Homeostasis and Thermoregulation

Although some organisms are able to meet all their needs via direct exchanges with the environment, this lifestyle has several limitations. For instance, no part of the body can be more than a few cell layers thick, every cell must be able to take care of all its own needs, and the animal is limited to environments that provide for all of its needs. As such, we only see this lifestyle in single-celled organisms and in some very simple multicellular animals.

The evolution of an **internal environment**, distinct from the external environment, made complex multicellular life possible. The internal environment consists of extracellular fluid that bathes all cells of an animal. It is important for animals to maintain a constant, optimal internal environment despite what changes may occur in the external environment, since it is the internal environment that provides for the needs of the cells. **Homeostasis** refers to the maintenance of a constant internal environment (constant internal milieu).

How is homeostasis maintained? With the evolution of an internal environment, it was no longer necessary that each cell provide for all of its own needs (as the needs are supplied by the internal environment). Therefore, cells could become dependent on one another and could become specialized for maintaining specific aspects of the internal environment. Furthermore, they formed more complex levels of organization, as follows (from simplest to most complex):

Cells -> tissues -> organs -> organ systems -> organism

At the organ systems level, we have each organ system contributing to homeostasis by controlling one or more components of the internal environment. For instance, a renal system to maintain salt/water balance or a respiratory system to maintain appropriate levels of carbon dioxide and oxygen.

Composition of the Internal Environment

As mentioned previously, extracellular fluid is the internal environment. What does this fluid consist of in humans? First, note that humans are roughly 60% water, and then consider a human who weighs 70 kg. This means that the person consists of 42 liters of water (60% of 70 kg = 42 kg water = 42 L water)

- 2/3 of total body water is intracellular fluid, meaning there's (2/3)*42L = 28 liters intracellular fluid.
- 1/3 of total body water is extracellular fluid, meaning there's (1/3)*42L = 14 liters extracellular fluid.
    - 80% of extracellular fluid is interstitial fluid. There's 80%*14L = 11 liters interstitial fluid.
    - 20% of extracellular fluid is plasma. There's 20%*14L = 3 liters plasma.

Interstitial fluid is the fluid that bathes cells in our body. **Plasma** is the liquid portion of blood.

The Effects of Temperature on Living Systems

The range of temperatures on earth (from the interior of Antarctica to boiling hot springs) far exceed the range compatible with life. Below 0 °C, ice crystals may form and damage the cells. Above 40 °C, many proteins will denature and lose their function. However, even within the temperature limits that cells can survive, temperature still matters because biological functions are temperature-sensitive. Physiological processes, like their underlying chemical reactions, are temperature-sensitive, proceeding faster at higher temperatures. (This relationship between rate and temperature is described by the Arrhenius equation).

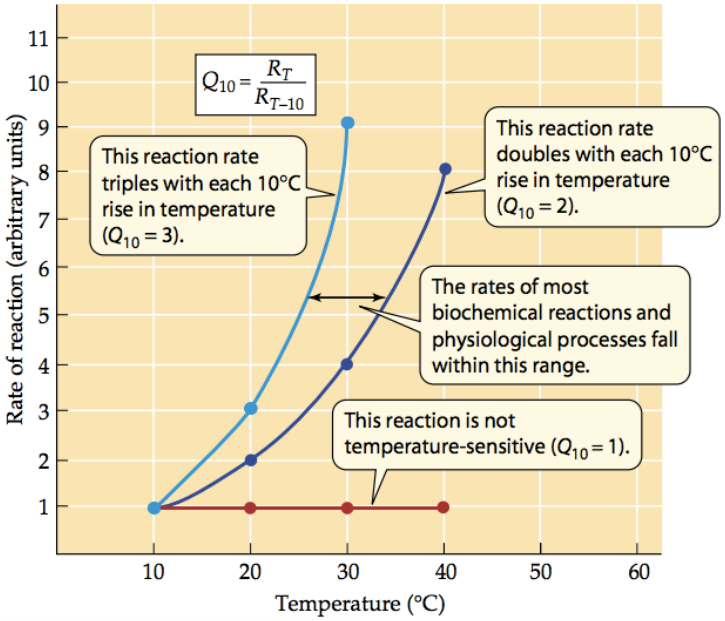
The Van't Hoff concept of **Q_{10}** is less rigorous than the Arrhenius equation, but it suffices to describe the effects of temperature in physiology. Q_{10} is a quotient calculated by dividing the rate of a reaction at a certain temperature (R_T) by the rate of that reaction at a temperature 10 °C lower (R_{T-10}). See below.

$Q_{10} = R_T / R_{T-10}$

- If $Q_{10} = 1$, then the reaction is not temperature-sensitive.
- If $Q_{10} = 2$, then that means the reaction rate doubles as temperature increases by 10 °C.
- If $Q_{10} = 3$, then that means the reaction rate triples as temperatures increases by 10 °C.

Most biological Q_{10} values are between 2 and 3.

Reactions linked together in a chain may have different Q_{10} values. As such, changes in temperature may shift the rates of some reactions more than those of others, which would be particularly disruptive to an animal's functioning.

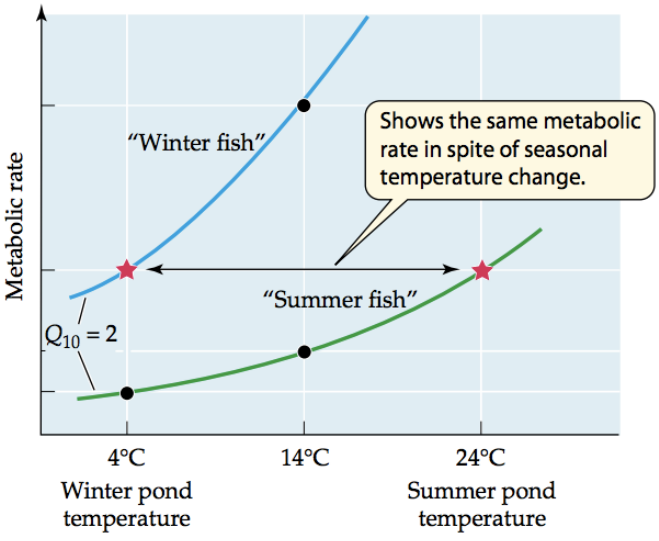


Dealing with Temperature Changes

Now, we will see what animals can do to resist the detrimental effects of temperature changes.

Metabolic compensation:

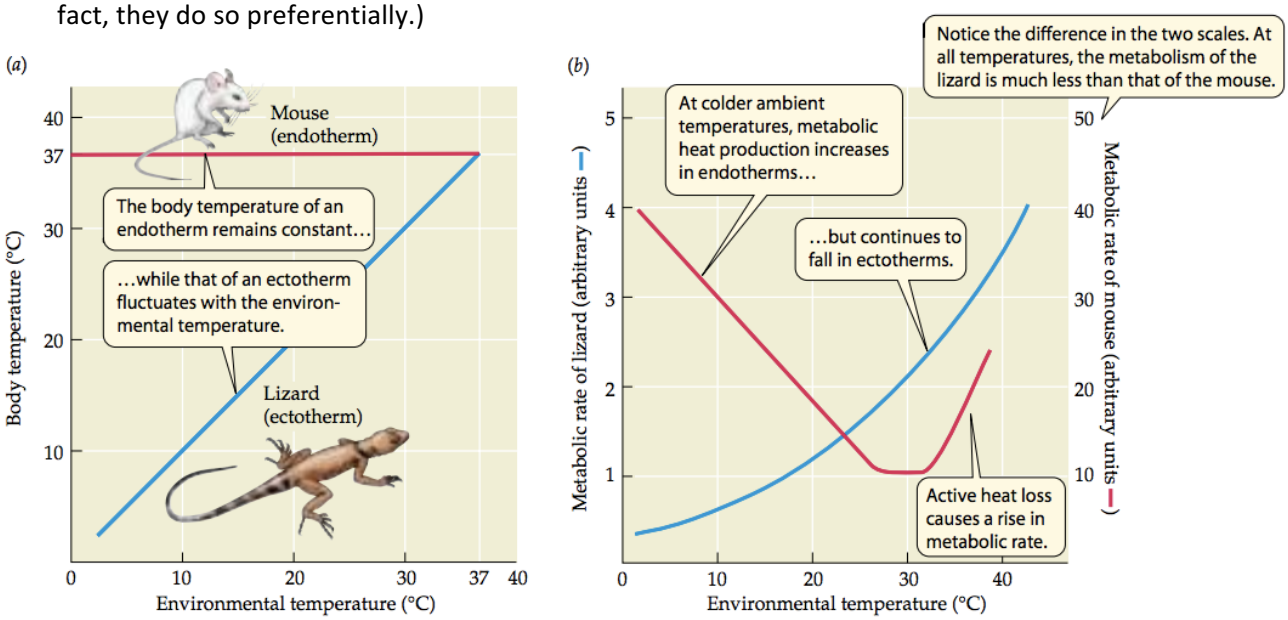
Metabolic compensation refers to molecular and biochemical changes that counter the effects of a temperature change. For instance, when the temperature changes, animals might alter their cell membrane composition so that their cell membranes retain the optimal level of fluidity despite the new temperature. Animals might also produce enzymes with different temperature optima in response to a temperature change; this is often seen in seasonal acclimation of fish. Temperate lake fish may express one set of enzymes in the summer and switch to another set of enzymes to catalyze the same reactions in the winter. The "winter fish" enzymes have different optimal temperatures than the "summer fish" enzymes. In this way, the fish may have the same metabolic rate in the summer and in the winter.



Thermoregulation:

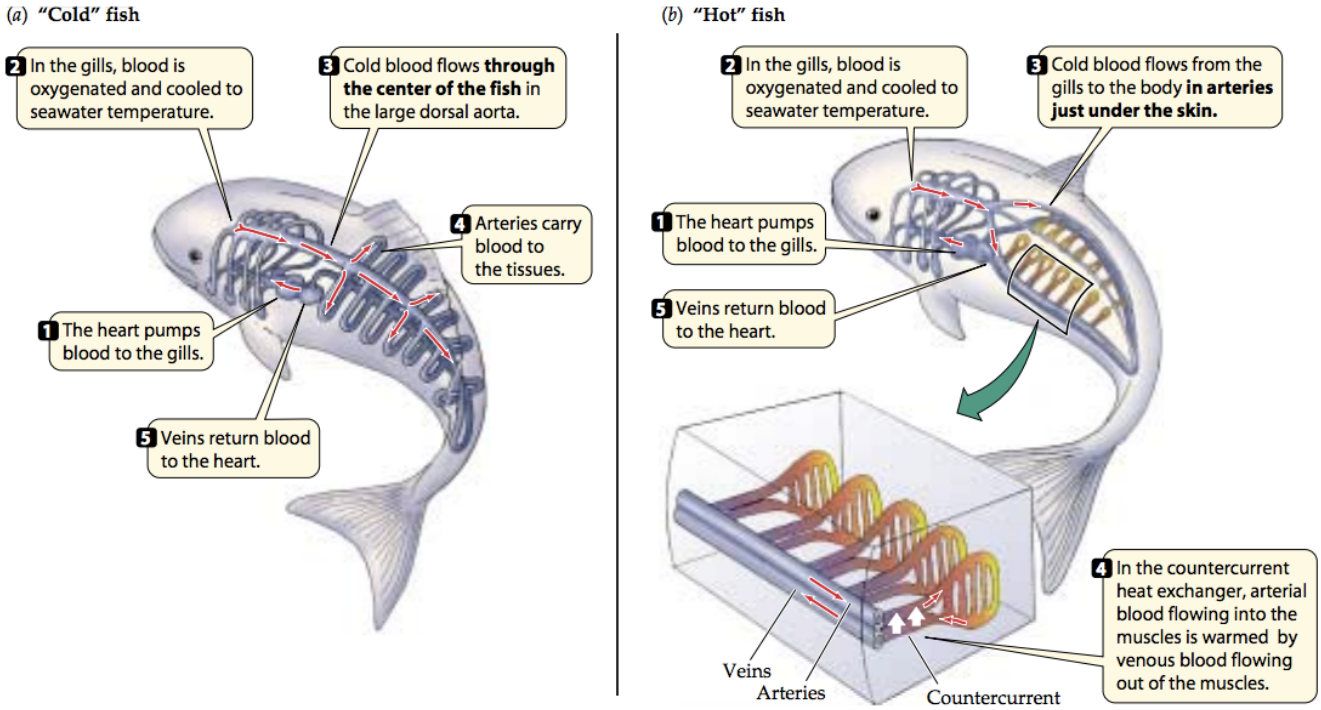
Many animals, rather than dealing with the effects of temperature changes via metabolic compensation, have physiological or behavioral adaptations that allow them to resist changes in temperature. These thermoregulatory animals can be classified into two groups:

- **Endotherms**: Generate internal heat to regulate body temperature. They may do so by increasing their metabolic rate (thereby getting heat from the inefficiencies of metabolism). Or, they may use energy to produce waste heat by shivering. Finally, they may make use of uncouplers to burn fuel without doing work (uncoupling proteins in brown fat tissue dissipate the H^+ gradient in the mitochondria so that the potential energy from the H^+ gradient is not used to make ATP but rather is lost as heat).
- **Ectotherms**: Depend on external heat and cannot regulate body temperature independently of environmental temperature. How do they thermoregulate then? They do so behaviorally – during daytime, they bask in the sun when the ambient temperature is cold but they will move into the shade when the temperature rises. (Note that endotherms can also use behavior to thermoregulate, and, in fact, they do so preferentially.)

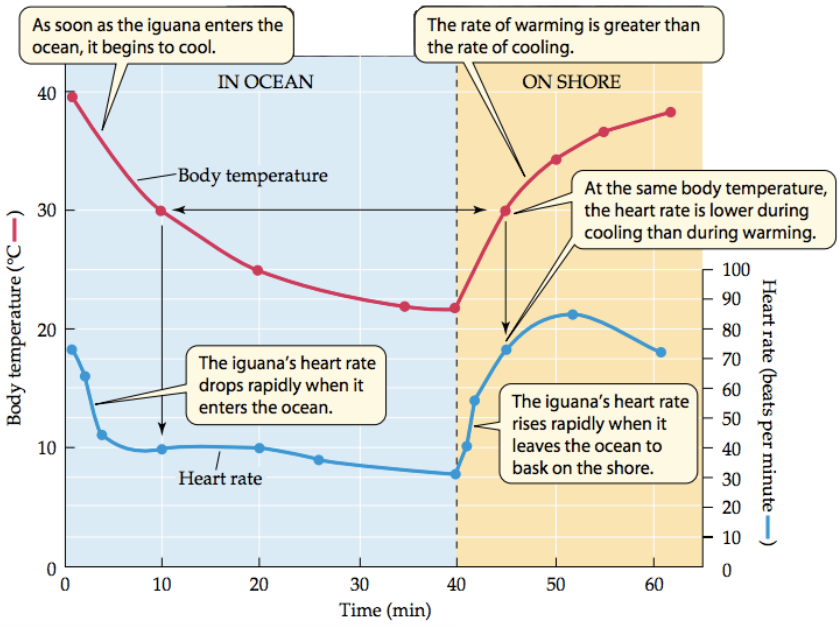


Ectotherms also have anatomical and physiological adaptations as means of thermoregulating:

- Conserving metabolic heat via countercurrent heat exchange: Most species of fish are "cold" fish species wherein their circulatory systems conduct cool, oxygenated blood from the gills through a large dorsal aorta to the rest of the body. Hence, any metabolic heat that the blood picks up from metabolically active muscles is not retained because the blood is cooled to seawater temperatures in the gills. In "hot" fish species, such as bluefin tuna and great white sharks, the cool, oxygenated blood from the gills are transported in large vessels just under the skin. Smaller vessels carrying this cold blood into the muscle mass run parallel to vessels transporting warm blood (the blood warmed by the heat produced by metabolism) from the muscles to the heart. Since heat flows from the warm blood to the cold blood, the heat is trapped in the muscle mass. This adaptation is called a **countercurrent heat exchanger** system since heat is exchanged between blood vessels carrying blood in opposite directions. See the diagram on the next page for an illustration of "hot" versus "cold" fish.



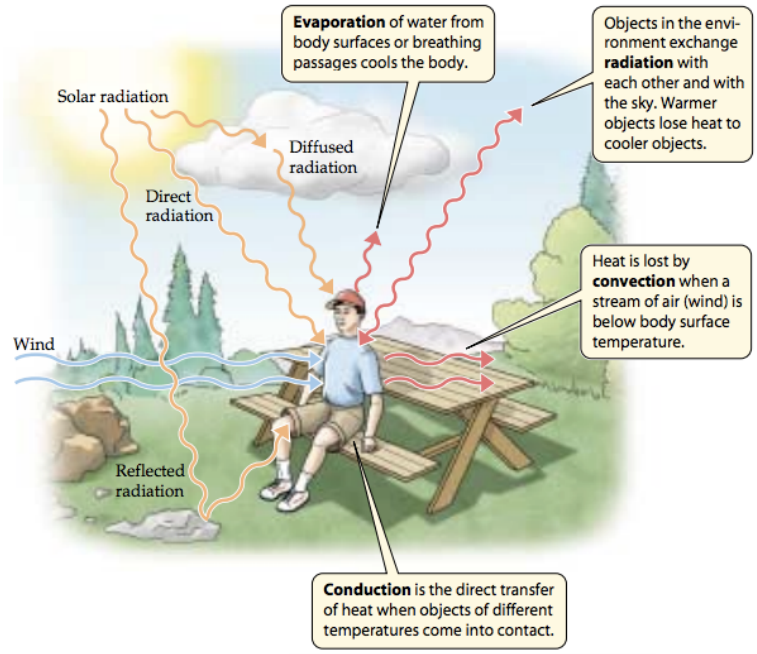
- <u>Control of blood flow to skin</u>: The marine iguana of the Galápagos is an ectothermic reptile that can thermoregulate by controlling blood flow to the skin. These iguanas need to enter the cold ocean water to feed on seaweed. When they enter the water, they experience bradycardia (a slowing down of their heart rate), which effectively reduces blood flow to the skin therefore conserving their body heat. However, upon returning to land, their heart rate rapidly rises (tachycardia), increasing blood flow to the skin therefore increasing heat exchange between their body's core and the hot rocks that they bask on under the sun. In effect, controlling blood flow to the skin ensures that they retain heat (cool down slowly) while feeding in water and warm up quickly while basking on land.



    - Note: Endotherms, like humans, also thermoregulate by controlling blood flow to the skin: When we're hot, our blood vessels dilate to increase blood flow to the skin and therefore heat loss to the environment; When we're cold, our blood vessels constrict to reduce heat loss to the environment.

The Energy Budget

The **energy budget** concept simply states that, in order for an animal's body temperature to remain constant, the heat entering the animal must equal the heat leaving the animal (Heat in = Heat out).



"Heat in" consists of:

- The heat produced by metabolism: M
- The heat absorbed from solar radiation: Q_{abs}

"Heat out" consists of:

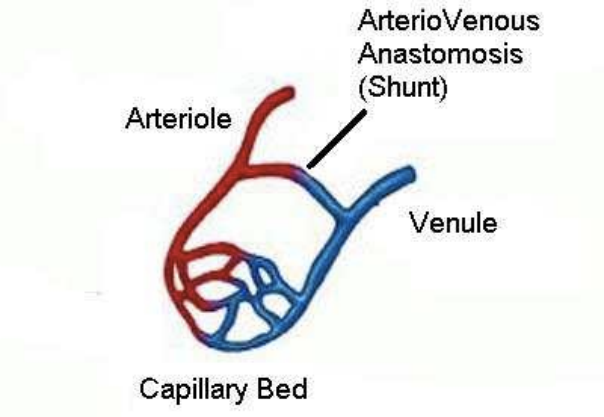
- Radiation emitted from body: $\varepsilon\sigma T_r^4$
- Heat lost from body by convection: $h_c(T_r - T_a)$
- Heat lost from body by conduction (C)
- Heat lost from body by evaporation (E)

The energy budget equation can be represented as:

$$M + Q_{abs} = \varepsilon\sigma T_r^4 + h_c(T_r - T_a) + C + E$$

Insulation versus Heat Exchange in Endotherms

As all components of the "Heat out" side of the energy budget equation are influenced by skin temperature, insulation (e.g. fur, feathers, etc.) is very important for preventing heat loss. However, on the other hand, insulation can pose a problem in animals when heat loss is required. Such animals may have certain areas of uninsulated skin dedicated to heat loss – these areas of skin may receive more blood flow (i.e. higher perfusion) and therefore act as radiators of heat. These radiator skin areas for furred mammals are the glabrous (non-hairy) skin. The uninsulated glabrous skin contains arteriovenous anastomoses (AVA) and retia venosa (RV), which are special vascular structures that act as radiators of heat. AVAs can shunt large quantities of hot blood to the retia venosa, a densely packed networks of vessels just below the surface of the glabrous skin, for heat dissipation. (Note: The term anastomosis refers to the connection between two neighboring vessels; in this case, between an artery and its neighboring vein).



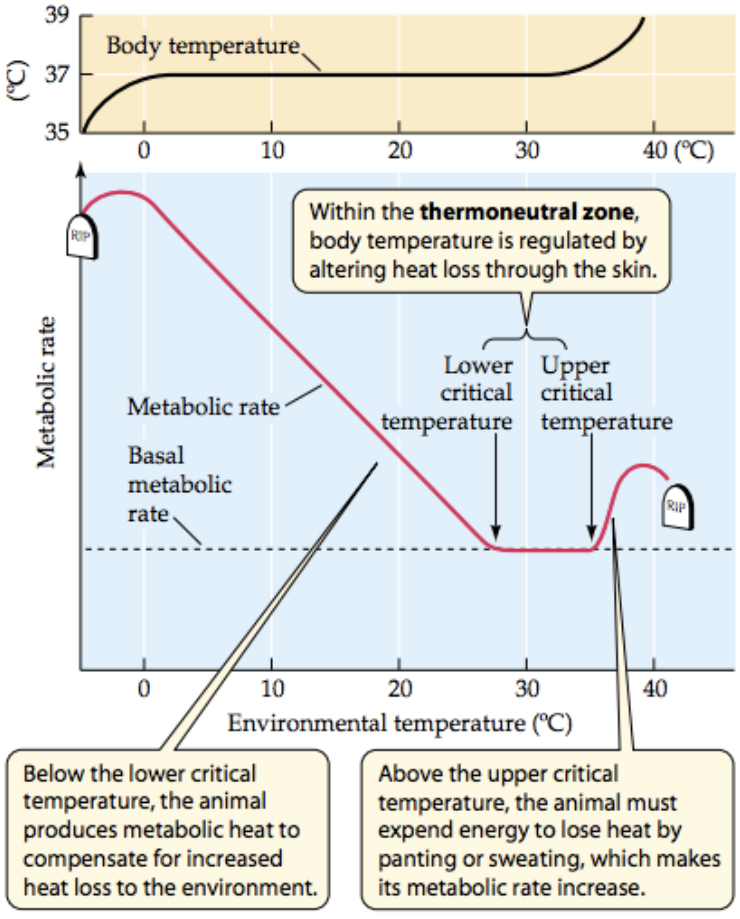
Thermoregulation in Endotherms

Although the metabolic rate of endotherms often changes when environmental temperature changes, within a narrow range of environmental temperatures, called the **thermoneutral zone (TNZ)**, the metabolic rate of endotherms is low and independent of temperature. The TNZ is bounded by a lower critical temperature (LCT) and an upper critical temperature (UCT). But outside the TNZ, energy expenditure (and thus, metabolic rate) increases, either for the purposes of warming up or cooling down:

- If environmental temperature falls below the LCT: Endotherms must actively produce heat (e.g. via shivering) to warm back up.
- If environmental temperature is above the UCT: Endotherms must expend energy to lose heat by panting or sweating. Metabolic rate goes up as a result (but the heat lost by panting or sweating will be greater than any heat gained from the resulting increase in metabolic activity, so panting and sweating still have net effect of cooling the animal).
- If environmental (ambient) temperature is within the TNZ (between LCT and UCT), endotherms passively (rather than actively) thermoregulate; they accomplish this via *vasomotor tone* (altering blood flow to the skin by constricting or dilating blood vessels).

The metabolic rate of a resting animal at a temperature within the thermoneutral zone is called the **basal metabolic rate (BMR)**. At the basal metabolic rate, metabolism is running just fast enough for an animal to carry out all of its minimal body functions. Again, to reiterate, when we venture outside the TNZ (on either side), metabolic rate will increase to be above the BMR. Note that although more massive animals have a higher BMR, smaller animals have a higher BMR *per unit body mass*.

The equation relating metabolic rate and ambient temperature is shown in the box below. This equation only applies to ambient temperatures below the LCT (as mentioned before, within the TNZ, MR = BMR). The steepness or slope (K) of the metabolic rate curve can give us info about how well insulated an animal is; if the slope of the left side of the graph is less steep, the animal is more insulated.



