermis of the skin are examples of neurons that have free nerve endings. Also located in the dermis of the skin are lamellated corpuscles, neurons with encapsulated nerve endings that respond to pressure and touch. The cells in the retina that respond to light stimuli are an example of a specialized receptor, a ***photoreceptor***.

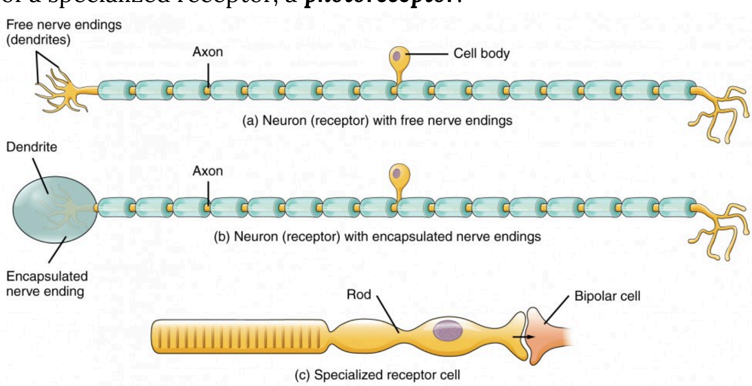


Figure 8.2. Receptor Classification by Cell Type
Receptor cell types can be classified on the basis of their structure. Sensory neurons can have either (a) free nerve endings or (b) encapsulated endings. Photoreceptors in the eyes, such as rod cells,

are examples of (c) specialized receptor cells. These cells release neurotransmitters onto a bipolar cell, which then synapses with the optic nerve neurons.

Another way that receptors can be classified is based on their location relative to the stimuli. An ***exteroceptor*** is a receptor that is located near a stimulus in the external environment, such as the somatosensory receptors that are located in the skin. An ***interoceptor*** is one that interprets stimuli from internal organs and tissues, such as the receptors that sense the increase in blood pressure in the aorta or carotid sinus. Finally, a ***proprioceptor*** is a receptor located near a moving part of the body, such as a muscle, that interprets the positions of the tissues as they move.

Functional Receptor Types

A third classification of receptors is by how the receptor transduces stimuli into membrane potential changes. Stimuli are of three general types. Some stimuli are ions and macromolecules that affect transmembrane receptor proteins when these chemicals diffuse across the cell membrane. Some stimuli are physical variations in the environment that affect receptor cell membrane potentials. Other stimuli include the electromagnetic radiation from visible light. For humans, the only electromagnetic energy that is perceived by our eyes is visible light. Some other organisms have receptors that humans lack, such as the heat sensors of snakes, the ultraviolet light sensors of bees, or magnetic receptors in migratory birds. Receptor cells can be further categorized on the basis of the type of stimuli they transduce. Chemical stimuli can be interpreted by a ***chemoreceptor*** that interprets chemical stimuli, such as an object's taste or smell. ***Osmoreceptors*** respond to solute concentrations of body fluids. Additionally, pain is primarily a chemical sense that interprets the presence of chemicals from tissue damage, or similar intense stimuli, through a ***nociceptor***. Physical stimuli, such as pressure and vibration, as well as the sensation of sound and body position (balance), are interpreted through a ***mechanoreceptor***. Another physical stimulus that has its own type of receptor is temperature, which is sensed through a ***thermoreceptor*** that is either sensitive to temperatures above (heat) or below (cold) normal body temperature.

Sensory Modalities

Ask anyone what the senses are, and they are likely to list the five major senses—taste, smell, touch, hearing, and sight. However, these are not all of the senses. The most obvious omission from this list is balance. Also, what is referred to simply as touch can be further subdivided into pressure, vibration, stretch, and hair-follicle position, on the basis of the type of mechanoreceptors that perceive these touch sensations. Other overlooked senses include temperature perception by thermoreceptors and pain perception by nociceptors. Within the realm of physiology, senses can be classified as either general or specific. A ***general sense*** is one that is distributed throughout the body and has receptor cells within the structures of other organs. Mechanoreceptors in the skin, muscles, or the walls of blood vessels are examples of this type. General senses often contribute to the sense of touch, as described above, or to ***proprioception*** (body movement) and ***kinesthesia*** (body movement), or to a ***visceral sense***, which is most important to autonomic functions. A ***special sense*** is one that has a specific organ devoted to it, namely the eye, inner ear, tongue, or nose. Each of the senses is referred to as a ***sensory modality***. Modality refers to the way that information is encoded, which is similar to the idea of transduction. The main sensory modalities can be described on the basis of how each is transduced. The chemical senses are taste and smell. The general sense that is usually referred to as touch includes chemical sensation in the form of nociception, or pain. Pressure, vibration, muscle stretch, and the movement of hair by an external stimulus, are all sensed by mechanoreceptors. Hearing and balance are also sensed by mechanoreceptors. Finally, vision involves the activation of photoreceptors. Listing all the different sensory modalities, which can number as many as 17, involves separating the five major senses into more specific categories, or ***submodalities***, of the larger sense. An individual sensory modality represents the sensation of a specific type of stimulus. For example, the general sense of touch, which is known ***assomatosensation***, can be separated into light pressure, deep pressure, vibration, itch, pain, temperature, or hair movement.

48. Taste

Gustation (Taste)

Only a few recognized submodalities exist within the sense of taste, or ***gustation***. Until recently, only four tastes were recognized: sweet, salty, sour, and bitter. Research at the turn of the 20th century led to recognition of the fifth taste, umami, during the mid-1980s. ***Umami*** is a Japanese word that means "delicious taste," and is often translated to mean savory.

Very recent research has suggested that there may also be a sixth taste for fats, or lipids. Gustation is the special sense associated with the tongue. The surface of the tongue, along with the rest of the oral cavity, is lined by a stratified squamous epithelium. Raised bumps called ***papillae*** (singular = papilla) contain the structures for gustatory transduction. There are four types of papillae, based on their appearance (Figure 8.3): circumvallate, foliate, filiform, and fungiform. Within the structure of the papillae are ***taste buds*** that contain specialized ***gustatory receptor cells*** for the transduction of taste stimuli. These receptor cells are sensitive to the chemicals contained within foods that are ingested, and they release neurotransmitters based on the amount of the chemical in the food. Neurotransmitters from the gustatory cells can activate sensory neurons in the facial, glossopharyngeal, and vagus cranial nerves.

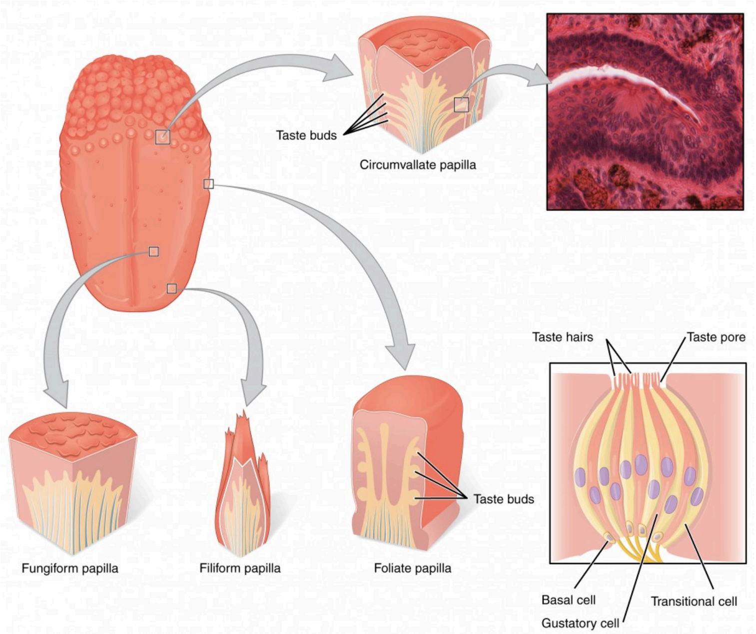


Figure 8.3. The Tongue
The tongue is covered with small bumps, called papillae, which contain taste buds that are sensitive to chemicals in ingested food or drink. Different types of papillae are found in different regions of the tongue. The taste buds contain specialized gustatory receptor cells that respond to chemical stimuli dissolved in the saliva. These receptor cells activate sensory neurons that are part of the facial and glossopharyngeal nerves. LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Salty taste is simply the perception of sodium ions (Na^+) in the saliva. When you eat something salty, the salt crystals dissociate into the component ions Na^+ and Cl^-, which dissolve into the saliva in your mouth. The Na^+ concentration becomes high outside the gustatory cells, creating a strong concentration gradient that drives the diffusion of the ion into the cells. The entry of Na^+ into these cells results in the depolarization of the cell membrane and the generation of a receptor potential. Sour taste is the perception of H^+ concentration. Just as with sodium ions in salty flavors, these hydrogen ions enter the cell and trigger depolarization. Sour flavors are, essentially, the perception of acids in our food. Increasing hydrogen ion concentrations in the saliva (lowering saliva pH) triggers progressively stronger graded potentials in the gustatory cells. For example, orange juice—which contains citric acid—will taste sour because it has a pH value of approximately 3. Of course, it is often sweetened so that the sour taste is masked. The first two tastes (salty and sour) are triggered by the cations Na^+ and H^+. The other tastes result from food molecules binding to a G protein–coupled receptor. A G protein signal transduction system ultimately leads to depolarization of the gustatory cell. The sweet taste is the sensitivity of gustatory cells to the presence of glucose dissolved in the saliva. Other monosaccharides such as fructose, or artificial sweeteners such as aspartame (NutraSweet™), saccharine, or sucralose (Splenda™) also activate the sweet receptors. The affinity for each of these molecules varies, and some will taste sweeter than glucose because they bind to the G protein–coupled receptor differently. Bitter taste is similar to sweet in that food molecules bind to G protein–coupled receptors. However, there are a number of different ways in which this can happen because there are a large diversity of bitter-tasting molecules. Some bitter molecules depolarize gustatory cells, whereas others hyperpolarize gustatory cells. Likewise, some bitter molecules increase G protein activation within the gustatory cells, whereas other bitter molecules decrease G protein activation. The specific response depends on which molecule is binding to the receptor. One major group of bitter-tasting molecules are alkaloids. ***Alkaloids*** are nitrogen-containing molecules that often have a basic pH. Alkaloids are commonly found in bitter-tasting plant products, such as coffee, hops (in beer), tannins (in wine), tea, and aspirin. By containing toxic alkaloids, the plant is less susceptible to microbe infection and less attractive to herbivores. Therefore, the function of bitter taste may primarily be related to stimulating the gag reflex to avoid ingesting poisons. Because of this, many bitter foods that are normally ingested are often combined with a sweet component to make them more palatable (cream and sugar in coffee, for example). The highest concentration of bitter receptors appear to be in the posterior tongue, where a gag reflex could still spit out poisonous food. The taste known as umami is often referred to as the savory taste. Like sweet and bitter, it is based on the activation of G protein–coupled receptors by a specific molecule. The molecule that activates this receptor is the amino acid L-glutamate. Therefore, the umami flavor is often perceived while eating protein-rich foods. Not surprisingly, dishes that contain meat are often described as savory. Once the gustatory cells are activated by the taste molecules, they release neurotransmitters onto the dendrites of sensory neurons. These neurons are part of the facial and glossopharyngeal cranial nerves, as well as a component within the vagus nerve dedicated to the gag reflex. The facial nerve connects to taste buds in the anterior third of the tongue. The glossopharyngeal nerve connects to taste buds in the posterior two thirds of the tongue. The vagus nerve connects to taste buds in the extreme posterior of the tongue, verging on the pharynx, which are more sensitive to noxious stimuli such as bitterness.

Age Related Changes to Taste

While the number of taste buds does not decline until after 75 years of age, there is a general decrease in taste perception as part of the aging process. Other factors that may contribute to the reduction in taste in older persons are a decrease in the volume of saliva secreted, an increases in the viscosity of saliva, and the formation of fissures and furrows on the tongue.

49. Smell

Olfaction (Smell)

Like taste, the sense of smell, or ***olfaction***, is also responsive to chemical stimuli. The olfactory receptor neurons are located in a small region within the superior nasal cavity (Figure 8.4). This region is referred to as the ***olfactory epithelium*** and contains bipolar sensory neurons. Each ***olfactory sensory neuron*** has dendrites that extend from the apical surface of the epithelium into the mucus lining the cavity. As airborne molecules are inhaled through the nose, they pass over the olfactory epithelial region and dissolve into the mucus. These ***odorant molecules*** bind to proteins that keep them dissolved in the mucus and help transport them to the olfactory dendrites. The odorant–protein complex binds to a receptor protein within the cell membrane of an olfactory dendrite. These receptors are G protein–coupled, and will produce a graded membrane potential in the olfactory neurons. The axon of an olfactory neuron extends from the basal surface of the epithelium, through an olfactory foramen in the cribriform plate of the ethmoid bone, and into the brain. The group of axons called the olfactory tract connect to the ***olfactory bulb*** on the ventral surface of the frontal lobe. From there, the axons split to travel to several brain regions. Some travel to the cerebrum, specifically to the primary olfactory cortex that is located in the inferior and medial areas of the temporal lobe. Others project to structures within the limbic system and hypothalamus, where smells become associated with long-term memory and emotional responses. This is how certain smells trigger emotional memories, such as the smell of food associated with one's birthplace. Smell is the one sensory modality that does not synapse in the thalamus before connecting to the cerebral cortex. This intimate connection between the olfactory system and the cerebral cortex is one reason why smell can be a potent trigger of memories and emotion. The nasal epithelium, including the olfactory cells, can be harmed by airborne toxic chemicals. Therefore, the olfactory neurons are regularly replaced within the nasal epithelium, after which the axons of the new neurons must find their appropriate connections in the olfactory bulb. These new axons grow along the axons that are already in place in the cranial nerve.

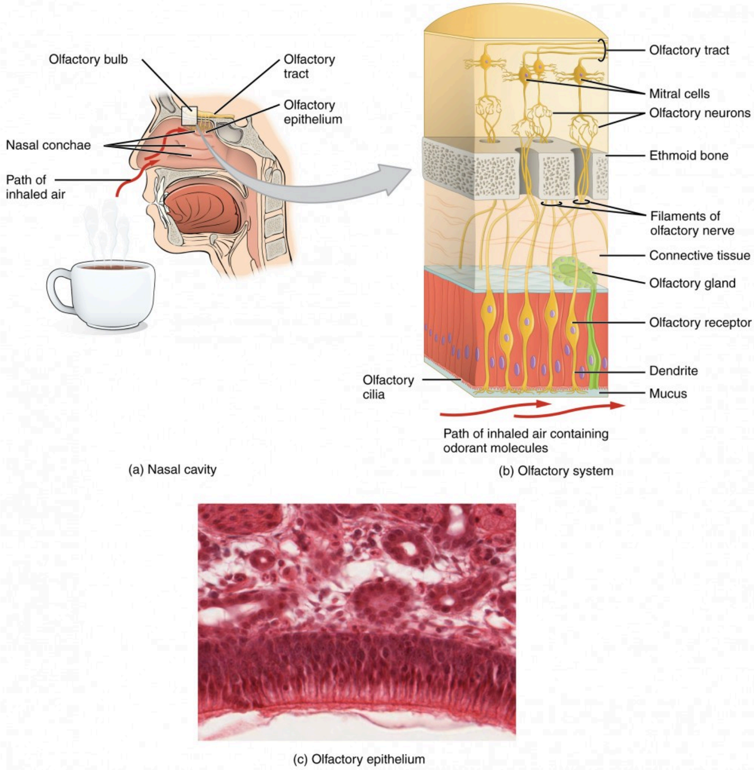


Figure 8.4. The Olfactory System
(a) The olfactory system begins in the peripheral structures of the nasal cavity. (b) The olfactory receptor neurons are within the olfactory epithelium. (c) Axons of the olfactory receptor neurons project through the cribriform plate of the ethmoid bone and synapse with the neurons of the olfactory bulb (tissue source: simian). LM ×

812. *(Micrograph provided by the Regents of University of Michigan Medical School © 2012)*

Disorders of the Olfactory System: Anosmia

Blunt force trauma to the face, such as that common in many car accidents, can lead to the loss of the olfactory nerve, and subsequently, loss of the sense of smell. This condition is known as ***anosmia***. When the frontal lobe of the brain moves relative to the ethmoid bone, the olfactory tract axons may be sheared apart. Professional fighters often experience anosmia because of repeated trauma to face and head. In addition, certain pharmaceuticals, such as antibiotics, can cause anosmia by killing all the olfactory neurons at once. If no axons are in place within the olfactory nerve, then the axons from newly formed olfactory neurons have no guide to lead them to their connections within the olfactory bulb. There are temporary causes of anosmia, as well, such as those caused by inflammatory responses related to respiratory infections or allergies. Loss of the sense of smell can result in food tasting bland. A person with an impaired sense of smell may require additional spice and seasoning levels for food to be tasted. Anosmia may also be related to some presentations of mild depression, because the loss of enjoyment of food may lead to a general sense of despair. The ability of olfactory neurons to replace themselves decreases with age, leading to age-related anosmia. This explains why some elderly people salt their food more than younger people do. However, this increased sodium intake can increase blood volume and blood pressure, increasing the risk of cardiovascular diseases in the elderly.

Aging and the Nervous System

Anosmia is the loss of the sense of smell. It is often the result of the olfactory nerve being severed, usually because of blunt force trauma to the head. The sensory neurons of the olfactory epithelium have a limited lifespan of approximately one to four months, and new ones are made on a regular basis. The new neurons extend their axons into the CNS by growing along the existing fibers of the olfactory nerve. The ability of these neurons to be replaced is lost with age. Age-related anosmia is not the result of impact trauma to the head, but rather a slow loss of the sensory neurons with no new neurons born to replace them. Smell is an important sense, especially for the enjoyment of food. There are only five tastes sensed by the tongue, and two of them are generally thought of as unpleasant tastes (sour and bitter). The rich sensory experience of food is the result of odor molecules associated with the food, both as food is moved into the mouth, and therefore passes under the nose, and when it is chewed and molecules are released to move up the pharynx into the posterior nasal cavity. Anosmia results in a loss of the enjoyment of food. As the replacement of olfactory neurons declines with age, anosmia can set in. Without the sense of smell, many sufferers complain of food tasting bland. Often, the only way to enjoy food is to add seasoning that can be sensed on the tongue, which usually means adding table salt. The problem with this solution, however, is that this increases sodium intake, which can lead to cardiovascular problems through water retention and the associated increase in blood pressure.

Age Related Changes to Smell

The sense of smell begins to decline in most people by middle age and continues to decline gradually into old age. This is most likely a result of a decrease in olfactory sensory cells and a loss of neurons in the olfactory bulb.

50. The Ear

Audition (Hearing)

Hearing, or ***audition***, is the transduction of sound waves into a neural signal that is made possible by the structures of the ear (Figure 8.5). The large, fleshy structure on the lateral aspect of the head is known as the ***auricle***. Some sources will also refer to this structure as the pinna, though that term is more appropriate for a structure that can be moved, such as the external ear of a cat. The C-shaped curves of the auricle direct sound waves toward the auditory canal. The canal enters the skull through the external auditory meatus of the temporal bone. At the end of the auditory canal is the ***tympanic membrane***, or ear drum, which vibrates after it is struck by sound waves. The auricle, ear canal, and tympanic membrane are often referred to as the ***external ear***. The ***middle ear*** consists of a space spanned by three small bones called the ***ossicles***. The three ossicles are the ***malleus***, ***incus***, and ***stapes***, which are Latin names that roughly translate to hammer, anvil, and stirrup. The malleus is attached to the tympanic membrane and articulates with the incus. The incus, in turn, articulates with the stapes. The stapes is then attached to the ***inner ear***, where the sound waves will be transduced into a neural signal. The middle ear is connected to the pharynx through the Eustachian tube, which helps equilibrate air pressure across the tympanic membrane. The tube is normally closed but will pop open when the muscles of the pharynx contract during swallowing or yawning.

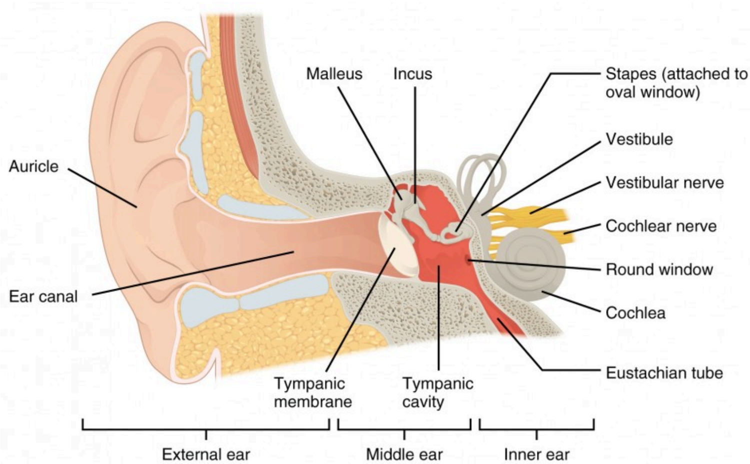


Figure 8.5. Structures of the Ear
The external ear contains the auricle, ear canal, and tympanic membrane. The middle ear contains the ossicles and is connected to the pharynx by the Eustachian tube. The inner ear contains the cochlea and vestibule, which are responsible for audition and equilibrium, respectively.

The inner ear is often described as a bony labyrinth, as it is composed of a series of canals embedded within the temporal bone. It has two separate regions, the ***cochlea*** and the ***vestibule***, which are responsible for hearing and balance, respectively. The neural signals from these two regions are relayed to the brain stem through separate fiber bundles. However, these two distinct bundles travel together from the inner ear to the brain stem as the vestibulocochlear nerve. Sound is transduced into neural signals within the cochlear region of the inner ear, which contains the sensory neurons of the ***spiral ganglia***. These ganglia are located within the spiral-shaped cochlea of the inner ear. The cochlea is attached to the stapes through the ***oval window***. The oval window is located at the beginning of a fluid-filled tube within the cochlea called the ***scala vestibuli***. The scala vestibuli extends from the oval window, travelling above the ***cochlear duct***, which is the central cavity of the cochlea that contains the sound-transducing neurons. At the uppermost tip of the cochlea, the scala vestibuli curves over the top of the cochlear duct. The fluid-filled tube, now called the ***scala tympani***, returns to the base of the cochlea, this time travelling under the cochlear duct. The scala tympani ends at the ***round window***, which is covered by a membrane that contains the fluid within the scala. As vibrations of the ossicles travel through the oval window, the fluid of the scala vestibuli and scala tympani moves in a wave-like motion. The frequency of the fluid waves match the frequencies of the sound waves (Figure 8.6). The membrane covering the round window will bulge out or pucker in with the movement of the fluid within the scala tympani.

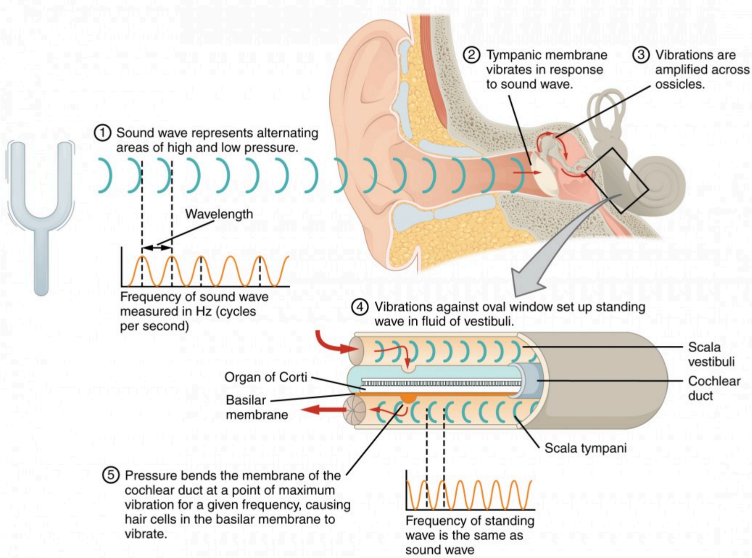


Figure 8.6. Transmission of Sound Waves to Cochlea

A sound wave causes the tympanic membrane to vibrate. This vibration is amplified as it moves across the malleus, incus, and stapes. The amplified vibration is picked up by the oval window causing pressure waves in the fluid of the scala vestibuli and scala tympani. The complexity of the pressure waves is determined by the changes in amplitude and frequency of the sound waves entering the ear.

A cross-sectional view of the cochlea shows that the scala vestibuli and scala tympani run along both sides of the cochlear duct (Figure 8.7). The cochlear duct contains several ***organs of Corti***, which tranduce the wave motion of the two scala into neural signals. The organs of Corti lie on top of the ***basilar membrane***, which is the side of the cochlear duct located between the organs of Corti and the scala tympani. As the fluid waves move through the scala vestibuli and scala tympani, the basilar membrane moves at a specific spot, depending on the frequency of the waves. Higher frequency waves move the region of the basilar membrane that is close to the base of the cochlea. Lower frequency waves move the region of the basilar membrane that is near the tip of the cochlea.

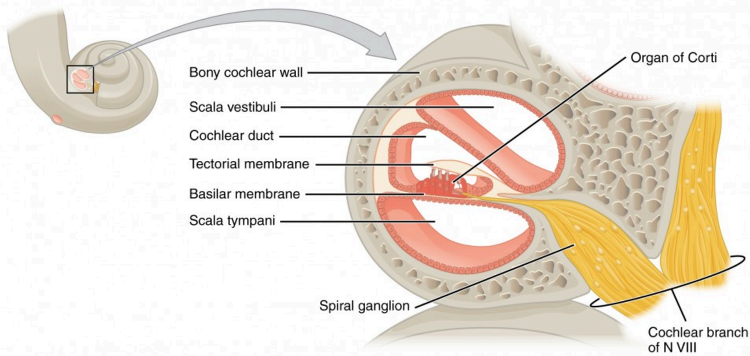


Figure 8.7. Cross Section of the Cochlea

The three major spaces within the cochlea are highlighted. The scala tympani and scala vestibuli lie on either side of the cochlear duct. The organ of Corti, containing the mechanoreceptor hair cells, is adjacent to the scala tympani, where it sits atop the basilar membrane.

The organs of Corti contain ***hair cells***, which are named for the hair-like ***stereocilia*** extending from the cell's apical surfaces (Figure 8.8). The stereocilia are an array of microvilli-like structures arranged from tallest to shortest. Protein fibers tether adjacent hairs together within each array, such that the array will bend in response to movements of the basilar membrane. The stereocilia extend up from the hair cells to the overlying ***tectorial membrane***, which is attached medially to the organ of Corti. When the pressure waves from the scala move the basilar membrane, the tectorial membrane slides across the stereocilia. This bends the stereocilia either toward or away from the tallest member of each array. When the stereocilia bend toward the tallest member of their array, tension in the protein tethers opens ion channels in the hair cell membrane. This will depolarize the hair cell membrane, triggering nerve impulses that travel down the afferent nerve fibers attached to the hair cells. When the stereocilia bend toward the shortest member of their array, the tension on the tethers slackens and the ion channels close. When no sound is present, and the stereocilia are standing straight, a small amount of tension still exists on the tethers, keeping the membrane potential of the hair cell slightly depolarized.

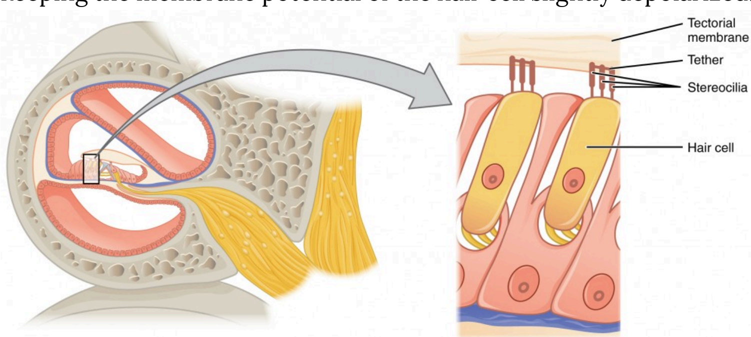


Figure 8.8. Hair Cell
The hair cell is a mechanoreceptor with an array of stereocilia emerging from its apical surface. The stereocilia are tethered together by proteins that open ion channels when the array is bent toward the tallest member of their array, and closed when the array is bent toward the shortest member of their array.

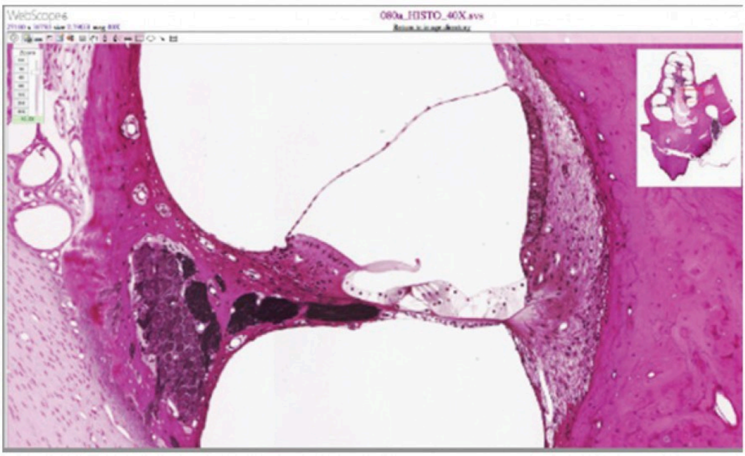


Figure 8.9. Cochlea and Organ of Corti
LM × 412. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

As stated above, a given region of the basilar membrane will only move if the incoming sound is at a specific frequency. Because the tectorial membrane only moves where the basilar membrane moves, the hair cells in this region will also only respond to sounds of this specific frequency. Therefore, as the frequency of a sound changes, different hair cells are activated all along the basilar membrane. The cochlea encodes auditory stimuli for frequencies between 20 and 20,000 Hz, which is the range of sound that human ears can detect. The unit of Hertz measures the frequency of sound waves in terms of cycles produced per second. Frequencies as low as 20 Hz are detected by hair cells at the apex, or tip, of the cochlea. Frequencies in the higher ranges of 20 KHz are encoded by hair cells at the base of the cochlea, close to the round and oval windows (Figure 8.10). Most auditory stimuli contain a mixture of sounds at a variety of frequencies and intensities (represented by the amplitude of the sound wave). The hair cells along the length of the cochlear duct, which are each sensitive to a particular frequency, allow the cochlea to separate auditory stimuli by frequency, just as a prism separates visible light into its component colors.

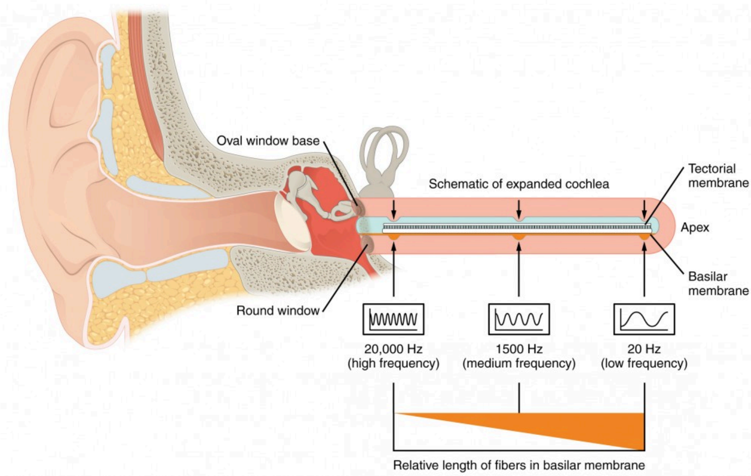


Figure 8.10. Frequency Coding in the Cochlea
The standing sound wave generated in the cochlea by the movement of the oval window deflects the basilar membrane on the basis of the frequency of sound. Therefore, hair cells at the base of the cochlea are activated only by high frequencies, whereas those at the apex of the cochlea are activated only by low frequencies.

Equilibrium (Balance)

Along with audition, the inner ear is responsible for encoding information about *equilibrium*, the sense of balance. A similar mechanoreceptor—a hair cell with stereocilia—senses head position, head movement, and whether our bodies are in motion. These cells are located within the vestibule of the inner ear. Head position is sensed by the *utricle* and *saccule*, whereas head movement is sensed by the *semicircular canals*. The neural signals generated in the*vestibular ganglion* are transmitted through the vestibulocochlear nerve to the brain stem and cerebellum. The utricle and saccule are both largely composed of *macula* tissue (plural = maculae). The macula is composed of hair cells surrounded by support cells. The stereocilia of the hair cells extend into a viscous gel called the *otolith* ([Figure 8.11](#)). The otolith contains calcium carbonate crystals, making it denser and giving it greater inertia than the macula. Therefore, gravity will cause the otolith to move separately from the macula in response to head movements. Tilting the head causes the otolith to slide over the macula in the direction of gravity. The moving otolith layer, in turn, bends the sterocilia to cause some hair cells to depolarize as others hyperpolarize. The exact tilt of the head is interpreted by the brain on the basis of the pattern of hair-cell depolarization.

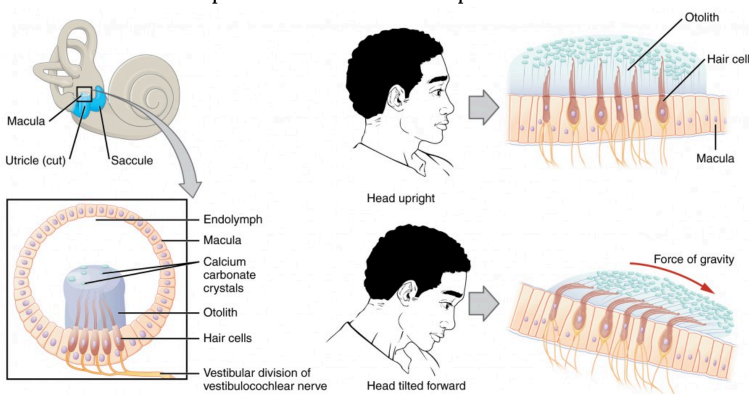


Figure 8.11. Linear Acceleration Coding by Maculae
The maculae are specialized for sensing linear acceleration, such as when gravity acts on the tilting head, or if the head starts moving in a straight line. The difference in inertia between the hair cell stereocilia and the otolith in which they are embedded leads to a shearing force that causes the stereocilia to bend in the direction of that linear acceleration.

The semicircular canals are three ring-like extensions of the vestibule. One is oriented in the horizontal plane, whereas the other two are oriented in the vertical plane. The anterior and posterior vertical canals are oriented at approximately 45 degrees relative to the sagittal plane (Figure 8.12). The base of each semicircular canal, where it meets with the vestibule, connects to an enlarged region known as the ***ampulla***. The ampulla contains the hair cells that respond to rotational movement, such as turning the head while saying "no." The stereocilia of these hair cells extend into the ***cupula***, a membrane that attaches to the top of the ampulla. As the head rotates in a plane parallel to the semicircular canal, the fluid lags, deflecting the cupula in the direction opposite to the head movement. The semicircular canals contain several ampullae, with some oriented horizontally and others oriented vertically. By comparing the relative movements of both the horizontal and vertical ampullae, the vestibular system can detect the direction of most head movements within three-dimensional (3-D) space.

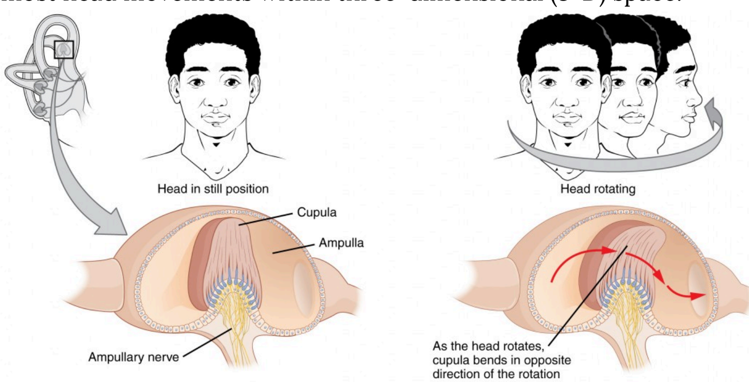


Figure 8.12. Rotational Coding by Semicircular Canals
Rotational movement of the head is encoded by the hair cells in the base of the semicircular canals. As one of the canals moves in an arc with the head, the internal fluid moves in the opposite direction, causing the cupula and stereocilia to bend. The movement of two canals within a plane results in information about the direction in which the head is moving, and activation of all six canals can give a very precise indication of head movement in three dimensions.

Age Related Changes to the Ear

While the external appearance of the ear does change as a part of aging, this does not affect hearing. The gradual loss of hearing that often begins by the age of 40 is due mostly to changes that occur in inner-ear structures. The vestibulocochlear nerve, which innervates the structures of the inner ear, is composed of two divisions- the cochlear division, which is associated with hearing, and the vestibular division, which is associated with balance and equilibrium.

Age Related Dysfunctions of the Ear

Presbycusis, indicating the loss of hearing that occurs normally with aging, is most often noticeable by the age of the age of 50. Typically high-pitched sounds are the first to be lost, followed by lower pitched sounds. As the majority of human speech is in the lower range of sounds initial hearing loss doesn't typically interfere with communication. It is thought that presbycusis is causes by long term exposure to environmental noise. People who have lived their life in relatively quiet environments are less likely to sure from this form of hearing loss.

Tinnitus, also known as ringing of the ears, affects 10% of people over the age of 65. While the cause of the ringing is unknown, the noise is generated somewhere within the auditory system.

Deafness, or complete hearing loss, is not a common condition of aging, but it does become more prevalent with aging. There are two types of deafness, conductive deafness and nerve deafness.

Conductive deafness occurs when the transmission of sound waves through the external or middle ear is hindered or blocked. The interference might be causes by a physical blockage of the external auditory meatus by earwax or a foreign object, inflammation of the tympanic membrane, calcification of the joints between the ossicles, or thickening of the oval window. All of these diminish the vibration reaching the inner-ear structures.

By contrast, nerve deafness is the result of disorders that affect the receptor cells of the spiral organ, the neurons of the vestibulocochlear nerve, or nerve pathways within the central nervous system. Ordinary hearing aids with not help correct nerve deafness, but improvement is possible by means of a cochlear implant.

Dizziness is often described as a disturbed sense of relationship to space or sensation of unsteadiness with a feeling of movement with the head. **Vertigo** is an illusion of movement, as if the external world was revolving around the person or as if the person was revolving in space. While the two terms are used interchangeably there are distinct difference between them. Older people have a greater tendency to be troubled with dizziness and vertigo. These conditions are often a result of inflammation of the parts of the inner ear associated with balance and equilibrium or of the nerve fibers of the vestibulocochlear nerve.

51. The Eye

Vision is the special sense of sight that is based on the transduction of light stimuli received through the eyes. The eyes are located within either orbit in the skull. The bony orbits surround the eyeballs, protecting them and anchoring the soft tissues of the eye (Figure 8.13). The eyelids, with lashes at their leading edges, help to protect the eye from abrasions by blocking particles that may land on the surface of the eye. The inner surface of each lid is a thin membrane known as the ***palpebral conjunctiva***. The conjunctiva extends over the white areas of the eye (the sclera), connecting the eyelids to the eyeball. Tears are produced by the ***lacrimal gland***, located beneath the lateral edges of the nose. Tears produced by this gland flow through the ***lacrimal duct*** to the medial corner of the eye, where the tears flow over the conjunctiva, washing away foreign particles.

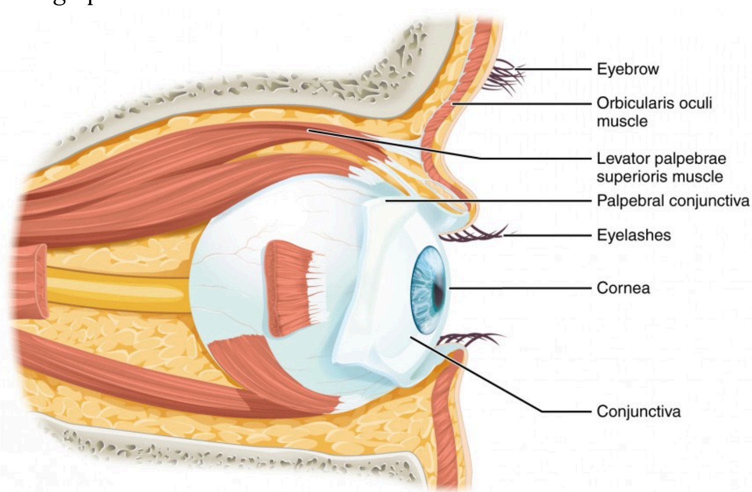


Figure 8.13. The Eye in the Orbit
The eye is located within the orbit and surrounded by soft tissues that protect and support its function. The orbit is surrounded by cranial bones of the skull.

Movement of the eye within the orbit is accomplished by the contraction of six ***extraocular muscles*** that originate from the bones of the orbit and insert into the surface of the eyeball (Figure 8.14). Four of the muscles are arranged at the cardinal points around the eye and are named for those locations. They are the ***superior rectus***, ***medial rectus***, ***inferior rectus***, and ***lateral rectus***. When each of these muscles contract, the eye to moves toward the contracting muscle. For example, when the superior rectus contracts, the eye rotates to look up. The ***superior oblique*** originates at the posterior orbit, near the origin of the four rectus muscles. However, the tendon of the oblique muscles threads through a pulley-like piece of cartilage known as the ***trochlea***. The tendon inserts obliquely into the superior surface of the eye. The angle of the tendon through the trochlea means that contraction of the superior oblique rotates the eye medially. The ***inferior oblique*** muscle originates from the floor of the orbit and inserts into the inferolateral surface of the eye. When it contracts, it laterally rotates the eye, in opposition to the superior oblique. Rotation of the eye by the two oblique muscles is necessary because the eye is not perfectly aligned on the sagittal plane. When the eye looks up or down, the eye must also rotate slightly to compensate for the superior rectus pulling at approximately a 20-degree angle, rather than straight up. The same is true for the inferior rectus, which is compensated by contraction of the inferior oblique. A seventh muscle in the orbit is the ***levator palpebrae superioris***, which is responsible for elevating and retracting the upper eyelid, a movement that usually occurs in concert with elevation of the eye by the superior rectus (see Figure 8.13). The extraocular muscles are innervated by three cranial nerves. The lateral rectus, which causes abduction of the eye, is innervated by the abducens nerve. The superior oblique is innervated by the trochlear nerve. All of the other muscles are innervated by the oculomotor nerve, as is the levator palpebrae superioris. The motor nuclei of these cranial nerves connect to the brain stem, which coordinates eye movements.

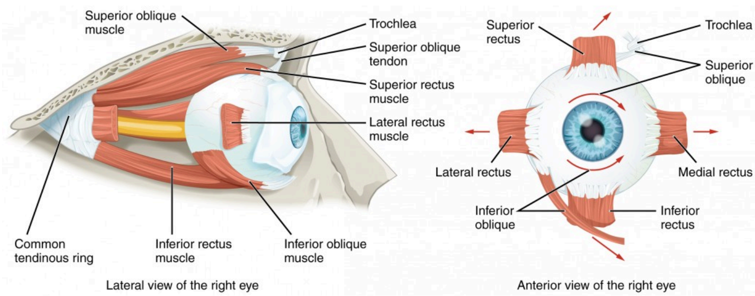


Figure 8.14. Extraocular Muscles
The extraocular muscles move the eye within the orbit.

The eye itself is a hollow sphere composed of three layers of tissue. The outermost layer is the ***fibrous tunic***, which includes the white ***sclera*** and clear ***cornea***. The sclera accounts for five sixths of the surface of the eye, most of which is not visible, though humans are unique compared with many other species in having so much of the "white of the eye" visible (Figure 8.15). The transparent cornea covers the anterior tip of the eye and allows light to enter the eye. The middle layer of the eye is the ***vascular tunic***, which is mostly composed of the choroid, ciliary body, and iris. The ***choroid*** is a layer of highly vascularized connective tissue that provides a blood supply to the eyeball. The choroid is posterior to the ***ciliary body***, a muscular structure that is attached to the ***lens*** by ***zonule fibers***. These two structures bend the lens, allowing it to focus light on the back of the eye. Overlaying the ciliary body, and visible in the anterior eye, is the ***iris***—the colored part of the eye. The iris is a smooth muscle that opens or closes the ***pupil***, which is the hole at the center of the eye that allows light to enter. The iris constricts the pupil in response to bright light and dilates the pupil in response to dim light. The innermost layer of the eye is the ***neural tunic***, or ***retina***, which contains the nervous tissue responsible for photoreception. The eye is also divided into two cavities: the anterior cavity and the posterior cavity. The anterior cavity is the space between the cornea and lens, including the iris and ciliary body. It is filled with a watery fluid called the ***aqueous humor***. The posterior cavity is the space behind the lens that extends to the posterior side of the interior eyeball, where the retina is located. The posterior cavity is filled with a more viscous fluid called the ***vitreous humor***. The retina is composed of several layers and contains specialized cells for the initial processing of visual stimuli. The photoreceptors (rods and cones) change their membrane potential when stimulated by light energy. The change in membrane potential alters the amount of neurotransmitter that the photoreceptor cells release onto ***bipolar cells*** in the ***outer synaptic layer***. It is the bipolar cell in the retina that connects a photoreceptor to a ***retinal ganglion cell*** **(RGC)** in the ***inner synaptic layer***. There, ***amacrine cells*** additionally contribute to retinal processing before an action potential is produced by the RGC. The axons of RGCs, which lie at the innermost layer of the retina, collect at the ***optic disc*** and leave the eye as the ***optic nerve*** (see Figure 8.15). Because these axons pass through the retina, there are no photoreceptors at the very back of the eye, where the optic nerve begins. This creates a "blind spot" in the retina, and a corresponding blind spot in our visual field.

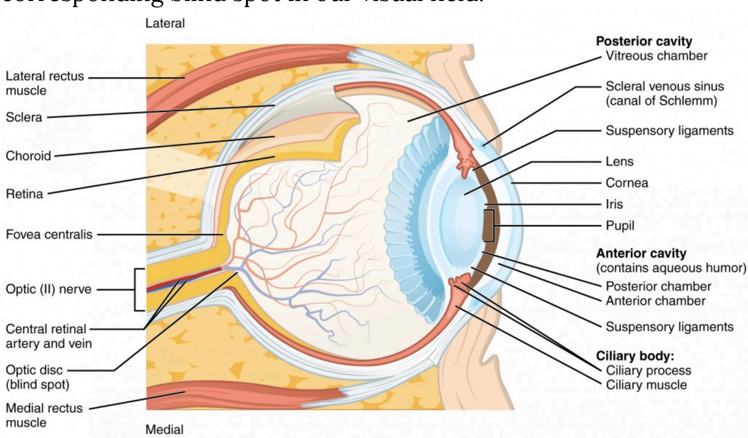


Figure 8.15. Structure of the Eye

The sphere of the eye can be divided into anterior and posterior chambers. The wall of the eye is composed of three layers: the fibrous tunic, vascular tunic, and neural tunic. Within the neural tunic is the *retina, with three layers of cells and two synaptic layers in between. The center of the retina has a small indentation known as the fovea.*

Note that the photoreceptors in the retina (rods and cones) are located behind the axons, RGCs, bipolar cells, and retinal blood vessels. A significant amount of light is absorbed by these structures before the light reaches the photoreceptor cells. However, at the exact center of the retina is a small area known as the ***fovea***. At the fovea, the retina lacks the supporting cells and blood vessels, and only contains photoreceptors. Therefore, ***visual acuity***, or the sharpness of vision, is greatest at the fovea. This is because the fovea is where the least amount of incoming light is absorbed by other retinal structures (see Figure 8.15). As one moves in either direction from this central point of the retina, visual acuity drops significantly. In addition, each photoreceptor cell of the fovea is connected to a single RGC. Therefore, this RGC does not have to integrate inputs from multiple photoreceptors, which reduces the accuracy of visual transduction. Toward the edges of the retina, several photoreceptors converge on RGCs (through the bipolar cells) up to a ratio of 50 to 1. The difference in visual acuity between the fovea and peripheral retina is easily evidenced by looking directly at a word in the middle of this paragraph. The visual stimulus in the middle of the field of view falls on the fovea and is in the sharpest focus. Without moving your eyes off that word, notice that words at the beginning or end of the paragraph are not in focus. The images in your peripheral vision are focused by the peripheral retina, and have vague, blurry edges and words that are not as clearly identified. As a result, a large part of the neural function of the eyes is concerned with moving the eyes and head so that important visual stimuli are centered on the fovea. Light falling on the retina causes chemical changes to pigment molecules in the photoreceptors, ultimately leading to a change in the activity of the RGCs. Photoreceptor cells have two parts, the ***inner segment*** and the ***outer segment*** (Figure 8.16). The inner segment contains the nucleus and other common organelles of a cell, whereas the outer segment is a specialized region in which photoreception takes place. There are two types of photoreceptors—rods and cones—which differ in the shape of their outer segment. The rod-shaped outer segments of the ***rod photoreceptor*** contain a stack of membrane-bound discs that contain the photosensitive pigment ***rhodopsin***. The cone-shaped outer segments of the ***cone photoreceptor*** contain their photosensitive pigments in infoldings of the cell membrane. There are three cone photopigments, called ***opsins***, which are each sensitive to a particular wavelength of light. The wavelength of visible light determines its color. The pigments in human eyes are specialized in perceiving three different primary colors: red, green, and blue.

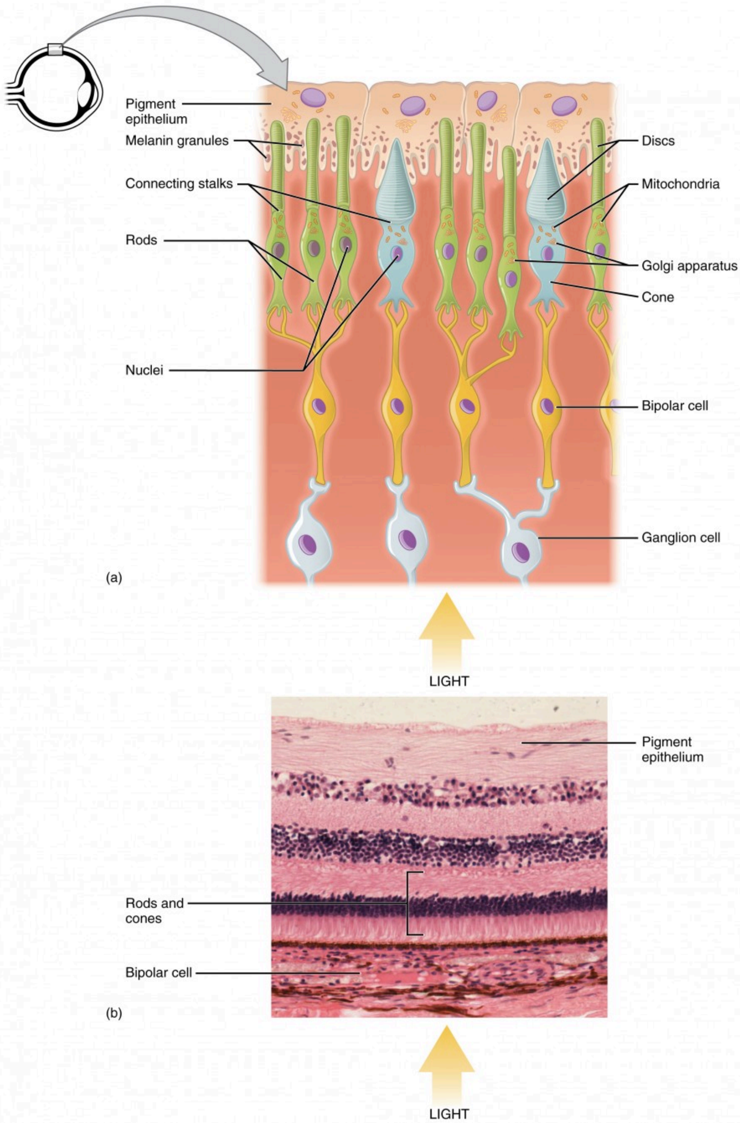


Figure 8.16. Photoreceptor

(a) All photoreceptors have inner segments containing the nucleus and other important organelles and outer segments with membrane arrays containing the photosensitive opsin molecules. Rod outer segments are long columnar shapes with stacks of membrane-bound

discs that contain the rhodopsin pigment. Cone outer segments are short, tapered shapes with folds of membrane in place of the discs in the rods. (b) Tissue of the retina shows a dense layer of nuclei of the rods and cones. LM × 800. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

At the molecular level, visual stimuli cause changes in the photopigment molecule that lead to changes in membrane potential of the photoreceptor cell. A single unit of light is called a ***photon***, which is described in physics as a packet of energy with properties of both a particle and a wave. The energy of a photon is represented by its wavelength, with each wavelength of visible light corresponding to a particular color. Visible light is electromagnetic radiation with a wavelength between 380 and 720 nm. Longer wavelengths of less than 380 nm fall into the infrared range, whereas shorter wavelengths of more than 720 nm fall into the ultraviolet range. Light with a wavelength of 380 nm is blue whereas light with a wavelength of 720 nm is dark red. All other colors fall between red and blue at various points along the wavelength scale. Opsin pigments are actually transmembrane proteins that contain a cofactor known as ***retinal***. Retinal is a hydrocarbon molecule related to vitamin A. When a photon hits retinal, the long hydrocarbon chain of the molecule is biochemically altered. Specifically, photons cause some of the double-bonded carbons within the chain to switch from a *cis* to a *trans* conformation. This process is called ***photoisomerization***. Before interacting with a photon, retinal's flexible double-bonded carbons are in the *cis* conformation. This molecule is referred to as 11-*cis*-retinal. A photon interacting with the molecule causes the flexible double-bonded carbons to change to the *trans*– conformation, forming all-*trans*-retinal, which has a straight hydrocarbon chain (Figure 8.17). The shape change of retinal in the photoreceptors initiates visual transduction in the retina. Activation of retinal and the opsin proteins result in activation of a G protein. The G protein changes the membrane potential of the photoreceptor cell, which then releases less neurotransmitter into the outer synaptic layer of the retina. Until the retinal molecule is changed back to the 11-*cis*-retinal shape, the opsin cannot respond to light energy, which is called bleaching. When a large group of photopigments is bleached, the retina will send information as if opposing visual information is being perceived. After a bright flash of light, afterimages are usually seen in negative. The photoisomerization is reversed by a series of enzymatic changes so that the retinal responds to more light energy.

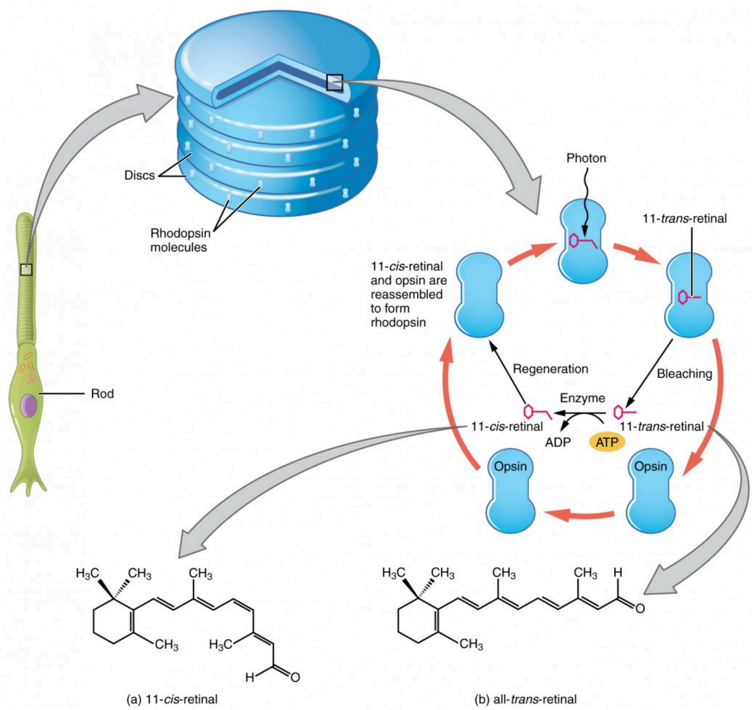


Figure 8.17. Retinal Isomers

The retinal molecule has two isomers, (a) one before a photon interacts with it and (b) one that is altered through photoisomerization.

The opsins are sensitive to limited wavelengths of light. Rhodopsin, the photopigment in rods, is most sensitive to light at a wavelength of 498 nm. The three color opsins have peak sensitivities of 564 nm, 534 nm, and 420 nm corresponding roughly to the primary colors of red, green, and blue (Figure 8.18). The absorbance of rhodopsin in the rods is much more sensitive than in the cone opsins; specifically, rods are sensitive to vision in low light conditions, and cones are sensitive to brighter conditions. In normal sunlight, rhodopsin will be constantly bleached while the cones are active. In a darkened room, there is not enough light to activate cone opsins, and vision is entirely dependent on rods. Rods are so sensitive to light that a single photon can result in an action potential from a rod's corresponding RGC. The three types of cone opsins, being sensitive to different wavelengths of light, provide us with color vision. By comparing the activity of the three different cones, the brain can extract color information from visual stimuli. For example, a bright blue light that has a wavelength of approximately 450 nm would activate the "red" cones minimally, the "green" cones marginally, and the "blue" cones predominantly. The relative activation of the three different cones is calculated by the brain, which perceives the color as blue. However, cones cannot react to low-intensity light, and rods do not sense the color of light. Therefore, our low-light vision is—in essence—in grayscale. In other words, in a dark room, everything appears as a shade of gray. If you think that you can see colors in the dark, it is most likely because your brain knows what color something is and is relying on that memory.

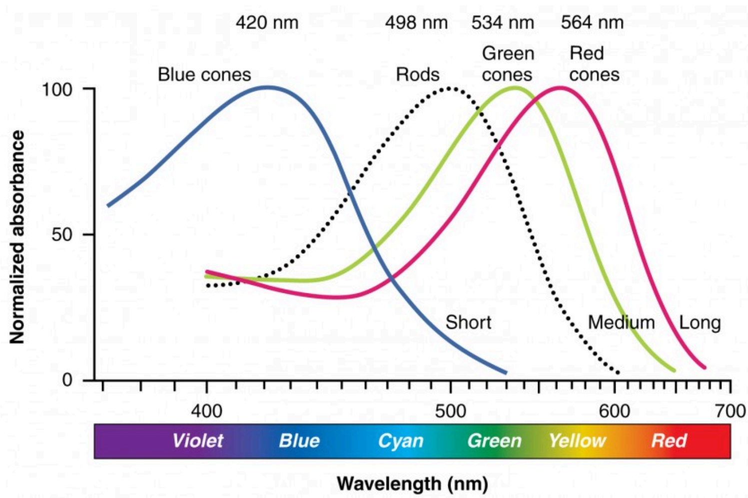


Figure 8.18. Comparison of Color Sensitivity of Photopigments
Comparing the peak sensitivity and absorbance spectra of the four photopigments suggests that they are most sensitive to particular wavelengths.

Age Related Changes to the Eye

While not true for all people, the changes that occur to the eye as a part of aging generally result in some type of vision problem. These changes are known to include a slight shrinkage of the eye, an increase in the amount of connective tissue present, degeneration of some cells, and reduced blood supply.

The loss of fat and connective tissue surround the eye causes wrinkles in the corners of the eyes and sagging skin around the eye. As muscles around the eye weaken eyelids no longer fully close causing the cornea to become dry, irritated, and inflamed.

Age Related Dysfunctions of the Eye

Presbyopia, also known as farsightedness, is the result of the gradual loss of lens elasticity, a flattening of its shape, and an increase in its density. Presbyopia is so common it affects nearly everyone over the age of 40.

Blindness affects 16% of the population over the age of 75 in one or both eyes. While blindness is not a result of aging the incidence of blindness does increase with age.

Glaucoma is the result of elevated pressure within the eye. The pressure is causes by deficient drainage of fluid from the anterior cavity of the eye. The pressure can squeeze shut blood vessels within the eye causing degeneration of the optic nerve fibers and resulting in blindness.

Diabetic retinopathy is another cause of blindness in the aging population. This condition is a complication of diabetes. In some diabetics contractile cells in the wall of retinal capillaries swell and rupture, weakening the vessels and allowing them to dilate and form small pouches called microaneurysms. As blood travels through the larger damaged capillaries adjacent capillaries carry less blood depriving areas of the eye of blood flow. Blindness may result as the disease progresses.

Cataracts are cloudy lens that block from entering the eye. About 90% of people over the age of 70 are said to have some degree of cataract formation. The lenses are composed of fibers that are continuously growing. As the lenses thicken the fibers condense and interfere with the passage of light. The most effective treatment for cataracts is surgical removal.

Age related macular degeneration is a disease of the macular area of the retina. The disease results in the loss of central vision. While the exact causes of macular degeneration are currently unknown, it is thought that the disease disrupts the blood flow between the retina and subretina.

The retina is largely held in place by pressure. As one ages and the retina no longer tightly fits in place. When this happens the nervous-tissue layer can separate from the pigment layer resulting in a **detached retina**.

52. Glossary: Special Senses

alkaloid
: substance, usually from a plant source, that is chemically basic with respect to pH and will stimulate bitter receptors

amacrine cell
: type of cell in the retina that connects to the bipolar cells near the outer synaptic layer and provides the basis for early image processing within the retina

ampulla
: in the ear, the structure at the base of a semicircular canal that contains the hair cells and cupula for transduction of rotational movement of the head

anosmia
: loss of the sense of smell; usually the result of physical disruption of the first cranial nerve

anterior corticospinal tract
: division of the corticospinal pathway that travels through the ventral (anterior) column of the spinal cord and controls axial musculature through the medial motor neurons in the ventral (anterior) horn

aqueous humor
: watery fluid that fills the anterior chamber containing the cornea, iris, ciliary body, and lens of the eye

ascending pathway
: fiber structure that relays sensory information from the periphery through the spinal cord and brain stem to other structures of the brain

association area
region of cortex connected to a primary sensory cortical area that further processes the information to generate more complex sensory perceptions

audition
sense of hearing

auricle
fleshy external structure of the ear

Betz cells
output cells of the primary motor cortex that cause musculature to move through synapses on cranial and spinal motor neurons

Broca's area
region of the frontal lobe associated with the motor commands necessary for speech production

basilar membrane
in the ear, the floor of the cochlear duct on which the organ of Corti sits

binocular depth cues
indications of the distance of visual stimuli on the basis of slight differences in the images projected onto either retina

bipolar cell
cell type in the retina that connects the photoreceptors to the RGCs

capsaicin
molecule that activates nociceptors by interacting with a temperature-sensitive ion channel and is the basis for "hot" sensations in spicy food

cerebral peduncles
segments of the descending motor pathway that make up the white matter of the ventral midbrain

cervical enlargement
region of the ventral (anterior) horn of the spinal cord that has a larger population of motor neurons for the greater number of and finer control of muscles of the upper limb

chemoreceptor
sensory receptor cell that is sensitive to chemical stimuli, such as in taste, smell, or pain

chief sensory nucleus
component of the trigeminal nuclei that is found in the pons

choroid
highly vascular tissue in the wall of the eye that supplies the outer retina with blood

ciliary body
smooth muscle structure on the interior surface of the iris that controls the shape of the lens through the zonule fibers

circadian rhythm
internal perception of the daily cycle of light and dark based on retinal activity related to sunlight

cochlea
auditory portion of the inner ear containing structures to transduce sound stimuli

cochlear duct
space within the auditory portion of the inner ear that contains the organ of Corti and is adjacent to the scala tympani and scala vestibuli on either side

cone photoreceptor
: one of the two types of retinal receptor cell that is specialized for color vision through the use of three photopigments distributed through three separate populations of cells

contralateral
: word meaning "on the opposite side," as in axons that cross the midline in a fiber tract

cornea
: fibrous covering of the anterior region of the eye that is transparent so that light can pass through it

corneal reflex
: protective response to stimulation of the cornea causing contraction of the orbicularis oculi muscle resulting in blinking of the eye

corticobulbar tract
: connection between the cortex and the brain stem responsible for generating movement

corticospinal tract
: connection between the cortex and the spinal cord responsible for generating movement

cupula
: specialized structure within the base of a semicircular canal that bends the stereocilia of hair cells when the head rotates by way of the relative movement of the enclosed fluid

decussate
: to cross the midline, as in fibers that project from one side of the body to the other

dorsal column system
: ascending tract of the spinal cord associated with fine touch and proprioceptive sensations

dorsal stream

connections between cortical areas from the occipital to parietal lobes that are responsible for the perception of visual motion and guiding movement of the body in relation to that motion

encapsulated ending

configuration of a sensory receptor neuron with dendrites surrounded by specialized structures to aid in transduction of a particular type of sensation, such as the lamellated corpuscles in the deep dermis and subcutaneous tissue

equilibrium

sense of balance that includes sensations of position and movement of the head

executive functions

cognitive processes of the prefrontal cortex that lead to directing goal-directed behavior, which is a precursor to executing motor commands

external ear

structures on the lateral surface of the head, including the auricle and the ear canal back to the tympanic membrane

exteroceptor

sensory receptor that is positioned to interpret stimuli from the external environment, such as photoreceptors in the eye or somatosensory receptors in the skin

extraocular muscle

one of six muscles originating out of the bones of the orbit and inserting into the surface of the eye which are responsible for moving the eye

extrapyramidal system

pathways between the brain and spinal cord that are separate from the corticospinal tract and are responsible for modulating the movements generated through that primary pathway

fasciculus cuneatus
lateral division of the dorsal column system composed of fibers from sensory neurons in the upper body

fasciculus gracilis
medial division of the dorsal column system composed of fibers from sensory neurons in the lower body

fibrous tunic
outer layer of the eye primarily composed of connective tissue known as the sclera and cornea

fovea
exact center of the retina at which visual stimuli are focused for maximal acuity, where the retina is thinnest, at which there is nothing but photoreceptors

free nerve ending
configuration of a sensory receptor neuron with dendrites in the connective tissue of the organ, such as in the dermis of the skin, that are most often sensitive to chemical, thermal, and mechanical stimuli

frontal eye fields
area of the prefrontal cortex responsible for moving the eyes to attend to visual stimuli

general sense
any sensory system that is distributed throughout the body and incorporated into organs of multiple other systems, such as the walls of the digestive organs or the skin

gustation
sense of taste

gustatory receptor cells
: sensory cells in the taste bud that transduce the chemical stimuli of gustation

hair cells
: mechanoreceptor cells found in the inner ear that transduce stimuli for the senses of hearing and balance

incus
: (also, anvil) ossicle of the middle ear that connects the malleus to the stapes

inferior colliculus
: last structure in the auditory brainstem pathway that projects to the thalamus and superior colliculus

inferior oblique
: extraocular muscle responsible for lateral rotation of the eye

inferior rectus
: extraocular muscle responsible for looking down

inner ear
: structure within the temporal bone that contains the sensory apparati of hearing and balance

inner segment
: in the eye, the section of a photoreceptor that contains the nucleus and other major organelles for normal cellular functions

inner synaptic layer
: layer in the retina where bipolar cells connect to RGCs

interaural intensity difference
: cue used to aid sound localization in the horizontal plane that compares the relative loudness of sounds at the two ears, because the ear closer to the sound source will hear a slightly

more intense sound

interaural time difference
: cue used to help with sound localization in the horizontal plane that compares the relative time of arrival of sounds at the two ears, because the ear closer to the sound source will receive the stimulus microseconds before the other ear

internal capsule
: segment of the descending motor pathway that passes between the caudate nucleus and the putamen

interoceptor
: sensory receptor that is positioned to interpret stimuli from internal organs, such as stretch receptors in the wall of blood vessels

ipsilateral
: word meaning on the same side, as in axons that do not cross the midline in a fiber tract

iris
: colored portion of the anterior eye that surrounds the pupil

kinesthesia
: sense of body movement based on sensations in skeletal muscles, tendons, joints, and the skin

lacrimal duct
: duct in the medial corner of the orbit that drains tears into the nasal cavity

lacrimal gland
: gland lateral to the orbit that produces tears to wash across the surface of the eye

lateral corticospinal tract
: division of the corticospinal pathway that travels through the

lateral column of the spinal cord and controls appendicular musculature through the lateral motor neurons in the ventral (anterior) horn

lateral geniculate nucleus
thalamic target of the RGCs that projects to the visual cortex

lateral rectus
extraocular muscle responsible for abduction of the eye

lens
component of the eye that focuses light on the retina

levator palpebrae superioris
muscle that causes elevation of the upper eyelid, controlled by fibers in the oculomotor nerve

lumbar enlargement
region of the ventral (anterior) horn of the spinal cord that has a larger population of motor neurons for the greater number of muscles of the lower limb

macula
enlargement at the base of a semicircular canal at which transduction of equilibrium stimuli takes place within the ampulla

malleus
(also, hammer) ossicle that is directly attached to the tympanic membrane

mechanoreceptor
receptor cell that transduces mechanical stimuli into an electrochemical signal

medial geniculate nucleus
thalamic target of the auditory brain stem that projects to the auditory cortex

medial lemniscus
fiber tract of the dorsal column system that extends from the nuclei gracilis and cuneatus to the thalamus, and decussates

medial rectus
extraocular muscle responsible for adduction of the eye

mesencephalic nucleus
component of the trigeminal nuclei that is found in the midbrain

middle ear
space within the temporal bone between the ear canal and bony labyrinth where the ossicles amplify sound waves from the tympanic membrane to the oval window

multimodal integration area
region of the cerebral cortex in which information from more than one sensory modality is processed to arrive at higher level cortical functions such as memory, learning, or cognition

neural tunic
layer of the eye that contains nervous tissue, namely the retina

nociceptor
receptor cell that senses pain stimuli

nucleus cuneatus
medullary nucleus at which first-order neurons of the dorsal column system synapse specifically from the upper body and arms

nucleus gracilis
medullary nucleus at which first-order neurons of the dorsal column system synapse specifically from the lower body and legs

odorant molecules
: volatile chemicals that bind to receptor proteins in olfactory neurons to stimulate the sense of smell

olfaction
: sense of smell

olfactory bulb
: central target of the first cranial nerve; located on the ventral surface of the frontal lobe in the cerebrum

olfactory epithelium
: region of the nasal epithelium where olfactory neurons are located

olfactory sensory neuron
: receptor cell of the olfactory system, sensitive to the chemical stimuli of smell, the axons of which compose the first cranial nerve

opsin
: protein that contains the photosensitive cofactor retinal for phototransduction

optic chiasm
: decussation point in the visual system at which medial retina fibers cross to the other side of the brain

optic disc
: spot on the retina at which RGC axons leave the eye and blood vessels of the inner retina pass

optic nerve
: second cranial nerve, which is responsible visual sensation

optic tract
: name for the fiber structure containing axons from the retina posterior to the optic chiasm representing their CNS location

organ of Corti
structure in the cochlea in which hair cells transduce movements from sound waves into electrochemical signals

osmoreceptor
receptor cell that senses differences in the concentrations of bodily fluids on the basis of osmotic pressure

ossicles
three small bones in the middle ear

otolith
gelatinous substance in the utricle and saccule of the inner ear that contains calcium carbonate crystals and into which the stereocilia of hair cells are embedded

outer segment
in the eye, the section of a photoreceptor that contains opsin molecules that transduce light stimuli

outer synaptic layer
layer in the retina at which photoreceptors connect to bipolar cells

oval window
membrane at the base of the cochlea where the stapes attaches, marking the beginning of the scala vestibuli

palpebral conjunctiva
membrane attached to the inner surface of the eyelids that covers the anterior surface of the cornea

papilla
for gustation, a bump-like projection on the surface of the tongue that contains taste buds

photoisomerization
chemical change in the retinal molecule that alters the bonding

so that it switches from the 11-*cis*-retinal isomer to the all-*trans*-retinal isomer

photon
individual "packet" of light

photoreceptor
receptor cell specialized to respond to light stimuli

premotor cortex
cortical area anterior to the primary motor cortex that is responsible for planning movements

primary sensory cortex
region of the cerebral cortex that initially receives sensory input from an ascending pathway from the thalamus and begins the processing that will result in conscious perception of that modality

proprioception
sense of position and movement of the body

proprioceptor
receptor cell that senses changes in the position and kinesthetic aspects of the body

pupil
open hole at the center of the iris that light passes through into the eye

pyramidal decussation
location at which corticospinal tract fibers cross the midline and segregate into the anterior and lateral divisions of the pathway

pyramids
segment of the descending motor pathway that travels in the anterior position of the medulla

receptor cell
: cell that transduces environmental stimuli into neural signals

red nucleus
: midbrain nucleus that sends corrective commands to the spinal cord along the rubrospinal tract, based on disparity between an original command and the sensory feedback from movement

reticulospinal tract
: extrapyramidal connections between the brain stem and spinal cord that modulate movement, contribute to posture, and regulate muscle tone

retinal ganglion cell (RGC)
: neuron of the retina that projects along the second cranial nerve

retinal
: cofactor in an opsin molecule that undergoes a biochemical change when struck by a photon (pronounced with a stress on the last syllable)

retina
: nervous tissue of the eye at which phototransduction takes place

rhodopsin
: photopigment molecule found in the rod photoreceptors

rod photoreceptor
: one of the two types of retinal receptor cell that is specialized for low-light vision

round window
: membrane that marks the end of the scala tympani

rubrospinal tract
: descending motor control pathway, originating in the red nucleus, that mediates control of the limbs on the basis of cerebellar processing

saccule
: structure of the inner ear responsible for transducing linear acceleration in the vertical plane

scala tympani
: portion of the cochlea that extends from the apex to the round window

scala vestibuli
: portion of the cochlea that extends from the oval window to the apex

sclera
: white of the eye

semicircular canals
: structures within the inner ear responsible for transducing rotational movement information

sensory homunculus
: topographic representation of the body within the somatosensory cortex demonstrating the correspondence between neurons processing stimuli and sensitivity

sensory modality
: a particular system for interpreting and perceiving environmental stimuli by the nervous system

solitary nucleus
: medullar nucleus that receives taste information from the facial and glossopharyngeal nerves

somatosensation
: general sense associated with modalities lumped together as touch

special sense
: any sensory system associated with a specific organ structure, namely smell, taste, sight, hearing, and balance

spinal trigeminal nucleus
: component of the trigeminal nuclei that is found in the medulla

spinothalamic tract
: ascending tract of the spinal cord associated with pain and temperature sensations

spiral ganglion
: location of neuronal cell bodies that transmit auditory information along the eighth cranial nerve

stapes
: (also, stirrup) ossicle of the middle ear that is attached to the inner ear

stereocilia
: array of apical membrane extensions in a hair cell that transduce movements when they are bent

stretch reflex
: response to activation of the muscle spindle stretch receptor that causes contraction of the muscle to maintain a constant length

submodality
: specific sense within a broader major sense such as sweet as a part of the sense of taste, or color as a part of vision

superior colliculus
: structure in the midbrain that combines visual, auditory, and somatosensory input to coordinate spatial and topographic representations of the three sensory systems

superior oblique
: extraocular muscle responsible for medial rotation of the eye

superior rectus
: extraocular muscle responsible for looking up

supplemental motor area
: cortical area anterior to the primary motor cortex that is responsible for planning movements

suprachiasmatic nucleus
: hypothalamic target of the retina that helps to establish the circadian rhythm of the body on the basis of the presence or absence of daylight

taste buds
: structures within a papilla on the tongue that contain gustatory receptor cells

tectorial membrane
: component of the organ of Corti that lays over the hair cells, into which the stereocilia are embedded

tectospinal tract
: extrapyramidal connections between the superior colliculus and spinal cord

thermoreceptor
: sensory receptor specialized for temperature stimuli

topographical
: relating to positional information

transduction
: process of changing an environmental stimulus into the electrochemical signals of the nervous system

trochlea
: cartilaginous structure that acts like a pulley for the superior oblique muscle

tympanic membrane
: ear drum

umami
: taste submodality for sensitivity to the concentration of amino acids; also called the savory sense

utricle
: structure of the inner ear responsible for transducing linear acceleration in the horizontal plane

vascular tunic
: middle layer of the eye primarily composed of connective tissue with a rich blood supply

ventral posterior nucleus
: nucleus in the thalamus that is the target of gustatory sensations and projects to the cerebral cortex

ventral stream
: connections between cortical areas from the occipital lobe to the temporal lobe that are responsible for identification of visual stimuli

vestibular ganglion
: location of neuronal cell bodies that transmit equilibrium information along the eighth cranial nerve

vestibular nuclei
: targets of the vestibular component of the eighth cranial nerve

vestibule

in the ear, the portion of the inner ear responsible for the sense of equilibrium

vestibulo-ocular reflex (VOR)

reflex based on connections between the vestibular system and the cranial nerves of eye movements that ensures images are stabilized on the retina as the head and body move

vestibulospinal tract

extrapyramidal connections between the vestibular nuclei in the brain stem and spinal cord that modulate movement and contribute to balance on the basis of the sense of equilibrium

visceral sense

sense associated with the internal organs

vision

special sense of sight based on transduction of light stimuli

visual acuity

property of vision related to the sharpness of focus, which varies in relation to retinal position

vitreous humor

viscous fluid that fills the posterior chamber of the eye

working memory

function of the prefrontal cortex to maintain a representation of information that is not in the immediate environment

zonule fibers

fibrous connections between the ciliary body and the lens

PART IX

CHAPTER 9: THE CIRCULATORY SYSTEM

53. Blood

Blood is a connective tissue. Like all connective tissues, it is made up of cellular elements and an extracellular matrix. The cellular elements—referred to as the formed elements—include red blood cells (RBCs), white blood cells (WBCs), and cell fragments called platelets. The extracellular matrix, called plasma, makes blood unique among connective tissues because it is fluid. This fluid, which is mostly water, perpetually suspends the formed elements and enables them to circulate throughout the body within the cardiovascular system.