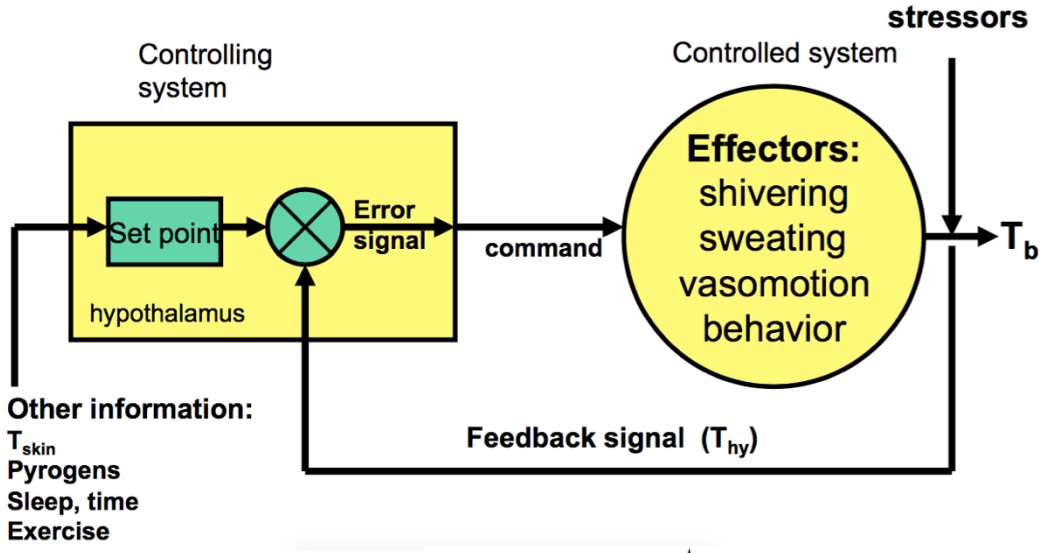
$$MR = K(T_b - T_a)$$

- MR = metabolic rate
- K = thermal conductance;
  - 1/K = thermal insulation
- T_b = body temperature
- T_a = ambient temperature

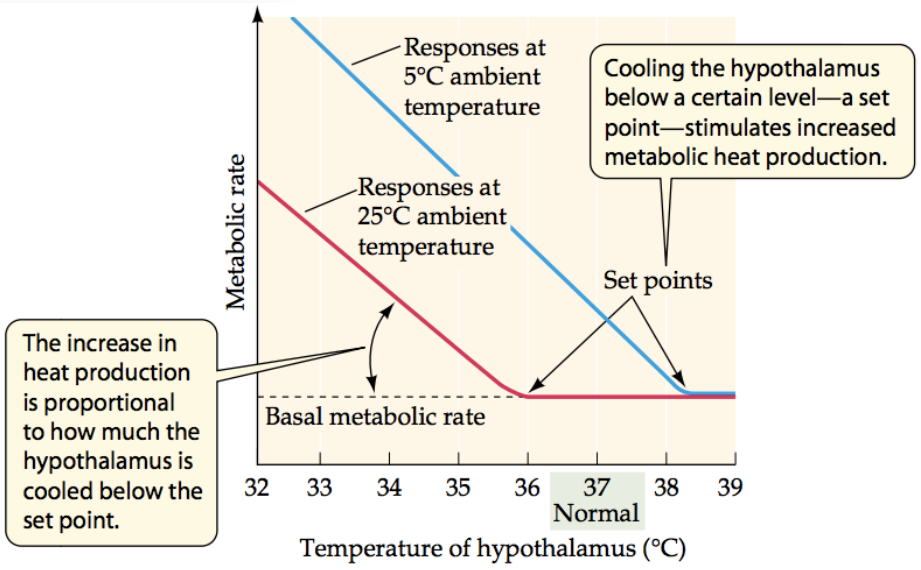
Different animals have different TNZs. The TNZs of tropical animals, which don't have much insulation, generally lie at higher temperature ranges. The TNZs of arctic animals, which have more insulation, generally lie at lower temperature ranges.

The Vertebrate Thermostat

How do animals know when it's time to increase or decrease body temperature? They have a thermostat control system, which makes use of feedback information (the temperature of the hypothalamus). The mammalian thermostat is the **preoptic anterior hypothalamus (POAH)**. The POAH is temperature-sensitive; when it is heated or cooled such that its temperature exceeds or drops below its **set point** (threshold), it generates **thermoregulatory responses** like shivering or sweating that work to reverse the direction of temperature change. (This is an example of negative feedback). The magnitude of the thermoregulatory response is proportional to the **error signal** (the difference between the temperature of the hypothalamus and the set point temperature). Thus, a small deviation from the set point will not cause a large thermoregulatory response. See below for a schematic of how the vertebrate thermostat works:



The set points of the POAH can be adjusted and are influenced by numerous factors such as sleep, time of day, pathogens (think about the increase in the set point during a fever), and exercise. Skin temperature also appears to affect the set points of the POAH, explaining how different set points exist for different ambient temperatures; see figure to the right. The influences of these factors on hypothalamic set points are known as **feed-forward information**. Using this information, the POAH can ensure that the appropriate effector responses are initiated to prevent the body temperature from increasing or decreasing. For example, in a cooler environment (right curve), the set point is raised. Notice that at a normal hypothalamic temperature of 37 degrees, the metabolic rate of the organism in this environment has increased, signifying increased metabolic heat production. The POAH measured the error



signal -- the difference between the hypothalamic temperature and the changed set point temperature -- and generated a heat production response. By changing the set point, the error signal will also change and cause the POAH to initiate heat production before the hypothalamic temperature actually changes. This increased heat production will compensate for the heat lost to the environment, allowing the body to stay at 37 degrees.

Hibernation is an extreme example of resetting the mammalian thermostat. During hibernation, the hypothalamic set point is turned down to an extremely low level to maximize energy conservation. Arousal from hibernation occurs when the set point returns to a normal level.

Hyperthermia

Insulation makes it difficult to lose heat during exercise, and, as a result, the heat that builds up causes our body temperatures to rise, leading to hyperthermia. Hyperthermia decreases athletic performance; the loss of muscle function associated with hyperthermia may be due to inactivation of enzymes like pyruvate kinase that are necessary for production of ATP. “The glove” is a device which increases blood flow to and extracts heat from glabrous skin areas, which contain vascular structures (arteriovenous anastomoses and retia venosa) that radiate heat effectively. This device has been shown to increase athletic performance in several trials.

The Reproductive System

A reproductive system is an organ system, containing both internal and external organs, that works towards procreation. We will discuss asexual reproduction, sexual reproduction, gametogenesis, sexual differentiation, sex determination, and human male/female reproductive physiology.

Sexual vs. Asexual Reproduction

Although many animals reproduce by sexual reproduction, some animals (mostly invertebrates) utilize an asexual mode of reproduction. There are several key advantages for each of these two modes of reproduction, delineated below:

Sexual Reproduction	Asexual Reproduction
➢ Generates genetic diversity	➢ Produces genetically identical offspring ➢ Efficient ▪ No time/energy wasted on mating ▪ Every individual can convert resources into offspring

Asexual Reproductive Systems:

Asexually reproducing animals are typically species that are attached to their substrate (i.e. growth surface) and cannot search for mates, or that live in sparse populations and rarely encounter potential mates. Asexually reproducing animals are more likely to be found in relatively constant environments (where genetic diversity is less important for species success). In fact, asexual reproduction is a good way to preserve a genotype that is successful in a particular environment, as long as that environment does not change. There are three common modes of asexual reproduction:

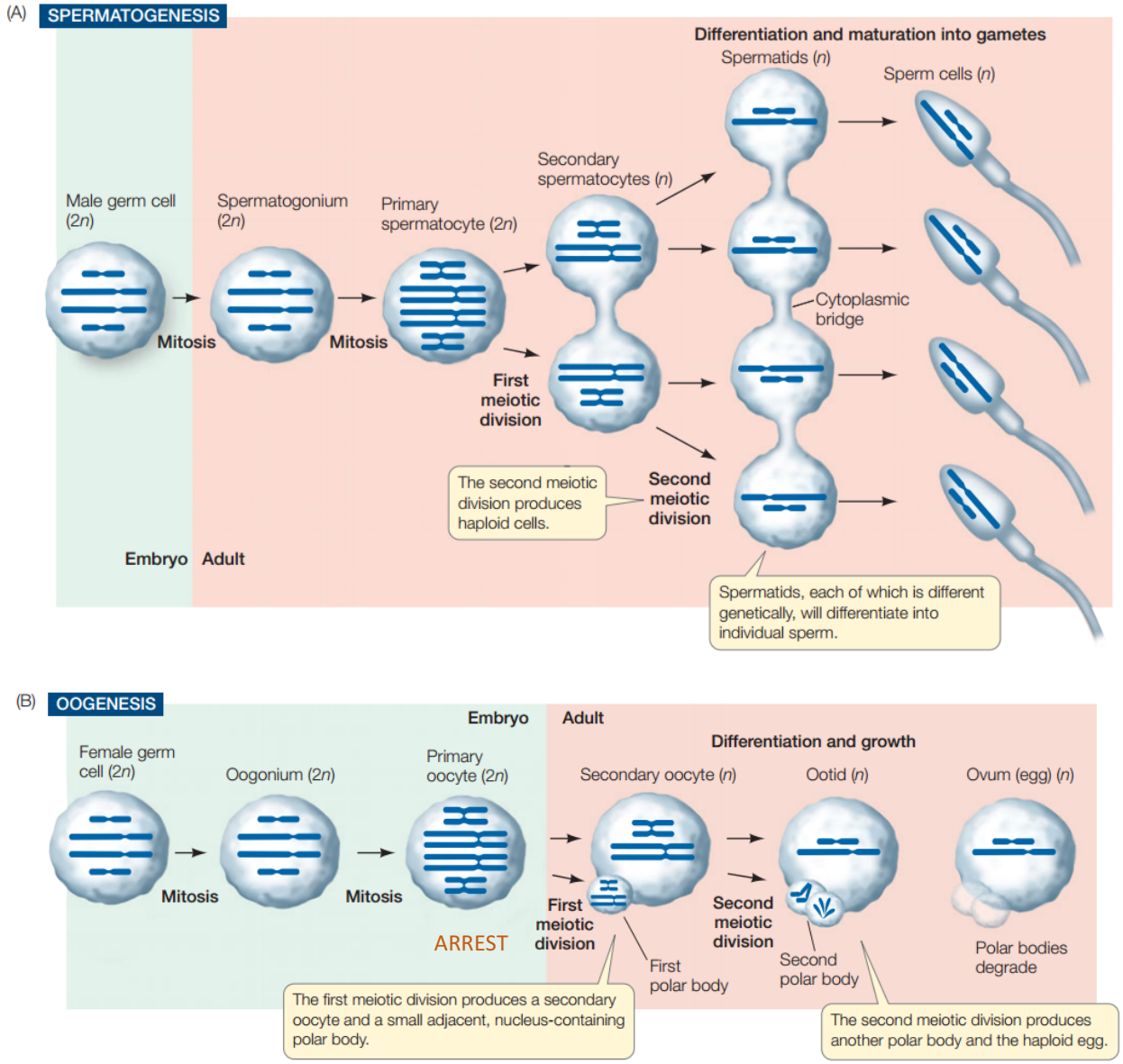
- **Budding**: New individuals form as outgrowths (buds) from the bodies of older organisms. The bud grows by mitosis and differentiates before finally breaking away from the parent. In some cases, the bud may grow to be as large as the parent before breaking off. (Example of budding: Hydras).
- **Regeneration**: Pieces of an organism can regenerate complete individuals. For example, in some echinoderms (a phylum of marine animals that includes sea stars), if a limb is torn off, that limb may develop into a complete individual.
- **Parthenogenesis**: Development of *unfertilized* eggs. For example, male honey bees develop parthenogenetically from unfertilized eggs and end up being haploid (in contrast, female honey bees develop from fertilized eggs and are diploid). In some species, parthenogenesis requires sex or sexual behavior. In a species of whiptail lizards, all lizards are females but they take turns acting the male role in reproductive behavior (to trigger other females to ovulate). This behavior depends on hormonal activity: a lizard acts as a female when estrogen is high and as a male when progesterone is high.

Sexual Reproductive Systems:

Sexual reproductive systems require two separate systems: male and female. Although these systems usually exist in separate bodies (**dioecious**), it is possible for these systems to exist in the same body (**monoecious**) as in **simultaneous hermaphrodites** (have both systems at the same time) or **serial hermaphrodites** (can switch between the two systems).

Gametogenesis and Fertilization

Gametogenesis is a hallmark of sexual reproduction and involves the formation of gametes (eggs and sperm). Let's review spermatogenesis (sperm formation) and oogenesis (egg formation) below:



Note: In males, spermatogonia continue to proliferate throughout life. Females are born with all of the primary oocytes they will have as adults (the primary oocytes are arrested in prophase of meiosis I).

Fertilization refers to the joining of gametes. External fertilization is the release of sperm into the environment and, by chance, the sperm encounters a nearby egg. Internal fertilization, the mode of fertilization used by terrestrial animals, is the release of sperm directly into the female reproductive tract.

Both gametogenesis and fertilization are similar across species (all other aspects of sexual reproduction involve an amazing diversity of adaptations).

Development of Sex Determinants

Where do sexes come from? How is one sex different from another? First, let's define some terms:

- **Primary sex organs**: The **gonads** (testes and ovaries)
- **Accessory sex organs**: Everything else (besides the gonads) necessary for reproduction.
- **Secondary sexual characteristics**: External differences between males and females that are not directly involved in reproduction.

Four types of sex:

There are four different types of sex, defined below:

- **Genetic sex**: Determined by chromosomes (e.g. XX or XY)
- **Gonadal sex**: Determined on the basis of the gonadal tissue present (ovarian or testicular).
- **Phenotypic sex**: Determined by internal and external genitalia (accessory sex organs) as well as secondary sexual characteristics.
- **Behavioral sex**: Determined by behavior.

Genetic sex is established at the time of gamete fertilization. From there, we will discuss how sex determination occurs to determine *gonadal sex*, followed by how sexual differentiation occurs to determine the *phenotypic sex*. Finally, we will discuss the development of *behavioral sex*.

Development of primary sex organs (Gonadal Sex):

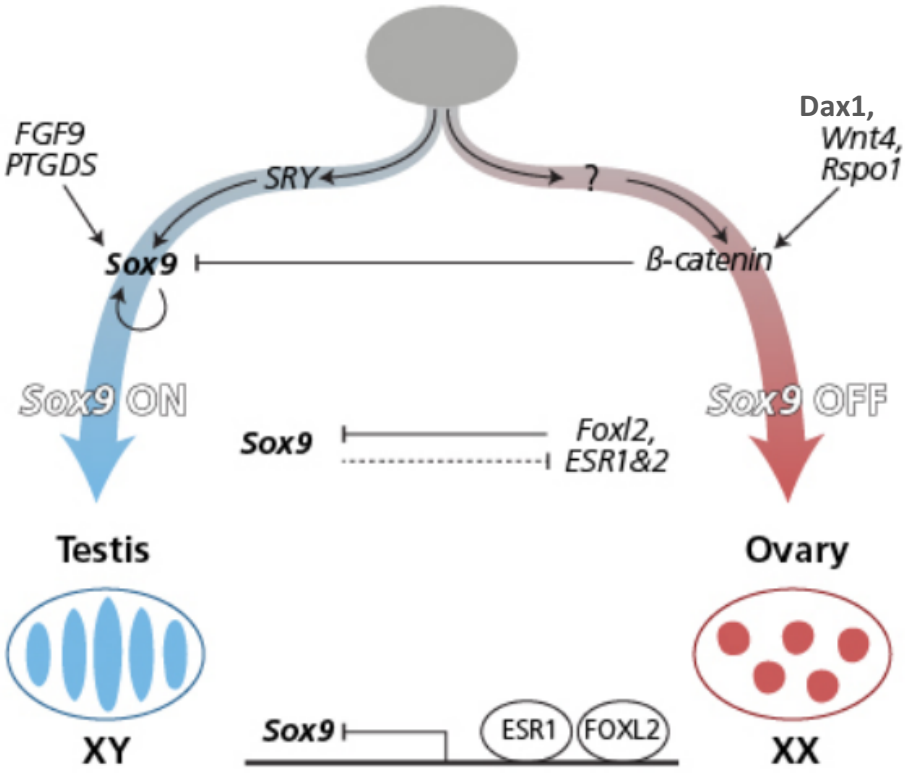
Up till the 7th week of gestation (pregnancy), there is no observable sexual difference in the gonads between males (XY) and females (XX). These undifferentiated gonads have the potential to form either ovaries or testes. Hence, this stage is called the **bipotential stage** (or the indifferent stage). Following this stage, gonads differentiate into testes or ovaries.

Around 7 weeks gestation, the **SRY** gene on the Y chromosome is activated. The product of this gene upregulates a transcription factor, **SOX9**, which is essential for gonads to differentiate into testes. Without SOX9, the gonads will differentiate into ovaries. Throughout a male person's adult life, Sox9 maintains the male system. In females, **Foxl2** and **estrogen receptors** (ESR1&2) repress Sox9 to maintain the female system, preventing ovaries from being reprogrammed into testes. (Think of primary sex organ determination as a lifelong "Sox versus Fox" battle).

Development of *internal* accessory sex organs (Phenotypic Sex):

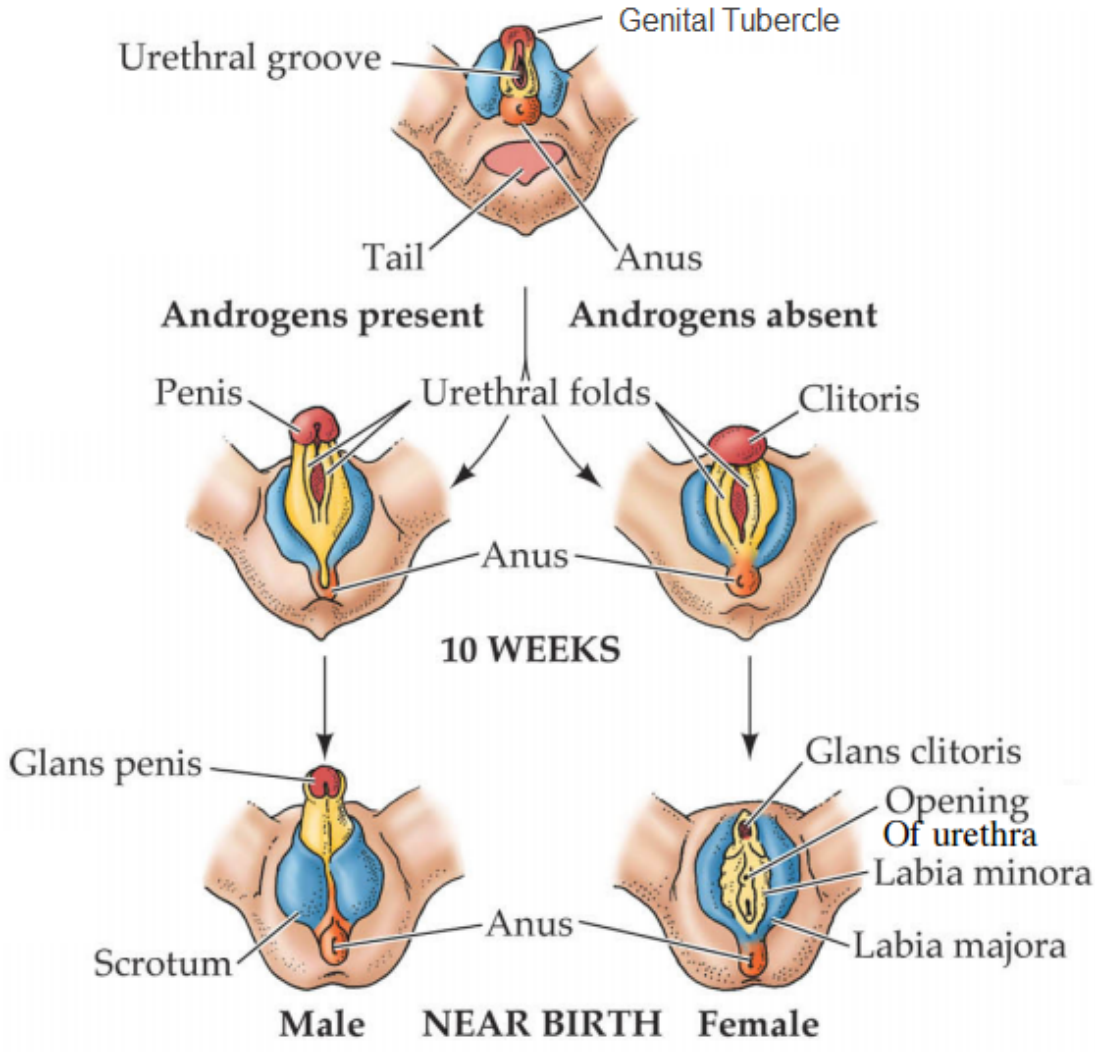
Previously, we discussed how the commitment to testes versus ovaries is made and maintained. Now, we will see how, starting from the bipotential stage, the internal accessory sex organs in males and females develop.

Bipotential stage 4-7 weeks gestation Both **Wolffian** and **Mullerian** ducts develop.	
Males (XY) Around 7 weeks gestation, when the SRY gene gets activated, **SOX9** expression results in the differentiation of gonads into testes. Testes produce **Mullerian inhibiting hormone (MIH)**, also known as Anti-Mullerian hormone (AMH), which degenerates Mullerian ducts. Testes also produce **testosterone**, which promotes the development of male accessory sex organs. Result: Mullerian ducts degenerate and Wolffian ducts remain (to become the male accessory internal genitalia: **vas deferens, seminal vesicles,** and **epididymis**).	Females (XX) **DAX1** gene on X chromosome as well as the genes: **Wnt4, Rspo1,** and **beta-catenin,** promote ovary development through repression of SOX9. Ovaries produce **estrogen**, which favors the development of Mullerian ducts and female accessory sex organs. Result: Wolffian ducts degenerate and Mullerian ducts remain (to become the female accessory internal genitalia: **oviducts** [**Fallopian tubes**], **uterus**, **cervix**, and **upper vagina**)



Development of *external* sex organs (Phenotypic Sex):

Male and female external genitalia develop from the same embryonic tissue, consisting of a **genital tubercle**, **urethral groove**, and **urethral folds**. The differentiation of external genitalia depends on androgens. As male gonads begin to form in the 7th week and begin producing androgens, by weeks 8-9, androgens determine phenotypic sex.



Development of secondary sexual characteristics (Phenotypic Sex):

Secondary sexual characteristics are features that appear during sexual maturity (puberty) and are sexually dimorphic traits that distinguish males from females. These features are not part of the reproductive system but rather are used for purposes such as courtship, child-bearing, etc. Such features include enlarged breasts for females and facial hair for males. The development of these features are stimulated by the sex hormones (estrogen in females and testosterone in males), which rise during puberty.

Ambiguous Sex Determination:

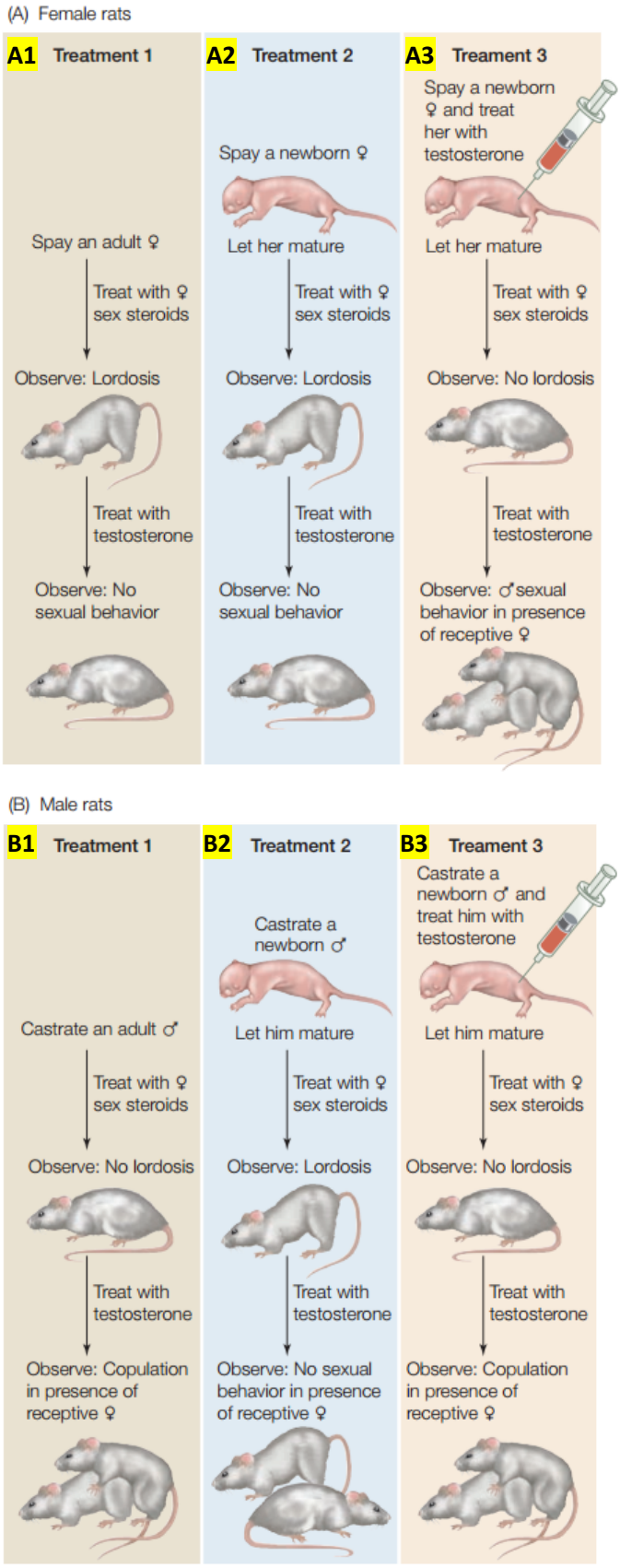
Certain genetic mutations or abnormalities, especially aneuploidy, can result in ambiguous sex determination. Let's look at a few examples:

- **Klinefelter's syndrome** (XXY): The presence of two X chromosomes impairs testes formation, leading to small (yet functional) testes and underproduction of testosterone. Although male primary sex organs and male accessory sex organs are present, there is a mix of male and female secondary sexual characteristics (due to decreased testosterone production).
- **Androgen insensitivity syndrome**: Normal XY genotype and functional internal male sex organs (including testes), but androgen receptors are lacking due to a genetic mutation. As a result, female external genitalia and female secondary sex characteristics are present.
- **Turner syndrome** (X0): Individuals develop as females but ovaries are not functional.
- **XX males and XY females**: Result of an unequal crossing over event between the X and Y chromosomes during meiosis. Consider the case that the Y chromosome's short arm, which contains SRY, is translocated to an X chromosome. A person who gets that Y chromosome would become an XY female (due to lack of SRY on the Y chromosome) and a person who gets that X chromosome (containing the translocated SRY) would become and XX male.
- **Male pseudohermaphroditism**: Results from a mutation of the 5-alpha-ketosteroid reductase (5AR) gene, which encodes an enzyme that converts testosterone to 5-alpha-dihydrotestosterone (DHT). Testosterone promotes development of epididymis, seminal vesicles, and vas deferens, but DHT is necessary for development of male urethra, prostate, penis, and scrotum until puberty. These individuals, called guevedoces, have female secondary sex characteristics and some female accessory sex organs (despite being XY males) until puberty (when there's a significant increase in testosterone levels).