Functions of Blood

The primary function of blood is to deliver oxygen and nutrients to and remove wastes from body cells, but that is only the beginning of the story. The specific functions of blood also include defense, distribution of heat, and maintenance of homeostasis.

Transportation

Nutrients from the foods you eat are absorbed in the digestive tract. Most of these travel in the bloodstream directly to the liver, where they are processed and released back into the bloodstream for delivery to body cells. Oxygen from the air you breathe diffuses into the blood, which moves from the lungs to the heart, which then pumps it out to the rest of the body. Moreover, endocrine glands scattered throughout the body release their products, called hormones, into the bloodstream, which carries them to distant target cells. Blood also picks up cellular wastes and byproducts, and transports them to various organs for removal. For instance, blood moves carbon dioxide to the lungs for exhalation from the body, and various waste products are transported to the kidneys and liver for excretion from the body in the form of urine or bile.

Defense

Many types of WBCs protect the body from external threats, such as disease-causing bacteria that have entered the bloodstream in a wound. Other WBCs seek out and destroy internal threats, such as cells with mutated DNA that could multiply to become cancerous, or body cells infected with viruses.

When damage to the vessels results in bleeding, blood platelets and certain proteins dissolved in the plasma, the fluid portion of the blood, interact to block the ruptured areas of the blood vessels involved. This protects the body from further blood loss.

Maintenance of Homeostasis

Body temperature is regulated via a classic negative-feedback loop. If you were exercising on a warm day, your rising core body temperature would trigger several homeostatic mechanisms, including increased transport of blood from your core to your body periphery, which is typically cooler. As blood passes through the vessels of the skin, heat would be dissipated to the environment, and the blood returning to your body core would be cooler. In contrast, on a cold day, blood is diverted away from the skin to maintain a warmer body core. In extreme cases, this may result in frostbite.

Blood also helps to maintain the chemical balance of the body. Proteins and other compounds in blood act as buffers, which thereby help to regulate the pH of body tissues. Blood also helps to regulate the water content of body cells.

Composition of Blood

You have probably had blood drawn from a superficial vein in your arm, which was then sent to a lab for analysis. Some of the most common blood tests—for instance, those measuring lipid or glucose levels in plasma—determine which substances are present within blood and in what quantities. Other blood tests check for the composition of the blood itself, including the quantities and types of formed elements.

One such test, called a hematocrit, measures the percentage of RBCs, clinically known as erythrocytes, in a blood sample. It is performed by spinning the blood sample in a specialized centrifuge, a process that causes the heavier elements suspended within the blood sample to separate from the lightweight, liquid plasma (Figure 9.1). Because the heaviest elements in blood are the erythrocytes, these settle at the very bottom of the hematocrit tube. Located above the erythrocytes is a pale, thin layer composed of the remaining formed elements of blood. These are the WBCs, clinically known as leukocytes, and the platelets, cell fragments also called thrombocytes. This layer is referred to as the buffy coat because of its color; it normally constitutes less than 1 percent of a blood sample. Above the buffy coat is the blood plasma, normally a pale, straw-colored fluid, which constitutes the remainder of the sample.

The volume of erythrocytes after centrifugation is also commonly referred to as packed cell volume (PCV). In normal blood, about 45 percent of a sample is erythrocytes. The hematocrit of any one sample can vary significantly, however, about 36–50 percent, according to gender and other factors. Normal hematocrit values for females range from 37 to 47, with a mean value of 41; for males, hematocrit ranges from 42 to 52, with a mean of 47. The percentage of other formed elements, the WBCs and platelets, is extremely small so it is not normally considered with the hematocrit. So the mean plasma percentage is the percent of blood that is not erythrocytes: for females, it is approximately 59 (or 100 minus 41), and for males, it is approximately 53 (or 100 minus 47).

Composition of Blood

The cellular elements of blood include a vast number of erythrocytes and comparatively fewer leukocytes and platelets. Plasma is the fluid in which the formed elements are suspended. A sample of blood spun in a centrifuge reveals that plasma is the lightest component. It floats at the top of the tube separated from the heaviest elements, the erythrocytes, by a buffy coat of leukocytes and platelets. Hematocrit is the percentage of the total sample that is comprised of erythrocytes. Depressed and elevated hematocrit levels are shown for comparison.

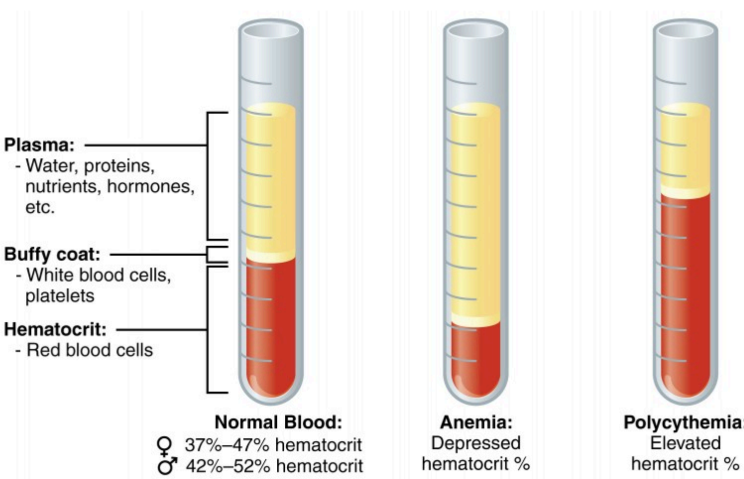


Figure 9.1: Composition of Blood

Characteristics of Blood

When you think about blood, the first characteristic that probably comes to mind is its color. Blood that has just taken up oxygen in the lungs is bright red, and blood that has released oxygen in the tissues is a more dusky red. This is because hemoglobin is a pigment that changes color, depending upon the degree of oxygen saturation.

Blood is viscous and somewhat sticky to the touch. It has a viscosity approximately five times greater than water. Viscosity is a measure of a fluid's thickness or resistance to flow, and is influenced by the presence of the plasma proteins and formed elements within the blood. The viscosity of blood has a dramatic impact on blood pressure and flow. Consider the difference in flow between water and honey. The more viscous honey would demonstrate a greater resistance to flow than the less viscous water. The same principle applies to blood.

The normal temperature of blood is slightly higher than normal body temperature—about 38 °C (or 100.4 °F), compared to 37 °C (or 98.6 °F) for an internal body temperature reading, although daily variations of 0.5 °C are normal. Although the surface of blood vessels is relatively smooth, as blood flows through them, it experiences some friction and resistance, especially as vessels age and lose their elasticity, thereby producing heat. This accounts for its slightly higher temperature.

The pH of blood averages about 7.4; however, it can range from 7.35 to 7.45 in a healthy person. Blood is therefore somewhat more basic (alkaline) on a chemical scale than pure water, which has a pH of 7.0. Blood contains numerous buffers that actually help to regulate pH.

Blood constitutes approximately 8 percent of adult body weight. Adult males typically average about 5 to 6 liters of blood. Females average 4–5 liters.

Blood Plasma

Like other fluids in the body, plasma is composed primarily of water: In fact, it is about 92 percent water. Dissolved or suspended within this water is a mixture of substances, most of which are proteins. There are literally hundreds of substances dissolved or suspended in the plasma, although many of them are found only in very small quantities.

Plasma Proteins

About 7 percent of the volume of plasma—nearly all that is not water—is made of proteins. These include several plasma proteins (proteins that are unique to the plasma), plus a much smaller number of regulatory proteins, including enzymes and some hormones. The major components of plasma are summarized in Table 9.1.

The three major groups of plasma proteins are as follows:

- Albumin is the most abundant of the plasma proteins. Manufactured by the liver, albumin molecules serve as binding proteins—transport vehicles for fatty acids and steroid hormones. Recall that lipids are hydrophobic; however, their binding to albumin enables their transport in the watery plasma. Albumin is also the most significant contributor to the osmotic pressure of blood; that is, its presence holds water inside the blood vessels and draws water from the tissues, across blood vessel walls, and into the bloodstream. This in turn helps to maintain both blood volume and blood pressure. Albumin normally accounts for approximately 54 percent of the total plasma protein content, in clinical levels of 3.5–5.0 g/dL blood.

- The second most common plasma proteins are the globulins. A heterogeneous group, there are three main subgroups known as alpha, beta, and gamma globulins. The alpha and beta globulins transport iron, lipids, and the fat-soluble vitamins A, D, E, and K to the cells; like albumin, they also contribute to osmotic pressure. The gamma globulins are proteins involved in immunity and are better known as an antibodies or immunoglobulins. Although other plasma proteins are produced by the liver, immunoglobulins are produced by specialized leukocytes known as plasma cells. (Seek additional content for more information about immunoglobulins.) Globulins make up approximately 38 percent of the total plasma protein volume, in clinical levels of 1.0–1.5 g/dL blood.
- The least abundant plasma protein is fibrinogen. Like albumin and the alpha and beta globulins, fibrinogen is produced by the liver. It is essential for blood clotting, a process described later in this chapter. Fibrinogen accounts for about 7 percent of the total plasma protein volume, in clinical levels of 0.2–0.45 g/dL blood.

Other Plasma Solutes

In addition to proteins, plasma contains a wide variety of other substances. These include various electrolytes, such as sodium, potassium, and calcium ions; dissolved gases, such as oxygen, carbon dioxide, and nitrogen; various organic nutrients, such as vitamins, lipids, glucose, and amino acids; and metabolic wastes. All of these nonprotein solutes combined contribute approximately 1 percent to the total volume of plasma.

Component and % of blood	Subcomponent and % of component	Type and % (where appropriate)	Site of production	Major function(s)
Plasma 46–63 percent	Water 92 percent	Fluid	Absorbed by intestinal tract or produced by metabolism	Transport medium
	Plasma proteins 7 percent	Albumin 54–60 percent	Liver	Maintain osmotic concentration, transport lipid molecules
		Globulins 35–38 percent	Alpha globulins—liver	Transport, maintain osmotic concentration
			Beta globulins—liver	Transport, maintain osmotic concentration
			Gamma globulins (immunoglobulins) —plasma cells	Immune responses
		Fibrinogen 4–7 percent	Liver	Blood clotting in hemostasis
	Regulatory proteins <1 percent	Hormones and enzymes	Various sources	Regulate various body functions
	Other solutes 1 percent	Nutrients, gases, and wastes	Absorbed by intestinal tract, exchanged in respiratory system, or produced by cells	Numerous and varied
Formed elements 37–54 percent	Erythrocytes 99 percent	Erythrocytes	Red bone marrow	Transport gases, primarily oxygen and some carbon dioxide
	Leukocytes <1 percent Platelets <1 percent	Granular leukocytes: neutrophils eosinophils basophils	Red bone marrow	Nonspecific immunity
		Agranular leukocytes: lymphocytes monocytes	Lymphocytes: bone marrow and lymphatic tissue	Lymphocytes: specific immunity
			Monocytes: red bone marrow	Monocytes: nonspecific immunity
	Platelets <1 percent		Megakaryocytes: red bone marrow	Hemostasis

Table 9.1: Major Blood Components

- Medical technologists (MT), also known as clinical laboratory technologists (CLT), typically hold a bachelor's degree and certification from an accredited training program. They perform a wide variety of tests on various body fluids, including blood. The information they provide is essential to the primary care providers in determining a diagnosis and in monitoring the course of a disease and response to treatment.
- Medical laboratory technicians (MLT) typically have an associate's degree but may perform duties similar to those of an MT.
- Medical laboratory assistants (MLA) spend the majority of their time processing samples and carrying out routine assignments within the lab. Clinical training is required, but a degree may not be essential to obtaining a position.

54. Heart

The vital importance of the heart is obvious. If one assumes an average rate of contraction of 75 contractions per minute, a human heart would contract approximately 108,000 times in one day, more than 39 million times in one year, and nearly 3 billion times during a 75-year lifespan. Each of the major pumping chambers of the heart ejects approximately 70 mL blood per contraction in a resting adult. This would be equal to 5.25 liters of fluid per minute and approximately 14,000 liters per day. Over one year, that would equal 10,000,000 liters or 2.6 million gallons of blood sent through roughly 60,000 miles of vessels. In order to understand how that happens, it is necessary to understand the anatomy and physiology of the heart.

Location of the Heart

The human heart is located within the thoracic cavity, medially between the lungs in the space known as the mediastinum. Figure 9.2 shows the position of the heart within the thoracic cavity. Within the mediastinum, the heart is separated from the other mediastinal structures by a tough membrane known as the pericardium, or pericardial sac, and sits in its own space called the pericardial cavity. The dorsal surface of the heart lies near the bodies of the vertebrae, and its anterior surface sits deep to the sternum and costal cartilages. The great veins, the superior and inferior venae cavae, and the great arteries, the aorta and pulmonary trunk, are attached to the superior surface of the heart, called the base. The base of the heart is located at the level of the third costal cartilage, as seen in Figure 9.2. The inferior tip of the heart, the apex, lies just to the left of the sternum between the junction of the fourth and fifth ribs near their articulation with the costal cartilages. The right side of the heart is deflected anteriorly, and the left side is deflected posteriorly. It is important to remember the position and orientation of the heart when placing a stethoscope on the chest of a patient and listening for heart sounds, and also when looking at images taken from a midsagittal perspective. The slight deviation of the apex to the left is reflected in a depression in the medial surface of the inferior lobe of the left lung, called the cardiac notch.

Position of the Heart in the Thorax

The heart is located within the thoracic cavity, medially between the lungs in the mediastinum. It is about the size of a fist, is broad at the top, and tapers toward the base.

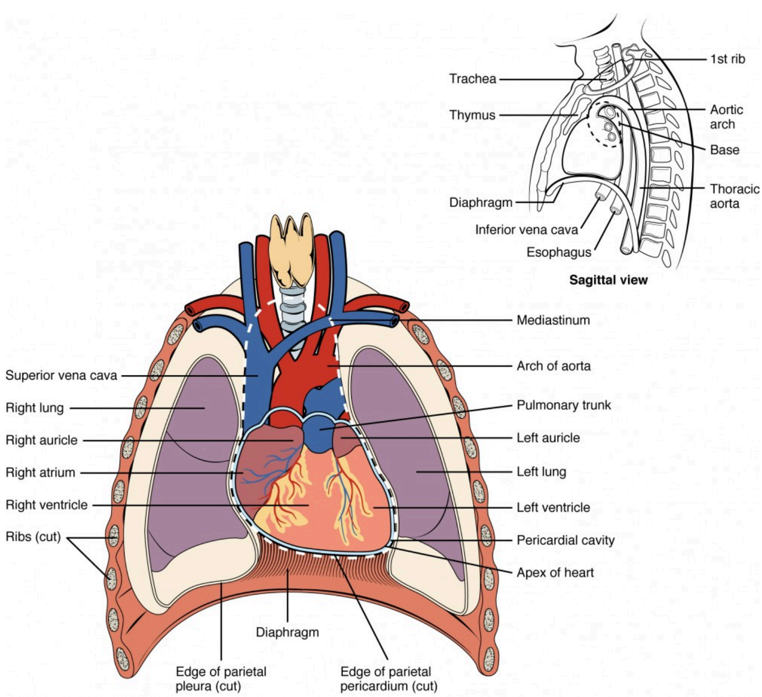


Figure 9.2: Location of the Heart

Everyday Connection

CPR

The position of the heart in the torso between the vertebrae and sternum (see Figure 9.2 above for the position of the heart within the thorax) allows for individuals to apply an emergency technique known as cardiopulmonary resuscitation (CPR) if the heart of a patient should stop. By applying pressure with the flat portion of one hand on the sternum in the area between the lines in Figure 9.3, it is possible to manually compress the blood within the heart enough to push some of the blood within it into the pulmonary and systemic circuits. This is particularly critical for the brain, as irreversible damage and death of neurons occur within minutes of loss of blood flow. Current standards call for compression of the chest at least 5 cm deep and at a rate of 100 compressions per minute, a rate equal to the beat in "Staying Alive," recorded in 1977 by the Bee Gees. If you are unfamiliar with this song, a version is available on www.youtube.com. At this stage, the emphasis is on performing high-quality chest compressions, rather than providing artificial respiration. CPR is generally performed until the patient regains spontaneous contraction or is declared dead by an experienced healthcare professional.

When performed by untrained or overzealous individuals, CPR can result in broken ribs or a broken sternum, and can inflict additional severe damage on the patient. It is also possible, if the hands are placed too low on the sternum, to manually drive the xiphoid process into the liver, a consequence that may prove fatal for the patient. Proper training is essential. This proven life-sustaining technique is so valuable that virtually all medical personnel as well as concerned members of the public should be certified and routinely recertified in its application. CPR courses are offered at a variety of locations, including colleges, hospitals, the American Red Cross, and some commercial companies. They normally include practice of the compression technique on a mannequin.

CPR Technique

If the heart should stop, CPR can maintain the flow of blood until the heart resumes beating. By applying pressure to the sternum, the blood within the heart will be squeezed out of the heart and into the circulation. Proper positioning of the hands on the sternum to perform CPR would be between the lines at T4 and T9.

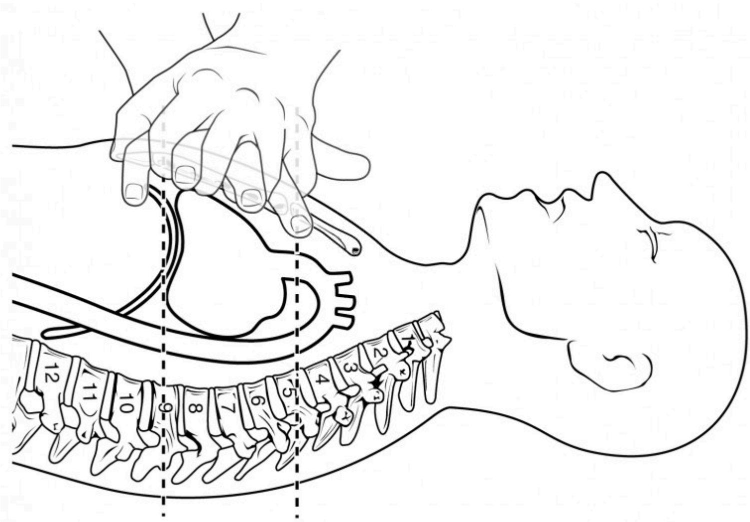


Figure 9.3: Proper CPR Position

Visit the [American Heart Association website](#)to help locate a course near your home in the United States. There are also many other national and regional heart associations that offer the same service, depending upon the location.

Shape and Size of the Heart

The shape of the heart is similar to a pinecone, rather broad at the superior surface and tapering to the apex. A typical heart is approximately the size of your fist: 12 cm (5 in) in length, 8 cm (3.5 in) wide, and 6 cm (2.5 in) in thickness. Given the size difference between most members of the sexes, the weight of a female heart is approximately 250–300 grams (9 to 11 ounces), and the weight of a male heart is approximately 300–350 grams (11 to 12 ounces). The heart of a well-trained athlete, especially one specializing in aerobic sports, can be considerably larger than this. Cardiac muscle responds to exercise in a manner similar to that of skeletal muscle. That is, exercise results in the addition of protein myofilaments that increase the size of the individual cells without increasing their numbers, a concept called hypertrophy. Hearts of athletes can pump blood more effectively at lower rates than those of nonathletes. Enlarged hearts are not always a result of exercise; they can result from pathologies, such as hypertrophic cardiomyopathy. The cause of an abnormally enlarged heart muscle is unknown, but the condition is often undiagnosed and can cause sudden death in apparently otherwise healthy young people.

Chambers and Circulation through the Heart

The human heart consists of four chambers: The left side and the right side each have one atrium and one ventricle. Each of the upper chambers, the right atrium (plural = atria) and the left atrium, acts as a receiving chamber and contracts to push blood into the lower chambers, the right ventricle and the left ventricle. The ventricles serve as the primary pumping chambers of the heart, propelling blood to the lungs or to the rest of the body.

There are two distinct but linked circuits in the human circulation called the pulmonary and systemic circuits. Although both circuits transport blood and everything it carries, we can initially view the circuits from the point of view of gases. The pulmonary circuit transports blood to and from the lungs, where it picks up oxygen and delivers carbon dioxide for exhalation. The systemic circuit transports oxygenated blood to virtually all of the tissues of the body and returns relatively deoxygenated blood and carbon dioxide to the heart to be sent back to the pulmonary circulation.

The right ventricle pumps deoxygenated blood into the pulmonary trunk, which leads toward the lungs and bifurcates into the left and right pulmonary arteries. These vessels in turn branch many times before reaching the pulmonary capillaries, where gas exchange occurs: Carbon dioxide exits the blood and oxygen enters. The pulmonary trunk arteries and their branches are the only arteries in the post-natal body that carry relatively deoxygenated blood. Highly oxygenated blood returning from the pulmonary capillaries in the lungs passes through a series of vessels that join together to form the pulmonary veins—the only post-natal veins in the body that carry highly oxygenated blood. The pulmonary veins conduct blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and on to the many branches of the systemic circuit. Eventually, these vessels will lead to the systemic capillaries, where exchange with the tissue fluid and cells of the body occurs. In this case, oxygen and nutrients exit the systemic capillaries to be used by the cells in their metabolic processes, and carbon dioxide and waste products will enter the blood.

The blood exiting the systemic capillaries is lower in oxygen concentration than when it entered. The capillaries will ultimately unite to form venules, joining to form ever-larger veins, eventually flowing into the two major systemic veins, the superior vena cava and the inferior vena cava, which return blood to the right atrium. The blood in the superior and inferior venae cavae flows into the right atrium, which pumps blood into the right ventricle. This process of blood circulation continues as long as the individual remains alive. Understanding the flow of blood through the pulmonary and systemic circuits is critical to all health professions.

Dual System of the Human Blood Circulation

Blood flows from the right atrium to the right ventricle, where it is pumped into the pulmonary circuit. The blood in the pulmonary artery branches is low in oxygen but relatively high in carbon dioxide. Gas exchange occurs in the pulmonary capillaries (oxygen into the blood, carbon dioxide out), and blood high in oxygen and low in carbon dioxide is returned to the left atrium. From here, blood enters the left ventricle, which pumps it into the systemic circuit. Following exchange in the systemic capillaries (oxygen and nutrients out of the capillaries and carbon dioxide and wastes in), blood returns to the right atrium and the cycle is repeated.

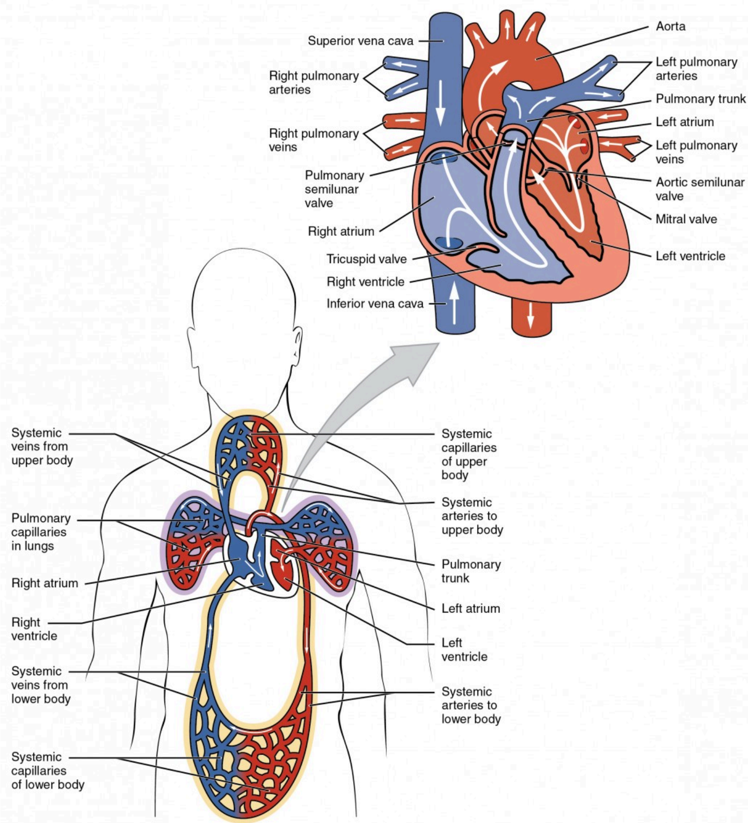


Figure 9.4: Dual System of the Human Blood Circulation

Membranes, Surface Features, and Layers

Our exploration of more in-depth heart structures begins by examining the membrane that surrounds the heart, the prominent surface features of the heart, and the layers that form the wall of the heart. Each of these components plays its own unique role in terms of function.

Membranes

The membrane that directly surrounds the heart and defines the pericardial cavity is called the pericardium or pericardial sac. It also surrounds the “roots” of the major vessels, or the areas of closest proximity to the heart. The pericardium, which literally translates as “around the heart,” consists of two distinct sublayers: the sturdy outer fibrous pericardium and the inner serous pericardium. The fibrous pericardium is made of tough, dense connective tissue that protects the heart and maintains its position in the thorax. The more delicate serous pericardium consists of two layers: the parietal pericardium, which is fused to the fibrous pericardium, and an inner visceral pericardium, or epicardium, which is fused to the heart and is part of the heart wall. The pericardial cavity, filled with lubricating serous fluid, lies between the epicardium and the pericardium.

In most organs within the body, visceral serous membranes such as the epicardium are microscopic. However, in the case of the heart, it is not a microscopic layer but rather a macroscopic layer, consisting of a simple squamous epithelium called a mesothelium, reinforced with loose, irregular, or areolar connective tissue that attaches to the pericardium. This mesothelium secretes the lubricating serous fluid that fills the pericardial cavity and reduces friction as the heart contracts.

Pericardial Membranes and Layers of the Heart Wall

The pericardial membrane that surrounds the heart consists of three layers and the pericardial cavity. The heart wall also consists of three layers. The pericardial membrane and the heart wall share the epicardium.

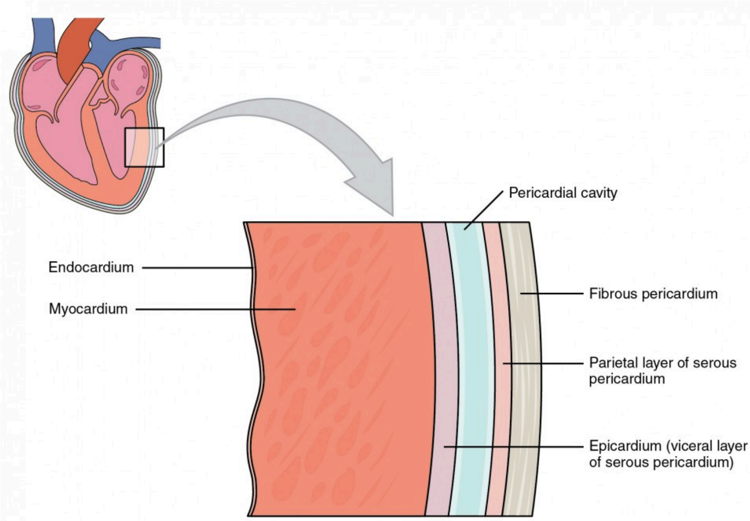


Figure 9.5: Pericardial Membranes and Layers of the Heart Wall

Surface Features of the Heart

Inside the pericardium, the surface features of the heart are visible, including the four chambers. There is a superficial leaf-like extension of the atria near the superior surface of the heart, one on each side, called an auricle—a name that means "ear like"—because its shape resembles the external ear of a human (Figure 9.6). Auricles are relatively thin-walled structures that can fill with blood and empty into the atria or upper chambers of the heart. You may also hear them referred to as atrial appendages. Also prominent is a series of fat-filled grooves, each of which is known as a sulcus (plural = sulci), along the superior surfaces of the heart. Major coronary blood vessels are located in these sulci. The deep coronary sulcus is located between the atria and ventricles. Located between the left and right ventricles are two additional sulci that are not as deep as the coronary sulcus. The anterior interventricular sulcus is visible on the anterior surface of the heart, whereas the posterior interventricular sulcus is visible on the posterior surface of the heart. Figure 9.6 illustrates anterior and posterior views of the surface of the heart.

External Anatomy of the Heart

Inside the pericardium, the surface features of the heart are visible.

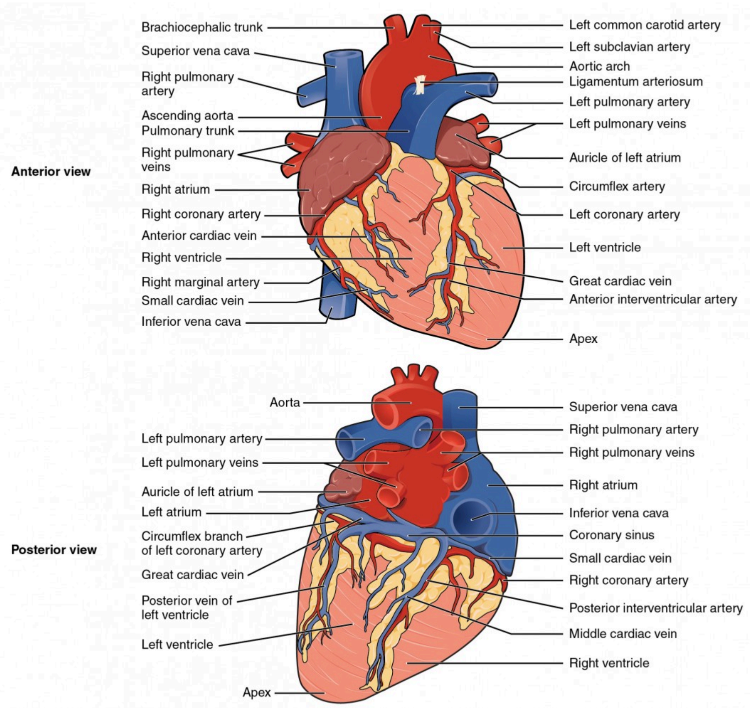


Figure 9.6: External Anatomy of the Heart

Layers

The wall of the heart is composed of three layers of unequal thickness. From superficial to deep, these are the epicardium, the myocardium, and the endocardium. The outermost layer of the wall of the heart is also the innermost layer of the pericardium, the epicardium, or the visceral pericardium discussed earlier.

The middle and thickest layer is the myocardium, made largely of cardiac muscle cells. It is built upon a framework of collagenous fibers, plus the blood vessels that supply the myocardium and the nerve fibers that help regulate the heart. It is the contraction of the myocardium that pumps blood through the heart and into the major arteries. The muscle pattern is elegant and complex, as the muscle cells swirl and spiral around the chambers of the heart. They form a figure 8 pattern around the atria and around the bases of the great vessels. Deeper ventricular muscles also form a figure 8 around the two ventricles and proceed toward the apex. More superficial layers of ventricular muscle wrap around both ventricles. This complex swirling pattern allows the heart to pump blood more effectively than a simple linear pattern would. The i mage belowillustrates the arrangement of muscle cells.

Heart Musculature

The swirling pattern of cardiac muscle tissue contributes significantly to the heart’s ability to pump blood effectively.

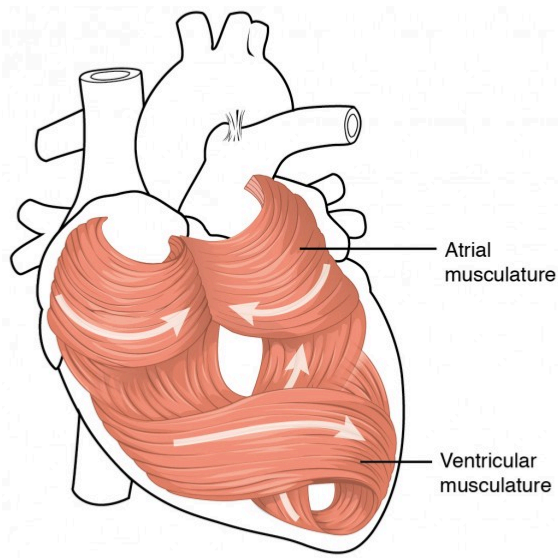


Figure 9.7: Heart Musculature

Although the ventricles on the right and left sides pump the same amount of blood per contraction, the muscle of the left ventricle is much thicker and better developed than that of the right ventricle. In order to overcome the high resistance required to pump blood into the long systemic circuit, the left ventricle must generate a great amount of pressure. The right ventricle does not need to generate as much pressure, since the pulmonary circuit is shorter and provides less resistance. The image below illustrates the differences in muscular thickness needed for each of the ventricles.

Differences in Ventricular Muscle Thickness

The myocardium in the left ventricle is significantly thicker than that of the right ventricle. Both ventricles pump the same amount of blood, but the left ventricle must generate a much greater pressure to overcome greater resistance in the systemic circuit. The ventricles are shown in both relaxed and contracting states. Note the differences in the relative size of the lumens, the region inside each ventricle where the blood is contained.

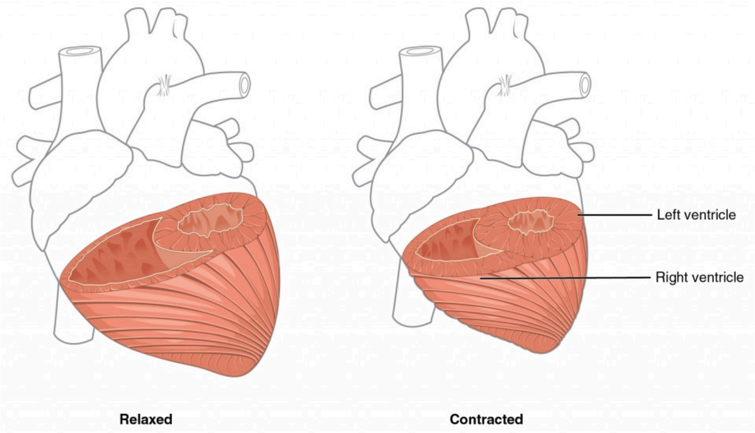


Figure 9.8: Differences in Ventricular Muscle Thickness

The innermost layer of the heart wall, the endocardium, is joined to the myocardium with a thin layer of connective tissue. The endocardium lines the chambers where the blood circulates and covers the heart valves. It is made of simple squamous epithelium called endothelium, which is continuous with the endothelial lining of the blood vessels.

Once regarded as a simple lining layer, recent evidence indicates that the endothelium of the endocardium and the coronary capillaries may play active roles in regulating the contraction of the muscle within the myocardium. The endothelium may also regulate the growth patterns of the cardiac muscle cells throughout life, and the endothelins it secretes create an environment in the surrounding tissue fluids that regulates ionic concentrations and states of contractility. Endothelins are potent vasoconstrictors and, in a normal individual, establish a homeostatic balance with other vasoconstrictors and vasodilators.

Internal Structure of the Heart

Recall that the heart's contraction cycle follows a dual pattern of circulation—the pulmonary and systemic circuits—because of the pairs of chambers that pump blood into the circulation. In order to develop a more precise understanding of cardiac function, it is first necessary to explore the internal anatomical structures in more detail.

Septa of the Heart

The word septum is derived from the Latin for "something that encloses;" in this case, a septum (plural = septa) refers to a wall or partition that divides the heart into chambers. The septa are physical extensions of the myocardium lined with endocardium. Located between the two atria is the interatrial septum. Normally in an adult heart, the interatrial septum bears an oval-shaped depression known as the fossa ovalis, a remnant of an opening in the fetal heart known as the foramen ovale. The foramen ovale allowed blood in the fetal heart to pass directly from the right atrium to the left atrium, allowing some blood to bypass the pulmonary circuit. Within seconds after birth, a flap of tissue known as the septum primum that previously acted as a valve closes the foramen ovale and establishes the typical cardiac circulation pattern.

Between the two ventricles is a second septum known as the interventricular septum. Unlike the interatrial septum, the interventricular septum is normally intact after its formation during fetal development. It is substantially thicker than the interatrial septum, since the ventricles generate far greater pressure when they contract.

The septum between the atria and ventricles is known as the atrioventricular septum. It is marked by the presence of four openings that allow blood to move from the atria into the ventricles and from the ventricles into the pulmonary trunk and aorta. Located in each of these openings between the atria and ventricles is a valve, a specialized structure that ensures one-way flow of blood. The valves between the atria and ventricles are known generically as atrioventricular valves. The valves at the openings that lead to the pulmonary trunk and aorta are known generically as semilunar valves. The interventricular septum is visible in the image below. In this figure, the atrioventricular septum has been removed to better show the bicupid and tricuspid valves; the interatrial septum is not visible, since its location is covered by the aorta and pulmonary trunk. Since these openings and valves structurally weaken the atrioventricular septum, the remaining tissue is heavily reinforced with dense connective tissue called the cardiac skeleton, or skeleton of the heart. It includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta, and serve as the point of attachment for the heart valves. The cardiac skeleton also provides an important boundary in the heart electrical conduction system.

Internal Structures of the Heart

This anterior view of the heart shows the four chambers, the major vessels and their early branches, as well as the valves. The presence of the pulmonary trunk and aorta covers the interatrial septum, and the atrioventricular septum is cut away to show the atrioventricular valves.

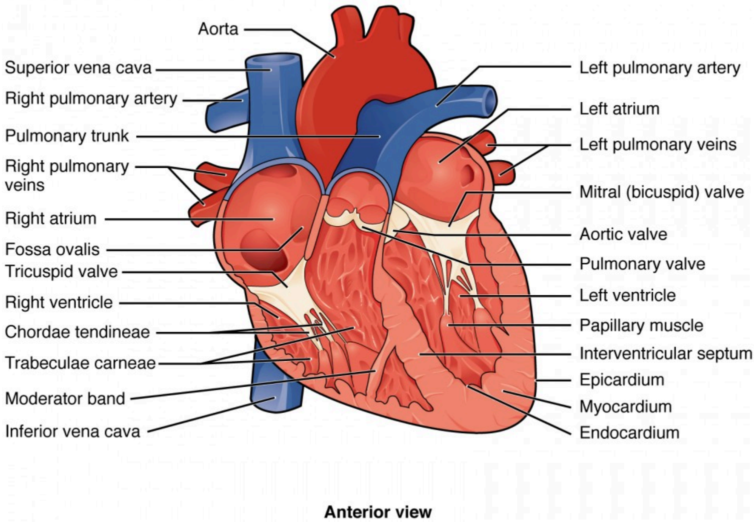


Figure 9.9: Interior Structure of the Heart

Right Atrium

The right atrium serves as the receiving chamber for blood returning to the heart from the systemic circulation. The two major systemic veins, the superior and inferior venae cavae, and the large coronary vein called the coronary sinus that drains the heart myocardium empty into the right atrium. The superior vena cava drains blood from regions superior to the diaphragm: the head, neck, upper limbs, and the thoracic region. It empties into the superior and posterior portions of the right atrium. The inferior vena cava drains blood from areas inferior to the diaphragm: the lower limbs and abdominopelvic region of the body. It, too, empties into the posterior portion of the atria, but inferior to the opening of the superior vena cava. Immediately superior and slightly medial to the opening of the inferior vena cava on the posterior surface of the atrium is the opening of the coronary sinus. This thin-walled vessel drains most of the coronary veins that return systemic blood from the heart. The majority of the internal heart structures discussed in this and subsequent sections are illustrated in the image above.

While the bulk of the internal surface of the right atrium is smooth, the depression of the fossa ovalis is medial, and the anterior surface demonstrates prominent ridges of muscle called the pectinate muscles. The right auricle also has pectinate muscles. The left atrium does not have pectinate muscles except in the auricle.

The atria receive venous blood on a nearly continuous basis, preventing venous flow from stopping while the ventricles are contracting. While most ventricular filling occurs while the atria are relaxed, they do demonstrate a contractile phase and actively pump blood into the ventricles just prior to ventricular contraction. The opening between the atrium and ventricle is guarded by the tricuspid valve.

Right Ventricle

The right ventricle receives blood from the right atrium through the tricuspid valve. Each flap of the valve is attached to strong strands of connective tissue, the chordae tendineae, literally "tendinous cords," or sometimes more poetically referred to as "heart strings." There are several chordae tendineae associated with each of the flaps. They are composed of approximately 80 percent collagenous fibers with the remainder consisting of elastic fibers and endothelium. They connect each of the flaps to a papillary muscle that extends from the inferior ventricular surface. There are three papillary muscles in the right ventricle, called the anterior, posterior, and septal muscles, which correspond to the three sections of the valves.

When the myocardium of the ventricle contracts, pressure within the ventricular chamber rises. Blood, like any fluid, flows from higher pressure to lower pressure areas, in this case, toward the pulmonary trunk and the atrium. To prevent any potential backflow, the papillary muscles also contract, generating tension on the chordae tendineae. This prevents the flaps of the valves from being forced into the atria and regurgitation of the blood back into the atria during ventricular contraction.The image below shows papillary muscles and chordae tendineae attached to the tricuspid valve.

Chordae Tendineae and Papillary Muscles

In this frontal section, you can see papillary muscles attached to the tricuspid valve on the right as well as the mitral valve on the left via chordae tendineae. (credit: modification of work by "PV KS"/flickr.com)

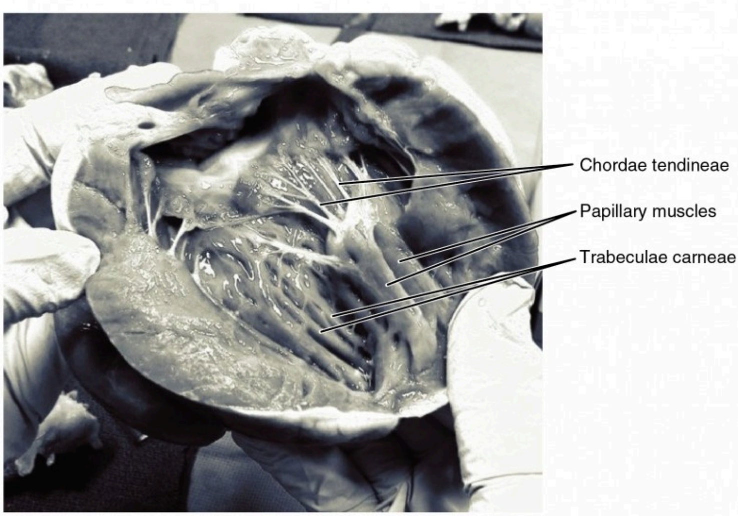


Figure 9.10: Chordae Tendineae and Papillary Muscles

The walls of the ventricle are lined with trabeculae carneae, ridges of cardiac muscle covered by endocardium. In addition to these muscular ridges, a band of cardiac muscle, also covered by endocardium, known as the moderator band reinforces the thin walls of the right ventricle and plays a crucial role in cardiac conduction. It arises from the inferior portion of the interventricular septum and crosses the interior space of the right ventricle to connect with the inferior papillary muscle.

When the right ventricle contracts, it ejects blood into the pulmonary trunk, which branches into the left and right pulmonary arteries that carry it to each lung. The superior surface of the right ventricle begins to taper as it approaches the pulmonary trunk. At the base of the pulmonary trunk is the pulmonary semilunar valve that prevents backflow from the pulmonary trunk.

Left Atrium

After exchange of gases in the pulmonary capillaries, blood returns to the left atrium high in oxygen via one of the four pulmonary veins. While the left atrium does not contain pectinate muscles, it does have an auricle that includes these pectinate ridges. Blood flows nearly continuously from the pulmonary veins back into the atrium, which acts as the receiving chamber, and from here through an opening into the left ventricle. Most blood flows passively into the heart while both the atria and ventricles are relaxed, but toward the end of the ventricular relaxation period, the left atrium will contract, pumping blood into the ventricle. This atrial contraction accounts for approximately 20 percent of ventricular filling. The opening between the left atrium and ventricle is guarded by the mitral valve.

Left Ventricle

Recall that, although both sides of the heart will pump the same amount of blood, the muscular layer is much thicker in the left ventricle compared to the right. Like the right ventricle, the left also has trabeculae carneae, but there is no moderator band. The mitral valve is connected to papillary muscles via chordae tendineae. There are two papillary muscles on the left—the anterior and posterior—as opposed to three on the right.

The left ventricle is the major pumping chamber for the systemic circuit; it ejects blood into the aorta through the aortic semilunar valve.

Heart Valve Structure and Function

A transverse section through the heart slightly above the level of the atrioventricular septum reveals all four heart valves along the same plane. The valves ensure unidirectional blood flow through the heart. Between the right atrium and the right ventricle is the right atrioventricular valve, or tricuspid valve. It typically consists of three flaps, or leaflets, made of endocardium reinforced with additional connective tissue. The flaps are connected by chordae tendineae to the papillary muscles, which control the opening and closing of the valves.

Heart Valves

With the atria and major vessels removed, all four valves are clearly visible, although it is difficult to distinguish the three separate cusps of the tricuspid valve.

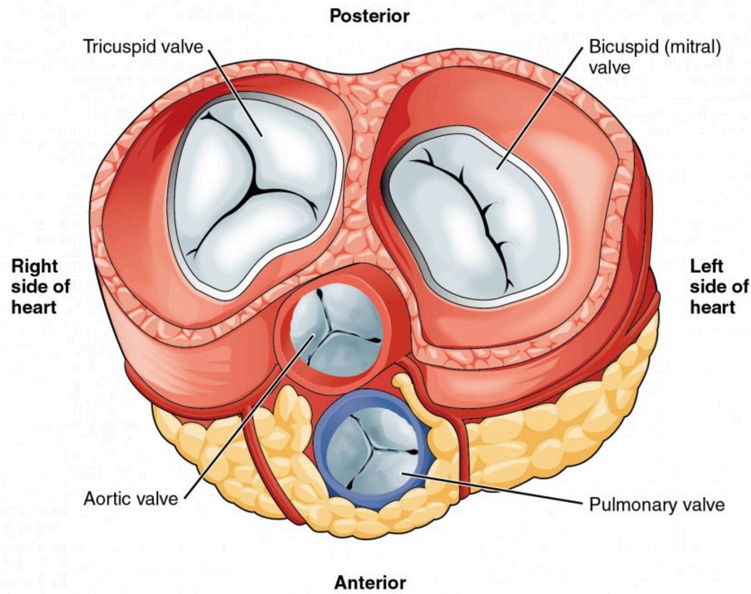


Figure 9.11: Heart Valves

Emerging from the right ventricle at the base of the pulmonary trunk is the pulmonary semilunar valve, or the pulmonary valve; it is also known as the pulmonic valve or the right semilunar valve. The pulmonary valve is comprised of three small flaps of endothelium reinforced with connective tissue. When the ventricle relaxes, the pressure differential causes blood to flow back into the ventricle from the pulmonary trunk. This flow of blood fills the pocket-like flaps of the pulmonary valve, causing the valve to close and producing an audible sound. Unlike the atrioventricular valves, there are no papillary muscles or chordae tendineae associated with the pulmonary valve.

Located at the opening between the left atrium and left ventricle is the mitral valve, also called the bicuspid valve or the left atrioventricular valve. Structurally, this valve consists of two cusps, known as the anterior medial cusp and the posterior medial cusp, compared to the three cusps of the tricuspid valve. In a clinical setting, the valve is referred to as the mitral valve, rather than the bicuspid valve. The two cusps of the mitral valve are attached by chordae tendineae to two papillary muscles that project from the wall of the ventricle.

At the base of the aorta is the aortic semilunar valve, or the aortic valve, which prevents backflow from the aorta. It normally is composed of three flaps. When the ventricle relaxes and blood attempts to flow back into the ventricle from the aorta, blood will fill the cusps of the valve, causing it to close and producing an audible sound.

In the image above, the two atrioventricular valves are open and the two semilunar valves are closed. This occurs when both atria and ventricles are relaxed and when the atria contract to pump blood into the ventricles. The image below shows a frontal view. Although only the left side of the heart is illustrated, the process is virtually identical on the right.

Blood Flow from the Left Atrium to the Left Ventricle

(a) A transverse section through the heart illustrates the four heart valves. The two atrioventricular valves are open; the two semilunar valves are closed. The atria and vessels have been removed. (b) A frontal section through the heart illustrates blood flow through the mitral valve. When the mitral valve is open, it allows blood to move from the left atrium to the left ventricle. The aortic semilunar valve is closed to prevent backflow of blood from the aorta to the left ventricle.

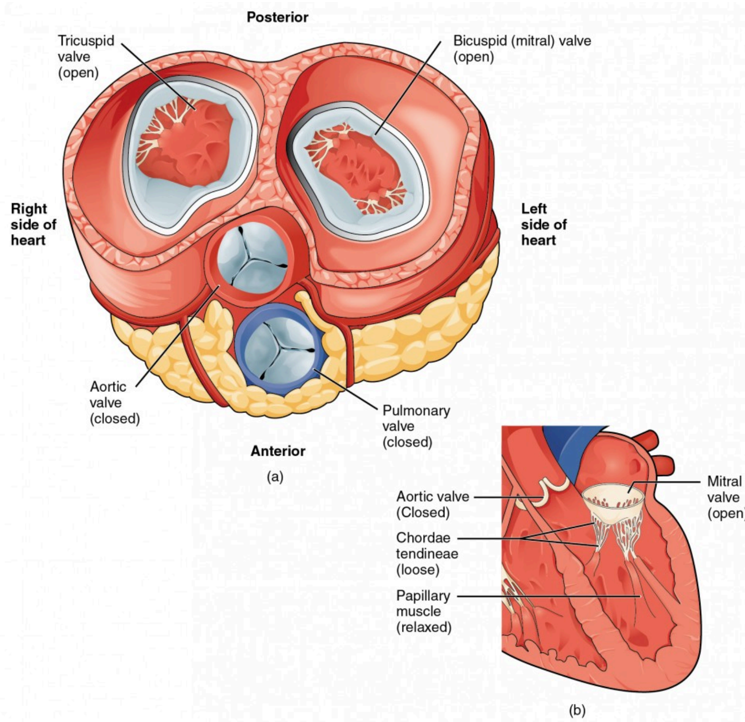


Figure 9.12: Blood Flow from the Left Atrium to the Left Ventricle

Image a above shows the atrioventricular valves closed while the two semilunar valves are open. This occurs when the ventricles contract to eject blood into the pulmonary trunk and aorta. Closure of the two atrioventricular valves prevents blood from being forced back into the atria. This stage can be seen from a frontal view in image b above.

Blood Flow from the Left Ventricle into the Great Vessels

(a) A transverse section through the heart illustrates the four heart valves during ventricular contraction. The two atrioventricular valves are closed, but the two semilunar valves are open. The atria and vessels have been removed. (b) A frontal view shows the closed mitral (bicuspid) valve that prevents backflow of blood into the left atrium. The aortic semilunar valve is open to allow blood to be ejected into the aorta.

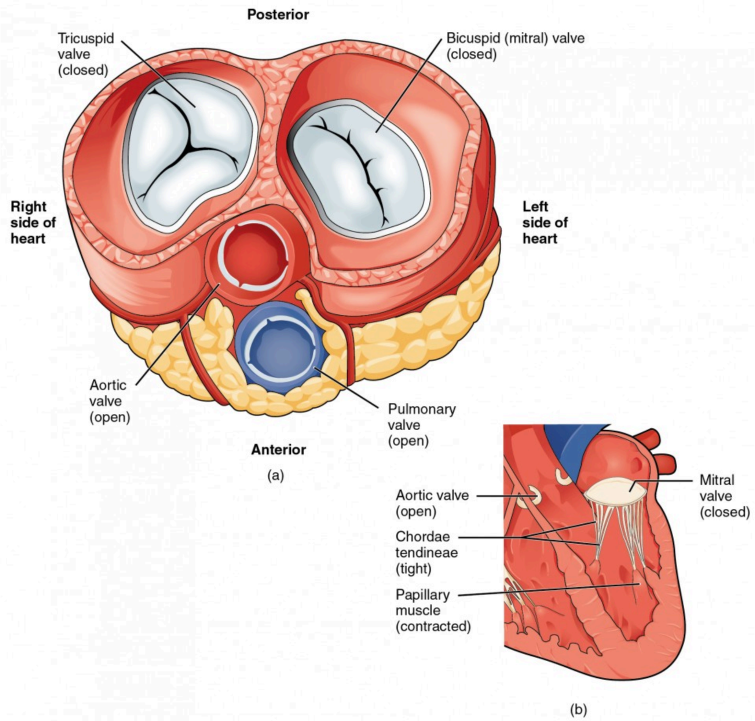


Figure 9.13: Blood Flow from the Left Ventricle into the Great Vessels

When the ventricles begin to contract, pressure within the ventricles rises and blood flows toward the area of lowest pressure, which is initially in the atria. This backflow causes the cusps of the tricuspid and mitral (bicuspid) valves to close. These valves are tied down to the papillary muscles by chordae tendineae. During the relaxation phase of the cardiac cycle, the papillary muscles are also relaxed and the tension on the chordae tendineae is slight (image b above). However, as the myocardium of the ventricle contracts, so do the papillary muscles. This creates tension on the chordae tendineae (image b above), helping to hold the cusps of the atrioventricular valves in place and preventing them from being blown back into the atria.

The aortic and pulmonary semilunar valves lack the chordae tendineae and papillary muscles associated with the atrioventricular valves. Instead, they consist of pocket-like folds of endocardium reinforced with additional connective tissue. When the ventricles relax and the change in pressure forces the blood toward the ventricles, the blood presses against these cusps and seals the openings.

55. Blood Vessels

Blood is carried through the body via blood vessels. An artery is a blood vessel that carries blood away from the heart, where it branches into ever-smaller vessels. Eventually, the smallest arteries, vessels called arterioles, further branch into tiny capillaries, where nutrients and wastes are exchanged, and then combine with other vessels that exit capillaries to form venules, small blood vessels that carry blood to a vein, a larger blood vessel that returns blood to the heart.

Arteries and veins transport blood in two distinct circuits: the systemic circuit and the pulmonary circuit. Systemic arteries provide blood rich in oxygen to the body's tissues. The blood returned to the heart through systemic veins has less oxygen, since much of the oxygen carried by the arteries has been delivered to the cells. In contrast, in the pulmonary circuit, arteries carry blood low in oxygen exclusively to the lungs for gas exchange. Pulmonary veins then return freshly oxygenated blood from the lungs to the heart to be pumped back out into systemic circulation. Although arteries and veins differ structurally and functionally, they share certain features.

Cardiovascular Circulation

The pulmonary circuit moves blood from the right side of the heart to the lungs and back to the heart. The systemic circuit moves blood from the left side of the heart to the head and body and returns it to the right side of the heart to repeat the cycle. The arrows indicate the direction of blood flow, and the colors show the relative levels of oxygen concentration.

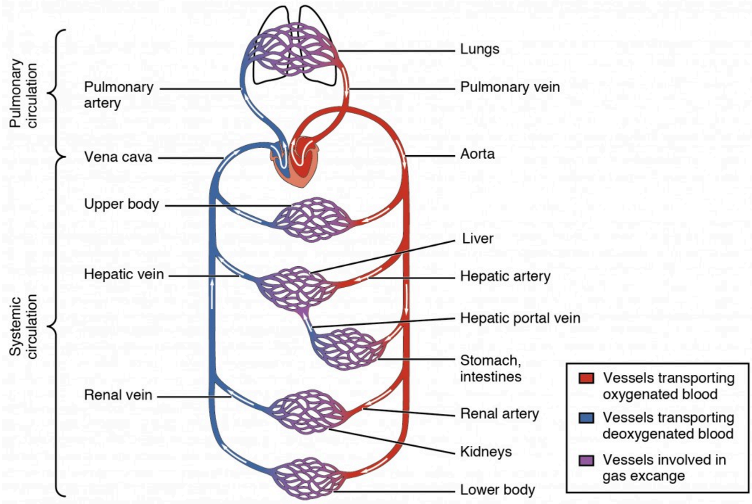


Figure 9.14: Cardiovascular Circulation

Shared Structures

Different types of blood vessels vary slightly in their structures, but they share the same general features. Arteries and arterioles have thicker walls than veins and venules because they are closer to the heart and receive blood that is surging at a far greater pressure. Each type of vessel has a lumen—a hollow passageway through which blood flows. Arteries have smaller lumens than veins, a characteristic that helps to maintain the pressure of blood moving through the system. Together, their thicker walls and smaller diameters give arterial lumens a more rounded appearance in cross section than the lumens of veins.

Structure of Blood Vessels

(a) Arteries and (b) veins share the same general features, but the walls of arteries are much thicker because of the higher pressure of the blood that flows through them. (c) A micrograph shows the relative differences in thickness. LM × 160. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

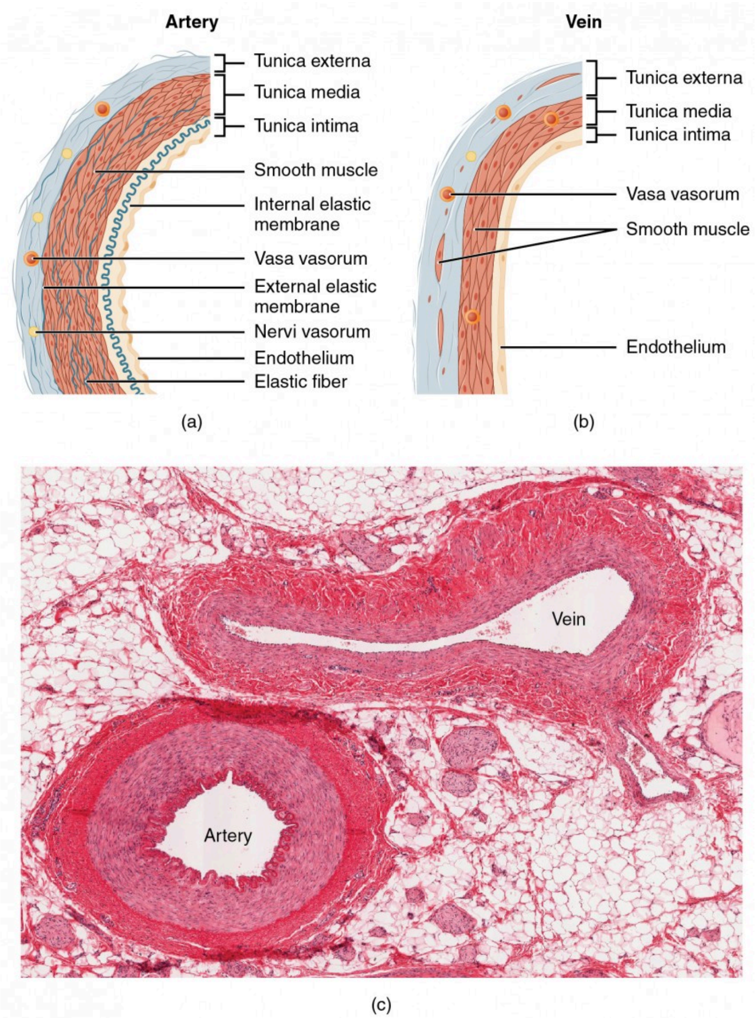


Figure 9.15: Structure of Blood Vessels

By the time blood has passed through capillaries and entered venules, the pressure initially exerted upon it by heart contractions has diminished. In other words, in comparison to arteries, venules and veins withstand a much lower pressure from the blood that flows through them. Their walls are considerably thinner and their lumens are correspondingly larger in diameter, allowing more blood to flow with less vessel resistance. In addition, many veins of the body, particularly those of the limbs, contain valves that assist the unidirectional flow of blood toward the heart. This is critical because blood flow becomes sluggish in the extremities, as a result of the lower pressure and the effects of gravity.

The walls of arteries and veins are largely composed of living cells and their products (including collagenous and elastic fibers); the cells require nourishment and produce waste. Since blood passes through the larger vessels relatively quickly, there is limited opportunity for blood in the lumen of the vessel to provide nourishment to or remove waste from the vessel's cells. Further, the walls of the larger vessels are too thick for nutrients to diffuse through to all of the cells. Larger arteries and veins contain small blood vessels within their walls known as the vasa vasorum—literally "vessels of the vessel"—to provide them with this critical exchange. Since the pressure within arteries is relatively high, the vasa vasorum must function in the outer layers of the vessel or the pressure exerted by the blood passing through the vessel would collapse it, preventing any exchange from occurring. The lower pressure within veins allows the vasa vasorum to be located closer to the lumen. The restriction of the vasa vasorum to the outer layers of arteries is thought to be one reason that arterial diseases are more common than venous diseases, since its location makes it more difficult to nourish the cells of the arteries and remove waste products. There are also minute nerves within the walls of both types of vessels that control the contraction and dilation of smooth muscle. These minute nerves are known as the nervi vasorum.

Both arteries and veins have the same three distinct tissue layers, called tunics (from the Latin term tunica), for the garments first worn by ancient Romans; the term tunic is also used for some modern garments. From the most interior layer to the outer, these tunics are the tunica intima, the tunica media, and the tunica externa.The following table compares and contrasts the tunics of the arteries and veins.

Table 9.2: Comparison of Tunics in Arteries and Veins

	Arteries	**Veins**
General appearance	Thick walls with small lumens Generally appear rounded	Thin walls with large lumens Generally appear flattened
Tunica intima	Endothelium usually appears wavy due to constriction of smooth muscle Internal elastic membrane present in larger vessels	Endothelium appears smooth Internal elastic membrane absent
Tunica media	Normally the thickest layer in arteries Smooth muscle cells and elastic fibers predominate (the proportions of these vary with distance from the heart) External elastic membrane present in larger vessels	Normally thinner than the tunica externa Smooth muscle cells and collagenous fibers predominate Nervi vasorum and vasa vasorum present External elastic membrane absent
Tunica externa	Normally thinner than the tunica media in all but the largest arteries Collagenous and elastic fibers Nervi vasorum and vasa vasorum present	Normally the thickest layer in veins Collagenous and smooth fibers predominate Some smooth muscle fibers Nervi vasorum and vasa vasorum present

Tunica Intima

The tunica intima (also called the tunica interna) is composed of epithelial and connective tissue layers. Lining the tunica intima is the specialized simple squamous epithelium called the endothelium, which is continuous throughout the entire vascular system, including the lining of the chambers of the heart. Damage to this endothelial lining and exposure of blood to the collagenous fibers beneath is one of the primary causes of clot formation. Until recently, the endothelium was viewed simply as the boundary between the blood in the lumen and the walls of the vessels. Recent studies, however, have shown that it is physiologically critical to such activities as helping to regulate capillary exchange and altering blood flow. The endothelium releases local chemicals called endothelins that can constrict the smooth muscle within the walls of the vessel to increase blood pressure. Uncompensated overproduction of endothelins may contribute to hypertension (high blood pressure) and cardiovascular disease.

Next to the endothelium is the basement membrane, or basal lamina, that effectively binds the endothelium to the connective tissue. The basement membrane provides strength while maintaining flexibility, and it is permeable, allowing materials to pass through it. The thin outer layer of the tunica intima contains a small amount of areolar connective tissue that consists primarily of elastic fibers to provide the vessel with additional flexibility; it also contains some collagenous fibers to provide additional strength.

In larger arteries, there is also a thick, distinct layer of elastic fibers known as the internal elastic membrane (also called the internal elastic lamina) at the boundary with the tunica media. Like the other components of the tunica intima, the internal elastic membrane provides structure while allowing the vessel to stretch. It is permeated with small openings that allow exchange of materials between the tunics. The internal elastic membrane is not apparent in veins. In addition, many veins, particularly in the lower limbs, contain valves formed by sections of thickened endothelium that are reinforced with connective tissue, extending into the lumen.

Under the microscope, the lumen and the entire tunica intima of a vein will appear smooth, whereas those of an artery will normally appear wavy because of the partial constriction of the smooth muscle in the tunica media, the next layer of blood vessel walls.

Tunica Media

The tunica media is the substantial middle layer of the vessel wall. It is generally the thickest layer in arteries, and it is much thicker in arteries than it is in veins. The tunica media consists of layers of smooth muscle supported by connective tissue that is primarily made up of elastic fibers, most of which are arranged in circular sheets. Toward the outer portion of the tunic, there are also layers of longitudinal muscle. Contraction and relaxation of the circular muscles decrease and increase the diameter of the vessel lumen, respectively. Specifically in arteries, vasoconstriction decreases blood flow as the smooth muscle in the walls of the tunica media contracts, making the lumen narrower and increasing blood pressure. Similarly, vasodilation increases blood flow as the smooth muscle relaxes, allowing the lumen to widen and blood pressure to drop. Both vasoconstriction and vasodilation are regulated in part by small vascular nerves, known as nervi vasorum, or "nerves of the vessel," that run within the walls of blood vessels. These are generally all sympathetic fibers, although some trigger vasodilation and others induce vasoconstriction, depending upon the nature of the neurotransmitter and receptors located on the target cell. Parasympathetic stimulation does trigger vasodilation as well as erection during sexual arousal in the external genitalia of both sexes. Nervous control over vessels tends to be more generalized than the specific targeting of individual blood vessels. Local controls, discussed later, account for this phenomenon. (Seek additional content for more information on these dynamic aspects of the autonomic nervous system.) Hormones and local chemicals also control blood vessels. Together, these neural and chemical mechanisms reduce or increase blood flow in response to changing body conditions, from exercise to hydration. Regulation of both blood flow and blood pressure is discussed in detail later in this chapter.

The smooth muscle layers of the tunica media are supported by a framework of collagenous fibers that also binds the tunica media to the inner and outer tunics. Along with the collagenous fibers are large numbers of elastic fibers that appear as wavy lines in prepared slides. Separating the tunica media from the outer tunica externa in larger arteries is the external elastic membrane (also called the external elastic lamina), which also appears wavy in slides. This structure is not usually seen in smaller arteries, nor is it seen in veins.

Tunica Externa

The outer tunic, the tunica externa (also called the tunica adventitia), is a substantial sheath of connective tissue composed primarily of collagenous fibers. Some bands of elastic fibers are found here as well. The tunica externa in veins also contains groups of smooth muscle fibers. This is normally the thickest tunic in veins and may be thicker than the tunica media in some larger arteries. The outer layers of the tunica externa are not distinct but rather blend with the surrounding connective tissue outside the vessel, helping to hold the vessel in relative position. If you are able to palpate some of the superficial veins on your upper limbs and try to move them, you will find that the tunica externa prevents this. If the tunica externa did not hold the vessel in place, any movement would likely result in disruption of blood flow.

Arteries

An artery is a blood vessel that conducts blood away from the heart. All arteries have relatively thick walls that can withstand the high pressure of blood ejected from the heart. However, those close to the heart have the thickest walls, containing a high percentage of elastic fibers in all three of their tunics. This type of artery is known as an elastic artery. Vessels larger than 10 mm in diameter are typically elastic. Their abundant elastic fibers allow them to expand, as blood pumped from the ventricles passes through them, and then to recoil after the surge has passed. If artery walls were rigid and unable to expand and recoil, their resistance to blood flow would greatly increase and blood pressure would rise to even higher levels, which would in turn require the heart to pump harder to increase the volume of blood expelled by each pump (the stroke volume) and maintain adequate pressure and flow. Artery walls would have to become even thicker in response to this increased pressure. The elastic recoil of the vascular wall helps to maintain the pressure gradient that drives the blood through the arterial system. An elastic artery is also known as a conducting artery, because the large diameter of the lumen enables it to accept a large volume of blood from the heart and conduct it to smaller branches.

Types of Arteries and Arterioles

Comparison of the walls of an elastic artery, a muscular artery, and an arteriole is shown. In terms of scale, the diameter of an arteriole is measured in micrometers compared to millimeters for elastic and muscular arteries.

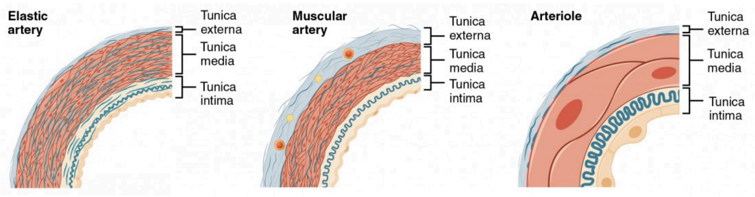


Figure 9.16: Types of Arteries and Arterioles

Farther from the heart, where the surge of blood has dampened, the percentage of elastic fibers in an artery's tunica intima decreases and the amount of smooth muscle in its tunica media increases. The artery at this point is described as a muscular artery. The diameter of muscular arteries typically ranges from 0.1 mm to 10 mm. Their thick tunica media allows muscular arteries to play a leading role in vasoconstriction. In contrast, their decreased quantity of elastic fibers limits their ability to expand. Fortunately, because the blood pressure has eased by the time it reaches these more distant vessels, elasticity has become less important.

Notice that although the distinctions between elastic and muscular arteries are important, there is no "line of demarcation" where an elastic artery suddenly becomes muscular. Rather, there is a gradual transition as the vascular tree repeatedly branches. In turn, muscular arteries branch to distribute blood to the vast network of arterioles. For this reason, a muscular artery is also known as a distributing artery.

Arterioles

An arteriole is a very small artery that leads to a capillary. Arterioles have the same three tunics as the larger vessels, but the thickness of each is greatly diminished. The critical endothelial lining of the tunica intima is intact. The tunica media is restricted to one or two smooth muscle cell layers in thickness. The tunica externa remains but is very thin.

With a lumen averaging 30 micrometers or less in diameter, arterioles are critical in slowing down—or resisting—blood flow and, thus, causing a substantial drop in blood pressure. Because of this, you may see them referred to as resistance vessels. The muscle fibers in arterioles are normally slightly contracted, causing arterioles to maintain a consistent muscle tone—in this case referred to as vascular tone—in a similar manner to the muscular tone of skeletal muscle. In reality, all blood vessels exhibit vascular tone due to the partial contraction of smooth muscle. The importance of the arterioles is that they will be the primary site of both resistance and regulation of blood pressure. The precise diameter of the lumen of an arteriole at any given moment is determined by neural and chemical controls, and vasoconstriction and vasodilation in the arterioles are the primary mechanisms for distribution of blood flow.

Capillaries

A capillary is a microscopic channel that supplies blood to the tissues themselves, a process called perfusion. Exchange of gases and other substances occurs in the capillaries between the blood and the surrounding cells and their tissue fluid (interstitial fluid). The diameter of a capillary lumen ranges from 5–10 micrometers; the smallest are just barely wide enough for an erythrocyte to squeeze through. Flow through capillaries is often described as microcirculation.

The wall of a capillary consists of the endothelial layer surrounded by a basement membrane with occasional smooth muscle fibers. There is some variation in wall structure: In a large capillary, several endothelial cells bordering each other may line the lumen; in a small capillary, there may be only a single cell layer that wraps around to contact itself.

For capillaries to function, their walls must be leaky, allowing substances to pass through. There are three major types of capillaries, which differ according to their degree of "leakiness:" continuous, fenestrated, and sinusoid capillaries.

Continuous Capillaries

The most common type of capillary, the continuous capillary, is found in almost all vascularized tissues. Continuous capillaries are characterized by a complete endothelial lining with tight junctions between endothelial cells. Although a tight junction is usually impermeable and only allows for the passage of water and ions, they are often incomplete in capillaries, leaving intercellular clefts that allow for exchange of water and other very small molecules between the blood plasma and the interstitial fluid. Substances that can pass between cells include metabolic products, such as glucose, water, and small hydrophobic molecules like gases and hormones, as well as various leukocytes. Continuous capillaries not associated with the brain are rich in transport vesicles, contributing to either endocytosis or exocytosis. Those in the brain are part of the blood-brain barrier. Here, there are tight junctions and no intercellular clefts, plus a thick basement membrane and astrocyte extensions called end feet; these structures combine to prevent the movement of nearly all substances.

Types of Capillaries

The three major types of capillaries: continuous, fenestrated, and sinusoid.

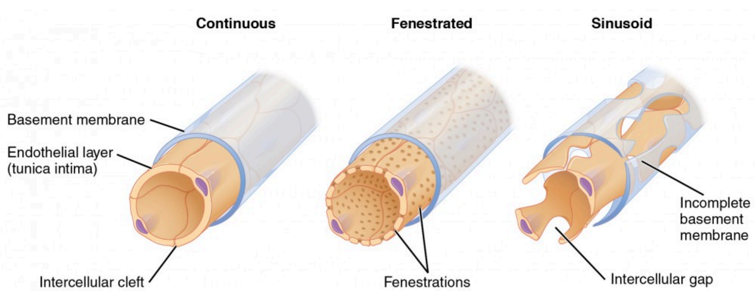


Figure 9.17: Types of Capillaries

Fenestrated Capillaries

A fenestrated capillary is one that has pores (or fenestrations) in addition to tight junctions in the endothelial lining. These make the capillary permeable to larger molecules. The number of fenestrations and their degree of permeability vary, however, according to their location. Fenestrated capillaries are common in the small intestine, which is the primary site of nutrient absorption, as well as in the kidneys, which filter the blood. They are also found in the choroid plexus of the brain and many endocrine structures, including the hypothalamus, pituitary, pineal, and thyroid glands.

Sinusoid Capillaries

A sinusoid capillary (or sinusoid) is the least common type of capillary. Sinusoid capillaries are flattened, and they have extensive intercellular gaps and incomplete basement membranes, in addition to intercellular clefts and fenestrations. This gives them an appearance not unlike Swiss cheese. These very large openings allow for the passage of the largest molecules, including plasma proteins and even cells. Blood flow through sinusoids is very slow, allowing more time for exchange of gases, nutrients, and wastes. Sinusoids are found in the liver and spleen, bone marrow, lymph nodes (where they carry lymph, not blood), and many endocrine glands including the pituitary and adrenal glands. Without these specialized capillaries, these organs would not be able to provide their myriad of functions. For example, when bone marrow forms new blood cells, the cells must enter the blood supply and can only do so through the large openings of a sinusoid capillary; they cannot pass through the small openings of continuous or fenestrated capillaries. The liver also requires extensive specialized sinusoid capillaries in order to process the materials brought to it by the hepatic portal vein from both the digestive tract and spleen, and to release plasma proteins into circulation.