Development of sexual behavior (Behavioral Sex):

Sexual behavior depends on development of circuits in the brain and can be independent of genotype or phenotype. Consider the experiment on the next page, which demonstrated the role of hormones in sexual behavior. This experiment demonstrated the following: Testosterone masculinizes the nervous system of both male and female newborn rats. Whether male or female sexual behavior develops depends on exposure to testosterone as a newborn. In adulthood, testosterone and estrogen control the expression of sexual behavior.

Further experiments showed that rodent sexual behavior depends on pheromones. Rodents have two olfactory systems: A main olfactory system, which includes the main olfactory epithelium and the main olfactory bulb, and an accessory olfactory system, which includes the vomeronasal organ and the accessory olfactory bulb. The **vomeronasal organ (VNO)** is thought to be responsible for the sensing of pheromones. With loss of an olfactory receptor in the vomeronasal organ, male mice cannot distinguish male from female individuals so will attempt to mate with both.



Experiment:

- Whether a female rat is spayed at birth (panel A2) or as an adult (panel A1) doesn't matter – either way, as an adult, she will exhibit lordosis (a female sexually receptive posture) when treated with female sex steroids.

Conclusion: Development of female sexual behavior does not require exposure to estrogen.

- A spayed newborn female rat exposed to testosterone will develop male sexual behavior as an adult (panel A3).

Conclusion: Exposure to testosterone at birth can cause females to develop male sexual behavior.

- A male rat castrated as an adult will not exhibit female sexual behavior (lordosis) even when treated with female sex steroids (panel B1). However, a male rat castrated at birth will develop lordosis as an adult when treated with female sex steroids (panel B2). This is rescued by exposure to testosterone as a newborn (panel B3).

Conclusion: Development of male sexual behavior in males requires exposure to testosterone at birth.

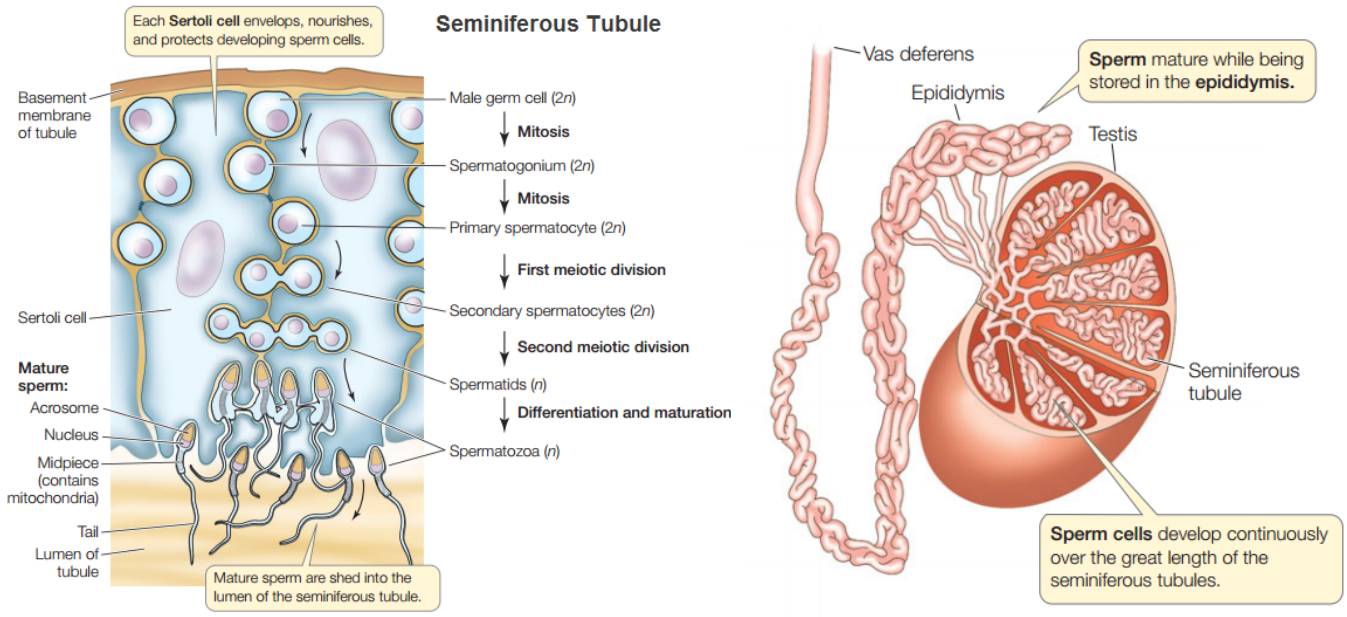
- Testosterone produces male sexual behavior only in adult rats whose brains were masculinized when they were newborns (i.e. exposed to testosterone as newborns) (panels A3, B1, and B3), and estrogen produces female sexual behavior (i.e. lordosis) only in adult rats whose brains were not masculinized when they were newborns (panels A1, A2, and B2).

Conclusion: In adulthood, sex steroid hormones determine when sexual behavior patterns are expressed and the sexual behavior patterns that are to be expressed have already been determined by exposure to testosterone at birth. Hence, the default circuitry is to exhibit female sexual behavior patterns; testosterone is necessary at birth to develop male circuitry.

Male Reproductive System

Sperm formation, maturation, and release:

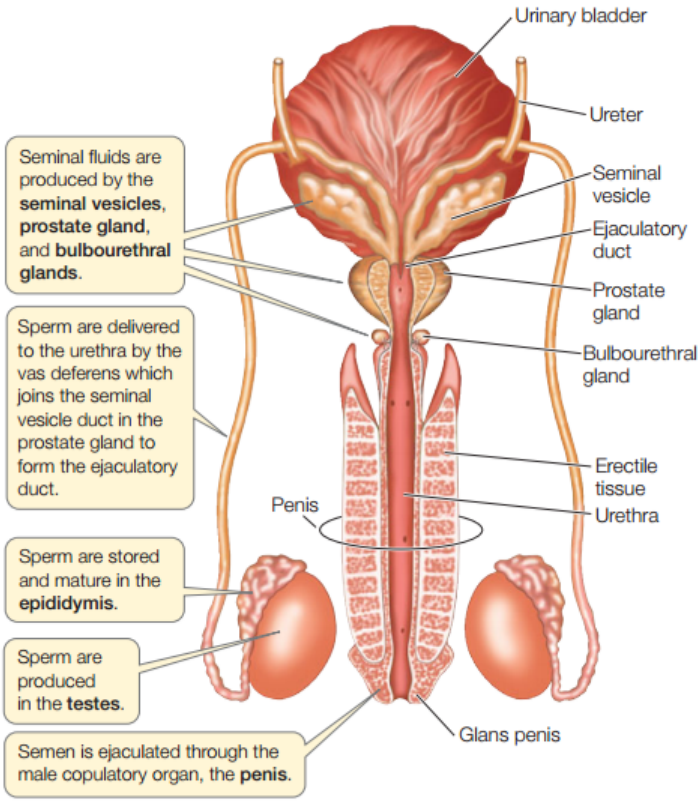
In the male reproductive system, spermatogenesis occurs in **seminiferous tubules** (500 half-meter segments) in each of the two testes. Between the seminiferous tubules are **Leydig cells**, which produce testosterone. The spermatogonia line the basement membrane of the seminiferous tubules and give rise to spermatocytes, which enter meiosis. Secondary spermatocytes (products of meiosis I) undergo meiosis II to become spermatids which are shed into the lumen of the seminiferous tubules. **Sertoli cells** of the tubules nurse and protect the developing spermatozoa. Tight junctions between Sertoli cells create a blood/sperm barrier. The sperm are propelled (by large volumes of fluid) to a tube called the **epididymis**, where they mature and become motile. Sperm are then delivered to the urethra by the **vas deferens** which joins the seminal vesicle duct to form the **ejaculatory duct**.



Accessory glands contribute over 90% of the volume of semen. The accessory glands are:

- **Seminal vesicles**: Empty into the vas deferens just before the vas deferens joins the urethra. Secretes mucus, nutrients (e.g. fructose), fibrinogen, and prostaglandins.
- **Prostate gland**: Surrounds the urethra and secretes an alkaline fluid (to neutralize acidity and make the environment more hospitable for sperm). Also secretes a clotting enzyme that causes the fibrinogen from the seminal vesicles to convert the semen into a coagulum (gelatinous mass), facilitating its propulsion into and retention in the upper regions of the female reproductive tract. Another enzyme in prostate fluid, called profibrinolysin, is inactive when secreted but is activated shortly after entering the female reproductive tract. It dissolves the clotted semen and liberates the sperm.
- **Bulbourethral gland**: Produces a small amount of an alkaline secretion that helps neutralize the acidity of the urethra.

The penis has three parts: the **shaft**, the **glans**, and the **foreskin**. Its erectile tissue consists of three cylinders of venous sinusoids.



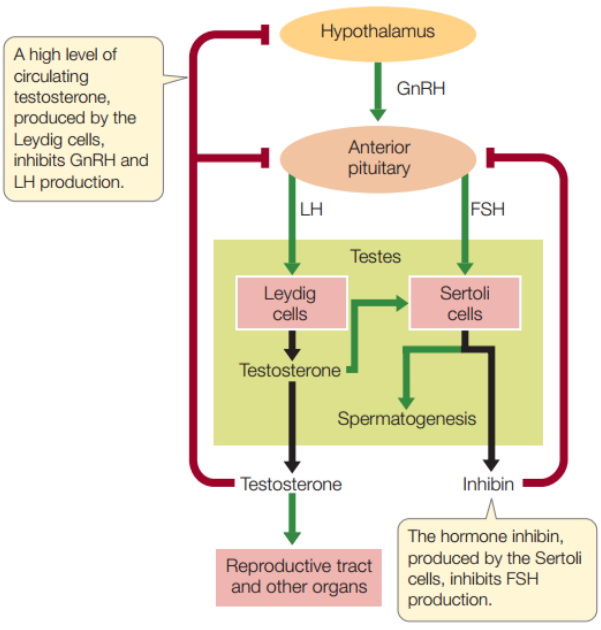
- Erection: During an erection, which is a nervous parasympathetic reflex, the arteries to the penis dilate and the venous sinusoids fill with blood and compress the veins draining the penis. How is the parasympathetic nervous system involved in an erection? Parasympathetic stimulation stimulates synthesis and release of nitric oxide (NO) from endothelial cells of penile arterioles. NO diffuses to smooth muscle and causes synthesis of cyclic GMP (cGMP) which causes relaxation of smooth muscle and vasodilation. cGMP is normally broken down by phosphodiesterase 5 (PDE5). Viagra inhibits PDE5 (preventing the breakdown of cGMP) and thereby sustains the vasodilation.

- Ejaculation is the expulsion of sperm from the penis and is a sympathetic reflex. **Emission** is the first stage of ejaculation wherein sympathetic stimulation causes accessory glands to secrete their contents into the urethra. The second stage is **peristaltic contractions** of the various accessory ducts and contractions of the muscles surrounding the base of the penis to force semen out.

(Note: Erection is a *parasympathetic* reflex whereas ejaculation is a *sympathetic* reflex).

Hormonal control of male sexual functions:

Spermatogenesis is regulated by hormones. **Gonadotropin-releasing hormone** (**GnRH**) is released by the hypothalamus and stimulates anterior pituitary cells to increase secretion of **luteinizing hormone** (**LH**) and **follicle-stimulating hormone** (**FSH**). Higher levels of LH stimulate Leydig cells to secrete more testosterone. Testosterone and FSH act on Sertoli cells in the seminiferous tubules to promote spermatogenesis.

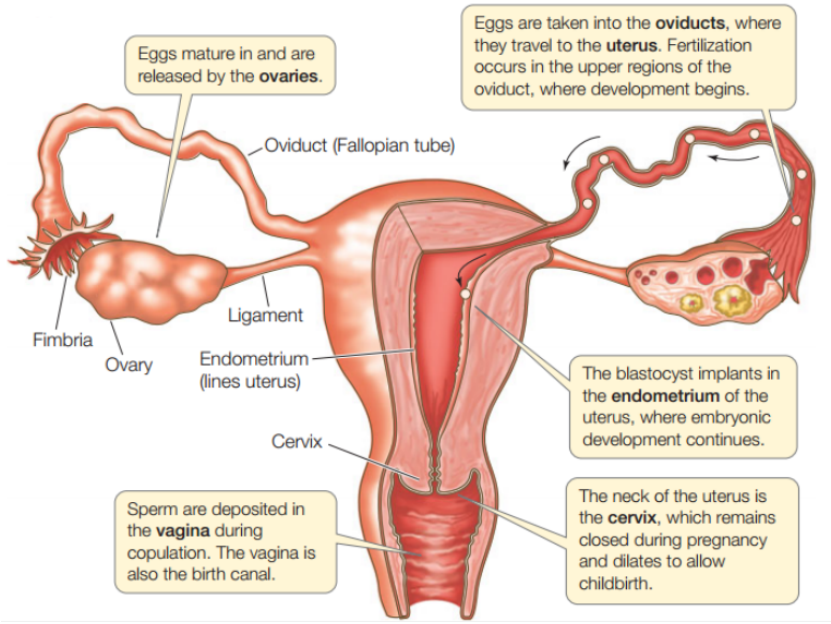


There are several negative feedback mechanisms going on. First, testosterone exerts negative feedback on the anterior pituitary and the hypothalamus. Also, Sertoli cells produce a hormone called inhibin, which exerts negative feedback on the anterior pituitary cells that secrete FSH. At puberty, the hypothalamus is less sensitive to testosterone, thus more GnRH (and, as a result, more LH and therefore more testosterone) is released.

Female Reproductive System

Ova production:

How are ova (eggs) produced in females? During fetal life, the ovary is covered by a germinal epithelium that produces primordial ova that migrate into the ovary and become surrounded by **granulosa cells** to form primordial **follicles**. There are 1 million primordial follicles at birth. Some die off and about 300,000 remain at puberty. About 400 mature during reproductive life, which ends at menopause.



Ova migration and fertilization:

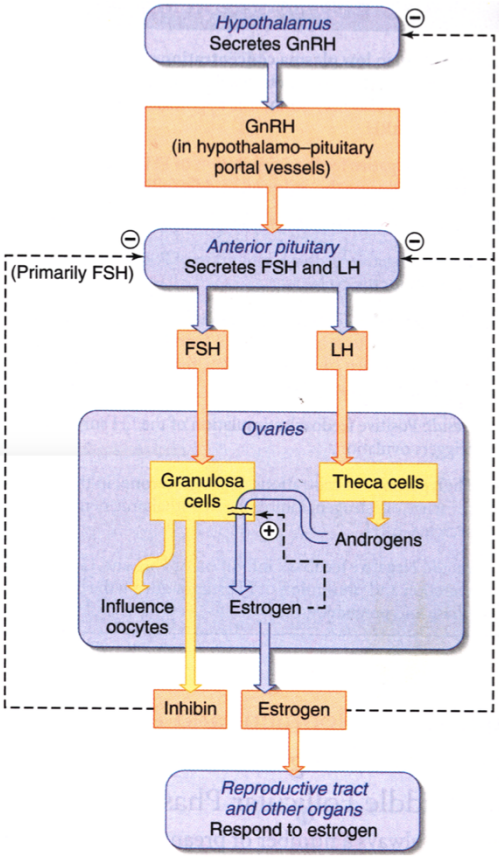
In the female reproductive system, ova are released from the ovaries monthly. They are swept by **fimbriae** (small fingerlike projections) into the opening of the **Fallopian tubes** (aka the **oviducts**). There, they are moved by cilia towards the **uterus**. Fertilization occurs when sperm meets the ovum in the upper third of the Fallopian tube. The **blastocyst** (mammalian blastula) that forms arrives in the uterus and implants in the **endometrium** (the uterine wall). The implanted blastocyst develops and also forms **extraembryonic membranes** (tissue that enclose and support the developing embryo).

The ovarian cycle:

The ovarian cycle is how hormones control the monthly maturation of follicles and release of ova.

1) It begins with rising GnRH and FSH (and LH), leading to the maturation of 6-12 follicles. FSH stimulates the development of follicles, and since the granulosa cells of the follicles release estrogen, estrogen levels rise. Estrogen puts negative feedback on GnRH (from the hypothalamus) and FSH (from the anterior pituitary), keeping levels of FSH low (so no new follicles mature) and LH low. Generally only one follicle survives and fully matures; the others undergo **atresia** (degeneration). The mature ovarian follicle consists of the primordial ovum, granulosa cells, and a surrounding layer of **thecal cells**.

> Why does only one follicle survive? Because LH stimulates thecal cells to produce androgens, which diffuses to granulosa cells. Granulosa cells convert androgens into estrogen. The estrogen stimulates production of more FSH receptors on granulosa cells. The follicle with the most FSH receptors will be the one that survives as that particular follicle will be most receptive to the low levels of FSH.



2) Midcycle: FSH and LH hormone levels rise sharply. This is because there is a switch from negative feedback of estrogen to positive feedback of estrogen. Estrogen begins to exert positive feedback on the pituitary, leading to a surge of LH and, to a lesser extent, FSH. The LH surge triggers **ovulation**, in which the one mature follicle ruptures and releases the ovum, and causes granulosa cells to become a structure called the **corpus luteum**, which secretes both estrogen and progesterone (crucial for the maintenance of the endometrium). LH helps maintain the corpus luteum.

3) The estrogen produced by the corpus luteum exerts negative feedback (once again!), keeping GnRH, FSH, and LH levels low (so no new follicles mature). If the egg is not fertilized, the corpus luteum degenerates (due to lack of LH). Since the corpus luteum secreted estrogen, with it gone, GnRH, FSH, and LH all begin to increase (since no more negative feedback from estrogen). The cycle repeats!

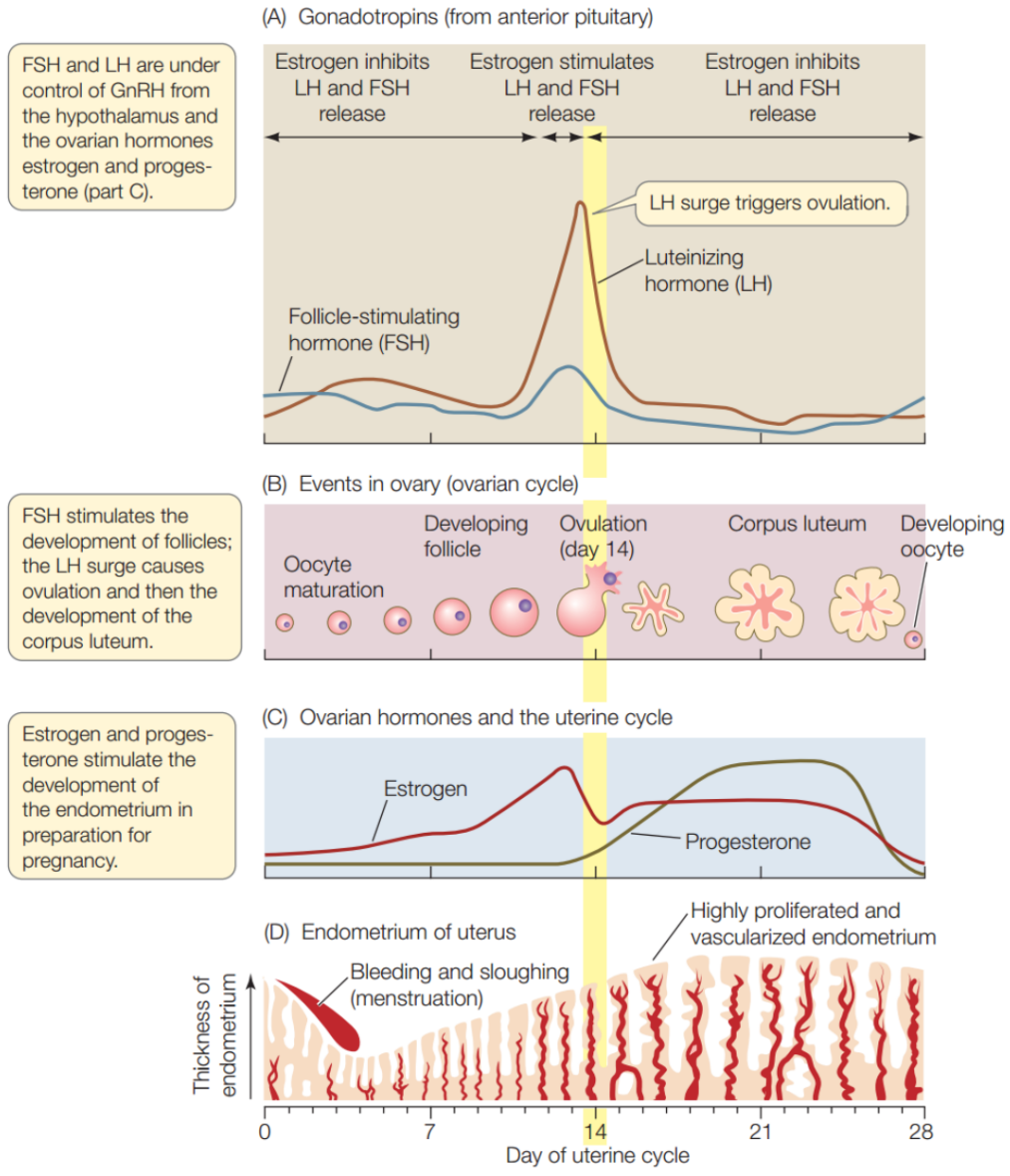
The uterine (menstrual) cycle:

This cycle begins with the sloughing off of the endometrium (see the end of step 3 from the ovarian cycle).

1) Follicular phase: Rising estrogen (secreted by granulosa cells of follicles) stimulates proliferation and vascularization of the endometrium.

2) Midcycle: Corpus luteum forms, producing estrogen and progesterone to maintain the endometrium.

3) Menstruation or pregnancy: If there's no pregnancy, the corpus luteum degenerates, and the endometrium is sloughed off (**menstruation**) due to falling levels of estrogen and progesterone. If implantation occurs, cells of the blastocyst produce **human chorionic gonadotropin (hCG)**, a hormone similar in structure to LH, which sustains the corpus luteum until the placenta takes over estrogen and progesterone production.



Contraception

Contraception, or birth control, is the deliberate use of artificial methods or techniques to prevent pregnancy as a consequence of sexual intercourse. Below are some common contraceptive methods.

METHOD	MODE OF ACTION	FAILURE RATE[a]
Rhythm method	Abstinence near time of ovulation	15–35
Coitus interruptus	Prevents sperm from reaching egg	10–40
Condom	Prevents sperm from entering vagina	3–20
Diaphragm/jelly	Prevents sperm from entering uterus; kills sperm	3–25
Vaginal jelly or foam	Kills sperm; blocks sperm movement	3–30
Douche	Supposedly flushes sperm from vagina	80
Birth control pills	Prevent ovulation	0–3
Vasectomy	Prevents release of sperm	0.0–0.15
Tubal ligation	Prevents egg from entering uterus	0.0–0.05
Intrauterine device (IUD)	Prevents implantation of fertilized egg	0.5–6
RU-486	Prevents development of fertilized egg	0–15
Unprotected	No form of birth control	85

[a] Number of pregnancies per 100 women per year

Sexual Arousal and Response

A variety of stimuli can lead to **arousal**. Those include visual stimuli, sound, smell, imagination, as well as the especially important: touching of erogenous zones. Note that parasympathetic tone is essential for sexual arousal and that arousal can be reversed or prevented by stress, fear, conflicting stimuli, and psychology.

When humans become sexually aroused and participate in sexual activities, they experience a sequence of events known as the sexual response cycle, comprised of stages as follows:

- **Excitement**: Blood flow to the genitals increases (erection occurs in males and engorgement of genital tissue occurs in females)
- **Plateau**: Sexual behavior will continue through an extended period of time
- **Orgasm**: Sudden switch from parasympathetic to sympathetic activation (ejaculation occurs)
- **Resolution**: Everything goes back down to a quiet state

Now, let's compare and contrast what happens in males vs. females.

In males: Arousal due to sight, smell, sound, touch, and ideation, leads to the excitement stage where there is an increase in blood flow to the penis, resulting in an erection. In this excitement stage, the erogenous zones (especially the penis) become more sensitive to touch and the heart rate, respiratory rate, and blood pressure increase. Sexual activity continues in what is known as the plateau stage, until orgasm occurs, which is a sudden burst of sympathetic activation involved in ejaculation accompanied by intense pleasure. Finally, there is a very rapid resolution, wherein the blood flow decreases to the penis, blood drains out of the penis, and things go back to normal. In males, resolution is accompanied by a **refractory period**, during which even with continued stimulation, the excitement phase cannot be triggered again. This refractory period is likely due to the release of **prolactin**, an anterior pituitary hormone.

In females: Arousal due to arousing stimuli results in vaginal lubrication (wetting) and increased blood flow to many tissues of the body, causing engorgement of the nipples, clitoral tissue, labia, and vagina, as well as sexual flushing in many parts of the body (due to increased skin blood flow). The excitement stage which follows is similar to that of males. During orgasm, there is rhythmic contraction of pelvic muscles and intense sexual pleasure -- and ejaculation may occur (this is a controversial point which we'll explore below). A major difference between the male and female sexual response is that females don't have a refractory period – they are capable of multiple orgasms. In fact, three different patterns of response are possible: 1) A response similar to the male response where there's excitement, plateau, then orgasm (except females can have multiple orgasms), 2) A very rapid transition from excitement to orgasm (no plateau), 3) A prolonged orgasmic state.

The **clitoris** is homologous to the glans penis (the highly sensitive part of the penis). The clitoris is composed of erectile tissue and is the primary organ of sexual stimulation in females. Although previously thought to be a very small structure, the clitoris is actually not such a small little structure. It turns out that the majority of the clitoris is actually internal to the body – only the very tip is exposed to the outside. This is in contrast to males where most of the erectile tissue is external to the body.

Are female orgasms clitoral or vaginal? The vagina, unlike the clitoris, is poorly innervated with sensory nerves. However, the **G spot** (Graffenberg spot) is a region of high sensitivity in the vagina – it's a not-so-clearly defined structure on the anterior wall of the vagina and is highly variable from individual to individual.

Do female ejaculations occur? A high percentage of women report releasing a small volume of fluid at the time of orgasm. This fluid has high levels of compounds associated with the prostate gland, including prostate-specific antigen, prostatic acid phosphatase, and glucose (which are not present in urine), and has low levels of creatinine (which occurs in urine). Hence, this fluid is not urine. It turns out that this fluid comes from **Skene's glands** – small glandular structures of unknown function that are highly anatomically variable from individual to individual (they don't even occur in some individuals).

The high variability from individual to individual of the G spot and the Skene's glands has led to controversy about whether those structures actually exist.

The Respiratory System

A respiratory system is an organ system that enables animals to participate in respiratory gas exchange. Cells need to obtain oxygen from the environment to produce ATP by cellular respiration. Carbon dioxide is a waste product of cellular respiration that must be removed from the body.

Diffusion

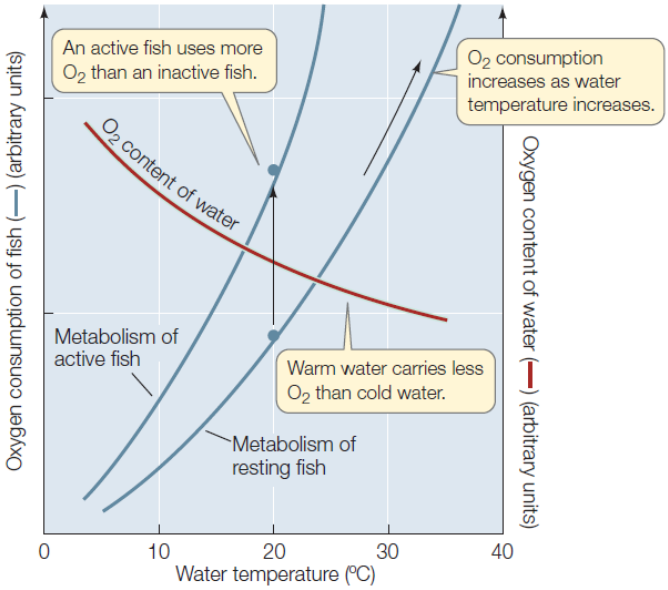
Diffusion, the net passive movement of molecules down the molecule's concentration gradient, is the only means by which respiratory gases are exchanged between an animal's internal *milieu* (environment) and the outside environment. No active transport is involved in moving respiratory gases across biological membranes.

The rate of diffusion is governed by **Fick's law of diffusion**: $Q = D\frac{A(C_1 - C_2)}{l}$

- Q = Rate at which a respiratory gas diffuses between two locations.
- D = Diffusion coefficient (a characteristic of the diffusing substance, the medium, and the temperature). CO_2 has a higher D than O_2 because CO_2 is more soluble in water. D is greater at higher temperatures and if air is the medium as opposed to water (substances diffuse faster at higher temperatures and faster in air than in water).
- A = Cross-sectional area through which the gas is diffusing.
- C_1 and C_2 = Concentrations (*partial pressures*) of the gas at the two locations.
- L = The path length (distance) between the two locations.

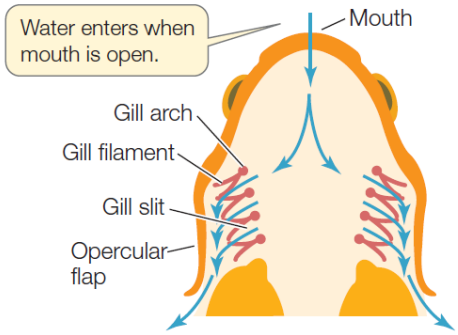
Air vs. Water:

It is better to breathe in air than in water: Air has higher O_2 content as well as lower density and lower viscosity compared to water; hence, gas exchange is more efficient in air. Furthermore, in water, as temperatures rise, dissolved oxygen levels in the water go down. This is problematic because ectothermic organisms (like most water-breathing animals) have higher metabolic rates when water temperature rises. So, at higher temperatures, ectothermic aquatic animals get less oxygen from water but have a higher demand for oxygen. This is compounded by the fact that, since these animals perform work to move water across gas exchange surfaces, more energy needs to be expended for breathing as water temperatures rise (since the water becomes more oxygen-deficient).



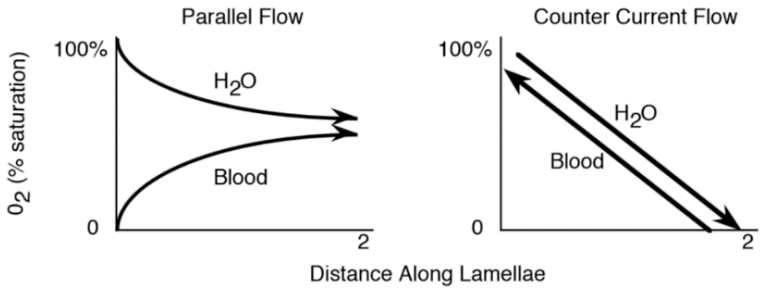
Fish Gills

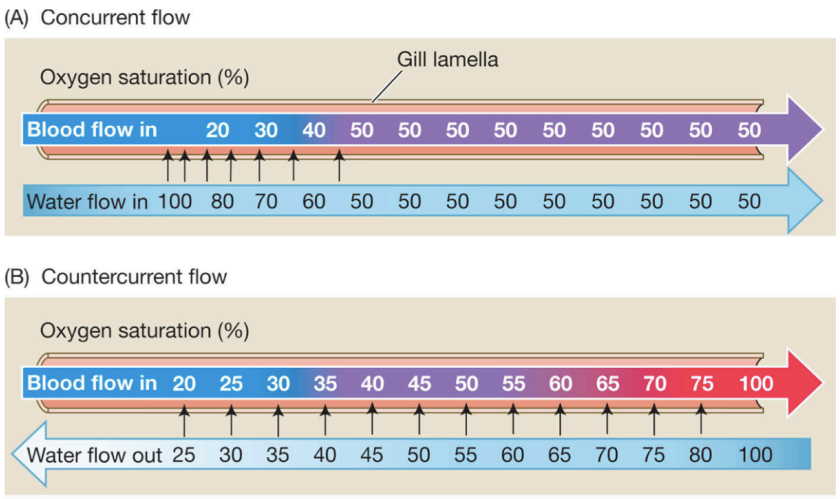
Gills are respiratory structures found in many water-dwelling animals. Water enters a fish's mouth when it is open and proceeds to flow unidirectionally over the gills, exiting under the opercular flaps. The unidirectional continuous flow of water over the gills maximizes the partial pressure of oxygen on the external gill surfaces. On the internal side of the gill membranes, the circulation of blood minimizes the partial pressure of oxygen by sweeping oxygen away as rapidly as it diffuses across.



Gills have an enormous surface area for gas exchange because they are so highly divided. Each gill consists of hundreds of gill filaments. The upper and lower flat surfaces of each gill filament are covered with rows of evenly spaced folds, or lamellae. The lamellae are the actual gas exchange surfaces. Because they are exceedingly thin, the path length (L) for diffusion of gases between blood and water is minimized.

The flow of blood perfusing the inner surfaces of the lamellae, like the flow of water over the gills, is unidirectional. Afferent blood vessels bring deoxygenated blood to the gills, while efferent blood vessels take oxygenated blood away from the gills. Blood flows through the lamellae in the direction opposite to the flow of water over the lamellae. This **countercurrent flow** optimizes the pO_2 gradient between water and blood, making gas exchange more efficient than it would be in a system using concurrent (parallel) flow.

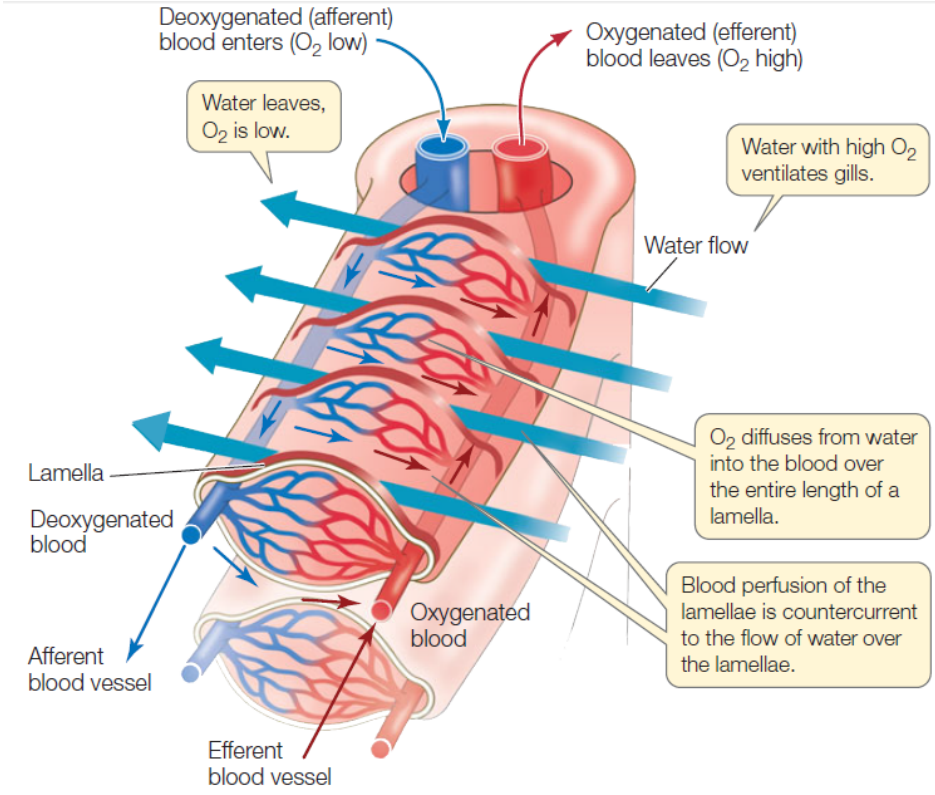




Some fishes ventilate their gills by swimming almost constantly with their mouths open. Most fishes, however, ventilate their gills by means of a <u>two-pump mechanism</u>:

1. <u>Buccal</u>: The closing and contracting of the mouth cavity pushes water over the gills.
2. <u>Opercular</u>: The expansion of the opercular cavity prior to opening of the opercular flaps pulls water over the gills.

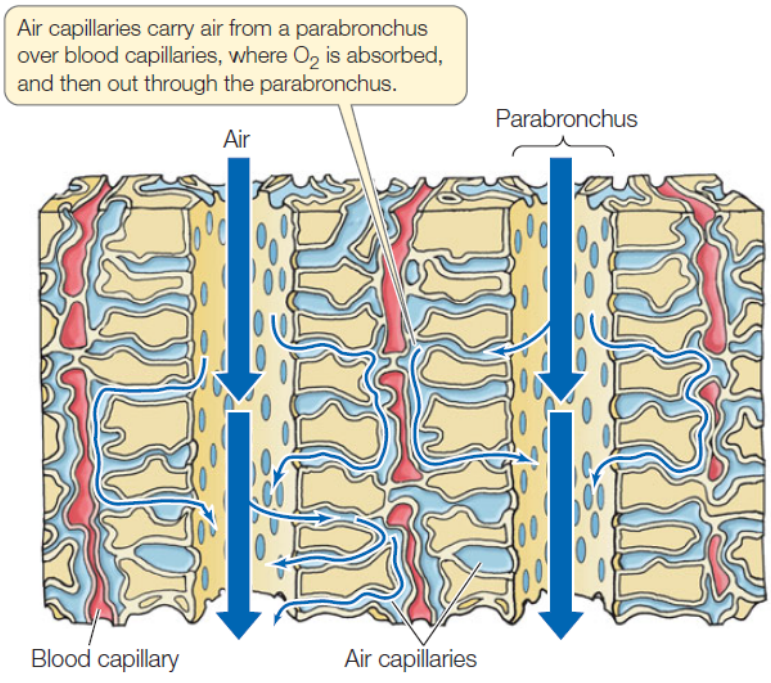
These pumps enable the fish to maintain a continuous and unidirectional flow of water across the gills



Avian Respiratory Systems

Respiratory demands on birds are extreme. Energy demands of flight are fifteen to twenty times the basal metabolic rate. Moreover, extended flights frequently take place at high altitudes where the concentration of oxygen is low. At all altitudes, the atmosphere is 20.9% oxygen (pO_2 = 20.9% of total air pressure). At sea level, 20.9% of atmospheric pressure (760 mm Hg) is ~160 mm Hg but on Mount Everest, 20.9% of atmospheric pressure (250 mm Hg) is only 52 mm Hg. The pO_2 on Mount Everest is clearly much lower than the pO_2 at sea level. So, what adaptations have birds evolved to keep up with such conditions?

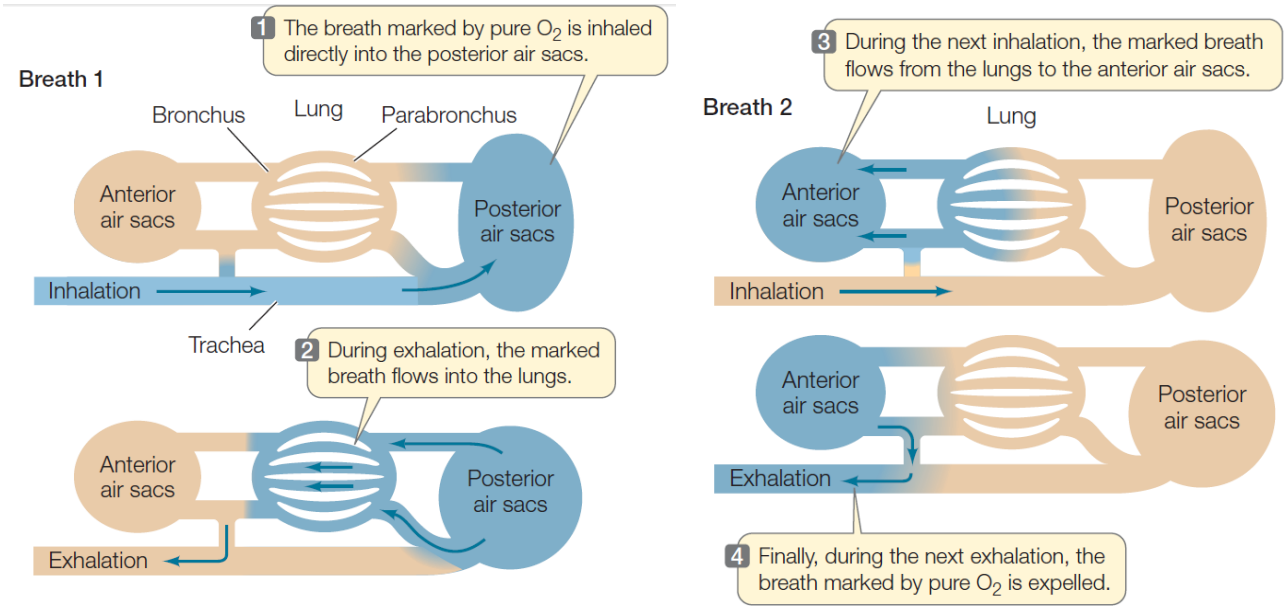
- **Lungs**: The structure of bird lungs allows air to flow unidirectionally through the airways, rather than bidirectionally through all the same airways (as it does in mammals). Because mammalian lungs are never completely emptied of air during exhalation, there is always some lung volume, called *dead space*, that is not ventilated with fresh air. In contrast, bird lungs have very little dead space, and the fresh incoming air is not mixed with stale air; this allows for a high pO_2 gradient to be maintained.



- **Air sacs**: Air sacs are structures that receive inhaled air but are not gas exchange surfaces themselves. Air sacs are interconnected with each other, with the lungs, and with air spaces in some of the bones. Birds have air sacs at several locations in their bodies.
- **Airways**: Air enters and leaves the bird's respiratory system through the trachea (windpipe), which divides into smaller airways called bronchi. The bronchi divide into tube-like parabronchi in the lungs that run parallel to one another. Branching off the parabronchi are numerous tiny air capillaries. Air flows through the parabronchi and diffuses into the air capillaries, which are the gas exchange surfaces. They are so numerous that they provide an enormous surface area for gas exchange. The parabronchi coalesce into larger bronchi that take the air out of the lungs and eventually back to the trachea.

Bird lungs are unusual in that they are smaller and less compliant than those of similar-sized mammals, and bird lungs expand and contract less during a breathing cycle than do mammalian lungs. Furthermore, bird lungs are compressed during inhalation and expand during exhalation. But bird respiratory systems are extremely efficient because the configuration of air sacs and lungs permits *unidirectional continuous* flow, as in fish gills. The air sacs act as bellows to maintain this continuous unidirectional flow of air (through the trachea, bronchi, posterior air sacs, parabronchi in the lungs, anterior air sacs, and out again via the trachea). Avian respiratory systems maximize the concentration of oxygen on the environmental side of the gas exchange membranes.

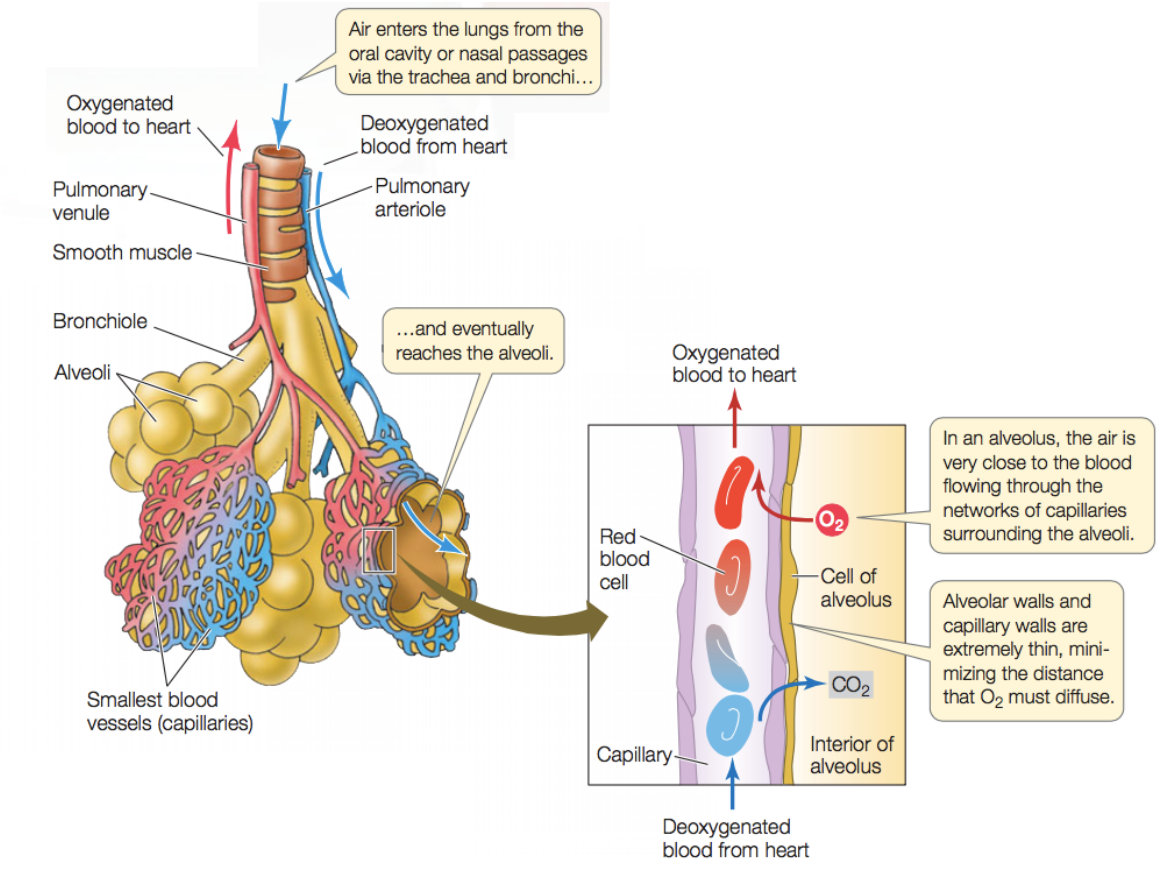
Each breath of air is in the avian respiratory system for 2 breathing cycles. Inhalation expands the air sacs and exhalation compresses the air sacs.



Mammalian Respiratory System

Air enters the mammalian lungs from the oral cavity or nasal passages via the **trachea**, the windpipe right below the *larynx* (voice box), and enters the branched **bronchi**. The trachea's thin walls are prevented from collapsing by C-shaped bands of cartilage as air pressure changes during the breathing cycle. The lungs lie within the **thoracic cavity**, which is bounded by the ribs and the diaphragm. **Pleural membranes** line the inner wall of the thoracic cavity and also cover the lungs.

Within each lung, the bronchi branch repeatedly to generate a treelike structure of progressively smaller airways extending to all regions of the lungs. After four branchings, the cartilage supports disappear, marking the transition to **bronchioles**. After about 16 branchings, tiny, thin-walled air sacs called alveoli begin to appear. **Alveoli** are the sites of gas exchange. The thin alveolar walls are made of pneumocytes and are surrounded by capillaries to minimize the path length of gas diffusion. Because the airways conduct air only to and from the alveoli and do not themselves participate in gas exchange, their volume is dead space.



Two features of gas exchange are particularly important to maximize the partial presssure gradients across the alveolar membranes:

Ventilation: Exchanging air between lungs and environment.

- Delivers oxygen to gas exchange surface.
- Delivers carbon dioxide away from gas exchange surface.

Perfusion: Delivery of blood.

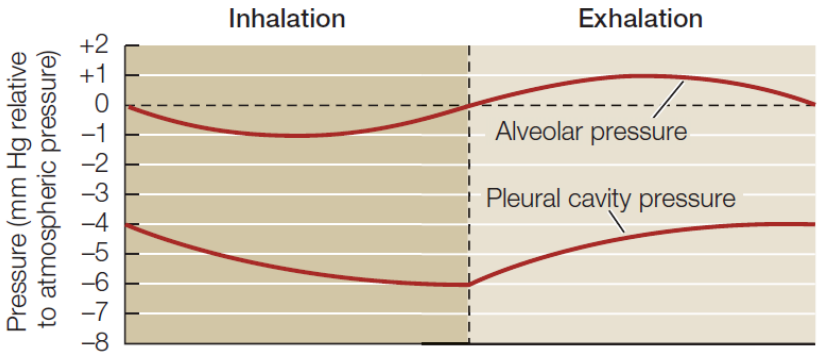
- Delivers oxygen from gas exchange surface to tissue.
- Delivers carbon dioxide from tissue to gas exchange surface.

Respiratory Mechanics: Negative Pressure Breathing

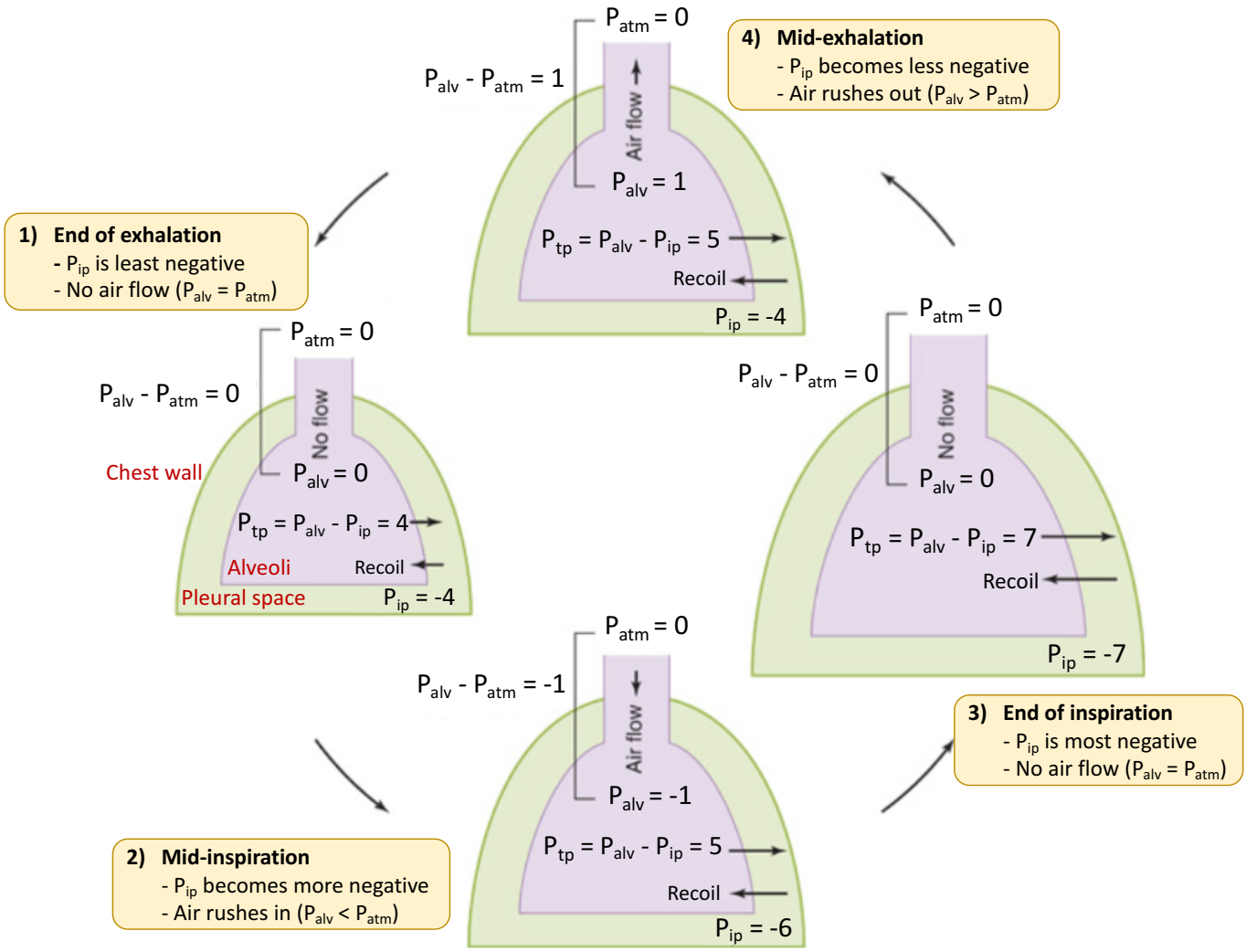
There is a little bit of fluid between the layer of pleural membrane (the parietal pleura) that lines the thoracic cavity wall and the layer of pleural membrane (the visceral pleura) that covers the lungs. This space is called the **pleural cavity.** This fluid, in addition to acting as a lubricant that allows the pleura to slide easily during breathing, also provides surface tension between the pleura. Attempting to increase the volume of the thoracic cavity will increase the tension between the pleural membranes and change the pressure in the pleural cavity. Even between breaths, there is tension between the pleural membranes because the rib cage is pulling outward and the elasticity of the lung tissue is pulling inward. This slight negative **intrapleural pressure** keeps the alveoli partly inflated even at the end of an exhalation. If the thoracic cavity is punctured, air can leak into the space between the pleural membranes and cause the lung to deflate. Breathing will then pull air in between the pleural membranes rather than into the lung (this condition is called "collapsed lung").