Metarterioles and Capillary Beds

A metarteriole is a type of vessel that has structural characteristics of both an arteriole and a capillary. Slightly larger than the typical capillary, the smooth muscle of the tunica media of the metarteriole is not continuous but forms rings of smooth muscle (sphincters) prior to the entrance to the capillaries. Each metarteriole arises from a terminal arteriole and branches to supply blood to a capillary bed that may consist of 10–100 capillaries.

The precapillary sphincters, circular smooth muscle cells that surround the capillary at its origin with the metarteriole, tightly regulate the flow of blood from a metarteriole to the capillaries it supplies. Their function is critical: If all of the capillary beds in the body were to open simultaneously, they would collectively hold every drop of blood in the body and there would be none in the arteries, arterioles, venules, veins, or the heart itself. Normally, the precapillary sphincters are closed. When the surrounding tissues need oxygen and have excess waste products, the precapillary sphincters open, allowing blood to flow through and exchange to occur before closing once more. If all of the precapillary sphincters in a capillary bed are closed, blood will flow from the metarteriole directly into a thoroughfare channel and then into the venous circulation, bypassing the capillary bed entirely. This creates what is known as a vascular shunt. In addition, an arteriovenous anastomosis may bypass the capillary bed and lead directly to the venous system.

Although you might expect blood flow through a capillary bed to be smooth, in reality, it moves with an irregular, pulsating flow. This pattern is called vasomotion and is regulated by chemical signals that are triggered in response to changes in internal conditions, such as oxygen, carbon dioxide, hydrogen ion, and lactic acid levels. For example, during strenuous exercise when oxygen levels decrease and carbon dioxide, hydrogen ion, and lactic acid levels all increase, the capillary beds in skeletal muscle are open, as they would be in the digestive system when nutrients are present in the digestive tract. During sleep or rest periods, vessels in both areas are largely closed; they open only occasionally to allow oxygen and nutrient supplies to travel to the tissues to maintain basic life processes.

Capillary Bed

In a capillary bed, arterioles give rise to metarterioles. Precapillary sphincters located at the junction of a metarteriole with a capillary regulate blood flow. A thoroughfare channel connects the metarteriole to a venule. An arteriovenous anastomosis, which directly connects the arteriole with the venule, is shown at the bottom.

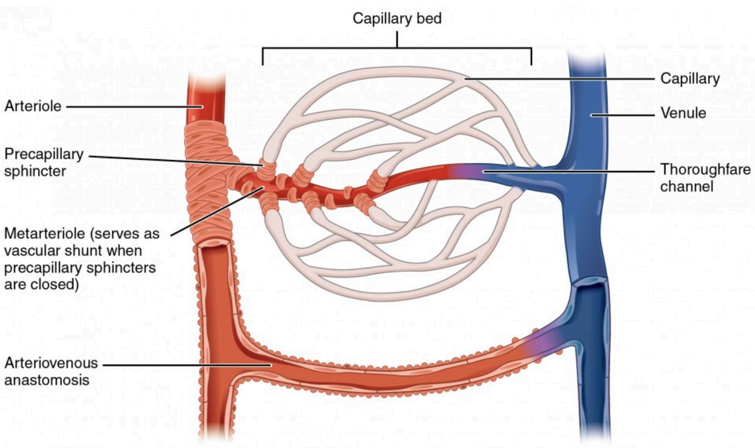


Figure 9.18: Capillary Bed

Venules

A venule is an extremely small vein, generally 8–100 micrometers in diameter. Postcapillary venules join multiple capillaries exiting from a capillary bed. Multiple venules join to form veins. The walls of venules consist of endothelium, a thin middle layer with a few muscle cells and elastic fibers, plus an outer layer of connective tissue fibers that constitute a very thin tunica externa. Venules as well as capillaries are the primary sites of emigration or diapedesis, in which the white blood cells adhere to the endothelial lining of the vessels and then squeeze through adjacent cells to enter the tissue fluid.

Veins

A vein is a blood vessel that conducts blood toward the heart. Compared to arteries, veins are thin-walled vessels with large and irregular lumens. Because they are low-pressure vessels, larger veins are commonly equipped with valves that promote the unidirectional flow of blood toward the heart and prevent backflow toward the capillaries caused by the inherent low blood pressure in veins as well as the pull of gravity.The following image compares the features of arteries and veins.

Comparison of Veins and Venules

Many veins have valves to prevent back flow of blood, whereas venules do not. In terms of scale, the diameter of a venule is measured in micrometers compared to millimeters for veins.

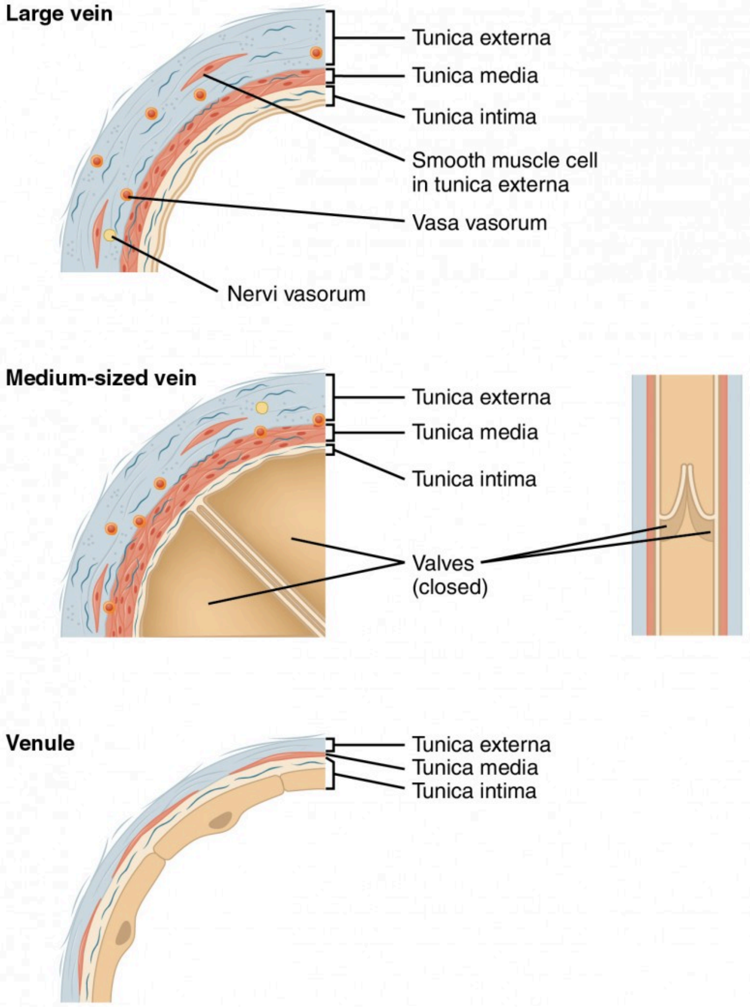


Figure 9.19: Comparison of Veins and Venules

Table 9.3: Comparison of Arteries and Veins		
	Arteries	**Veins**
Direction of blood flow	Conducts blood away from the heart	Conducts blood toward the heart
General appearance	Rounded	Irregular, often collapsed
Pressure	High	Low
Wall thickness	Thick	Thin
Relative oxygen concentration	Higher in systemic arteries Lower in pulmonary arteries	Lower in systemic veins Higher in pulmonary veins
Valves	Not present	Present most commonly in limbs and in veins inferior to the heart

Veins as Blood Reservoirs

In addition to their primary function of returning blood to the heart, veins may be considered blood reservoirs, since systemic veins contain approximately 64 percent of the blood volume at any given time. Their ability to hold this much blood is due to their high capacitance, that is, their capacity to distend (expand) readily to store a high volume of blood, even at a low pressure. The large lumens and relatively thin walls of veins make them far more distensible than arteries; thus, they are said to be capacitance vessels.

Table 9.4: Blood Flow

Systemic circulation 84%	Systemic veins 64%	Large veins 18%
		Large venous networks (liver, bone marrow, and integument) 21%
		Venules and medium-sized veins 25%
	Systemic arteries 13%	Arterioles 2%
		Muscular arteries 5%
		Elastic arteries 4%
		Aorta 2%
	Systemic capillaries 7%	Systemic capillaries 7%
Pulmonary circulation 9%	Pulmonary veins 4%	
	Pulmonary capillaries 2%	
	Pulmonary arteries 3%	
Heart 7%		

When blood flow needs to be redistributed to other portions of the body, the vasomotor center located in the medulla oblongata sends sympathetic stimulation to the smooth muscles in the walls of the veins, causing constriction—or in this case, venoconstriction. Less dramatic than the vasoconstriction seen in smaller arteries and arterioles, venoconstriction may be likened to a “stiffening” of the vessel wall. This increases pressure on the blood within the veins, speeding its return to the heart. As you will note in the image above, approximately 21 percent of the venous blood is located in venous networks within the liver, bone marrow, and integument. This volume of blood is referred to as venous reserve. Through venoconstriction, this “reserve” volume of blood can get back to the heart more quickly for redistribution to other parts of the circulation.

56. Age Related Changes to the Circulatory System

Blood

There is no major changes to blood with age, but there is a reduction of red bone marrow. This means that there is a diminished capacity for blood cell formation in the elderly.

Heart

In the absence of heart disease the heart remains essentially the same size, or diminishes slightly in size. The is a reduction in the number and size of cardiac muscle cells with aging and an increase in fibrous tissue.

Blood Vessels

Blood vessels reduce in elasticity with age. This is due to a reduced elastic fiber content in the wall of the arteries.

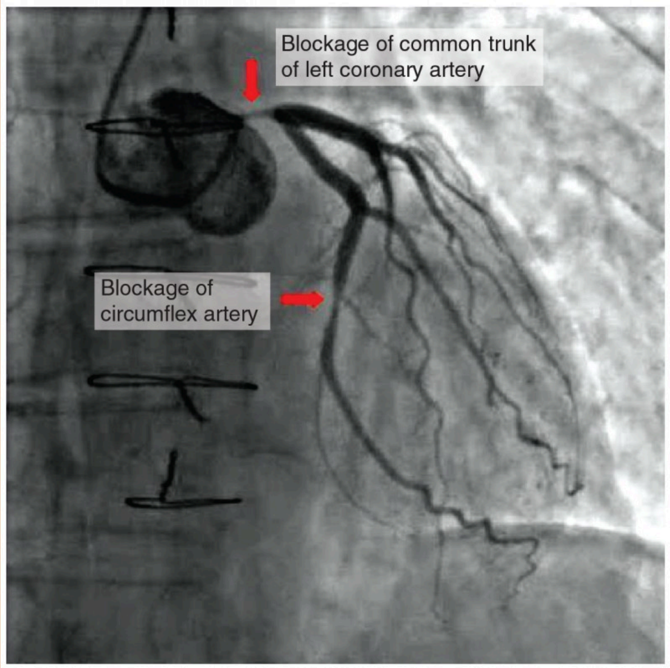
57. Age Related Dysfunctions to The Circulatory System

Atherosclerosis, Arteriosclerosis, & Coronary Artery Disease

Coronary artery disease is the leading cause of death worldwide. It occurs when the buildup of plaque—a fatty material including cholesterol, connective tissue, white blood cells, and some smooth muscle cells—within the walls of the arteries obstructs the flow of blood and decreases the flexibility or compliance of the vessels. This condition is called **atherosclerosis**, a hardening of the arteries that involves the accumulation of plaque. In advanced cases, atherosclerotic plaques can become hardened by the deposition of calcium, and fibrous tissue may proliferate in the arterial walls. This leads to a condition known as **arteriosclerosis**, or hardening of the arteries. As the coronary blood vessels become occluded, the flow of blood to the tissues will be restricted, a condition called ischemia that causes the cells to receive insufficient amounts of oxygen, called hypoxia. The image below shows the blockage of coronary arteries highlighted by the injection of dye. Some individuals with coronary artery disease report pain radiating from the chest called angina pectoris, but others remain asymptomatic. If untreated, coronary artery disease can lead to MI or a heart attack.

Atherosclerotic Coronary Arteries

In this coronary angiogram (X-ray), the dye makes visible two occluded coronary arteries. Such blockages can lead to decreased blood flow (ischemia) and insufficient oxygen (hypoxia) delivered to the cardiac tissues. If uncorrected, this can lead to cardiac muscle death (myocardial infarction).



The disease progresses slowly and often begins in children and can be seen as fatty "streaks" in the vessels. It then gradually progresses throughout life. Well-documented risk factors include smoking, family history, hypertension, obesity, diabetes, high alcohol consumption, lack of exercise, stress, and hyperlipidemia or high circulating levels of lipids in the blood. Treatments may include medication, changes to diet and exercise, angioplasty with a balloon catheter, insertion of a stent, or coronary bypass procedure.

Angioplasty is a procedure in which the occlusion is mechanically widened with a balloon. A specialized catheter with an expandable tip is inserted into a superficial vessel, normally in the leg, and then directed to the site of the occlusion. At this point, the balloon is inflated to compress the plaque material and to open the vessel to increase blood flow. Then, the balloon is deflated and retracted. A stent consisting of a specialized mesh is typically inserted at the site of occlusion to reinforce the weakened and damaged walls. Stent insertions have been routine in cardiology for more than 40 years.

Coronary bypass surgery may also be performed. This surgical procedure grafts a replacement vessel obtained from another, less vital portion of the body to bypass the occluded area. This procedure is clearly effective in treating patients experiencing a MI, but overall does not increase longevity. Nor does it seem advisable in patients with stable although diminished cardiac capacity since frequently loss of mental acuity occurs following the procedure. Long-term changes to behavior, emphasizing diet and exercise plus a medicine regime tailored to lower blood pressure, lower cholesterol and lipids, and reduce clotting are equally as effective.

Hypertension

Hypertension, or high blood pressure, is a potentially serious because it can contribute to heart attack, heart failure, kidney damage, or rupture blood vessels. In general systolic arterial blood pressures above 170 mm Hg and diastolic pressure above 90 mm Hg are considered hypertensive. While hypertension is not restricted to older person, the incidences tend to increase with age.

Myocardial Infarction

Myocardial infarction (MI) is the formal term for what is commonly referred to as a heart attack. It normally results from a lack of blood flow (ischemia) and oxygen (hypoxia) to a region of the heart, resulting in death of the cardiac muscle cells. An MI often occurs when a coronary artery is blocked by the buildup of atherosclerotic plaque consisting of lipids, cholesterol and fatty acids, and white blood cells, primarily macrophages. It can also occur when a portion of an unstable atherosclerotic plaque travels through the coronary arterial system and lodges in one of the smaller vessels. The resulting blockage restricts the flow of blood and oxygen to the myocardium and causes death of the tissue. MIs may be triggered by excessive exercise, in which the partially occluded artery is no longer able to pump sufficient quantities of blood, or severe stress, which may induce spasm of the smooth muscle in the walls of the vessel.

In the case of acute MI, there is often sudden pain beneath the sternum (retrosternal pain) called angina pectoris, often radiating down the left arm in males but not in female patients. Until this anomaly between the sexes was discovered, many female patients suffering MIs were misdiagnosed and sent home. In addition, patients typically present with difficulty breathing and shortness of breath (dyspnea), irregular heartbeat (palpations), nausea and vomiting, sweating (diaphoresis), anxiety, and fainting (syncope), although not all of these symptoms may be present. Many of the symptoms are shared with other medical conditions, including anxiety attacks and simple indigestion, so differential diagnosis is critical. It is estimated that between 22 and 64 percent of MIs present without any symptoms.

An MI can be confirmed by examining the patient's ECG, which frequently reveals alterations in the ST and Q components. Some classification schemes of MI are referred to as ST-elevated MI (STEMI) and non-elevated MI (non-STEMI). In addition, echocardiography or cardiac magnetic resonance imaging may be employed. Common blood tests indicating an MI include elevated levels of creatine kinase MB (an enzyme that catalyzes the conversion of creatine to phosphocreatine, consuming ATP) and cardiac troponin (the regulatory protein for muscle contraction), both of which are released by damaged cardiac muscle cells.

Immediate treatments for MI are essential and include administering supplemental oxygen, aspirin that helps to break up clots, and nitroglycerine administered sublingually (under the tongue) to facilitate its absorption. Despite its unquestioned success in treatments and use since the 1880s, the mechanism of nitroglycerine is still incompletely understood but is believed to involve the release of nitric oxide, a known vasodilator, and endothelium-derived releasing factor, which also relaxes the smooth muscle in the tunica media of coronary vessels. Longer-term treatments include injections of thrombolytic agents such as streptokinase that dissolve the clot, the anticoagulant heparin, balloon angioplasty and stents to open blocked vessels, and bypass surgery to allow blood to pass around the site of blockage. If the damage is extensive, coronary replacement with a donor heart or coronary assist device, a sophisticated mechanical device that supplements the pumping activity of the heart, may be employed. Despite the attention, development of artificial hearts to augment the severely limited supply of heart donors has proven less than satisfactory but will likely improve in the future.

MIs may trigger cardiac arrest, but the two are not synonymous. Important risk factors for MI include cardiovascular disease, age, smoking, high blood levels of the low-density lipoprotein (LDL, often referred to as "bad" cholesterol), low levels of high-density lipoprotein (HDL, or "good" cholesterol), hypertension, diabetes mellitus, obesity, lack of physical exercise, chronic kidney disease, excessive alcohol consumption, and use of illegal drugs.

Stroke

The supply of blood to the brain is crucial to its ability to perform many functions. Without a steady supply of oxygen, and to a lesser extent glucose, the nervous tissue in the brain cannot keep up its extensive electrical activity. These nutrients get into the brain through the blood, and if blood flow is interrupted, neurological function is compromised. The common name for a disruption of blood supply to the brain is a stroke. It is caused by a blockage to an artery in the brain. The blockage is from some type of embolus: a blood clot, a fat embolus, or an air bubble. When the blood cannot travel through the artery, the surrounding tissue that is deprived starves and dies. Strokes will often result in the loss of very specific functions. A stroke in the lateral medulla, for example, can cause a loss in the ability to swallow. Sometimes, seemingly unrelated functions will be lost because they are dependent on structures in the same region. Along with the swallowing in the previous example, a stroke in that region could affect sensory functions from the face or extremities because important white matter pathways also pass through the lateral medulla. Loss of blood flow to specific regions of the cortex can lead to the loss of specific higher functions, from the ability to recognize faces to the ability to move a particular region of the body. Severe or limited memory loss can be the result of a temporal lobe stroke. Related to strokes are transient ischemic attacks (TIAs), which can also be called “mini-strokes.” These are events in which a physical blockage may be temporary, cutting off the blood supply and oxygen to a region, but not to the extent that it causes cell death in that region. While the neurons in that area are recovering from the event, neurological function may be lost. Function can return if the area is able to recover from the event. Recovery from a stroke (or TIA) is strongly dependent on the speed of treatment. Often, the person who is present and notices something is wrong must then make a decision. The mnemonic **FAST** helps people remember what to look for when someone is dealing with sudden losses of neurological function. If someone complains of feeling “funny,” check these things quickly: Look at the person’s face. Does he or she have problems moving **F**ace muscles and making regular facial expressions? Ask the person to raise his or her **A**rms above the head. Can the person lift one arm but not the other? Has the person’s **S**peech changed? Is he or she slurring words or having trouble saying things? If any of these things have happened, then it is **T**ime to call for help. Sometimes, treatment with blood-thinning drugs can alleviate the problem, and recovery is possible. If the tissue is damaged, the amazing thing about the nervous system is that it is adaptable. With physical, occupational, and speech therapy, victims of strokes can recover, or more accurately relearn, functions.

Angina Pectoris

Angina pectoris refers to short episodes of cardiac pain that result from progressive constriction of the coronary arteries. The pain appears whenever the heart is called upon to contract more strenuously than can be supported by the restricted coronary blood flow. Incidents of angina actually reduce with age, most likely due to decreases in exercise.

Cardiac Arrhythmias

Irregular beats that occur outside the normal sequence are referred to as cardiac arrhythmias. Arrhythmias may occur at an age but are more common in older persons. Arrhythmias may result from extra systoles, when an atrium or ventricle contracts more often than it should, or from delayed heartbeats, when the chambers contract less frequently than normal.

Congestive Heart Failure

Congestive heart failure is a condition in which the heart is unable to pump enough blood to meet the needs of the body. The condition is a result of other cardiovascular diseases that have damaged the heart to the extent that it can no longer function efficiently. Kidney function is profoundly affected by congestive heart failure. Because of the small cardiac output, the production of urine is reduced and fluid is retained, causing an increase in the volume of tissue fluid and blood.

Edema and Varicose Veins

Despite the presence of valves and the contributions of other anatomical and physiological adaptations we will cover shortly, over the course of a day, some blood will inevitably pool, especially in the lower limbs, due to the pull of gravity. Any blood that accumulates in a vein will increase the pressure within it, which can then be reflected back into the smaller veins, venules, and eventually even the capillaries. Increased pressure will promote the flow of fluids out of the capillaries and into the interstitial fluid. The presence of excess tissue fluid around the cells leads to a condition called edema.

Most people experience a daily accumulation of tissue fluid, especially if they spend much of their work life on their feet (like most health professionals). However, clinical edema goes beyond normal swelling and requires medical treatment. Edema has many potential causes, including hypertension and heart failure, severe protein deficiency, renal failure, and many others. In order to treat edema, which is a sign rather than a discrete disorder, the underlying cause must be diagnosed and alleviated.

Varicose Veins

Varicose veins are commonly found in the lower limbs. (credit: Thomas Kriese)

Edema may be accompanied by varicose veins, especially in the superficial veins of the legs. This disorder arises when defective valves allow blood to accumulate within the veins, causing them to distend, twist, and become visible on the surface of the integument. Varicose veins may occur in both sexes, but are more common in women and are often related to pregnancy. More than simple cosmetic blemishes, varicose veins are often painful and sometimes itchy or throbbing. Without treatment, they tend to grow worse over time. The use of support hose, as well as elevating the feet and legs whenever possible, may be helpful in alleviating this condition. Laser surgery and interventional radiologic procedures can reduce the size and severity of varicose veins. Severe cases may require conventional surgery to remove the damaged vessels. As there are typically redundant circulation patterns, that is, anastomoses, for the smaller and more superficial veins, removal does not typically impair the circulation. There is evidence that patients with varicose veins suffer a greater risk of developing a thrombus or clot.

58. Glossary: The Circulatory System

Glossary

albumin most abundant plasma protein, accounting for most of the osmotic pressure of plasma

anastomosis (plural = anastomoses) area where vessels unite to allow blood to circulate even if there may be partial blockage in another branch

anterior cardiac veins vessels that parallel the small cardiac arteries and drain the anterior surface of the right ventricle; bypass the coronary sinus and drain directly into the right atrium

anterior interventricular artery (also, left anterior descending artery or LAD) major branch of the left coronary artery that follows the anterior interventricular sulcus

anterior interventricular sulcus sulcus located between the left and right ventricles on the anterior surface of the heart

antibodies (also, immunoglobulins or gamma globulins) antigen-specific proteins produced by specialized B lymphocytes that protect the body by binding to foreign objects such as bacteria and viruses

aortic valve (also, aortic semilunar valve) valve located at the base of the aorta

arteriole (also, resistance vessel) very small artery that leads to a capillary

arteriovenous anastomosis short vessel connecting an arteriole directly to a venule and bypassing the capillary beds

artery blood vessel that conducts blood away from the heart; may be a conducting or distributing vessel

atrioventricular septum cardiac septum located between the atria and ventricles; atrioventricular valves are located here

atrioventricular valves one-way valves located between the atria and ventricles; the valve on the right is called the tricuspid valve, and the one on the left is the mitral or bicuspid valve

atrium (plural = atria) upper or receiving chamber of the heart that pumps blood into the lower chambers just prior to their contraction; the right atrium receives blood from the systemic circuit that flows into the right ventricle; the left atrium receives blood from the pulmonary circuit that flows into the left ventricle

auricle extension of an atrium visible on the superior surface of the heart

bicuspid valve (also, mitral valve or left atrioventricular valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

blood liquid connective tissue composed of formed elements—erythrocytes, leukocytes, and platelets—and a fluid extracellular matrix called plasma; component of the cardiovascular system

buffy coat thin, pale layer of leukocytes and platelets that separates the erythrocytes from the plasma in a sample of centrifuged blood

capacitance ability of a vein to distend and store blood

capacitance vessels veins

capillary smallest of blood vessels where physical exchange occurs between the blood and tissue cells surrounded by interstitial fluid

capillary bed network of 10–100 capillaries connecting arterioles to venules

cardiac notch depression in the medial surface of the inferior lobe of the left lung where the apex of the heart is located

cardiac skeleton (also, skeleton of the heart) reinforced connective tissue located within the atrioventricular septum; includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta; the point of attachment for the heart valves

cardiomyocyte muscle cell of the heart

chordae tendineae string-like extensions of tough connective tissue that extend from the flaps of the atrioventricular valves to the papillary muscles

circumflex artery

continuous capillary most common type of capillary, found in virtually all tissues except epithelia and cartilage; contains very small gaps in the endothelial lining that permit exchange

coronary arteries branches of the ascending aorta that supply blood to the heart; the left coronary artery feeds the left side of the heart, the left atrium and ventricle, and the interventricular septum; the right coronary artery feeds the right atrium, portions of both ventricles, and the heart conduction system

coronary sinus large, thin-walled vein on the posterior surface of the heart that lies within the atrioventricular sulcus and drains the heart myocardium directly into the right atrium

coronary sulcus sulcus that marks the boundary between the atria and ventricles

coronary veins vessels that drain the heart and generally parallel the large surface arteries

elastic artery (also, conducting artery) artery with abundant elastic fibers located closer to the heart, which maintains the pressure gradient and conducts blood to smaller branches

endocardium innermost layer of the heart lining the heart chambers and heart valves; composed of endothelium reinforced with a thin layer of connective tissue that binds to the myocardium

endothelium layer of smooth, simple squamous epithelium that lines the endocardium and blood vessels

epicardial coronary arteries surface arteries of the heart that generally follow the sulci

epicardium innermost layer of the serous pericardium and the outermost layer of the heart wall

external elastic membrane membrane composed of elastic fibers that separates the tunica media from the tunica externa; seen in larger arteries

fenestrated capillary type of capillary with pores or fenestrations in the endothelium that allow for rapid passage of certain small materials

fibrinogen plasma protein produced in the liver and involved in blood clotting

foramen ovale opening in the fetal heart that allows blood to flow directly from the right atrium to the left atrium, bypassing the fetal pulmonary circuit

formed elements cellular components of blood; that is, erythrocytes, leukocytes, and platelets

fossa ovalis oval-shaped depression in the interatrial septum that marks the former location of the foramen ovale

globulins heterogeneous group of plasma proteins that includes transport proteins, clotting factors, immune proteins, and others

great cardiac vein vessel that follows the interventricular sulcus on the anterior surface of the heart and flows along the coronary sulcus into the coronary sinus on the posterior surface; parallels the anterior interventricular artery and drains the areas supplied by this vessel

hematocrit (also, packed cell volume) volume percentage of erythrocytes in a sample of centrifuged blood

hypertrophic cardiomyopathy pathological enlargement of the heart, generally for no known reason

immunoglobulins (also, antibodies or gamma globulins) antigen-specific proteins produced by specialized B lymphocytes that protect the body by binding to foreign objects such as bacteria and viruses

inferior vena cava large systemic vein that returns blood to the heart from the inferior portion of the body

interatrial septum cardiac septum located between the two atria; contains the fossa ovalis after birth

internal elastic membrane membrane composed of elastic fibers that separates the tunica intima from the tunica media; seen in larger arteries

interventricular septum cardiac septum located between the two ventricles

left atrioventricular valve (also, mitral valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

lumen interior of a tubular structure such as a blood vessel or a portion of the alimentary canal through which blood, chyme, or other substances travel

marginal arteries branches of the right coronary artery that supply blood to the superficial portions of the right ventricle

mesothelium simple squamous epithelial portion of serous membranes, such as the superficial portion of the epicardium (the visceral pericardium) and the deepest portion of the pericardium (the parietal pericardium)

metarteriole short vessel arising from a terminal arteriole that branches to supply a capillary bed

microcirculation blood flow through the capillaries

middle cardiac vein vessel that parallels and drains the areas supplied by the posterior interventricular artery; drains into the great cardiac vein

mitral valve (also, left atrioventricular valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

moderator band band of myocardium covered by endocardium that arises from the inferior portion of the interventricular septum

in the right ventricle and crosses to the anterior papillary muscle; contains conductile fibers that carry electrical signals followed by contraction of the heart
myocardium thickest layer of the heart composed of cardiac muscle cells built upon a framework of primarily collagenous fibers and blood vessels that supply it and the nervous fibers that help to regulate it

nervi vasorum small nerve fibers found in arteries and veins that trigger contraction of the smooth muscle in their walls

packed cell volume (PCV) (also, hematocrit) volume percentage of erythrocytes present in a sample of centrifuged blood
papillary muscle extension of the myocardium in the ventricles to which the chordae tendineae attach
pectinate muscles muscular ridges seen on the anterior surface of the right atrium
perfusion distribution of blood into the capillaries so the tissues can be supplied
pericardial cavity cavity surrounding the heart filled with a lubricating serous fluid that reduces friction as the heart contracts
pericardial sac (also, pericardium) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium
pericardium (also, pericardial sac) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium

plasma in blood, the liquid extracellular matrix composed mostly of water that circulates the formed elements and dissolved materials throughout the cardiovascular system

platelets (also, thrombocytes) one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes

posterior cardiac vein vessel that parallels and drains the areas supplied by the marginal artery branch of the circumflex artery; drains into the great cardiac vein
posterior interventricular artery (also, posterior descending artery) branch of the right coronary artery that runs along the posterior portion of the interventricular sulcus toward the apex of the heart and gives rise to branches that supply the interventricular septum and portions of both ventricles
posterior interventricular sulcus sulcus located between the left and right ventricles on the anterior surface of the heart
precapillary sphincters circular rings of smooth muscle that surround the entrance to a capillary and regulate blood flow into that capillary
pulmonary arteries left and right branches of the pulmonary trunk that carry deoxygenated blood from the heart to each of the lungs
pulmonary capillaries capillaries surrounding the alveoli of the lungs where gas exchange occurs: carbon dioxide exits the blood and oxygen enters
pulmonary circuit blood flow to and from the lungs
pulmonary trunk large arterial vessel that carries blood ejected from the right ventricle; divides into the left and right pulmonary arteries
pulmonary valve (also, pulmonary semilunar valve, the pulmonic valve, or the right semilunar valve) valve at the base of the pulmonary trunk that prevents backflow of blood into the right ventricle; consists of three flaps
pulmonary veins veins that carry highly oxygenated blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and to the many branches of the systemic circuit

red blood cells (RBCs) (also, erythrocytes) one of the formed elements of blood that transports oxygen
right atrioventricular valve (also, tricuspid valve) valve located between the right atrium and ventricle; consists of three flaps of

tissue

semilunar valves valves located at the base of the pulmonary trunk and at the base of the aorta

septum (plural = septa) walls or partitions that divide the heart into chambers

septum primum flap of tissue in the fetus that covers the foramen ovale within a few seconds after birth

sinusoid capillary rarest type of capillary, which has extremely large intercellular gaps in the basement membrane in addition to clefts and fenestrations; found in areas such as the bone marrow and liver where passage of large molecules occurs

small cardiac vein parallels the right coronary artery and drains blood from the posterior surfaces of the right atrium and ventricle; drains into the great cardiac vein

sulcus (plural = sulci) fat-filled groove visible on the surface of the heart; coronary vessels are also located in these areas

superior vena cava large systemic vein that returns blood to the heart from the superior portion of the body

systemic circuit blood flow to and from virtually all of the tissues of the body

thoroughfare channel continuation of the metarteriole that enables blood to bypass a capillary bed and flow directly into a venule, creating a vascular shunt

trabeculae carneae ridges of muscle covered by endocardium located in the ventricles

tricuspid valve term used most often in clinical settings for the right atrioventricular valve

tunica externa (also, tunica adventitia) outermost layer or tunic of a vessel (except capillaries)

tunica intima (also, tunica interna) innermost lining or tunic of a vessel

tunica media middle layer or tunic of a vessel (except capillaries)

valve in the cardiovascular system, a specialized structure located within the heart or vessels that ensures one-way flow of blood

vasa vasorum small blood vessels located within the walls or tunics of larger vessels that supply nourishment to and remove wastes from the cells of the vessels

vascular shunt continuation of the metarteriole and thoroughfare channel that allows blood to bypass the capillary beds to flow directly from the arterial to the venous circulation

vasoconstriction constriction of the smooth muscle of a blood vessel, resulting in a decreased vascular diameter

vasodilation relaxation of the smooth muscle in the wall of a blood vessel, resulting in an increased vascular diameter

vasomotion irregular, pulsating flow of blood through capillaries and related structures

vein blood vessel that conducts blood toward the heart

venous reserve volume of blood contained within systemic veins in the integument, bone marrow, and liver that can be returned to the heart for circulation, if needed

ventricle one of the primary pumping chambers of the heart located in the lower portion of the heart; the left ventricle is the major pumping chamber on the lower left side of the heart that ejects blood into the systemic circuit via the aorta and receives blood from the left atrium; the right ventricle is the major pumping chamber on the lower right side of the heart that ejects blood into the pulmonary circuit via the pulmonary trunk and receives blood from the right atrium

venule small vessel leading from the capillaries to veins

white blood cells (WBCs) (also, leukocytes) one of the formed elements of blood that provides defense against disease agents and foreign materials

PART X

CHAPTER 10: THE IMMUNE SYSTEM

59. Anatomy of the Lymphatic and Immune Systems

The immune system is the complex collection of cells and organs that destroys or neutralizes pathogens that would otherwise cause disease or death. The lymphatic system, for most people, is associated with the immune system to such a degree that the two systems are virtually indistinguishable. The lymphatic system is the system of vessels, cells, and organs that carries excess fluids to the bloodstream and filters pathogens from the blood. The swelling of lymph nodes during an infection and the transport of lymphocytes via the lymphatic vessels are but two examples of the many connections between these critical organ systems.

Functions of the Lymphatic System

A major function of the lymphatic system is to drain body fluids and return them to the bloodstream. Blood pressure causes leakage of fluid from the capillaries, resulting in the accumulation of fluid in the interstitial space—that is, spaces between individual cells in the tissues. In humans, 20 liters of plasma is released into the interstitial space of the tissues each day due to capillary filtration. Once this filtrate is out of the bloodstream and in the tissue spaces, it is referred to as interstitial fluid. Of this, 17 liters is reabsorbed directly by the blood vessels. But what happens to the remaining three liters? This is where the lymphatic system comes into play. It drains the excess fluid and empties it back into the bloodstream via a series of vessels, trunks, and ducts. Lymph is the term used to describe interstitial fluid once it has entered the lymphatic system. When the lymphatic system is damaged in some way, such as by being blocked by cancer cells or destroyed by injury, protein-rich interstitial fluid accumulates (sometimes "backs up" from the lymph vessels) in the tissue spaces. This inappropriate accumulation of fluid referred to as lymphedema may lead to serious medical consequences.

As the vertebrate immune system evolved, the network of lymphatic vessels became convenient avenues for transporting the cells of the immune system. Additionally, the transport of dietary lipids and fat-soluble vitamins absorbed in the gut uses this system.

Cells of the immune system not only use lymphatic vessels to make their way from interstitial spaces back into the circulation, but they also use lymph nodes as major staging areas for the development of critical immune responses. A lymph node is one of the small, bean-shaped organs located throughout the lymphatic system.

Structure of the Lymphatic System

The lymphatic vessels begin as open-ended capillaries, which feed into larger and larger lymphatic vessels, and eventually empty into the bloodstream by a series of ducts. Along the way, the lymph travels through the lymph nodes, which are commonly found near the groin, armpits, neck, chest, and abdomen. Humans have about 500–600 lymph nodes throughout the body.

Anatomy of the Lymphatic System

Lymphatic vessels in the arms and legs convey lymph to the larger lymphatic vessels in the torso.

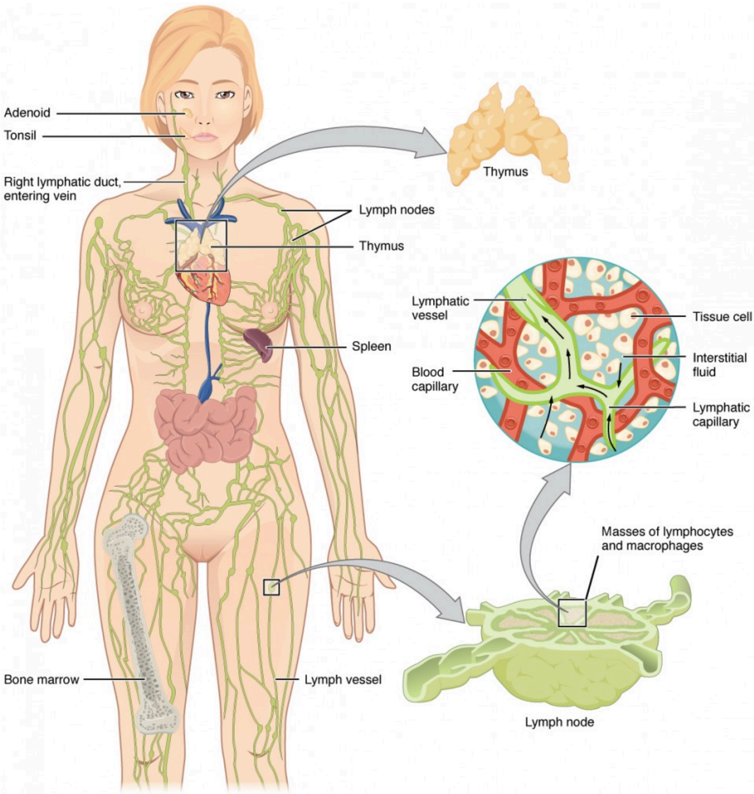


Figure 10.1: Anatomy of the Lymphatic System

A major distinction between the lymphatic and cardiovascular systems in humans is that lymph is not actively pumped by the heart, but is forced through the vessels by the movements of the body, the contraction of skeletal muscles during body movements, and breathing. One-way valves (semi-lunar valves) in lymphatic vessels keep the lymph moving toward the heart. Lymph flows from the lymphatic capillaries, through lymphatic vessels, and then is dumped into the circulatory system via the lymphatic ducts located at the junction of the jugular and subclavian veins in the neck.

Lymphatic Capillaries

Lymphatic capillaries, also called the terminal lymphatics, are vessels where interstitial fluid enters the lymphatic system to become lymph fluid. Located in almost every tissue in the body, these vessels are interlaced among the arterioles and venules of the circulatory system in the soft connective tissues of the body. Exceptions are the central nervous system, bone marrow, bones, teeth, and the cornea of the eye, which do not contain lymph vessels.

Lymphatic Capillaries

Lymphatic capillaries are interlaced with the arterioles and venules of the cardiovascular system. Collagen fibers anchor a lymphatic capillary in the tissue (inset). Interstitial fluid slips through spaces between the overlapping endothelial cells that compose the lymphatic capillary.

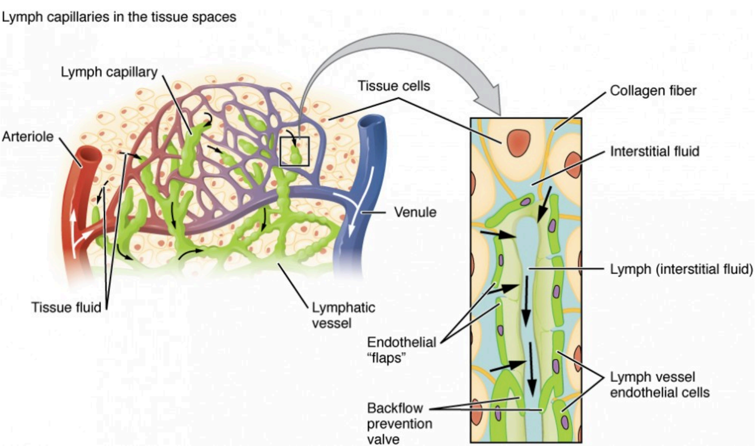


Figure 10.2: Lymph Capillaries in the Tissue Spaces

Lymphatic capillaries are formed by a one cell-thick layer of endothelial cells and represent the open end of the system, allowing interstitial fluid to flow into them via overlapping cells. When interstitial pressure is low, the endothelial flaps close to prevent "backflow." As interstitial pressure increases, the spaces between the cells open up, allowing the fluid to enter. Entry of fluid into lymphatic capillaries is also enabled by the collagen filaments that anchor the capillaries to surrounding structures. As interstitial pressure increases, the filaments pull on the endothelial cell flaps, opening up them even further to allow easy entry of fluid.

In the small intestine, lymphatic capillaries called lacteals are critical for the transport of dietary lipids and lipid-soluble vitamins to the bloodstream. In the small intestine, dietary triglycerides combine with other lipids and proteins, and enter the lacteals to form a milky fluid called chyle. The chyle then travels through the lymphatic system, eventually entering the liver and then the bloodstream.

Larger Lymphatic Vessels, Trunks, and Ducts

The lymphatic capillaries empty into larger lymphatic vessels, which are similar to veins in terms of their three-tunic structure and the presence of valves. These one-way valves are located fairly close to one another, and each one causes a bulge in the lymphatic vessel, giving the vessels a beaded appearance.

The superficial and deep lymphatics eventually merge to form larger lymphatic vessels known as lymphatic trunks. On the right side of the body, the right sides of the head, thorax, and right upper limb drain lymph fluid into the right subclavian vein via the right lymphatic duct. On the left side of the body, the remaining portions of the body drain into the larger thoracic duct, which drains into the left subclavian vein. The thoracic duct itself begins just beneath the diaphragm in the cisterna chyli, a sac-like chamber that receives lymph from the lower abdomen, pelvis, and lower limbs by way of the left and right lumbar trunks and the intestinal trunk.

Major Trunks and Ducts of the Lymphatic System

The thoracic duct drains a much larger portion of the body than does the right lymphatic duct.

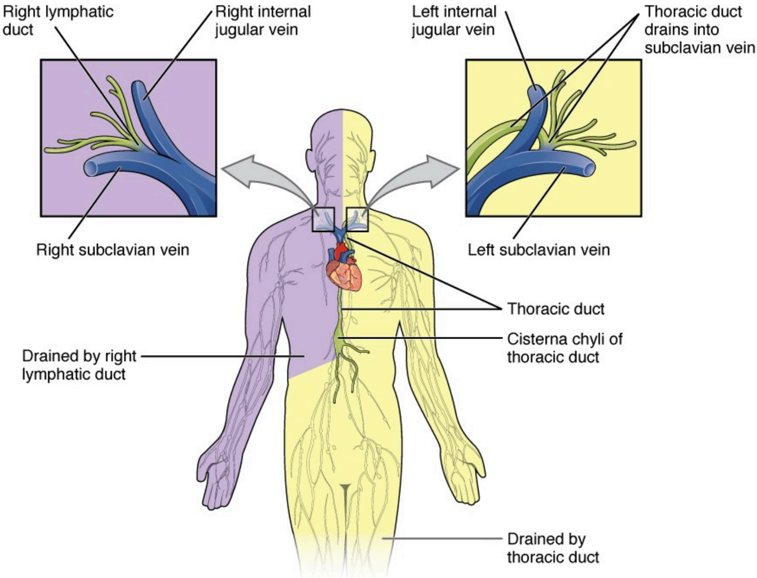


Figure 10.3: Major Trunks and Ducts of the Lymphatic System

The overall drainage system of the body is asymmetrical. The right lymphatic duct receives lymph from only the upper right side of the body. The lymph from the rest of the body enters the bloodstream through the thoracic duct via all the remaining lymphatic trunks. In general, lymphatic vessels of the subcutaneous tissues of the skin, that is, the superficial lymphatics, follow the same routes as veins, whereas the deep lymphatic vessels of the viscera generally follow the paths of arteries.

The Organization of Immune Function

The immune system is a collection of barriers, cells, and soluble proteins that interact and communicate with each other in extraordinarily complex ways. The modern model of immune function is organized into three phases based on the timing of their effects. The three temporal phases consist of the following:

- Barrier defenses such as the skin and mucous membranes, which act instantaneously to prevent pathogenic invasion into the body tissues
- The rapid but nonspecific innate immune response, which consists of a variety of specialized cells and soluble factors
- The slower but more specific and effective adaptive immune response, which involves many cell types and soluble factors, but is primarily controlled by white blood cells (leukocytes) known as lymphocytes, which help control immune responses

The cells of the blood, including all those involved in the immune response, arise in the bone marrow via various differentiation pathways from hematopoietic stem cells. In contrast with embryonic stem cells, hematopoietic stem cells are present throughout adulthood and allow for the continuous differentiation of blood cells to replace those lost to age or function. These cells can be divided into three classes based on function:

- Phagocytic cells, which ingest pathogens to destroy them
- Lymphocytes, which specifically coordinate the activities of adaptive immunity
- Cells containing cytoplasmic granules, which help mediate immune responses against parasites and intracellular pathogens such as viruses

Hematopoietic System of the Bone Marrow

All the cells of the immune response as well as of the blood arise by differentiation from hematopoietic stem cells. Platelets are cell fragments involved in the clotting of blood.

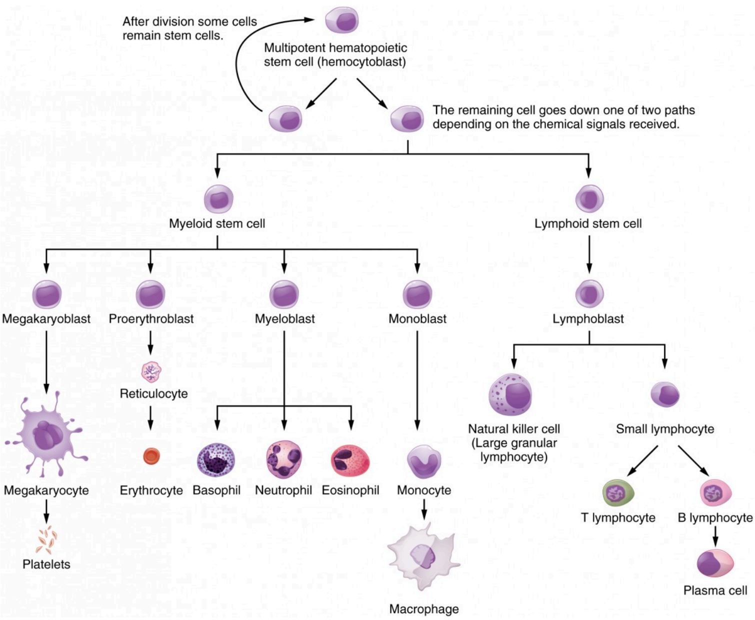


Figure 10.4: Hematopoietic System of the Bone Marrow

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

As stated above, lymphocytes are the primary cells of adaptive immune responses ([link]). The two basic types of lymphocytes, B cells and T cells, are identical morphologically with a large central nucleus surrounded by a thin layer of cytoplasm. They are distinguished from each other by their surface protein markers as well as by the molecules they secrete. While B cells mature in red bone marrow and T cells mature in the thymus, they both initially develop from bone marrow. T cells migrate from bone marrow to the thymus gland where they further mature. B cells and T cells are found in many parts of the body, circulating in the bloodstream and lymph, and residing in secondary lymphoid organs, including the spleen and lymph nodes, which will be described later in this section. The human body contains approximately 10^{12} lymphocytes.

B Cells

B cells are immune cells that function primarily by producing antibodies. An antibody is any of the group of proteins that binds specifically to pathogen-associated molecules known as antigens. An antigen is a chemical structure on the surface of a pathogen that binds to T or B lymphocyte antigen receptors. Once activated by binding to antigen, B cells differentiate into cells that secrete a soluble form of their surface antibodies. These activated B cells are known as plasma cells.

T Cells

The T cell, on the other hand, does not secrete antibody but performs a variety of functions in the adaptive immune response. Different T cell types have the ability to either secrete soluble factors that communicate with other cells of the adaptive immune response or destroy cells infected with intracellular pathogens. The roles of T and B lymphocytes in the adaptive immune response will be discussed further in this chapter.

Plasma Cells

Another type of lymphocyte of importance is the plasma cell. A plasma cell is a B cell that has differentiated in response to antigen binding, and has thereby gained the ability to secrete soluble antibodies. These cells differ in morphology from standard B and T cells in that they contain a large amount of cytoplasm packed with the protein-synthesizing machinery known as rough endoplasmic reticulum.

Natural Killer Cells

A fourth important lymphocyte is the natural killer cell, a participant in the innate immune response. A natural killer cell (NK) is a circulating blood cell that contains cytotoxic (cell-killing) granules in its extensive cytoplasm. It shares this mechanism with the cytotoxic T cells of the adaptive immune response. NK cells are among the body's first lines of defense against viruses and certain types of cancer.

Lymphocytes

Type of lymphocyte	Primary function
B lymphocyte	Generates diverse antibodies
T lymphocyte	Secretes chemical messengers
Plasma cell	Secretes antibodies
NK cell	Destroys virally infected cells

Primary Lymphoid Organs and Lymphocyte Development

Understanding the differentiation and development of B and T cells is critical to the understanding of the adaptive immune response. It is through this process that the body (ideally) learns to destroy only pathogens and leaves the body's own cells relatively intact. The primary lymphoid organs are the bone marrow, spleen, and thymus gland. The lymphoid organs are where lymphocytes mature, proliferate, and are selected, which enables them to attack pathogens without harming the cells of the body.

Bone Marrow

In the embryo, blood cells are made in the yolk sac. As development proceeds, this function is taken over by the spleen, lymph nodes, and liver. Later, the bone marrow takes over most hematopoietic functions, although the final stages of the differentiation of some cells may take place in other organs. The red bone marrow is a loose collection of cells where hematopoiesis occurs, and the yellow bone marrow is a site of energy storage, which consists largely of fat cells. The B cell undergoes nearly all of its development in the red bone marrow, whereas the immature T cell, called a thymocyte, leaves the bone marrow and matures largely in the thymus gland.

Bone Marrow

Red bone marrow fills the head of the femur, and a spot of yellow bone marrow is visible in the center. The white reference bar is 1 cm.

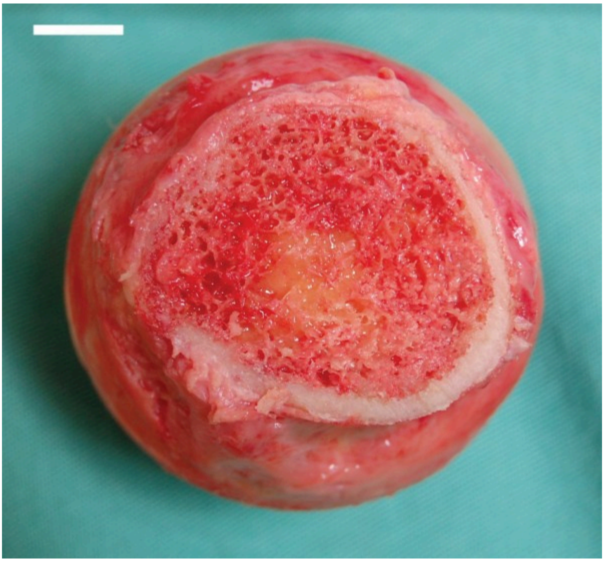


Figure 10.5: Bone Marrow

Thymus

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

Location, Structure, and Histology of the Thymus

The thymus lies above the heart. The trabeculae and lobules, including the darkly staining cortex and the lighter staining medulla of each lobule, are clearly visible in the light micrograph of the thymus of a newborn. LM × 100. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

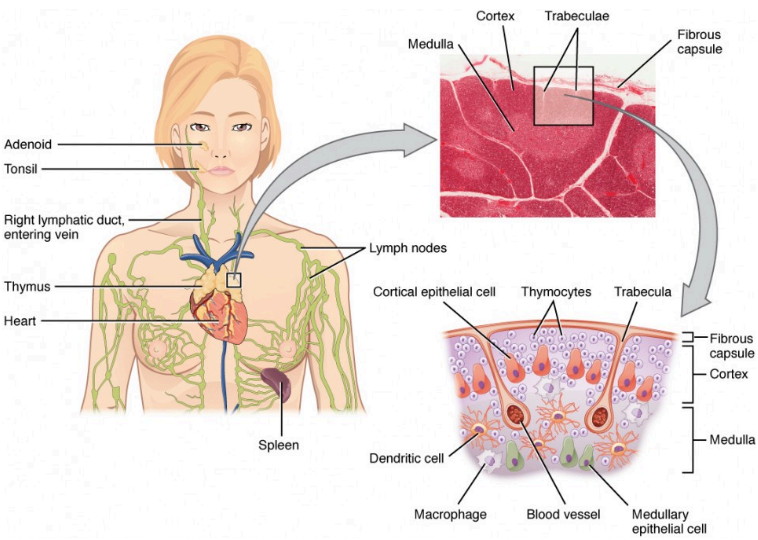


Figure 10.6: Location, Structure, and Histology of the Thymus

The connective tissue capsule further divides the thymus into lobules via extensions called trabeculae. The outer region of the organ is known as the cortex and contains large numbers of thymocytes with some epithelial cells, macrophages, and dendritic cells (two types of phagocytic cells that are derived from monocytes). The cortex is densely packed so it stains more intensely than the rest of the thymus. The medulla, where thymocytes migrate before leaving the thymus, contains a less dense collection of thymocytes, epithelial cells, and dendritic cells.

Secondary Lymphoid Organs and their Roles in Active Immune Responses

Lymphocytes develop and mature in the primary lymphoid organs, but they mount immune responses from the secondary lymphoid organs. A naïve lymphocyte is one that has left the primary organ and entered a secondary lymphoid organ. Naïve lymphocytes are fully functional immunologically, but have yet to encounter an antigen to respond to. In addition to circulating in the blood and lymph, lymphocytes concentrate in secondary lymphoid organs, which include the lymph nodes, spleen, and lymphoid nodules. All of these tissues have many features in common, including the following:

- The presence of lymphoid follicles, the sites of the formation of lymphocytes, with specific B cell-rich and T cell-rich areas
- An internal structure of reticular fibers with associated fixed macrophages
- Germinal centers, which are the sites of rapidly dividing B lymphocytes and plasma cells, with the exception of the spleen
- Specialized post-capillary vessels known as high endothelial venules; the cells lining these venules are thicker and more columnar than normal endothelial cells, which allow cells from the blood to directly enter these tissues

Lymph Nodes

Lymph nodes function to remove debris and pathogens from the lymph, and are thus sometimes referred to as the "filters of the lymph". Any bacteria that infect the interstitial fluid are taken up by the lymphatic capillaries and transported to a regional lymph node. Dendritic cells and macrophages within this organ internalize and kill many of the pathogens that pass through, thereby removing them from the body. The lymph node is also the site of adaptive immune responses mediated by T cells, B cells, and accessory cells of the adaptive immune system. Like the thymus, the bean-shaped lymph nodes are surrounded by a tough capsule of connective tissue and are separated into compartments by trabeculae, the extensions of the capsule. In addition to the structure provided by the capsule and trabeculae, the structural support of the lymph node is provided by a series of reticular fibers laid down by fibroblasts.

Structure and Histology of a Lymph Node

Lymph nodes are masses of lymphatic tissue located along the larger lymph vessels. The micrograph of the lymph nodes shows a germinal center, which consists of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. LM × 128. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

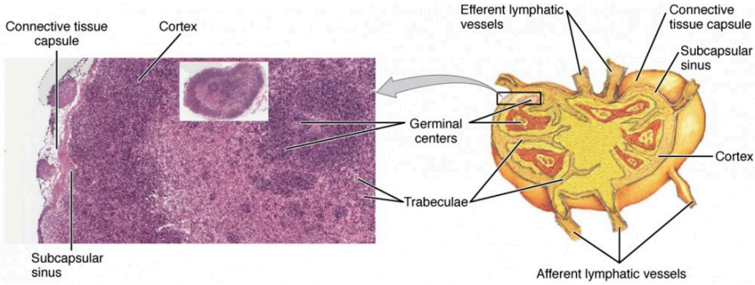


Figure 10.7: Structure and Histology of a Lymph Node

The major routes into the lymph node are via afferent lymphatic vessels. Cells and lymph fluid that leave the lymph node may do so by another set of vessels known as the efferent lymphatic vessels. Lymph enters the lymph node via the subcapsular sinus, which is occupied by dendritic cells, macrophages, and reticular fibers. Within the cortex of the lymph node are lymphoid follicles, which consist of germinal centers of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. As the lymph continues to flow through the node, it enters the medulla, which consists of medullary cords of B cells and plasma cells, and the medullary sinuses where the lymph collects before leaving the node via the efferent lymphatic vessels.

Spleen

In addition to the lymph nodes, the spleen is a major secondary lymphoid organ. It is about 12 cm (5 in) long and is attached to the lateral border of the stomach via the gastrosplenic ligament. The spleen is a fragile organ without a strong capsule, and is dark red due to its extensive vascularization. The spleen is sometimes called the “filter of the blood” because of its extensive vascularization and the presence of macrophages and dendritic cells that remove microbes and other materials from the blood, including dying red blood cells. The spleen also functions as the location of immune responses to blood-borne pathogens.

Spleen

(a) The spleen is attached to the stomach. (b) A micrograph of spleen tissue shows the germinal center. The marginal zone is the region between the red pulp and white pulp, which sequesters particulate antigens from the circulation and presents these antigens to lymphocytes in the white pulp. EM × 660. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

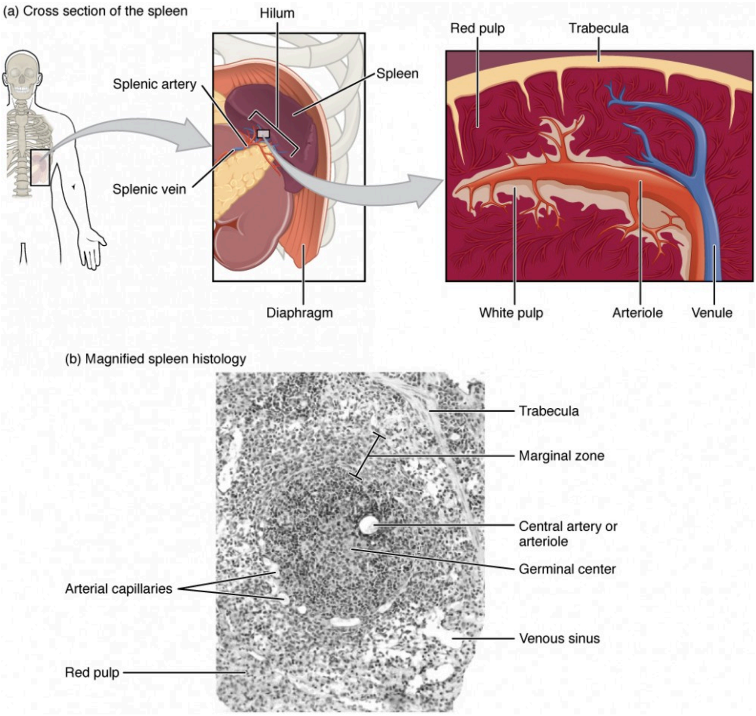


Figure 10.8: Spleen

The spleen is also divided by trabeculae of connective tissue, and within each splenic nodule is an area of red pulp, consisting of mostly red blood cells, and white pulp, which resembles the lymphoid follicles of the lymph nodes. Upon entering the spleen, the splenic artery splits into several arterioles (surrounded by white pulp) and eventually into sinusoids. Blood from the capillaries subsequently collects in the venous sinuses and leaves via the splenic vein. The red pulp consists of reticular fibers with fixed macrophages attached, free macrophages, and all of the other cells typical of the blood, including some lymphocytes. The white pulp surrounds a central arteriole and consists of germinal centers of dividing B cells surrounded by T cells and accessory cells, including macrophages and dendritic cells. Thus, the red pulp primarily functions as a filtration system of the blood, using cells of the relatively nonspecific immune response, and white pulp is where adaptive T and B cell responses are mounted.

Lymphoid Nodules

The other lymphoid tissues, the lymphoid nodules, have a simpler architecture than the spleen and lymph nodes in that they consist of a dense cluster of lymphocytes without a surrounding fibrous capsule. These nodules are located in the respiratory and digestive tracts, areas routinely exposed to environmental pathogens.

Tonsils are lymphoid nodules located along the inner surface of the pharynx and are important in developing immunity to oral pathogens. The tonsil located at the back of the throat, the pharyngeal tonsil, is sometimes referred to as the adenoid when swollen. Such swelling is an indication of an active immune response to infection. Histologically, tonsils do not contain a complete capsule, and the epithelial layer invaginates deeply into the interior of the tonsil to form tonsillar crypts. These structures, which accumulate all sorts of materials taken into the body through eating and breathing, actually "encourage" pathogens to penetrate deep into the tonsillar tissues where they are acted upon by numerous lymphoid follicles and eliminated. This seems to be the major function of tonsils—to help children's bodies recognize, destroy, and develop immunity to common environmental pathogens so that they will be protected in their later lives. Tonsils are often removed in those children who have recurring throat infections, especially those involving the palatine tonsils on either side of the throat, whose swelling may interfere with their breathing and/or swallowing.

Locations and Histology of the Tonsils

(a) The pharyngeal tonsil is located on the roof of the posterior superior wall of the nasopharynx. The palatine tonsils lay on each side of the pharynx. (b) A micrograph shows the palatine tonsil tissue. LM × 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

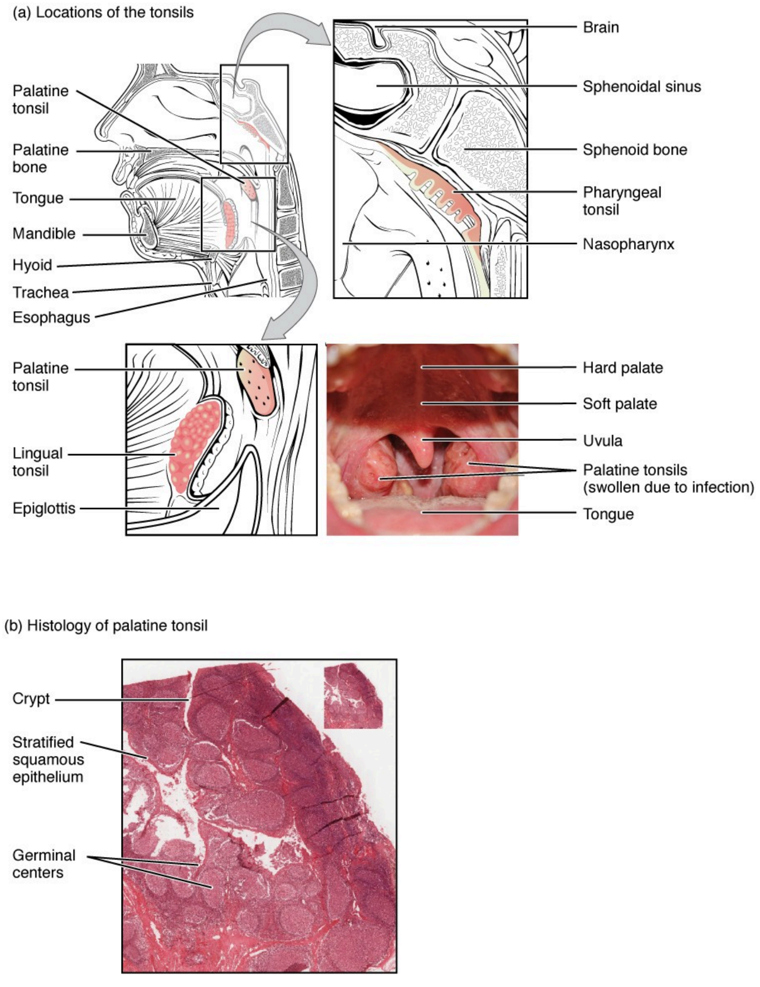


Figure 10.9: Locations and Histology of the Tonsils

Mucosa-associated lymphoid tissue (MALT) consists of an aggregate of lymphoid follicles directly associated with the mucous membrane epithelia. MALT makes up dome-shaped structures found underlying the mucosa of the gastrointestinal tract, breast tissue, lungs, and eyes. Peyer's patches, a type of MALT in the small intestine, are especially important for immune responses against ingested substances. Peyer's patches contain specialized endothelial cells called M (or microfold) cells that sample material from the intestinal lumen and transport it to nearby follicles so that adaptive immune responses to potential pathogens can be mounted.

Mucosa-associated Lymphoid Tissue (MALT) Nodule

LM × 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

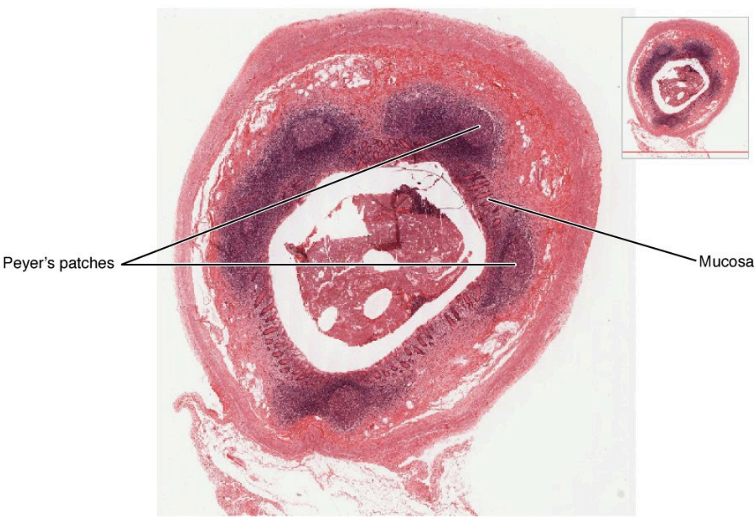


Figure 10.10: Mucosa-associated Lymphoid Tissue (MALT) Nodule

Bronchus-associated lymphoid tissue (BALT) consists of lymphoid follicular structures with an overlying epithelial layer found along the bifurcations of the bronchi, and between bronchi and arteries. They also have the typically less-organized structure of other lymphoid nodules. These tissues, in addition to the tonsils, are effective against inhaled pathogens.

60. Age Related Changes to the Immune System

Aging and the Immune System

By the year 2050, 25 percent of the population of the United States will be 60 years of age or older. The CDC estimates that 80 percent of those 60 years and older have one or more chronic disease associated with deficiencies of the immune systems. This loss of immune function with age is called immunosenescence. To treat this growing population, medical professionals must better understand the aging process. One major cause of age-related immune deficiencies is thymic involution, the shrinking of the thymus gland that begins at birth, at a rate of about three percent tissue loss per year, and continues until 35–45 years of age, when the rate declines to about one percent loss per year for the rest of one's life. At that pace, the total loss of thymic epithelial tissue and thymocytes would occur at about 120 years of age. Thus, this age is a theoretical limit to a healthy human lifespan.

Thymic involution has been observed in all vertebrate species that have a thymus gland. Animal studies have shown that transplanted thymic grafts between inbred strains of mice involuted according to the age of the donor and not of the recipient, implying the process is genetically programmed. There is evidence that the thymic microenvironment, so vital to the development of naïve T cells, loses thymic epithelial cells according to the decreasing expression of the FOXN1 gene with age.

It is also known that thymic involution can be altered by hormone levels. Sex hormones such as estrogen and testosterone enhance involution, and the hormonal changes in pregnant women cause a temporary thymic involution that reverses itself, when the size of the thymus and its hormone levels return to normal, usually after lactation ceases. What does all this tell us? Can we reverse immunosenescence, or at least slow it down? The potential is there for using thymic transplants from younger donors to keep thymic output of naïve T cells high. Gene therapies that target gene expression are also seen as future possibilities. The more we learn through immunosenescence research, the more opportunities there will be to develop therapies, even though these therapies will likely take decades to develop. The ultimate goal is for everyone to live and be healthy longer, but there may be limits to immortality imposed by our genes and hormones.

61. Age Related Dysfunctions of the Immune System

General Decrease in Immune Responses

The interactions of the immune system are very complex. This makes it impossible to fully understand how the dysfunctions of individual components affect the system as a whole. That being said, it is well known that there is a general decrease in immune response with age. Simultaneously autoimmune responses increase with age. This means that the body's ability to fight invading pathogens is decreasing, while it becomes more likely that the immune system will attack the body's own healthy tissue.

Age Associated T-Lymphocyte Defects

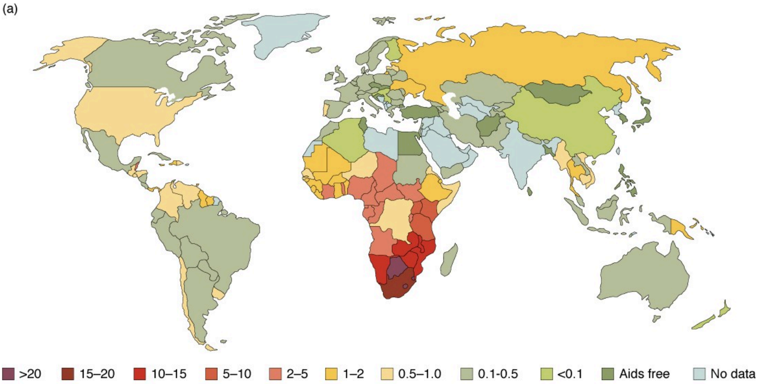
The reduced activity of T lymphocytes and the reduction in cell-mediated immunity that results in considered to be a factor in the reactivation of lymphoma, tuberculosis, and shingles that occurs most often in older people.

Acquired Immune Deficiency Syndrome

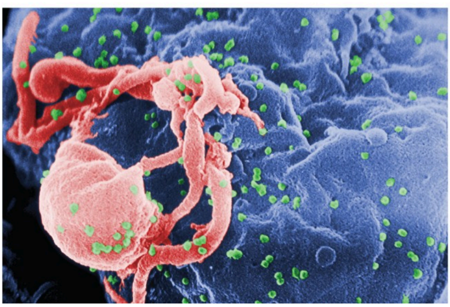
The Worldwide AIDS Epidemic
(a) As of 2008, more than 15 percent of adults were infected with HIV in certain African countries. This grim picture had changed little by 2012. (b) In this scanning electron micrograph, HIV virions

(green particles) are budding off the surface of a macrophage (pink structure). (credit b: C. Goldsmith)

(a)



(b)



In June 1981, the Centers for Disease Control and Prevention (CDC), in Atlanta, Georgia, published a report of an unusual cluster of five patients in Los Angeles, California. All five were diagnosed with a rare pneumonia caused by a fungus called *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*).

Why was this unusual? Although commonly found in the lungs of healthy individuals, this fungus is an opportunistic pathogen that causes disease in individuals with suppressed or underdeveloped immune systems. The very young, whose immune systems have yet to mature, and the elderly, whose immune systems have declined with age, are particularly susceptible. The five patients from LA, though, were between 29 and 36 years of age and should have been in the prime of their lives, immunologically speaking. What could be going on?

A few days later, a cluster of eight cases was reported in New York City, also involving young patients, this time exhibiting a rare form of skin cancer known as Kaposi's sarcoma. This cancer of the cells that line the blood and lymphatic vessels was previously observed as a relatively innocuous disease of the elderly. The disease that doctors saw in 1981 was frighteningly more severe, with multiple, fast-growing lesions that spread to all parts of the body, including the trunk and face. Could the immune systems of these young patients have been compromised in some way? Indeed, when they were tested, they exhibited extremely low numbers of a specific type of white blood cell in their bloodstreams, indicating that they had somehow lost a major part of the immune system.

Acquired immune deficiency syndrome, or AIDS, turned out to be a new disease caused by the previously unknown human immunodeficiency virus (HIV). Although nearly 100 percent fatal in those with active HIV infections in the early years, the development of anti-HIV drugs has transformed HIV infection into a chronic, manageable disease and not the certain death sentence it once was. One positive outcome resulting from the emergence of HIV disease was that the public's attention became focused as never before on the importance of having a functional and healthy immune system.

Although many viruses cause suppression of the immune system, only one wipes it out completely, and that is HIV. It is worth discussing the biology of this virus, which can lead to the well-known AIDS, so that its full effects on the immune system can be understood. The virus is transmitted through semen, vaginal fluids, and blood, and can be caught by risky sexual behaviors and the sharing of needles by intravenous drug users. There are sometimes, but not always, flu-like symptoms in the first 1 to 2 weeks after infection. This is later followed by seroconversion. The anti-HIV antibodies formed during seroconversion are the basis for most initial HIV screening done in the United States. Because seroconversion takes different lengths of time in different individuals, multiple AIDS tests are given months apart to confirm or eliminate the possibility of infection.

After seroconversion, the amount of virus circulating in the blood drops and stays at a low level for several years. During this time, the levels of $CD4^+$ cells, especially helper T cells, decline steadily, until at some point, the immune response is so weak that opportunistic disease and eventually death result. CD4 is the receptor that HIV uses to get inside T cells and reproduce. Given that $CD4^+$ helper T cells play an important role in other in T cell immune responses and antibody responses, it should be no surprise that both types of immune responses are eventually seriously compromised.

Treatment for the disease consists of drugs that target virally encoded proteins that are necessary for viral replication but are absent from normal human cells. By targeting the virus itself and sparing the cells, this approach has been successful in significantly prolonging the lives of HIV-positive individuals. On the other hand, an HIV vaccine has been 30 years in development and is still years away. Because the virus mutates rapidly to evade the immune system, scientists have been looking for parts of the virus that do not change and thus would be good targets for a vaccine candidate.

Lymphomas

Lymphomas are malignancies of the lymph nodes. Typical symptoms include swollen lymph nodes, persistent fever, night sweat sweats, and weight loss. Lymphomas are classifies as either Hodgkin's disease or non-Hodgkin's lymphoma bases on different patterns of spread, clinical behavior, and cells or origin. Hodgkin's disease shows a bimodal age distribution, with one peak occurring between 15 and 35 years of age and another peak between ages 50 and 80. The incidence of non-Hodgkin's lymphoma increases progressively with age.

62. Glossary: The Immune System

Glossary

adaptive immune response relatively slow but very specific and effective immune response controlled by lymphocytes

afferent lymphatic vessels lead into a lymph node

antibody antigen-specific protein secreted by plasma cells; immunoglobulin

antigen molecule recognized by the receptors of B and T lymphocytes

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

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

bone marrow tissue found inside bones; the site of all blood cell differentiation and maturation of B lymphocytes

bronchus-associated lymphoid tissue (BALT) lymphoid nodule associated with the respiratory tract

chyle lipid-rich lymph inside the lymphatic capillaries of the small intestine

cisterna chyli bag-like vessel that forms the beginning of the thoracic duct

efferent lymphatic vessels lead out of a lymph node

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

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

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

innate immune response rapid but relatively nonspecific immune response

lymph fluid contained within the lymphatic system

lymph node one of the bean-shaped organs found associated with the lymphatic vessels

lymphatic capillaries smallest of the lymphatic vessels and the origin of lymph flow

lymphatic system network of lymphatic vessels, lymph nodes, and ducts that carries lymph from the tissues and back to the bloodstream.

lymphatic trunks large lymphatics that collect lymph from smaller lymphatic vessels and empties into the blood via lymphatic ducts

lymphocytes white blood cells characterized by a large nucleus and small rim of cytoplasm

lymphoid nodules unencapsulated patches of lymphoid tissue found throughout the body

mucosa-associated lymphoid tissue (MALT) lymphoid nodule associated with the mucosa

naïve lymphocyte mature B or T cell that has not yet encountered antigen for the first time

natural killer cell (NK) cytotoxic lymphocyte of innate immune response

plasma cell differentiated B cell that is actively secreting antibody

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

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

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

spleen secondary lymphoid organ that filters pathogens from the blood (white pulp) and removes degenerating or damaged blood cells (red pulp)

T cell lymphocyte that acts by secreting molecules that regulate the immune system or by causing the destruction of foreign cells, viruses, and cancer cells

thoracic duct large duct that drains lymph from the lower limbs, left thorax, left upper limb, and the left side of the head

thymocyte immature T cell found in the thymus

thymus primary lymphoid organ; where T lymphocytes proliferate and mature

tonsils lymphoid nodules associated with the nasopharynx

PART XI

CHAPTER 11: THE RESPIRATORY SYSTEM

63. Organs and Structures of the Respiratory System

Hold your breath. Really! See how long you can hold your breath as you continue reading…How long can you do it? Chances are you are feeling uncomfortable already. A typical human cannot survive without breathing for more than 3 minutes, and even if you wanted to hold your breath longer, your autonomic nervous system would take control. This is because every cell in the body needs to run the oxidative stages of cellular respiration, the process by which energy is produced in the form of adenosine triphosphate (ATP). For oxidative phosphorylation to occur, oxygen is used as a reactant and carbon dioxide is released as a waste product. You may be surprised to learn that although oxygen is a critical need for cells, it is actually the accumulation of carbon dioxide that primarily drives your need to breathe. Carbon dioxide is exhaled and oxygen is inhaled through the respiratory system, which includes muscles to move air into and out of the lungs, passageways through which air moves, and microscopic gas exchange surfaces covered by capillaries. The circulatory system transports gases from the lungs to tissues throughout the body and vice versa. A variety of diseases can affect the respiratory system, such as asthma, emphysema, chronic obstruction pulmonary disorder (COPD), and lung cancer. All of these conditions affect the gas exchange process and result in labored breathing and other difficulties.

The major organs of the respiratory system function primarily to provide oxygen to body tissues for cellular respiration, remove the waste product carbon dioxide, and help to maintain acid-base balance. Portions of the respiratory system are also used for non-vital functions, such as sensing odors, speech production, and for straining, such as during childbirth or coughing.

Major Respiratory Structures

The major respiratory structures span the nasal cavity to the diaphragm.

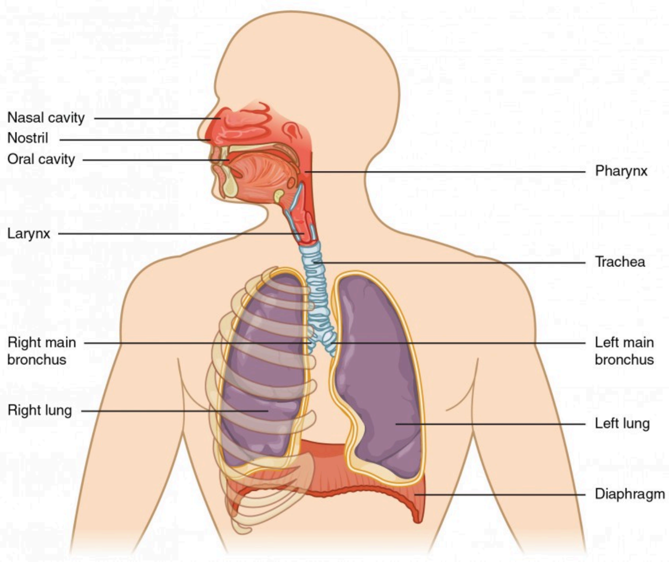


Figure 11.1: Major Respiratory Structures

Functionally, the respiratory system can be divided into a conducting zone and a respiratory zone. The conducting zone of the respiratory system includes the organs and structures not directly involved in gas exchange. The gas exchange occurs in the respiratory zone.

Conducting Zone

The major functions of the conducting zone are to provide a route for incoming and outgoing air, remove debris and pathogens from the incoming air, and warm and humidify the incoming air. Several structures within the conducting zone perform other functions as well. The epithelium of the nasal passages, for example, is essential to sensing odors, and the bronchial epithelium that lines the lungs can metabolize some airborne carcinogens.

The Nose and its Adjacent Structures

The major entrance and exit for the respiratory system is through the nose. When discussing the nose, it is helpful to divide it into two major sections: the external nose, and the nasal cavity or internal nose.

The external nose consists of the surface and skeletal structures that result in the outward appearance of the nose and contribute to its numerous functions. The root is the region of the nose located between the eyebrows. The bridge is the part of the nose that connects the root to the rest of the nose. The dorsum nasi is the length of the nose. The apex is the tip of the nose. On either side of the apex, the nostrils are formed by the alae (singular = ala). An ala is a cartilaginous structure that forms the lateral side of each naris (plural = nares), or nostril opening. The philtrum is the concave surface that connects the apex of the nose to the upper lip.

Nose

This illustration shows features of the external nose (top) and skeletal features of the nose (bottom).

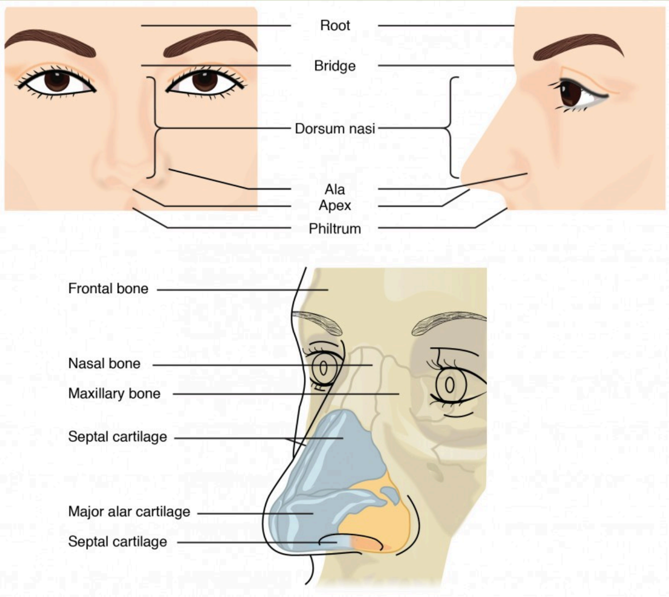


Figure 11.2: Nose

Underneath the thin skin of the nose are its skeletal features. While the root and bridge of the nose consist of bone, the protruding portion of the nose is composed of cartilage. As a result, when looking at a skull, the nose is missing. The nasal bone is one of a pair of bones that lies under the root and bridge of the nose. The nasal bone articulates superiorly with the frontal bone and laterally with the maxillary bones. Septal cartilage is flexible hyaline cartilage connected to the nasal bone, forming the dorsum nasi. The alar cartilage consists of the apex of the nose; it surrounds the naris.

The nares open into the nasal cavity, which is separated into left and right sections by the nasal septum. The nasal septum is formed anteriorly by a portion of the septal cartilage (the flexible portion you can touch with your fingers) and posteriorly by the perpendicular plate of the ethmoid bone (a cranial bone located just posterior to the nasal bones) and the thin vomer bones (whose name refers to its plough shape). Each lateral wall of the nasal cavity has three bony projections, called the superior, middle, and inferior nasal conchae. The inferior conchae are separate bones, whereas the superior and middle conchae are portions of the ethmoid bone. Conchae serve to increase the surface area of the nasal cavity and to disrupt the flow of air as it enters the nose, causing air to bounce along the epithelium, where it is cleaned and warmed. The conchae and meatuses also conserve water and prevent dehydration of the nasal epithelium by trapping water during exhalation. The floor of the nasal cavity is composed of the palate. The hard palate at the anterior region of the nasal cavity is composed of bone. The soft palate at the posterior portion of the nasal cavity consists of muscle tissue. Air exits the nasal cavities via the internal nares and moves into the pharynx.

Upper Airway

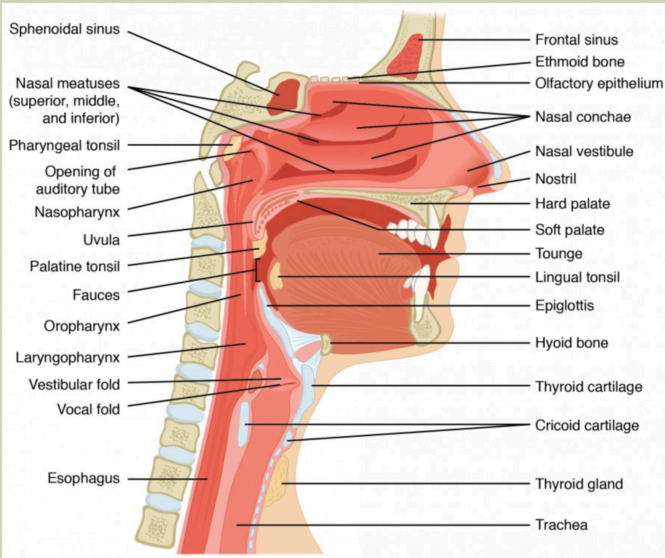


Figure 11.3: Upper Airway

Several bones that help form the walls of the nasal cavity have air-containing spaces called the paranasal sinuses, which serve to warm and humidify incoming air. Sinuses are lined with a mucosa. Each paranasal sinus is named for its associated bone: frontal sinus, maxillary sinus, sphenoidal sinus, and ethmoidal sinus. The sinuses produce mucus and lighten the weight of the skull.

The nares and anterior portion of the nasal cavities are lined with mucous membranes, containing sebaceous glands and hair follicles that serve to prevent the passage of large debris, such as dirt, through the nasal cavity. An olfactory epithelium used to detect odors is found deeper in the nasal cavity.

The conchae, meatuses, and paranasal sinuses are lined by respiratory epithelium composed of pseudostratified ciliated columnar epithelium. The epithelium contains goblet cells, one of the specialized, columnar epithelial cells that produce mucus to trap debris. The cilia of the respiratory epithelium help remove the mucus and debris from the nasal cavity with a constant beating motion, sweeping materials towards the throat to be swallowed. Interestingly, cold air slows the movement of the cilia, resulting in accumulation of mucus that may in turn lead to a runny nose during cold weather. This moist epithelium functions to warm and humidify incoming air. Capillaries located just beneath the nasal epithelium warm the air by convection. Serous and mucus-producing cells also secrete the lysozyme enzyme and proteins called defensins, which have antibacterial properties. Immune cells that patrol the connective tissue deep to the respiratory epithelium provide additional protection.

Pseudostratified Ciliated Columnar Epithelium

Respiratory epithelium is pseudostratified ciliated columnar epithelium. Seromucous glands provide lubricating mucus. LM × 680. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

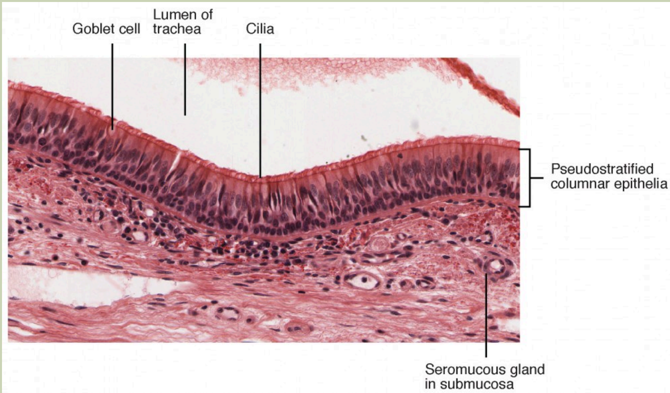


Figure 11.4: Pseudostratified Ciliated Columnar Epithelium

Pharynx

The pharynx is a tube formed by skeletal muscle and lined by mucous membrane that is continuous with that of the nasal cavities. The pharynx is divided into three major regions: the nasopharynx, the oropharynx, and the laryngopharynx.

Divisions of the Pharynx

The pharynx is divided into three regions: the nasopharynx, the oropharynx, and the laryngopharynx.

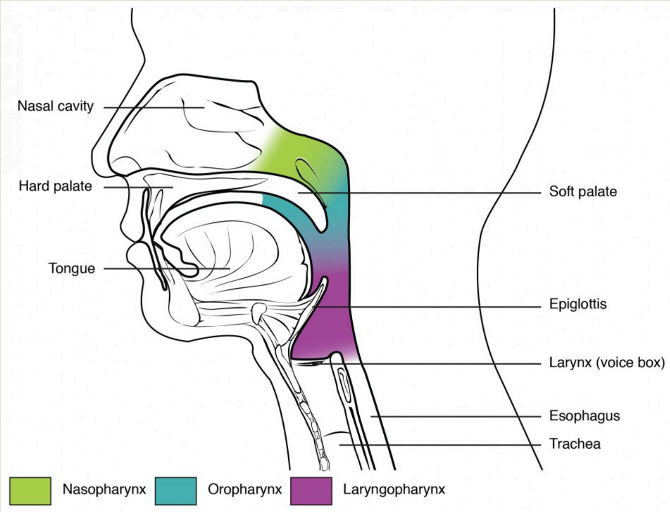


Figure 11.5: Divisions of the Pharynx

The nasopharynx is flanked by the conchae of the nasal cavity, and it serves only as an airway. At the top of the nasopharynx are the pharyngeal tonsils. A pharyngeal tonsil, also called an adenoid, is an aggregate of lymphoid reticular tissue similar to a lymph node that lies at the superior portion of the nasopharynx. The function of the pharyngeal tonsil is not well understood, but it contains a rich supply of lymphocytes and is covered with ciliated epithelium that traps and destroys invading pathogens that enter during inhalation. The pharyngeal tonsils are large in children, but interestingly, tend to regress with age and may even disappear. The uvula is a small bulbous, teardrop-shaped structure located at the apex of the soft palate. Both the uvula and soft palate move like a pendulum during swallowing, swinging upward to close off the nasopharynx to prevent ingested materials from entering the nasal cavity. In addition, auditory (Eustachian) tubes that connect to each middle ear cavity open into the nasopharynx. This connection is why colds often lead to ear infections.

The oropharynx is a passageway for both air and food. The oropharynx is bordered superiorly by the nasopharynx and anteriorly by the oral cavity. The fauces is the opening at the connection between the oral cavity and the oropharynx. As the nasopharynx becomes the oropharynx, the epithelium changes from pseudostratified ciliated columnar epithelium to stratified squamous epithelium. The oropharynx contains two distinct sets of tonsils, the palatine and lingual tonsils. A palatine tonsil is one of a pair of structures located laterally in the oropharynx in the area of the fauces. The lingual tonsil is located at the base of the tongue. Similar to the pharyngeal tonsil, the palatine and lingual tonsils are composed of lymphoid tissue, and trap and destroy pathogens entering the body through the oral or nasal cavities.

The laryngopharynx is inferior to the oropharynx and posterior to the larynx. It continues the route for ingested material and air until its inferior end, where the digestive and respiratory systems diverge. The stratified squamous epithelium of the oropharynx is continuous with the laryngopharynx. Anteriorly, the laryngopharynx opens into the larynx, whereas posteriorly, it enters the esophagus.

Larynx

The larynx is a cartilaginous structure inferior to the laryngopharynx that connects the pharynx to the trachea and helps regulate the volume of air that enters and leaves the lungs. The structure of the larynx is formed by several pieces of cartilage. Three large cartilage pieces—the thyroid cartilage (anterior), epiglottis (superior), and cricoid cartilage (inferior)—form the major structure of the larynx. The thyroid cartilage is the largest piece of cartilage that makes up the larynx. The thyroid cartilage consists of the laryngeal prominence, or "Adam's apple," which tends to be more prominent in males. The thick cricoid cartilage forms a ring, with a wide posterior region and a thinner anterior region. Three smaller, paired cartilages—the arytenoids, corniculates, and cuneiforms—attach to the epiglottis and the vocal cords and muscle that help move the vocal cords to produce speech.

Larynx

The larynx extends from the laryngopharynx and the hyoid bone to the trachea.

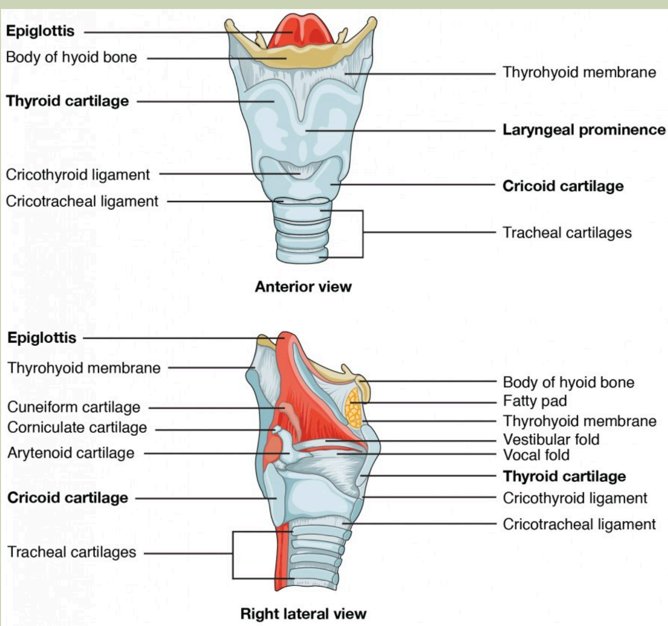


Figure 11.6: Larynx

The epiglottis, attached to the thyroid cartilage, is a very flexible piece of elastic cartilage that covers the opening of the trachea. When in the "closed" position, the unattached end of the epiglottis rests on the glottis. The glottis is composed of the vestibular folds, the true vocal cords, and the space between these folds. A vestibular fold, or false vocal cord, is one of a pair of folded sections of mucous membrane. A true vocal cord is one of the white, membranous folds attached by muscle to the thyroid and arytenoid cartilages of the larynx on their outer edges. The inner edges of the true vocal cords are free, allowing oscillation to produce sound. The size of the membranous folds of the true vocal cords differs between individuals, producing voices with different pitch ranges. Folds in males tend to be larger than those in females, which create a deeper voice. The act of swallowing causes the pharynx and larynx to lift upward, allowing the pharynx to expand and the epiglottis of the larynx to swing downward, closing the opening to the trachea. These movements produce a larger area for food to pass through, while preventing food and beverages from entering the trachea.

Vocal Cords

The true vocal cords and vestibular folds of the larynx are viewed inferiorly from the laryngopharynx.

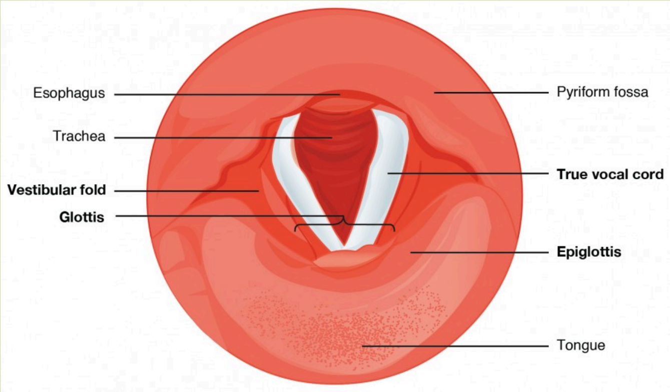


Figure 11.7: Vocal Cords

Continuous with the laryngopharynx, the superior portion of the larynx is lined with stratified squamous epithelium, transitioning into pseudostratified ciliated columnar epithelium that contains goblet cells. Similar to the nasal cavity and nasopharynx, this specialized epithelium produces mucus to trap debris and pathogens as they enter the trachea. The cilia beat the mucus upward towards the laryngopharynx, where it can be swallowed down the esophagus.

Trachea

The trachea (windpipe) extends from the larynx toward the lungs. The trachea is formed by 16 to 20 stacked, C-shaped pieces of hyaline cartilage that are connected by dense connective tissue. The trachealis muscle and elastic connective tissue together form the fibroelastic membrane, a flexible membrane that closes the posterior surface of the trachea, connecting the C-shaped cartilages. The fibroelastic membrane allows the trachea to stretch and expand slightly during inhalation and exhalation, whereas the rings of cartilage provide structural support and prevent the trachea from collapsing. In addition, the trachealis muscle can be contracted to force air through the trachea during exhalation. The trachea is lined with pseudostratified ciliated columnar epithelium, which is continuous with the larynx. The esophagus borders the trachea posteriorly.

Trachea

(a) The tracheal tube is formed by stacked, C-shaped pieces of hyaline cartilage. (b) The layer visible in this cross-section of tracheal wall tissue between the hyaline cartilage and the lumen of the trachea is the mucosa, which is composed of pseudostratified ciliated columnar epithelium that contains goblet cells. LM × 1220. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

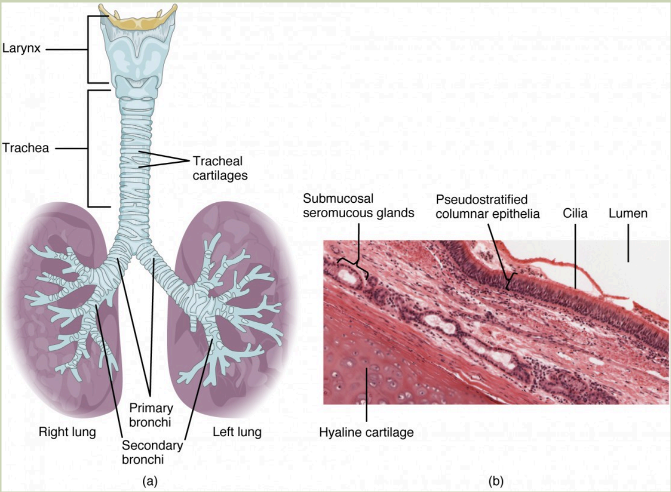


Figure 11.8: Trachea

Bronchial Tree

The trachea branches into the right and left primary bronchi at the carina. These bronchi are also lined by pseudostratified ciliated columnar epithelium containing mucus-producing goblet cells. The carina is a raised structure that contains specialized nervous tissue that induces violent coughing if a foreign body, such as food, is present. Rings of cartilage, similar to those of the trachea, support the structure of the bronchi and prevent their collapse. The primary bronchi enter the lungs at the hilum, a concave region where blood vessels, lymphatic vessels, and nerves also enter the lungs. The bronchi continue to branch into bronchial a tree. A bronchial tree (or respiratory tree) is the collective term used for these multiple-branched bronchi. The main function of the bronchi, like other conducting zone structures, is to provide a passageway for air to move into and out of each lung. In addition, the mucous membrane traps debris and pathogens.

A bronchiole branches from the tertiary bronchi. Bronchioles, which are about 1 mm in diameter, further branch until they become the tiny terminal bronchioles, which lead to the structures of gas exchange. There are more than 1000 terminal bronchioles in each lung. The muscular walls of the bronchioles do not contain cartilage like those of the bronchi. This muscular wall can change the size of the tubing to increase or decrease airflow through the tube.

Respiratory Zone

In contrast to the conducting zone, the respiratory zone includes structures that are directly involved in gas exchange. The respiratory zone begins where the terminal bronchioles join a respiratory bronchiole, the smallest type of bronchiole, which then leads to an alveolar duct, opening into a cluster of alveoli.

Respiratory Zone

Bronchioles lead to alveolar sacs in the respiratory zone, where gas exchange occurs.

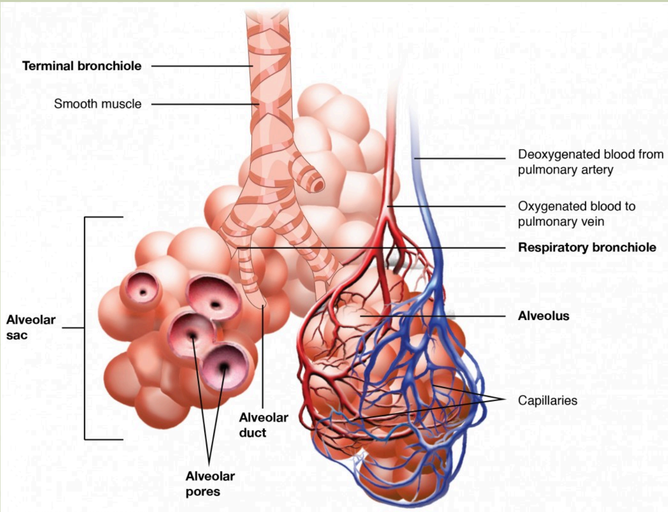


Figure 11.9: Respiratory Zone

Alveoli

An alveolar duct is a tube composed of smooth muscle and connective tissue, which opens into a cluster of alveoli. An alveolus is one of the many small, grape-like sacs that are attached to the alveolar ducts.

An alveolar sac is a cluster of many individual alveoli that are responsible for gas exchange. An alveolus is approximately 200 mm in diameter with elastic walls that allow the alveolus to stretch during air intake, which greatly increases the surface area available for gas exchange. Alveoli are connected to their neighbors by alveolar pores, which help maintain equal air pressure throughout the alveoli and lung.

Structures of the Respiratory Zone

(a) The alveolus is responsible for gas exchange. (b) A micrograph shows the alveolar structures within lung tissue. LM × 178. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

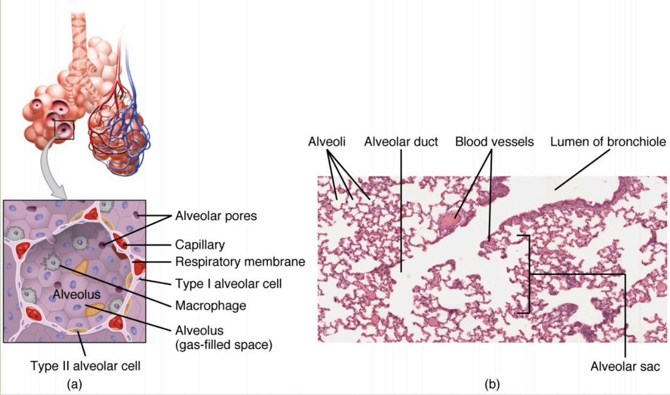


Figure 11.10: Structures of the Respiratory Zone

The alveolar wall consists of three major cell types: type I alveolar cells, type II alveolar cells, and alveolar macrophages. A type I alveolar cell is a squamous epithelial cell of the alveoli, which constitute up to 97 percent of the alveolar surface area. These cells are about 25 nm thick and are highly permeable to gases. A type II alveolar cell is interspersed among the type I cells and secretes pulmonary surfactant, a substance composed of phospholipids and proteins that reduces the surface tension of the alveoli. Roaming around the alveolar wall is the alveolar macrophage, a phagocytic cell of the immune system that removes debris and pathogens that have reached the alveoli.

The simple squamous epithelium formed by type I alveolar cells is attached to a thin, elastic basement membrane. This epithelium is extremely thin and borders the endothelial membrane of capillaries. Taken together, the alveoli and capillary membranes form a respiratory membrane that is approximately 0.5 mm thick. The respiratory membrane allows gases to cross by simple diffusion, allowing oxygen to be picked up by the blood for transport and CO_2 to be released into the air of the alveoli.

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64. The Lungs

A major organ of the respiratory system, each lung houses structures of both the conducting and respiratory zones. The main function of the lungs is to perform the exchange of oxygen and carbon dioxide with air from the atmosphere. To this end, the lungs exchange respiratory gases across a very large epithelial surface area—about 70 square meters—that is highly permeable to gases.

Gross Anatomy of the Lungs

The lungs are pyramid-shaped, paired organs that are connected to the trachea by the right and left bronchi; on the inferior surface, the lungs are bordered by the diaphragm. The diaphragm is the flat, dome-shaped muscle located at the base of the lungs and thoracic cavity. The lungs are enclosed by the pleurae, which are attached to the mediastinum. The right lung is shorter and wider than the left lung, and the left lung occupies a smaller volume than the right. The cardiac notch is an indentation on the surface of the left lung, and it allows space for the heart. The apex of the lung is the superior region, whereas the base is the opposite region near the diaphragm. The costal surface of the lung borders the ribs. The mediastinal surface faces the midline.

Gross Anatomy of the Lungs

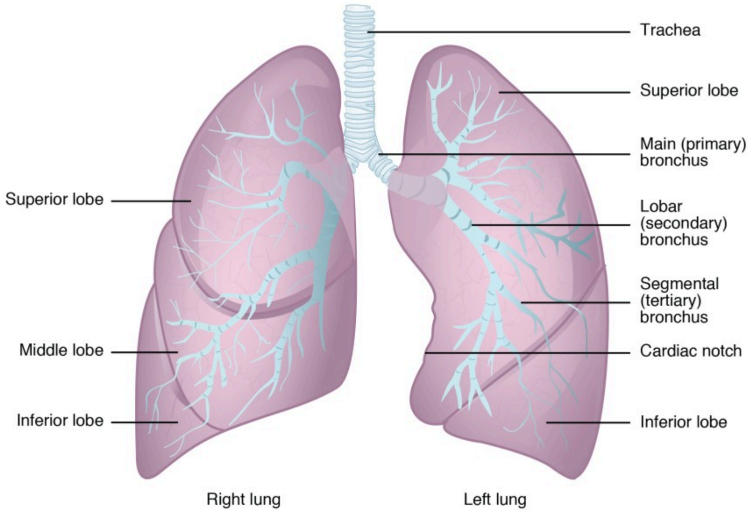


Figure 11.11: Gross Anatomy of the Lungs

Each lung is composed of smaller units called lobes. Fissures separate these lobes from each other. The right lung consists of three lobes: the superior, middle, and inferior lobes. The left lung consists of two lobes: the superior and inferior lobes. A bronchopulmonary segment is a division of a lobe, and each lobe houses multiple bronchopulmonary segments. Each segment receives air from its own tertiary bronchus and is supplied with blood by its own artery. Some diseases of the lungs typically affect one or more bronchopulmonary segments, and in some cases, the diseased segments can be surgically removed with little influence on neighboring segments. A pulmonary lobule is a subdivision formed as the bronchi branch into bronchioles. Each lobule receives its own large bronchiole that has multiple branches. An interlobular septum is a wall, composed of connective tissue, which separates lobules from one another.

Blood Supply and Nervous Innervation of the

Lungs

The blood supply of the lungs plays an important role in gas exchange and serves as a transport system for gases throughout the body. In addition, innervation by the both the parasympathetic and sympathetic nervous systems provides an important level of control through dilation and constriction of the airway.

Blood Supply

The major function of the lungs is to perform gas exchange, which requires blood from the pulmonary circulation. This blood supply contains deoxygenated blood and travels to the lungs where erythrocytes, also known as red blood cells, pick up oxygen to be transported to tissues throughout the body. The pulmonary artery is an artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli. The pulmonary artery branches multiple times as it follows the bronchi, and each branch becomes progressively smaller in diameter. One arteriole and an accompanying venule supply and drain one pulmonary lobule. As they near the alveoli, the pulmonary arteries become the pulmonary capillary network. The pulmonary capillary network consists of tiny vessels with very thin walls that lack smooth muscle fibers. The capillaries branch and follow the bronchioles and structure of the alveoli. It is at this point that the capillary wall meets the alveolar wall, creating the respiratory membrane. Once the blood is oxygenated, it drains from the alveoli by way of multiple pulmonary veins, which exit the lungs through the hilum.

Nervous Innervation

Dilation and constriction of the airway are achieved through nervous control by the parasympathetic and sympathetic nervous systems. The parasympathetic system causes bronchoconstriction, whereas the sympathetic nervous system stimulates bronchodilation. Reflexes such as coughing, and the ability of the lungs to regulate oxygen and carbon dioxide levels, also result from this autonomic nervous system control. Sensory nerve fibers arise from the vagus nerve, and from the second to fifth thoracic ganglia. The pulmonary plexus is a region on the lung root formed by the entrance of the nerves at the hilum. The nerves then follow the bronchi in the lungs and branch to innervate muscle fibers, glands, and blood vessels.

Pleura of the Lungs

Each lung is enclosed within a cavity that is surrounded by the pleura. The pleura (plural = pleurae) is a serous membrane that surrounds the lung. The right and left pleurae, which enclose the right and left lungs, respectively, are separated by the mediastinum. The pleurae consist of two layers. The visceral pleura is the layer that is superficial to the lungs, and extends into and lines the lung fissures. In contrast, the parietal pleura is the outer layer that connects to the thoracic wall, the mediastinum, and the diaphragm. The visceral and parietal pleurae connect to each other at the hilum. The pleural cavity is the space between the visceral and parietal layers.

Parietal and Visceral Pleurae of the Lungs

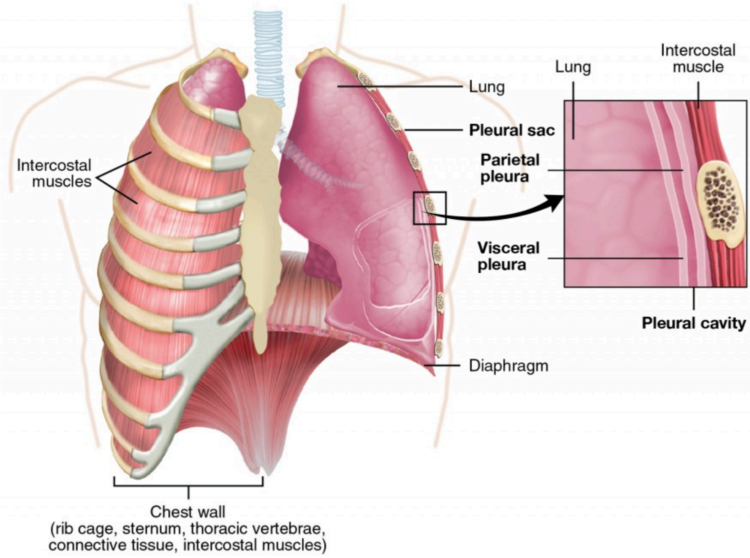


Figure 11.12: Parietal and Visceral Pleurae of the Lungs

The pleurae perform two major functions: They produce pleural fluid and create cavities that separate the major organs. Pleural fluid is secreted by mesothelial cells from both pleural layers and acts to lubricate their surfaces. This lubrication reduces friction between the two layers to prevent trauma during breathing, and creates surface tension that helps maintain the position of the lungs against the thoracic wall. This adhesive characteristic of the pleural fluid causes the lungs to enlarge when the thoracic wall expands during ventilation, allowing the lungs to fill with air. The pleurae also create a division between major organs that prevents interference due to the movement of the organs, while preventing the spread of infection.

65. Age Related Changes to the Respiratory System

One common sign of aging is when a person cannot maintain as high a level of physical activity as in the past. One of the major causes of this decease in activity is the deceased ability of the respiratory organs to acquire and deliver oxygen to the arterial blood. This is due to a number of structural changes to the respiratory system.

The cartilage in the walls of the trachea and bronchi undergoes a progressive calcification causing them to become increasingly rigid with aging. These changes cause a gradual decrease in maximum breathing capacity. Additionally the walls of the alveoli deteriorate. This reduces the surface area of the alveoli where gas exchange takes place. Finally with age the lungs lose some of their elastic recoil and thus offer less resistance to expansion.

66. Age Related Dysfunctions to the Respiratory System

Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is a group of diseases characterized by chronic air flow obstruction in the lungs. People who suffer from COPD experience difficulty breathing, wheezing, and coughing. Thy symptoms increase rapidly in those over 50 years of age and most frequent in men. The most common contributing factor is cigarette smoke, but there is a possible genetic predisposition.

Emphysema is one of the diseases which causes COPD. Emphysema is characterized by the accumulation of excessive air in the lungs as they lose their ability to ventilate properly. Chronic irritation of the bronchial tree damages the cilia of the airway while other cells become inflamed and over produce mucus. This hinders airflow and traps air in the alveoli, which eventually become damaged. Emphysema places an extra load on the heart as it attempts to pump more blood to the lungs in an effort to compensate for the deficiency of oxygen in the blood leaving the lungs. It develops gradually and is therefore much more prevalent in older persons.

Chronic bronchitis is another of the diseases which causes COPD. Chronic bronchitis is characterized by the chronic inflammation of the bronchial tree caused by long-term exposure to environmental irritants or a bacterial infection. Like in emphysema the chronic inflammation causes the over production of mucus. As the mucus secretions accumulate within the bronchi, they are removed by coughing, which can become persistent and irritating.

Pneumonia

Pneumonia is an inflammation of the lower airways of the lung in which the alveoli become filled. This causes the affected portion of the lung to become less spongy and restricts air from reaching the alveoli. The inflammation may be caused by several different viruses or bacteria. While these infections can affect people of all ages, they are more frequent in those over 65 whose are less able to fight off the infections.

Tuberculosis

Thanks to the development of antibiotics the incidences of tuberculosis has declined greatly. Prior to the development of antibiotics tuberculosis was very common bacterial disease. As many of today's elderly people were alive during the time period when tuberculosis was prevalent they may have been exposed to this bacteria. Due to the behavior of this bacteria it is possible that an elderly person inhaled this bacteria years prior and the bacteria was controlled by the immune system. The bacteria is able to survive for years within tubercles of the lungs. Due to the weakened immune systems of the elderly the bacteria is able to reinfect the lungs. While tuberculosis can now be treated with a six to nine month treatment of drug therapy the lungs may be permanently damaged.

Pulmonary Embolism

A pulmonary embolism refers to a clot that blocks a branch of a pulmonary artery. The tendency is for emboli to become lodged in the small branches of the pulmonary artery and restrict blood flow to some region of the lung. Pulmonary embolisms most commonly occur in patients who are bedridden. This is because the rate of blood flow deceases which generally increases the developments of blood clots.

67. Glossary: The Respiratory System

Glossary

ala (plural = alae) small, flaring structure of a nostril that forms the lateral side of the nares

alar cartilage cartilage that supports the apex of the nose and helps shape the nares; it is connected to the septal cartilage and connective tissue of the alae

alveolar duct small tube that leads from the terminal bronchiole to the respiratory bronchiole and is the point of attachment for alveoli

alveolar macrophage immune system cell of the alveolus that removes debris and pathogens

alveolar pore opening that allows airflow between neighboring alveoli

alveolar sac cluster of alveoli

alveolus small, grape-like sac that performs gas exchange in the lungs

apex tip of the external nose

bronchial tree collective name for the multiple branches of the bronchi and bronchioles of the respiratory system

bronchoconstriction decrease in the size of the bronchiole due to contraction of the muscular wall

bronchodilation increase in the size of the bronchiole due to contraction of the muscular wall

bridge portion of the external nose that lies in the area of the nasal bones

bronchiole branch of bronchi that are 1 mm or less in diameter and terminate at alveolar sacs

bronchus tube connected to the trachea that branches into many subsidiaries and provides a passageway for air to enter and leave the lungs

cardiac notch indentation on the surface of the left lung that allows space for the heart

conducting zone region of the respiratory system that includes the organs and structures that provide passageways for air and are not directly involved in gas exchange

cricoid cartilage portion of the larynx composed of a ring of cartilage with a wide posterior region and a thinner anterior region; attached to the esophagus

dorsum nasi intermediate portion of the external nose that connects the bridge to the apex and is supported by the nasal bone

epiglottis leaf-shaped piece of elastic cartilage that is a portion of the larynx that swings to close the trachea during swallowing

external nose region of the nose that is easily visible to others

fauces portion of the posterior oral cavity that connects the oral cavity to the oropharynx

fibroelastic membrane specialized membrane that connects the ends of the C-shape cartilage in the trachea; contains smooth muscle fibers

glottis opening between the vocal folds through which air passes when producing speech

hilum concave structure on the mediastinal surface of the lungs where blood vessels, lymphatic vessels, nerves, and a bronchus enter the lung

laryngeal prominence region where the two lamina of the thyroid cartilage join, forming a protrusion known as "Adam's apple"

laryngopharynx portion of the pharynx bordered by the oropharynx superiorly and esophagus and trachea inferiorly; serves as a route for both air and food

larynx cartilaginous structure that produces the voice, prevents food and beverages from entering the trachea, and regulates the volume of air that enters and leaves the lungs

lingual tonsil lymphoid tissue located at the base of the tongue

lung organ of the respiratory system that performs gas exchange

meatus one of three recesses (superior, middle, and inferior) in the nasal cavity attached to the conchae that increase the surface area of the nasal cavity

naris (plural = nares) opening of the nostrils

nasal bone bone of the skull that lies under the root and bridge of the nose and is connected to the frontal and maxillary bones

nasal septum wall composed of bone and cartilage that separates the left and right nasal cavities

nasopharynx portion of the pharynx flanked by the conchae and oropharynx that serves as an airway

oropharynx portion of the pharynx flanked by the nasopharynx, oral cavity, and laryngopharynx that is a passageway for both air and food

palatine tonsil one of the paired structures composed of lymphoid tissue located anterior to the uvula at the roof of isthmus of the fauces

paranasal sinus one of the cavities within the skull that is connected to the conchae that serve to warm and humidify incoming air, produce mucus, and lighten the weight of the skull; consists of frontal, maxillary, sphenoidal, and ethmoidal sinuses

parietal pleura outermost layer of the pleura that connects to the thoracic wall, mediastinum, and diaphragm

pharyngeal tonsil structure composed of lymphoid tissue located in the nasopharynx

pharynx region of the conducting zone that forms a tube of skeletal muscle lined with respiratory epithelium; located between the nasal conchae and the esophagus and trachea

philtrum concave surface of the face that connects the apex of the nose to the top lip

pleural cavity space between the visceral and parietal pleurae

pleural fluid substance that acts as a lubricant for the visceral and parietal layers of the pleura during the movement of breathing

pulmonary artery artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli

pulmonary plexus network of autonomic nervous system fibers found near the hilum of the lung

pulmonary surfactant substance composed of phospholipids and proteins that reduces the surface tension of the alveoli; made by type II alveolar cells

respiratory bronchiole specific type of bronchiole that leads to alveolar sacs

respiratory epithelium ciliated lining of much of the conducting zone that is specialized to remove debris and pathogens, and produce mucus

respiratory membrane alveolar and capillary wall together, which form an air-blood barrier that facilitates the simple diffusion of gases

respiratory zone includes structures of the respiratory system that are directly involved in gas exchange

root region of the external nose between the eyebrows

thyroid cartilage largest piece of cartilage that makes up the larynx and consists of two lamina

trachea tube composed of cartilaginous rings and supporting tissue that connects the lung bronchi and the larynx; provides a route for air to enter and exit the lung

trachealis muscle smooth muscle located in the fibroelastic membrane of the trachea

true vocal cord one of the pair of folded, white membranes that have a free inner edge that oscillates as air passes through to produce sound

type I alveolar cell squamous epithelial cells that are the major cell type in the alveolar wall; highly permeable to gases

type II alveolar cell cuboidal epithelial cells that are the minor cell type in the alveolar wall; secrete pulmonary surfactant

vestibular fold part of the folded region of the glottis composed of mucous membrane; supports the epiglottis during swallowing

visceral pleura innermost layer of the pleura that is superficial to the lungs and extends into the lung fissures

PART XII

CHAPTER 12: THE DIGESTIVE SYSTEM

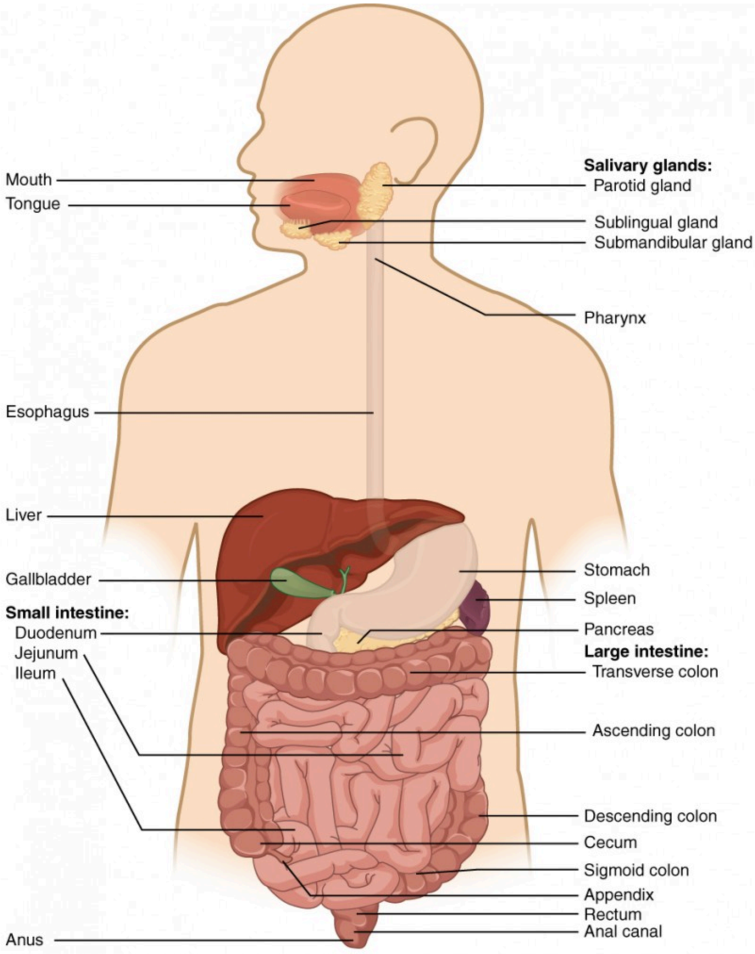
68. Overview of the Digestive System

The digestive system is continually at work, yet people seldom appreciate the complex tasks it performs in a choreographed biologic symphony. Consider what happens when you eat an apple. Of course, you enjoy the apple's taste as you chew it, but in the hours that follow, unless something goes amiss and you get a stomachache, you don't notice that your digestive system is working. You may be taking a walk or studying or sleeping, having forgotten all about the apple, but your stomach and intestines are busy digesting it and absorbing its vitamins and other nutrients. By the time any waste material is excreted, the body has appropriated all it can use from the apple. In short, whether you pay attention or not, the organs of the digestive system perform their specific functions, allowing you to use the food you eat to keep you going. This chapter examines the structure and functions of these organs, and explores the mechanics and chemistry of the digestive processes.

The function of the digestive system is to break down the foods you eat, release their nutrients, and absorb those nutrients into the body. Although the small intestine is the workhorse of the system, where the majority of digestion occurs, and where most of the released nutrients are absorbed into the blood or lymph, each of the digestive system organs makes a vital contribution to this process.

Components of the Digestive System

All digestive organs play integral roles in the life-sustaining process of digestion.



As is the case with all body systems, the digestive system does not work in isolation; it functions cooperatively with the other systems of the body. Consider for example, the interrelationship between the digestive and cardiovascular systems. Arteries supply the digestive organs with oxygen and processed nutrients, and veins drain the digestive tract. These intestinal veins, constituting the hepatic portal system, are unique; they do not return blood directly to the heart. Rather, this blood is diverted to the liver where its nutrients are off-loaded for processing before blood completes its circuit back to the heart. At the same time, the digestive system provides nutrients to the heart muscle and vascular tissue to support their functioning. The interrelationship of the digestive and endocrine systems is also critical. Hormones secreted by several endocrine glands, as well as endocrine cells of the pancreas, the stomach, and the small intestine, contribute to the control of digestion and nutrient metabolism. In turn, the digestive system provides the nutrients to fuel endocrine function. The following table gives a quick glimpse at how these other systems contribute to the functioning of the digestive system.

Contribution of Other Body Systems to the Digestive System

Body system	**Benefits received by the digestive system**
Cardiovascular	Blood supplies digestive organs with oxygen and processed nutrients
Endocrine	Endocrine hormones help regulate secretion in digestive glands and accessory organs
Integumentary	Skin helps protect digestive organs and synthesizes vitamin D for calcium absorption
Lymphatic	Mucosa-associated lymphoid tissue and other lymphatic tissue defend against entry of pathogens; lacteals absorb lipids; and lymphatic vessels transport lipids to bloodstream
Muscular	Skeletal muscles support and protect abdominal organs
Nervous	Sensory and motor neurons help regulate secretions and muscle contractions in the digestive tract
Respiratory	Respiratory organs provide oxygen and remove carbon dioxide
Skeletal	Bones help protect and support digestive organs
Urinary	Kidneys convert vitamin D into its active form, allowing calcium absorption in the small intestine

Digestive System Organs

The easiest way to understand the digestive system is to divide its organs into two main categories. The first group is the organs that make up the alimentary canal. Accessory digestive organs comprise the second group and are critical for orchestrating the breakdown of food and the assimilation of its nutrients into the body. Accessory digestive organs, despite their name, are critical to the function of the digestive system.

Alimentary Canal Organs

Also called the gastrointestinal (GI) tract or gut, the alimentary canal (aliment- = "to nourish") is a one-way tube about 7.62 meters (25 feet) in length during life and closer to 10.67 meters (35 feet) in length when measured after death, once smooth muscle tone is lost. The main function of the organs of the alimentary canal is to nourish the body. This tube begins at the mouth and terminates at the anus. Between those two points, the canal is modified as the pharynx, esophagus, stomach, and small and large intestines to fit the functional needs of the body. Both the mouth and anus are open to the external environment; thus, food and wastes within the alimentary canal are technically considered to be outside the body. Only through the process of absorption do the nutrients in food enter into and nourish the body's "inner space."

Accessory Structures

Each accessory digestive organ aids in the breakdown of food. Within the mouth, the teeth and tongue begin mechanical digestion, whereas the salivary glands begin chemical digestion. Once food products enter the small intestine, the gallbladder, liver, and pancreas release secretions—such as bile and enzymes—essential for digestion to continue. Together, these are called accessory organs because they sprout from the lining cells of the developing gut (mucosa) and augment its function; indeed, you could not live without their vital contributions, and many significant diseases result from their malfunction. Even after development is complete, they maintain a connection to the gut by way of ducts.

Nerve Supply

As soon as food enters the mouth, it is detected by receptors that send impulses along the sensory neurons of cranial nerves. Without these nerves, not only would your food be without taste, but you would also be unable to feel either the food or the structures of your mouth, and you would be unable to avoid biting yourself as you chew, an action enabled by the motor branches of cranial nerves.

Intrinsic innervation of much of the alimentary canal is provided by the enteric nervous system, which runs from the esophagus to the anus, and contains approximately 100 million motor, sensory, and interneurons (unique to this system compared to all other parts of the peripheral nervous system). These enteric neurons are grouped into two plexuses. The myenteric plexus (plexus of Auerbach) lies in the muscularis layer of the alimentary canal and is responsible for motility, especially the rhythm and force of the contractions of the muscularis. The submucosal plexus (plexus of Meissner) lies in the submucosal layer and is responsible for regulating digestive secretions and reacting to the presence of food.

Extrinsic innervations of the alimentary canal are provided by the autonomic nervous system, which includes both sympathetic and parasympathetic nerves. In general, sympathetic activation (the fight-or-flight response) restricts the activity of enteric neurons, thereby decreasing GI secretion and motility. In contrast, parasympathetic activation (the rest-and-digest response) increases GI secretion and motility by stimulating neurons of the enteric nervous system.

Blood Supply

The blood vessels serving the digestive system have two functions. They transport the protein and carbohydrate nutrients absorbed by mucosal cells after food is digested in the lumen. Lipids are absorbed via lacteals, tiny structures of the lymphatic system. The blood vessels' second function is to supply the organs of the alimentary canal with the nutrients and oxygen needed to drive their cellular processes.

Specifically, the more anterior parts of the alimentary canal are supplied with blood by arteries branching off the aortic arch and thoracic aorta. Below this point, the alimentary canal is supplied with blood by arteries branching from the abdominal aorta. The celiac trunk services the liver, stomach, and duodenum, whereas the superior and inferior mesenteric arteries supply blood to the remaining small and large intestines.

The veins that collect nutrient-rich blood from the small intestine (where most absorption occurs) empty into the hepatic portal system. This venous network takes the blood into the liver where the nutrients are either processed or stored for later use. Only then does the blood drained from the alimentary canal viscera circulate back to the heart. To appreciate just how demanding the digestive process is on the cardiovascular system, consider that while you are "resting and digesting," about one-fourth of the blood pumped with each heartbeat enters arteries serving the intestines.

69. Digestive System Processes and Regulation

Functions of the Digestive Organs

Organ	Major functions	Other functions
Mouth	• Ingests food • Chews and mixes food • Begins chemical breakdown of carbohydrates • Moves food into the pharynx • Begins breakdown of lipids via lingual lipase	• Moistens and dissolves food, allowing you to taste it • Cleans and lubricates the teeth and oral cavity • Has some antimicrobial activity
Pharynx	• Propels food from the oral cavity to the esophagus	• Lubricates food and passageways
Esophagus	• Propels food to the stomach	• Lubricates food and passageways
Stomach	• Mixes and churns food with gastric juices to form chyme • Begins chemical breakdown of proteins • Releases food into the duodenum as chyme • Absorbs some fat-soluble substances (for example, alcohol, aspirin) • Possesses antimicrobial functions	• Stimulates protein-digesting enzymes • Secretes intrinsic factor required for vitamin B_{12} absorption in small intestine

Functions of the Digestive Organs

Organ	Major functions	Other functions
Small intestine	• Mixes chyme with digestive juices • Propels food at a rate slow enough for digestion and absorption • Absorbs breakdown products of carbohydrates, proteins, lipids, and nucleic acids, along with vitamins, minerals, and water • Performs physical digestion via segmentation	• Provides optimal medium for enzymatic activity
Accessory organs	• Liver: produces bile salts, which emulsify lipids, aiding their digestion and absorption • Gallbladder: stores, concentrates, and releases bile • Pancreas: produces digestive enzymes and bicarbonate	• Bicarbonate-rich pancreatic juices help neutralize acidic chyme and provide optimal environment for enzymatic activity
Large intestine	• Further breaks down food residues • Absorbs most residual water, electrolytes, and vitamins produced by enteric bacteria • Propels feces toward rectum • Eliminates feces	• Food residue is concentrated and temporarily stored prior to defecation • Mucus eases passage of feces through colon

Digestive Processes

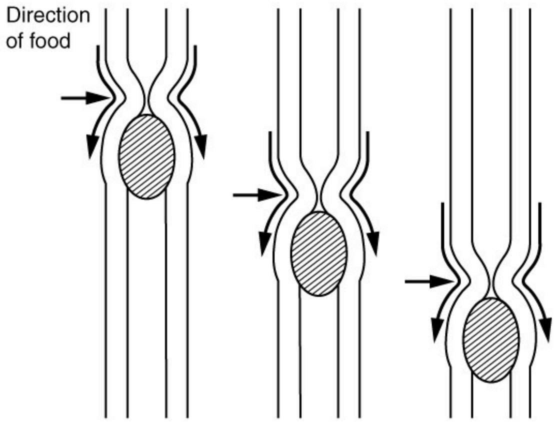
The processes of digestion include six activities: ingestion, propulsion, mechanical or physical digestion, chemical digestion, absorption, and defecation.

The first of these processes, ingestion, refers to the entry of food into the alimentary canal through the mouth. There, the food is chewed and mixed with saliva, which contains enzymes that begin breaking down the carbohydrates in the food plus some lipid digestion via lingual lipase. Chewing increases the surface area of the food and allows an appropriately sized bolus to be produced.

Food leaves the mouth when the tongue and pharyngeal muscles propel it into the esophagus. This act of swallowing, the last voluntary act until defecation, is an example of propulsion, which refers to the movement of food through the digestive tract. It includes both the voluntary process of swallowing and the involuntary process of peristalsis. Peristalsis consists of sequential, alternating waves of contraction and relaxation of alimentary wall smooth muscles, which act to propel food along. These waves also play a role in mixing food with digestive juices. Peristalsis is so powerful that foods and liquids you swallow enter your stomach even if you are standing on your head.

Peristalsis

Peristalsis moves food through the digestive tract with alternating waves of muscle contraction and relaxation.



Digestion includes both mechanical and chemical processes. Mechanical digestion is a purely physical process that does not change the chemical nature of the food. Instead, it makes the food smaller to increase both surface area and mobility. It includes mastication, or chewing, as well as tongue movements that help break food into smaller bits and mix food with saliva. Although there may be a tendency to think that mechanical digestion is limited to the first steps of the digestive process, it occurs after the food leaves the mouth, as well. The mechanical churning of food in the stomach serves to further break it apart and expose more of its surface area to digestive juices, creating an acidic "soup" called chyme. Segmentation, which occurs mainly in the small intestine, consists of localized contractions of circular muscle of the muscularis layer of the alimentary canal. These contractions isolate small sections of the intestine, moving their contents back and forth while continuously subdividing, breaking up, and mixing the contents. By moving food back and forth in the intestinal lumen, segmentation mixes food with digestive juices and facilitates absorption.

In chemical digestion, starting in the mouth, digestive secretions break down complex food molecules into their chemical building blocks (for example, proteins into separate amino acids). These secretions vary in composition, but typically contain water, various enzymes, acids, and salts. The process is completed in the small intestine.

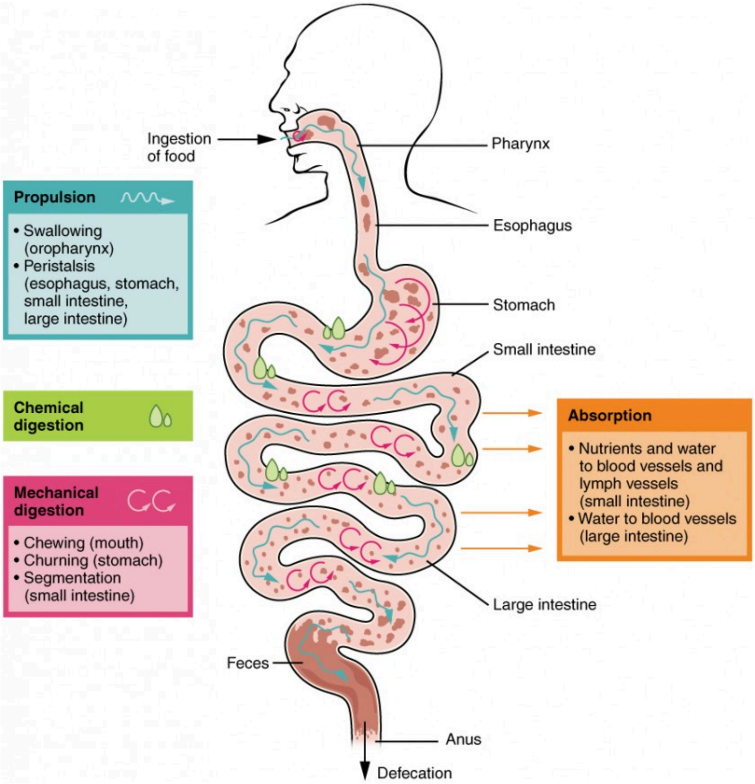
Food that has been broken down is of no value to the body unless it enters the bloodstream and its nutrients are put to work. This occurs through the process of absorption, which takes place primarily within the small intestine. There, most nutrients are absorbed from the lumen of the alimentary canal into the bloodstream through the epithelial cells that make up the mucosa. Lipids are absorbed into lacteals and are transported via the lymphatic vessels to the bloodstream (the subclavian veins near the heart). The details of these processes will be discussed later.

In defecation, the final step in digestion, undigested materials are removed from the body as feces.

In some cases, a single organ is in charge of a digestive process. For example, ingestion occurs only in the mouth and defecation only in the anus. However, most digestive processes involve the interaction of several organs and occur gradually as food moves through the alimentary canal.

Digestive Processes

The digestive processes are ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation.



Some chemical digestion occurs in the mouth. Some absorption can occur in the mouth and stomach, for example, alcohol and aspirin.

70. The Mouth, Pharynx, and Esophagus

The Mouth

The cheeks, tongue, and palate frame the mouth, which is also called the oral cavity (or buccal cavity). The structures of the mouth are illustrated in.

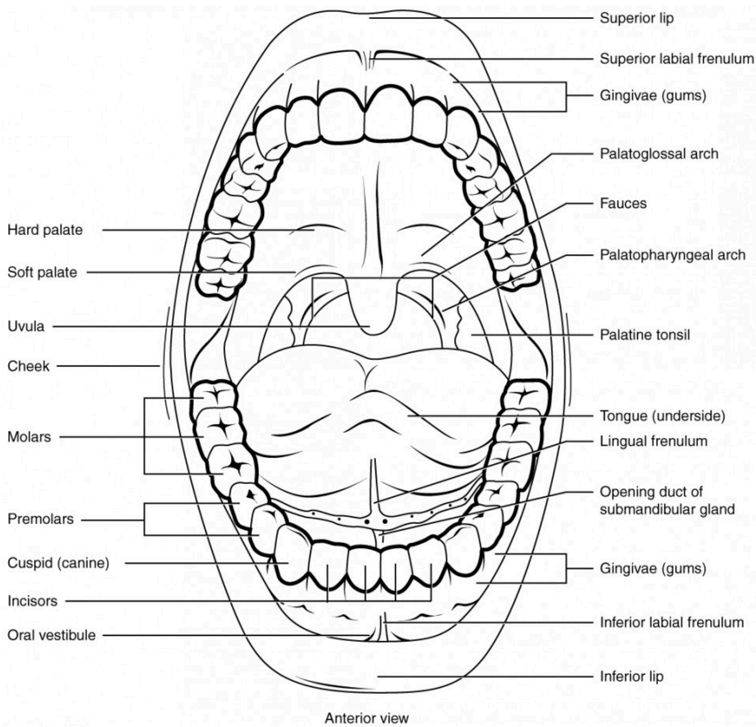
At the entrance to the mouth are the lips, or labia (singular = labium). Their outer covering is skin, which transitions to a mucous membrane in the mouth proper. Lips are very vascular with a thin layer of keratin; hence, the reason they are "red." They have a huge representation on the cerebral cortex, which probably explains the human fascination with kissing! The lips cover the orbicularis oris muscle, which regulates what comes in and goes out of the mouth. The labial frenulum is a midline fold of mucous membrane that attaches the inner surface of each lip to the gum. The cheeks make up the oral cavity's sidewalls. While their outer covering is skin, their inner covering is mucous membrane. This membrane is made up of non-keratinized, stratified squamous epithelium. Between the skin and mucous membranes are connective tissue and buccinator muscles. The next time you eat some food, notice how the buccinator muscles in your cheeks and the orbicularis oris muscle in your lips contract, helping you keep the food from falling out of your mouth. Additionally, notice how these muscles work when you are speaking.

The pocket-like part of the mouth that is framed on the inside by the gums and teeth, and on the outside by the cheeks and lips is called the oral vestibule. Moving farther into the mouth, the opening between the oral cavity and throat (oropharynx) is called the fauces (like the kitchen "faucet"). The main open area of the mouth, or oral cavity proper, runs from the gums and teeth to the fauces.

When you are chewing, you do not find it difficult to breathe simultaneously. The next time you have food in your mouth, notice how the arched shape of the roof of your mouth allows you to handle both digestion and respiration at the same time. This arch is called the palate. The anterior region of the palate serves as a wall (or septum) between the oral and nasal cavities as well as a rigid shelf against which the tongue can push food. It is created by the maxillary and palatine bones of the skull and, given its bony structure, is known as the hard palate. If you run your tongue along the roof of your mouth, you'll notice that the hard palate ends in the posterior oral cavity, and the tissue becomes fleshier. This part of the palate, known as the soft palate, is composed mainly of skeletal muscle. You can therefore manipulate, subconsciously, the soft palate—for instance, to yawn, swallow, or sing.

Mouth

The mouth includes the lips, tongue, palate, gums, and teeth.



A fleshy bead of tissue called the uvula drops down from the center of the posterior edge of the soft palate. Although some have suggested that the uvula is a vestigial organ, it serves an important purpose. When you swallow, the soft palate and uvula move upward, helping to keep foods and liquid from entering the nasal cavity. Unfortunately, it can also contribute to the sound produced by snoring. Two muscular folds extend downward from the soft palate, on either side of the uvula. Toward the front, the palatoglossal arch lies next to the base of the tongue; behind it, the palatopharyngeal arch forms the superior and lateral margins of the fauces. Between these two arches are the palatine tonsils, clusters of lymphoid tissue that protect the pharynx. The lingual tonsils are located at the base of the tongue.

The Tongue

Perhaps you have heard it said that the tongue is the strongest muscle in the body. Those who stake this claim cite its strength proportionate to its size. Although it is difficult to quantify the relative strength of different muscles, it remains indisputable that the tongue is a workhorse, facilitating ingestion, mechanical digestion, chemical digestion (lingual lipase), sensation (of taste, texture, and temperature of food), swallowing, and vocalization.

The tongue is attached to the mandible, the styloid processes of the temporal bones, and the hyoid bone. The hyoid is unique in that it only distantly/indirectly articulates with other bones. The tongue is positioned over the floor of the oral cavity. A medial septum extends the entire length of the tongue, dividing it into symmetrical halves.

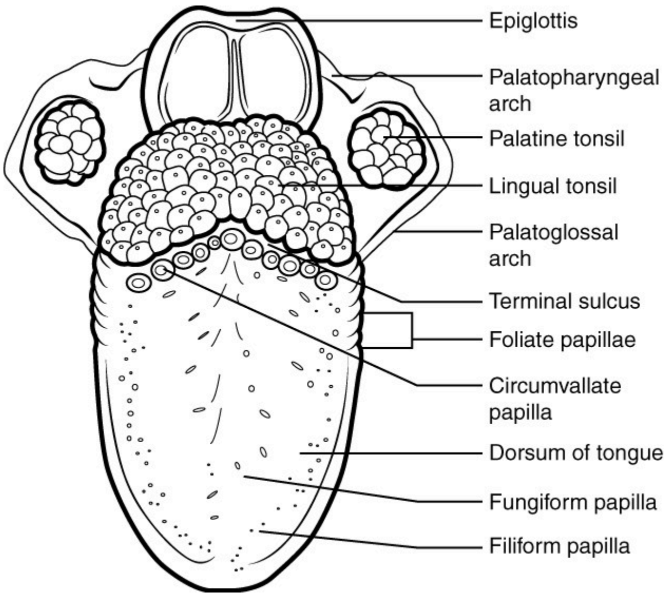
Beneath its mucous membrane covering, each half of the tongue is composed of the same number and type of intrinsic and extrinsic skeletal muscles. The intrinsic muscles (those within the tongue) are the longitudinalis inferior, longitudinalis superior, transversus linguae, and verticalis linguae muscles. These allow you to change the size and shape of your tongue, as well as to stick it out, if you wish. Having such a flexible tongue facilitates both swallowing and speech.

As you learned in your study of the muscular system, the extrinsic muscles of the tongue are the mylohyoid, hyoglossus, styloglossus, and genioglossus muscles. These muscles originate outside the tongue and insert into connective tissues within the tongue. The mylohyoid is responsible for raising the tongue, the hyoglossus pulls it down and back, the styloglossus pulls it up and back, and the genioglossus pulls it forward. Working in concert, these muscles perform three important digestive functions in the mouth: (1) position food for optimal chewing, (2) gather food into a bolus (rounded mass), and (3) position food so it can be swallowed.

The top and sides of the tongue are studded with papillae, extensions of lamina propria of the mucosa, which are covered in stratified squamous epithelium. Fungiform papillae, which are mushroom shaped, cover a large area of the tongue; they tend to be larger toward the rear of the tongue and smaller on the tip and sides. In contrast, filiform papillae are long and thin. Fungiform papillae contain taste buds, and filiform papillae have touch receptors that help the tongue move food around in the mouth. The filiform papillae create an abrasive surface that performs mechanically, much like a cat's rough tongue that is used for grooming. Lingual glands in the lamina propria of the tongue secrete mucus and a watery serous fluid that contains the enzyme lingual lipase, which plays a minor role in breaking down triglycerides but does not begin working until it is activated in the stomach. A fold of mucous membrane on the underside of the tongue, the lingual frenulum, tethers the tongue to the floor of the mouth. People with the congenital anomaly ankyloglossia, also known by the non-medical term "tongue tie," have a lingual frenulum that is too short or otherwise malformed. Severe ankyloglossia can impair speech and must be corrected with surgery.

Tongue

This superior view of the tongue shows the locations and types of lingual papillae.



The Salivary Glands

Many small salivary glands are housed within the mucous membranes of the mouth and tongue. These minor exocrine glands are constantly secreting saliva, either directly into the oral cavity or indirectly through ducts, even while you sleep. In fact, an average of 1 to 1.5 liters of saliva is secreted each day. Usually just enough saliva is present to moisten the mouth and teeth. Secretion increases when you eat, because saliva is essential to moisten food and initiate the chemical breakdown of carbohydrates. Small amounts of saliva are also secreted by the labial glands in the lips. In addition, the buccal glands in the cheeks, palatal glands in the palate, and lingual glands in the tongue help ensure that all areas of the mouth are supplied with adequate saliva.

The Major Salivary Glands

Outside the oral mucosa are three pairs of major salivary glands, which secrete the majority of saliva into ducts that open into the mouth:

- The submandibular glands, which are in the floor of the mouth, secrete saliva into the mouth through the submandibular ducts.
- The sublingual glands, which lie below the tongue, use the lesser sublingual ducts to secrete saliva into the oral cavity.
- The parotid glands lie between the skin and the masseter muscle, near the ears. They secrete saliva into the mouth through the parotid duct, which is located near the second upper molar tooth.

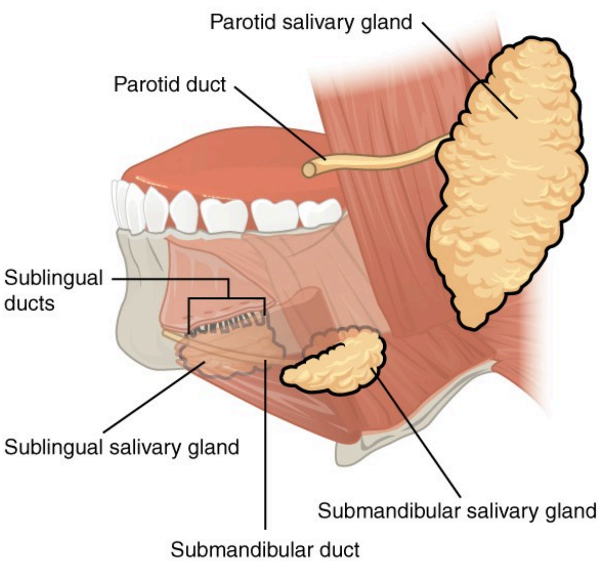
Saliva

Saliva is essentially (95.5 percent) water. The remaining 4.5 percent is a complex mixture of ions, glycoproteins, enzymes, growth factors, and waste products. Perhaps the most important ingredient in salvia from the perspective of digestion is the enzyme salivary amylase, which initiates the breakdown of carbohydrates. Food does not spend enough time in the mouth to allow all the carbohydrates to break down, but salivary amylase continues acting until it is inactivated by stomach acids. Bicarbonate and phosphate ions function as chemical buffers, maintaining saliva at a pH between 6.35 and 6.85. Salivary mucus helps lubricate food, facilitating movement in the mouth, bolus formation, and swallowing. Saliva contains immunoglobulin A, which prevents microbes from penetrating the epithelium, and lysozyme, which makes saliva antimicrobial. Saliva also contains epidermal growth factor, which might have given rise to the adage "a mother's kiss can heal a wound."

Each of the major salivary glands secretes a unique formulation of saliva according to its cellular makeup. For example, the parotid glands secrete a watery solution that contains salivary amylase. The submandibular glands have cells similar to those of the parotid glands, as well as mucus-secreting cells. Therefore, saliva secreted by the submandibular glands also contains amylase but in a liquid thickened with mucus. The sublingual glands contain mostly mucous cells, and they secrete the thickest saliva with the least amount of salivary amylase.

Salivary glands

The major salivary glands are located outside the oral mucosa and deliver saliva into the mouth through ducts.



Regulation of Salivation

The autonomic nervous system regulates salivation (the secretion of saliva). In the absence of food, parasympathetic stimulation keeps saliva flowing at just the right level for comfort as you speak, swallow, sleep, and generally go about life. Over-salivation can occur, for example, if you are stimulated by the smell of food, but that food is not available for you to eat. Drooling is an extreme instance of the overproduction of saliva. During times of stress, such as before speaking in public, sympathetic stimulation takes over, reducing salivation and producing the symptom of dry mouth often associated with anxiety. When you are dehydrated, salivation is reduced, causing the mouth to feel dry and prompting you to take action to quench your thirst.

Salivation can be stimulated by the sight, smell, and taste of food. It can even be stimulated by thinking about food. You might notice whether reading about food and salivation right now has had any effect on your production of saliva.

How does the salivation process work while you are eating? Food contains chemicals that stimulate taste receptors on the tongue, which send impulses to the superior and inferior salivatory nuclei in the brain stem. These two nuclei then send back parasympathetic impulses through fibers in the glossopharyngeal and facial nerves, which stimulate salivation. Even after you swallow food, salivation is increased to cleanse the mouth and to water down and neutralize any irritating chemical remnants, such as that hot sauce in your burrito. Most saliva is swallowed along with food and is reabsorbed, so that fluid is not lost.

The Teeth

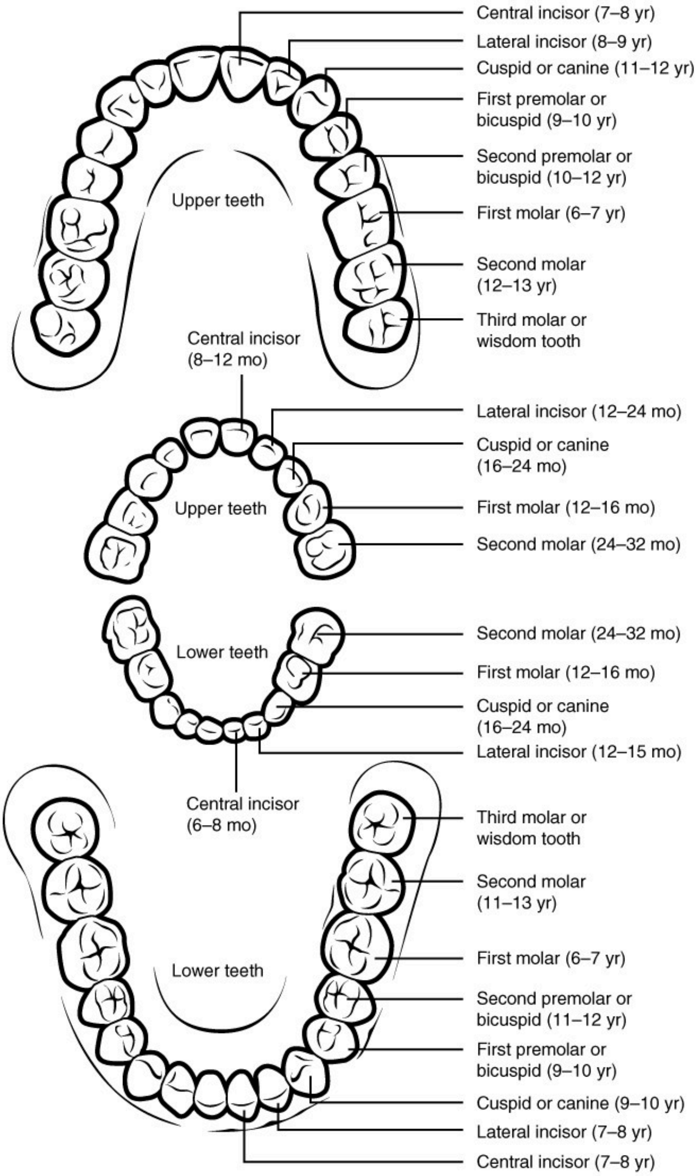
The teeth, or dentes (singular = dens), are organs similar to bones that you use to tear, grind, and otherwise mechanically break down food.