Muscles involved in inhalation and exhalation:

- **Diaphragm**: A dome-shaped sheet of skeletal muscle that extends across the bottom of the thoracic cavity.
    - During inhalation, as the diaphragm contracts, it pulls down, expanding the thoracic cavity and causing intrapleural pressure to become more negative. The pleural membranes cannot separate and will pull on the lungs, causing the lungs to expand and air to rush in (air flows from higher pressure [atmosphere] to lower pressure [expanded lungs]).
    - During exhalation, the diaphragm relaxes, the thoracic cavity contracts, intrapleural pressure becomes less negative, lungs undergo **elastic recoil** (that is, they rebound back to their original size), and the diaphragm is pulled up (by the elastic recoil of the lungs) causing air in the lungs to rush out (air flows from higher pressure [lungs] to lower pressure [atmosphere]).
    - Air is therefore pulled in during inhalation and pushed out during exhalation. Note that for a healthy person at rest, inhalation is an active process and exhalation is passive.



The diagram on the next page describes the respiration cycle in more detail.



P_{atm} = Atmospheric pressure (0 atm).

P_{alv} = Alveolar pressure.

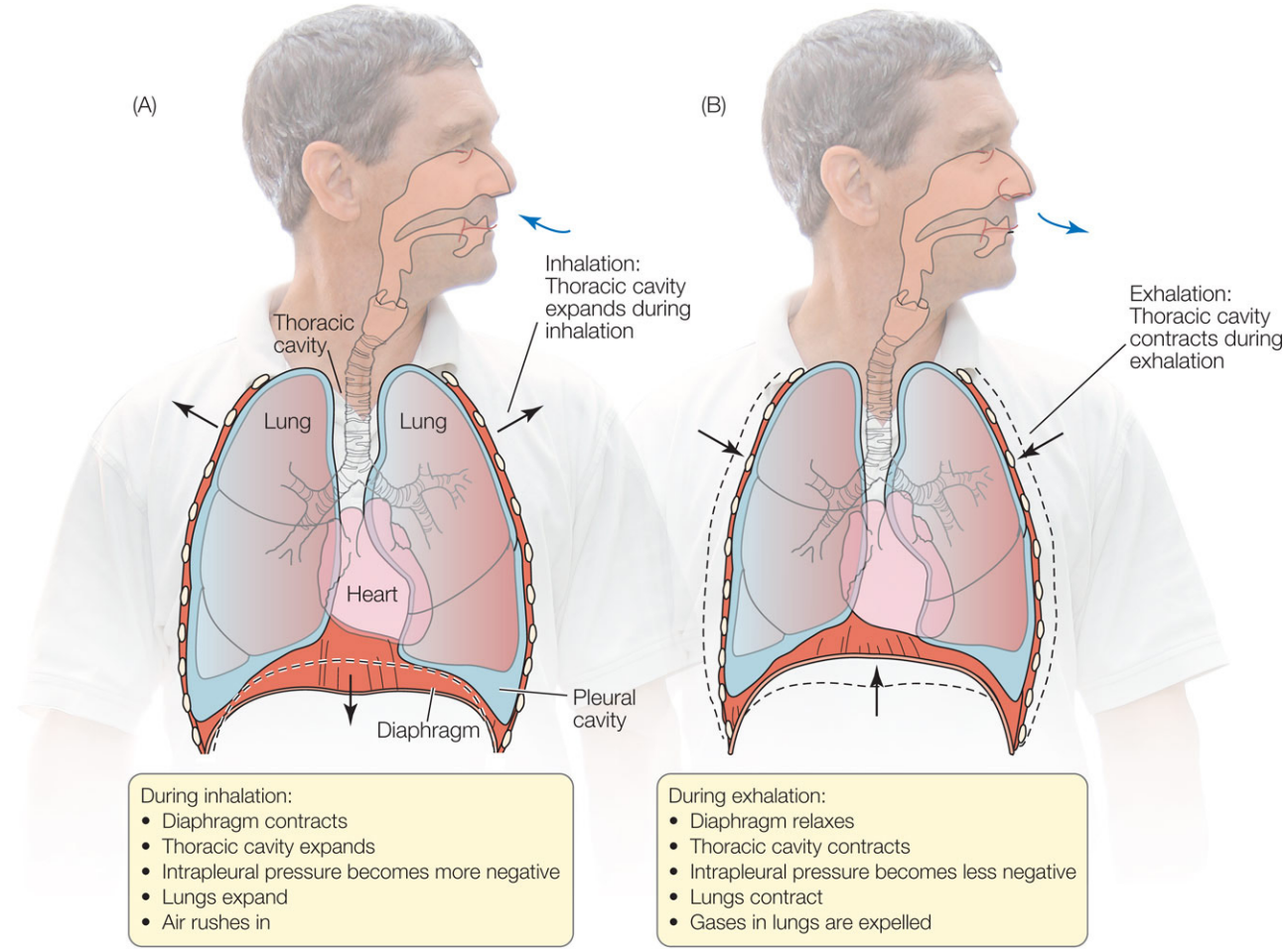
P_{ip} = Intrapleural pressure.

P_{tp} = Transpulmonary pressure: P_{alv} - P_{ip}. This is the pressure that keeps the lungs inflated (it is the net distending pressure on the alveolar walls). This should always be greater than zero (otherwise the lungs will collapse). This pressure is equal and opposite to the elastic recoil pressure of the lung.

(All numbers in the above diagram are relative to P_{atm} which is set to 0).

- **Intercostal muscles**: Located between the ribs.
    - **External intercostals**: Expand the thoracic cavity by lifting the ribs up and outward.
    - **Internal intercostals**: Decrease thoracic cavity volume by pulling ribs down and inward.
    - During strenuous exercise, the external intercostal muscles increase the volume of air inhaled, making use of the inspiratory reserve volume, and the internal intercostal muscles increase the amount of air exhaled, making use of the expiratory reserve volume.
- **Abdominal muscles:** The abdominal muscles can also aid in breathing. When they contract, they cause the abdominal contents to push up on the diaphragm and thereby contribute to the expiratory reserve volume.

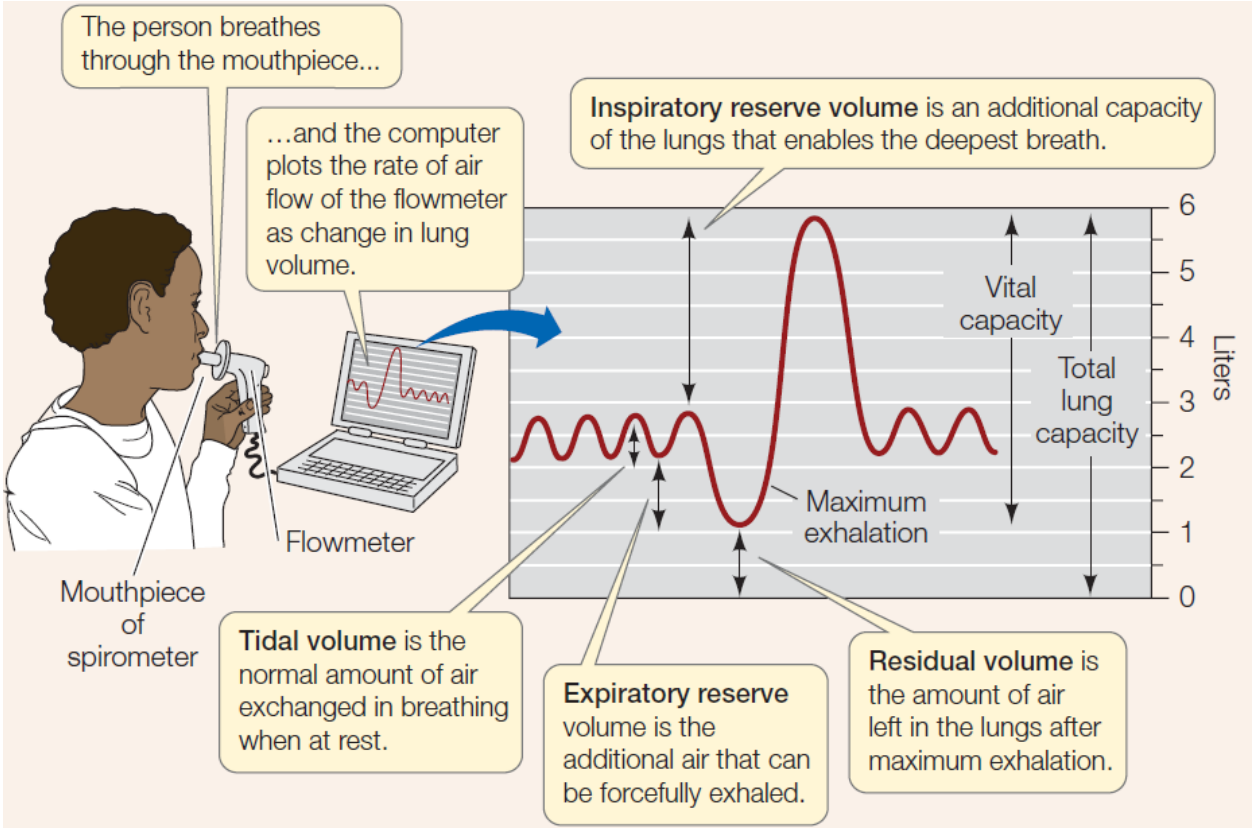
The image below shows another view of respiration.



***LIFE 10e*, Figure 49.11**

Lung Volume Measurements

A **spirometer** is a device that measures the volume of air a person breathes through a mouthpiece. The combined tidal volume (TV), inspiratory reserve volume (IRV), and expiratory reserve volume (ERV) are the lungs' vital capacity. In other words, **VC = TV + IRV + ERV.**



We can't measure residual volume (RV) directly with the spirometer since RV is the dead space, but we can measure it indirectly using the **helium dilution method** as follows:

1. Prepare a spirometer of known volume (V_{spir}). The reservoir should be filled with air mixed with helium at a known concentration ($[He]_i$).
2. Beginning with normal end expiration, a person breathes the helium-air mixture in the spirometer in a closed system. The helium is not absorbed from the lungs, so it becomes evenly distributed between the lungs and the reservoir as the subject inhales and exhales.
3. After several breaths the spirometer is sealed off at end expiration.
4. Because the fixed amount of He became dispersed in a larger volume of air, its concentration in the spirometer ($[He]_f$) will have decreased. Initially, the amount of helium we had is given by the following: $[He]_i \times V_{spir}$. At the end, the amount of helium we have is: $[He]_f \times (V_{spir} + FRV)$ where FRV is the **functional residual volume**, which is volume of air present in the lungs at the end of passive expiration. **FRV = ERV + RV**. (From FRV, we can easily find the residual volume [RV]).
5. Setting initial and final helium amounts equal, we get an equation in which we can solve for FRV: $\mathbf{[He]_i \times V_{spir} = [He]_f \times (V_{spir} + FRV)}$

Alveolar Surface Tension

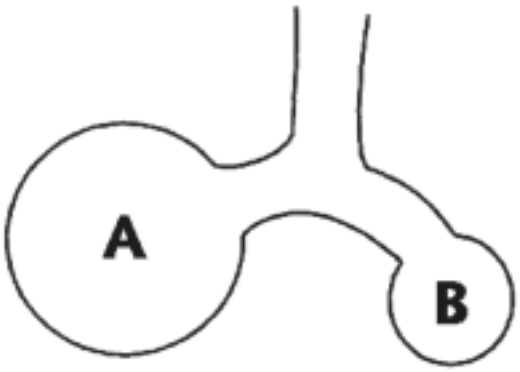
Previously, we discussed how surface tension maintains a negative pressure within the pleural cavity. Now, we will discuss surface tension of the alveoli. Specifically, the liquid lining the alveoli creates surface tension, which is responsible for the decreased **compliance** (ability to stretch/expand) of lungs filled with air. Although most pneumocytes (cells lining the alveoli) function in gas exchange at the blood-air barrier, some pneumocytes function in secreting **surfactants** (substances that reduce surface tension).

Alveolar pressure is given by the following:

$P = \frac{2T}{R}$ *(T represents tension and R represents radius).*

Alveoli are of different sizes, yet all are in communication with one another. Therefore, all alveoli share the same pressure. But, in the absence of surfactants, small alveoli require more pressure to inflate, and hence, compared to large alveoli, tend not to inflate when inhalation occurs. How do surfactants solve this problem? Surfactants reduce the surface tension of smaller alveoli *to a greater extent* than that of larger alveoli (since surfactants are more concentrated around smaller alveoli). This allows smaller alveoli to be inflatable as the larger alveoli are.

Take a look at the two alveoli below:



- Surfactants absent: Alveolus B would tend to remain near the same size during inhalation (because it takes a higher pressure to inflate B compared to A). In other words, alveolus B wouldn't get inflated like alveolus A does during inhalation.
- Surfactants present: Surface tension of alveolus B is reduced to a larger extent than that of alveolus A, allowing for both alveolus A and alveolus B to be filled upon inhalation. It will take about the same pressure to inflate both the small (B) and large (A) alveoli. For that reason, surfactants are sometimes referred to as “The Great Equalizer”.

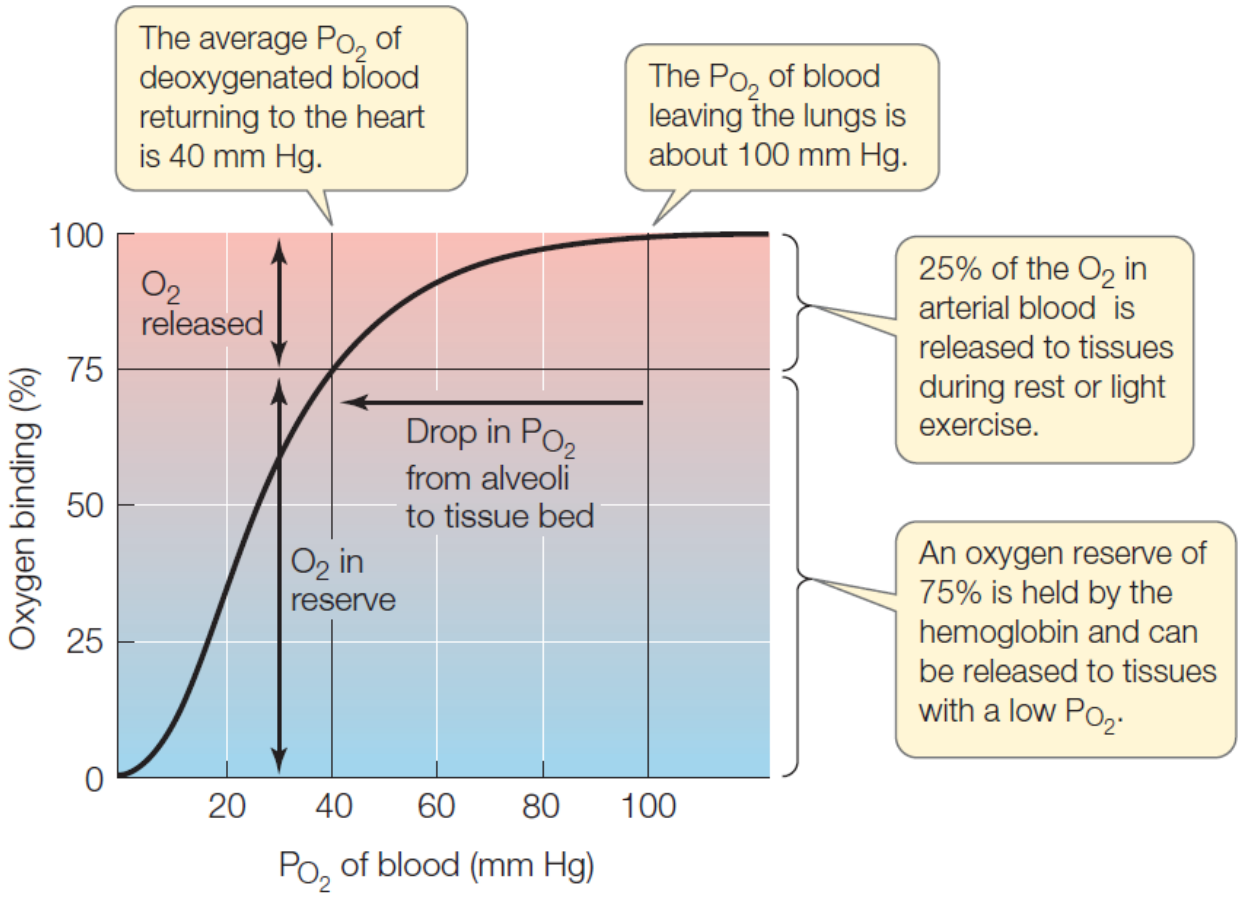
Transport of Respiratory Gases: Oxygen

Dissolved oxygen in blood plasma alone is insufficient to meet even basal metabolic demands. Hence, most oxygen in blood is transported in red blood cells via **hemoglobin**. Hemoglobin (Hb) is a protein made up of 4 subunits, each with a heme moiety attached to a polypeptide chain (globin). Heme is a porphyrin group with 1 atom of ferrous iron at the center. Each of the 4 atoms of iron in the Hb molecule can bind reversibly with 1 molecule of O_2. There are 17 varieties of hemoglobin known (only two of them are normal):

- HbA = Normal adult hemoglobin which has two *alpha* chains and two *beta* chains.
- HbF = Normal fetal hemoglobin which has two *alpha* chains and two *gamma* chains.

The abnormal hemoglobin found in people with sickle-cell anemia (HbS) has valine in place of glutamic acid at position 6 of the beta-globin subunits. This reduces the solubility of deoxygenated hemoglobin which then crystallizes out and results in sickling of red blood cells.

The binding of hemoglobin to oxygen depends on pO_2. See figure below. The sigmoidal shape of the curve is due to positive cooperativity (oxygen binding by one subunit increases the affinity of other subunits for oxygen).

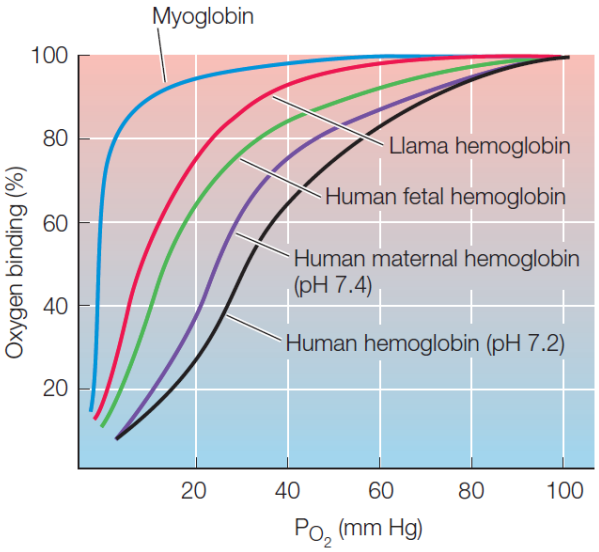


Other factors also influence oxygen binding to hemoglobin:

- **Bohr effect**: When blood pH falls, the excess H^+ binds preferentially to deoxygenated hemoglobin and decreases its affinity for O_2 and the O_2-binding/dissociation curve of hemoglobin shifts to the right. This shift means the hemoglobin will release more O_2 in tissues where pH is low—another way that O_2 is supplied where and when it is most needed.
- **2,3-Bisphosphoglyceric Acid** (DPG): Like H^+, DPG reduces the affinity of hemoglobin for oxygen.

$$HbO_2 \Leftrightarrow Hb + O_2$$
$$\Updownarrow$$
$$Hb + DPG \Leftrightarrow HbDPG$$

Llamas, having evolved to live at high altitude, have low DPG. Human fetal hemoglobin has lower affinity for DPG (hence a higher affinity for oxygen) than does maternal hemoglobin (facilitating O_2 transfer to the fetus in the placenta).



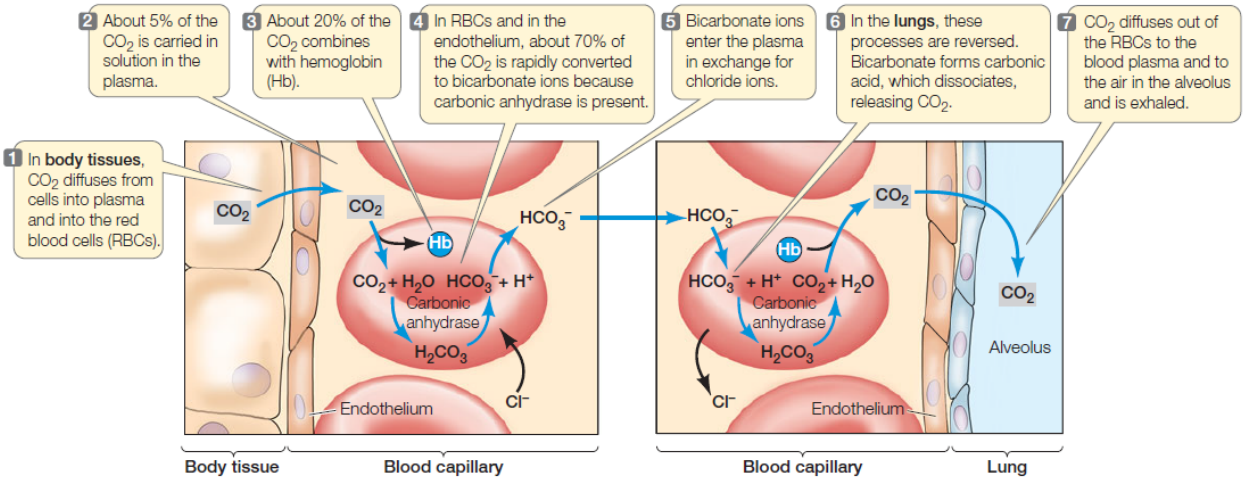
Transport of Respiratory Gases: Carbon Dioxide

Carbon dioxide is transported as follows:

- 5% in solution
- 20% as carbamino compounds
- 75% as bicarbonate

  Reaction: $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

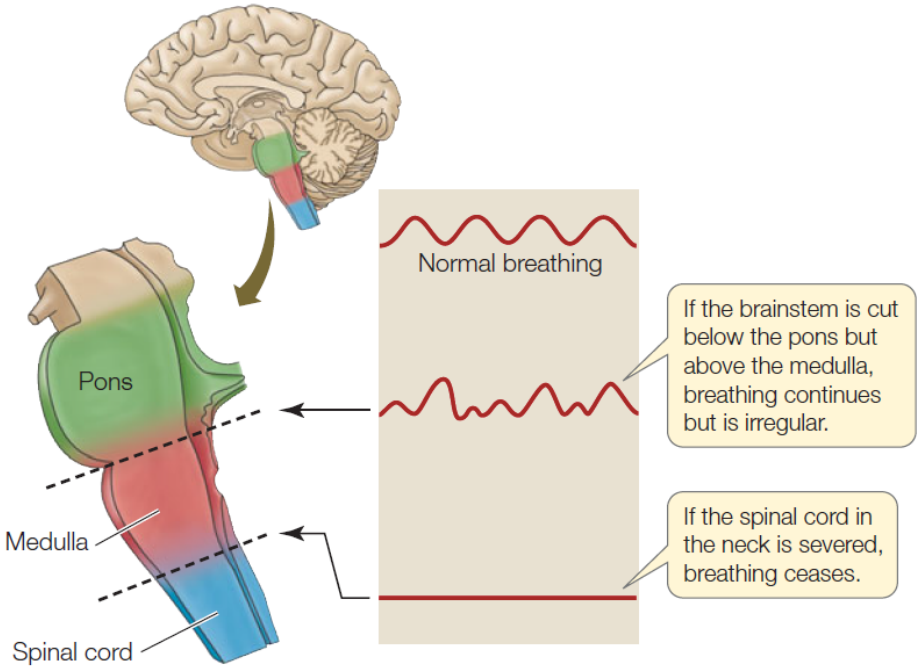
  Conversion of CO_2 to H_2CO_3 is catalyzed by carbonic anhydrase.



Regulation of Breathing

Breathing is autonomically controlled in the **brainstem**, specifically in the medulla oblongata and the pons.

- **Medulla oblongata**: Generates basic breathing rhythm (pacemaker). Sends neuronal projections to the diaphragm and intercostals. Two important groups of neurons in the medulla are:
    - **Dorsal Respiratory Group**: Group of neurons responsible for generating inspiration (inhalation) by sending impulses to the motor neurons of the diaphragm and external intercostals. As more of these neurons fire faster and faster, the diaphragm contracts and inhalation begins. Once they stop firing, the diaphragm relaxes and exhalation begins.
    - **Ventral Respiratory Group**: Group of neurons that becomes active when breathing demand is high. Can send both expiratory impulses (during active expiration) and inspiratory impulses (it sends inspiratory impulses as the dorsal group is driven harder) to the intercostal muscles. This can increase both the exhalation and inhalation volumes, respectively.
- **Pons**: Modifies the breathing rhythm generated by the medulla.
    - **Pneumotaxic center**: Part of the upper pons that sends inhibitory signals to the medulla's inspiratory center to make sure that inspiration does not continue too long.



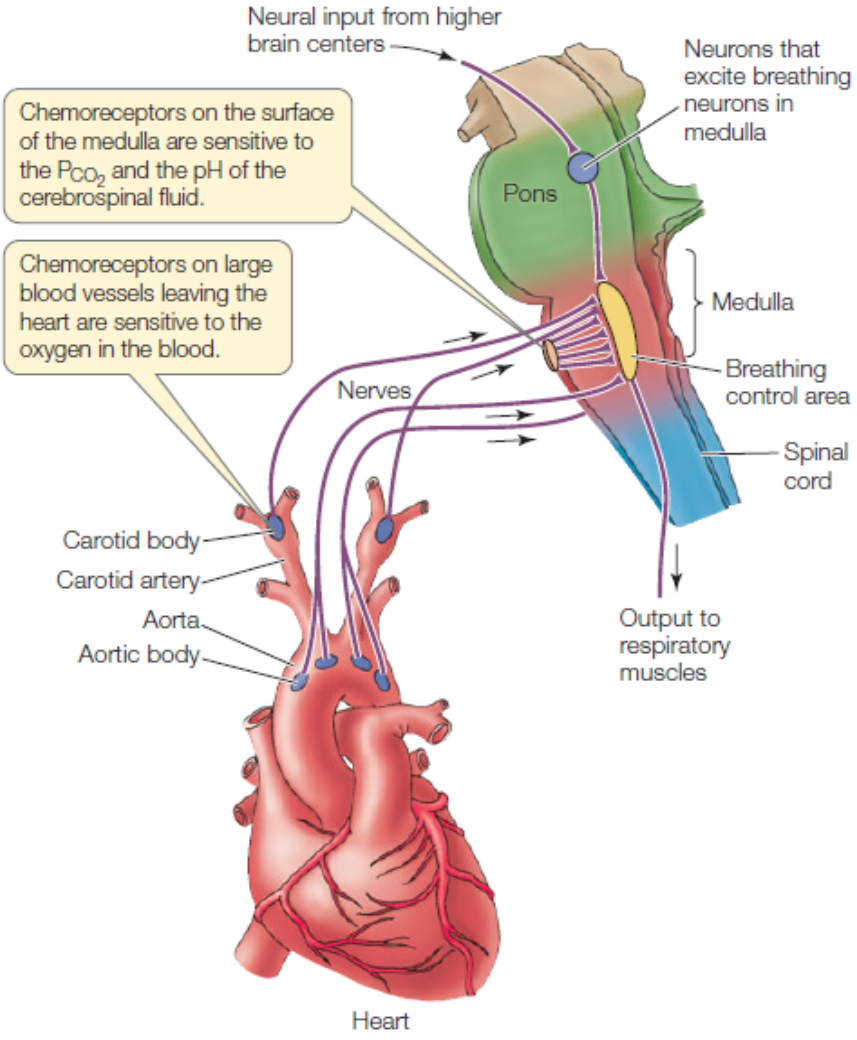
Hering Breuer reflexes: When stretch receptors in walls of lungs, intercostal muscles, and diaphragm are stretched, they stimulate a reflex exhalation.

Other higher brain areas can also modify breathing rates for speech, singing, coughing, etc.

Feedback

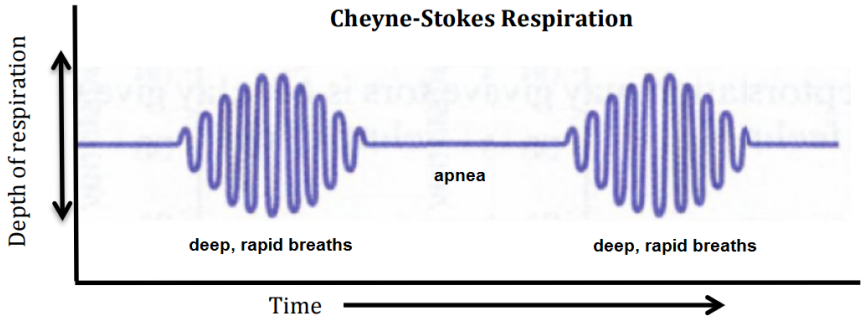
The most important feedback stimulus for breathing is the level of CO_2 in the blood. However, we are also sensitive to changes in blood oxygen levels, though to a much lesser extent. Where are the partial pressures of the respiratory gases sensed?

- **Central Chemoreceptors:**
  - **Ventral surface of the medulla**: Contains chemosensors sensitive to H^+ ions. pH is a direct reflection of blood pCO_2; recall that CO_2 combines with H_2O to form carbonic acid (lowering the blood pH). Low pH stimulates these chemosensitive cells to increase respiratory gas exchange.
- **Peripheral Chemoreceptors:**
  - **Carotid and aortic bodies**: Chemosensors on the large blood vessels leaving the heart. They are sensitive to oxygen partial pressure. If blood supply to these structures decreases or if blood pO_2 falls dramatically, these bodies trigger the breathing control center to increase respiration. Although we are not very sensitive to changes in blood pO_2, these bodies can stimulate increases in breathing during exposure to very high altitudes or when blood pressure or volume is very low. Note: O_2 and CO_2 sensors act synergistically; when blood pCO_2 decreases, sensitivity to low O_2 increases and vice versa.



Cheyne-Stokes Breathing

Cheyne-Stokes respiration is characterized by periods of deep, rapid breathing followed by periods of apnea (cessation of breathing). This can happen at high altitudes because the concentration gradient for O_2 uptake decreases (there's less O_2 at high altitudes) but the concentration gradient for CO_2 loss remains the same (the amount of CO_2 in the air is extremely small so regardless of altitude, there will always be a steep gradient for CO_2 loss). Apnea leads to buildup of CO_2 (thereby lowering blood pH) which stimulates rapid breathing. The rapid breathing causes too much CO_2 to be blown off (raising blood pH) which leads to apnea (since the pH of the blood is too high to stimulate respiration).



The Effects of Diving on Respiration

Previously, we discussed the effects of high-altitude hypoxia on breathing. Now, we will move our discussion to what happens to our respiratory system when we go diving way below sea level. For every 33 feet we dive underwater, the pressure we experience increases by 1 atm (remember: water weighs a lot more than air does so it exerts much more pressure). According to Boyle's law, the volume of a gas is inversely proportional to pressure. Furthermore, according to Henry's law, the solubility of a gas increases with pressure. Where does that lead us?

1. **Nitrogen narcosis**: Symptoms of joviality, intoxication, drowsiness, and loss of fine motor control that begin to occur when a person is at about 120 feet under water for an hour. This is due to nitrogen gas dissolving into nerve cell membranes, resulting in a disruption in nerve transmissions.
2. **Decompression sickness** (also known as the bends): After nitrogen dissolves into tissues (especially fat tissue) due to high pressures under water, when we ascend back toward sea level, nitrogen comes out of solution. If our ascent is too rapid, then the pressure decreases too fast, causing bubbles to form that block small blood vessels (air embolism). This is a consequence of Boyle's law – the gas expands during ascent as pressure drops. (Along similar lines, it's dangerous to hold your breath while scuba diving because when you ascend, the gases within your lungs expand and can rupture your lungs).

How do marine animals stay submerged for long periods of time at great depths? They have several adaptations that enable them to do this:

1. They dive with empty lungs
2. Their tissues have a higher capacity to store oxygen than those of humans; a diving seal can store 7 times more oxygen in blood and 3 times more oxygen in muscle compared to man. As a result, the total oxygen reserves per kilogram of a diving seal is double that of a human.
3. They are capable of undergoing diving bradycardia: When they dive, their heart rate falls (a parasympathetic response), causing blood pressure to drop. The sympathetic nervous system counteracts the drop in blood pressure by inducing vasoconstriction of peripheral arteries. This results in the shunting of blood to vital organs such as the brain and the heart. The other tissues of the body, which receive less blood now, switch to anaerobic metabolism and also experience reduced metabolism (a hypometabolic state). This hypometabolism prevents too much "oxygen debt" accumulation from lactic acid fermentation. Note: The diving reflex described here also occurs in other mammals – in humans, it occurs when the face is submerged in water and is particularly strong in infants.

Respiratory Insufficiency

Respiratory insufficiency is the inability to satisfy the body's need for oxygen.

Most causes are grouped under:

1. Inadequate perfusion: Not enough blood flow to alveolar capillaries.
2. Inadequate ventilation: Not enough gas exchange between lungs and the environment.
3. Inadequate diffusion: Not enough movement of gases between alveoli and blood.

All of these causes are due to alterations in the **ventilation (V_A) to perfusion (Q) ratio**:

- V_A / Q = 1 is normal.
- Normal V_A but low Q (high V_A / Q ratio) means perfusion is less than ventilation. Alveoli that are not perfused by blood and therefore can't exchange gases with the blood are known as **dead spaces**.
    - This can be caused by the blockage of blood vessels by a tumor or blood clot, heart failure, or emphysema (damage to alveolar tissue).
- Low V_A but normal Q (low V_A / Q ratio) means ventilation is less than perfusion, which is known as a **pulmonary shunt**. In a pulmonary shunt, the alveoli are perfused with blood as normal but ventilation fails to supply perfused alveoli.
    - This can be caused by airway construction (as in asthma), emphysema, decreased lung compliance (as in COPD or fibrosis), pulmonary edema (excess fluid in lungs), a collapsed lung, or infectious diseases (such as tuberculosis or pneumonia).

The Circulatory System

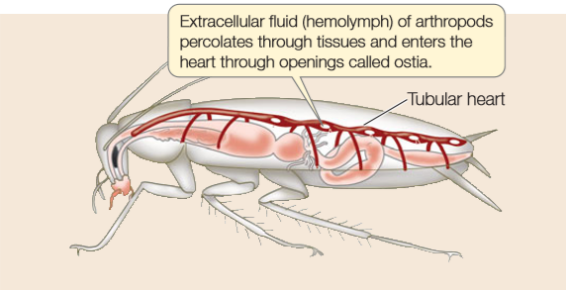
A circulatory system is an organ system that consists of a mechanical pump called the **heart**, fluid (**blood**), and a network of **blood vessels**. It is essential for transporting nutrients, respiratory gases, hormones, blood cells, heat, waste products, and various other things around the body. Not all organisms possess a circulatory system; unicellular organisms and some multicellular organisms are able to get nutrients and other necessities through direct exchanges with the environment. Flatworms and jellyfishes, for example, don't have a circulatory system; instead, they have a highly branched digestive system (called a gastrovascular cavity) that allows for direct diffusion of nutrients from the environment into the cell.

Open Circulatory Systems

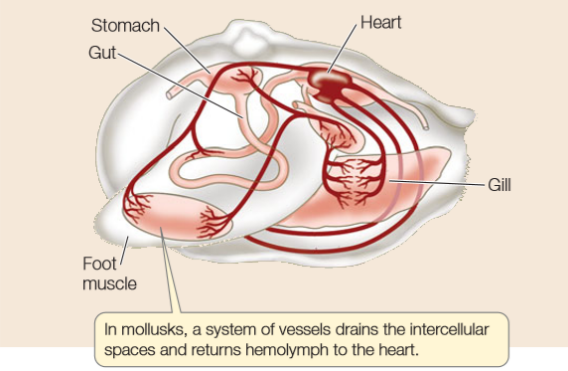
In open circulatory systems, interstitial fluid (the extracellular fluid that bathes tissue) is the fluid that circulates. The interstitial fluid, called **hemolymph**, is pumped through vessels via the heart. Hemolymph leaves vessels, flows through tissue spaces (so that exchange occurs between tissue and fluid), and then is returned to the heart to be pumped out again. Most invertebrates have open circulatory systems.

Comparison of invertebrate circulatory systems:

- In insects, a dorsal vessel (which contains a tubular heart) contracts to distribute hemolymph throughout the body. Ostia (openings with valves to prevent backflow) in the tubular heart open during relaxation so that hemolymph can refill the vessel.



- In bivalve mollusks (e.g. clams), open vessels collect hemolymph from different parts of the body and return it to the heart, therefore the bivalve mollusk heart has multiple **atria** to receive the returning hemolymph.



Closed Circulatory Systems

In closed circulatory systems, a closed system of vessels keeps the circulating fluid (blood) separate from interstitial fluid. Only the smallest vessels, called capillaries, permit exchange between blood and interstitial fluid. This type of circulatory system is found in all vertebrates and some invertebrates (e.g. earthworms).

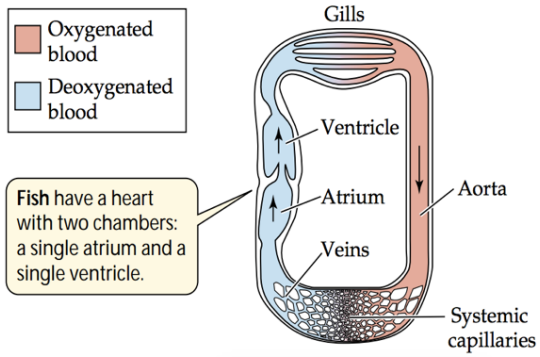
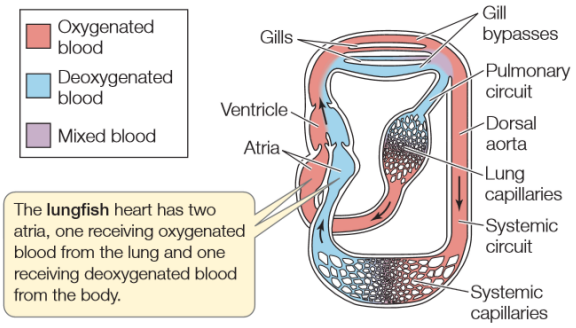
There are several advantages of closed circulatory systems:

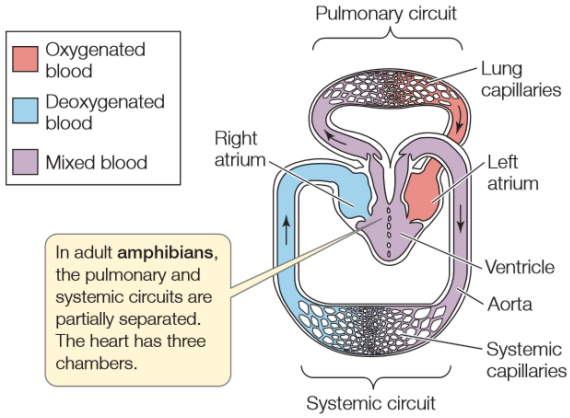
- Transport is quicker because fluid flow is more rapid through vessels than through tissue spaces (higher pressures can be generated).
- Changing the diameter of specific vessels can control the flow of blood to selective tissue to match their needs.
- Cells and molecules that help transport nutrients and hormones can be kept in the blood vessels and can drop their cargo in the tissues where it is needed.

Evolution of the vertebrate circulatory system

The table below outlines six types of circulatory systems. When comparing these systems, consider the:

- number of **atria** (chambers that receive blood returning to heart)
- number of **ventricles** (chambers that pump blood out of heart)
- separation of oxygenated and deoxygenated blood
- presence or absence of a complete **pulmonary circuit** (which travels from heart to lung to heart)
- overall pressure in the **systemic circuit** (which travels from heart to body to heart) and pulmonary circuit (if applicable)

Animal	**Circulatory system**
Fish	Heart has two chambers: 1) The **atrium** which receives deoxygenated blood from body tissue, 2) The **ventricle**, which receives blood from atrium and pumps the blood to gills, where gases are exchanged. Blood leaving gills enters the **aorta**, an artery which distributes blood to smaller arteries and arterioles to reach body tissues. High pressure cannot be generated because the pressure generated by the contraction of the ventricle is lost when the blood enters the narrow spaces of the gills. 
Lungfish	Able to breathe air; evolved a gas exchange organ (a **lung**) as an outpocketing of the gut to adapt to waters with low oxygen content. Modified gill arches send blood to the lung where the blood picks up oxygen. The heart has a partially divided atrium: The left side picks up oxygenated blood from the lungs and the right side picks deoxygenated blood from the body. The oxygenated and deoxygenated blood remain mostly separate as they flow through the ventricle so that the deoxygenated blood goes preferentially to the lungs. Note: Some gill arches remain that are not modified so the lungfish is still able to breathe water through the gills, not just air. Pressure is low as the blood must move through the gills. 

<table>
<tr>
<td>Amphibians</td>
<td>Three-chambered heart with pulmonary (lungs) and systemic (body) circulation largely separated. A single ventricle pumps blood to lungs and to the rest of the body. Two atria receive blood returning back to the heart; one atria receives oxygenated blood from the lungs and the other atria receives deoxygenated blood from the body. The atria deliver blood to the single ventricle. Although oxygenated blood and deoxygenated blood end up mixing in the ventricle, mixing is limited by anatomical features of the ventricle which direct the flow of deoxygenated blood from the right atrium to the pulmonary circuit and the flow of oxygenated blood from the left atrium to the aorta. The partial separation of pulmonary and systemic circulation is beneficial because there is a huge pressure drop when the blood passes through the lungs for gas exchange. Though blood leaves the heart at the same pressures as it leaves the lone ventricle, the systemic circulation (separate from the pulmonary) can bypass the pressure drop that occurs in the pulmonary circuit. Amphibians have another adaptation for oxygenating their blood: they can pick up a considerable amount of oxygen in blood flowing through small blood vessels in their skin.


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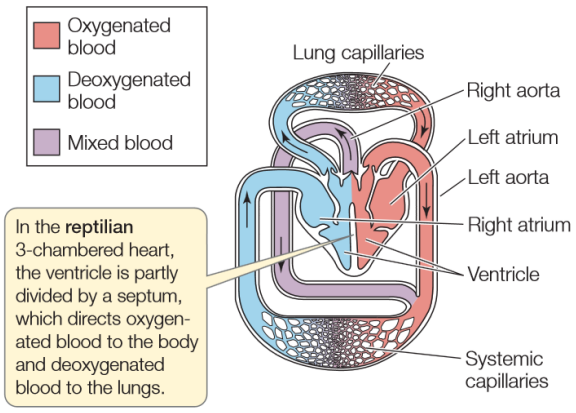
<tr>
<td>Reptiles (excluding crocodiles)</td>
<td>Three-chambered heart with the ventricle partially divided by a septum (the septum can divide oxygenated blood and deoxygenated blood). Two aortas are present: The left aorta receives oxygenated blood from the left side of the ventricle and the right aorta receives blood from both sides of the ventricle (thus, the right aorta receives a mixture of oxygenated and deoxygenated blood). This system can accommodate the following two situations:


Animal is breathing (active): Resistance in the pulmonary circuit is lower than resistance in the systemic circuit so blood from the right side of the ventricle tends to flow into the pulmonary artery to the lungs rather than the right aorta to the body.
Animal is not breathing (at rest): Resistance in the pulmonary circuit increases (from constriction of pulmonary vessels) so blood from the right side of the ventricle tends to flow into the right aorta. As a result, blood from both sides of the ventricle flows through both aortas to the systemic circuit.

Reptiles, being ectotherms, are often very active. They have bursts of high activity (more breathing) interspersed with periods of low activity (less breathing). Also, some species are "divers" which spend a lot of time under water (during which they can’t breathe air). When there's no need to breathe air, what a waste of energy it would be to pump blood through the pulmonary circuit! That's why they evolved this system (called shunting) wherein when the animal is not breathing at rest, more blood gets to the systemic circuit (because blood gets directed to both aortas) and when the animal is breathing, some blood gets diverted to the pulmonary circuit (blood is directed to flow more towards the pulmonary artery than the right aorta).</td>
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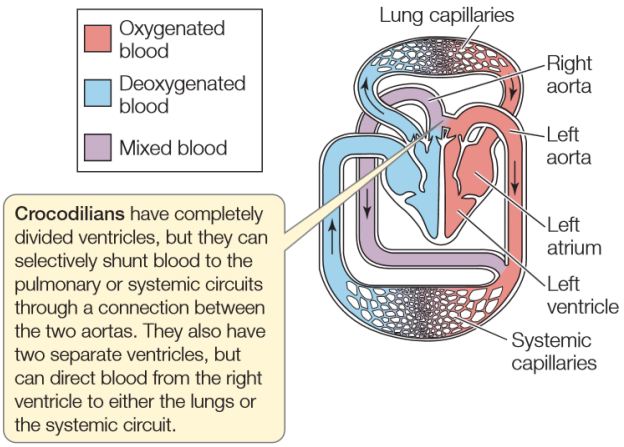
<tr>
<td>Crocodiles</td>
<td>Crocodiles, although ectothermic reptiles, have a different system. One main difference is that their ventricle is completely divided in two (thus, they have two ventricles and therefore a four-chambered heart). Because of this, pressures can differ in the pulmonary and systemic circuits. Crocodiles, like other reptiles, are still capable of selectively shunting blood to the pulmonary or systemic circuits. This is made possible by a foramen that connects the right and left aorta. Thus, in crocodiles, even though the ventricles are completely divided, the right aorta can still receive oxygenated blood just as in other reptiles thanks to this foramen!


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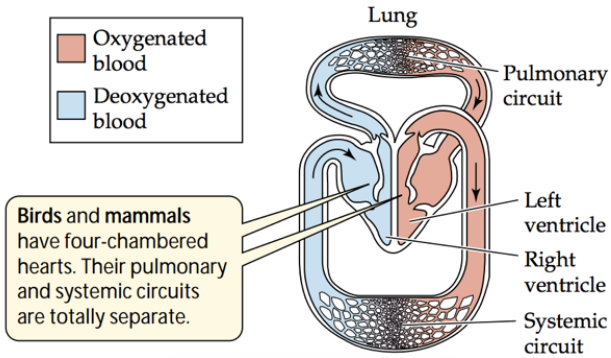
<tr>
<td>Birds and mammals</td>
<td>Four-chambered heart. Unlike crocodiles, they only have one aorta so they don't have an aorta that contains "mixed" oxygenated and deoxygenated blood. Pulmonary and systemic circuits are completely separate and can operate at different pressures, and the systemic circuit operates at a higher pressure.


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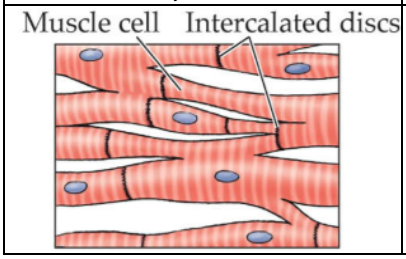
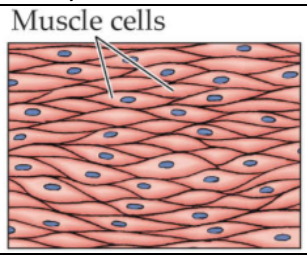
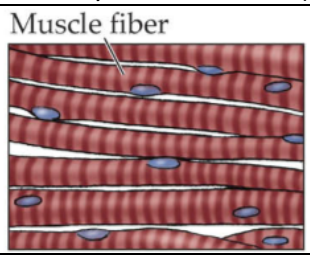
Cardiac Muscle

Cardiac muscle has several distinguishing features:

- Cardiac muscle cells are connected to each other at their ends by **intercalated discs**, which consist of gap junctions that allow action potentials to spread rapidly from cell to cell. Hence, cardiac muscle cells are electrically coupled to one another. As a result, large groups of cardiac muscle cells can contract in unison.
- Some cardiac muscle cells are **pacemaker cells** that can initiate action potentials without stimulation from the nervous system. Note: The autonomic nervous system (ANS) innervates cardiac muscle cells so it can influence the depolarization rate, however, it is not needed for initiating action potentials.
- Cardiac muscle cells are uninucleate and are striated due to the presence of sarcomeres.
- Cardiac muscle fibers branch and interdigitate into a meshwork that prevents tearing.

Comparison of cardiac muscle, smooth muscle, and skeletal muscle:

Cardiac Muscle	Smooth Muscle	Skeletal Muscle
Sarcomeres present (striated)	Myofibrils not organized in sarcomeres	Sarcomeres present (striated)
Uninucleate cells	Uninucleate cells	Multinucleate cells
Branched	Unbranched	Unbranched
Gap junctions	Gap junctions	No cell-cell junctions
Innervated by ANS	Innervated by ANS	Innervated by somatic nerves (VNS)
		

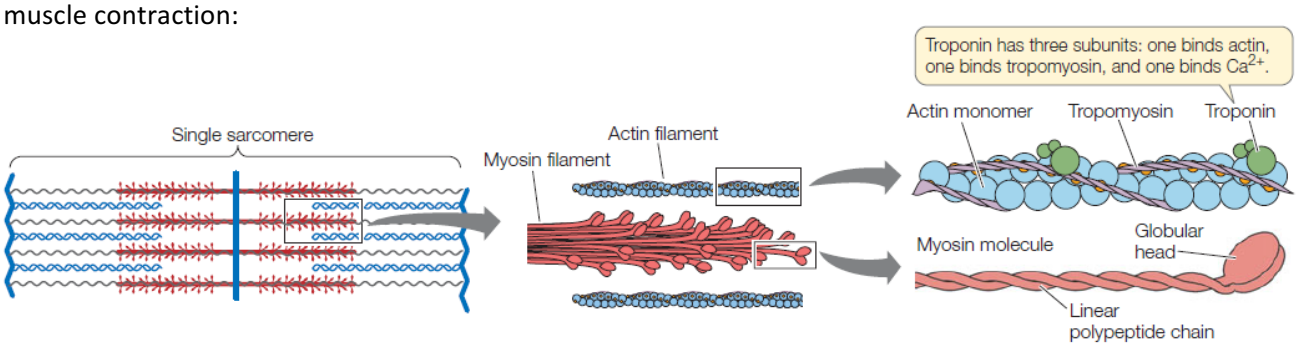
ATP in muscle contraction:

To review, there are 3 roles that ATP plays in muscle contraction:

1. Interaction with myosin
    a. When ATP binds to myosin, the connection between actin and myosin is broken
    b. When myosin's ATPase activity hydrolyzes its bound ATP, myosin's globular head undergoes a conformational change; the myosin head pivots so that it can bind to a new location on the actin filament when the phosphate group is lost.
    c. When the ADP is lost, the myosin head returns to its original position, sliding the actin filament along with it (the "power stroke").
2. Sequestering Ca^{2+} in the sarcoplasmic reticulum (SR)
    a. Specifically, a Ca^{2+}-ATPase embedded in the SR membrane uses ATP to pump Ca^{2+} back into the SR after Ca^{2+} is released into the sarcoplasm. More details on this later.
3. Establishing a membrane potential
    a. A Na^{+}/K^{+} gradient is established across the muscle cell membrane; depolarization of muscle cells leads to contraction, as we will see in a little bit.