Types of Teeth

During the course of your lifetime, you have two sets of teeth (one set of teeth is a dentition). Your 20 deciduous teeth, or baby teeth, first begin to appear at about 6 months of age. Between approximately age 6 and 12, these teeth are replaced by 32 permanent teeth. Moving from the center of the mouth toward the side, these are as follows:

- The eight incisors, four top and four bottom, are the sharp front teeth you use for biting into food.
- The four cuspids (or canines) flank the incisors and have a pointed edge (cusp) to tear up food. These fang-like teeth are superb for piercing tough or fleshy foods.
- Posterior to the cuspids are the eight premolars (or bicuspids), which have an overall flatter shape with two rounded cusps useful for mashing foods.
- The most posterior and largest are the 12 molars, which have several pointed cusps used to crush food so it is ready for swallowing. The third members of each set of three molars, top and bottom, are commonly referred to as the wisdom teeth, because their eruption is commonly delayed until early adulthood. It is not uncommon for wisdom teeth to fail to erupt; that is, they remain impacted. In these cases, the teeth are typically removed by orthodontic surgery.

Permanent and Deciduous Teeth
This figure of two human dentitions shows the arrangement of teeth in the maxilla and mandible, and the relationship between the deciduous and permanent teeth.


Central incisor (7–8 yr)
Lateral incisor (8–9 yr)
Cuspid or canine (11–12 yr)
First premolar or bicuspid (9–10 yr)
Second premolar or bicuspid (10–12 yr)
First molar (6–7 yr)
Second molar (12–13 yr)
Third molar or wisdom tooth
Upper teeth
Central incisor (8–12 mo)
Lateral incisor (12–24 mo)
Cuspid or canine (16–24 mo)
Upper teeth
First molar (12–16 mo)
Second molar (24–32 mo)
Lower teeth
Second molar (24–32 mo)
First molar (12–16 mo)
Cuspid or canine (16–24 mo)
Lateral incisor (12–15 mo)
Central incisor (6–8 mo)
Third molar or wisdom tooth
Second molar (11–13 yr)
First molar (6–7 yr)
Lower teeth
Second premolar or bicuspid (11–12 yr)
First premolar or bicuspid (9–10 yr)
Cuspid or canine (9–10 yr)
Lateral incisor (7–8 yr)
Central incisor (7–8 yr)

Anatomy of a Tooth

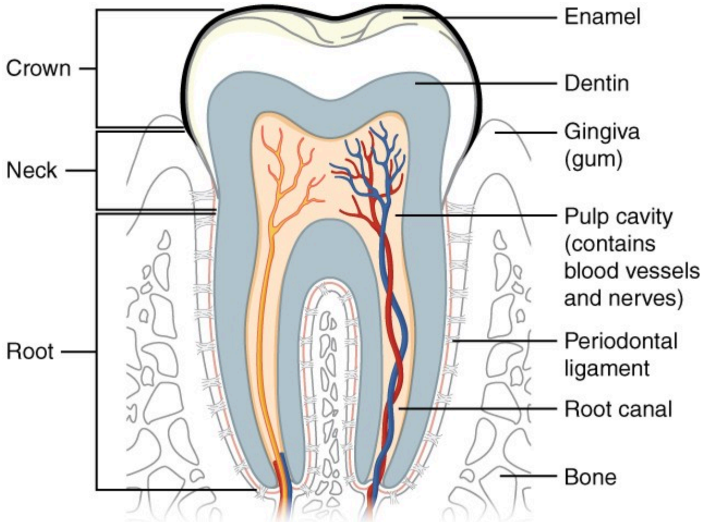
The teeth are secured in the alveolar processes (sockets) of the maxilla and the mandible. Gingivae (commonly called the gums) are soft tissues that line the alveolar processes and surround the necks of the teeth. Teeth are also held in their sockets by a connective tissue called the periodontal ligament.

The two main parts of a tooth are the crown, which is the portion projecting above the gum line, and the root, which is embedded within the maxilla and mandible. Both parts contain an inner pulp cavity, containing loose connective tissue through which run nerves and blood vessels. The region of the pulp cavity that runs through the root of the tooth is called the root canal. Surrounding the pulp cavity is dentin, a bone-like tissue. In the root of each tooth, the dentin is covered by an even harder bone-like layer called cementum. In the crown of each tooth, the dentin is covered by an outer layer of enamel, the hardest substance in the body.

Although enamel protects the underlying dentin and pulp cavity, it is still nonetheless susceptible to mechanical and chemical erosion, or what is known as tooth decay. The most common form, dental caries (cavities) develops when colonies of bacteria feeding on sugars in the mouth release acids that cause soft tissue inflammation and degradation of the calcium crystals of the enamel. The digestive functions of the mouth are summarized in.

The Structure of the Tooth

This longitudinal section through a molar in its alveolar socket shows the relationships between enamel, dentin, and pulp.


Crown
Neck
Root
Enamel
Dentin
Gingiva
(gum)
Pulp cavity
(contains
blood vessels
and nerves)
Periodontal
ligament
Root canal
Bone

Digestive Functions of the Mouth

Structure	Action	Outcome
Lips and cheeks	Confine food between teeth	• Food is chewed evenly during mastication
Salivary glands	Secrete saliva	• Moisten and lubricate the lining of the mouth and pharynx • Moisten, soften, and dissolve food • Clean the mouth and teeth • Salivary amylase breaks down starch
Tongue's extrinsic muscles	Move tongue sideways, and in and out	• Manipulate food for chewing • Shape food into a bolus • Manipulate food for swallowing
Tongue's intrinsic muscles	Change tongue shape	• Manipulate food for swallowing
Taste buds	Sense food in mouth and sense taste	• Nerve impulses from taste buds are conducted to salivary nuclei in the brain stem and then to salivary glands, stimulating saliva secretion
Lingual glands	Secrete lingual lipase	• Activated in the stomach • Break down triglycerides into fatty acids and diglycerides
Teeth	Shred and crush food	• Break down solid food into smaller particles for deglutition

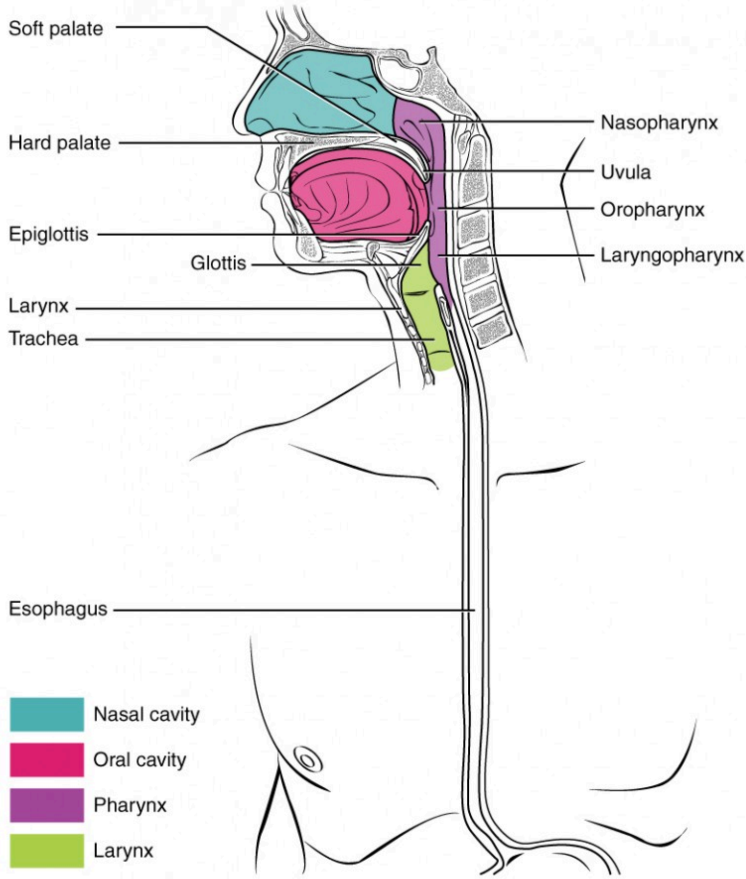
The Pharynx

The pharynx (throat) is involved in both digestion and respiration. It receives food and air from the mouth, and air from the nasal cavities. When food enters the pharynx, involuntary muscle contractions close off the air passageways.

A short tube of skeletal muscle lined with a mucous membrane, the pharynx runs from the posterior oral and nasal cavities to the opening of the esophagus and larynx. It has three subdivisions. The most superior, the nasopharynx, is involved only in breathing and speech. The other two subdivisions, the oropharynx and the laryngopharynx, are used for both breathing and digestion. The oropharynx begins inferior to the nasopharynx and is continuous below with the laryngopharynx. The inferior border of the laryngopharynx connects to the esophagus, whereas the anterior portion connects to the larynx, allowing air to flow into the bronchial tree.

Pharynx

The pharynx runs from the nostrils to the esophagus and the larynx.



Histologically, the wall of the oropharynx is similar to that of the oral cavity. The mucosa includes a stratified squamous epithelium that is endowed with mucus-producing glands. During swallowing, the elevator skeletal muscles of the pharynx contract, raising and expanding the pharynx to receive the bolus of food. Once received, these muscles relax and the constrictor muscles of the pharynx contract, forcing the bolus into the esophagus and initiating peristalsis.

Usually during swallowing, the soft palate and uvula rise reflexively to close off the entrance to the nasopharynx. At the same time, the larynx is pulled superiorly and the cartilaginous epiglottis, its most superior structure, folds inferiorly, covering the glottis (the opening to the larynx); this process effectively blocks access to the trachea and bronchi. When the food "goes down the wrong way," it goes into the trachea. When food enters the trachea, the reaction is to cough, which usually forces the food up and out of the trachea, and back into the pharynx.

The Esophagus

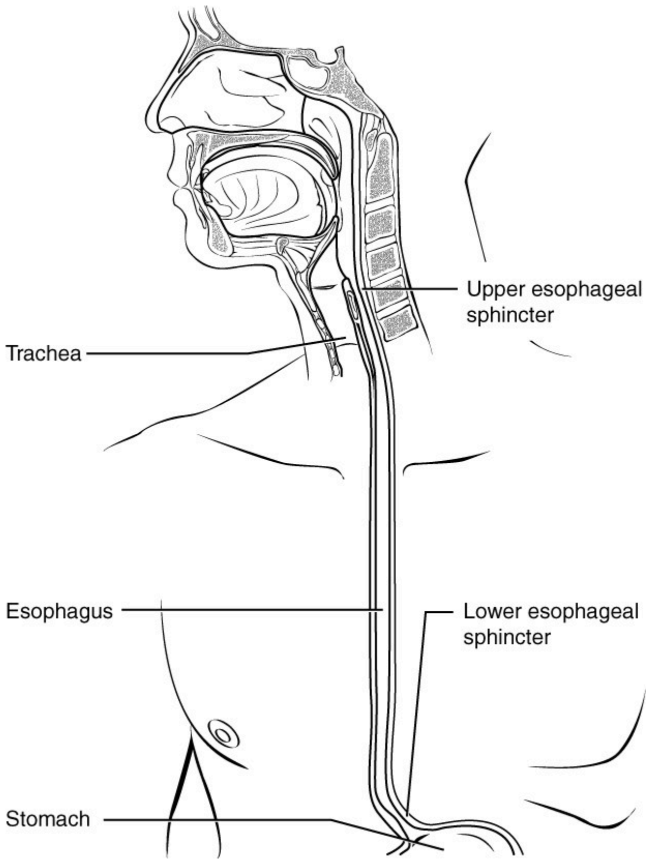
The esophagus is a muscular tube that connects the pharynx to the stomach. It is approximately 25.4 cm (10 in) in length, located posterior to the trachea, and remains in a collapsed form when not engaged in swallowing. As you can see in the image below, the esophagus runs a mainly straight route through the mediastinum of the thorax. To enter the abdomen, the esophagus penetrates the diaphragm through an opening called the esophageal hiatus.

Passage of Food through the Esophagus

The upper esophageal sphincter, which is continuous with the inferior pharyngeal constrictor, controls the movement of food from the pharynx into the esophagus. The upper two-thirds of the esophagus consists of both smooth and skeletal muscle fibers, with the latter fading out in the bottom third of the esophagus. Rhythmic waves of peristalsis, which begin in the upper esophagus, propel the bolus of food toward the stomach. Meanwhile, secretions from the esophageal mucosa lubricate the esophagus and food. Food passes from the esophagus into the stomach at the lower esophageal sphincter (also called the gastroesophageal or cardiac sphincter). Recall that sphincters are muscles that surround tubes and serve as valves, closing the tube when the sphincters contract and opening it when they relax. The lower esophageal sphincter relaxes to let food pass into the stomach, and then contracts to prevent stomach acids from backing up into the esophagus. Surrounding this sphincter is the muscular diaphragm, which helps close off the sphincter when no food is being swallowed. When the lower esophageal sphincter does not completely close, the stomach's contents can reflux (that is, back up into the esophagus), causing heartburn or gastroesophageal reflux disease (GERD).

Esophagus

The upper esophageal sphincter controls the movement of food from the pharynx to the esophagus. The lower esophageal sphincter controls the movement of food from the esophagus to the stomach.

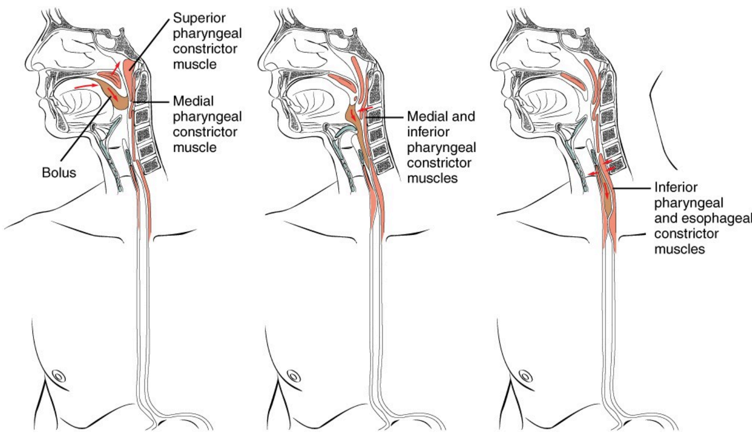


Deglutition

Deglutition is another word for swallowing—the movement of food from the mouth to the stomach. The entire process takes about 4 to 8 seconds for solid or semisolid food, and about 1 second for very soft food and liquids. Although this sounds quick and effortless, deglutition is, in fact, a complex process that involves both the skeletal muscle of the tongue and the muscles of the pharynx and esophagus. It is aided by the presence of mucus and saliva. There are three stages in deglutition: the voluntary phase, the pharyngeal phase, and the esophageal phase. The autonomic nervous system controls the latter two phases.

Deglutition

Deglutition includes the voluntary phase and two involuntary phases: the pharyngeal phase and the esophageal phase.



The Voluntary Phase

The voluntary phase of deglutition (also known as the oral or buccal phase) is so called because you can control when you swallow food. In this phase, chewing has been completed and swallowing is set in motion. The tongue moves upward and backward against the palate, pushing the bolus to the back of the oral cavity and into the oropharynx. Other muscles keep the mouth closed and prevent food from falling out. At this point, the two involuntary phases of swallowing begin.

The Pharyngeal Phase

In the pharyngeal phase, stimulation of receptors in the oropharynx sends impulses to the deglutition center (a collection of neurons that controls swallowing) in the medulla oblongata. Impulses are then sent back to the uvula and soft palate, causing them to move upward and close off the nasopharynx. The laryngeal muscles also constrict to prevent aspiration of food into the trachea. At this point, deglutition apnea takes place, which means that breathing ceases for a very brief time. Contractions of the pharyngeal constrictor muscles move the bolus through the oropharynx and laryngopharynx. Relaxation of the upper esophageal sphincter then allows food to enter the esophagus.

The Esophageal Phase

The entry of food into the esophagus marks the beginning of the esophageal phase of deglutition and the initiation of peristalsis. As in the previous phase, the complex neuromuscular actions are controlled by the medulla oblongata. Peristalsis propels the bolus through the esophagus and toward the stomach. The circular muscle layer of the muscularis contracts, pinching the esophageal wall and forcing the bolus forward. At the same time, the longitudinal muscle layer of the muscularis also contracts, shortening this area and pushing out its walls to receive the bolus. In this way, a series of contractions keeps moving food toward the stomach. When the bolus nears the stomach, distention of the esophagus initiates a short reflex relaxation of the lower esophageal sphincter that allows the bolus to pass into the stomach. During the esophageal phase, esophageal glands secrete mucus that lubricates the bolus and minimizes friction.

References

van Loon FPL, Holmes SJ, Sirotkin B, Williams W, Cochi S, Hadler S, Lindegren ML. Morbidity and Mortality Weekly Report: Mumps surveillance — United States, 1988–1993 [Internet]. Atlanta, GA: Center for Disease Control; [cited 2013 Apr 3]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/00038546.htm.

71. The Stomach

Although a minimal amount of carbohydrate digestion occurs in the mouth, chemical digestion really gets underway in the stomach. An expansion of the alimentary canal that lies immediately inferior to the esophagus, the stomach links the esophagus to the first part of the small intestine (the duodenum) and is relatively fixed in place at its esophageal and duodenal ends. In between, however, it can be a highly active structure, contracting and continually changing position and size. These contractions provide mechanical assistance to digestion. The empty stomach is only about the size of your fist, but can stretch to hold as much as 4 liters of food and fluid, or more than 75 times its empty volume, and then return to its resting size when empty. Although you might think that the size of a person's stomach is related to how much food that individual consumes, body weight does not correlate with stomach size. Rather, when you eat greater quantities of food—such as at holiday dinner—you stretch the stomach more than when you eat less.

Popular culture tends to refer to the stomach as the location where all digestion takes place. Of course, this is not true. An important function of the stomach is to serve as a temporary holding chamber. You can ingest a meal far more quickly than it can be digested and absorbed by the small intestine. Thus, the stomach holds food and parses only small amounts into the small intestine at a time. Foods are not processed in the order they are eaten; rather, they are mixed together with digestive juices in the stomach until they are converted into chyme, which is released into the small intestine.

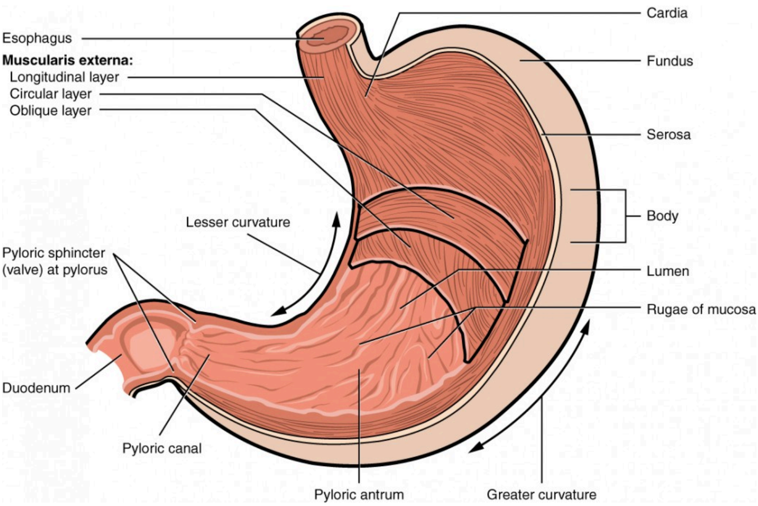
As you will see in the sections that follow, the stomach plays several important roles in chemical digestion, including the continued digestion of carbohydrates and the initial digestion of proteins and triglycerides. Little if any nutrient absorption occurs in the stomach, with the exception of the negligible amount of nutrients in alcohol.

Structure

There are four main regions in the stomach: the cardia, fundus, body, and pylorus. The cardia (or cardiac region) is the point where the esophagus connects to the stomach and through which food passes into the stomach. Located inferior to the diaphragm, above and to the left of the cardia, is the dome-shaped fundus. Below the fundus is the body, the main part of the stomach. The funnel-shaped pylorus connects the stomach to the duodenum. The wider end of the funnel, the pyloric antrum, connects to the body of the stomach. The narrower end is called the pyloric canal, which connects to the duodenum. The smooth muscle pyloric sphincter is located at this latter point of connection and controls stomach emptying. In the absence of food, the stomach deflates inward, and its mucosa and submucosa fall into a large fold called a ruga.

Stomach

The stomach has four major regions: the cardia, fundus, body, and pylorus. The addition of an inner oblique smooth muscle layer gives the muscularis the ability to vigorously churn and mix food.



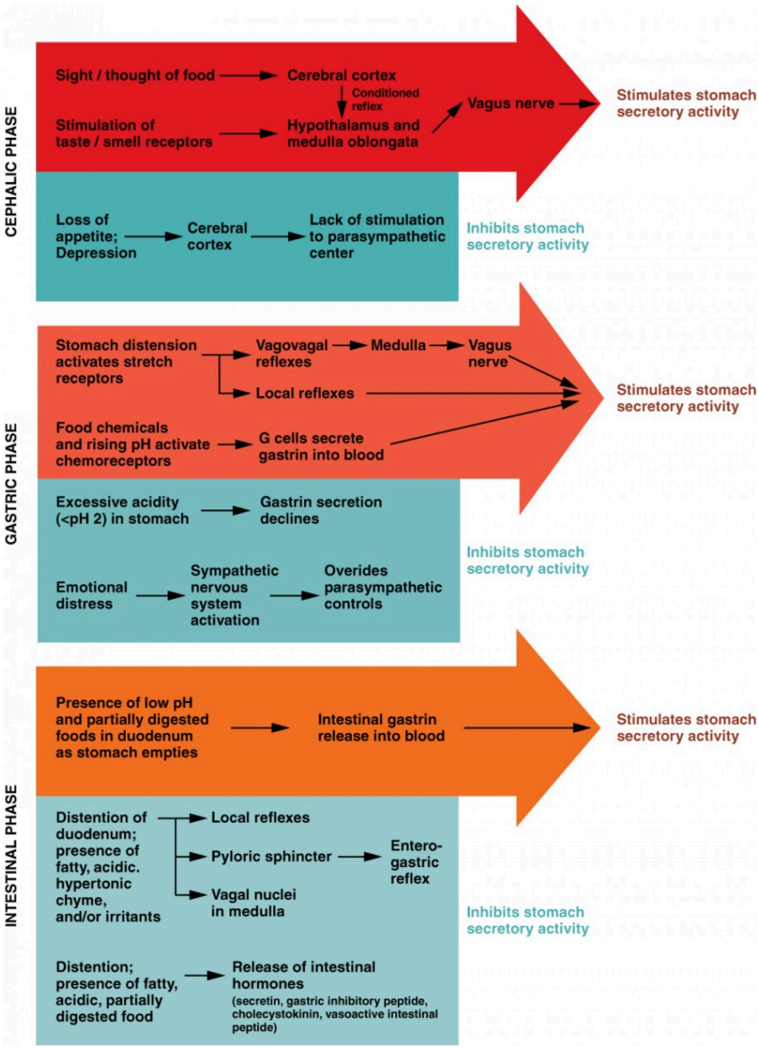
The convex lateral surface of the stomach is called the greater curvature; the concave medial border is the lesser curvature. The stomach is held in place by the lesser omentum, which extends from the liver to the lesser curvature, and the greater omentum, which runs from the greater curvature to the posterior abdominal wall.

Gastric Secretion

The secretion of gastric juice is controlled by both nerves and hormones. Stimuli in the brain, stomach, and small intestine activate or inhibit gastric juice production. This is why the three phases of gastric secretion are called the cephalic, gastric, and intestinal phases. However, once gastric secretion begins, all three phases can occur simultaneously.

The Three Phases of Gastric Secretion

Gastric secretion occurs in three phases: cephalic, gastric, and intestinal. During each phase, the secretion of gastric juice can be stimulated or inhibited.



The cephalic phase (reflex phase) of gastric secretion, which is relatively brief, takes place before food enters the stomach. The smell, taste, sight, or thought of food triggers this phase. For example, when you bring a piece of sushi to your lips, impulses from receptors in your taste buds or the nose are relayed to your brain, which returns signals that increase gastric secretion to prepare your stomach for digestion. This enhanced secretion is a conditioned reflex, meaning it occurs only if you like or want a particular food. Depression and loss of appetite can suppress the cephalic reflex.

The gastric phase of secretion lasts 3 to 4 hours, and is set in motion by local neural and hormonal mechanisms triggered by the entry of food into the stomach. For example, when your sushi reaches the stomach, it creates distention that activates the stretch receptors. This stimulates parasympathetic neurons to release acetylcholine, which then provokes increased secretion of gastric juice. Partially digested proteins, caffeine, and rising pH stimulate the release of gastrin from enteroendocrine G cells, which in turn induces parietal cells to increase their production of HCl, which is needed to create an acidic environment for the conversion of pepsinogen to pepsin, and protein digestion. Additionally, the release of gastrin activates vigorous smooth muscle contractions. However, it should be noted that the stomach does have a natural means of avoiding excessive acid secretion and potential heartburn. Whenever pH levels drop too low, cells in the stomach react by suspending HCl secretion and increasing mucous secretions.

The intestinal phase of gastric secretion has both excitatory and inhibitory elements. The duodenum has a major role in regulating the stomach and its emptying. When partially digested food fills the duodenum, intestinal mucosal cells release a hormone called intestinal (enteric) gastrin, which further excites gastric juice secretion. This stimulatory activity is brief, however, because when the intestine distends with chyme, the enterogastric reflex inhibits secretion. One of the effects of this reflex is to close the pyloric sphincter, which blocks additional chyme from entering the duodenum.

The Mucosal Barrier

The mucosa of the stomach is exposed to the highly corrosive acidity of gastric juice. Gastric enzymes that can digest protein can also digest the stomach itself. The stomach is protected from self-digestion by the mucosal barrier. This barrier has several components. First, the stomach wall is covered by a thick coating of bicarbonate-rich mucus. This mucus forms a physical barrier, and its bicarbonate ions neutralize acid. Second, the epithelial cells of the stomach's mucosa meet at tight junctions, which block gastric juice from penetrating the underlying tissue layers. Finally, stem cells located where gastric glands join the gastric pits quickly replace damaged epithelial mucosal cells, when the epithelial cells are shed. In fact, the surface epithelium of the stomach is completely replaced every 3 to 6 days.

Digestive Functions of the Stomach

The stomach participates in virtually all the digestive activities with the exception of ingestion and defecation. Although almost all absorption takes place in the small intestine, the stomach does absorb some nonpolar substances, such as alcohol and aspirin.

Mechanical Digestion

Within a few moments after food after enters your stomach, mixing waves begin to occur at intervals of approximately 20 seconds. A mixing wave is a unique type of peristalsis that mixes and softens the food with gastric juices to create chyme. The initial mixing waves are relatively gentle, but these are followed by more intense waves, starting at the body of the stomach and increasing in force as they reach the pylorus. It is fair to say that long before your sushi exits through the pyloric sphincter, it bears little resemblance to the sushi you ate.

The pylorus, which holds around 30 mL (1 fluid ounce) of chyme, acts as a filter, permitting only liquids and small food particles to pass through the mostly, but not fully, closed pyloric sphincter. In a process called gastric emptying, rhythmic mixing waves force about 3 mL of chyme at a time through the pyloric sphincter and into the duodenum. Release of a greater amount of chyme at one time would overwhelm the capacity of the small intestine to handle it. The rest of the chyme is pushed back into the body of the stomach, where it continues mixing. This process is repeated when the next mixing waves force more chyme into the duodenum.

Gastric emptying is regulated by both the stomach and the duodenum. The presence of chyme in the duodenum activates receptors that inhibit gastric secretion. This prevents additional chyme from being released by the stomach before the duodenum is ready to process it.

Chemical Digestion

The fundus plays an important role, because it stores both undigested food and gases that are released during the process of chemical digestion. Food may sit in the fundus of the stomach for a while before being mixed with the chyme. While the food is in the fundus, the digestive activities of salivary amylase continue until the food begins mixing with the acidic chyme. Ultimately, mixing waves incorporate this food with the chyme, the acidity of which inactivates salivary amylase and activates lingual lipase. Lingual lipase then begins breaking down triglycerides into free fatty acids, and mono- and diglycerides.

The breakdown of protein begins in the stomach through the actions of HCl and the enzyme pepsin. During infancy, gastric glands also produce rennin, an enzyme that helps digest milk protein.

Its numerous digestive functions notwithstanding, there is only one stomach function necessary to life: the production of intrinsic factor. The intestinal absorption of vitamin B_{12}, which is necessary for both the production of mature red blood cells and normal neurological functioning, cannot occur without intrinsic factor. People who undergo total gastrectomy (stomach removal)—for life-threatening stomach cancer, for example—can survive with minimal digestive dysfunction if they receive vitamin B_{12} injections.

The contents of the stomach are completely emptied into the duodenum within 2 to 4 hours after you eat a meal. Different types of food take different amounts of time to process. Foods heavy in carbohydrates empty fastest, followed by high-protein foods. Meals with a high triglyceride content remain in the stomach the longest. Since enzymes in the small intestine digest fats slowly, food can stay in the stomach for 6 hours or longer when the duodenum is processing fatty chyme. However, note that this is still a fraction of the 24 to 72 hours that full digestion typically takes from start to finish.

72. The Small and Large Intestines

The word intestine is derived from a Latin root meaning "internal," and indeed, the two organs together nearly fill the interior of the abdominal cavity. In addition, called the small and large bowel, or colloquially the "guts," they constitute the greatest mass and length of the alimentary canal and, with the exception of ingestion, perform all digestive system functions.

The Small Intestine

Chyme released from the stomach enters the small intestine, which is the primary digestive organ in the body. Not only is this where most digestion occurs, it is also where practically all absorption occurs. The longest part of the alimentary canal, the small intestine is about 3.05 meters (10 feet) long in a living person (but about twice as long in a cadaver due to the loss of muscle tone). Since this makes it about five times longer than the large intestine, you might wonder why it is called "small." In fact, its name derives from its relatively smaller diameter of only about 2.54 cm (1 in), compared with 7.62 cm (3 in) for the large intestine. As we'll see shortly, in addition to its length, the folds and projections of the lining of the small intestine work to give it an enormous surface area, which is approximately 200 m^2, more than 100 times the surface area of your skin. This large surface area is necessary for complex processes of digestion and absorption that occur within it.

Structure

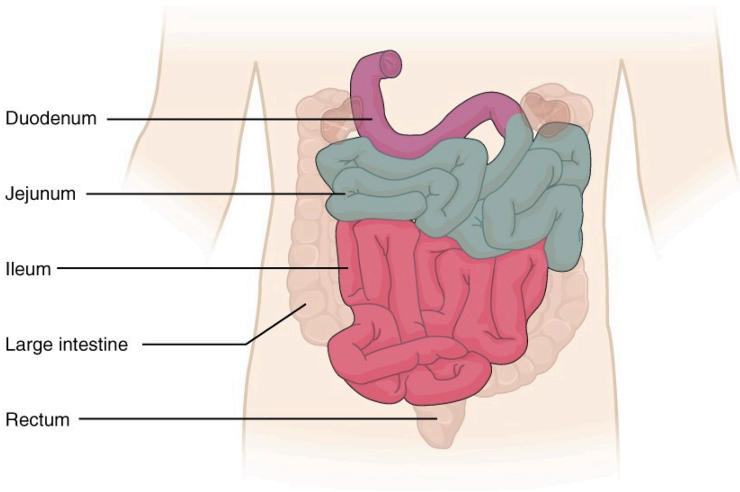
The coiled tube of the small intestine is subdivided into three regions. From proximal (at the stomach) to distal, these are the duodenum, jejunum, and ileum.

The shortest region is the 25.4-cm (10-in) duodenum, which begins at the pyloric sphincter. Just past the pyloric sphincter, it bends posteriorly behind the peritoneum, becoming retroperitoneal, and then makes a C-shaped curve around the head of the pancreas before ascending anteriorly again to return to the peritoneal cavity and join the jejunum. The duodenum can therefore be subdivided into four segments: the superior, descending, horizontal, and ascending duodenum.

Of particular interest is the hepatopancreatic ampulla (ampulla of Vater). Located in the duodenal wall, the ampulla marks the transition from the anterior portion of the alimentary canal to the mid-region, and is where the bile duct (through which bile passes from the liver) and the main pancreatic duct (through which pancreatic juice passes from the pancreas) join. This ampulla opens into the duodenum at a tiny volcano-shaped structure called the major duodenal papilla. The hepatopancreatic sphincter (sphincter of Oddi) regulates the flow of both bile and pancreatic juice from the ampulla into the duodenum.

Small Intestine

The three regions of the small intestine are the duodenum, jejunum, and ileum.



The jejunum is about 0.9 meters (3 feet) long (in life) and runs from the duodenum to the ileum. Jejunum means “empty” in Latin and supposedly was so named by the ancient Greeks who noticed it was always empty at death. No clear demarcation exists between the jejunum and the final segment of the small intestine, the ileum.

The ileum is the longest part of the small intestine, measuring about 1.8 meters (6 feet) in length. It is thicker, more vascular, and has more developed mucosal folds than the jejunum. The ileum joins the cecum, the first portion of the large intestine, at the ileocecal sphincter (or valve). The jejunum and ileum are tethered to the posterior abdominal wall by the mesentery. The large intestine frames these three parts of the small intestine.

Parasympathetic nerve fibers from the vagus nerve and sympathetic nerve fibers from the thoracic splanchnic nerve provide extrinsic innervation to the small intestine. The superior mesenteric artery is its main arterial supply. Veins run parallel to the arteries and drain into the superior mesenteric vein. Nutrient-rich blood from the small intestine is then carried to the liver via the hepatic portal vein.

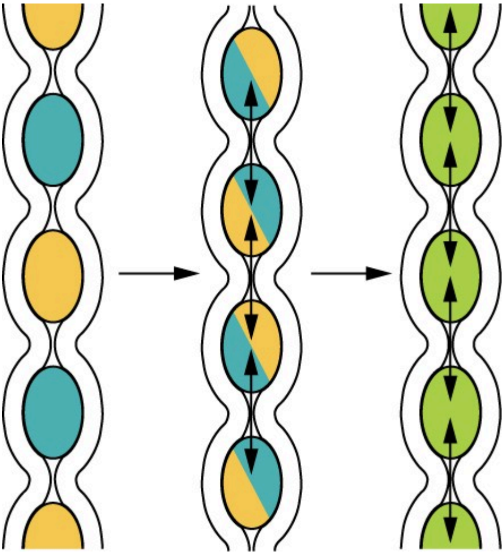
Mechanical Digestion in the Small Intestine

The movement of intestinal smooth muscles includes both segmentation and a form of peristalsis called migrating motility complexes. The kind of peristaltic mixing waves seen in the stomach are not observed here.

If you could see into the small intestine when it was going through segmentation, it would look as if the contents were being shoved incrementally back and forth, as the rings of smooth muscle repeatedly contract and then relax. Segmentation in the small intestine does not force chyme through the tract. Instead, it combines the chyme with digestive juices and pushes food particles against the mucosa to be absorbed. The duodenum is where the most rapid segmentation occurs, at a rate of about 12 times per minute. In the ileum, segmentations are only about eight times per minute .

Segmentation

Segmentation separates chyme and then pushes it back together, mixing it and providing time for digestion and absorption.



When most of the chyme has been absorbed, the small intestinal wall becomes less distended. At this point, the localized segmentation process is replaced by transport movements. The duodenal mucosa secretes the hormone motilin, which initiates peristalsis in the form of a migrating motility complex. These complexes, which begin in the duodenum, force chyme through a short section of the small intestine and then stop. The next contraction begins a little bit farther down than the first, forces chyme a bit farther through the small intestine, then stops. These complexes move slowly down the small intestine, forcing chyme on the way, taking around 90 to 120 minutes to finally reach the end of the ileum. At this point, the process is repeated, starting in the duodenum.

The ileocecal valve, a sphincter, is usually in a constricted state, but when motility in the ileum increases, this sphincter relaxes, allowing food residue to enter the first portion of the large intestine, the cecum. Relaxation of the ileocecal sphincter is controlled by both nerves and hormones. First, digestive activity in the stomach provokes the gastroileal reflex, which increases the force of ileal segmentation. Second, the stomach releases the hormone gastrin, which enhances ileal motility, thus relaxing the ileocecal sphincter. After chyme passes through, backward pressure helps close the sphincter, preventing backflow into the ileum. Because of this reflex, your lunch is completely emptied from your stomach and small intestine by the time you eat your dinner. It takes about 3 to 5 hours for all chyme to leave the small intestine.

Chemical Digestion in the Small Intestine

The digestion of proteins and carbohydrates, which partially occurs in the stomach, is completed in the small intestine with the aid of intestinal and pancreatic juices. Lipids arrive in the intestine largely undigested, so much of the focus here is on lipid digestion, which is facilitated by bile and the enzyme pancreatic lipase.

Moreover, intestinal juice combines with pancreatic juice to provide a liquid medium that facilitates absorption. The intestine is also where most water is absorbed, via osmosis. The small intestine's absorptive cells also synthesize digestive enzymes and then place them in the plasma membranes of the microvilli. This distinguishes the small intestine from the stomach; that is, enzymatic digestion occurs not only in the lumen, but also on the luminal surfaces of the mucosal cells.

For optimal chemical digestion, chyme must be delivered from the stomach slowly and in small amounts. This is because chyme from the stomach is typically hypertonic, and if large quantities were forced all at once into the small intestine, the resulting osmotic water loss from the blood into the intestinal lumen would result in potentially life-threatening low blood volume. In addition, continued digestion requires an upward adjustment of the low pH of stomach chyme, along with rigorous mixing of the chyme with bile and pancreatic juices. Both processes take time, so the pumping action of the pylorus must be carefully controlled to prevent the duodenum from being overwhelmed with chime.

The Large Intestine

The large intestine is the terminal part of the alimentary canal. The primary function of this organ is to finish absorption of nutrients and water, synthesize certain vitamins, form feces, and eliminate feces from the body.

Structure

The large intestine runs from the appendix to the anus. It frames the small intestine on three sides. Despite its being about one-half as long as the small intestine, it is called large because it is more than twice the diameter of the small intestine, about 3 inches.

Subdivisions

The large intestine is subdivided into four main regions: the cecum, the colon, the rectum, and the anus. The ileocecal valve, located at the opening between the ileum and the large intestine, controls the flow of chyme from the small intestine to the large intestine.

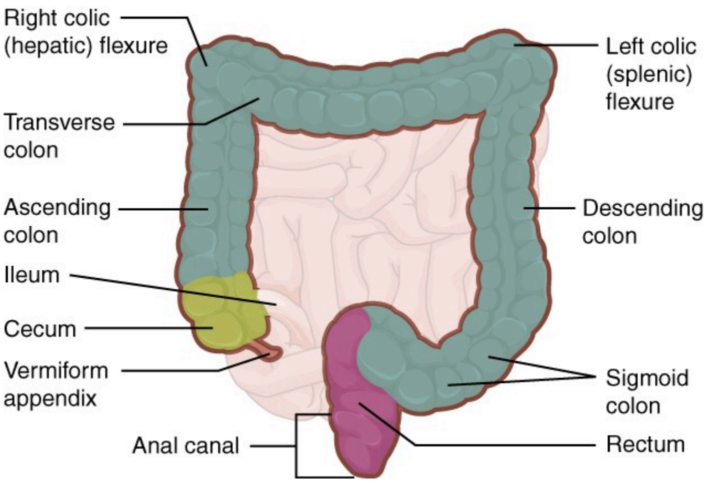
Cecum

The first part of the large intestine is the cecum, a sac-like structure that is suspended inferior to the ileocecal valve. It is about 6 cm (2.4 in) long, receives the contents of the ileum, and continues the absorption of water and salts. The appendix (or vermiform appendix) is a winding tube that attaches to the cecum. Although the 7.6-cm (3-in) long appendix contains lymphoid tissue, suggesting an immunologic function, this organ is generally considered vestigial. However, at least one recent report postulates a survival advantage conferred by the appendix: In diarrheal illness, the appendix may serve as a bacterial reservoir to repopulate the enteric bacteria for those surviving the initial phases of the illness. Moreover, its twisted anatomy provides a haven for the accumulation and multiplication of enteric bacteria. The mesoappendix, the mesentery of the appendix, tethers it to the mesentery of the ileum.

Colon

The cecum blends seamlessly with the colon. Upon entering the colon, the food residue first travels up the ascending colon on the right side of the abdomen. At the inferior surface of the liver, the colon bends to form the right colic flexure (hepatic flexure) and becomes the transverse colon. The region defined as hindgut begins with the last third of the transverse colon and continues on. Food residue passing through the transverse colon travels across to the left side of the abdomen, where the colon angles sharply immediately inferior to the spleen, at the left colic flexure (splenic flexure). From there, food residue passes through the descending colon, which runs down the left side of the posterior abdominal wall. After entering the pelvis inferiorly, it becomes the s-shaped sigmoid colon, which extends medially to the midline. The ascending and descending colon, and the rectum (discussed next) are located in the retroperitoneum. The transverse and sigmoid colon are tethered to the posterior abdominal wall by the mesocolon.

Large Intestine
The large intestine includes the cecum, colon, and rectum.



Rectum

Food residue leaving the sigmoid colon enters the rectum in the pelvis, near the third sacral vertebra. The final 20.3 cm (8 in) of the alimentary canal, the rectum extends anterior to the sacrum and coccyx. Even though rectum is Latin for "straight," this structure follows the curved contour of the sacrum and has three lateral bends that create a trio of internal transverse folds called the rectal valves. These valves help separate the feces from gas to prevent the simultaneous passage of feces and gas.

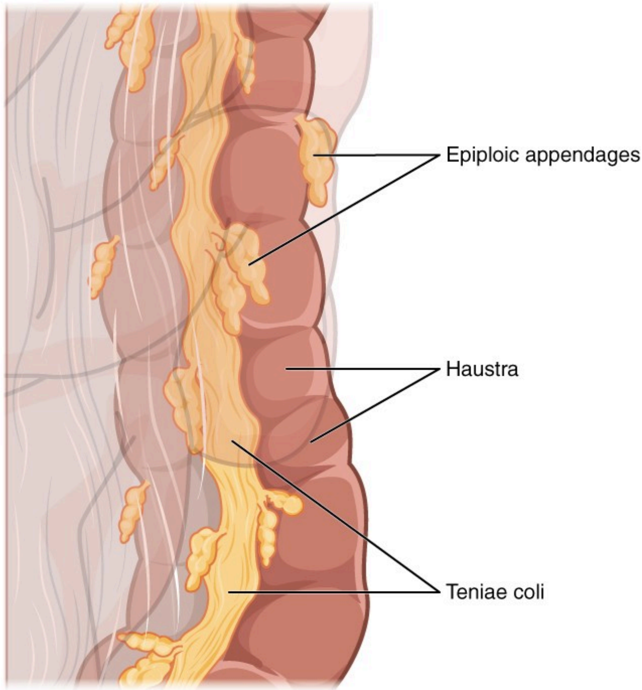
Anal Canal

Finally, food residue reaches the last part of the large intestine, the anal canal, which is located in the perineum, completely outside of the abdominopelvic cavity. This 3.8–5 cm (1.5–2 in) long structure opens to the exterior of the body at the anus. The anal canal includes two sphincters. The internal anal sphincter is made of smooth muscle, and its contractions are involuntary. The external anal sphincter is made of skeletal muscle, which is under voluntary control. Except when defecating, both usually remain closed.

Anatomy

Three features are unique to the large intestine: teniae coli, haustra, and epiploic appendages ([link]). The teniae coli are three bands of smooth muscle that make up the longitudinal muscle layer of the muscularis of the large intestine, except at its terminal end. Tonic contractions of the teniae coli bunch up the colon into a succession of pouches called haustra (singular = hostrum), which are responsible for the wrinkled appearance of the colon. Attached to the teniae coli are small, fat-filled sacs of visceral peritoneum called epiploic appendages. The purpose of these is unknown. Although the rectum and anal canal have neither teniae coli nor haustra, they do have well-developed layers of muscularis that create the strong contractions needed for defecation.

Teniae Coli, Haustra, and Epiploic Appendages



The stratified squamous epithelial mucosa of the anal canal connects to the skin on the outside of the anus. This mucosa varies considerably from that of the rest of the colon to accommodate the high level of abrasion as feces pass through. The anal canal's mucous membrane is organized into longitudinal folds, each called an anal column, which house a grid of arteries and veins. Two superficial venous plexuses are found in the anal canal: one within the anal columns and one at the anus.

Depressions between the anal columns, each called an anal sinus, secrete mucus that facilitates defecation. The pectinate line (or dentate line) is a horizontal, jagged band that runs circumferentially just below the level of the anal sinuses, and represents the junction between the hindgut and external skin. The mucosa above this line is fairly insensitive, whereas the area below is very sensitive. The resulting difference in pain threshold is due to the fact that the upper region is innervated by visceral sensory fibers, and the lower region is innervated by somatic sensory fibers.

Bacterial Flora

Most bacteria that enter the alimentary canal are killed by lysozyme, defensins, HCl, or protein-digesting enzymes. However, trillions of bacteria live within the large intestine and are referred to as the bacterial flora. Most of the more than 700 species of these bacteria are nonpathogenic commensal organisms that cause no harm as long as they stay in the gut lumen. In fact, many facilitate chemical digestion and absorption, and some synthesize certain vitamins, mainly biotin, pantothenic acid, and vitamin K. Some are linked to increased immune response. A refined system prevents these bacteria from crossing the mucosal barrier. First, peptidoglycan, a component of bacterial cell walls, activates the release of chemicals by the mucosa's epithelial cells, which draft immune cells, especially dendritic cells, into the mucosa. Dendritic cells open the tight junctions between epithelial cells and extend probes into the lumen to evaluate the microbial antigens. The dendritic cells with antigens then travel to neighboring lymphoid follicles in the mucosa where T cells inspect for antigens. This process triggers an IgA-mediated response, if warranted, in the lumen that blocks the commensal organisms from infiltrating the mucosa and setting off a far greater, widespread systematic reaction.

Digestive Functions of the Large Intestine

The residue of chyme that enters the large intestine contains few nutrients except water, which is reabsorbed as the residue lingers in the large intestine, typically for 12 to 24 hours. Thus, it may not surprise you that the large intestine can be completely removed without significantly affecting digestive functioning. For example, in severe cases of inflammatory bowel disease, the large intestine can be removed by a procedure known as a colectomy. Often, a new fecal pouch can be crafted from the small intestine and sutured to the anus, but if not, an ileostomy can be created by bringing the distal ileum through the abdominal wall, allowing the watery chyme to be collected in a bag-like adhesive appliance.

Mechanical Digestion

In the large intestine, mechanical digestion begins when chyme moves from the ileum into the cecum, an activity regulated by the ileocecal sphincter. Right after you eat, peristalsis in the ileum forces chyme into the cecum. When the cecum is distended with chyme, contractions of the ileocecal sphincter strengthen. Once chyme enters the cecum, colon movements begin.

Mechanical digestion in the large intestine includes a combination of three types of movements. The presence of food residues in the colon stimulates a slow-moving haustral contraction. This type of movement involves sluggish segmentation, primarily in the transverse and descending colons. When a haustrum is distended with chyme, its muscle contracts, pushing the residue into the next haustrum. These contractions occur about every 30 minutes, and each last about 1 minute. These movements also mix the food residue, which helps the large intestine absorb water. The second type of movement is peristalsis, which, in the large intestine, is slower than in the more proximal portions of the alimentary canal. The third type is a mass movement. These strong waves start midway through the transverse colon and quickly force the contents toward the rectum. Mass movements usually occur three or four times per day, either while you eat or immediately afterward. Distension in the stomach and the breakdown products of digestion in the small intestine provoke the gastrocolic reflex, which increases motility, including mass movements, in the colon. Fiber in the diet both softens the stool and increases the power of colonic contractions, optimizing the activities of the colon.

Chemical Digestion

Although the glands of the large intestine secrete mucus, they do not secrete digestive enzymes. Therefore, chemical digestion in the large intestine occurs exclusively because of bacteria in the lumen of the colon. Through the process of saccharolytic fermentation, bacteria break down some of the remaining carbohydrates. This results in the discharge of hydrogen, carbon dioxide, and methane gases that create flatus (gas) in the colon; flatulence is excessive flatus. Each day, up to 1500 mL of flatus is produced in the colon. More is produced when you eat foods such as beans, which are rich in otherwise indigestible sugars and complex carbohydrates like soluble dietary fiber.

Absorption, Feces Formation, and Defecation

The small intestine absorbs about 90 percent of the water you ingest (either as liquid or within solid food). The large intestine absorbs most of the remaining water, a process that converts the liquid chyme residue into semisolid feces ("stool"). Feces is composed of undigested food residues, unabsorbed digested substances, millions of bacteria, old epithelial cells from the GI mucosa, inorganic salts, and enough water to let it pass smoothly out of the body. Of every 500 mL (17 ounces) of food residue that enters the cecum each day, about 150 mL (5 ounces) become feces.

Feces are eliminated through contractions of the rectal muscles.

You help this process by a voluntary procedure called Valsalva's maneuver, in which you increase intra-abdominal pressure by contracting your diaphragm and abdominal wall muscles, and closing your glottis.

The process of defecation begins when mass movements force feces from the colon into the rectum, stretching the rectal wall and provoking the defecation reflex, which eliminates feces from the rectum. This parasympathetic reflex is mediated by the spinal cord. It contracts the sigmoid colon and rectum, relaxes the internal anal sphincter, and initially contracts the external anal sphincter. The presence of feces in the anal canal sends a signal to the brain, which gives you the choice of voluntarily opening the external anal sphincter (defecating) or keeping it temporarily closed. If you decide to delay defecation, it takes a few seconds for the reflex contractions to stop and the rectal walls to relax. The next mass movement will trigger additional defecation reflexes until you defecate.

If defecation is delayed for an extended time, additional water is absorbed, making the feces firmer and potentially leading to constipation. On the other hand, if the waste matter moves too quickly through the intestines, not enough water is absorbed, and diarrhea can result. This can be caused by the ingestion of foodborne pathogens. In general, diet, health, and stress determine the frequency of bowel movements. The number of bowel movements varies greatly between individuals, ranging from two or three per day to three or four per week.

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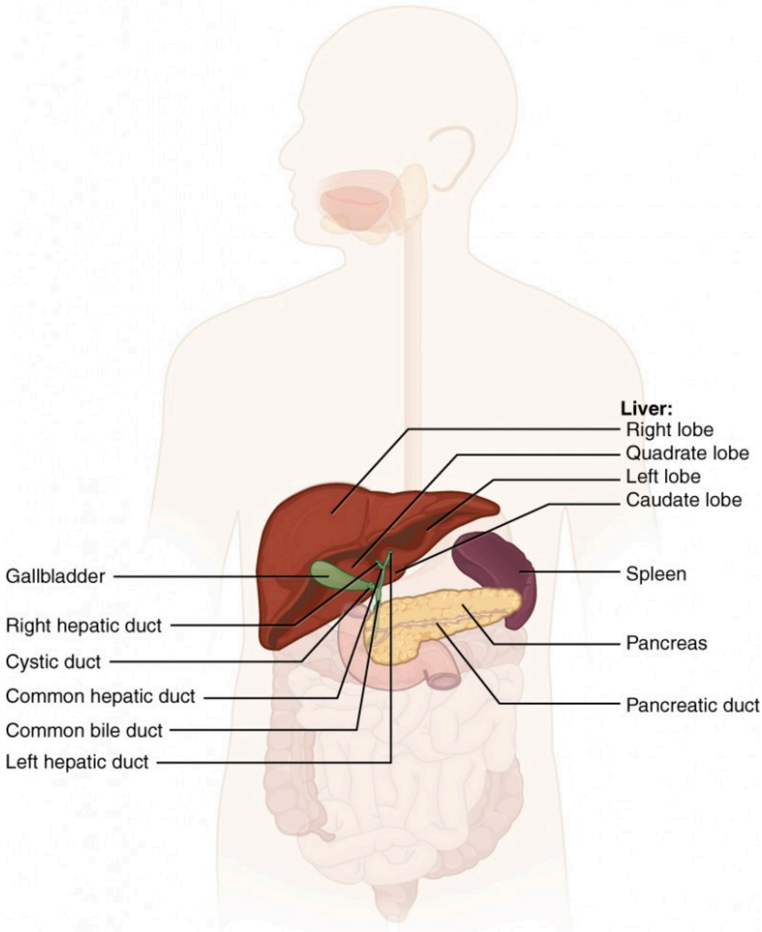
73. Accessory Organs in Digestion: The Liver, Pancreas, and Gallbladder

Chemical digestion in the small intestine relies on the activities of three accessory digestive organs: the liver, pancreas, and gallbladder. The digestive role of the liver is to produce bile and export it to the duodenum. The gallbladder primarily stores, concentrates, and releases bile. The pancreas produces pancreatic juice, which contains digestive enzymes and bicarbonate ions, and delivers it to the duodenum.

Accessory Organs

The liver, pancreas, and gallbladder are considered accessory digestive organs, but their roles in the digestive system are vital.



The Liver

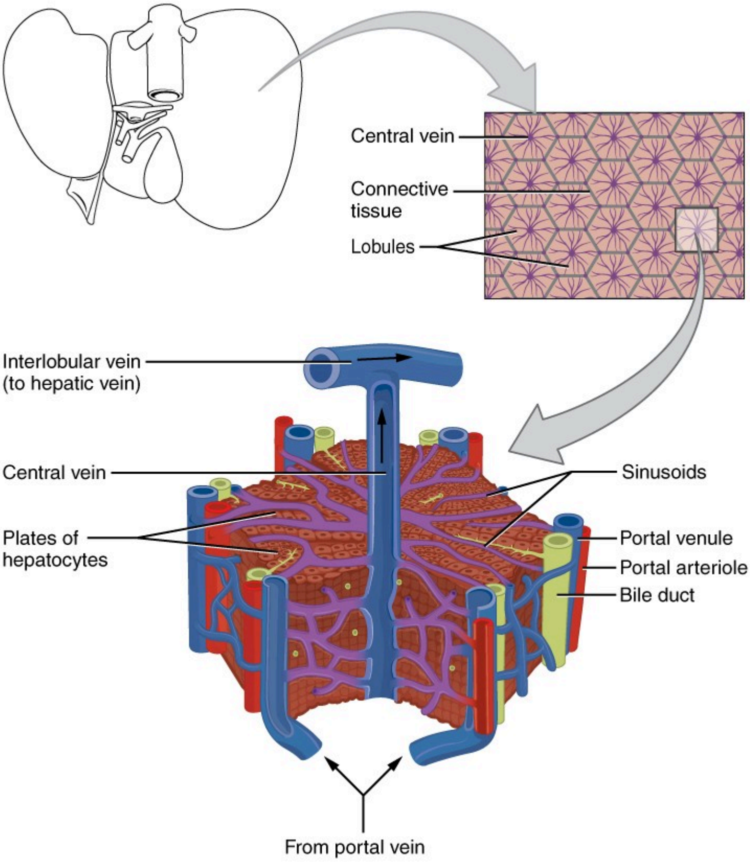
The liver is the largest gland in the body, weighing about three pounds in an adult. It is also one of the most important organs. In addition to being an accessory digestive organ, it plays a number of roles in metabolism and regulation. The liver lies inferior to the diaphragm in the right upper quadrant of the abdominal cavity and receives protection from the surrounding ribs.

The liver is divided into two primary lobes: a large right lobe and a much smaller left lobe. In the right lobe, some anatomists also identify an inferior quadrate lobe and a posterior caudate lobe, which are defined by internal features. The liver is connected to the abdominal wall and diaphragm by five peritoneal folds referred to as ligaments. These are the falciform ligament, the coronary ligament, two lateral ligaments, and the ligamentum teres hepatis. The falciform ligament and ligamentum teres hepatis are actually remnants of the umbilical vein, and separate the right and left lobes anteriorly. The lesser omentum tethers the liver to the lesser curvature of the stomach.

The porta hepatis ("gate to the liver") is where the hepatic artery and hepatic portal vein enter the liver. These two vessels, along with the common hepatic duct, run behind the lateral border of the lesser omentum on the way to their destinations. As shown in, the hepatic artery delivers oxygenated blood from the heart to the liver. The hepatic portal vein delivers partially deoxygenated blood containing nutrients absorbed from the small intestine and actually supplies more oxygen to the liver than do the much smaller hepatic arteries. In addition to nutrients, drugs and toxins are also absorbed. After processing the bloodborne nutrients and toxins, the liver releases nutrients needed by other cells back into the blood, which drains into the central vein and then through the hepatic vein to the inferior vena cava. With this hepatic portal circulation, all blood from the alimentary canal passes through the liver. This largely explains why the liver is the most common site for the metastasis of cancers that originate in the alimentary canal.

Microscopic Anatomy of the Liver

The liver receives oxygenated blood from the hepatic artery and nutrient-rich deoxygenated blood from the hepatic portal vein.



Bile

Recall that lipids are hydrophobic, that is, they do not dissolve in water. Thus, before they can be digested in the watery environment of the small intestine, large lipid globules must be broken down into smaller lipid globules, a process called emulsification. Bile is a mixture secreted by the liver to accomplish the emulsification of lipids in the small intestine.

Hepatocytes secrete about one liter of bile each day. A yellow-brown or yellow-green alkaline solution (pH 7.6 to 8.6), bile is a mixture of water, bile salts, bile pigments, phospholipids (such as lecithin), electrolytes, cholesterol, and triglycerides. The components most critical to emulsification are bile salts and phospholipids, which have a nonpolar (hydrophobic) region as well as a polar (hydrophilic) region. The hydrophobic region interacts with the large lipid molecules, whereas the hydrophilic region interacts with the watery chyme in the intestine. This results in the large lipid globules being pulled apart into many tiny lipid fragments of about 1 μm in diameter. This change dramatically increases the surface area available for lipid-digesting enzyme activity. This is the same way dish soap works on fats mixed with water.

Bile salts act as emulsifying agents, so they are also important for the absorption of digested lipids. While most constituents of bile are eliminated in feces, bile salts are reclaimed by the enterohepatic circulation. Once bile salts reach the ileum, they are absorbed and returned to the liver in the hepatic portal blood. The hepatocytes then excrete the bile salts into newly formed bile. Thus, this precious resource is recycled.

Bilirubin, the main bile pigment, is a waste product produced when the spleen removes old or damaged red blood cells from the circulation. These breakdown products, including proteins, iron, and toxic bilirubin, are transported to the liver via the splenic vein of the hepatic portal system. In the liver, proteins and iron are recycled, whereas bilirubin is excreted in the bile. It accounts for the green color of bile. Bilirubin is eventually transformed by intestinal bacteria into stercobilin, a brown pigment that gives your stool its characteristic color! In some disease states, bile does not enter the intestine, resulting in white ('acholic') stool with a high fat content, since virtually no fats are broken down or absorbed.

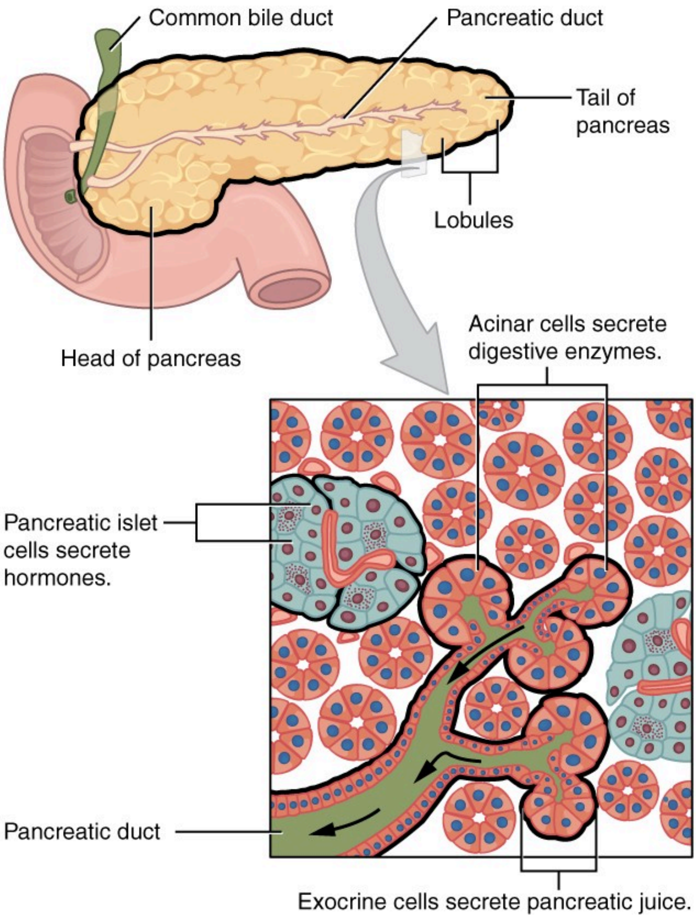
Hepatocytes work non-stop, but bile production increases when fatty chyme enters the duodenum and stimulates the secretion of the gut hormone secretin. Between meals, bile is produced but conserved. The valve-like hepatopancreatic ampulla closes, allowing bile to divert to the gallbladder, where it is concentrated and stored until the next meal.

The Pancreas

The soft, oblong, glandular pancreas lies transversely in the retroperitoneum behind the stomach. Its head is nestled into the “c-shaped” curvature of the duodenum with the body extending to the left about 15.2 cm (6 in) and ending as a tapering tail in the hilum of the spleen. It is a curious mix of exocrine (secreting digestive enzymes) and endocrine (releasing hormones into the blood) functions.

Exocrine and Endocrine Pancreas

The pancreas has a head, a body, and a tail. It delivers pancreatic juice to the duodenum through the pancreatic duct.



The exocrine part of the pancreas arises as little grape-like cell clusters, each called an acinus (plural = acini), located at the terminal ends of pancreatic ducts. These acinar cells secrete enzyme-rich pancreatic juice into tiny merging ducts that form two dominant ducts. The larger duct fuses with the common bile duct (carrying bile from the liver and gallbladder) just before entering the duodenum via a common opening (the hepatopancreatic ampulla). The smooth muscle sphincter of the hepatopancreatic ampulla controls the release of pancreatic juice and bile into the small intestine. The second and smaller pancreatic duct, the accessory duct (duct of Santorini), runs from the pancreas directly into the duodenum, approximately 1 inch above the hepatopancreatic ampulla. When present, it is a persistent remnant of pancreatic development.

Scattered through the sea of exocrine acini are small islands of endocrine cells, the islets of Langerhans. These vital cells produce the hormones pancreatic polypeptide, insulin, glucagon, and somatostatin.

Pancreatic Juice

The pancreas produces over a liter of pancreatic juice each day. Unlike bile, it is clear and composed mostly of water along with some salts, sodium bicarbonate, and several digestive enzymes. Sodium bicarbonate is responsible for the slight alkalinity of pancreatic juice (pH 7.1 to 8.2), which serves to buffer the acidic gastric juice in chyme, inactivate pepsin from the stomach, and create an optimal environment for the activity of pH-sensitive digestive enzymes in the small intestine. Pancreatic enzymes are active in the digestion of sugars, proteins, and fats.

The pancreas produces protein-digesting enzymes in their inactive forms. These enzymes are activated in the duodenum. If produced in an active form, they would digest the pancreas (which is exactly what occurs in the disease, pancreatitis). The intestinal brush border enzyme enteropeptidase stimulates the activation of trypsin from trypsinogen of the pancreas, which in turn changes the pancreatic enzymes procarboxypeptidase and chymotrypsinogen into their active forms, carboxypeptidase and chymotrypsin.

The enzymes that digest starch (amylase), fat (lipase), and nucleic acids (nuclease) are secreted in their active forms, since they do not attack the pancreas as do the protein-digesting enzymes.

Pancreatic Secretion

Regulation of pancreatic secretion is the job of hormones and the parasympathetic nervous system. The entry of acidic chyme into the duodenum stimulates the release of secretin, which in turn causes the duct cells to release bicarbonate-rich pancreatic juice. The presence of proteins and fats in the duodenum stimulates the secretion of CCK, which then stimulates the acini to secrete enzyme-rich pancreatic juice and enhances the activity of secretin. Parasympathetic regulation occurs mainly during the cephalic and gastric phases of gastric secretion, when vagal stimulation prompts the secretion of pancreatic juice.

Usually, the pancreas secretes just enough bicarbonate to counterbalance the amount of HCl produced in the stomach. Hydrogen ions enter the blood when bicarbonate is secreted by the pancreas. Thus, the acidic blood draining from the pancreas neutralizes the alkaline blood draining from the stomach, maintaining the pH of the venous blood that flows to the liver.

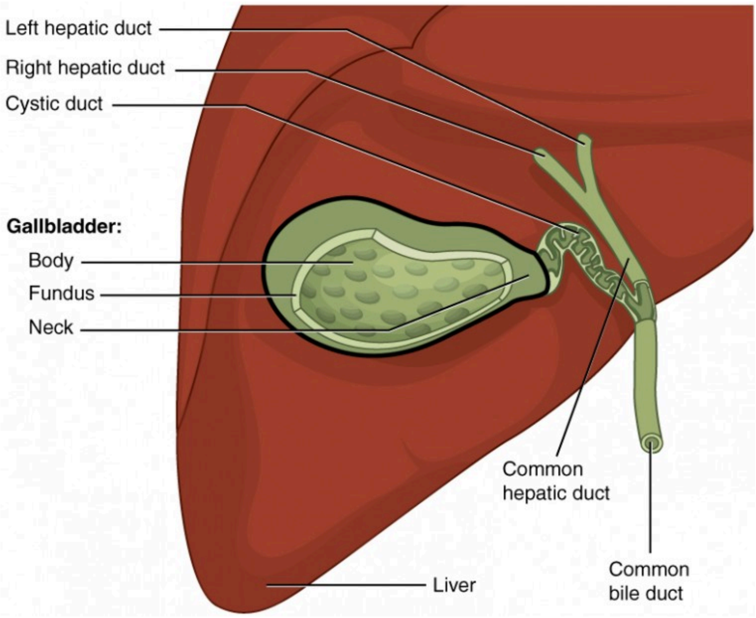
The Gallbladder

The gallbladder is 8–10 cm (~3–4 in) long and is nested in a shallow area on the posterior aspect of the right lobe of the liver. This muscular sac stores, concentrates, and, when stimulated, propels the bile into the duodenum via the common bile duct. It is divided into three regions. The fundus is the widest portion and tapers medially into the body, which in turn narrows to become the neck. The neck angles slightly superiorly as it approaches the hepatic duct. The cystic duct is 1–2 cm (less than 1 in) long and turns inferiorly as it bridges the neck and hepatic duct.

The simple columnar epithelium of the gallbladder mucosa is organized in rugae, similar to those of the stomach. There is no submucosa in the gallbladder wall. The wall's middle, muscular coat is made of smooth muscle fibers. When these fibers contract, the gallbladder's contents are ejected through the cystic duct and into the bile duct. Visceral peritoneum reflected from the liver capsule holds the gallbladder against the liver and forms the outer coat of the gallbladder. The gallbladder's mucosa absorbs water and ions from bile, concentrating it by up to 10-fold.

Gallbladder

The gallbladder stores and concentrates bile, and releases it into the two-way cystic duct when it is needed by the small intestine.



74. Age Related Changes to the Digestive System

Mouth

The most significant change to the mouth with age is the loss of teeth. This is caused by a combination of bone loss from the jaw, which occurs with age, and gum disease. Both result in a loosening of teeth. While lost teeth can be replaced with dentures these are not equivalent to natural teeth. Dentures can make it difficult to chew comfortably. This can result in a change of eating habits and long term deficits in nutrition.

Additional changes to the mouth include a decreased level of saliva production, thicker mucus production, and a diminished sense of taste.

Esophagus

Many other people experience difficultly in swallowing. Most often this is a result from incomplete relaxation of the lower esophageal sphincter, but it could be a result of a neurological disorder.

Other issues with esophagus include heartburn caused by stomach acid entering the esophagus through a weakened esophageal sphincter.

Stomach

The mucus membrane of the stomach thins with age resulting in lower levels of mucus, hydrochloric acid, and digestive enzymes. This reduces the digestion of proteins and may result in chronic atrophic gastritis.

Small Intestine

The walls of the small intestines atrophy with age. This alters the shape of the villi and reduces the surface area across which absorption occurs. Along with the atrophy these is a decrease in the production of digestive enzymes. Surprisingly these changes do not result in decreased rate of the absorption of digested food.

Large Intestine

The walls of the large intestines atrophy with age. The thinning of the walls results in outpockets from the wall, a condition known as diverticulosis.

Pancreas

The number of secretory cells in the pancreas decreases with age. This results in a decrease in the level of fat digestion.

Liver

While the liver reduces in size with age it does not show any significant reduction in the ability to perform its various functions in healthy elderly people.

75. Age Relate Dysfunctions of the Digestive System

Age-related changes in the digestive system begin in the mouth and can affect virtually every aspect of the digestive system. Taste buds become less sensitive, so food isn't as appetizing as it once was. A slice of pizza is a challenge, not a treat, when you have lost teeth, your gums are diseased, and your salivary glands aren't producing enough saliva. Swallowing can be difficult, and ingested food moves slowly through the alimentary canal because of reduced strength and tone of muscular tissue. Neurosensory feedback is also dampened, slowing the transmission of messages that stimulate the release of enzymes and hormones.

Pathologies that affect the digestive organs—such as hiatal hernia, gastritis, and peptic ulcer disease—can occur at greater frequencies as you age. Problems in the small intestine may include duodenal ulcers, maldigestion, and malabsorption. Problems in the large intestine include hemorrhoids, diverticular disease, and constipation. Conditions that affect the function of accessory organs—and their abilities to deliver pancreatic enzymes and bile to the small intestine—include jaundice, acute pancreatitis, cirrhosis, and gallstones.

Hiatal Hernia

A hiatal hernia occurs when the hiatus becomes weakened and the junction of the esophagus and the upper portion of the stomach protrudes from the abdominal cavity into the thoracic cavity by way of the hiatus. This condition is most common in obese people over the age of 50. While the condition is initially treated with surgery it is likely to reoccur. To prevent reoccurrence the condition is treated with medication and individuals are encouraged to eat small less frequent meals and elevate the head and chest while sleeping.

Colorectal Cancer

Each year, approximately 140,000 Americans are diagnosed with colorectal cancer, and another 49,000 die from it, making it one of the most deadly malignancies. People with a family history of colorectal cancer are at increased risk. Smoking, excessive alcohol consumption, and a diet high in animal fat and protein also increase the risk. Despite popular opinion to the contrary, studies support the conclusion that dietary fiber and calcium do not reduce the risk of colorectal cancer.

Colorectal cancer may be signaled by constipation or diarrhea, cramping, abdominal pain, and rectal bleeding. Bleeding from the rectum may be either obvious or occult (hidden in feces). Since most colon cancers arise from benign mucosal growths called polyps, cancer prevention is focused on identifying these polyps. The colonoscopy is both diagnostic and therapeutic. Colonoscopy not only allows identification of precancerous polyps, the procedure also enables them to be removed before they become malignant. Screening for fecal occult blood tests and colonoscopy is recommended for those over 50 years of age.

Diverticulitis

Diverticula are tiny herniations in the wall of the intestines, producing pouches that protrude outward through the muscular layer. Fecal matter can collect in the diverticula. This causes inflammation and possible infection. The infection is called diverticulitis. Diverticulitis is common in individuals over 40 in developed countries. This is believed to be a result of diets too low in fiber.

Constipation

Constipation refers to infrequent or difficult evacuation of feces from the bowel. It is often associated with large quantities of dry, hard faces in the descending colon and rectum. This slows the movement of digestive residue. The longer the fecal matter remains in the colon the more water is removed from the matter. This exacerbates the problem.

Fecal Incontinence

Fecal incontinence, or loss of control of bowels, is a problem for many older people. The major concern for people suffering from fecal incontinence is hygiene. Additionally, fecal incontinence can be embarrassing and has been known to cause depression.

Hemorrhoids

Hemorrhoids are swollen or ruptured blood vessels in the lower bowel. Most older people suffer from this condition, and while they may not cause any discomfort hemorrhoids often cause pain, itching, and bleeding. Constipation is the most common cause of hemorrhoids.