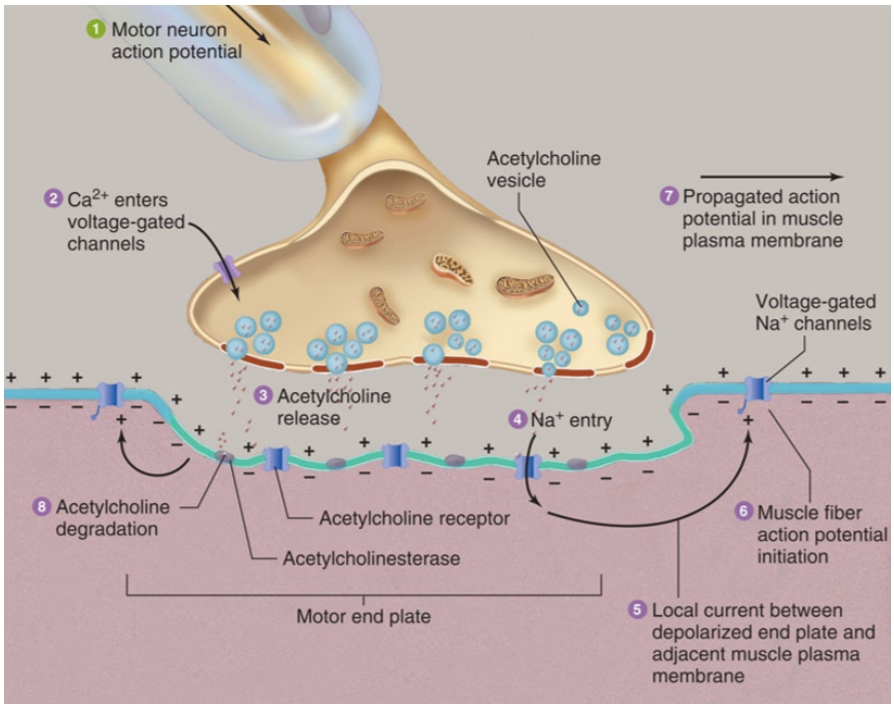
Calcium regulation of muscle contraction:

Recall the role of calcium in muscle contraction: Two strands of the fibrous protein, tropomyosin, twist around an actin filament. When a muscle is at rest, the tropomyosin strands block the sites on the actin filament where myosin heads can bind. When calcium ions are released from the sarcoplasmic reticulum into the muscle fiber cytoplasm (the sarcoplasm), the calcium ions bind to the globular protein, troponin, changing the conformation of troponin. Since troponin is bound to tropomyosin, this conformational change shifts the tropomyosin's position so that the actin-myosin binding sites are exposed, allowing muscle contraction to proceed. When calcium ions are removed from the sarcoplasm and returned to the sarcoplasmic reticulum, the tropomyosin shifts back to its original position, blocking the binding of myosin heads to actin and ending contraction. The diagram below shows the structure of the filaments involved in muscle contraction:



What happens at the neuromuscular junction?

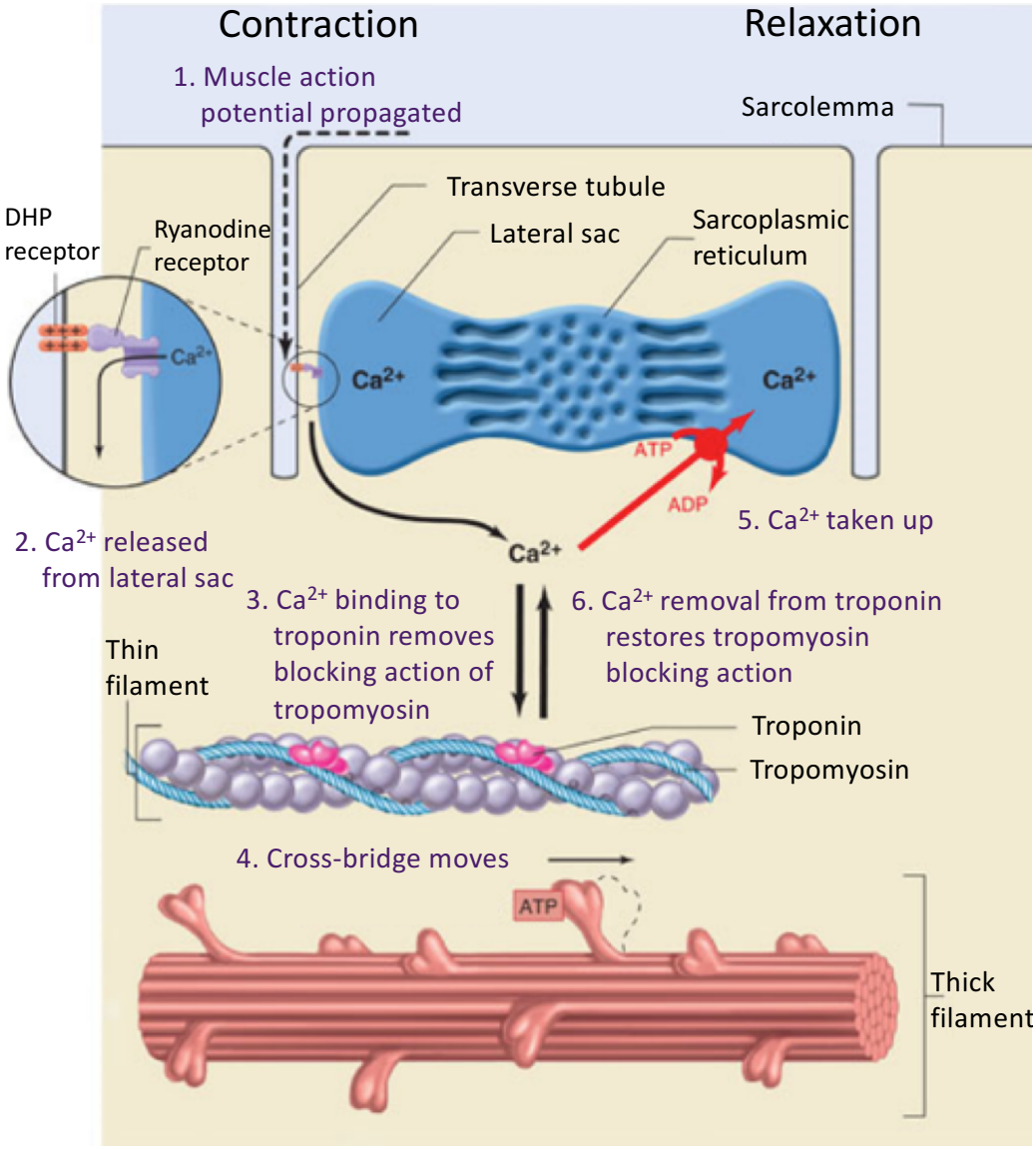
Acetylcholine is released at the motor end plate (the postsynaptic membrane) in response to an action potential arriving at the axon terminal of the motor neuron. Nicotinic cholinergic receptors in the motor end plate allow Na^+ to enter the muscle fiber and depolarize the membrane. Depolarization spreads to adjacent plasma membrane regions and activates voltage-gated Na^+ channels, which propagate the action potential throughout the plasma membranes (the **sarcolemma**) of the muscle fiber.



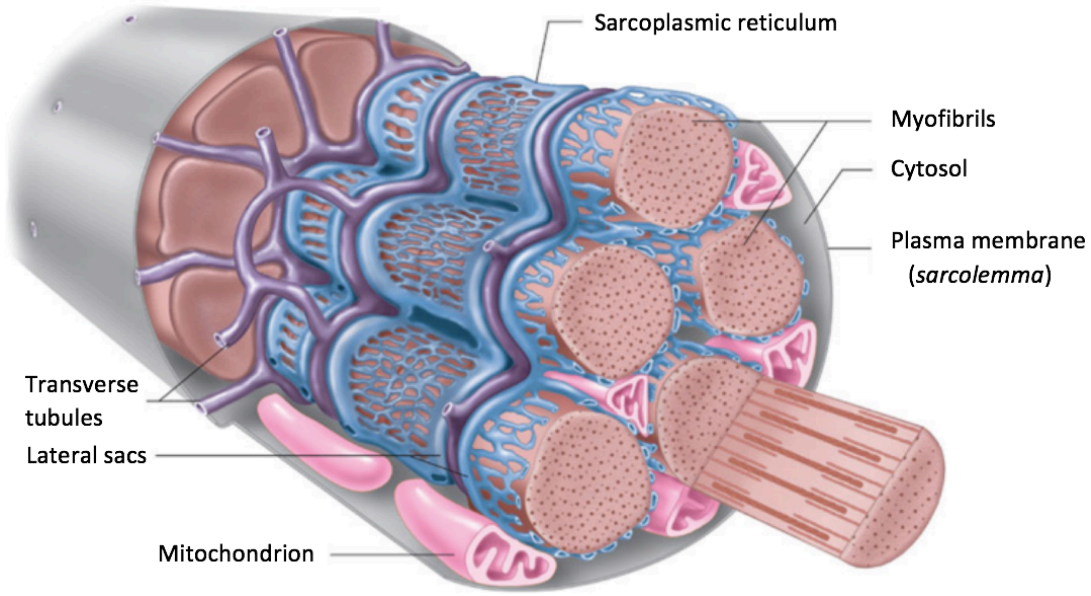
Excitation-Contraction Coupling in Skeletal Muscle:

How does the depolarization of skeletal muscle lead to contraction? First, some anatomy: **T-tubules** (transverse tubules), which are invaginations of the sarcolemma, run into the depths of the fiber and surround the myofibrils. The **sarcoplasmic reticulum** (the endoplasmic reticulum of muscle cells), which sequesters Ca^{2+}, also surrounds the myofibrils. The T-tubules are indirectly connected to the lateral sacs of the sarcoplasmic reticulum: embedded in the T-tubule membrane are voltage-sensitive receptors, called **dihydropyridine (DHP) receptors**. Connected to a DHP receptor is a **ryanodine receptor**, which is a Ca^{2+} channel embedded in the sarcoplasmic reticulum membrane.

When an action potential propagates down the membrane via the T-tubules, a DHP receptor undergoes a conformational change. This activates its attached ryanodine receptor, allowing calcium ions to flow out of the channel from the sarcoplasmic reticulum into the sarcoplasm where it can bind troponin. A Ca^{2+} ATPase then uses the energy from ATP hydrolysis to pump Ca^{2+} back into the sarcoplasmic reticulum.



The diagram below shows the anatomy of a skeletal muscle cell:

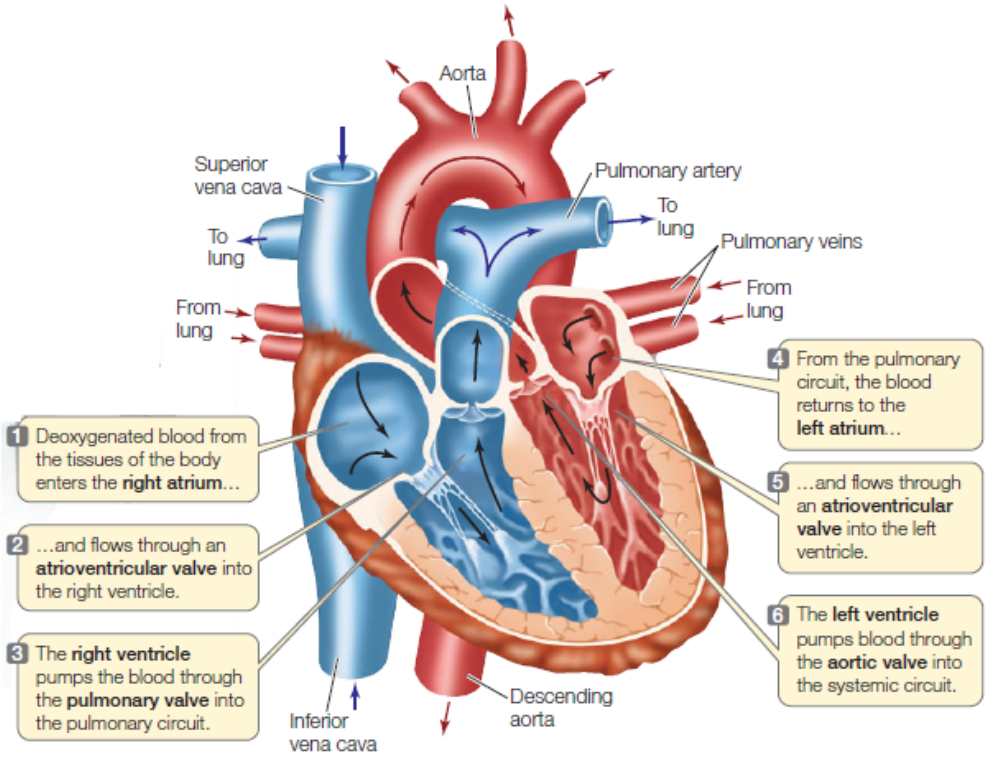


Excitation-Contraction Coupling in Cardiac Muscle (Calcium-induced-calcium-release):

The excitation-contraction coupling mechanism described previously applies to skeletal muscle. For cardiac muscle, the mechanism is slightly different. In cardiac muscle, the T tubules are larger and the DHP proteins are not just voltage sensors but are also calcium ion channels which, unlike the DHP proteins in skeletal muscle, are **not** physically connected with ryanodine receptors. Instead, the isoform of ryanodine receptors found in cardiac muscle are ion-gated Ca^{2+} channels. When an action potential spreads down the T tubules, voltage-gated Ca^{2+} channels in the T tubules (DHP receptor proteins) open, allowing Ca^{2+} to flow into the cell. This rise in sarcoplasmic Ca^{2+} triggers the opening of Ca^{2+} channels (ryanodine receptor calcium channels) in the sarcoplasmic reticulum, releasing even more Ca^{2+} into the sarcoplasm. Thus, the influx of Ca^{2+} into the cell induces Ca^{2+} release from the sarcoplasmic reticulum – this is called **calcium-induced-calcium release**.

The Anatomy of the Mammalian Heart

The diagram below shows the circulation of blood through the mammalian heart. Blood flows from the right heart to the lungs to the left heart to the body and back to the right heart. *Deoxygenated* blood enters the heart from the lower body through the inferior vena cava and enters the heart from the upper body through the superior vena cava. *Oxygenated* blood leaves the heart and is distributed to the body from the aorta. The **atrioventricular valves** prevent blood from flowing back into the atria when the ventricles contract. The **pulmonary valve** and the **aortic valve**, together known as the semilunar valves, prevent blood from flowing back into the ventricles from the arteries when the ventricles relax. Refer to the diagram for a detailed depiction of the flow of blood through the heart.



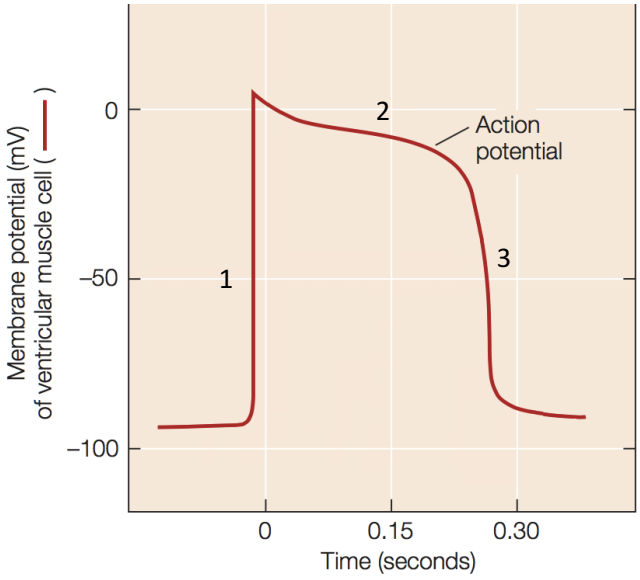
Cardiac Action Potentials

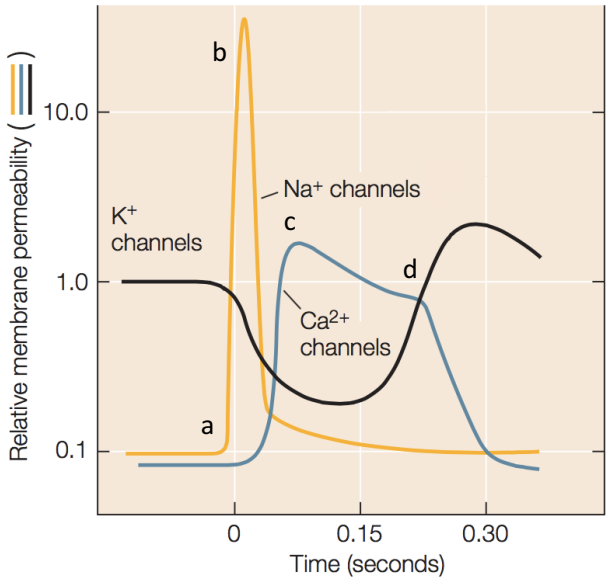
Calcium plays an essential role in cardiac muscle contraction, as we have seen. Before we investigate the role Ca^{2+} plays in cardiac action potentials, let us first distinguish between two types of *voltage-gated* Ca^{2+} channels:

- **L-Type Ca^{2+} channels**: Voltage-gated Ca^{2+} channels with long-lasting action potentials. Voltage-gated Ca^{2+} channels in T tubules (DHP receptors) are L-type Ca^{2+} channels.
- **T-Type Ca^{2+} channels**: Voltage-gated Ca^{2+} channels with shorter action potentials. Activated at a lower voltage than their L-type counterparts.

Now, we will examine how action potentials in cardiac cells of the ventricle occur, which lead to a rise in intracellular Ca^{2+} levels and therefore contraction of these cardiac muscle cells. We will then see how Ca^{2+} is involved in the establishing action potentials in the heart's pacemaker cells.

Ventricular cardiac cell





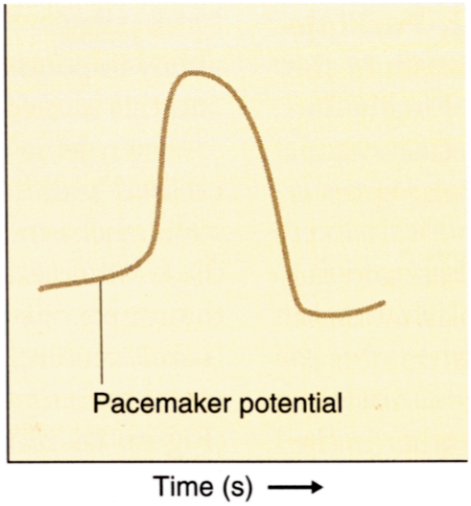
The depolarized state is broad thus stimulating sustained contractions.

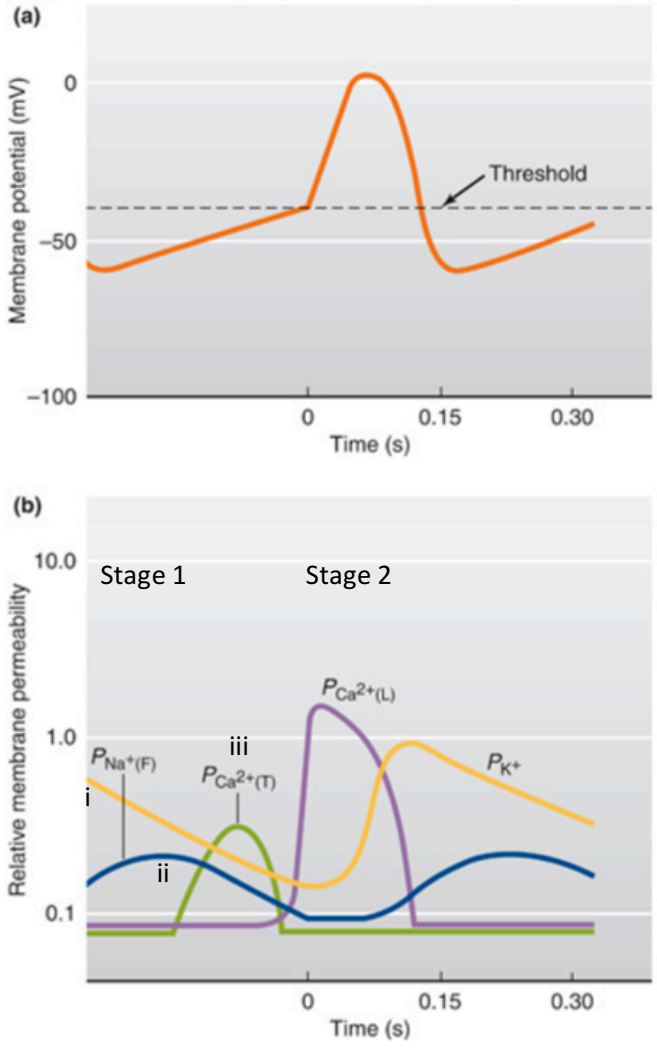
There are a few phases of the ventricular action potential, as follows:
1. Rising phase: Na^+ rushes in through voltage-gated sodium channels, depolarizing the cell.
2. Plateau: Opening of voltage-gated L-type Ca^{2+} channels & closing of K^+ channels. Ca^{2+} rushes in and K^+ is unable to leave, maintaining the depolarization.
3. Falling phase: Closing of Ca^{2+} channels and the reopening of K^+ channels. K^+ rushes out, repolarizing the cell.

What causes the ventricular action potential and how does that action potential result in cardiac muscle contraction?
a) An action potential is initiated by pacemaker cells (described on next page).
b) The action potential (depolarization) spreads to ventricular cardiac cells via gap junctions, opening voltage-gated Na^+ channels.
c) The resulting depolarization of the sarcolemma opens L-type calcium channels (DHP channels) in the T tubules, leading to calcium-induced-calcium-release. Sarcoplasmic Ca^{2+} concentrations rise, leading to contraction. K^+ channels also close.
d) L-type Ca^{2+} channels (DHP channels) close and K^+ channels open, repolarizing the cell and ending the contraction.

The duration of the Ca^{2+} pulse determines the duration of contraction, and a longer pulse of Ca^{2+} means a longer contraction.

Pacemaker cell of the sinoatrial node





The sinoatrial node is the pacemaker of the heart (responsible for your heartbeat). It is a group of pacemaker cells in the right atrium.

How are action potentials generated in pacemaker cells? There are two stages: 1) a period of gradual depolarization followed by 2) a large depolarization accompanied with the opening of L-type Ca^{2+} channels once the threshold voltage is reached. See these two stages in more detail below:

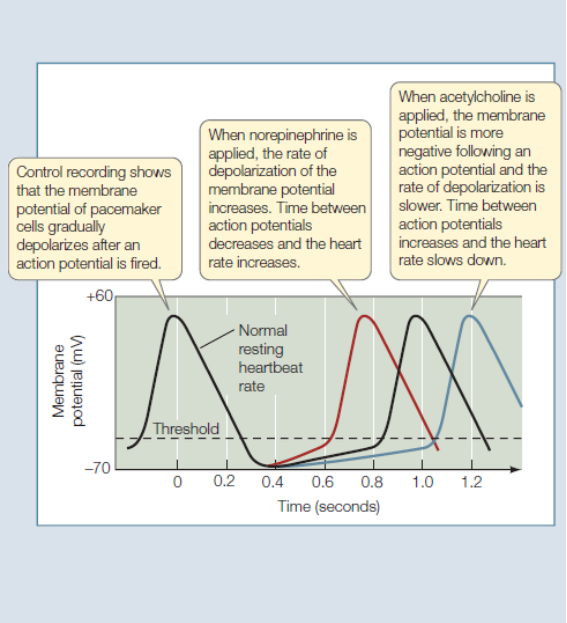
Stage 1. Pacemaker cells have an unstable resting potential that will lead to spontaneous action potentials. The gradual depolarization is due to:
i) Voltage-gated K^+ channels close after the previous action potential resulting in a progressive decline in K^+ permeability. This results in a more depolarized cell as K^+ cannot leave.
ii) Voltage-gated Na^+ channels open following i). This results in slightly increased Na^+ permeability and an even more depolarized cell as Na^+ enters. Note that the voltage-gated Na^+ channels begin to close shortly after opening (they are called "funny" channels) and Na^+ permeability will decline again.
iii) Voltage-gated T-type calcium ion channels eventually open (following depolarization from open Na^+ channels and closed K+ channels). Ca^{2+} enters, further depolarizing the cell. This allows the cell to reach threshold.
To summarize stage 1: the resting potential gradually depolarizes due to a decline in the permeability of K^+, a slow influx of Na^+, and the opening of T-type Ca^{2+} channels.

Stage 2. L-type Ca^{2+} channels open, resulting in the action potential.

The Autonomic Nervous System Controls the Heartbeat

The autonomic nervous system controls the heartbeat by influencing the firing rate of pacemaker cells:

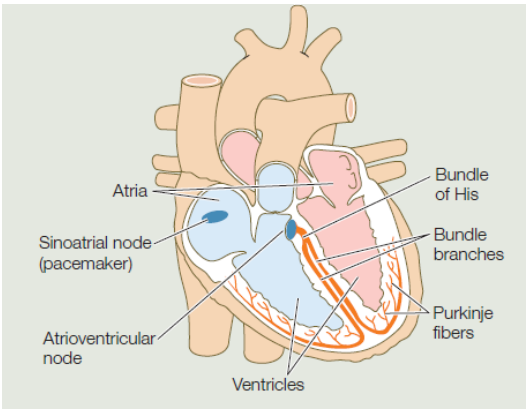
- Increase heartbeat: Norepinephrine released onto pacemaker cells by sympathetic nerve fibers increases the permeability of Na^+ channels and Ca^{2+} channels. As a result, the membrane potential of the pacemaker cells goes up more rapidly (more rapid depolarization) and the interval between action potentials is decreased.
- Decrease heartbeat: Acetylcholine released onto pacemaker cells by parasympathetic nerve fibers increases the permeability of K^+ channels so that the membrane potential becomes even more negative following an action potential (greater hyperpolarization) and rises more slowly. Acetylcholine also decreases the permeability of the Ca^{2+} channels so that the rate of rise of the membrane potential slows and the interval between pacemaker action potentials lengthens.