76. Glossary: The Digestive System

absorption passage of digested products from the intestinal lumen through mucosal cells and into the bloodstream or lacteals

accessory digestive organ includes teeth, tongue, salivary glands, gallbladder, liver, and pancreas

accessory duct (also, duct of Santorini) duct that runs from the pancreas into the duodenum

acinus cluster of glandular epithelial cells in the pancreas that secretes pancreatic juice in the pancreas

alimentary canal continuous muscular digestive tube that extends from the mouth to the anus

anal canal final segment of the large intestine

anal column long fold of mucosa in the anal canal

anal sinus between anal columns

appendix (vermiform appendix) coiled tube attached to the cecum

ascending colon first region of the colon

bacterial flora bacteria in the large intestine

bile alkaline solution produced by the liver and important for the emulsification of lipids

bile canaliculus small duct between hepatocytes that collects bile

bilirubin main bile pigment, which is responsible for the brown color of feces

body mid-portion of the stomach

bolus mass of chewed food

brush border fuzzy appearance of the small intestinal mucosa created by microvilli

cardia (also, cardiac region) part of the stomach surrounding the cardiac orifice (esophageal hiatus)

cecum pouch forming the beginning of the large intestine

cementum bone-like tissue covering the root of a tooth

central vein vein that receives blood from hepatic sinusoids

cephalic phase (also, reflex phase) initial phase of gastric secretion that occurs before food enters the stomach

chemical digestion enzymatic breakdown of food

chief cell gastric gland cell that secretes pepsinogen

chyme soupy liquid created when food is mixed with digestive juices

circular fold (also, plica circulare) deep fold in the mucosa and submucosa of the small intestine

colon part of the large intestine between the cecum and the rectum

common bile duct structure formed by the union of the common hepatic duct and the gallbladder's cystic duct

common hepatic duct duct formed by the merger of the two hepatic ducts

crown portion of tooth visible superior to the gum line

cuspid (also, canine) pointed tooth used for tearing and shredding food

cystic duct duct through which bile drains and enters the gallbladder

deciduous tooth one of 20 "baby teeth"

defecation elimination of undigested substances from the body in the form of feces

deglutition three-stage process of swallowing

dens tooth

dentin bone-like tissue immediately deep to the enamel of the crown or cementum of the root of a tooth

dentition set of teeth

descending colon part of the colon between the transverse colon and the sigmoid colon

duodenal gland (also, Brunner's gland) mucous-secreting gland in the duodenal submucosa

duodenum first part of the small intestine, which starts at the pyloric sphincter and ends at the jejunum

enamel covering of the dentin of the crown of a tooth

enteroendocrine cell gastric gland cell that releases hormones

enterohepatic circulation recycling mechanism that conserves bile salts

enteropeptidase intestinal brush-border enzyme that activates trypsinogen to trypsin

epiploic appendage small sac of fat-filled visceral peritoneum attached to teniae coli

esophagus muscular tube that runs from the pharynx to the stomach

external anal sphincter voluntary skeletal muscle sphincter in the anal canal

fauces opening between the oral cavity and the oropharynx

feces semisolid waste product of digestion

flatus gas in the intestine

fundus dome-shaped region of the stomach above and to the left of the cardia

G cell gastrin-secreting enteroendocrine cell

gallbladder accessory digestive organ that stores and concentrates bile

gastric emptying process by which mixing waves gradually cause the release of chyme into the duodenum

gastric gland gland in the stomach mucosal epithelium that produces gastric juice

gastric phase phase of gastric secretion that begins when food enters the stomach

gastric pit narrow channel formed by the epithelial lining of the stomach mucosa

gastrin peptide hormone that stimulates secretion of hydrochloric acid and gut motility

gastrocolic reflex propulsive movement in the colon activated by the presence of food in the stomach

gastroileal reflex long reflex that increases the strength of segmentation in the ileum

gingiva gum

haustrum small pouch in the colon created by tonic contractions of teniae coli

haustral contraction slow segmentation in the large intestine

hepatic artery artery that supplies oxygenated blood to the liver

hepatic lobule hexagonal-shaped structure composed of hepatocytes that radiate outward from a central vein

hepatic portal vein vein that supplies deoxygenated nutrient-rich blood to the liver

hepatic sinusoid blood capillaries between rows of hepatocytes that receive blood from the hepatic portal vein and the branches of the hepatic artery

hepatic vein vein that drains into the inferior vena cava

hepatocytes major functional cells of the liver

hepatopancreatic ampulla (also, ampulla of Vater) bulb-like point in the wall of the duodenum where the bile duct and main pancreatic duct unite

hepatopancreatic sphincter (also, sphincter of Oddi) sphincter regulating the flow of bile and pancreatic juice into the duodenum

hydrochloric acid (HCl) digestive acid secreted by parietal cells in the stomach

ileocecal sphincter sphincter located where the small intestine joins with the large intestine

ileum end of the small intestine between the jejunum and the large intestine

incisor midline, chisel-shaped tooth used for cutting into food

ingestion taking food into the GI tract through the mouth

internal anal sphincter involuntary smooth muscle sphincter in the anal canal

intestinal gland (also, crypt of Lieberkühn) gland in the small intestinal mucosa that secretes intestinal juice

intestinal juice mixture of water and mucus that helps absorb nutrients from chyme

intrinsic factor glycoprotein required for vitamin B_{12} absorption in the small intestine

intestinal phase phase of gastric secretion that begins when chyme enters the intestine

jejunum middle part of the small intestine between the duodenum and the ileum

labium lip

labial frenulum midline mucous membrane fold that attaches the inner surface of the lips to the gums

lacteal lymphatic capillary in the villi

large intestine terminal portion of the alimentary canal

laryngopharynx part of the pharynx that functions in respiration and digestion

left colic flexure (also, splenic flexure) point where the transverse colon curves below the inferior end of the spleen

lingual frenulum mucous membrane fold that attaches the bottom of the tongue to the floor of the mouth

lingual lipase digestive enzyme from glands in the tongue that acts on triglycerides

liver largest gland in the body whose main digestive function is the production of bile

lower esophageal sphincter smooth muscle sphincter that regulates food movement from the esophagus to the stomach

main pancreatic duct (also, duct of Wirsung) duct through which pancreatic juice drains from the pancreas

major duodenal papilla point at which the hepatopancreatic ampulla opens into the duodenum

mass movement long, slow, peristaltic wave in the large intestine

mastication chewing

mechanical digestion chewing, mixing, and segmentation that prepares food for chemical digestion

mesoappendix mesentery of the appendix

microvillus small projection of the plasma membrane of the absorptive cells of the small intestinal mucosa

migrating motility complex form of peristalsis in the small intestine

mixing wave unique type of peristalsis that occurs in the stomach

molar tooth used for crushing and grinding food

motilin hormone that initiates migrating motility complexes

motility movement of food through the GI tract

mucosa innermost lining of the alimentary canal

mucosal barrier protective barrier that prevents gastric juice from destroying the stomach itself

mucous neck cell gastric gland cell that secretes a uniquely acidic mucus

muscularis muscle (skeletal or smooth) layer of the alimentary canal wall

myenteric plexus (plexus of Auerbach) major nerve supply to alimentary canal wall; controls motility

oral cavity (also, buccal cavity) mouth

oral vestibule part of the mouth bounded externally by the cheeks and lips, and internally by the gums and teeth

oropharynx part of the pharynx continuous with the oral cavity that functions in respiration and digestion

palatoglossal arch muscular fold that extends from the lateral side of the soft palate to the base of the tongue

palatopharyngeal arch muscular fold that extends from the lateral side of the soft palate to the side of the pharynx

pancreas accessory digestive organ that secretes pancreatic juice

pancreatic juice secretion of the pancreas containing digestive enzymes and bicarbonate

parietal cell gastric gland cell that secretes hydrochloric acid and intrinsic factor

parotid gland one of a pair of major salivary glands located inferior and anterior to the ears

pectinate line horizontal line that runs like a ring, perpendicular to the inferior margins of the anal sinuses

pepsinogen inactive form of pepsin

peristalsis muscular contractions and relaxations that propel food through the GI tract

permanent tooth one of 32 adult teeth

pharynx throat

porta hepatis "gateway to the liver" where the hepatic artery and hepatic portal vein enter the liver

portal triad bile duct, hepatic artery branch, and hepatic portal vein branch

premolar (also, bicuspid) transitional tooth used for mastication, crushing, and grinding food

propulsion voluntary process of swallowing and the involuntary process of peristalsis that moves food through the digestive tract

pulp cavity deepest portion of a tooth, containing nerve endings and blood vessels

pyloric antrum wider, more superior part of the pylorus

pyloric canal narrow, more inferior part of the pylorus

pyloric sphincter sphincter that controls stomach emptying

pylorus lower, funnel-shaped part of the stomach that is continuous with the duodenum

rectal valve one of three transverse folds in the rectum where feces is separated from flatus

rectum part of the large intestine between the sigmoid colon and anal canal

reticuloendothelial cell (also, Kupffer cell) phagocyte in hepatic sinusoids that filters out material from venous blood from the alimentary canal

retroperitoneal located posterior to the peritoneum

right colic flexure (also, hepatic flexure) point, at the inferior surface of the liver, where the ascending colon turns abruptly to the left

root portion of a tooth embedded in the alveolar processes beneath the gum line

ruga fold of alimentary canal mucosa and submucosa in the empty stomach and other organs

saccharolytic fermentation anaerobic decomposition of carbohydrates

saliva aqueous solution of proteins and ions secreted into the mouth by the salivary glands

salivary amylase digestive enzyme in saliva that acts on starch

salivary gland an exocrine gland that secretes a digestive fluid called saliva

salivation secretion of saliva

segmentation alternating contractions and relaxations of non-adjacent segments of the intestine that move food forward and backward, breaking it apart and mixing it with digestive juices

serosa outermost layer of the alimentary canal wall present in regions within the abdominal cavity

sigmoid colon end portion of the colon, which terminates at the rectum

small intestine section of the alimentary canal where most digestion and absorption occurs

soft palate posterior region of the bottom portion of the nasal cavity that consists of skeletal muscle

stomach alimentary canal organ that contributes to chemical and mechanical digestion of food from the esophagus before releasing it, as chyme, to the small intestine

sublingual gland one of a pair of major salivary glands located beneath the tongue

submandibular gland one of a pair of major salivary glands located in the floor of the mouth

submucosa layer of dense connective tissue in the alimentary canal wall that binds the overlying mucosa to the underlying muscularis

submucosal plexus (plexus of Meissner) nerve supply that regulates activity of glands and smooth muscle

tenia coli one of three smooth muscle bands that make up the longitudinal muscle layer of the muscularis in all of the large intestine except the terminal end

tongue accessory digestive organ of the mouth, the bulk of which is composed of skeletal muscle

transverse colon part of the colon between the ascending colon and the descending colon

upper esophageal sphincter skeletal muscle sphincter that regulates food movement from the pharynx to the esophagus

Valsalva's maneuver voluntary contraction of the diaphragm and abdominal wall muscles and closing of the glottis, which increases intra-abdominal pressure and facilitates defecation

villus projection of the mucosa of the small intestine

PART XIII

CHAPTER 13: THE URINARY SYSTEM

77. Introduction

The urinary system has roles you may be well aware of: cleansing the blood and ridding the body of wastes probably come to mind. However, there are additional, equally important functions played by the system. Take for example, regulation of pH, a function shared with the lungs and the buffers in the blood. Additionally, the regulation of blood pressure is a role shared with the heart and blood vessels. What about regulating the concentration of solutes in the blood? Did you know that the kidney is important in determining the concentration of red blood cells? Eighty-five percent of the erythropoietin (EPO) produced to stimulate red blood cell production is produced in the kidneys. The kidneys also perform the final synthesis step of vitamin D production, converting calcidiol to calcitriol, the active form of vitamin D.

If the kidneys fail, these functions are compromised or lost altogether, with devastating effects on homeostasis. The affected individual might experience weakness, lethargy, shortness of breath, anemia, widespread edema (swelling), metabolic acidosis, rising potassium levels, heart arrhythmias, and more. Each of these functions is vital to your well-being and survival. The urinary system, controlled by the nervous system, also stores urine until a convenient time for disposal and then provides the anatomical structures to transport this waste liquid to the outside of the body. Failure of nervous control or the anatomical structures leading to a loss of control of urination results in a condition called incontinence.

This chapter will help you to understand the anatomy of the urinary system and how it enables the physiologic functions critical to homeostasis. It is best to think of the kidney as a regulator of plasma makeup rather than simply a urine producer. As you read each section, ask yourself this question: “What happens if this does not work?” This question will help you to understand how the urinary system maintains homeostasis and affects all the other systems of the body and the quality of one’s life.

78. Physical Characteristics of Urine

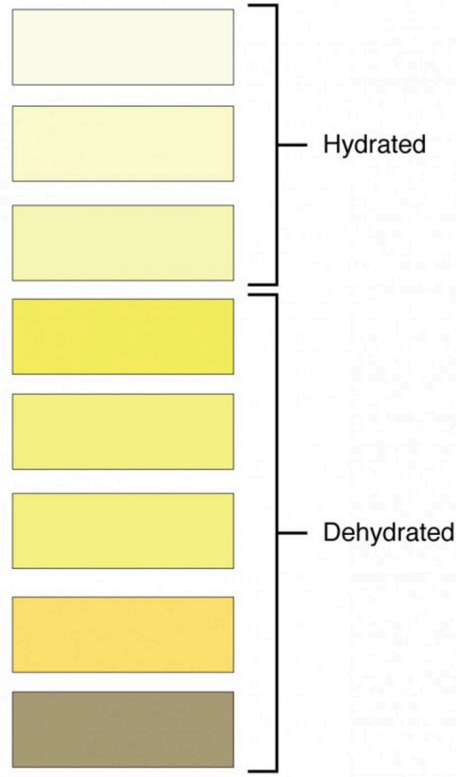
The urinary system's ability to filter the blood resides in about 2 to 3 million tufts of specialized capillaries—the glomeruli—distributed more or less equally between the two kidneys. Because the glomeruli filter the blood based mostly on particle size, large elements like blood cells, platelets, antibodies, and albumen are excluded. The glomerulus is the first part of the nephron, which then continues as a highly specialized tubular structure responsible for creating the final urine composition. All other solutes, such as ions, amino acids, vitamins, and wastes, are filtered to create a filtrate composition very similar to plasma. The glomeruli create about 200 liters (189 quarts) of this filtrate every day, yet you excrete less than two liters of waste you call urine.

Characteristics of the urine change, depending on influences such as water intake, exercise, environmental temperature, nutrient intake, and other factors. Some of the characteristics such as color and odor are rough descriptors of your state of hydration. For example, if you exercise or work outside, and sweat a great deal, your urine will turn darker and produce a slight odor, even if you drink plenty of water. Athletes are often advised to consume water until their urine is clear. This is good advice; however, it takes time for the kidneys to process body fluids and store it in the bladder. Another way of looking at this is that the quality of the urine produced is an average over the time it takes to make that urine. Producing clear urine may take only a few minutes if you are drinking a lot of water or several hours if you are working outside and not drinking much.

Normal Urine Characteristics	
Characteristic	**Normal values**
Color	Pale yellow to deep amber
Odor	Odorless
Volume	750–2000 mL/24 hour
pH	4.5–8.0
Specific gravity	1.003–1.032
Osmolarity	40–1350 mOsmol/kg
Urobilinogen	0.2–1.0 mg/100 mL
White blood cells	0–2 HPF (per high-power field of microscope)
Leukocyte esterase	None
Protein	None or trace
Bilirubin	<0.3 mg/100 mL
Ketones	None
Nitrites	None
Blood	None
Glucose	None

Urinalysis (urine analysis) often provides clues to renal disease. Normally, only traces of protein are found in urine, and when higher amounts are found, damage to the glomeruli is the likely basis. Unusually large quantities of urine may point to diseases like diabetes mellitus or hypothalamic tumors that cause diabetes insipidus. The color of urine is determined mostly by the breakdown products of red blood cell destruction. The “heme” of hemoglobin is converted by the liver into water-soluble forms that can be excreted into the bile and indirectly into the urine. This yellow pigment is urochrome. Urine color may also be affected by certain foods like beets, berries, and fava beans. A kidney stone or a cancer of the urinary system may produce sufficient bleeding to manifest as pink or even bright red urine. Diseases of the liver or obstructions of bile drainage from the liver impart a dark “tea” or “cola” hue to the urine. Dehydration produces darker, concentrated urine that may also possess the slight odor of ammonia. Most of the ammonia produced from protein breakdown is converted into urea by the liver, so ammonia is rarely detected in fresh urine. The strong ammonia odor you may detect in bathrooms or alleys is due to the breakdown of urea into ammonia by bacteria in the environment. About one in five people detect a distinctive odor in their urine after consuming asparagus; other foods such as onions, garlic, and fish can impart their own aromas! These food-caused odors are harmless.

Urine Color



Urine volume varies considerably. The normal range is one to two liters per day. The kidneys must produce a minimum urine volume of about 500 mL/day to rid the body of wastes. Output below this level may be caused by severe dehydration or renal disease and is termed oliguria. The virtual absence of urine production is termed anuria. Excessive urine production is polyuria, which may be due to diabetes mellitus or diabetes insipidus. In diabetes mellitus, blood glucose levels exceed the number of available sodium-glucose transporters in the kidney, and glucose appears in the urine. The osmotic nature of glucose attracts water, leading to its loss in the urine. In the case of diabetes insipidus, insufficient pituitary antidiuretic hormone (ADH) release or insufficient numbers of ADH receptors in the collecting ducts means that too few water channels are inserted into the cell membranes that line the collecting ducts of the kidney. Insufficient numbers of water channels (aquaporins) reduce water absorption, resulting in high volumes of very dilute urine.

Urine Volumes

Volume condition	**Volume**	**Causes**
Normal	1–2 L/day	
Polyuria	>2.5 L/day	Diabetes mellitus; diabetes insipidus; excess caffeine or alcohol; kidney disease; certain drugs, such as diuretics; sickle cell anemia; excessive water intake
Oliguria	300–500 mL/day	Dehydration; blood loss; diarrhea; cardiogenic shock; kidney disease; enlarged prostate
Anuria	<50 mL/day	Kidney failure; obstruction, such as kidney stone or tumor; enlarged prostate

The pH (hydrogen ion concentration) of the urine can vary more than 1000-fold, from a normal low of 4.5 to a maximum of 8.0. Diet can influence pH; meats lower the pH, whereas citrus fruits, vegetables, and dairy products raise the pH. Chronically high or low pH can lead to disorders, such as the development of kidney stones or osteomalacia.

Specific gravity is a measure of the quantity of solutes per unit volume of a solution and is traditionally easier to measure than osmolarity. Urine will always have a specific gravity greater than pure water (water = 1.0) due to the presence of solutes. Laboratories can now measure urine osmolarity directly, which is a more accurate indicator of urinary solutes than specific gravity. Remember that osmolarity is the number of osmoles or milliosmoles per liter of fluid (mOsmol/L). Urine osmolarity ranges from a low of 50–100 mOsmol/L to as high as 1200 mOsmol/L H_2O.

Cells are not normally found in the urine. The presence of leukocytes may indicate a urinary tract infection. Leukocyte esterase is released by leukocytes; if detected in the urine, it can be taken as indirect evidence of a urinary tract infection (UTI).

Protein does not normally leave the glomerular capillaries, so only trace amounts of protein should be found in the urine, approximately 10 mg/100 mL in a random sample. If excessive protein is detected in the urine, it usually means that the glomerulus is damaged and is allowing protein to “leak” into the filtrate.

Ketones are byproducts of fat metabolism. Finding ketones in the urine suggests that the body is using fat as an energy source in preference to glucose. In diabetes mellitus when there is not enough insulin (type I diabetes mellitus) or because of insulin resistance (type II diabetes mellitus), there is plenty of glucose, but without the action of insulin, the cells cannot take it up, so it remains in the bloodstream. Instead, the cells are forced to use fat as their energy source, and fat consumed at such a level produces excessive ketones as byproducts. These excess ketones will appear in the urine. Ketones may also appear if there is a severe deficiency of proteins or carbohydrates in the diet.

Nitrates (NO_3^-) occur normally in the urine. Gram-negative bacteria metabolize nitrate into nitrite (NO_2^-), and its presence in the urine is indirect evidence of infection.

There should be no blood found in the urine. It may sometimes appear in urine samples as a result of menstrual contamination, but this is not an abnormal condition. Now that you understand what the normal characteristics of urine are, the next section will introduce you to how you store and dispose of this waste product and how you make it.

79. Gross Anatomy of Urine Transport

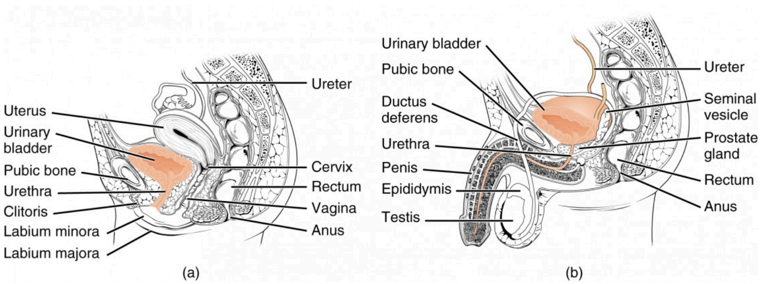
Rather than start with urine formation, this section will start with urine excretion. Urine is a fluid of variable composition that requires specialized structures to remove it from the body safely and efficiently. Blood is filtered, and the filtrate is transformed into urine at a relatively constant rate throughout the day. This processed liquid is stored until a convenient time for excretion. All structures involved in the transport and storage of the urine are large enough to be visible to the naked eye. This transport and storage system not only stores the waste, but it protects the tissues from damage due to the wide range of pH and osmolarity of the urine, prevents infection by foreign organisms, and for the male, provides reproductive functions.

Urethra

The urethra transports urine from the bladder to the outside of the body for disposal. The urethra is the only urologic organ that shows any significant anatomic difference between males and females; all other urine transport structures are identical.

Female and Male Urethras

The urethra transports urine from the bladder to the outside of the body. This image shows (a) a female urethra and (b) a male urethra.



The urethra in both males and females begins inferior and central to the two ureteral openings forming the three points of a triangular-shaped area at the base of the bladder called the trigone (Greek tri- = "triangle" and the root of the word "trigonometry"). The urethra tracks posterior and inferior to the pubic symphysis. In both males and females, the proximal urethra is lined by transitional epithelium, whereas the terminal portion is a nonkeratinized, stratified squamous epithelium. In the male, pseudostratified columnar epithelium lines the urethra between these two cell types. Voiding is regulated by an involuntary autonomic nervous system-controlled internal urinary sphincter, consisting of smooth muscle and voluntary skeletal muscle that forms the external urinary sphincter below it.

Female Urethra

The external urethral orifice is embedded in the anterior vaginal wall inferior to the clitoris, superior to the vaginal opening (introitus), and medial to the labia minora. Its short length, about 4 cm, is less of a barrier to fecal bacteria than the longer male urethra and the best explanation for the greater incidence of UTI in women. Voluntary control of the external urethral sphincter is a function of the pudendal nerve. It arises in the sacral region of the spinal cord, traveling via the S2–S4 nerves of the sacral plexus.

Male Urethra

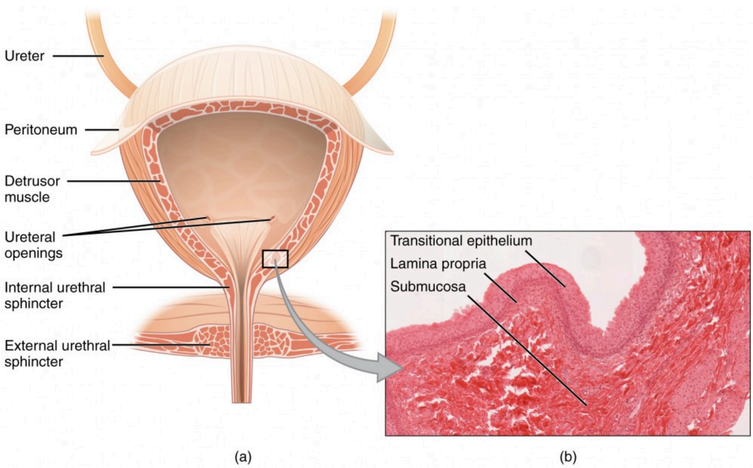
The male urethra passes through the prostate gland immediately inferior to the bladder before passing below the pubic symphysis . The length of the male urethra varies between men but averages 20 cm in length. It is divided into four regions: the preprostatic urethra, the prostatic urethra, the membranous urethra, and the spongy or penile urethra. The preprostatic urethra is very short and incorporated into the bladder wall. The prostatic urethra passes through the prostate gland. During sexual intercourse, it receives sperm via the ejaculatory ducts and secretions from the seminal vesicles. Paired Cowper's glands (bulbourethral glands) produce and secrete mucus into the urethra to buffer urethral pH during sexual stimulation. The mucus neutralizes the usually acidic environment and lubricates the urethra, decreasing the resistance to ejaculation. The membranous urethra passes through the deep muscles of the perineum, where it is invested by the overlying urethral sphincters. The spongy urethra exits at the tip (external urethral orifice) of the penis after passing through the corpus spongiosum. Mucous glands are found along much of the length of the urethra and protect the urethra from extremes of urine pH. Innervation is the same in both males and females.

Bladder

The urinary bladder collects urine from both ureters. The bladder lies anterior to the uterus in females, posterior to the pubic bone and anterior to the rectum. During late pregnancy, its capacity is reduced due to compression by the enlarging uterus, resulting in increased frequency of urination. In males, the anatomy is similar, minus the uterus, and with the addition of the prostate inferior to the bladder. The bladder is partially retroperitoneal (outside the peritoneal cavity) with its peritoneal-covered "dome" projecting into the abdomen when the bladder is distended with urine.

Bladder

(a) Anterior cross section of the bladder. (b) The detrusor muscle of the bladder (source: monkey tissue) LM × 448. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)



The bladder is a highly distensible organ comprised of irregular crisscrossing bands of smooth muscle collectively called the detrusor muscle. The interior surface is made of transitional cellular epithelium that is structurally suited for the large volume fluctuations of the bladder. When empty, it resembles columnar epithelia, but when stretched, it "transitions" (hence the name) to a squamous appearance. Volumes in adults can range from nearly zero to 500–600 mL.

The detrusor muscle contracts with significant force in the young. The bladder's strength diminishes with age, but voluntary contractions of abdominal skeletal muscles can increase intra-abdominal pressure to promote more forceful bladder emptying. Such voluntary contraction is also used in forceful defecation and childbirth.

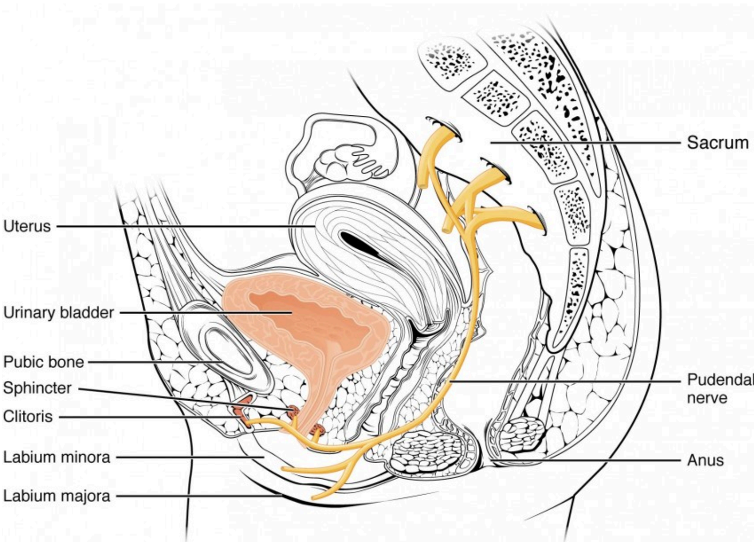
Micturition Reflex

Micturition is a less-often used, but proper term for urination or voiding. It results from an interplay of involuntary and voluntary actions by the internal and external urethral sphincters. When bladder volume reaches about 150 mL, an urge to void is sensed but is easily overridden. Voluntary control of urination relies on consciously preventing relaxation of the external urethral sphincter to maintain urinary continence. As the bladder fills, subsequent urges become harder to ignore. Ultimately, voluntary constraint fails with resulting incontinence, which will occur as bladder volume approaches 300 to 400 mL.

Normal micturition is a result of stretch receptors in the bladder wall that transmit nerve impulses to the sacral region of the spinal cord to generate a spinal reflex. The resulting parasympathetic neural outflow causes contraction of the detrusor muscle and relaxation of the involuntary internal urethral sphincter. At the same time, the spinal cord inhibits somatic motor neurons, resulting in the relaxation of the skeletal muscle of the external urethral sphincter. The micturition reflex is active in infants but with maturity, children learn to override the reflex by asserting external sphincter control, thereby delaying voiding (potty training). This reflex may be preserved even in the face of spinal cord injury that results in paraplegia or quadriplegia. However, relaxation of the external sphincter may not be possible in all cases, and therefore, periodic catheterization may be necessary for bladder emptying.

Nerves involved in the control of urination include the hypogastric, pelvic, and pudendal. Voluntary micturition requires an intact spinal cord and functional pudendal nerve arising from the sacral micturition center. Since the external urinary sphincter is voluntary skeletal muscle, actions by cholinergic neurons maintain contraction (and thereby continence) during filling of the bladder. At the same time, sympathetic nervous activity via the hypogastric nerves suppresses contraction of the detrusor muscle. With further bladder stretch, afferent signals traveling over sacral pelvic nerves activate parasympathetic neurons. This activates efferent neurons to release acetylcholine at the neuromuscular junctions, producing detrusor contraction and bladder emptying.

Nerves Innervating the Urinary System



Ureters

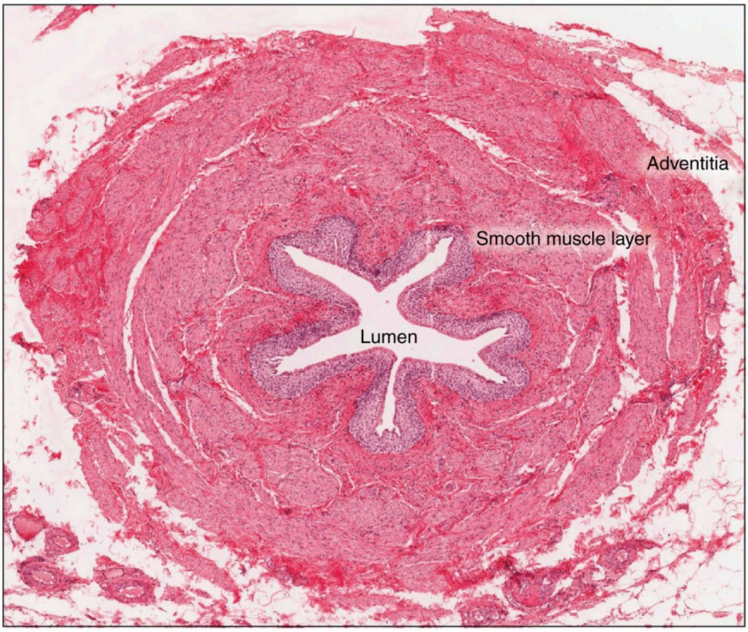
The kidneys and ureters are completely retroperitoneal, and the bladder has a peritoneal covering only over the dome. As urine is formed, it drains into the calyces of the kidney, which merge to form the funnel-shaped renal pelvis in the hilum of each kidney. The hilum narrows to become the ureter of each kidney. As urine passes through the ureter, it does not passively drain into the bladder but rather is propelled by waves of peristalsis. As the ureters enter the pelvis, they sweep laterally, hugging the pelvic walls. As they approach the bladder, they turn medially and pierce the bladder wall obliquely. This is important because it creates an one-way valve (a physiological sphincter rather than an anatomical sphincter) that allows urine into the bladder but prevents reflux of urine from the bladder back into the ureter. Children born lacking this oblique course of the ureter through the bladder wall are susceptible to "vesicoureteral reflux," which dramatically increases their risk of serious UTI. Pregnancy also increases the likelihood of reflux and UTI.

The ureters are approximately 30 cm long. The inner mucosa is lined with transitional epithelium and scattered goblet cells that secrete protective mucus. The muscular layer of the ureter consists of longitudinal and circular smooth muscles that create the peristaltic contractions to move the urine into the bladder without the aid of gravity. Finally, a loose adventitial layer composed of collagen and fat anchors the ureters between the parietal peritoneum and the posterior abdominal wall.

Ureter

Peristaltic contractions help to move urine through the lumen with contributions from fluid pressure and gravity. LM × 128.

(Micrograph provided by the Regents of the University of Michigan Medical School © 2012)


Adventitia
Smooth muscle layer
Lumen

80. Gross Anatomy of the Kidney

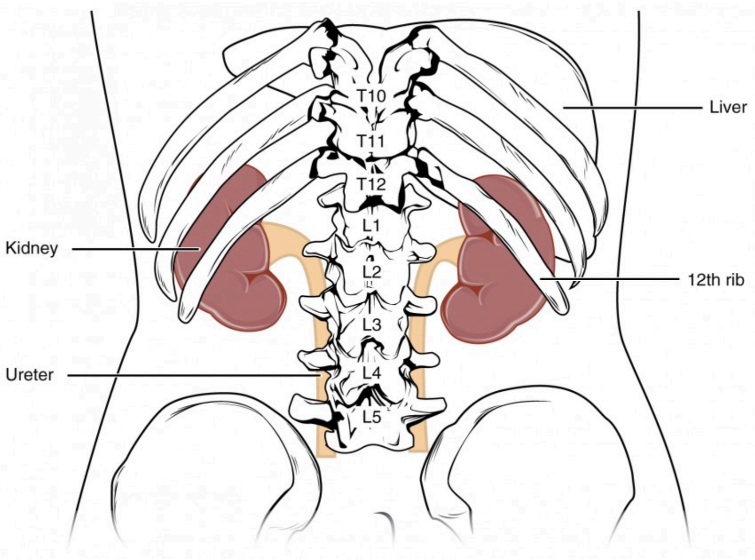
The kidneys lie on either side of the spine in the retroperitoneal space between the parietal peritoneum and the posterior abdominal wall, well protected by muscle, fat, and ribs. They are roughly the size of your fist, and the male kidney is typically a bit larger than the female kidney. The kidneys are well vascularized, receiving about 25 percent of the cardiac output at rest.

External Anatomy

The left kidney is located at about the T12 to L3 vertebrae, whereas the right is lower due to slight displacement by the liver. Upper portions of the kidneys are somewhat protected by the eleventh and twelfth ribs. Each kidney weighs about 125–175 g in males and 115–155 g in females. They are about 11–14 cm in length, 6 cm wide, and 4 cm thick, and are directly covered by a fibrous capsule composed of dense, irregular connective tissue that helps to hold their shape and protect them. This capsule is covered by a shock-absorbing layer of adipose tissue called the renal fat pad, which in turn is encompassed by a tough renal fascia. The fascia and, to a lesser extent, the overlying peritoneum serve to firmly anchor the kidneys to the posterior abdominal wall in a retroperitoneal position.

Kidneys

The kidneys are slightly protected by the ribs and are surrounded by fat for protection (not shown).



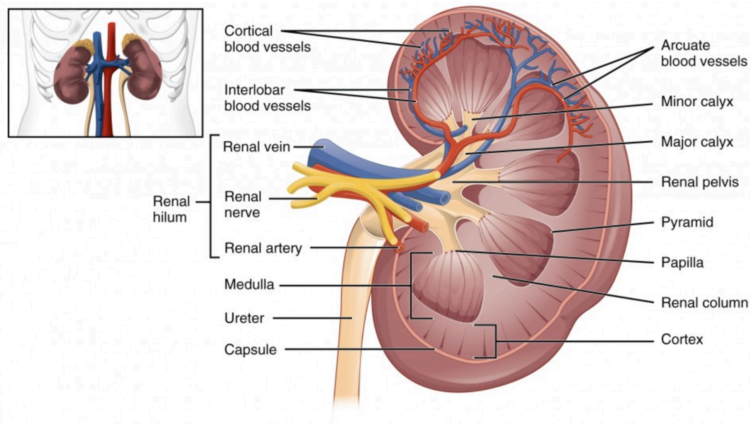
On the superior aspect of each kidney is the adrenal gland. The adrenal cortex directly influences renal function through the production of the hormone aldosterone to stimulate sodium reabsorption.

Internal Anatomy

A frontal section through the kidney reveals an outer region called the renal cortex and an inner region called the medulla. The renal columns are connective tissue extensions that radiate downward from the cortex through the medulla to separate the most characteristic features of the medulla, the renal pyramids and renal papillae. The papillae are bundles of collecting ducts that transport urine made by nephrons to the calyces of the kidney for excretion.

The renal columns also serve to divide the kidney into 6–8 lobes and provide a supportive framework for vessels that enter and exit the cortex. The pyramids and renal columns taken together constitute the kidney lobes.

Left Kidney



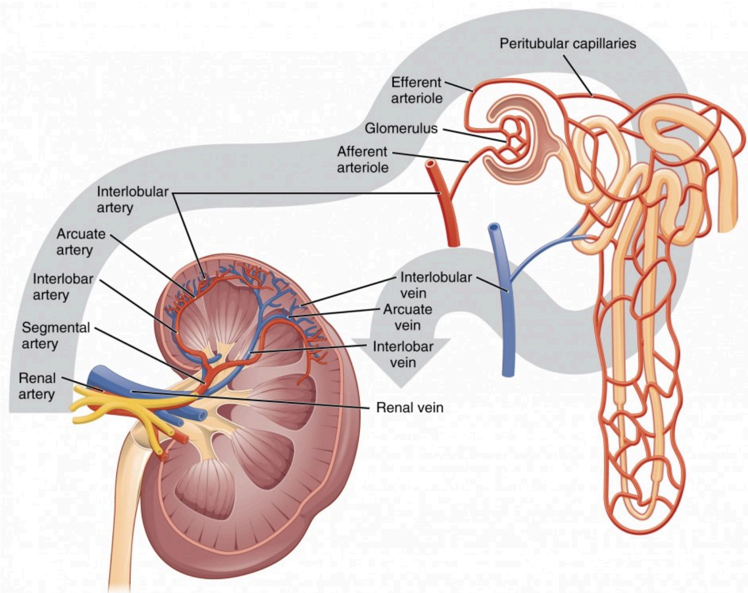
Renal Hilum

The renal hilum is the entry and exit site for structures servicing the kidneys: vessels, nerves, lymphatics, and ureters. The medial-facing hila are tucked into the sweeping convex outline of the cortex. Emerging from the hilum is the renal pelvis, which is formed from the major and minor calyxes in the kidney. The smooth muscle in the renal pelvis funnels urine via peristalsis into the ureter. The renal arteries form directly from the descending aorta, whereas the renal veins return cleansed blood directly to the inferior vena cava. The artery, vein, and renal pelvis are arranged in an anterior-to-posterior order.

Nephrons and Vessels

The renal artery first divides into segmental arteries, followed by further branching to form interlobar arteries that pass through the renal columns to reach the cortex. The interlobar arteries, in turn, branch into arcuate arteries, cortical radiate arteries, and then into afferent arterioles. The afferent arterioles service about 1.3 million nephrons in each kidney.

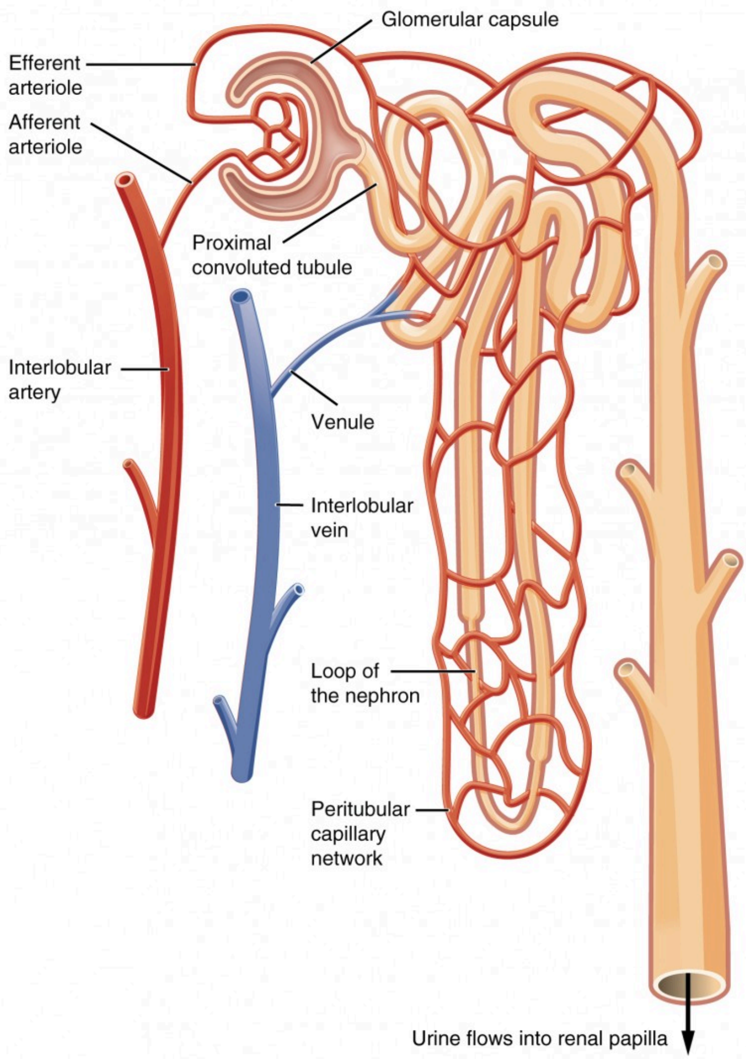
Blood Flow in the Kidney



Nephrons are the "functional units" of the kidney; they cleanse the blood and balance the constituents of the circulation. The afferent arterioles form a tuft of high-pressure capillaries about 200 µm in diameter, the glomerulus. The rest of the nephron consists of a continuous sophisticated tubule whose proximal end surrounds the glomerulus in an intimate embrace—this is Bowman's capsule. The glomerulus and Bowman's capsule together form the renal corpuscle. As mentioned earlier, these glomerular capillaries filter the blood based on particle size. After passing through the renal corpuscle, the capillaries form a second arteriole, the efferent arteriole. These will next form a capillary network around the more distal portions of the nephron tubule, the peritubular capillaries and vasa recta, before returning to the venous system. As the glomerular filtrate progresses through the nephron, these capillary networks recover most of the solutes and water, and return them to the circulation. Since a capillary bed (the glomerulus) drains into a vessel that in turn forms a second capillary bed, the definition of a portal system is met. This is the only portal system in which an arteriole is found between the first and second capillary beds. (Portal systems also link the hypothalamus to the anterior pituitary, and the blood vessels of the digestive viscera to the liver.)

Blood Flow in the Nephron

The two capillary beds are clearly shown in this figure. The efferent arteriole is the connecting vessel between the glomerulus and the peritubular capillaries and vasa recta.



Cortex

In a dissected kidney, it is easy to identify the cortex; it appears lighter in color compared to the rest of the kidney. All of the renal corpuscles as well as both the proximal convoluted tubules (PCTs) and distal convoluted tubules are found here. Some nephrons have a short loop of Henle that does not dip beyond the cortex. These nephrons are called cortical nephrons. About 15 percent of nephrons have long loops of Henle that extend deep into the medulla and are called juxtamedullary nephrons.

81. Microscopic Anatomy of the Kidney

Learning Objectives

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

- Distinguish the histological differences between the renal cortex and medulla
- Describe the structure of the filtration membrane
- Identify the major structures and subdivisions of the renal corpuscles, renal tubules, and renal capillaries
- Discuss the function of the peritubular capillaries and vasa recta
- Identify the location of the juxtaglomerular apparatus and describe the cells that line it
- Describe the histology of the proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting ducts

The renal structures that conduct the essential work of the kidney cannot be seen by the naked eye. Only a light or electron microscope can reveal these structures. Even then, serial sections and computer reconstruction are necessary to give us a comprehensive view of the functional anatomy of the nephron and its associated blood vessels.

Nephrons: The Functional Unit

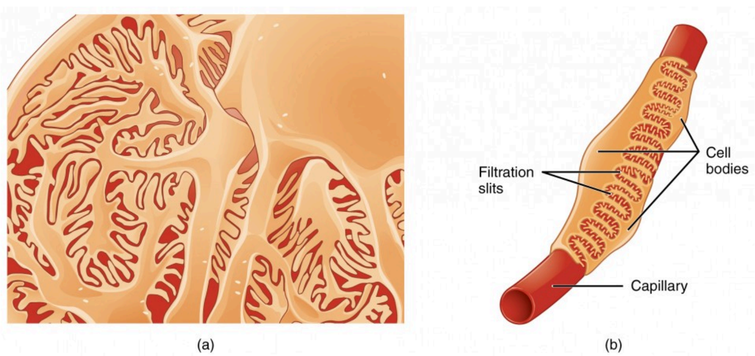
Nephrons take a simple filtrate of the blood and modify it into urine. Many changes take place in the different parts of the nephron before urine is created for disposal. The term forming urine will be used hereafter to describe the filtrate as it is modified into true urine. The principle task of the nephron population is to balance the plasma to homeostatic set points and excrete potential toxins in the urine. They do this by accomplishing three principle functions—filtration, reabsorption, and secretion. They also have additional secondary functions that exert control in three areas: blood pressure (via production of renin), red blood cell production (via the hormone EPO), and calcium absorption (via conversion of calcidiol into calcitriol, the active form of vitamin D).

Renal Corpuscle

As discussed earlier, the renal corpuscle consists of a tuft of capillaries called the glomerulus that is largely surrounded by Bowman's (glomerular) capsule. The glomerulus is a high-pressure capillary bed between afferent and efferent arterioles. Bowman's capsule surrounds the glomerulus to form a lumen, and captures and directs this filtrate to the PCT. The outermost part of Bowman's capsule, the parietal layer, is a simple squamous epithelium. It transitions onto the glomerular capillaries in an intimate embrace to form the visceral layer of the capsule. Here, the cells are not squamous, but uniquely shaped cells (podocytes) extending finger-like arms (pedicels) to cover the glomerular capillaries. These projections interdigitate to form filtration slits, leaving small gaps between the digits to form a sieve. As blood passes through the glomerulus, 10 to 20 percent of the plasma filters between these sieve-like fingers to be captured by Bowman's capsule and funneled to the PCT. Where the fenestrae (windows) in the glomerular capillaries match the spaces between the podocyte "fingers," the only thing separating the capillary lumen and the lumen of Bowman's capsule is their shared basement membrane. These three features comprise what is known as the filtration membrane. This membrane permits very rapid movement of filtrate from capillary to capsule though pores that are only 70 nm in diameter.

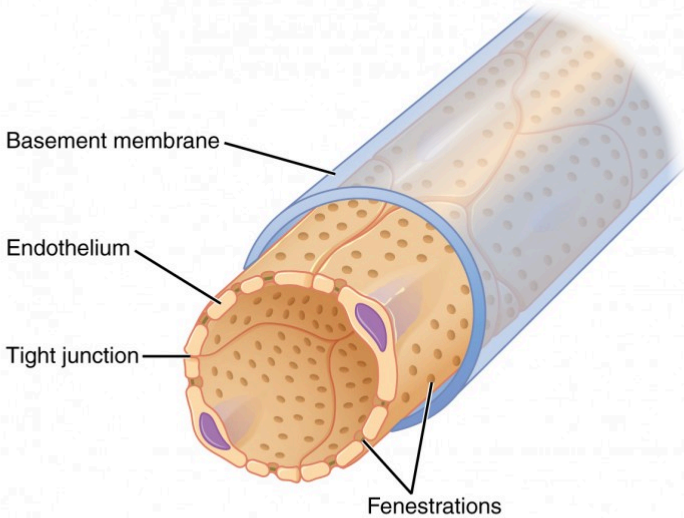
Podocytes

Podocytes interdigitate with structures called pedicels and filter substances in a way similar to fenestrations. In (a), the large cell body can be seen at the top right corner, with branches extending from the cell body. The smallest finger-like extensions are the pedicels. Pedicels on one podocyte always interdigitate with the pedicels of another podocyte. (b) This capillary has three podocytes wrapped around it.



Fenestrated Capillary

Fenestrations allow many substances to diffuse from the blood based primarily on size.

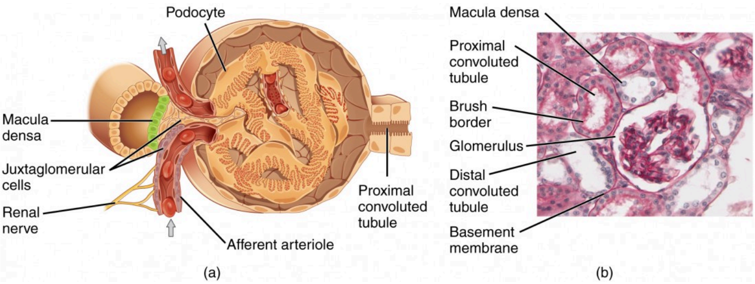


The fenestrations prevent filtration of blood cells or large proteins, but allow most other constituents through. These substances cross readily if they are less than 4 nm in size and most pass freely up to 8 nm in size. An additional factor affecting the ability of substances to cross this barrier is their electric charge. The proteins associated with these pores are negatively charged, so they tend to repel negatively charged substances and allow positively charged substances to pass more readily. The basement membrane prevents filtration of medium-to-large proteins such as globulins. There are also mesangial cells in the filtration membrane that can contract to help regulate the rate of filtration of the glomerulus. Overall, filtration is regulated by fenestrations in capillary endothelial cells, podocytes with filtration slits, membrane charge, and the basement membrane between capillary cells. The result is the creation of a filtrate that does not contain cells or large proteins, and has a slight predominance of positively charged substances.

Lying just outside Bowman's capsule and the glomerulus is the juxtaglomerular apparatus (JGA). At the juncture where the afferent and efferent arterioles enter and leave Bowman's capsule, the initial part of the distal convoluted tubule (DCT) comes into direct contact with the arterioles. The wall of the DCT at that point forms a part of the JGA known as the macula densa. This cluster of cuboidal epithelial cells monitors the fluid composition of fluid flowing through the DCT. In response to the concentration of Na^+ in the fluid flowing past them, these cells release paracrine signals. They also have a single, nonmotile cilium that responds to the rate of fluid movement in the tubule. The paracrine signals released in response to changes in flow rate and Na^+ concentration are adenosine triphosphate (ATP) and adenosine.

Juxtaglomerular Apparatus and Glomerulus

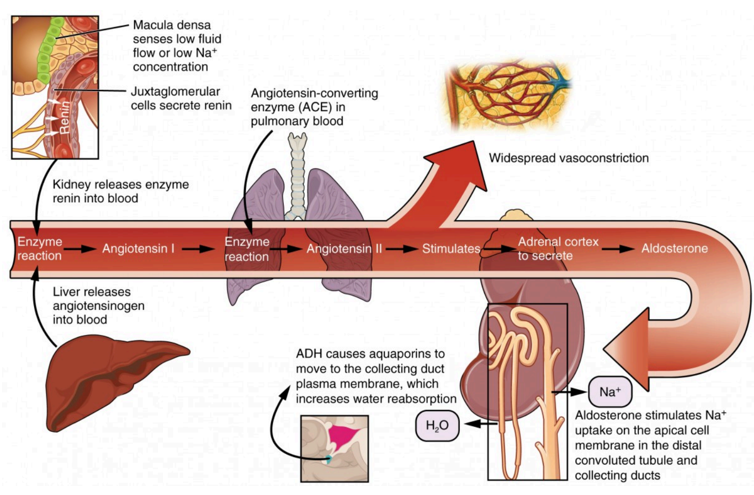
(a) The JGA allows specialized cells to monitor the composition of the fluid in the DCT and adjust the glomerular filtration rate. (b) This micrograph shows the glomerulus and surrounding structures. LM × 1540. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



A second cell type in this apparatus is the juxtaglomerular cell. This is a modified, smooth muscle cell lining the afferent arteriole that can contract or relax in response to ATP or adenosine released by the macula densa. Such contraction and relaxation regulate blood flow to the glomerulus. If the osmolarity of the filtrate is too high (hyperosmotic), the juxtaglomerular cells will contract, decreasing the glomerular filtration rate (GFR) so less plasma is filtered, leading to less urine formation and greater retention of fluid. This will ultimately decrease blood osmolarity toward the physiologic norm. If the osmolarity of the filtrate is too low, the juxtaglomerular cells will relax, increasing the GFR and enhancing the loss of water to the urine, causing blood osmolarity to rise. In other words, when osmolarity goes up, filtration and urine formation decrease and water is retained. When osmolarity goes down, filtration and urine formation increase and water is lost by way of the urine. The net result of these opposing actions is to keep the rate of filtration relatively constant. A second function of the macula densa cells is to regulate renin release from the juxtaglomerular cells of the afferent arteriole. Active renin is a protein comprised of 304 amino acids that cleaves several amino acids from angiotensinogen to produce angiotensin I. Angiotensin I is not biologically active until converted to angiotensin II by angiotensin-converting enzyme (ACE) from the lungs. Angiotensin II is a systemic vasoconstrictor that helps to regulate blood pressure by increasing it. Angiotensin II also stimulates the release of the steroid hormone aldosterone from the adrenal cortex. Aldosterone stimulates Na^+ reabsorption by the kidney, which also results in water retention and increased blood pressure.

Conversion of Angiotensin I to Angiotensin II

The enzyme renin converts the pro-enzyme angiotensin I; the lung-derived enzyme ACE converts angiotensin I into active angiotensin II.



Proximal Convoluted Tubule (PCT)

Filtered fluid collected by Bowman's capsule enters into the PCT. It is called convoluted due to its tortuous path. Simple cuboidal cells form this tubule with prominent microvilli on the luminal surface, forming a brush border. These microvilli create a large surface area to maximize the absorption and secretion of solutes (Na^+, Cl^-, glucose, etc.), the most essential function of this portion of the nephron. These cells actively transport ions across their membranes, so they possess a high concentration of mitochondria in order to produce sufficient ATP.

Loop of Henle

The descending and ascending portions of the loop of Henle (sometimes referred to as the nephron loop) are, of course, just continuations of the same tubule. They run adjacent and parallel to each other after having made a hairpin turn at the deepest point of their descent. The descending loop of Henle consists of an initial short, thick portion and long, thin portion, whereas the ascending loop consists of an initial short, thin portion followed by a long, thick portion. The descending thick portion consists of simple cuboidal epithelium similar to that of the PCT. The descending and ascending thin portions consists of simple squamous epithelium. As you will see later, these are important differences, since different portions of the loop have different permeabilities for solutes and water. The ascending thick portion consists of simple cuboidal epithelium similar to the DCT.

Distal Convoluted Tubule (DCT)

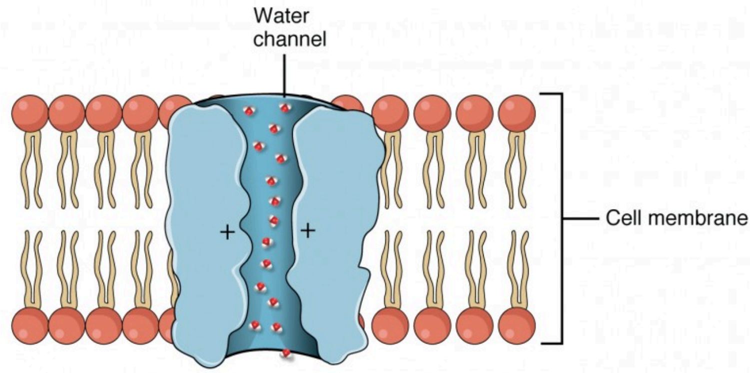
The DCT, like the PCT, is very tortuous and formed by simple cuboidal epithelium, but it is shorter than the PCT. These cells are not as active as those in the PCT; thus, there are fewer microvilli on the apical surface. However, these cells must also pump ions against their concentration gradient, so you will find of large numbers of mitochondria, although fewer than in the PCT.

Collecting Ducts

The collecting ducts are continuous with the nephron but not technically part of it. In fact, each duct collects filtrate from several nephrons for final modification. Collecting ducts merge as they descend deeper in the medulla to form about 30 terminal ducts, which empty at a papilla. They are lined with simple squamous epithelium with receptors for ADH. When stimulated by ADH, these cells will insert aquaporin channel proteins into their membranes, which as their name suggests, allow water to pass from the duct lumen through the cells and into the interstitial spaces to be recovered by the vasa recta. This process allows for the recovery of large amounts of water from the filtrate back into the blood. In the absence of ADH, these channels are not inserted, resulting in the excretion of water in the form of dilute urine. Most, if not all, cells of the body contain aquaporin molecules, whose channels are so small that only water can pass. At least 10 types of aquaporins are known in humans, and six of those are found in the kidney. The function of all aquaporins is to allow the movement of water across the lipid-rich, hydrophobic cell membrane.

Aquaporin Water Channel

Positive charges inside the channel prevent the leakage of electrolytes across the cell membrane, while allowing water to move due to osmosis.



Chapter Review

The functional unit of the kidney, the nephron, consists of the renal corpuscle, PCT, loop of Henle, and DCT. Cortical nephrons have short loops of Henle, whereas juxtamedullary nephrons have long loops of Henle extending into the medulla. About 15 percent of nephrons are juxtamedullary. The glomerulus is a capillary bed that filters blood principally based on particle size. The filtrate is captured by Bowman's capsule and directed to the PCT. A filtration membrane is formed by the fused basement membranes of the podocytes and the capillary endothelial cells that they embrace. Contractile mesangial cells further perform a role in regulating the rate at which the blood is filtered. Specialized cells in the JGA produce paracrine signals to regulate blood flow and filtration rates of the glomerulus. Other JGA cells produce the enzyme renin, which plays a central role in blood pressure regulation. The filtrate enters the PCT where absorption and secretion of several substances occur. The descending and ascending limbs of the loop of Henle consist of thick and thin segments. Absorption and secretion continue in the DCT but to a lesser extent than in the PCT. Each collecting duct collects forming urine from several nephrons and responds to the posterior pituitary hormone ADH by inserting aquaporin water channels into the cell membrane to fine tune water recovery.

Critical Thinking Questions

1. Which structures make up the renal corpuscle?
2. What are the major structures comprising the filtration membrane?

Answers: Critical Thinking

1. The structures that make up the renal corpuscle are the glomerulus, Bowman's capsule, and PCT.
2. The major structures comprising the filtration

membrane are fenestrations and podocyte fenestra, fused basement membrane, and filtration slits.

Glossary

angiotensin-converting enzyme (ACE) enzyme produced by the lungs that catalyzes the reaction of inactive angiotensin I into active angiotensin II

angiotensin I protein produced by the enzymatic action of renin on angiotensinogen; inactive precursor of angiotensin II

angiotensin II protein produced by the enzymatic action of ACE on inactive angiotensin I; actively causes vasoconstriction and stimulates aldosterone release by the adrenal cortex

angiotensinogen inactive protein in the circulation produced by the liver; precursor of angiotensin I; must be modified by the enzymes renin and ACE to be activated

aquaporin protein-forming water channels through the lipid bilayer of the cell; allows water to cross; activation in the collecting ducts is under the control of ADH

brush border formed by microvilli on the surface of certain cuboidal cells; in the kidney it is found in the PCT; increases surface area for absorption in the kidney

fenestrations small windows through a cell, allowing rapid filtration based on size; formed in such a way as to allow substances to cross through a cell without mixing with cell contents

filtration slits formed by pedicels of podocytes; substances filter between the pedicels based on size

forming urine filtrate undergoing modifications through secretion and reabsorption before true urine is produced

juxtaglomerular apparatus (JGA) located at the juncture of the DCT and the afferent and efferent arterioles of the glomerulus; plays a role in the regulation of renal blood flow and GFR

juxtaglomerular cell modified smooth muscle cells of the afferent arteriole; secretes renin in response to a drop in blood pressure

macula densa cells found in the part of the DCT forming the JGA; sense Na^+ concentration in the forming urine

mesangial contractile cells found in the glomerulus; can contract or relax to regulate filtration rate

pedicels finger-like projections of podocytes surrounding glomerular capillaries; interdigitate to form a filtration membrane

podocytes cells forming finger-like processes; form the visceral layer of Bowman's capsule; pedicels of the podocytes interdigitate to form a filtration membrane

renin enzyme produced by juxtaglomerular cells in response to decreased blood pressure or sympathetic nervous activity; catalyzes the conversion of angiotensinogen into angiotensin I

82. Age Related Changes to the Urinary System

Kidneys

After the age of 40 there is a decrease in the number of cells within the kidney. As this is happening there is a thickening of the connective tissue capsule surrounding the organ and a decrease in the thickness of the cortical region.

The loss of kidney cells is explained mostly by a loss of glomeruli. As glomeruli are responsible for filtration, the loss of cells is associated with a loss of kidney functioning.

Bladder and Urethra

The walls of the bladder and urethra are made of smooth muscle. With age this muscle tissue weakens and is less elastic. This means that the bladder is less able to expand and contract in older people. As a result, the bladders of elderly people have a capacity of approximately one-half of young adults and the bladders are unable to fully evacuate during urination.

83. Age Related Dysfunctions of the Urinary System

Urinary Incontinence

Urinary incontinence is the involuntary passing of urine through the urethra. Between 30 and 50% of elderly people suffer from urinary incontinence. Incontinence is caused by weakening of the urethral sphincters and the muscles of the pelvic floor.

Nocturia

Nocturia is defined as excessive urination at night. While having to urinate multiple times in the night is not serious in itself it can contribute to insomnia. Between 60 and 80% of people over the age of 65 experience nocturia.

Benign Hyperplasia

Benign hyperplasia is defined as the enlargement of the prostate gland. The prostate gland is an organ of the male reproductive system. When it enlarges the prostate gland puts pressure on the urethra. Over time the increased pressure on the urethra makes it difficult for the bladder to be fully evacuated. In sever cases urine can back up into the ureters and interfere with kidney functioning.

Carcinoma of the Prostate

Carcinoma of the prostate is the most common cancer in older men. Over 50% of men over 70 years of age show signs of prostate cancer. According to the Centers for Disease Control and Prevention (CDC), prostate cancer is the second most common cancer in men. However, some forms of prostate cancer grow very slowly and thus may not ever require treatment. Aggressive forms of prostate cancer, in contrast, involve metastasis to vulnerable organs like the lungs and brain. There is no link between BPH and prostate cancer, but the symptoms are similar. Prostate cancer is detected by a medical history, a blood test, and a rectal exam that allows physicians to palpate the prostate and check for unusual masses. If a mass is detected, the cancer diagnosis is confirmed by biopsy of the cells.

Pyelonephritis

Pyelonephritis is an inflammation of the kidney caused by a bacterial infection or viral infection. The initial infection may be caused by a urinary tract infection, or travel to the kidney in the blood or lymph. While the infections are generally easily treatable with antibiotics repeated infections can cause permanent scarring of the kidney tissue. This affects the kidney function and can cause kidney failure.

Renal Calculi

Renal calculi, also know as kidney stones, become progressively more common with age. The presence of stones in the kidney do not typically cause problems severe enough to be detected.

However, the passage of renal calculi from the kidney through the ureters, bladder, and urethra can be extremely painful. Additionally the stones may become lodged in the ureter or cause ulcerations in the lining of the urinary tract.

84. Glossary: The Urinary System

Glossary

anatomical sphincter smooth or skeletal muscle surrounding the lumen of a vessel or hollow organ that can restrict flow when contracted

anuria absence of urine produced; production of 50 mL or less per day

Bowman's capsule cup-shaped sack lined by a simple squamous epithelium (parietal surface) and specialized cells called podocytes (visceral surface) that participate in the filtration process; receives the filtrate which then passes on to the PCTs

calyces cup-like structures receiving urine from the collecting ducts where it passes on to the renal pelvis and ureter

cortical nephrons nephrons with loops of Henle that do not extend into the renal medulla

detrusor muscle smooth muscle in the bladder wall; fibers run in all directions to reduce the size of the organ when emptying it of urine

distal convoluted tubules portions of the nephron distal to the loop of Henle that receive hyposmotic filtrate from the loop of Henle and empty into collecting ducts

efferent arteriole arteriole carrying blood from the glomerulus to the capillary beds around the convoluted tubules and loop of Henle; portion of the portal system

external urinary sphincter skeletal muscle; must be relaxed consciously to void urine

glomerulus tuft of capillaries surrounded by Bowman's capsule; filters the blood based on size

internal urinary sphincter smooth muscle at the juncture of the bladder and urethra; relaxes as the bladder fills to allow urine into the urethra

incontinence loss of ability to control micturition

juxtamedullary nephrons nephrons adjacent to the border of the cortex and medulla with loops of Henle that extend into the renal medulla

leukocyte esterase enzyme produced by leukocytes that can be detected in the urine and that serves as an indirect indicator of urinary tract infection

loop of Henle descending and ascending portions between the proximal and distal convoluted tubules; those of cortical nephrons do not extend into the medulla, whereas those of juxtamedullary nephrons do extend into the medulla

medulla inner region of kidney containing the renal pyramids

micturition also called urination or voiding

nephrons functional units of the kidney that carry out all filtration and modification to produce urine; consist of renal corpuscles, proximal and distal convoluted tubules, and descending and ascending loops of Henle; drain into collecting ducts

oliguria below normal urine production of 400–500 mL/day

peritubular capillaries second capillary bed of the renal portal system; surround the proximal and distal convoluted tubules; associated with the vasa recta

physiological sphincter sphincter consisting of circular smooth muscle indistinguishable from adjacent muscle but possessing differential innervations, permitting its function as a sphincter; structurally weak

polyuria urine production in excess of 2.5 L/day; may be caused by diabetes insipidus, diabetes mellitus, or excessive use of diuretics

proximal convoluted tubules (PCTs) tortuous tubules receiving filtrate from Bowman's capsule; most active part of the nephron in reabsorption and secretion

renal columns extensions of the renal cortex into the renal medulla; separates the renal pyramids; contains blood vessels and connective tissues

renal corpuscle consists of the glomerulus and Bowman's capsule

renal cortex outer part of kidney containing all of the nephrons; some nephrons have loops of Henle extending into the medulla

renal fat pad adipose tissue between the renal fascia and the renal capsule that provides protective cushioning to the kidney

renal hilum recessed medial area of the kidney through which the renal artery, renal vein, ureters, lymphatics, and nerves pass

renal papillae medullary area of the renal pyramids where collecting ducts empty urine into the minor calyces

renal pyramids six to eight cone-shaped tissues in the medulla of the kidney containing collecting ducts and the loops of Henle of juxtamedullary nephrons

retroperitoneal outside the peritoneal cavity; in the case of the kidney and ureters, between the parietal peritoneum and the abdominal wall

sacral micturition center group of neurons in the sacral region of the spinal cord that controls urination; acts reflexively unless its action is modified by higher brain centers to allow voluntary urination

specific gravity weight of a liquid compared to pure water, which has a specific gravity of 1.0; any solute added to water will increase its specific gravity

trigone area at the base of the bladder marked by the two ureters in the posterior–lateral aspect and the urethral orifice in the anterior aspect oriented like points on a triangle

urethra transports urine from the bladder to the outside environment

urinalysis analysis of urine to diagnose disease

urochrome heme-derived pigment that imparts the typical yellow color of urine

vasa recta branches of the efferent arterioles that parallel the course of the loops of Henle and are continuous with the peritubular capillaries; with the glomerulus, form a portal system

PART XIV

CHAPTER 14: THE REPRODUCTIVE SYSTEM

85. Development of the Male and Female Reproductive Systems

The development of the reproductive systems begins soon after fertilization of the egg, with primordial gonads beginning to develop approximately one month after conception. Reproductive development continues in utero, but there is little change in the reproductive system between infancy and puberty.

Development of the Sexual Organs in the Embryo and Fetus

Females are considered the "fundamental" sex—that is, without much chemical prompting, all fertilized eggs would develop into females. To become a male, an individual must be exposed to the cascade of factors initiated by a single gene on the male Y chromosome. This is called the SRY (Sex-determining Region of the Y chromosome). Because females do not have a Y chromosome, they do not have the SRY gene. Without a functional SRY gene, an individual will be female.

In both male and female embryos, the same group of cells has the potential to develop into either the male or female gonads; this tissue is considered bipotential. The SRY gene actively recruits other genes that begin to develop the testes, and suppresses genes that are important in female development. As part of this SRY-prompted cascade, germ cells in the bipotential gonads differentiate into spermatogonia. Without SRY, different genes are expressed, oogonia form, and primordial follicles develop in the primitive ovary.

Soon after the formation of the testis, the Leydig cells begin to secrete testosterone. Testosterone can influence tissues that are bipotential to become male reproductive structures. For example, with exposure to testosterone, cells that could become either the glans penis or the glans clitoris form the glans penis. Without testosterone, these same cells differentiate into the clitoris.

Not all tissues in the reproductive tract are bipotential. The internal reproductive structures (for example the uterus, uterine tubes, and part of the vagina in females; and the epididymis, ductus deferens, and seminal vesicles in males) form from one of two rudimentary duct systems in the embryo. For proper reproductive function in the adult, one set of these ducts must develop properly, and the other must degrade. In males, secretions from sustentacular cells trigger a degradation of the female duct, called the Müllerian duct. At the same time, testosterone secretion stimulates growth of the male tract, the Wolffian duct. Without such sustentacular cell secretion, the Müllerian duct will develop; without testosterone, the Wolffian duct will degrade. Thus, the developing offspring will be female. For more information and a figure of differentiation of the gonads, seek additional content on fetal development.

Further Sexual Development Occurs at Puberty

Puberty is the stage of development at which individuals become sexually mature. Though the outcomes of puberty for boys and girls are very different, the hormonal control of the process is very similar. In addition, though the timing of these events varies between individuals, the sequence of changes that occur is predictable for male and female adolescents. As shown in the image below, a concerted release of hormones from the hypothalamus (GnRH), the anterior pituitary (LH and FSH), and the gonads (either testosterone or estrogen) is responsible for the maturation of the reproductive systems and the development of secondary sex characteristics, which are physical changes that serve auxiliary roles in reproduction.

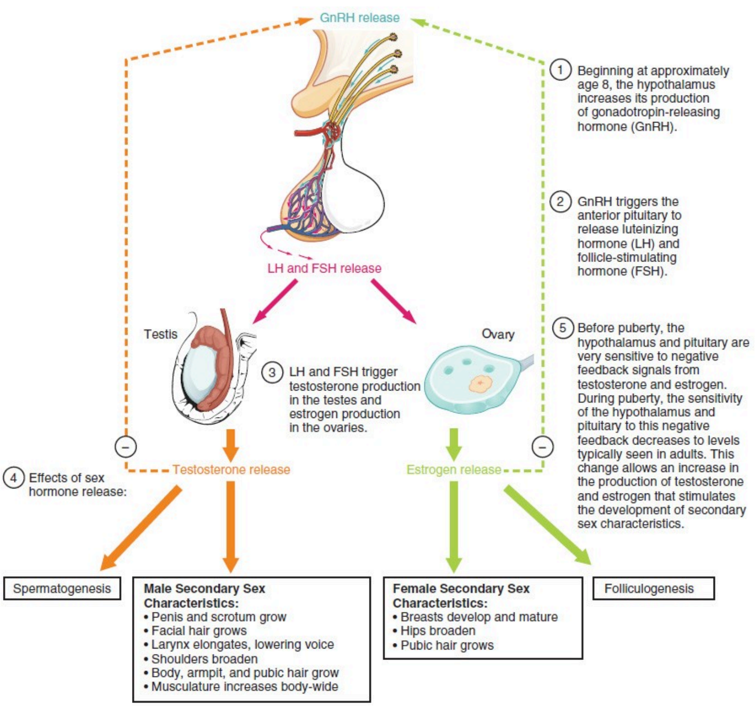
The first changes begin around the age of eight or nine when the production of LH becomes detectable. The release of LH occurs primarily at night during sleep and precedes the physical changes of puberty by several years. In pre-pubertal children, the sensitivity of the negative feedback system in the hypothalamus and pituitary is very high. This means that very low concentrations of androgens or estrogens will negatively feed back onto the hypothalamus and pituitary, keeping the production of GnRH, LH, and FSH low.

As an individual approaches puberty, two changes in sensitivity occur. The first is a decrease of sensitivity in the hypothalamus and pituitary to negative feedback, meaning that it takes increasingly larger concentrations of sex steroid hormones to stop the production of LH and FSH. The second change in sensitivity is an increase in sensitivity of the gonads to the FSH and LH signals, meaning the gonads of adults are more responsive to gonadotropins than are the gonads of children. As a result of these two changes, the levels of LH and FSH slowly increase and lead to the enlargement and maturation of the gonads, which in turn leads to secretion of higher levels of sex hormones and the initiation of spermatogenesis and folliculogenesis.

In addition to age, multiple factors can affect the age of onset of puberty, including genetics, environment, and psychological stress. One of the more important influences may be nutrition; historical data demonstrate the effect of better and more consistent nutrition on the age of menarche in girls in the United States, which decreased from an average age of approximately 17 years of age in 1860 to the current age of approximately 12.75 years in 1960, as it remains today. Some studies indicate a link between puberty onset and the amount of stored fat in an individual. This effect is more pronounced in girls, but has been documented in both sexes. Body fat, corresponding with secretion of the hormone leptin by adipose cells, appears to have a strong role in determining menarche. This may reflect to some extent the high metabolic costs of gestation and lactation. In girls who are lean and highly active, such as gymnasts, there is often a delay in the onset of puberty.

Hormones of Puberty

During puberty, the release of LH and FSH from the anterior pituitary stimulates the gonads to produce sex hormones in both male and female adolescents.



Signs of Puberty

Different sex steroid hormone concentrations between the sexes also contribute to the development and function of secondary sexual characteristics. Examples of secondary sexual characteristics are listed in the table below.

Development of the Secondary Sexual Characteristics

Male	Female
Increased larynx size and deepening of the voice	Deposition of fat, predominantly in breasts and hips
Increased muscular development	Breast development
Growth of facial, axillary, and pubic hair, and increased growth of body hair	Broadening of the pelvis and growth of axillary and pubic hair

As a girl reaches puberty, typically the first change that is visible is the development of the breast tissue. This is followed by the growth of axillary and pubic hair. A growth spurt normally starts at approximately age 9 to 11, and may last two years or more. During this time, a girl's height can increase 3 inches a year. The next step in puberty is menarche, the start of menstruation.

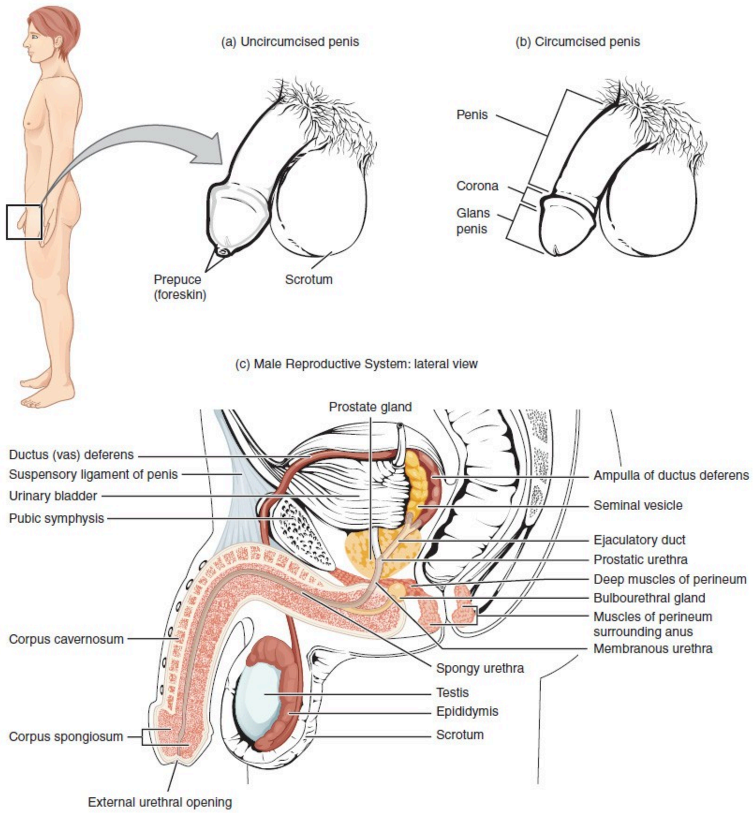
In boys, the growth of the testes is typically the first physical sign of the beginning of puberty, which is followed by growth and pigmentation of the scrotum and growth of the penis. The next step is the growth of hair, including armpit, pubic, chest, and facial hair. Testosterone stimulates the growth of the larynx and thickening and lengthening of the vocal folds, which causes the voice to drop in pitch. The first fertile ejaculations typically appear at approximately 15 years of age, but this age can vary widely across individual boys. Unlike the early growth spurt observed in females, the male growth spurt occurs toward the end of puberty, at approximately age 11 to 13, and a boy's height can increase as much as 4 inches a year. In some males, pubertal development can continue through the early 20s.

86. Anatomy and Physiology of the Male Reproductive System

Unique for its role in human reproduction, a gamete is a specialized sex cell carrying 23 chromosomes—one half the number in body cells. At fertilization, the chromosomes in one male gamete, called a sperm (or spermatozoon), combine with the chromosomes in one female gamete, called an oocyte. The function of the male reproductive system is to produce sperm and transfer them to the female reproductive tract. The paired testes are a crucial component in this process, as they produce both sperm and androgens, the hormones that support male reproductive physiology. In humans, the most important male androgen is testosterone. Several accessory organs and ducts aid the process of sperm maturation and transport the sperm and other seminal components to the penis, which delivers sperm to the female reproductive tract. In this section, we examine each of these different structures, and discuss the process of sperm production and transport.

Male Reproductive System

The structures of the male reproductive system include the testes, the epididymides, the penis, and the ducts and glands that produce and carry semen. Sperm exit the scrotum through the ductus deferens, which is bundled in the spermatic cord. The seminal vesicles and prostate gland add fluids to the sperm to create semen.



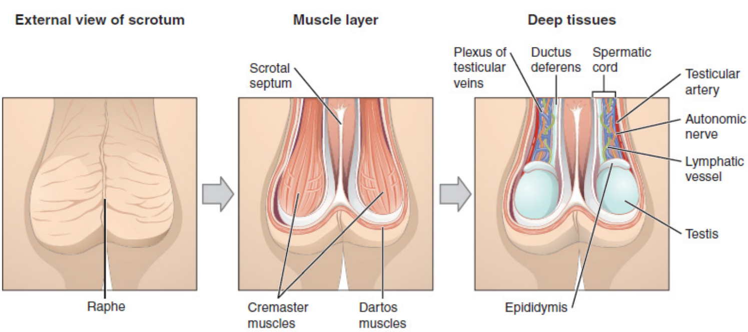
Scrotum

The testes are located in a skin-covered, highly pigmented, muscular sack called the scrotum that extends from the body behind the penis. This location is important in sperm production, which occurs within the testes, and proceeds more efficiently when the testes are kept 2 to 4°C below core body temperature.

The dartos muscle makes up the subcutaneous muscle layer of the scrotum. It continues internally to make up the scrotal septum, a wall that divides the scrotum into two compartments, each housing one testis. Descending from the internal oblique muscle of the abdominal wall are the two cremaster muscles, which cover each testis like a muscular net. By contracting simultaneously, the dartos and cremaster muscles can elevate the testes in cold weather (or water), moving the testes closer to the body and decreasing the surface area of the scrotum to retain heat. Alternatively, as the environmental temperature increases, the scrotum relaxes, moving the testes farther from the body core and increasing scrotal surface area, which promotes heat loss. Externally, the scrotum has a raised medial thickening on the surface called the raphae.

The Scrotum and Testes

This anterior view shows the structures of the scrotum and testes.



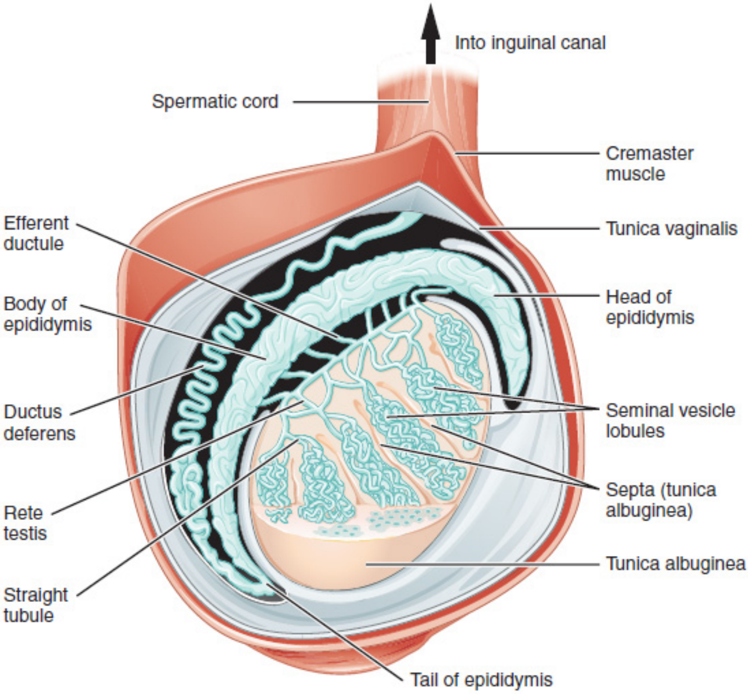
Testes

The testes (singular = testis) are the male gonads—that is, the male reproductive organs. They produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan of the male.

Paired ovals, the testes are each approximately 4 to 5 cm in length and are housed within the scrotum. They are surrounded by two distinct layers of protective connective tissue. The outer tunica vaginalis is a serous membrane that has both a parietal and a thin visceral layer. Beneath the tunica vaginalis is the tunica albuginea, a tough, white, dense connective tissue layer covering the testis itself. Not only does the tunica albuginea cover the outside of the testis, it also invaginates to form septa that divide the testis into 300 to 400 structures called lobules. Within the lobules, sperm develop in structures called seminiferous tubules. During the seventh month of the developmental period of a male fetus, each testis moves through the abdominal musculature to descend into the scrotal cavity. This is called the "descent of the testis." Cryptorchidism is the clinical term used when one or both of the testes fail to descend into the scrotum prior to birth.

Anatomy of the Testis

This sagittal view shows the seminiferous tubules, the site of sperm production. Formed sperm are transferred to the epididymis, where they mature. They leave the epididymis during an ejaculation via the ductus deferens.



The tightly coiled seminiferous tubules form the bulk of each testis. They are composed of developing sperm cells surrounding a lumen, the hollow center of the tubule, where formed sperm are released into the duct system of the testis. Specifically, from the lumens of the seminiferous tubules, sperm move into the straight tubules (or tubuli recti), and from there into a fine meshwork of tubules called the rete testes. Sperm leave the rete testes, and the testis itself, through the 15 to 20 efferent ductules that cross the tunica albuginea.

Inside the seminiferous tubules are six different cell types. These include supporting cells called sustentacular cells, as well as five types of developing sperm cells called germ cells. Germ cell development progresses from the basement membrane—at the perimeter of the tubule—toward the lumen. Let's look more closely at these cell types.

Sertoli Cells

Surrounding all stages of the developing sperm cells are elongate, branching Sertoli cells. Sertoli cells are a type of supporting cell called a sustentacular cell, or sustenocyte, that are typically found in epithelial tissue. Sertoli cells secrete signaling molecules that promote sperm production and can control whether germ cells live or die. They extend physically around the germ cells from the peripheral basement membrane of the seminiferous tubules to the lumen. Tight junctions between these sustentacular cells create the blood–testis barrier, which keeps bloodborne substances from reaching the germ cells and, at the same time, keeps surface antigens on developing germ cells from escaping into the bloodstream and prompting an autoimmune response.

Germ Cells

The least mature cells, the spermatogonia (singular = spermatogonium), line the basement membrane inside the tubule. Spermatogonia are the stem cells of the testis, which means that they are still able to differentiate into a variety of different cell types throughout adulthood. Spermatogonia divide to produce primary and secondary spermatocytes, then spermatids, which finally produce formed sperm. The process that begins with spermatogonia and concludes with the production of sperm is called spermatogenesis.

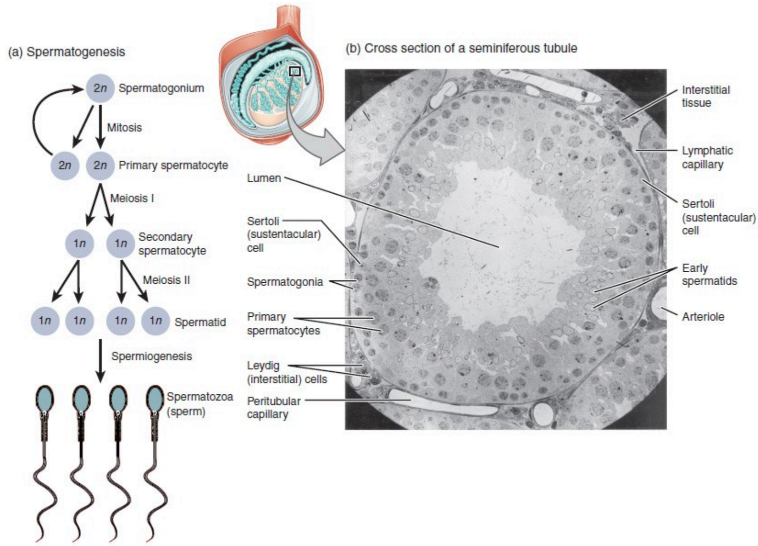
Spermatogenesis

As just noted, spermatogenesis occurs in the seminiferous tubules that form the bulk of each testis. The process begins at puberty, after which time sperm are produced constantly throughout a man's life. One production cycle, from spermatogonia through formed sperm, takes approximately 64 days. A new cycle starts approximately every 16 days, although this timing is not synchronous across the seminiferous tubules. Sperm counts—the total number of sperm a man produces—slowly decline after age 35, and some studies suggest that smoking can lower sperm counts irrespective of age.

The process of spermatogenesis begins with mitosis of the diploid spermatogonia. Because these cells are diploid ($2n$), they each have a complete copy of the father's genetic material, or 46 chromosomes. However, mature gametes are haploid ($1n$), containing 23 chromosomes—meaning that daughter cells of spermatogonia must undergo a second cellular division through the process of meiosis.

Spermatogenesis

(a) Mitosis of a spermatogonial stem cell involves a single cell division that results in two identical, diploid daughter cells (spermatogonia to primary spermatocyte). Meiosis has two rounds of cell division: primary spermatocyte to secondary spermatocyte, and then secondary spermatocyte to spermatid. This produces four haploid daughter cells (spermatids). (b) In this electron micrograph of a cross-section of a seminiferous tubule from a rat, the lumen is the light-shaded area in the center of the image. The location of the primary spermatocytes is near the basement membrane, and the early spermatids are approaching the lumen (tissue source: rat). EM × 900. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



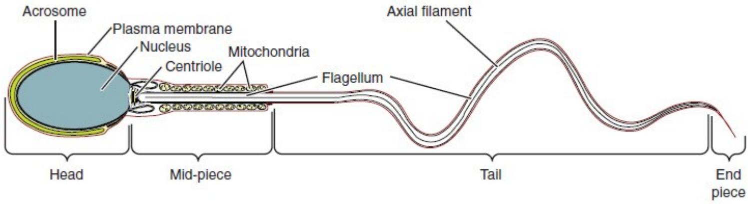
Two identical diploid cells result from spermatogonia mitosis. One of these cells remains a spermatogonium, and the other becomes a primary spermatocyte, the next stage in the process of spermatogenesis. As in mitosis, DNA is replicated in a primary spermatocyte, and the cell undergoes cell division to produce two cells with identical chromosomes. Each of these is a secondary spermatocyte. Now a second round of cell division occurs in both of the secondary spermatocytes, separating the chromosome pairs. This second meiotic division results in a total of four cells with only half of the number of chromosomes. Each of these new cells is a spermatid. Although haploid, early spermatids look very similar to cells in the earlier stages of spermatogenesis, with a round shape, central nucleus, and large amount of cytoplasm. A process called spermiogenesis transforms these early spermatids, reducing the cytoplasm, and beginning the formation of the parts of a true sperm. The fifth stage of germ cell formation—spermatozoa, or formed sperm—is the end result of this process, which occurs in the portion of the tubule nearest the lumen. Eventually, the sperm are released into the lumen and are moved along a series of ducts in the testis toward a structure called the epididymis for the next step of sperm maturation.

Structure of Formed Sperm

Sperm are smaller than most cells in the body; in fact, the volume of a sperm cell is 85,000 times less than that of the female gamete. Approximately 100 to 300 million sperm are produced each day, whereas women typically ovulate only one oocyte per month as is true for most cells in the body, the structure of sperm cells speaks to their function. Sperm have a distinctive head, mid-piece, and tail region. The head of the sperm contains the extremely compact haploid nucleus with very little cytoplasm. These qualities contribute to the overall small size of the sperm (the head is only 5 μm long). A structure called the acrosome covers most of the head of the sperm cell as a "cap" that is filled with lysosomal enzymes important for preparing sperm to participate in fertilization. Tightly packed mitochondria fill the mid-piece of the sperm. ATP produced by these mitochondria will power the flagellum, which extends from the neck and the mid-piece through the tail of the sperm, enabling it to move the entire sperm cell. The central strand of the flagellum, the axial filament, is formed from one centriole inside the maturing sperm cell during the final stages of spermatogenesis.

Structure of Sperm

Sperm cells are divided into a head, containing DNA; a mid-piece, containing mitochondria; and a tail, providing motility. The acrosome is oval and somewhat flattened.



Sperm Transport

To fertilize an egg, sperm must be moved from the seminiferous tubules in the testes, through the epididymis, and—later during ejaculation—along the length of the penis and out into the female reproductive tract.

Role of the Epididymis

From the lumen of the seminiferous tubules, the immotile sperm are surrounded by testicular fluid and moved to the epididymis (plural = epididymides), a coiled tube attached to the testis where newly formed sperm continue to mature. Though the epididymis does not take up much room in its tightly coiled state, it would be approximately 6 m (20 feet) long if straightened. It takes an average of 12 days for sperm to move through the coils of the epididymis, with the shortest recorded transit time in humans being one day. Sperm enter the head of the epididymis and are moved along predominantly by the contraction of smooth muscles lining the epididymal tubes. As they are moved along the length of the epididymis, the sperm further mature and acquire the ability to move under their own power. Once inside the female reproductive tract, they will use this ability to move independently toward the unfertilized egg. The more mature sperm are then stored in the tail of the epididymis (the final section) until ejaculation occurs.

Duct System

During ejaculation, sperm exit the tail of the epididymis and are pushed by smooth muscle contraction to the ductus deferens (also called the vas deferens). The ductus deferens is a thick, muscular tube that is bundled together inside the scrotum with connective tissue, blood vessels, and nerves into a structure called the spermatic cord. Because the ductus deferens is physically accessible within the scrotum, surgical sterilization to interrupt sperm delivery can be performed by cutting and sealing a small section of the ductus (vas) deferens. This procedure is called a vasectomy, and it is an effective form of male birth control. Although it may be possible to reverse a vasectomy, clinicians consider the procedure permanent, and advise men to undergo it only if they are certain they no longer wish to father children.

From each epididymis, each ductus deferens extends superiorly into the abdominal cavity through the inguinal canal in the abdominal wall. From here, the ductus deferens continues posteriorly to the pelvic cavity, ending posterior to the bladder where it dilates in a region called the ampulla (meaning "flask").

Sperm make up only 5 percent of the final volume of semen, the thick, milky fluid that the male ejaculates. The bulk of semen is produced by three critical accessory glands of the male reproductive system: the seminal vesicles, the prostate, and the bulbourethral glands.

Seminal Vesicles

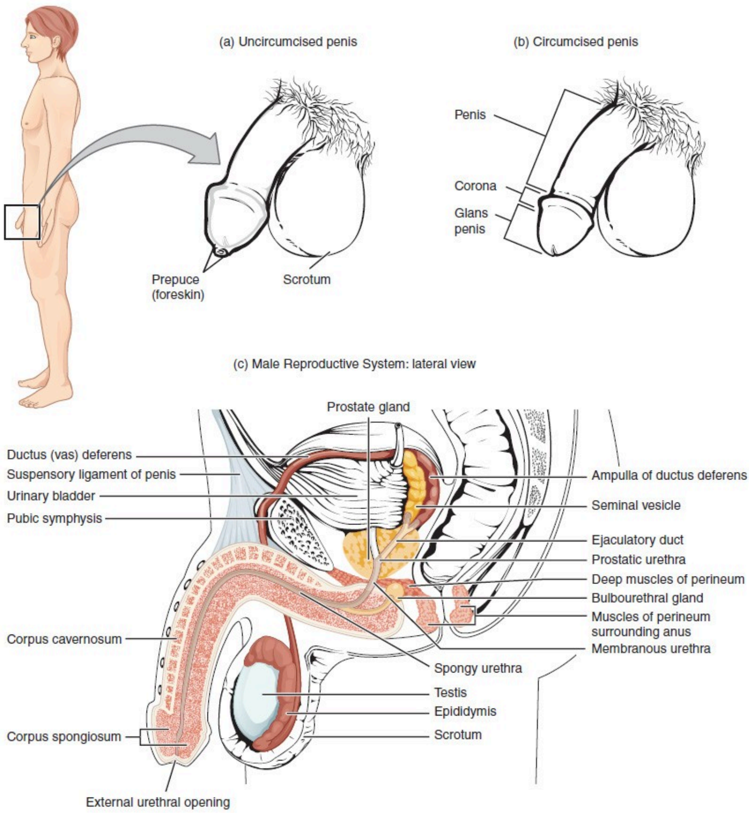
As sperm pass through the ampulla of the ductus deferens at ejaculation, they mix with fluid from the associated seminal vesicle. The paired seminal vesicles are glands that contribute approximately 60 percent of the semen volume. Seminal vesicle fluid contains large amounts of fructose, which is used by the sperm mitochondria to generate ATP to allow movement through the female reproductive tract.

The fluid, now containing both sperm and seminal vesicle secretions, next moves into the associated ejaculatory duct, a short structure formed from the ampulla of the ductus deferens and the duct of the seminal vesicle. The paired ejaculatory ducts transport the seminal fluid into the next structure, the prostate gland.

Prostate Gland

As shown in the image below, the centrally located prostate gland sits anterior to the rectum at the base of the bladder surrounding the prostatic urethra (the portion of the urethra that runs within the prostate). About the size of a walnut, the prostate is formed of both muscular and glandular tissues. It excretes an alkaline, milky fluid to the passing seminal fluid—now called semen—that is critical to first coagulate and then decoagulate the semen following ejaculation. The temporary thickening of semen helps retain it within the female reproductive tract, providing time for sperm to utilize the fructose provided by seminal vesicle secretions. When the semen regains its fluid state, sperm can then pass farther into the female reproductive tract.

Male Reproductive System



The prostate normally doubles in size during puberty. At approximately age 25, it gradually begins to enlarge again. This enlargement does not usually cause problems; however, abnormal growth of the prostate, or benign prostatic hyperplasia (BPH), can cause constriction of the urethra as it passes through the middle of the prostate gland, leading to a number of lower urinary tract symptoms, such as a frequent and intense urge to urinate, a weak stream, and a sensation that the bladder has not emptied completely. By age 60, approximately 40 percent of men have some degree of BPH. By age 80, the number of affected individuals has jumped to as many as 80 percent. Treatments for BPH attempt to relieve the pressure on the urethra so that urine can flow more normally. Mild to moderate symptoms are treated with medication, whereas severe enlargement of the prostate is treated by surgery in which a portion of the prostate tissue is removed.

Bulbourethral Glands

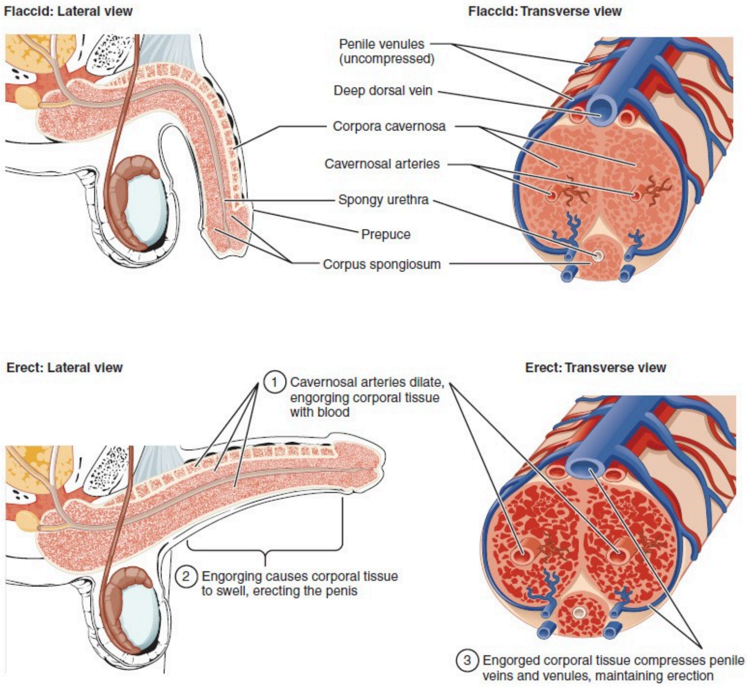
The final addition to semen is made by two bulbourethral glands (or Cowper's glands) that release a thick, salty fluid that lubricates the end of the urethra and the vagina, and helps to clean urine residues from the penile urethra. The fluid from these accessory glands is released after the male becomes sexually aroused, and shortly before the release of the semen. It is therefore sometimes called pre-ejaculate. It is important to note that, in addition to the lubricating proteins, it is possible for bulbourethral fluid to pick up sperm already present in the urethra, and therefore it may be able to cause pregnancy.

The Penis

The penis is the male organ of copulation (sexual intercourse). It is flaccid for non-sexual actions, such as urination, and turgid and rod-like with sexual arousal. When erect, the stiffness of the organ allows it to penetrate into the vagina and deposit semen into the female reproductive tract.

Cross-Sectional Anatomy of the Penis

Three columns of erectile tissue make up most of the volume of the penis.



The shaft of the penis surrounds the urethra. The shaft is composed of three column-like chambers of erectile tissue that span the length of the shaft. Each of the two larger lateral chambers is called a corpus cavernosum (plural = corpora cavernosa). Together, these make up the bulk of the penis. The corpus spongiosum, which can be felt as a raised ridge on the erect penis, is a smaller chamber that surrounds the spongy, or penile, urethra. The end of the penis, called the glans penis, has a high concentration of nerve endings, resulting in very sensitive skin that influences the likelihood of ejaculation. The skin from the shaft extends down over the glans and forms a collar called the prepuce (or foreskin). The foreskin also contains a dense concentration of nerve endings, and both lubricate and protect the sensitive skin of the glans penis. A surgical procedure called circumcision, often performed for religious or social reasons, removes the prepuce, typically within days of birth.

Both sexual arousal and REM sleep (during which dreaming occurs) can induce an erection. Penile erections are the result of vasocongestion, or engorgement of the tissues because of more arterial blood flowing into the penis than is leaving in the veins. During sexual arousal, nitric oxide (NO) is released from nerve endings near blood vessels within the corpora cavernosa and spongiosum. Release of NO activates a signaling pathway that results in relaxation of the smooth muscles that surround the penile arteries, causing them to dilate. This dilation increases the amount of blood that can enter the penis and induces the endothelial cells in the penile arterial walls to also secrete NO and perpetuate the vasodilation. The rapid increase in blood volume fills the erectile chambers, and the increased pressure of the filled chambers compresses the thin-walled penile venules, preventing venous drainage of the penis. The result of this increased blood flow to the penis and reduced blood return from the penis is erection. Depending on the flaccid dimensions of a penis, it can increase in size slightly or greatly during erection, with the average length of an erect penis measuring approximately 15 cm.

Testosterone

Testosterone, an androgen, is a steroid hormone produced by Leydig cells. The alternate term for Leydig cells, interstitial cells, reflects their location between the seminiferous tubules in the testes. In male embryos, testosterone is secreted by Leydig cells by the seventh week of development, with peak concentrations reached in the second trimester. This early release of testosterone results in the anatomical differentiation of the male sexual organs. In childhood, testosterone concentrations are low. They increase during puberty, activating characteristic physical changes and initiating spermatogenesis.

Functions of Testosterone

The continued presence of testosterone is necessary to keep the male reproductive system working properly, and Leydig cells produce approximately 6 to 7 mg of testosterone per day. Testicular steroidogenesis (the manufacture of androgens, including testosterone) results in testosterone concentrations that are 100 times higher in the testes than in the circulation. Maintaining these normal concentrations of testosterone promotes spermatogenesis, whereas low levels of testosterone can lead to infertility. In addition to intratesticular secretion, testosterone is also released into the systemic circulation and plays an important role in muscle development, bone growth, the development of secondary sex characteristics, and maintaining libido (sex drive) in both males and females. In females, the ovaries secrete small amounts of testosterone, although most is converted to estradiol. A small amount of testosterone is also secreted by the adrenal glands in both sexes.

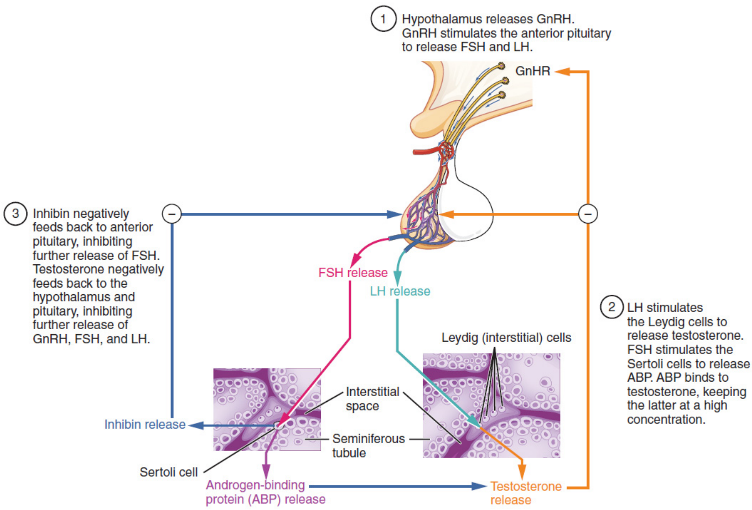
Control of Testosterone

The regulation of testosterone concentrations throughout the body is critical for male reproductive function. The intricate interplay between the endocrine system and the reproductive system is shown in the image below.

Regulation of Testosterone Production

The hypothalamus and pituitary gland regulate the production of testosterone and the cells that assist in spermatogenesis. GnRH activates the anterior pituitary to produce LH and FSH, which in turn stimulate Leydig cells and Sertoli cells, respectively. The system is a negative feedback loop because the end products of the pathway, testosterone and inhibin, interact with the activity of

GnRH to inhibit their own production.



The regulation of Leydig cell production of testosterone begins outside of the testes. The hypothalamus and the pituitary gland in the brain integrate external and internal signals to control testosterone synthesis and secretion. The regulation begins in the hypothalamus. Pulsatile release of a hormone called gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the endocrine release of hormones from the pituitary gland. Binding of GnRH to its receptors on the anterior pituitary gland stimulates release of the two gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These two hormones are critical for reproductive function in both men and women. In men, FSH binds predominantly to the Sertoli cells within the seminiferous tubules to promote spermatogenesis. FSH also stimulates the Sertoli cells to produce hormones called inhibins, which function to inhibit FSH release from the pituitary, thus reducing testosterone secretion. These polypeptide hormones correlate directly with Sertoli cell function and sperm number; inhibin B can be used as a marker of spermatogenic activity. In men, LH binds to receptors on Leydig cells in the testes and upregulates the production of testosterone.

A negative feedback loop predominantly controls the synthesis and secretion of both FSH and LH. Low blood concentrations of testosterone stimulate the hypothalamic release of GnRH. GnRH then stimulates the anterior pituitary to secrete LH into the bloodstream. In the testis, LH binds to LH receptors on Leydig cells and stimulates the release of testosterone. When concentrations of testosterone in the blood reach a critical threshold, testosterone itself will bind to androgen receptors on both the hypothalamus and the anterior pituitary, inhibiting the synthesis and secretion of GnRH and LH, respectively. When the blood concentrations of testosterone once again decline, testosterone no longer interacts with the receptors to the same degree and GnRH and LH are once again secreted, stimulating more testosterone production. This same process occurs with FSH and inhibin to control spermatogenesis.

Aging and the Male Reproductive System

Declines in Leydig cell activity can occur in men beginning at 40 to 50 years of age. The resulting reduction in circulating testosterone concentrations can lead to symptoms of andropause, also known as male menopause. While the reduction in sex steroids in men is akin to female menopause, there is no clear sign—such as a lack of a menstrual period—to denote the initiation of andropause. Instead, men report feelings of fatigue, reduced muscle mass, depression, anxiety, irritability, loss of libido, and insomnia. A reduction in spermatogenesis resulting in lowered fertility is also reported, and sexual dysfunction can also be associated with andropausal symptoms.

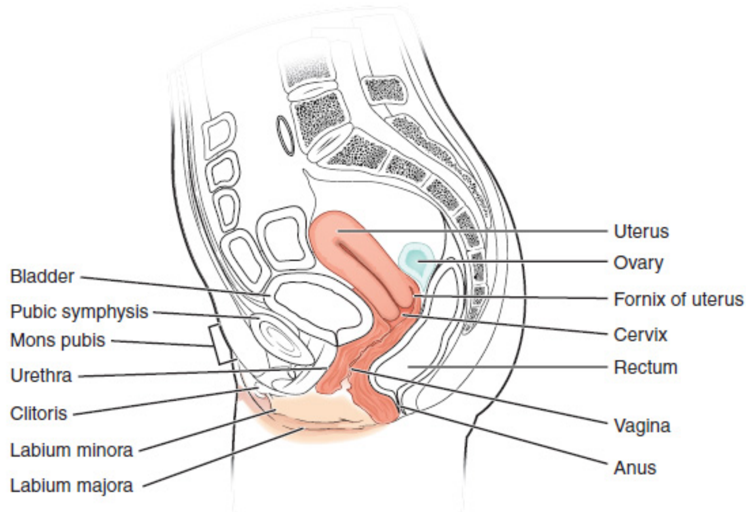
Whereas some researchers believe that certain aspects of andropause are difficult to tease apart from aging in general, testosterone replacement is sometimes prescribed to alleviate some symptoms. Recent studies have shown a benefit from androgen replacement therapy on the new onset of depression in elderly men;

however, other studies caution against testosterone replacement for long-term treatment of andropause symptoms, showing that high doses can sharply increase the risk of both heart disease and prostate cancer.

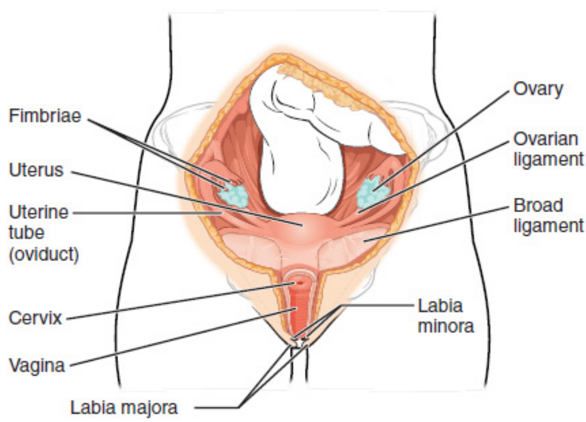
87. Anatomy and Physiology of the Female Reproductive System

The female reproductive system functions to produce gametes and reproductive hormones, just like the male reproductive system; however, it also has the additional task of supporting the developing fetus and delivering it to the outside world. Unlike its male counterpart, the female reproductive system is located primarily inside the pelvic cavity. Recall that the ovaries are the female gonads. The gamete they produce is called an oocyte. We'll discuss the production of oocytes in detail shortly. First, let's look at some of the structures of the female reproductive system.

Female Reproductive System
The major organs of the female reproductive system are located inside the pelvic cavity.



(a) Human female reproductive system: lateral view



(b) Human female reproductive system: anterior view

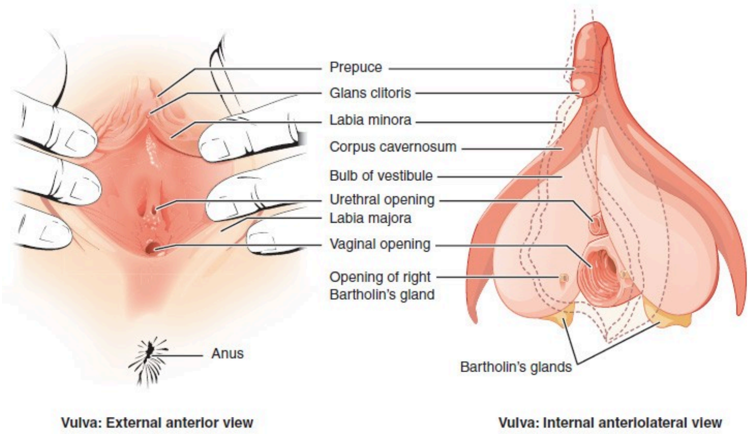
External Female Genitals

The external female reproductive structures are referred to collectively as the vulva. The mons pubis is a pad of fat that is located at the anterior, over the pubic bone. After puberty, it becomes covered in pubic hair. The labia majora (labia = “lips”; majora = “larger”) are folds of hair-covered skin that begin just posterior to the mons pubis. The thinner and more pigmented labia minora (labia = “lips”; minora = “smaller”) extend medial to the labia majora. Although they naturally vary in shape and size from woman to woman, the labia minora serve to protect the female urethra and the entrance to the female reproductive tract.

The superior, anterior portions of the labia minora come together to encircle the clitoris (or glans clitoris), an organ that originates from the same cells as the glans penis and has abundant nerves that make it important in sexual sensation and orgasm. The hymen is a thin membrane that sometimes partially covers the entrance to the vagina. An intact hymen cannot be used as an indication of “virginity”; even at birth, this is only a partial membrane, as menstrual fluid and other secretions must be able to exit the body, regardless of penile–vaginal intercourse. The vaginal opening is located between the opening of the urethra and the anus. It is flanked by outlets to the Bartholin’s glands (or greater vestibular glands).

The Vulva

The external female genitalia are referred to collectively as the vulva.



Vagina

The vagina is a muscular canal (approximately 10 cm long) that serves as the entrance to the reproductive tract. It also serves as the exit from the uterus during menses and childbirth. The outer walls of the anterior and posterior vagina are formed into longitudinal columns, or ridges, and the superior portion of the vagina—called the fornix—meets the protruding uterine cervix. The walls of the vagina are lined with an outer, fibrous adventitia; a middle layer of smooth muscle; and an inner mucous membrane with transverse folds called rugae. Together, the middle and inner layers allow the expansion of the vagina to accommodate intercourse and childbirth. The thin, perforated hymen can partially surround the opening to the vaginal orifice. The hymen can be ruptured with strenuous physical exercise, penile–vaginal intercourse, and childbirth. The Bartholin's glands and the lesser vestibular glands (located near the clitoris) secrete mucus, which keeps the vestibular area moist.

The vagina is home to a normal population of microorganisms that help to protect against infection by pathogenic bacteria, yeast, or other organisms that can enter the vagina. In a healthy woman, the most predominant type of vaginal bacteria is from the genus *Lactobacillus*. This family of beneficial bacterial flora secretes lactic acid, and thus protects the vagina by maintaining an acidic pH (below 4.5). Potential pathogens are less likely to survive in these acidic conditions. Lactic acid, in combination with other vaginal secretions, makes the vagina a self-cleansing organ. However, douching—or washing out the vagina with fluid—can disrupt the normal balance of healthy microorganisms, and actually increase a woman's risk for infections and irritation. Indeed, the American College of Obstetricians and Gynecologists recommend that women do not douche, and that they allow the vagina to maintain its normal healthy population of protective microbial flora.

Ovaries

The ovaries are the female gonads. Paired ovals, they are each about 2 to 3 cm in length, about the size of an almond. The ovaries are located within the pelvic cavity, and are supported by the mesovarium, an extension of the peritoneum that connects the ovaries to the broad ligament. Extending from the mesovarium itself is the suspensory ligament that contains the ovarian blood and lymph vessels. Finally, the ovary itself is attached to the uterus via the ovarian ligament.

The ovary comprises an outer covering of cuboidal epithelium called the ovarian surface epithelium that is superficial to a dense connective tissue covering called the tunica albuginea. Beneath the tunica albuginea is the cortex, or outer portion, of the organ. The cortex is composed of a tissue framework called the ovarian stroma that forms the bulk of the adult ovary. Oocytes develop within the outer layer of this stroma, each surrounded by supporting cells. This grouping of an oocyte and its supporting cells is called a follicle. The growth and development of ovarian follicles will be described shortly. Beneath the cortex lies the inner ovarian medulla, the site of blood vessels, lymph vessels, and the nerves of the ovary. You will learn more about the overall anatomy of the female reproductive system at the end of this section.

The Ovarian Cycle

The ovarian cycle is a set of predictable changes in a female's oocytes and ovarian follicles. During a woman's reproductive years, it is a roughly 28-day cycle that can be correlated with, but is not the same as, the menstrual cycle (discussed shortly). The cycle includes two interrelated processes: oogenesis (the production of female gametes) and folliculogenesis (the growth and development of ovarian follicles).

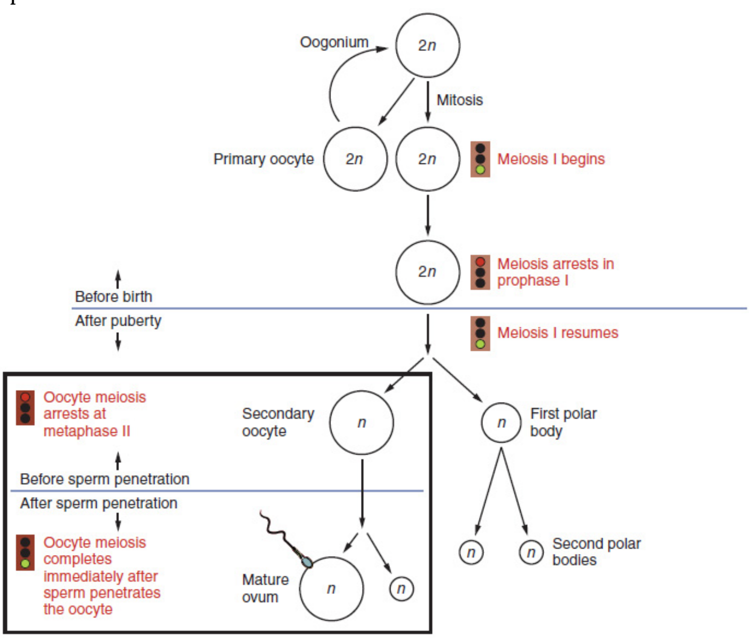
Oogenesis

Gametogenesis in females is called oogenesis. The process begins with the ovarian stem cells, or oogonia. Oogonia are formed during fetal development, and divide via mitosis, much like spermatogonia in the testis. Unlike spermatogonia, however, oogonia form primary oocytes in the fetal ovary prior to birth. These primary oocytes are then arrested in this stage of meiosis I, only to resume it years later, beginning at puberty and continuing until the woman is near menopause (the cessation of a woman's reproductive functions). The number of primary oocytes present in the ovaries declines from one to two million in an infant, to approximately 400,000 at puberty, to zero by the end of menopause.

The initiation of ovulation—the release of an oocyte from the ovary—marks the transition from puberty into reproductive maturity for women. From then on, throughout a woman's reproductive years, ovulation occurs approximately once every 28 days. Just prior to ovulation, a surge of luteinizing hormone triggers the resumption of meiosis in a primary oocyte. This initiates the transition from primary to secondary oocyte. However, as you can see in the diagram below, this cell division does not result in two identical cells. Instead, the cytoplasm is divided unequally, and one daughter cell is much larger than the other. This larger cell, the secondary oocyte, eventually leaves the ovary during ovulation. The smaller cell, called the first polar body, may or may not complete meiosis and produce second polar bodies; in either case, it eventually disintegrates. Therefore, even though oogenesis produces up to four cells, only one survives.

Oogenesis

The unequal cell division of oogenesis produces one to three polar bodies that later degrade, as well as a single haploid ovum, which is produced only if there is penetration of the secondary oocyte by a sperm cell.



How does the diploid secondary oocyte become an ovum—the haploid female gamete? Meiosis of a secondary oocyte is completed only if a sperm succeeds in penetrating its barriers. Meiosis II then resumes, producing one haploid ovum that, at the instant of fertilization by a (haploid) sperm, becomes the first diploid cell of the new offspring (a zygote). Thus, the ovum can be thought of as a brief, transitional, haploid stage between the diploid oocyte and diploid zygote.

The larger amount of cytoplasm contained in the female gamete is used to supply the developing zygote with nutrients during the period between fertilization and implantation into the uterus. Interestingly, sperm contribute only DNA at fertilization —not cytoplasm. Therefore, the cytoplasm and all of the cytoplasmic organelles in the developing embryo are of maternal origin. This includes mitochondria, which contain their own DNA. Scientific research in the 1980s determined that mitochondrial DNA was maternally inherited, meaning that you can trace your mitochondrial DNA directly to your mother, her mother, and so on back through your female ancestors.

Everyday Connections

Mapping Human History with Mitochondrial DNAWhen we talk about human DNA, we're usually referring to nuclear DNA; that is, the DNA coiled into chromosomal bundles in the nucleus of our cells. We inherit half of our nuclear DNA from our father, and half from our mother. However, mitochondrial DNA (mtDNA) comes only from the mitochondria in the cytoplasm of the fat ovum we inherit from our mother. She received her mtDNA from her mother, who got it from her mother, and so on. Each of our cells contains approximately 1700 mitochondria, with each mitochondrion packed with mtDNA containing approximately 37 genes.

Mutations (changes) in mtDNA occur spontaneously in a somewhat organized pattern at regular intervals in human history. By analyzing these mutational relationships, researchers have been able to determine that we can all trace our ancestry back to one woman who lived in Africa about 200,000 years ago. Scientists have given this woman the biblical name Eve, although she is not, of course, the first *Homo sapiens* female. More precisely, she is our most recent common ancestor through matrilineal descent.

This doesn't mean that everyone's mtDNA today looks exactly like that of our ancestral Eve. Because of the spontaneous mutations in mtDNA that have occurred over the centuries, researchers can map different "branches" off of the "main trunk" of our mtDNA family tree. Your mtDNA might have a pattern of mutations that aligns more closely with one branch, and your neighbor's may align with another branch. Still, all branches eventually lead back to Eve.

But what happened to the mtDNA of all of the other *Homo sapiens* females who were living at the time of Eve? Researchers explain that, over the centuries, their female descendants died childless or with only male children, and thus, their maternal line—and its mtDNA—ended.

Folliculogenesis

Again, ovarian follicles are oocytes and their supporting cells. They grow and develop in a process called folliculogenesis, which typically leads to ovulation of one follicle approximately every 28 days, along with death to multiple other follicles. The death of ovarian follicles is called atresia, and can occur at any point during follicular development. Recall that, a female infant at birth will have one to two million oocytes within her ovarian follicles, and that this number declines throughout life until menopause, when no follicles remain. As you'll see next, follicles progress from primordial, to primary, to secondary and tertiary stages prior to ovulation—with the oocyte inside the follicle remaining as a primary oocyte until right before ovulation.

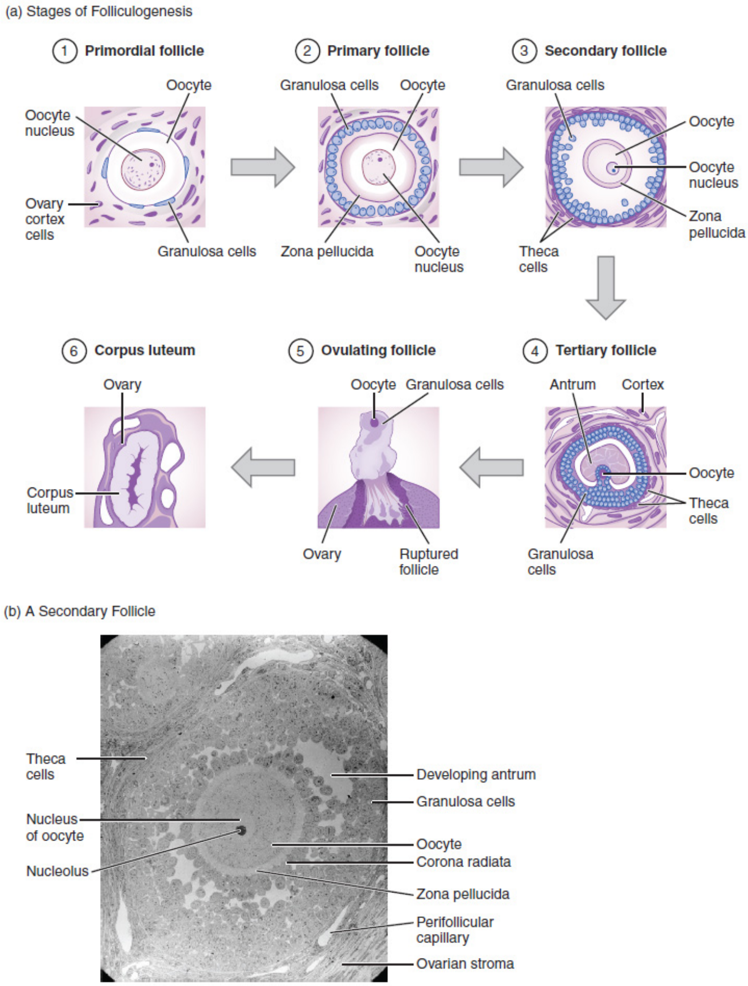
Folliculogenesis begins with follicles in a resting state. These small primordial follicles are present in newborn females and are the prevailing follicle type in the adult ovary. Primordial follicles have only a single flat layer of support cells, called granulosa cells, that surround the oocyte, and they can stay in this resting state for years—some until right before menopause.

After puberty, a few primordial follicles will respond to a recruitment signal each day, and will join a pool of immature growing follicles called primary follicles. Primary follicles start with a single layer of granulosa cells, but the granulosa cells then become active and transition from a flat or squamous shape to a rounded, cuboidal shape as they increase in size and proliferate. As the granulosa cells divide, the follicles—now called secondary follicles—increase in diameter, adding a new outer layer of connective tissue, blood vessels, and theca cells—cells that work with the granulosa cells to produce estrogens.

Within the growing secondary follicle, the primary oocyte now secretes a thin acellular membrane called the zona pellucida that will play a critical role in fertilization. A thick fluid, called follicular fluid, that has formed between the granulosa cells also begins to collect into one large pool, or antrum. Follicles in which the antrum has become large and fully formed are considered tertiary follicles (or antral follicles). Several follicles reach the tertiary stage at the same time, and most of these will undergo atresia. The one that does not die will continue to grow and develop until ovulation, when it will expel its secondary oocyte surrounded by several layers of granulosa cells from the ovary. Keep in mind that most follicles don't make it to this point. In fact, roughly 99 percent of the follicles in the ovary will undergo atresia, which can occur at any stage of folliculogenesis.

Folliculogenesis

(a) The maturation of a follicle is shown in a clockwise direction proceeding from the primordial follicles. FSH stimulates the growth of a tertiary follicle, and LH stimulates the production of estrogen by granulosa and theca cells. Once the follicle is mature, it ruptures and releases the oocyte. Cells remaining in the follicle then develop into the corpus luteum. (b) In this electron micrograph of a secondary follicle, the oocyte, theca cells (thecae folliculi), and developing antrum are clearly visible. EM × 1100. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



Hormonal Control of the Ovarian Cycle

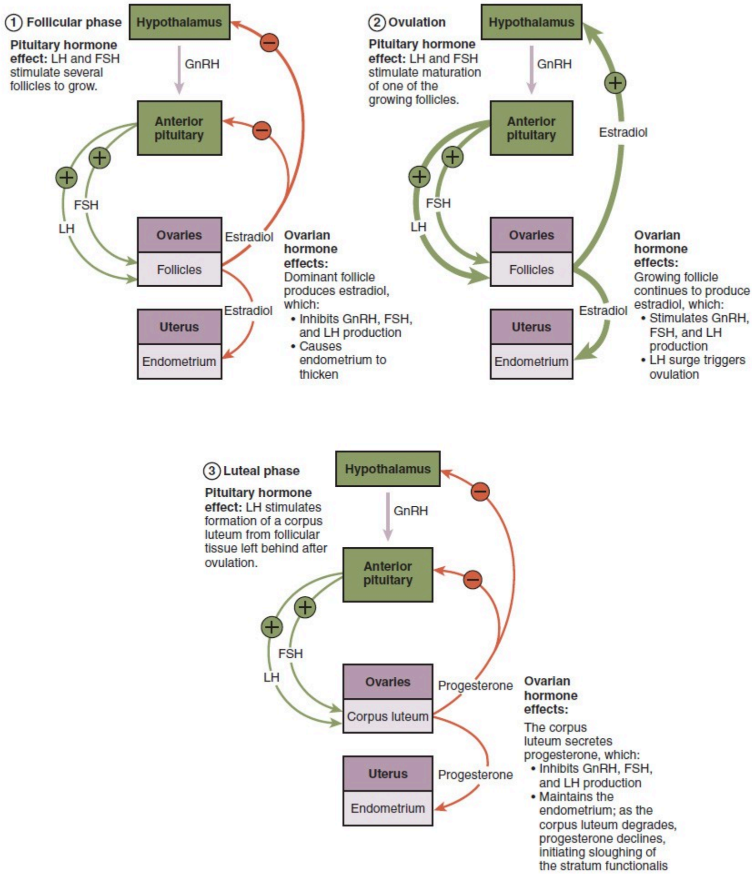
The process of development that we have just described, from primordial follicle to early tertiary follicle, takes approximately two months in humans. The final stages of development of a small cohort of tertiary follicles, ending with ovulation of a secondary oocyte, occur over a course of approximately 28 days. These changes are regulated by many of the same hormones that regulate the male reproductive system, including GnRH, LH, and FSH.

As in men, the hypothalamus produces GnRH, a hormone that signals the anterior pituitary gland to produce the gonadotropins FSH and LH. These gonadotropins leave the pituitary and travel through the bloodstream to the ovaries, where they bind to receptors on the granulosa and theca cells of the follicles. FSH stimulates the follicles to grow (hence its name of follicle-stimulating hormone), and the five or six tertiary follicles expand in diameter. The release of LH also stimulates the granulosa and theca cells of the follicles to produce the sex steroid hormone estradiol, a type of estrogen. This phase of the ovarian cycle, when the tertiary follicles are growing and secreting estrogen, is known as the follicular phase.

The more granulosa and theca cells a follicle has (that is, the larger and more developed it is), the more estrogen it will produce in response to LH stimulation. As a result of these large follicles producing large amounts of estrogen, systemic plasma estrogen concentrations increase. Following a classic negative feedback loop, the high concentrations of estrogen will stimulate the hypothalamus and pituitary to reduce the production of GnRH, LH, and FSH. Because the large tertiary follicles require FSH to grow and survive at this point, this decline in FSH caused by negative feedback leads most of them to die (atresia). Typically only one follicle, now called the dominant follicle, will survive this reduction in FSH, and this follicle will be the one that releases an oocyte. Scientists have studied many factors that lead to a particular follicle becoming dominant: size, the number of granulosa cells, and the number of FSH receptors on those granulosa cells all contribute to a follicle becoming the one surviving dominant follicle.

Hormonal Regulation of Ovulation

The hypothalamus and pituitary gland regulate the ovarian cycle and ovulation. GnRH activates the anterior pituitary to produce LH and FSH, which stimulate the production of estrogen and progesterone by the ovaries.



When only the one dominant follicle remains in the ovary, it again begins to secrete estrogen. It produces more estrogen than all of the developing follicles did together before the negative feedback occurred. It produces so much estrogen that the normal negative feedback doesn't occur. Instead, these extremely high concentrations of systemic plasma estrogen trigger a regulatory switch in the anterior pituitary that responds by secreting large amounts of LH and FSH into the bloodstream. The positive feedback loop by which more estrogen triggers release of more LH and FSH only occurs at this point in the cycle.

It is this large burst of LH (called the LH surge) that leads to ovulation of the dominant follicle. The LH surge induces many changes in the dominant follicle, including stimulating the resumption of meiosis of the primary oocyte to a secondary oocyte. As noted earlier, the polar body that results from unequal cell division simply degrades. The LH surge also triggers proteases (enzymes that cleave proteins) to break down structural proteins in the ovary wall on the surface of the bulging dominant follicle. This degradation of the wall, combined with pressure from the large, fluid-filled antrum, results in the expulsion of the oocyte surrounded by granulosa cells into the peritoneal cavity. This release is ovulation.

In the next section, you will follow the ovulated oocyte as it travels toward the uterus, but there is one more important event that occurs in the ovarian cycle. The surge of LH also stimulates a change in the granulosa and theca cells that remain in the follicle after the oocyte has been ovulated. This change is called luteinization (recall that the full name of LH is luteinizing hormone), and it transforms the collapsed follicle into a new endocrine structure called the corpus luteum, a term meaning "yellowish body". Instead of estrogen, the luteinized granulosa and theca cells of the corpus luteum begin to produce large amounts of the sex steroid hormone progesterone, a hormone that is critical for the establishment and maintenance of pregnancy. Progesterone triggers negative feedback at the hypothalamus and pituitary, which keeps GnRH, LH, and FSH secretions low, so no new dominant follicles develop at this time.

The post-ovulatory phase of progesterone secretion is known as the luteal phase of the ovarian cycle. If pregnancy does not occur within 10 to 12 days, the corpus luteum will stop secreting progesterone and degrade into the corpus albicans, a nonfunctional "whitish body" that will disintegrate in the ovary over a period of several months. During this time of reduced progesterone secretion, FSH and LH are once again stimulated, and the follicular phase begins again with a new cohort of early tertiary follicles beginning to grow and secrete estrogen.

The Uterine Tubes

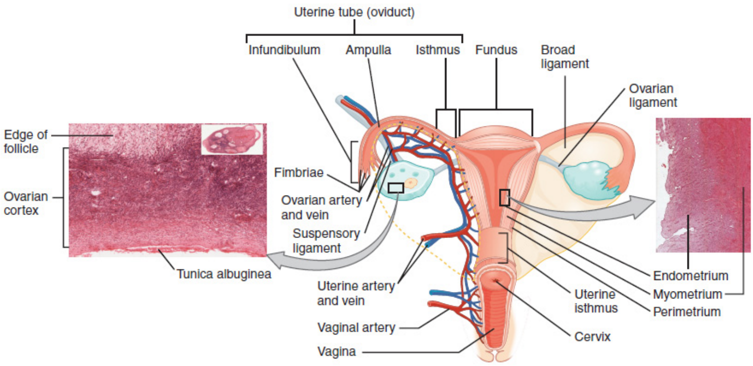
The uterine tubes (also called fallopian tubes or oviducts) serve as the conduit of the oocyte from the ovary to the uterus. Each of the two uterine tubes is close to, but not directly connected to, the ovary and divided into sections. The isthmus is the narrow medial end of each uterine tube that is connected to the uterus. The wide distal infundibulum flares out with slender, finger-like projections called fimbriae. The middle region of the tube, called the ampulla, is where fertilization often occurs. The uterine tubes also have three layers: an outer serosa, a middle smooth muscle layer, and an inner mucosal layer. In addition to its mucus-secreting cells, the inner mucosa contains ciliated cells that beat in the direction of the uterus, producing a current that will be critical to move the oocyte.

Following ovulation, the secondary oocyte surrounded by a few granulosa cells is released into the peritoneal cavity. The nearby uterine tube, either left or right, receives the oocyte. Unlike sperm, oocytes lack flagella, and therefore cannot move on their own. So how do they travel into the uterine tube and toward the uterus? High concentrations of estrogen that occur around the time of ovulation induce contractions of the smooth muscle along the length of the uterine tube. These contractions occur every 4 to 8 seconds, and the result is a coordinated movement that sweeps the surface of the ovary and the pelvic cavity. Current flowing toward the uterus is generated by coordinated beating of the cilia that line the outside and lumen of the length of the uterine tube. These cilia beat more strongly in response to the high estrogen concentrations that occur around the time of ovulation. As a result of these mechanisms, the oocyte–granulosa cell complex is pulled into the interior of the tube. Once inside, the muscular contractions and beating cilia move the oocyte slowly toward the uterus. When fertilization does occur, sperm typically meet the egg while it is still moving through the ampulla.

If the oocyte is successfully fertilized, the resulting zygote will begin to divide into two cells, then four, and so on, as it makes its way through the uterine tube and into the uterus. There, it will implant and continue to grow. If the egg is not fertilized, it will simply degrade—either in the uterine tube or in the uterus, where it may be shed with the next menstrual period.

Ovaries, Uterine Tubes, and Uterus

This anterior view shows the relationship of the ovaries, uterine tubes (oviducts), and uterus. Sperm enter through the vagina, and fertilization of an ovulated oocyte usually occurs in the distal uterine tube. From left to right, LM × 400, LM × 20. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)



The open-ended structure of the uterine tubes can have significant health consequences if bacteria or other contagions enter through the vagina and move through the uterus, into the tubes, and then into the pelvic cavity. If this is left unchecked, a bacterial infection (sepsis) could quickly become life-threatening. The spread of an infection in this manner is of special concern when unskilled practitioners perform abortions in non-sterile conditions. Sepsis is also associated with sexually transmitted bacterial infections, especially gonorrhea and chlamydia. These increase a woman's risk for pelvic inflammatory disease (PID), infection of the uterine tubes or other reproductive organs. Even when resolved, PID can leave scar tissue in the tubes, leading to infertility.

The Uterus and Cervix

The uterus is the muscular organ that nourishes and supports the growing embryo. Its average size is approximately 5 cm wide by 7 cm long (approximately 2 in by 3 in) when a female is not pregnant. It has three sections. The portion of the uterus superior to the opening of the uterine tubes is called the fundus. The middle section of the uterus is called the body of uterus (or corpus). The cervix is the narrow inferior portion of the uterus that projects into the vagina. The cervix produces mucus secretions that become thin and stringy under the influence of high systemic plasma estrogen concentrations, and these secretions can facilitate sperm movement through the reproductive tract.

Several ligaments maintain the position of the uterus within the abdominopelvic cavity. The broad ligament is a fold of peritoneum that serves as a primary support for the uterus, extending laterally from both sides of the uterus and attaching it to the pelvic wall. The round ligament attaches to the uterus near the uterine tubes, and extends to the labia majora. Finally, the uterosacral ligament stabilizes the uterus posteriorly by its connection from the cervix to the pelvic wall.

The wall of the uterus is made up of three layers. The most superficial layer is the serous membrane, or perimetrium, which consists of epithelial tissue that covers the exterior portion of the uterus. The middle layer, or myometrium, is a thick layer of smooth muscle responsible for uterine contractions. Most of the uterus is myometrial tissue, and the muscle fibers run horizontally, vertically, and diagonally, allowing the powerful contractions that occur during labor and the less powerful contractions (or cramps) that help to expel menstrual blood during a woman's period. Anteriorly directed myometrial contractions also occur near the time of ovulation, and are thought to possibly facilitate the transport of sperm through the female reproductive tract.

The innermost layer of the uterus is called the endometrium. The endometrium contains a connective tissue lining, the lamina propria, which is covered by epithelial tissue that lines the lumen. Structurally, the endometrium consists of two layers: the stratum basalis and the stratum functionalis (the basal and functional layers). The stratum basalis layer is part of the lamina propria and is adjacent to the myometrium; this layer does not shed during menses. In contrast, the thicker stratum functionalis layer contains the glandular portion of the lamina propria and the endothelial tissue that lines the uterine lumen. It is the stratum functionalis that grows and thickens in response to increased levels of estrogen and progesterone. In the luteal phase of the menstrual cycle, special branches off of the uterine artery called spiral arteries supply the thickened stratum functionalis. This inner functional layer provides the proper site of implantation for the fertilized egg, and—should fertilization not occur—it is only the stratum functionalis layer of the endometrium that sheds during menstruation.

Recall that during the follicular phase of the ovarian cycle, the tertiary follicles are growing and secreting estrogen. At the same time, the stratum functionalis of the endometrium is thickening to prepare for a potential implantation. The post-ovulatory increase in progesterone, which characterizes the luteal phase, is key for maintaining a thick stratum functionalis. As long as a functional corpus luteum is present in the ovary, the endometrial lining is prepared for implantation. Indeed, if an embryo implants, signals are sent to the corpus luteum to continue secreting progesterone to maintain the endometrium, and thus maintain the pregnancy. If an embryo does not implant, no signal is sent to the corpus luteum and it degrades, ceasing progesterone production and ending the luteal phase. Without progesterone, the endometrium thins and, under the influence of prostaglandins, the spiral arteries of the endometrium constrict and rupture, preventing oxygenated blood from reaching the endometrial tissue. As a result, endometrial tissue dies and blood, pieces of the endometrial tissue, and white blood cells are shed through the vagina during menstruation, or the menses. The first menses after puberty, called menarche, can occur either before or after the first ovulation.

The Menstrual Cycle

Now that we have discussed the maturation of the cohort of tertiary follicles in the ovary, the build-up and then shedding of the endometrial lining in the uterus, and the function of the uterine tubes and vagina, we can put everything together to talk about the three phases of the menstrual cycle—the series of changes in which the uterine lining is shed, rebuilds, and prepares for implantation.

The timing of the menstrual cycle starts with the first day of menses, referred to as day one of a woman's period. Cycle length is determined by counting the days between the onset of bleeding in two subsequent cycles. Because the average length of a woman's menstrual cycle is 28 days, this is the time period used to identify the timing of events in the cycle. However, the length of the menstrual cycle varies among women, and even in the same woman from one cycle to the next, typically from 21 to 32 days.

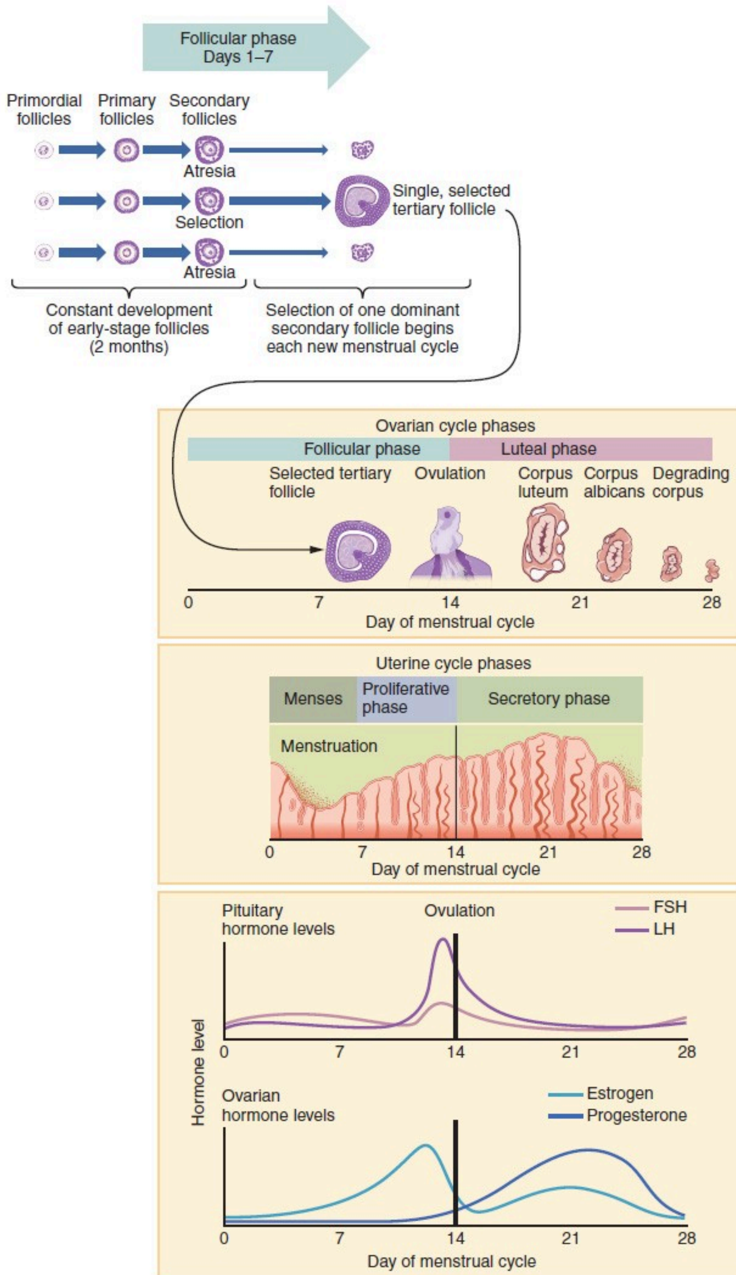
Just as the hormones produced by the granulosa and theca cells of the ovary "drive" the follicular and luteal phases of the ovarian cycle, they also control the three distinct phases of the menstrual cycle. These are the menses phase, the proliferative phase, and the secretory phase.

Menses Phase

The menses phase of the menstrual cycle is the phase during which the lining is shed; that is, the days that the woman menstruates. Although it averages approximately five days, the menses phase can last from 2 to 7 days, or longer. As shown in the diagram below, the menses phase occurs during the early days of the follicular phase of the ovarian cycle, when progesterone, FSH, and LH levels are low. Recall that progesterone concentrations decline as a result of the degradation of the corpus luteum, marking the end of the luteal phase. This decline in progesterone triggers the shedding of the stratum functionalis of the endometrium.

Hormone Levels in Ovarian and Menstrual Cycles

The correlation of the hormone levels and their effects on the female reproductive system is shown in this timeline of the ovarian and menstrual cycles. The menstrual cycle begins at day one with the start of menses. Ovulation occurs around day 14 of a 28-day cycle, triggered by the LH surge.


Follicular phase
Days 1–7
Primordial follicles
Primary follicles
Secondary follicles
Atresia
Selection
Atresia
Single, selected tertiary follicle
Constant development of early-stage follicles (2 months)
Selection of one dominant secondary follicle begins each new menstrual cycle
Ovarian cycle phases
Follicular phase
Luteal phase
Selected tertiary follicle
Ovulation
Corpus luteum
Corpus albicans
Degrading corpus
0
7
14
21
28
Day of menstrual cycle
Uterine cycle phases
Menses
Proliferative phase
Secretory phase
Menstruation
0
7
14
21
28
Day of menstrual cycle
Pituitary hormone levels
Ovulation
FSH
LH
Hormone level
0
7
14
21
28
Ovarian hormone levels
Estrogen
Progesterone
0
7
14
21
28
Day of menstrual cycle

Proliferative Phase

Once menstrual flow ceases, the endometrium begins to proliferate again, marking the beginning of the proliferative phase of the menstrual cycle. It occurs when the granulosa and theca cells of the tertiary follicles begin to produce increased amounts of estrogen. These rising estrogen concentrations stimulate the endometrial lining to rebuild.

Recall that the high estrogen concentrations will eventually lead to a decrease in FSH as a result of negative feedback, resulting in atresia of all but one of the developing tertiary follicles. The switch to positive feedback—which occurs with the elevated estrogen production from the dominant follicle—then stimulates the LH surge that will trigger ovulation. In a typical 28-day menstrual cycle, ovulation occurs on day 14. Ovulation marks the end of the proliferative phase as well as the end of the follicular phase.

Secretory Phase

In addition to prompting the LH surge, high estrogen levels increase the uterine tube contractions that facilitate the pick-up and transfer of the ovulated oocyte. High estrogen levels also slightly decrease the acidity of the vagina, making it more hospitable to sperm. In the ovary, the luteinization of the granulosa cells of the collapsed follicle forms the progesterone-producing corpus luteum, marking the beginning of the luteal phase of the ovarian cycle. In the uterus, progesterone from the corpus luteum begins the secretory phase of the menstrual cycle, in which the endometrial lining prepares for implantation. Over the next 10 to 12 days, the endometrial glands secrete a fluid rich in glycogen. If fertilization has occurred, this fluid will nourish the ball of cells now developing from the zygote.

At the same time, the spiral arteries develop to provide blood to the thickened stratum functionalis.

If no pregnancy occurs within approximately 10 to 12 days, the corpus luteum will degrade into the corpus albicans. Levels of both estrogen and progesterone will fall, and the endometrium will grow thinner. Prostaglandins will be secreted that cause constriction of the spiral arteries, reducing oxygen supply. The endometrial tissue will die, resulting in menses—or the first day of the next cycle.

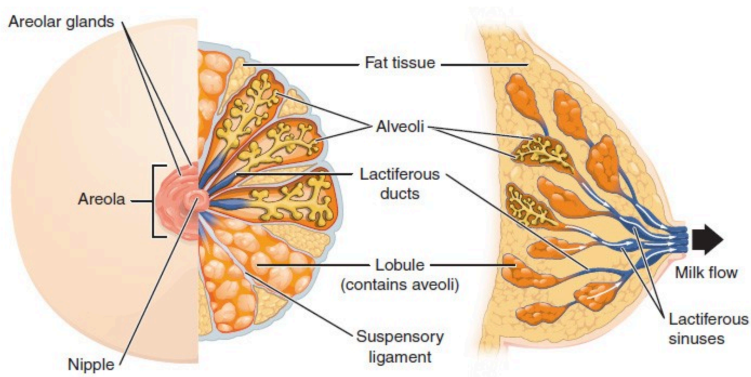
The Breasts

Whereas the breasts are located far from the other female reproductive organs, they are considered accessory organs of the female reproductive system. The function of the breasts is to supply milk to an infant in a process called lactation. The external features of the breast include a nipple surrounded by a pigmented areola, whose coloration may deepen during pregnancy. The areola is typically circular and can vary in size from 25 to 100 mm in diameter. The areolar region is characterized by small, raised areolar glands that secrete lubricating fluid during lactation to protect the nipple from chafing. When a baby nurses, or draws milk from the breast, the entire areolar region is taken into the mouth.

Breast milk is produced by the mammary glands, which are modified sweat glands. The milk itself exits the breast through the nipple via 15 to 20 lactiferous ducts that open on the surface of the nipple. These lactiferous ducts each extend to a lactiferous sinus that connects to a glandular lobe within the breast itself that contains groups of milk-secreting cells in clusters called alveoli. The clusters can change in size depending on the amount of milk in the alveolar lumen. Once milk is made in the alveoli, stimulated myoepithelial cells that surround the alveoli contract to push the milk to the lactiferous sinuses. From here, the baby can draw milk through the lactiferous ducts by suckling. The lobes themselves are surrounded by fat tissue, which determines the size of the breast; breast size differs between individuals and does not affect the amount of milk produced. Supporting the breasts are multiple bands of connective tissue called suspensory ligaments that connect the breast tissue to the dermis of the overlying skin.

Anatomy of the Breast

During lactation, milk moves from the alveoli through the lactiferous ducts to the nipple.



During the normal hormonal fluctuations in the menstrual cycle, breast tissue responds to changing levels of estrogen and progesterone, which can lead to swelling and breast tenderness in some individuals, especially during the secretory phase. If pregnancy occurs, the increase in hormones leads to further development of the mammary tissue and enlargement of the breasts.

Hormonal Birth Control

Birth control pills take advantage of the negative feedback system that regulates the ovarian and menstrual cycles to stop ovulation and prevent pregnancy. Typically they work by providing a constant level of both estrogen and progesterone, which negatively feeds back onto the hypothalamus and pituitary, thus preventing the release of FSH and LH. Without FSH, the follicles do not mature, and without the LH surge, ovulation does not occur. Although the estrogen in birth control pills does stimulate some thickening of the endometrial wall, it is reduced compared with a normal cycle and is less likely to support implantation.

Some birth control pills contain 21 active pills containing hormones, and 7 inactive pills (placebos). The decline in hormones during the week that the woman takes the placebo pills triggers menses, although it is typically lighter than a normal menstrual flow because of the reduced endometrial thickening. Newer types of birth control pills have been developed that deliver low-dose estrogens and progesterone for the entire cycle (these are meant to be taken 365 days a year), and menses never occurs. While some women prefer to have the proof of a lack of pregnancy that a monthly period provides, menstruation every 28 days is not required for health reasons, and there are no reported adverse effects of not having a menstrual period in an otherwise healthy individual.

Because birth control pills function by providing constant estrogen and progesterone levels and disrupting negative feedback, skipping even just one or two pills at certain points of the cycle (or even being several hours late taking the pill) can lead to an increase in FSH and LH and result in ovulation. It is important, therefore, that the woman follow the directions on the birth control pill package to successfully prevent pregnancy.

88. Age Related Changes to the Reproductive System

Female Reproductive System

Female fertility (the ability to conceive) peaks when women are in their twenties, and is slowly reduced until a women reaches 35 years of age. After that time, fertility declines more rapidly, until it ends completely at the end of menopause. Menopause is the cessation of the menstrual cycle that occurs as a result of the loss of ovarian follicles and the hormones that they produce. A woman is considered to have completed menopause if she has not menstruated in a full year. After that point, she is considered postmenopausal. The average age for this change is consistent worldwide at between 50 and 52 years of age, but it can normally occur in a woman's forties, or later in her fifties. Poor health, including smoking, can lead to earlier loss of fertility and earlier menopause.

As a woman reaches the age of menopause, depletion of the number of viable follicles in the ovaries due to atresia affects the hormonal regulation of the menstrual cycle. During the years leading up to menopause, there is a decrease in the levels of the hormone inhibin, which normally participates in a negative feedback loop to the pituitary to control the production of FSH. The menopausal decrease in inhibin leads to an increase in FSH. The presence of FSH stimulates more follicles to grow and secrete estrogen. Because small, secondary follicles also respond to increases in FSH levels, larger numbers of follicles are stimulated to grow; however, most undergo atresia and die. Eventually, this process leads to the depletion of all follicles in the ovaries, and the production of estrogen falls off dramatically. It is primarily the lack of estrogens that leads to the symptoms of menopause.

The earliest changes occur during the menopausal transition, often referred to as peri-menopause, when a women's cycle becomes irregular but does not stop entirely. Although the levels of estrogen are still nearly the same as before the transition, the level of progesterone produced by the corpus luteum is reduced. This decline in progesterone can lead to abnormal growth, or hyperplasia, of the endometrium. This condition is a concern because it increases the risk of developing endometrial cancer. Two harmless conditions that can develop during the transition are uterine fibroids, which are benign masses of cells, and irregular bleeding. As estrogen levels change, other symptoms that occur are hot flashes and night sweats, trouble sleeping, vaginal dryness, mood swings, difficulty focusing, and thinning of hair on the head along with the growth of more hair on the face. Depending on the individual, these symptoms can be entirely absent, moderate, or severe.

After menopause, lower amounts of estrogens can lead to other changes. Cardiovascular disease becomes as prevalent in women as in men, possibly because estrogens reduce the amount of cholesterol in the blood vessels. When estrogen is lacking, many women find that they suddenly have problems with high cholesterol and the cardiovascular issues that accompany it. Osteoporosis is another problem because bone density decreases rapidly in the first years after menopause. The reduction in bone density leads to a higher incidence of fractures.

Hormone therapy (HT), which employs medication (synthetic estrogens and progestins) to increase estrogen and progestin levels, can alleviate some of the symptoms of menopause. In 2002, the Women's Health Initiative began a study to observe women for the long-term outcomes of hormone replacement therapy over 8.5 years. However, the study was prematurely terminated after 5.2 years because of evidence of a higher than normal risk of breast cancer in patients taking estrogen-only HT. The potential positive effects on cardiovascular disease were also not realized in the estrogen-only patients. The results of other hormone replacement studies over the last 50 years, including a 2012 study that followed over 1,000 menopausal women for 10 years, have shown cardiovascular benefits from estrogen and no increased risk for cancer. Some researchers believe that the age group tested in the 2002 trial may have been too old to benefit from the therapy, thus skewing the results. In the meantime, intense debate and study of the benefits and risks of replacement therapy is ongoing. Current guidelines approve HT for the reduction of hot flashes or flushes, but this treatment is generally only considered when women first start showing signs of menopausal changes, is used in the lowest dose possible for the shortest time possible (5 years or less), and it is suggested that women on HT have regular pelvic and breast exams.

Male Reproductive System

As a result of the cumulative changes to the male reproductive system many men experience depression, mood swings, and a general feeling of uneasiness as they approach their 50s or 60s. This time period is referred to as andropause, or male menopause. While the testes continue to function during and after this period men may experience impotence. Regardless, even at advanced ages, some men are able to have sexual relationships and may even remain fertile.

Physiologically the testes decrease in size and firmness with age. This is associated with a gradual age related decline in the secretion of testosterone. Simultaneously there is a decrease in sexual desire. By the age of 60 there is a 30% reduction in sperm count. The prostate gland atrophies between the ages of 50 and 60 years of age, which reduces the secretory capacity. By the age of 70 the prostate gland may enlarge due to masses of potentially cancerous tissue. Additionally the seminal vesicles decrease in weight and storage capacity after age 60 and the penis undergoes some atrophy with age.

89. Age Related Dysfunctions to the Reproductive System

Cancer

Research over many years has confirmed that cervical cancer is most often caused by a sexually transmitted infection with human papillomavirus (HPV). There are over 100 related viruses in the HPV family, and the characteristics of each strain determine the outcome of the infection. In all cases, the virus enters body cells and uses its own genetic material to take over the host cell's metabolic machinery and produce more virus particles.

HPV infections are common in both men and women. Indeed, a recent study determined that 42.5 percent of females had HPV at the time of testing. These women ranged in age from 14 to 59 years and differed in race, ethnicity, and number of sexual partners. Of note, the prevalence of HPV infection was 53.8 percent among women aged 20 to 24 years, the age group with the highest infection rate.

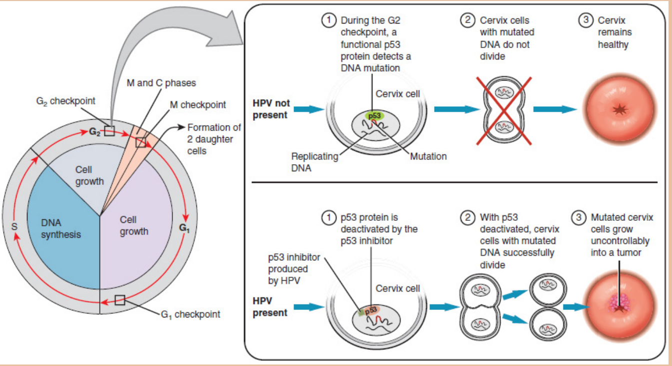
HPV strains are classified as high or low risk according to their potential to cause cancer.

Though most HPV infections do not cause disease, the disruption of normal cellular functions in the low-risk forms of HPV can cause the male or female human host to develop genital warts. Often, the body is able to clear an HPV infection by normal immune responses within 2 years. However, the more serious, high-risk infection by certain types of HPV can result in cancer of the cervix. Infection with either of the cancer-causing variants HPV 16 or HPV 18 has been linked to more than 70 percent of all cervical cancer diagnoses. Although even these high-risk HPV strains can be cleared from the body over time, infections persist in some individuals. If this happens, the HPV infection can influence the cells of the cervix to develop precancerous changes.

Risk factors for cervical cancer include having unprotected sex; having multiple sexual partners; a first sexual experience at a younger age, when the cells of the cervix are not fully mature; failure to receive the HPV vaccine; a compromised immune system; and smoking. The risk of developing cervical cancer is doubled with cigarette smoking.

Development of Cervical Cancer

In most cases, cells infected with the HPV virus heal on their own. In some cases, however, the virus continues to spread and becomes an invasive cancer.



When the high-risk types of HPV enter a cell, two viral proteins are used to neutralize proteins that the host cells use as checkpoints in the cell cycle. The best studied of these proteins is p53. In a normal cell, p53 detects DNA damage in the cell's genome and either halts the progression of the cell cycle—allowing time for DNA repair to occur—or initiates apoptosis. Both of these processes prevent the accumulation of mutations in a cell's genome. High-risk HPV can neutralize p53, keeping the cell in a state in which fast growth is possible and impairing apoptosis, allowing mutations to accumulate in the cellular DNA.

The prevalence of cervical cancer in the United States is very low because of regular screening exams called pap smears. Pap smears sample cells of the cervix, allowing the detection of abnormal cells. If pre-cancerous cells are detected, there are several highly effective techniques that are currently in use to remove them before they pose a danger. However, women in developing countries often do not have access to regular pap smears. As a result, these women account for as many as 80 percent of the cases of cervical cancer worldwide.

In 2006, the first vaccine against the high-risk types of HPV was approved. There are now two HPV vaccines available: Gardasil® and Cervarix®. Whereas these vaccines were initially only targeted for women, because HPV is sexually transmitted, both men and women require vaccination for this approach to achieve its maximum efficacy. A recent study suggests that the HPV vaccine has cut the rates of HPV infection by the four targeted strains at least in half. Unfortunately, the high cost of manufacturing the vaccine is currently limiting access to many women worldwide.

Atrophic Vaginitis

Atrophic vaginitis is inflammation of the vagina due to degenerative changes. This is dues to the age related thinning and dryness of the vaginal walls in postmenopausal women.

Prolapse of the Uterus

Prolapse of the uterus is a result of weakness of the ligaments supporting the organ. It is characterized by the uterus dropping through the cervical canal and protrudes into the vagina. Uterine prolapse may be corrected surgically or by the placement of a supportive instrument called a pessary in the vagina.

Impotence

Impotence, or Erectile dysfunction (ED), is a condition in which a man has difficulty either initiating or maintaining an erection. The combined prevalence of minimal, moderate, and complete ED is approximately 40 percent in men at age 40, and reaches nearly 70 percent by 70 years of age. In addition to aging, ED is associated with diabetes, vascular disease, psychiatric disorders, prostate disorders, the use of some drugs such as certain antidepressants, and problems with the testes resulting in low testosterone concentrations. These physical and emotional conditions can lead to interruptions in the vasodilation pathway and result in an inability to achieve an erection.

Recall that the release of NO induces relaxation of the smooth muscles that surround the penile arteries, leading to the vasodilation necessary to achieve an erection. To reverse the process of vasodilation, an enzyme called phosphodiesterase (PDE) degrades a key component of the NO signaling pathway called cGMP. There are several different forms of this enzyme, and PDE type 5 is the type of PDE found in the tissues of the penis. Scientists discovered that inhibiting PDE5 increases blood flow, and allows vasodilation of the penis to occur.

PDEs and the vasodilation signaling pathway are found in the vasculature in other parts of the body. In the 1990s, clinical trials of a PDE5 inhibitor called sildenafil were initiated to treat hypertension and angina pectoris (chest pain caused by poor blood flow through the heart). The trial showed that the drug was not effective at treating heart conditions, but many men experienced erection and priapism (erection lasting longer than 4 hours). Because of this, a clinical trial was started to investigate the ability of sildenafil to promote erections in men suffering from ED. In 1998, the FDA approved the drug, marketed as Viagra®. Since approval of the drug, sildenafil and similar PDE inhibitors now generate over a billion dollars a year in sales, and are reported to be effective in treating approximately 70 to 85 percent of cases of ED. Importantly, men with health problems—especially those with cardiac disease taking nitrates—should avoid Viagra or talk to their physician to find out if they are a candidate for the use of this drug, as deaths have been reported for at-risk users.

90. Glossary: The Reproductive System

Glossary

alveoli (of the breast) milk-secreting cells in the mammary gland

ampulla (of the uterine tube) middle portion of the uterine tube in which fertilization often occurs

antrum fluid-filled chamber that characterizes a mature tertiary (antral) follicle

areola highly pigmented, circular area surrounding the raised nipple and containing areolar glands that secrete fluid important for lubrication during suckling

Bartholin's glands (also, greater vestibular glands) glands that produce a thick mucus that maintains moisture in the vulva area; also referred to as the greater vestibular glands

blood–testis barrier tight junctions between Sertoli cells that prevent bloodborne pathogens from gaining access to later stages of spermatogenesis and prevent the potential for an autoimmune reaction to haploid sperm

body of uterus middle section of the uterus

broad ligament wide ligament that supports the uterus by attaching laterally to both sides of the uterus and pelvic wall

bulbourethral glands (also, Cowper's glands) glands that secrete a lubricating mucus that cleans and lubricates the urethra prior to and during ejaculation

cervix elongate inferior end of the uterus where it connects to the vagina

clitoris (also, glans clitoris) nerve-rich area of the vulva that contributes to sexual sensation during intercourse

corpus albicans nonfunctional structure remaining in the ovarian stroma following structural and functional regression of the corpus luteum

corpus cavernosum either of two columns of erectile tissue in the penis that fill with blood during an erection

corpus luteum transformed follicle after ovulation that secretes progesterone

corpus spongiosum (plural = corpora cavernosa) column of erectile tissue in the penis that fills with blood during an erection and surrounds the penile urethra on the ventral portion of the penis

ductus deferens (also, vas deferens) duct that transports sperm from the epididymis through the spermatic cord and into the ejaculatory duct; also referred as the vas deferens

ejaculatory duct duct that connects the ampulla of the ductus deferens with the duct of the seminal vesicle at the prostatic urethra

endometrium inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses

epididymis (plural = epididymides) coiled tubular structure in which sperm start to mature and are stored until ejaculation

fimbriae fingerlike projections on the distal uterine tubes

follicle ovarian structure of one oocyte and surrounding granulosa (and later theca) cells

folliculogenesis development of ovarian follicles from primordial to tertiary under the stimulation of gonadotropins

fundus (of the uterus) domed portion of the uterus that is superior to the uterine tubes

gamete haploid reproductive cell that contributes genetic material to form an offspring

glans penis bulbous end of the penis that contains a large number of nerve endings

gonadotropin-releasing hormone (GnRH) hormone released by the hypothalamus that regulates the production of follicle-stimulating hormone and luteinizing hormone from the pituitary gland

gonads reproductive organs (testes in men and ovaries in women) that produce gametes and reproductive hormones

granulosa cells supportive cells in the ovarian follicle that produce estrogen

hymen membrane that covers part of the opening of the vagina

infundibulum (of the uterine tube) wide, distal portion of the uterine tube terminating in fimbriae

inguinal canal opening in abdominal wall that connects the testes to the abdominal cavity

isthmus narrow, medial portion of the uterine tube that joins the uterus

labia majora hair-covered folds of skin located behind the mons pubis

labia minora thin, pigmented, hairless flaps of skin located medial and deep to the labia majora

lactiferous ducts ducts that connect the mammary glands to the nipple and allow for the transport of milk

lactiferous sinus area of milk collection between alveoli and lactiferous duct

Leydig cells cells between the seminiferous tubules of the testes that produce testosterone; a type of interstitial cell

mammary glands glands inside the breast that secrete milk

menarche first menstruation in a pubertal female

menses shedding of the inner portion of the endometrium out though the vagina; also referred to as menstruation

menses phase phase of the menstrual cycle in which the endometrial lining is shed

menstrual cycle approximately 28-day cycle of changes in the uterus consisting of a menses phase, a proliferative phase, and a secretory phase

mons pubis mound of fatty tissue located at the front of the vulva

Müllerian duct duct system present in the embryo that will eventually form the internal female reproductive structures

myometrium smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood

oocyte cell that results from the division of the oogonium and undergoes meiosis I at the LH surge and meiosis II at fertilization to become a haploid ovum

oogenesis process by which oogonia divide by mitosis to primary oocytes, which undergo meiosis to produce the secondary oocyte and, upon fertilization, the ovum

oogonia ovarian stem cells that undergo mitosis during female fetal development to form primary oocytes

ovarian cycle approximately 28-day cycle of changes in the ovary consisting of a follicular phase and a luteal phase

ovaries female gonads that produce oocytes and sex steroid hormones (notably estrogen and progesterone)

ovulation release of a secondary oocyte and associated granulosa cells from an ovary

ovum haploid female gamete resulting from completion of meiosis II at fertilization

penis male organ of copulation

perimetrium outer epithelial layer of uterine wall

polar body smaller cell produced during the process of meiosis in oogenesis

prepuce (also, foreskin) flap of skin that forms a collar around, and thus protects and lubricates, the glans penis; also referred as the foreskin

primary follicles ovarian follicles with a primary oocyte and one layer of cuboidal granulosa cells

primordial follicles least developed ovarian follicles that consist of a single oocyte and a single layer of flat (squamous) granulosa cells

proliferative phase phase of the menstrual cycle in which the endometrium proliferates

prostate gland doughnut-shaped gland at the base of the bladder surrounding the urethra and contributing fluid to semen during ejaculation

puberty life stage during which a male or female adolescent becomes anatomically and physiologically capable of reproduction

rugae (of the vagina) folds of skin in the vagina that allow it to stretch during intercourse and childbirth

scrotum external pouch of skin and muscle that houses the testes

secondary follicles ovarian follicles with a primary oocyte and multiple layers of granulosa cells

secondary sex characteristics physical characteristics that are influenced by sex steroid hormones and have supporting roles in reproductive function

secretory phase phase of the menstrual cycle in which the endometrium secretes a nutrient-rich fluid in preparation for implantation of an embryo

semen ejaculatory fluid composed of sperm and secretions from the seminal vesicles, prostate, and bulbourethral glands

seminal vesicle gland that produces seminal fluid, which contributes to semen

seminiferous tubules tube structures within the testes where spermatogenesis occurs

Sertoli cells cells that support germ cells through the process of spermatogenesis; a type of sustentacular cell

sperm (also, spermatozoon) male gamete

spermatic cord bundle of nerves and blood vessels that supplies the testes; contains ductus deferens

spermatid immature sperm cells produced by meiosis II of secondary spermatocytes

spermatocyte cell that results from the division of spermatogonium and undergoes meiosis I and meiosis II to form spermatids

spermatogenesis formation of new sperm, occurs in the seminiferous tubules of the testes

spermatogonia (singular = spermatogonium) diploid precursor cells that become sperm

spermiogenesis transformation of spermatids to spermatozoa during spermatogenesis

suspensory ligaments bands of connective tissue that suspend the breast onto the chest wall by attachment to the overlying dermis

tertiary follicles (also, antral follicles) ovarian follicles with a primary or secondary oocyte, multiple layers of granulosa cells, and a fully formed antrum

testes (singular = testis) male gonads

theca cells estrogen-producing cells in a maturing ovarian follicle

uterine tubes (also, fallopian tubes or oviducts) ducts that facilitate transport of an ovulated oocyte to the uterus

uterus muscular hollow organ in which a fertilized egg develops into a fetus

vagina tunnel-like organ that provides access to the uterus for the insertion of semen and from the uterus for the birth of a baby

vulva external female genitalia

Wolffian duct duct system present in the embryo that will eventually form the internal male reproductive structures

PART XV

CHAPTER 15: THE ENDOCRINE SYSTEM

91. The Endocrine System

Neural and Endocrine Signaling

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

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

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

The Following Chart compares the Endocrine and Nervous Systems.

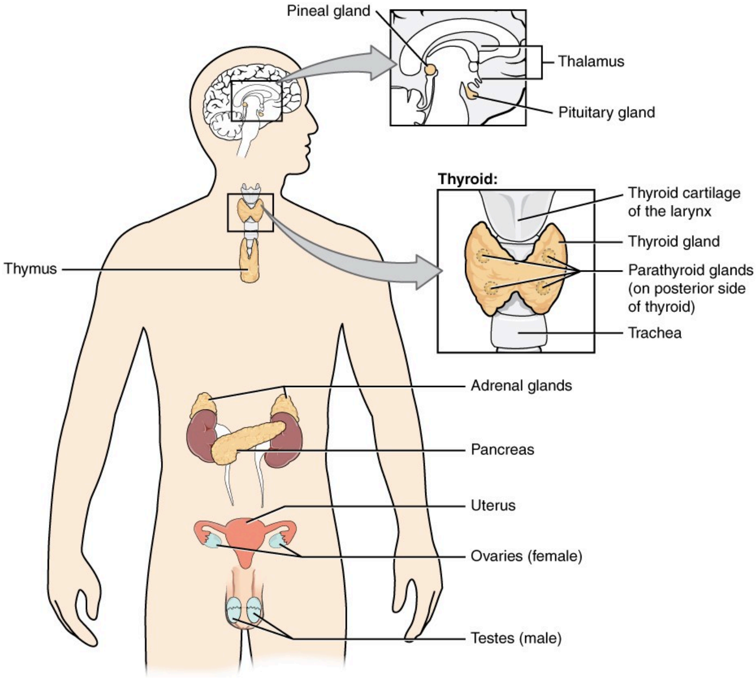
Endocrine and Nervous Systems		
	Endocrine system	**Nervous system**
Signaling mechanism(s)	Chemical	Chemical/electrical
Primary chemical signal	Hormones	Neurotransmitters
Distance traveled	Long or short	Always short
Response time	Fast or slow	Always fast
Environment targeted	Internal	Internal and external

Structures of the Endocrine System

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

Endocrine System

Endocrine glands and cells are located throughout the body and play an important role in homeostasis.



The ductless endocrine glands are not to be confused with the body's exocrine system, whose glands release their secretions through ducts. Examples of exocrine glands include the sebaceous and sweat glands of the skin. As just noted, the pancreas also has an exocrine function: most of its cells secrete pancreatic juice through the pancreatic and accessory ducts to the lumen of the small intestine.

Other Types of Chemical Signaling

In endocrine signaling, hormones secreted into the extracellular fluid diffuse into the blood or lymph, and can then travel great distances throughout the body. In contrast, autocrine signaling takes place within the same cell. An autocrine (auto- = “self”) is a chemical that elicits a response in the same cell that secreted it. Interleukin-1, or IL-1, is a signaling molecule that plays an important role in inflammatory response. The cells that secrete IL-1 have receptors on their cell surface that bind these molecules, resulting in autocrine signaling.

Local intercellular communication is the province of the paracrine, also called a paracrine factor, which is a chemical that induces a response in neighboring cells. Although paracrines may enter the bloodstream, their concentration is generally too low to elicit a response from distant tissues. A familiar example to those with asthma is histamine, a paracrine that is released by immune cells in the bronchial tree. Histamine causes the smooth muscle cells of the bronchi to constrict, narrowing the airways. Another example is the neurotransmitters of the nervous system, which act only locally within the synaptic cleft.

92. Hormones

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

Endocrine Glands and Their Major Hormones

Endocrine gland	Associated hormones	Chemical class	Effect
Pituitary (anterior)	Growth hormone (GH)	Protein	Promotes growth of body tissues
Pituitary (anterior)	Prolactin (PRL)	Peptide	Promotes milk production
Pituitary (anterior)	Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates thyroid hormone release
Pituitary (anterior)	Adrenocorticotropic hormone (ACTH)	Peptide	Stimulates hormone release by adrenal cortex
Pituitary (anterior)	Follicle-stimulating hormone (FSH)	Glycoprotein	Stimulates gamete production
Pituitary (anterior)	Luteinizing hormone (LH)	Glycoprotein	Stimulates androgen production by gonads
Pituitary (posterior)	Antidiuretic hormone (ADH)	Peptide	Stimulates water reabsorption by kidneys
Pituitary (posterior)	Oxytocin	Peptide	Stimulates uterine contractions during childbirth
Thyroid	Thyroxine (T_4), triiodothyronine (T_3)	Amine	Stimulate basal metabolic rate
Thyroid	Calcitonin	Peptide	Reduces blood Ca^{2+} levels
Parathyroid	Parathyroid hormone (PTH)	Peptide	Increases blood Ca^{2+} levels
Adrenal (cortex)	Aldosterone	Steroid	Increases blood Na^{+} levels
Adrenal (cortex)	Cortisol, corticosterone, cortisone	Steroid	Increase blood glucose levels
Adrenal (medulla)	Epinephrine, norepinephrine	Amine	Stimulate fight-or-flight response
Pineal	Melatonin	Amine	Regulates sleep cycles

Endocrine Glands and Their Major Hormones			
Endocrine gland	**Associated hormones**	**Chemical class**	**Effect**
Pancreas	Insulin	Protein	Reduces blood glucose levels
Pancreas	Glucagon	Protein	Increases blood glucose levels
Testes	Testosterone	Steroid	Stimulates development of male secondary sex characteristics and sperm production
Ovaries	Estrogens and progesterone	Steroid	Stimulate development of female secondary sex characteristics and prepare the body for childbirth

Types of Hormones

The hormones of the human body can be divided into two major groups on the basis of their chemical structure. Hormones derived from amino acids include amines, peptides, and proteins. Those derived from lipids include steroids. These chemical groups affect a hormone's distribution, the type of receptors it binds to, and other aspects of its function.

This table shows the chemical structure of amine hormones, peptide hormones, protein hormones, and steroid hormones. Amine hormones are amino acids with modified side groups. The example given is norepinephrine, which contains the NH two group typical of an amino acid, along with a hydroxyl (OH) group. The carboxyl group typical of most amino acids is replaced with a benzene ring, depicted as a hexagon of carbons that are connected by alternating single and double bonds. Peptide hormones are composed of short chains of amino acids. The example given is oxytocin, which has a chain of the following amino acids: GLY, LEU, PRO. The PRO is the bottom of the chain, which connects to a ring of the following amino acids: CYS, CYS, TYR, ILE, GLU, and ASP. Protein hormones are composed of long chains of linked amino acids. The example given is human growth hormone, which is composed of a bundle of amino acid strands, some thread-like, some coiled, and some in flat, folded sheets. Finally, steroid hormones are derived from the lipid cholesterol. Testosterone and progesterone are given as examples, which each contain several hexagonal and pentagonal carbon rings linked together.

Amine, Peptide, Protein, and Steroid Hormone Structure

Amine Hormones

Hormones derived from the modification of amino acids are referred to as amine hormones. Typically, the original structure of the amino acid is modified such that a –COOH, or carboxyl, group is removed, whereas the $-NH_3^+$, or amine, group remains.

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

Peptide and Protein Hormones

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

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

Steroid Hormones

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

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

Pathways of Hormone Action

The message a hormone sends is received by a hormone receptor, a protein located either inside the cell or within the cell membrane. The receptor will process the message by initiating other signaling events or cellular mechanisms that result in the target cell's response. Hormone receptors recognize molecules with specific shapes and side groups, and respond only to those hormones that are recognized. The same type of receptor may be located on cells in different body tissues, and trigger somewhat different responses. Thus, the response triggered by a hormone depends not only on the hormone, but also on the target cell.

Once the target cell receives the hormone signal, it can respond in a variety of ways. The response may include the stimulation of protein synthesis, activation or deactivation of enzymes, alteration in the permeability of the cell membrane, altered rates of mitosis and cell growth, and stimulation of the secretion of products. Moreover, a single hormone may be capable of inducing different responses in a given cell.

Pathways Involving Intracellular Hormone Receptors

Intracellular hormone receptors are located inside the cell. Hormones that bind to this type of receptor must be able to cross the cell membrane. Steroid hormones are derived from cholesterol and therefore can readily diffuse through the lipid bilayer of the cell membrane to reach the intracellular receptor. Thyroid hormones, which contain benzene rings studded with iodine, are also lipid-soluble and can enter the cell.

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

This illustration shows the steps involved with the binding of lipid-soluble hormones. Lipid-soluble hormones, such as steroid hormones, easily diffuse through the cell membrane. The hormone binds to its receptor in the cytosol, forming a receptor-hormone complex. The receptor-hormone complex then enters the nucleus and binds to the target gene on the cell's DNA. Transcription of the gene creates a messenger RNA that is translated into the desired protein within the cytoplasm. It is these proteins that alter the cell's activity.

Binding of Lipid-Soluble Hormones

A steroid hormone directly initiates the production of proteins within a target cell. Steroid hormones easily diffuse through the cell membrane. The hormone binds to its receptor in the cytosol, forming a receptor–hormone complex. The receptor–hormone complex then enters the nucleus and binds to the target gene on the DNA. Transcription of the gene creates a messenger RNA that is translated into the desired protein within the cytoplasm.

Pathways Involving Cell Membrane Hormone Receptors

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

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

This illustration shows the binding of water-soluble hormones. Water-soluble hormones cannot diffuse through the cell membrane. These hormones must bind to a receptor on the outer surface of the cell membrane. The receptor then activates a G protein in the cytoplasm, which travels to and activates adenylyl cyclase. Adenylyl cyclase catalyzes the conversion of ATP to CAMP, the secondary messenger in this pathway. CAMP, in turn, activates protein kinases, which phosphorylate proteins in the cytoplasm. This phosphorylation, shown as a P being added to a polypeptide chain, activates the proteins, allowing them to alter cell activity.

Binding of Water-Soluble Hormones

Water-soluble hormones cannot diffuse through the cell membrane. These hormones must bind to a surface cell-membrane receptor. The receptor then initiates a cell-signaling pathway within the cell involving G proteins, adenylyl cyclase, the secondary messenger cyclic AMP (cAMP), and protein kinases. In the final step, these protein kinases phosphorylate proteins in the cytoplasm. This activates proteins in the cell that carry out the changes specified by the hormone.

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

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

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

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

Factors Affecting Target Cell Response

You will recall that target cells must have receptors specific to a given hormone if that hormone is to trigger a response. But several other factors influence the target cell response. For example, the presence of a significant level of a hormone circulating in the bloodstream can cause its target cells to decrease their number of receptors for that hormone. This process is calleddownregulation, and it allows cells to become less reactive to the excessive hormone levels. When the level of a hormone is chronically reduced, target cells engage in upregulation to increase their number of receptors. This process allows cells to be more sensitive to the hormone that is present. Cells can also alter the sensitivity of the receptors themselves to various hormones.

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

- The permissive effect, in which the presence of one hormone enables another hormone to act. For example, thyroid hormones have complex permissive relationships with certain reproductive hormones. A dietary deficiency of iodine, a component of thyroid hormones, can therefore affect reproductive system development and functioning.
- The synergistic effect, in which two hormones with similar effects produce an amplified response. In some cases, two hormones are required for an adequate response. For example, two different reproductive hormones—FSH from the pituitary gland and estrogens from the ovaries—are required for the maturation of female ova (egg cells).

- The antagonistic effect, in which two hormones have opposing effects. A familiar example is the effect of two pancreatic hormones, insulin and glucagon. Insulin increases the liver's storage of glucose as glycogen, decreasing blood glucose, whereas glucagon stimulates the breakdown of glycogen stores, increasing blood glucose.

Regulation of Hormone Secretion

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

Role of Feedback Loops

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

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

This diagram shows a negative feedback loop using the example of glucocorticoid regulation in the blood. Step 1 in the cycle is when an imbalance occurs. The hypothalamus perceives low blood concentrations of glucocorticoids in the blood. This is illustrated by there being only 5 glucocorticoids floating in a cross section of an artery. Step 2 in the cycle is hormone release, where the hypothalamus releases corticotropin-releasing hormone (CRH). Step 3 is labeled correction. Here, the CRH release starts a hormone cascade that triggers the adrenal gland to release glucocorticoid into the blood. This allows the blood concentration of glucocorticoid to increase, as illustrated by 8 glucocorticoid molecules now being present in the cross section of the artery. Step 4 is labeled negative feedback. Here, the hypothalamus perceives normal concentrations of glucocorticoids in the blood and stops releasing CRH. This brings blood glucocorticoid levels back to homeostasis.

Negative Feedback Loop

The release of adrenal glucocorticoids is stimulated by the release of hormones from the hypothalamus and pituitary gland. This signaling is inhibited when glucocorticoid levels become elevated by causing negative signals to the pituitary gland and hypothalamus.

Role of Endocrine Gland Stimuli

Reflexes triggered by both chemical and neural stimuli control endocrine activity. These reflexes may be simple, involving only one hormone response, or they may be more complex and involve many hormones, as is the case with the hypothalamic control of various anterior pituitary–controlled hormones.

Humoral stimuli are changes in blood levels of non-hormone chemicals, such as nutrients or ions, which cause the release or inhibition of a hormone to, in turn, maintain homeostasis. For example, osmoreceptors in the hypothalamus detect changes in blood osmolarity (the concentration of solutes in the blood plasma). If blood osmolarity is too high, meaning that the blood is not dilute enough, osmoreceptors signal the hypothalamus to release ADH. The hormone causes the kidneys to reabsorb more water and reduce the volume of urine produced. This reabsorption causes a reduction of the osmolarity of the blood, diluting the blood to the appropriate level. The regulation of blood glucose is another example. High blood glucose levels cause the release of insulin from the pancreas, which increases glucose uptake by cells and liver storage of glucose as glycogen.

An endocrine gland may also secrete a hormone in response to the presence of another hormone produced by a different endocrine gland. Such hormonal stimuli often involve the hypothalamus, which produces releasing and inhibiting hormones that control the secretion of a variety of pituitary hormones.

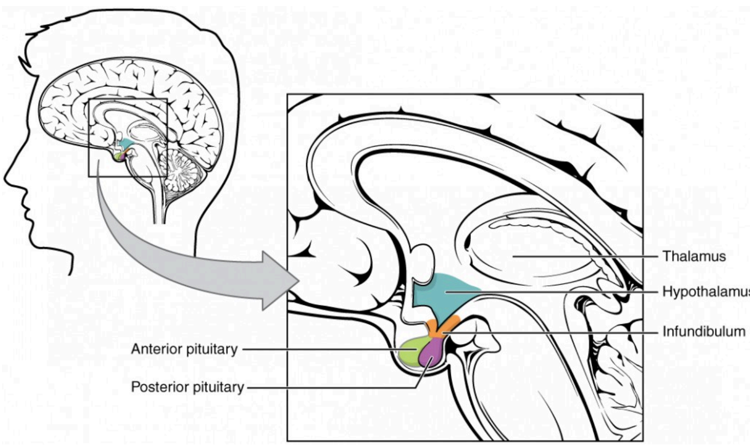
In addition to these chemical signals, hormones can also be released in response to neural stimuli. A common example of neural stimuli is the activation of the fight-or-flight response by the sympathetic nervous system. When an individual perceives danger, sympathetic neurons signal the adrenal glands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

93. The Pituitary Gland and Hypothalamus

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

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

Hypothalamus–Pituitary Complex
The hypothalamus region lies inferior and anterior to the thalamus. It connects to the pituitary gland by the stalk-like infundibulum. The pituitary gland consists of an anterior and posterior lobe, with each lobe secreting different hormones in response to signals from the hypothalamus.



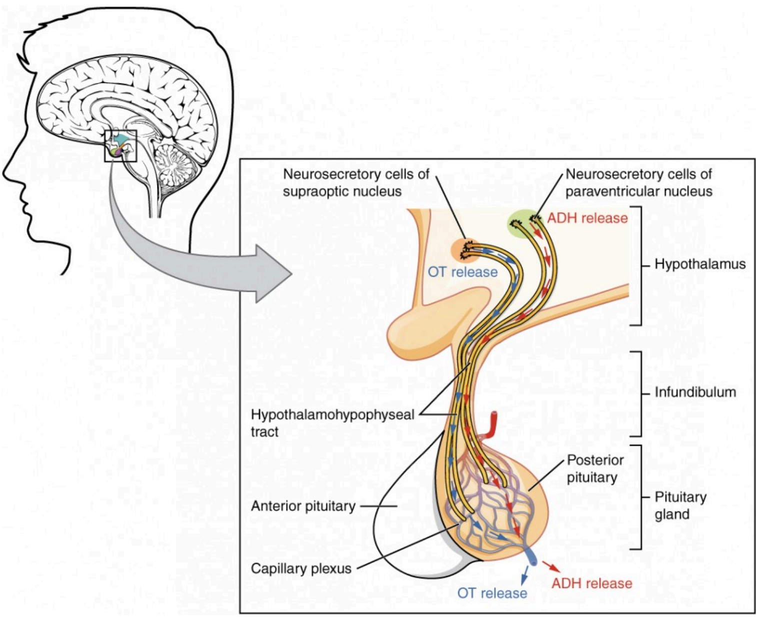
Pituitary Hormones			
Pituitary lobe	**Associated hormones**	**Chemical class**	**Effect**
Anterior	Growth hormone (GH)	Protein	Promotes growth of body tissues
Anterior	Prolactin (PRL)	Peptide	Promotes milk production from mammary glands
Anterior	Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates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

Posterior Pituitary

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

Posterior Pituitary

Neurosecretory cells in the hypothalamus release oxytocin (OT) or ADH into the posterior lobe of the pituitary gland. These hormones are stored or released into the blood via the capillary plexus.



Posterior Pituitary

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

Oxytocin

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

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

Antidiuretic Hormone (ADH)

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

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

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

Anterior Pituitary

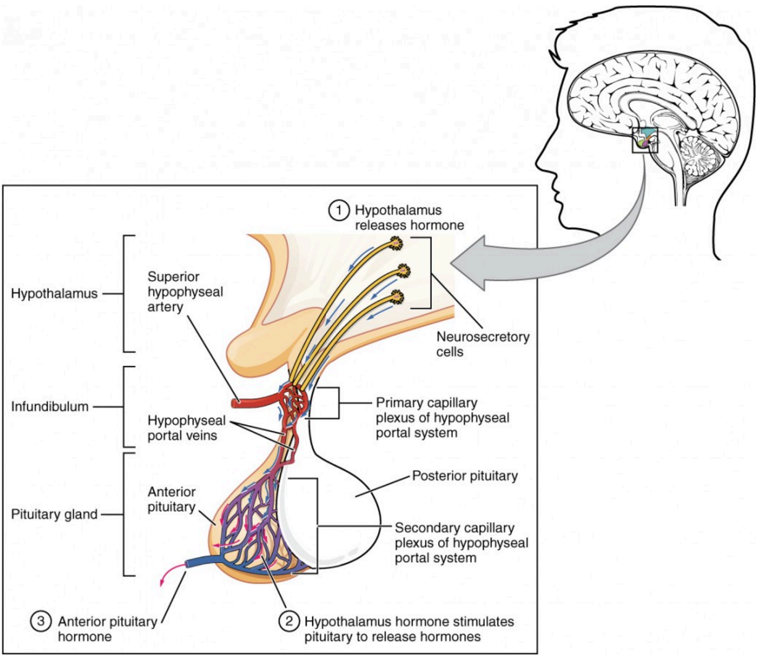
The anterior pituitary originates from the digestive tract in the embryo and migrates toward the brain during fetal development. There are three regions: the pars distalis is the most anterior, the pars intermedia is adjacent to the posterior pituitary, and the pars tuberalis is a slender “tube” that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

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

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

Anterior Pituitary

The anterior pituitary manufactures seven hormones. The hypothalamus produces separate hormones that stimulate or inhibit hormone production in the anterior pituitary. Hormones from the hypothalamus reach the anterior pituitary via the hypophyseal portal system.



Anterior Pituitary

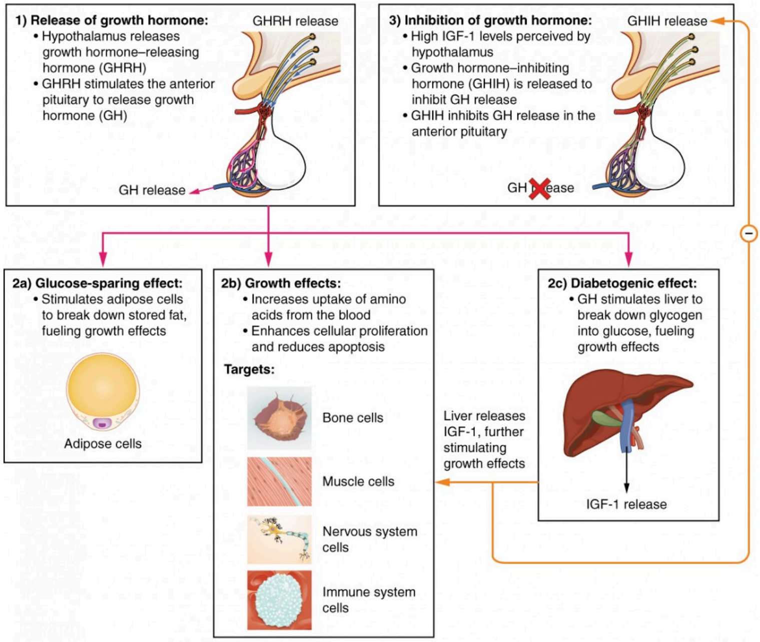
The anterior pituitary produces seven hormones. These are the growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), beta endorphin, and prolactin. Of the hormones of the anterior pituitary, TSH, ACTH,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

Growth Hormone

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

Hormonal Regulation of Growth

Growth hormone (GH) directly accelerates the rate of protein synthesis in skeletal muscle and bones. Insulin-like growth factor 1 (IGF-1) is activated by growth hormone and indirectly supports the formation of new proteins in muscle cells and bone.



Hormonal Regulation of Growth

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

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

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

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

Thyroid-Stimulating Hormone

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

Adrenocorticotropic Hormone

The adrenocorticotropic hormone (ACTH), also called corticotropin, stimulates the adrenal cortex (the more superficial "bark" of the adrenal glands) to secrete corticosteroid hormones such as cortisol.

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

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

Follicle-Stimulating Hormone and Luteinizing Hormone

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

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

Prolactin

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

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

Intermediate Pituitary: Melanocyte-Stimulating Hormone

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

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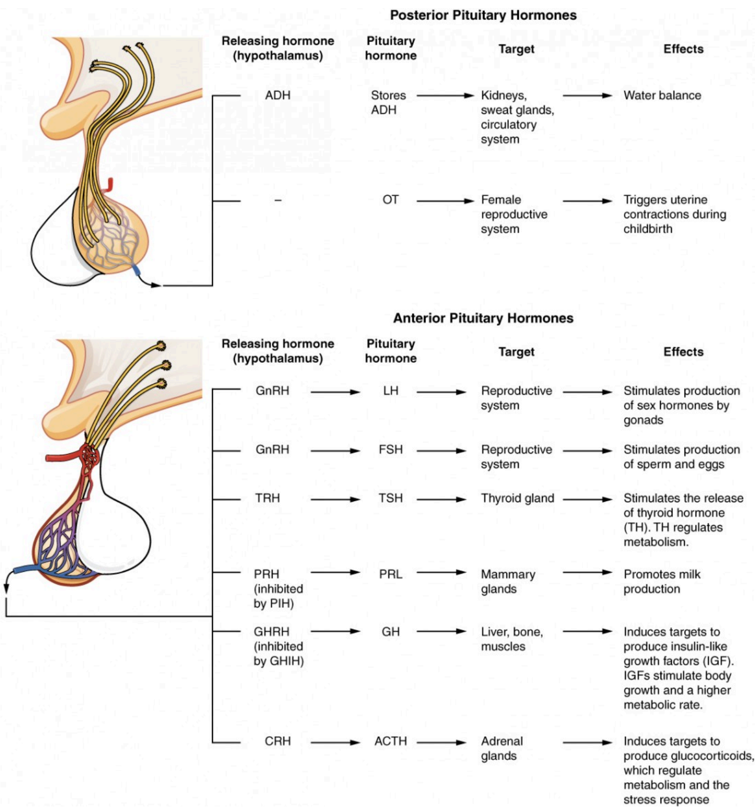


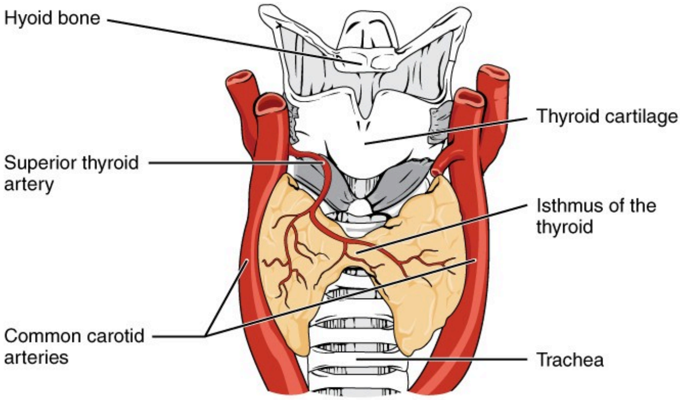
Major Pituitary Hormones Major pituitary hormones and their target organs

94. The Thyroid Gland

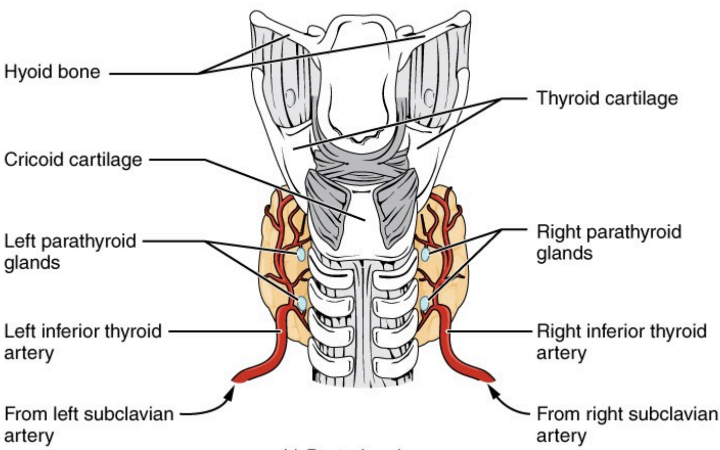
A butterfly-shaped organ, the thyroid gland is located anterior to the trachea, just inferior to the larynx. The medial region, called the isthmus, is flanked by wing-shaped left and right lobes. Each of the thyroid lobes are embedded with parathyroid glands, primarily on their posterior surfaces. The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

Thyroid Gland

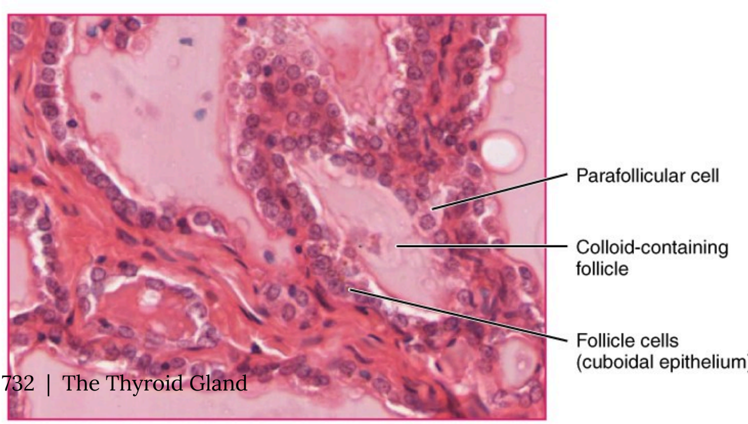
The thyroid gland is located in the neck where it wraps around the trachea. (a) Anterior view of the thyroid gland. (b) Posterior view of the thyroid gland. (c) The glandular tissue is composed primarily of thyroid follicles. The larger parafollicular cells often appear within the matrix of follicle cells. LM × 1332. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



a) Anterior view



b) Posterior view



c) Thyroid follicle cells

Synthesis and Release of Thyroid Hormones

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

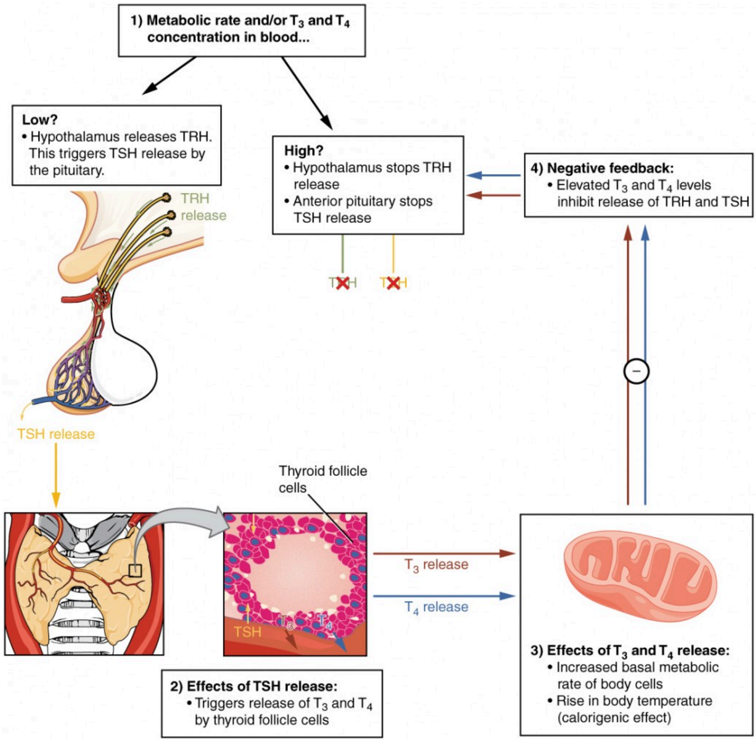
1. Binding of TSH to its receptors in the follicle cells of the thyroid gland causes the cells to actively transport iodide ions (I^{-}) across their cell membrane, from the bloodstream into the cytosol. As a result, the concentration of iodide ions "trapped" in the follicular cells is many times higher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

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

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

Regulation of TH Synthesis

The release of T_3 and T_4 from the thyroid gland is regulated by thyroid-stimulating hormone (TSH). Low blood levels of T_3 and T_4 stimulate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus, which triggers secretion of TSH from the anterior pituitary. In turn, TSH stimulates the thyroid gland to secrete T_3 and T_4. The levels of TRH, TSH, T_3, and T_4 are regulated by a negative feedback system in which increasing levels of T_3 and T_4 decrease the production and secretion of TSH.
Classic Negative Feedback Loop
A classic negative feedback loop controls the regulation of thyroid hormone levels.



Functions of Thyroid Hormones

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

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

Calcitonin

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

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

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

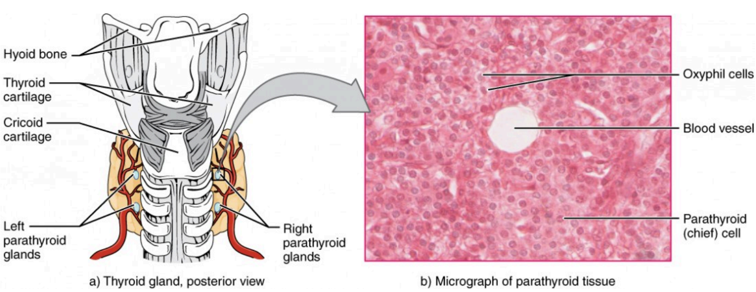
Thyroid Hormones		
Associated hormones	**Chemical class**	**Effect**
Thyroxine (T_4), triiodothyronine (T_3)	Amine	Stimulate basal metabolic rate
Calcitonin	Peptide	Reduces blood Ca^{2+} levels

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

95. The Parathyroid Glands

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

Parathyroid Glands
The small parathyroid glands are embedded in the posterior surface of the thyroid gland. LM × 760. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

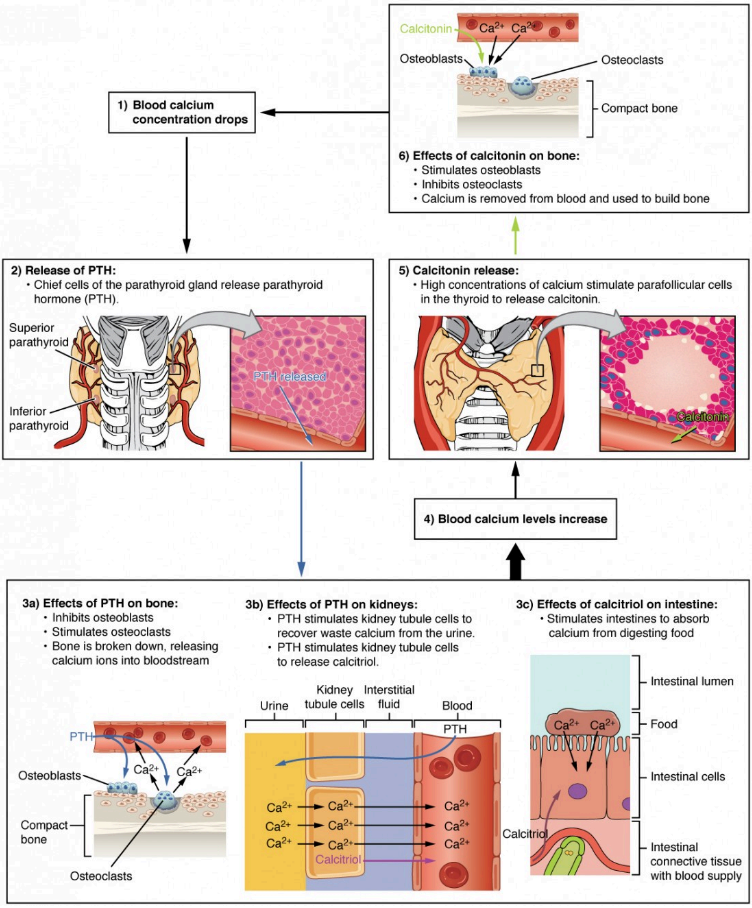


View the University of Michigan WebScope at http://141.214.65.171/Histology/Endocrine%20System/217_HISTO_40X.svs/view.apml to explore the tissue sample in greater detail.

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

Parathyroid Hormone in Maintaining Blood Calcium Homeostasis

Parathyroid hormone increases blood calcium levels when they drop too low. Conversely, calcitonin, which is released from the thyroid gland, decreases blood calcium levels when they become too high. These two mechanisms constantly maintain blood calcium concentration at homeostasis.



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

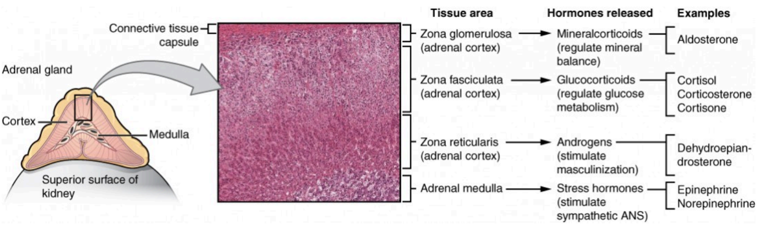
In contrast, abnormally low blood calcium levels may be caused by parathyroid hormone deficiency, called hypoparathyroidism, which may develop following injury or surgery involving the thyroid gland. Low blood calcium increases membrane permeability to sodium, resulting in muscle twitching, cramping,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

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

96. The Adrenal Glands

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

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



Adrenal Glands

View the University of Michigan WebScope at http://141.214.65.171/Histology/Endocrine%20System/New%20Scans/230_HISTO_40x.svs/view.apml to explore the tissue sample in greater detail.

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

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

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

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

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

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

If the stress continues for a longer term however, the body responds with symptoms quite different than the fight-or-flight response. During the stage of exhaustion, individuals may begin to suffer depression, the suppression of their immune response, severe fatigue, or even a fatal heart attack. These symptoms are mediated by the hormones of the adrenal cortex, especially cortisol, released as a result of signals from the HPA axis.

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

Adrenal Cortex

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

Hormones of the Zona Glomerulosa

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

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

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

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

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

Hormones of the Zona Fasciculata

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

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

Hormones of the Zona Reticularis

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

Adrenal Medulla

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

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

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

Hormones of the Adrenal Glands

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

Disorders Involving the Adrenal Glands

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

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

97. The Pineal Gland

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

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

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

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

98. Gonadal and Placental Hormones

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

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

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

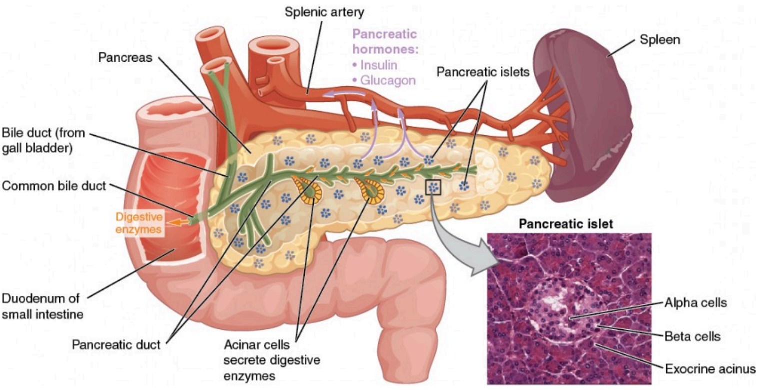
Reproductive Hormones

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

99. Pancreas

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

Pancreas
The pancreatic exocrine function involves the acinar cells secreting digestive enzymes that are transported into the small intestine by the pancreatic duct. Its endocrine function involves the secretion of insulin (produced by beta cells) and glucagon (produced by alpha cells) within the pancreatic islets. These two hormones regulate the rate of glucose metabolism in the body. The micrograph reveals pancreatic islets. LM × 760. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



View the University of Michigan WebScope at http://141.214.65.171/Histology/Digestive%20System/Liver%20and%20Pancreas/188B_HISTO_40X.svs/view.apml to explore the tissue sample in greater detail.

Cells and Secretions of the Pancreatic Islets

The pancreatic islets each contain four varieties of cells:

- The alpha cell produces the hormone glucagon and makes up approximately 20 percent of each islet. Glucagon plays an important role in blood glucose regulation; low blood glucose levels stimulate its release.
- The beta cell produces the hormone insulin and makes up approximately 75 percent of each islet. Elevated blood glucose levels stimulate the release of insulin.
- The delta cell accounts for four percent of the islet cells and secretes the peptide hormone somatostatin. Recall that somatostatin is also released by the hypothalamus (as GHIH), and the stomach and intestines also secrete it. An inhibiting hormone, pancreatic somatostatin inhibits the release of both

glucagon and insulin.
- The PP cell accounts for about one percent of islet cells and secretes the pancreatic polypeptide hormone. It is thought to play a role in appetite, as well as in the regulation of pancreatic exocrine and endocrine secretions. Pancreatic polypeptide released following a meal may reduce further food consumption; however, it is also released in response to fasting.

Regulation of Blood Glucose Levels by Insulin and Glucagon

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

Glucagon

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

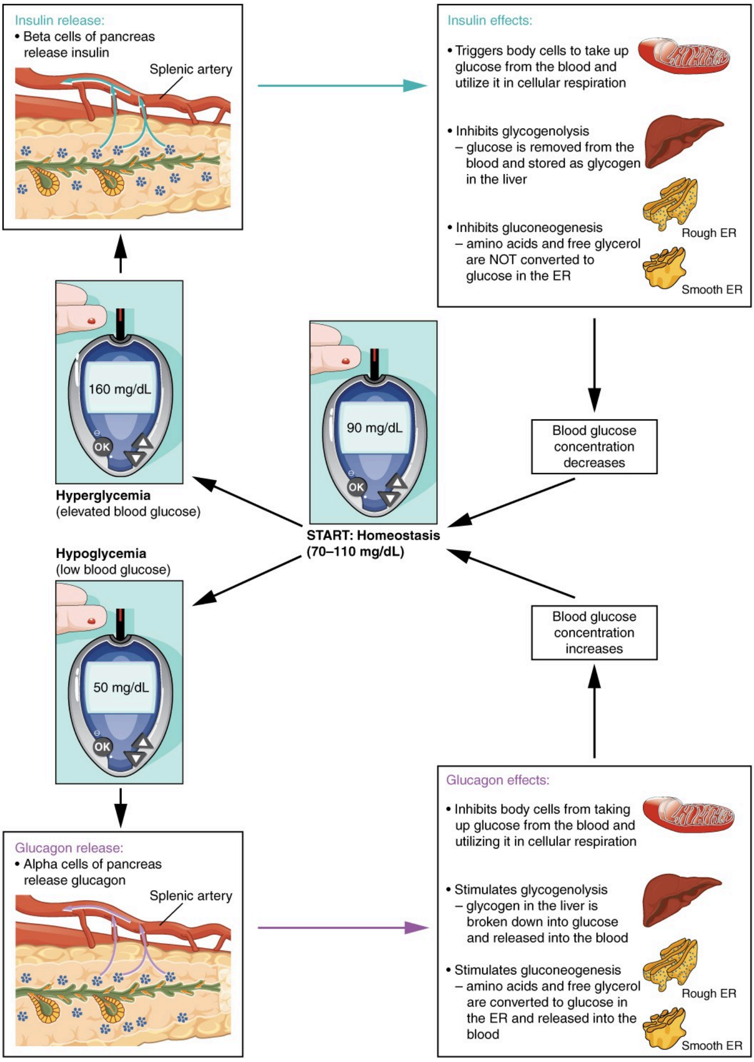
- It stimulates the liver to convert its stores of glycogen back

into glucose. This response is known as glycogenolysis. The glucose is then released into the circulation for use by body cells.
- It stimulates the liver to take up amino acids from the blood and convert them into glucose. This response is known as gluconeogenesis.
- It stimulates lipolysis, the breakdown of stored triglycerides into free fatty acids and glycerol. Some of the free glycerol released into the bloodstream travels to the liver, which converts it into glucose. This is also a form of gluconeogenesis.

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

Homeostatic Regulation of Blood Glucose Levels

Blood glucose concentration is tightly maintained between 70 mg/dL and 110 mg/dL. If blood glucose concentration rises above this range, insulin is released, which stimulates body cells to remove glucose from the blood. If blood glucose concentration drops below this range, glucagon is released, which stimulates body cells to release glucose into the blood.



Insulin

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

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

Precisely how insulin facilitates glucose uptake is not entirely clear. However, insulin appears to activate a tyrosine kinase receptor, triggering the phosphorylation of many substrates within the cell. These multiple biochemical reactions converge to support the movement of intracellular vesicles containing facilitative glucose transporters to the cell membrane. In the absence of insulin, these transport proteins are normally recycled slowly between the cell membrane and cell interior. Insulin triggers the rapid movement of a pool of glucose transporter vesicles to the cell membrane, where they fuse and expose the glucose transporters to the extracellular fluid. The transporters then move glucose by facilitated diffusion into the cell interior.

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

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

100. Age Related Changes to the Endocrine System

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

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

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

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

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

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

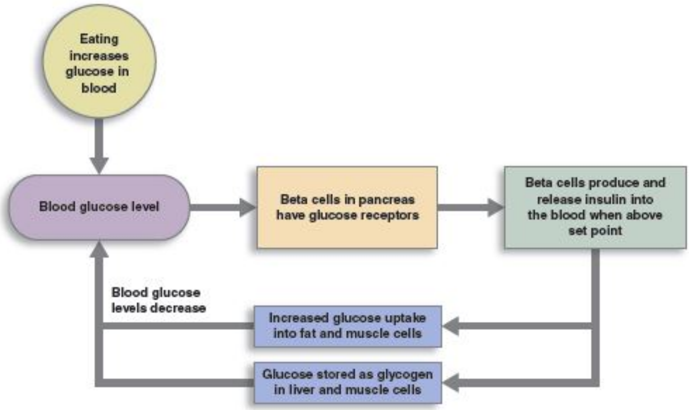
Increasing age also affects glucose metabolism, as blood glucose levels spike more rapidly and take longer to return to normal in the elderly. In addition, increasing glucose intolerance may occur because of a gradual decline in cellular insulin sensitivity. Almost 27 percent of Americans aged 65 and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

101. Age Related Dysfunctions of the Endocrine System

Diabetes Mellitus

An important example of negative feedback is the control of blood sugar.

1. After a meal, the small intestine absorbs glucose from digested food. Blood glucose levels rise.
2. Increased blood glucose levels stimulate beta cells in the pancreas to produce insulin.
3. Insulin triggers liver, muscle, and fat tissue cells to absorb glucose, where it is stored. As glucose is absorbed, blood glucose levels fall.
4. Once glucose levels drop below a threshold, there is no longer a sufficient stimulus for insulin release, and the beta cells stop releasing insulin.



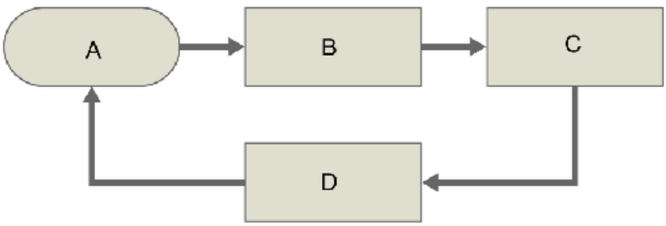
Due to synchronization of insulin release among the beta cells, basal insulin concentration oscillates in the blood following a meal. The oscillations are clinically important, since they are believed to help maintain sensitivity of insulin receptors in target cells. This loss of sensitivity is the basis for insulin resistance. Thus, failure of the negative feedback mechanism can result in high blood glucose levels, which have a variety of negative health effects.

Let's take a closer look at diabetes. In particular, we will discuss diabetes type 1 and type 2. Diabetes can be caused by too little insulin, resistance to insulin, or both.

Type 1 Diabetes occurs when the pancreatic beta cells are destroyed by an immune-mediated process. Because the pancreatic beta cells sense plasma glucose levels and respond by releasing insulin, individuals with type 1 diabetes have a complete lack of insulin. In this disease, daily injections of insulin are needed.

Also affected are those who lose their pancreas. Once the pancreas has been removed (because of cancer, for example), diabetes type 1 is always present.

Type 2 Diabetes is far more common than type 1. It makes up most of diabetes cases. It usually occurs in adulthood, but young people are increasingly being diagnosed with this disease. In type 2 diabetes, the pancreas still makes insulin, but the tissues do not respond effectively to normal levels of insulin, a condition termed insulin resistance. Over many years the pancreas will decrease the levels of insulin it secretes, but that is not the main problem when the disease initiates. Many people with type 2 diabetes do not know they have it, although it is a serious condition. Type 2 diabetes is becoming more common due to increasing obesity and failure to exercise, both of which contribute to insulin resistance.



Hypothyroidism

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

Stress Responses

Stress responses are not unique to older persons. People of all ages must respond to stress. However, the physiological changes that contribute to aging can be quite stressful, and how people respond to stress can change with age.

What goes on inside our bodies when we experience stress? The physiological mechanisms of stress are extremely complex, but they generally involve the work of two systems—the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. When a person first perceives something as stressful (Selye's alarm reaction), the sympathetic nervous system triggers arousal via the release of adrenaline from the adrenal glands. Release of these hormones activates the fight-or-flight responses to stress, such as accelerated heart rate and respiration. At the same time, the HPA axis, which is primarily endocrine in nature, becomes especially active, although it works much more slowly than the sympathetic nervous system. In response to stress, the hypothalamus (one of the limbic structures in the brain) releases corticotrophin-releasing factor, a hormone that causes the pituitary gland to release adrenocorticotropic hormone (ACTH). The ACTH then activates the adrenal glands to secrete a number of hormones into the bloodstream; an important one is cortisol, which can affect virtually every organ within the body. Cortisol is commonly known as a stress hormone and helps provide that boost of energy when we first encounter a stressor, preparing us to run away or fight. However, sustained elevated levels of cortisol weaken the immune system.

A figure shows an outline of the human body that indicates various pa
adrenal axis. The hypothalamus, pituitary gland, and adrenal glands are
gland and another arrow from pituitary gland to adrenal glands. The
This diagram shows the functioning of the hypothalamic-pituitary-adre

gland, which in turn activates the adrenal glands, i

Evidence suggests that due to the cumulative stresses that accompany aging the hypothalamic-pituitary-adrenal axis tends to be hyperactive in older people.

102. Glossary: The Endocrine System

GLOSSARY

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

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

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

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

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

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

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

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

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

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

alpha cell pancreatic islet cell type that produces the hormone glucagon

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

beta cell pancreatic islet cell type that produces the hormone insulin

calcitonin peptide hormone produced and secreted by the parafollicular cells (C cells) of the thyroid gland that functions to decrease blood calcium levels

chromaffin neuroendocrine cells of the adrenal medulla

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

gonadotropins hormones that regulate the function of the gonads

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

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

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

hyperglycemia abnormally high blood glucose levels

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

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

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

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

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

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

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

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

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

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

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

luteinizing hormone (LH) anterior pituitary hormone that triggers ovulation and the production of ovarian hormones in females, and the production of testosterone in males

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

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

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

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

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

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

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

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

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

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

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

phosphodiesterase (PDE) cytosolic enzyme that deactivates and degrades cAMP

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

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

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

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

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

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

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

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

protein kinase enzyme that initiates a phosphorylation cascade upon activation

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

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

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

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

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

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

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

triiodothyronine (also, T_3) amino acid–derived thyroid hormone that is less abundant but more potent than T_4
upregulation increase in the number of hormone receptors, typically in response to chronically reduced levels of a hormone

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

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

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

PART XVI

COURSE INFORMATION

These are all original documents

103. Welcome to the Class!

Throughout the documents found in this "Course Information" folder, you'll find syllabus-like information (Overview, Course Reading and Materials, Course Schedule, etc.). You should read these documents in order and feel free to ask any questions you might have along the way by clicking on the "Ask a Question" discussion forum at the bottom of each module. **However, this area is not for just for asking questions. I encourage you to respond to any questions posted to help each other out along the way.** After reading through the Course Information documents, you should have a clear understanding of my expectations of you in this course. You may want to print out some of the documents, if you are more comfortable reading or keeping the course information off-line.

After you have read through the Course Information documents, return to the main Learning Modules screen, this area contains all the content and areas for interaction in this course. Look at the "guide" area to the left-hand side of your screen, this "guide" is a course "map" and directs you to "what's new" in the course by providing quick links to help you navigate around the course. The Learning Modules contain the all content, reading assignments, and learning activities for this course. The Learning Module section is where you "attend class" on a weekly basis. Rely on the Course Schedule found in this course information section to plan your participation, work, and to find out when all course learning activities/assignments will begin, end, or are due. Please be sure you review and refer to all the "Student How To's" documentation for instructions on how to navigate and participate in course activities. If you have any technical questions or problems, please contact the SLN HelpDesk.

Important notice: If something in the course seems odd, or if you are not clear what you are expected to do, let me know.

104. Contact Information

Instructor:	Jessica Kelly
Course Number:	SC 113
Mailing Address:	100 Reservoir Road, Herkimer,
Ways to communicate with me and other students:	The general practice in SLN is fo There are several ways to comm **Discussion Forums** are whe read the responses of others. Y the course, and part of the lear within the Learning Modules. Us interest for the whole class. **Course Mail**, is available in t on-one way for you to commun questions or comments to me o for private communication. **'Talk with the Professor/A** contact and communication wit found within each module of th in which they are found. The **Bulletin Board**, found a is a public area in the course fo not tied to the content in a spe
Phone:	315.866.0300 ext. 8222
Private Communications:	Contact me through ANGEL Co
Logon Schedule:	I will logon frequently and do my best

105. Course Schedule

You may wish to print this out.

All assignments are due by midnight on the last date of the work period. No late assignments will be accepted.

If you have a question about the course schedule, please post a question in the " Ask a Question" area located at the bottom of the "Course Information" section of this course. Please be sure to give your post a meaningful subject and to check that area frequently for replies and new posts.

106. Overview

Official course description:	This course is designed to explore the biological aging process as part of the normal developmental sequence and process of change from conception to death. This aging process will be viewed as the developmental continuum that occurs in all human beings. Typical biological aging changes in all body systems, as well as some disease processes, will be discussed.
Credits:	3
Course prerequisites:	None

This course is fully online. This course is divided into seven scheduled modules, a course information area, an ice breaking module, and a course survey section. Each scheduled module may include readings, discussion, quizzes, and written assignments.

Module 1: Introduction to Human Again, Theories of Aging, and Cellular Aging

Module 2: The Integumentary System, Skeletal System, and Muscular System

Module 3: The Nervous System & Special Senses

Module 4: The Circulatory, Immune, and Respiratory System

Module 5: The Digestive and Urinary System

Module 6: The Reproductive and Endocrine System

Module 7: Term Research Project

107. Course Readings & Materials

book	**Required Course Materials** The standard text for this course is: Biology of Aging The text is an open source textbook and available under the textbook tab at the top of this page.

Required Software

In this course you will be using conventional productivity software, such as word processor and graphic presentation tool. *Microsoft Word* and PowerPoint would be appropriate, or similar programs that can convert files to the RTF or PDF format. In addition, you may require certain Internet plug-ins for using articles, simulations, or videos inserted in some documents of this course. These are:

1. Adobe Reader
2. Macromedia Flash Player
3. Macromedia Shockwave Player

Click to download and install these plug-ins.

Additional Resources

Each module of the course contains many links to Internet resources that are relevant to the specific content. In addition, students can benefit from the HCCC Library.

If you have a question about the readings and materials for this course, please post a question in the " Ask a Question" area located at the bottom of the "Course Information" section of this course. Please be sure to give your post a meaningful subject and to check that area frequently for replies and new posts.

108. Learning Activities

The course is divided into Learning Modules. In each module there are several graded learning activities, including a written assignment, a written assignment discussion, 2 or more textbook chapter discussions, and a 2-part learning audit. In addition there is a term paper module to be completed throughout the course. These various learning activities are detailed below.

Written Assignments and Related Discussions:

Each module includes a written assignment and a written assignment discussion activity. In each module, there is a written assignment folder – the dropbox is in that folder, as is the written assignment discussion forum. In addition to leading the discussion on your own assignment, you must also participate in the discussions of other students.

Student-led Discussions:

In every module you will find two or more Student-led Discussions. This is the way we cover the content of the textbook. For each chapter you must ask an original "critical thinking" question about some topic in the chapter. Other students will respond to your question, and you will then reply back to those students. In addition you leading your own discussion thread, you are required to answer some of the questions posed by other students, and they are required to reply to your answers. You are encouraged to keep up these "virtual discussions" as long as they are productive. The idea here is for each student to **lead** one discussion with the other students about some important and/or controversial issue introduced in each chapter, and **participate** in a few others. A large percentage of your final grade is determined by your participation in these discussions. I will grade these discussions, but I will not be a participant. If the discussion you are leading gets off track, it is your responsibility to refocus it. You are responsible for maintaining the quality of the discussion threads you lead. Every posting to a discussion should add something substantive to that discussion.

Knowledge Audits:

In each module your appreciation for and understanding of the important content issues and concepts will be assessed two ways:

Module Exams:

There is an objective exam on the textbook chapters for each module. Although you may use your textbook, the exams have a time limit.

Module Recaps:

You are asked to write a brief overview of the most important things that you have learned in each module.

Term Paper:

You are required to complete a three part term paper as part of this course. Part one of this project requires you to interview a person over the age of 75 on their experiences with the agin process. Part two of this project requires you to write a research paper. Your interview will be one of the sources for this paper, but you will be required to do additional research on any conditions your interviewee may have experienced in their lifetime. Part three of the term paper will require you to lead a discussion on your term paper. You are encouraged to keep up these "virtual discussions" as long as they are productive.

Extra Credit / Make-up Work / Incomplete Grades

1. The major requirement in this course is to discuss, with other students, the contents of each chapter in the text. There is no substitute for this requirement, and I do not permit "extra credit" or "alternative credit" assignments.
2. Also, there is no way to "go back" after a module has ended and "make-up" missed discussion activity, because there are no other students left to learn from your posts and discuss the content with you.
3. Finally, an incomplete in the course is not appropriate, as there is no way to complete the course once it has ended and all of

the other students are gone.

If you have a question about the learning activities for this course, please post a question in the " Ask a Question" area located at the bottom of the "Course Information" section of this course. Please be sure to give your post a meaningful subject and to check that area frequently for replies and new posts.

109. How You Will Be Evaluated

Final course evaluation

I will use both qualitative and quantitative evaluation in all courses and learning activities. The qualitative evaluation is represented by my comments to your assignments and discussions. The quantitative evaluation is represented through grades that follow the conventional letter system, and they are based on specific criteria for the course and each learning activity in the course. This page summarizes what you need to know about both the qualitative and quantitative evaluations in this course. You may want to print it for future reference.

Final course evaluation

Final course evaluation will be based on the following percentage weight of each type of Learning Activity:

Written Assignments	24%
Chapter Discussions	24%
Module Recaps	12%
Module Exams	18%
Term Paper	22%
Total	100%

See the detail of these evaluation moments below:

Module	Aspects to Evaluate	Percentage of Grade	Cumulative
1	Written Assignment 1	4.0%	13.8%
	Chapter 1 Discussion	1.6%	
	Chapter 2 Discussion	1.6%	
	Chapter 3 Discussion	1.6%	
	Module 1 Recap	2.0%	
	Module 1 Exam	3.0%	
2	Written Assignment 2	4.0%	27.6%
	Chapter 4 Discussion	1.6%	
	Chapter 5 Discussion	1.6%	
	Chapter 6 Discussion	1.6%	
	Module 2 Recap	2.0%	
	Module 2 Exam	3.0%	
3	Written Assignment 3	4.0%	39.8%
	Chapter 7 Discussion	1.6%	
	Chapter 8 Discussion	1.6%	
	Module 3 Recap	2.0%	
	Module 3 Exam	3.0%	
4	Written Assignment 4	4.0%	53.6%
	Chapter 9 Discussion	1.6%	
	Chapter 10 Discussion	1.6%	
	Chapter 11 Discussion	1.6%	
	Module 4 Recap	2.0%	
	Module 4 Exam	3.0%	

5	Written Assignment 5 Chapter 12 Discussion Chapter 13 Discussion Module 5 Recap Module 5 Exam	4.0% 1.6% 1.6% 2.0% 3.0%	65.8%
6	Written Assignment 6 Chapter 14 Discussion Chapter 15 Discussion Module 6 Recap Module 6 Exam	4.0% 1.6% 1.6% 2.0% 3.0%	78.0%
7	Term Paper Part 1 Term Paper Part 2 Term Paper Part 3	6.0% 10.0% 6.0%	100 %

The sum of the four groups of percentages will determine your final course grade according to the following table:

90-100 = A- or A

80 – 89 = B-, B or B+

70 – 79 = C-, C or C+

60 – 69 = D-, D or D+

59 and under = F

The Gradebook

This course has special features that allows you to see your progress at every moment. Access is through the “Grades” nugget on the course homepage, or you can access the gradebook through the “Report” tab.

If you have a question about how you will be evaluated, please post a question in the " Ask a Question" area located at the bottom of the "Course Information" section of this course. Please be sure to give your post a meaningful subject and to check that area frequently for replies and new posts.

110. My Expectations

My Expectations

This is a regular college course. I expect the same commitment to time and quality as I do in the classroom. The big difference is that Internet study is student centered rather than teacher centered. This means that you are responsible for your own learning and success. If you are highly motivated and produce high quality work – you will be successful. However, if you logon sporadically, participate minimally, or submit poor work – you will not. Online higher education is aimed at independent learners. If you require the structure of a classroom, this method will not suit you.

I expect the successful student will spend an **average** of about ***15-18 hours per module*** on this course. Although that may seem like a lot – remember this: A traditional classroom-based course requires 45 hours of "seat time" plus 2-3 hours outside of class for each hour in class. It adds up to around 150 total hours.

Do you have a plan if you have a technical problem? If your computer crashes, or if your Internet connection fails – these events do not excuse you from your course responsibilities.You can access this online course from any computer that has an Internet connection. I suggest that you make a plan now for events such as these. If you ever have a technical problem connecting to your course, submitting work to your course, or any other course-related issue, call the SLN Student Helpdesk at (800) 875-6269. If the problem is with the SLN system, you will be granted a time extension for submitting assignments affected by the problem.

However, if you do not report the problem to SLN, no time extension will be granted.

If you have a question about my expectations, please post a question in the " Ask a Question" area located at the bottom of the "Course Information" section of this course. Please be sure to give your post a meaningful subject and to check that area frequently for replies and new posts.

111. Course Objectives

Objectives:

1. This course is designed to provide the student with information regarding developmental changes as they occur during the aging process.

Students who complete this course will gain knowledge regarding developmental changes as they occur during the aging process. This will be assessed through Chapter Discussions (1-15), and Module Recaps and Examinations (1-6).

2. This course is designed to enable the student to evaluate current issues related to the aging process.

Students who complete this course will be able to evaluate current issues related to the aging process. This will be assessed through Written Assignment Reviews and Discussions (1-6), and the Term Project (Parts 1-3).

PART XVII

TERM RESEARCH PROJECT

All content is original.

112. Requirements

Overview of Term Research Project:

1. Interview a person over the age of 75 on their personal experience in aging and research each of the conditions the individual is experiencing.
2. Write a research paper that summarizes the individual's personal experiences and the conditions the individual is experiencing.
3. Discuss the research papers

Please check the Course Scheduleforall due dates.

Purpose:

Your term research project assignment is to write an original research paper on an individual's experience with aging and the specific conditions they suffer from. The assignment is divided into into three parts. Each part is graded separately.

Part 1 – Interview:

1. Select an individual over the age of 75 to interview on their experience with aging.
2. Complete the interview and transcribe the conversation. Post to your Term Paper Part 1 dropbox.

Part 2 – Write the paper:
Write and submit your paper.

Paper Requirements:

1. The minimum acceptable length of your paper is 2500 original words.

2. The content of your paper will be evaluated using two criteria:

Have you addressed the significant issues?

Have you added significant teaching value to the course?

3. Include a Works Cited page:

Use the textbook as one of your resources and specifically reference the pages used in your paper.

Use a minimum of 5 websites as resources and include a working link to each website in your paper.

4. Submit your paper to the ANGEL Term Paper Drop Box.

Part 3 – Discussion of all papers:

Paste your paper into the Term Paper 3 forum. Read and discuss the papers you find most interesting and valuable. You are expected to provide constructive criticism and insightful teaching presence for these papers, and respond to most of the students who comment on your paper. You need to logon and be an active participant in the forum. This blog will be graded using the same grading scale as the chapter and written assignment forums. I will grade your first 12 posts.