- **Baroreceptors** (mechanoreceptors that sense pressure changes in the heart) signal the autonomic nervous system to slow down or speed up heartbeat depending on the changes in blood pressure.

The Electrical Conduction System of the Heart

How does a heartbeat occur? Depolarization begins in the **sinoatrial node** via the mechanism described on the previous page and spreads throughout atrial muscles. As there are no gap junctions between cells of the atria and cells of the ventricles, the action potential does not spread directly to the ventricles. Hence, the ventricles and the atria do not contract in unison – the atria contract first. The action potential moves from the atria to the ventricles via the **atrioventricular node** (AV node), a group of pacemaker cells situated at the junction of the atria and the ventricles. When the AV node is stimulated by the depolarization of the atria, the AV node, after a slight delay, generates action potentials that are conducted to the ventricles via the **bundle of His**, a collection of cardiac muscles that do not contract but are rather specialized for electrical conduction. These fibers divide into left and right bundle branches that run to the tips of the ventricles and then spread throughout the ventricular muscle mass as **Purkinje fibers**. The Purkinje fibers ensure that the cardiac action potential spreads rapidly and evenly throughout the ventricular muscle mass, starting at the very bottom of the ventricles. The short delay in the spread of the action potential imposed by the AV node ensures that the atria contract before the ventricles do, so that the blood passes progressively from the atria to the ventricles to the arteries.



The Cardiac Cycle

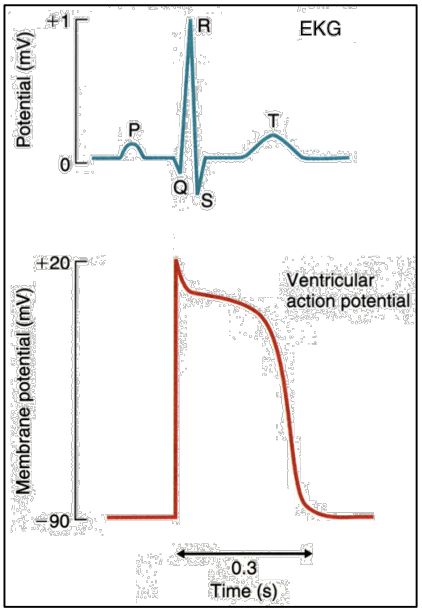
The **cardiac cycle** consists of contraction of the two atria, followed by contraction of the two ventricles, and then relaxation. The two atria contract at the same time and the two ventricles contract at the same time. The cardiac cycle is divided into two phases:

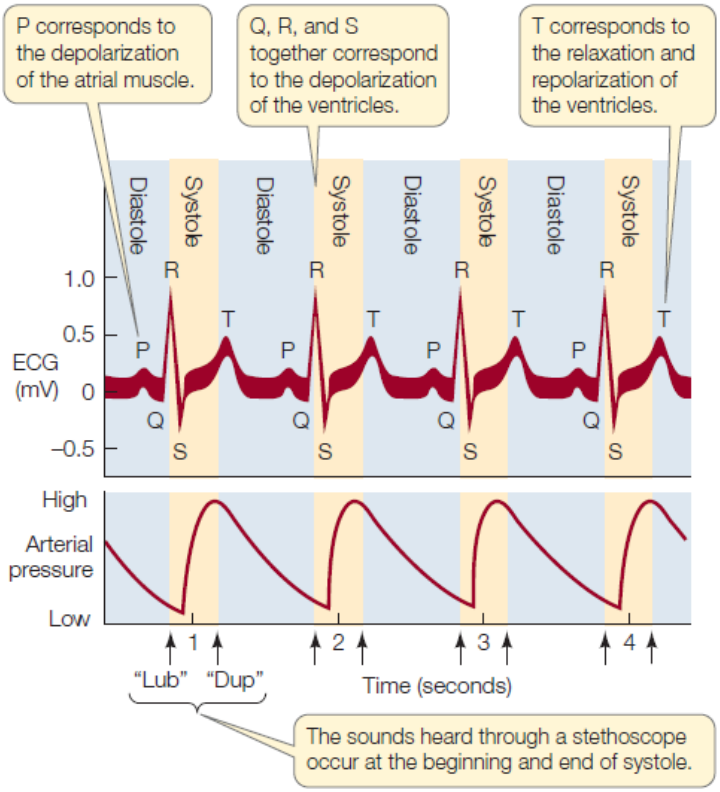
- **Systole** = Period of ventricular contraction.
- **Diastole** = Period of ventricular relaxation.

The **lub-dup** sounds heard through stethoscope are due to the closing of valves as follows:

- **Lub**: Beginning of systole. As the ventricles begin to contract, the pressure in them rises above the pressure in the atria, causing the AV valves to close.
- **Dup**: Beginning of diastole. When the ventricles begin to relax, the high pressure in the aorta and pulmonary artery closes the semilunar valves.

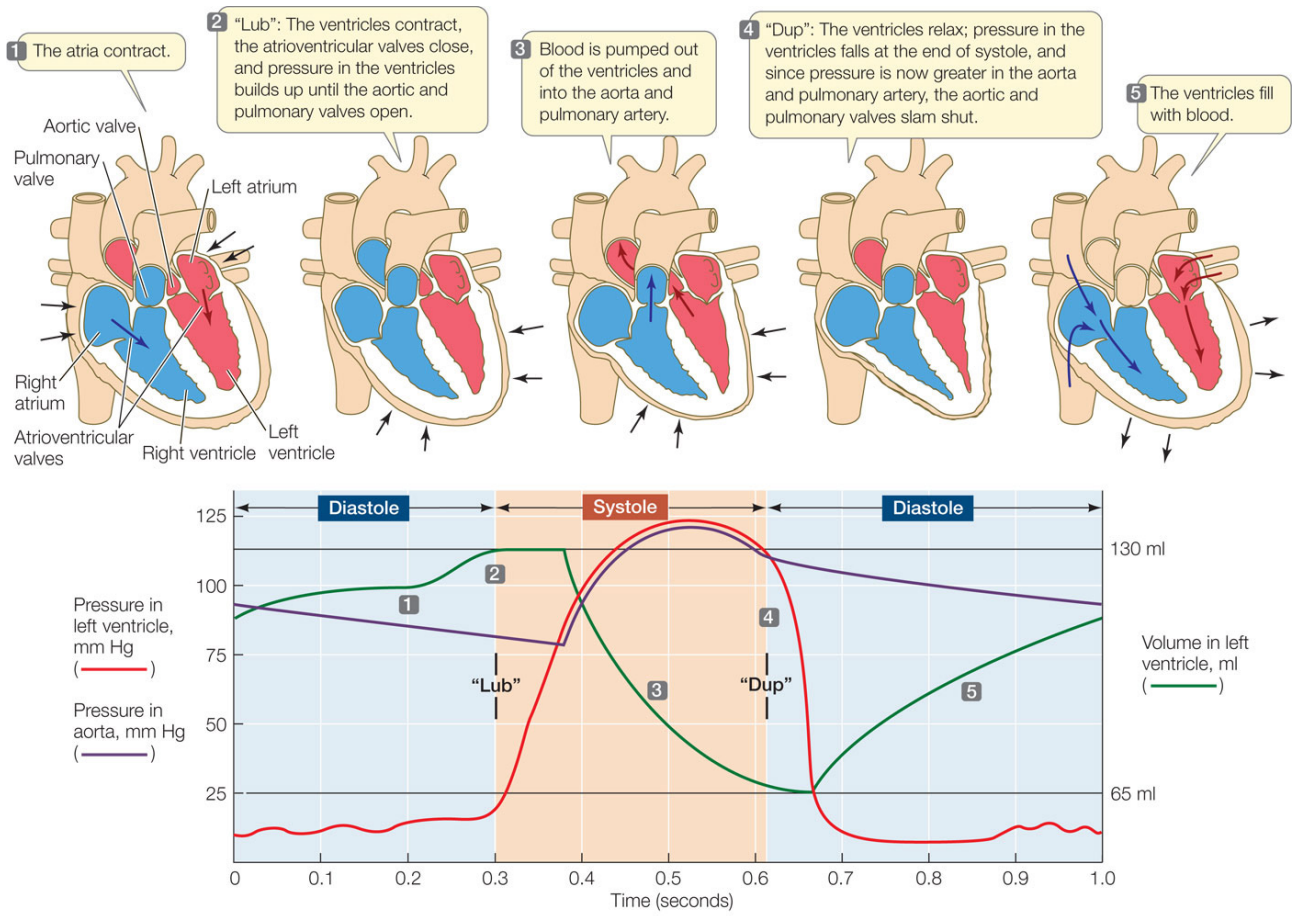
Electrocardiogram (EKG): Reflects voltage changes in the cardiac muscle mass that are conducted throughout the body. See the following figures.





P wave	atria depolarize & contract
QRS complex	ventricles depolarize (atria repolarize) - **SYSTOLE**
T wave	ventricles repolarize - **DIASTOLE**
PR interval	AV nodal delay
PR segment	atria contract, ventricles have not contracted yet
ST segment	ventricles are emptying
Q-T interval	ventricles contract

The figure and table on the next page summarize the steps of the cardiac cycle. You should be able to work through each stage and explain what is happening in detail.

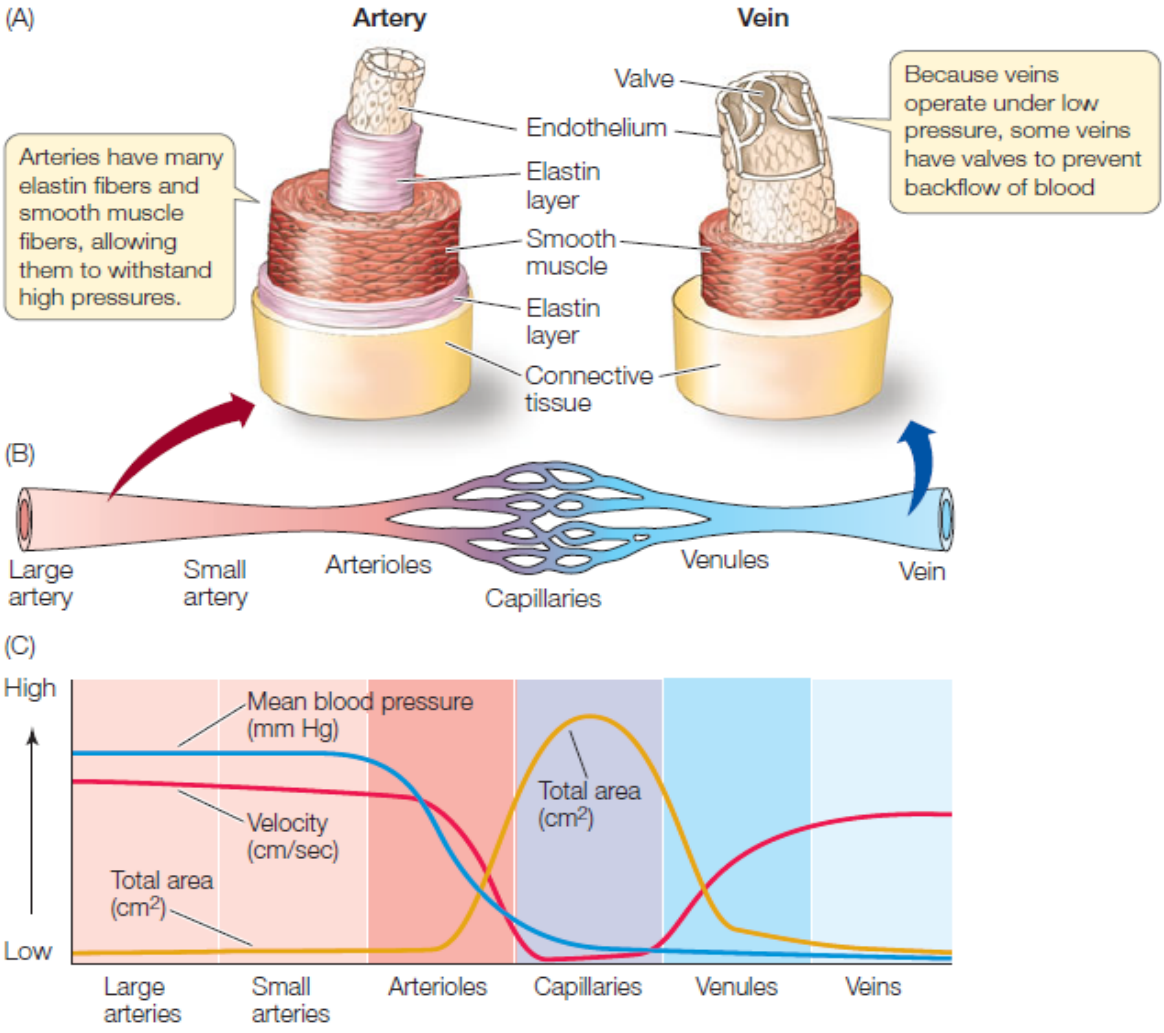


The summary table below (for the ventricles) matches the numbers on the figure above:

Stage in Cardiac Cycle	**AV Valves**	**Semilunar Valves**	**Open Ion Channels**	**Status of ventricles and atria**	**EKG region**
1. Ventricular filling **(atrial contraction)**	**Open**	Closed	K+ (leaky) (membrane potential at rest)	Atria contract & pump blood Additional filling of ventricles	**PR segment**
2. Isovolumetric ventricular contraction **(systole begins, atria relax)**	**Closed (lub sound)**	Closed	Na+ (membrane potential rising)	Ventricles begin to contract (pressure ↑) Ventricle volume unchanged Atria repolarize	**QRS complex**
3. Ventricular ejection	Closed	**Open**	Ca++ (plateau phase)	Ventricles fully contract Pump blood to rest of body	**ST segment**
4. Isovolumetric ventricular relaxation **(diastole begins)**	Closed	**Closed (dup sound)**	K+ (membrane potential falls)	Ventricles relax (pressure ↓) Ventricle volume unchanged Atria expand and are filling	**T wave**
5. Ventricular filling **(atria relaxed)**	**Open**	Closed	K+ (leaky) (membrane potential at rest)	Whole heart is relaxed Ventricles are expanding and filling	**TP interval**

The Vascular System

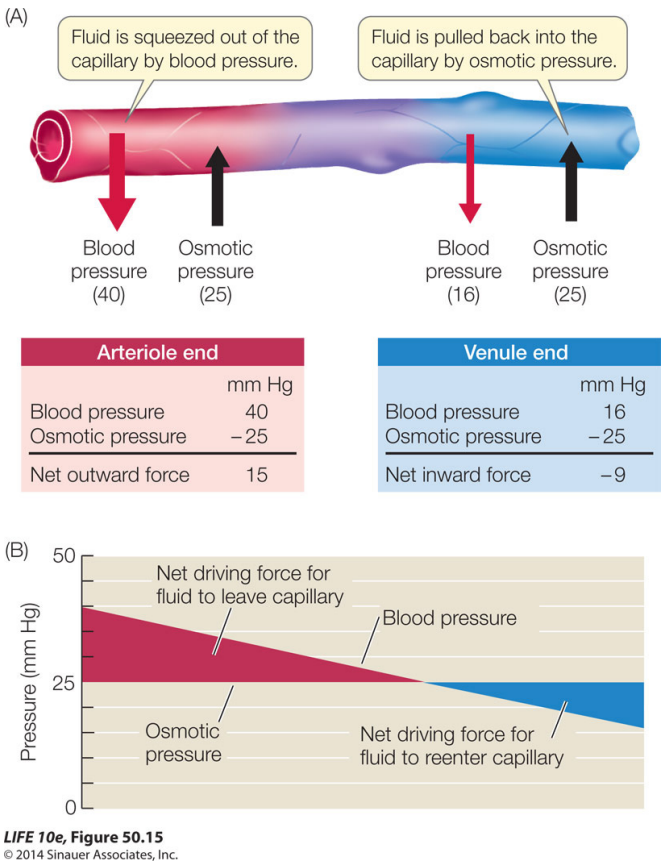
Blood circulation through the body is accomplished via a system of closed vessels. Blood leaves the heart in arteries and is distributed throughout the body's tissues in arterioles, which feed capillary beds. Exchange of material (nutrients, waste, respiratory gases, and hormones) occur in the capillaries. Blood leaving capillary beds collect in venules, which empty into veins that conduct blood back to the heart. The figure below shows the structure of arteries and veins, as well as the relative pressures, surface areas, and velocities of blood flow in different vessels.



Let's have a closer look at the various types of blood vessels:

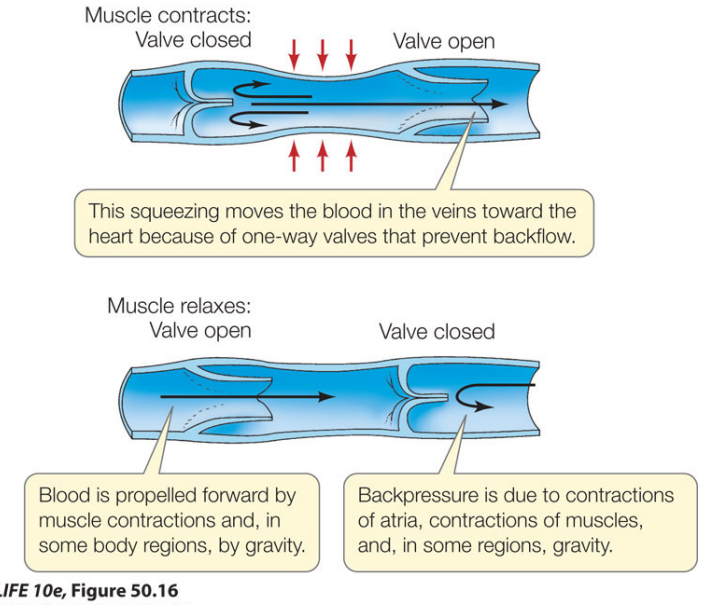
- **Large arteries** (such as the aorta, the largest artery in the body) have lots of smooth muscle and elastic fibers, enabling them to withstand the high pressures generated by the heart. The elasticity also permits stretching of the vessels during systole so that elastic recoil during diastole can push the blood forward.
- **Arterioles** are *resistance vessels*; smooth muscle can constrict or dilate arterioles (and arteries) in response to neural and hormonal cues, allowing modulation of blood flow to specific tissue.

- **Capillaries** are thin-walled and very permeable; they are made up of **endothelial cells** only (note: endothelial cells make up the endothelium—the inner lining of blood vessels). Because the total cross-sectional area of capillaries (not just one capillary but the many capillaries that branch out from arterioles) is extremely large, blood flows slowly through the capillaries so that material can be exchanged between blood and **interstitial fluid** (the fluid that bathes tissue) across the thin capillary walls. At the arterial end of capillaries, hydrostatic pressure (blood pressure) is higher than the osmotic pressure (which drives water back into vessels) so fluid tends to flow out from capillaries into tissue space. At the venous end of capillaries, hydrostatic pressure is lower than osmotic pressure so fluid tends to flow from tissue space into capillaries. See the figure to the right for a pictorial representation of this relationship.



***LIFE 10e*, Figure 50.15**

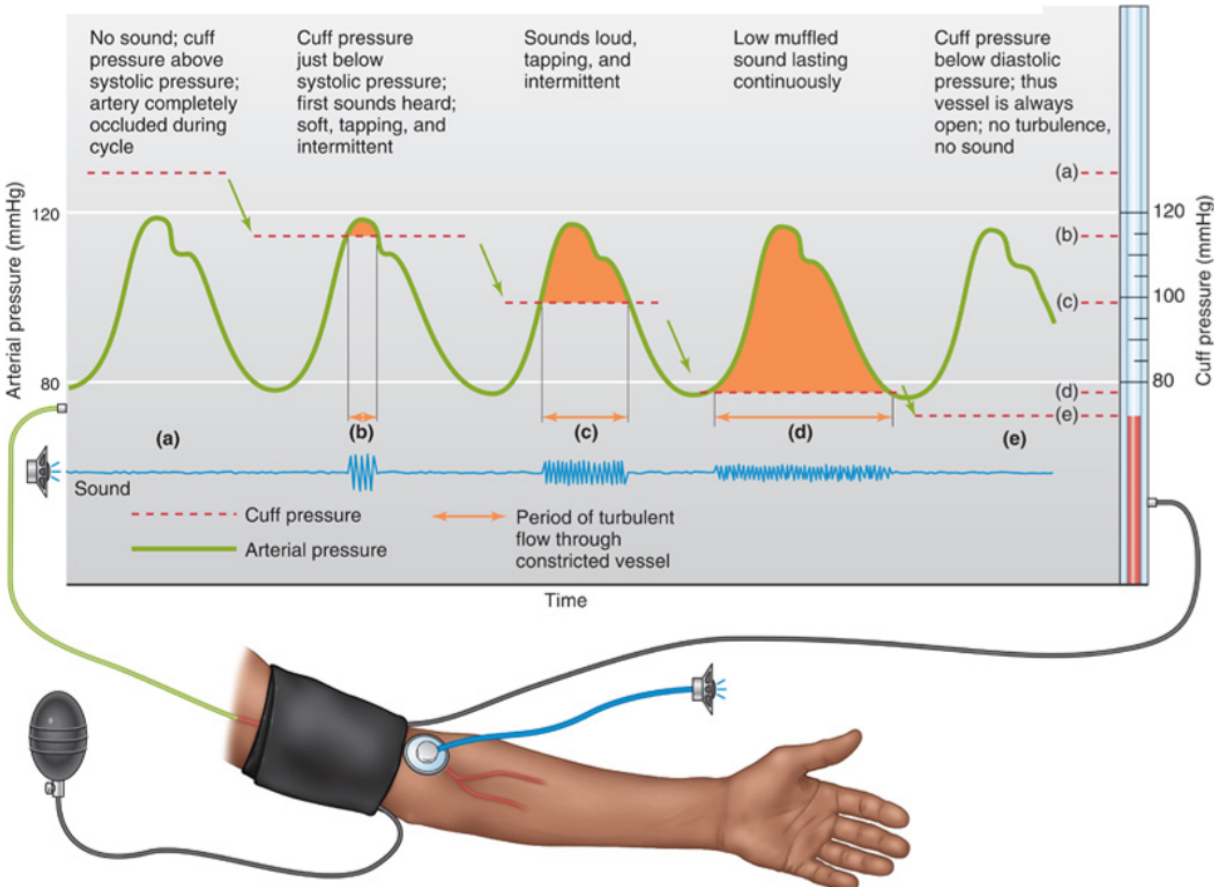
- **Venules** are thin-walled vessels that collect blood from the capillaries and join to form veins.
- **Veins** are *capacitance vessels*; they have high capacity to stretch (due to their many elastic fibers) and to store blood. At rest, about 60% of your blood volume is in your systemic veins, and only 18% is in arteries. How does blood return to the heart from the veins? Above the level of the heart, gravity aids return. Below the level of the heart, skeletal muscles serve as auxiliary pumps; one-way valves in *peripheral veins* (veins in the body's extremities) cause blood to flow toward heart when muscles squeeze veins. For example, contractions of leg muscles act as auxiliary vascular pumps when an animal walks or runs and facilitate the return of blood to the heart from the veins of the lower body (see figure).



***LIFE 10e*, Figure 50.16**

Blood Pressure

Blood pressure is measured with a device called a sphygmomanometer. See the diagram below.



Blood flow through capillary beds is largely autoregulated. Two autoregulatory mechanisms that control blood flow through capillary beds are:

- Precapillary sphincters can shut off blood supply to the capillary bed.
- Constriction of smooth muscles in the arteries and arterioles.

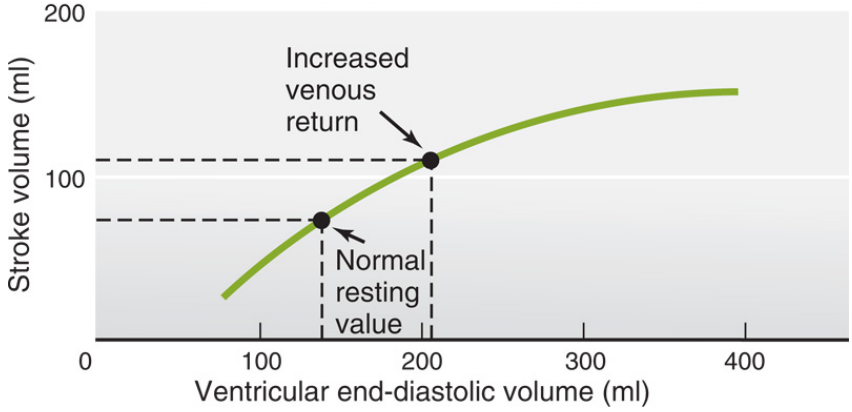
The Relationship Between Blood Flow, Blood Pressure, and Resistance:

The follow equations describe the relationship between blood flow, blood pressure, and resistance to blood flow:

- **MAP = CO x TPR**
  - Mean Arterial Pressure (MAP) is the average arterial pressure during a single cardiac cycle
  - Cardiac Output (CO) is the volume of blood pumped by the heart per unit time
  - Total Peripheral Resistance (TPR) is the total resistance opposing blood flow in the systemic circuit
    - TPR is controlled by local factors, hormones, and the autonomic nervous system.
- **CO = HR x SV**
  - Cardiac Output (CO) depends on heart rate and stroke volume
  - Heart Rate (HR) is controlled by the ANS
  - Stroke Volume (SV) is controlled by the ANS and the Frank-Starling law of the heart

Frank-Starling Law of the Heart: Stroke volume increases as the **end-diastolic volume** (pre-load) increases

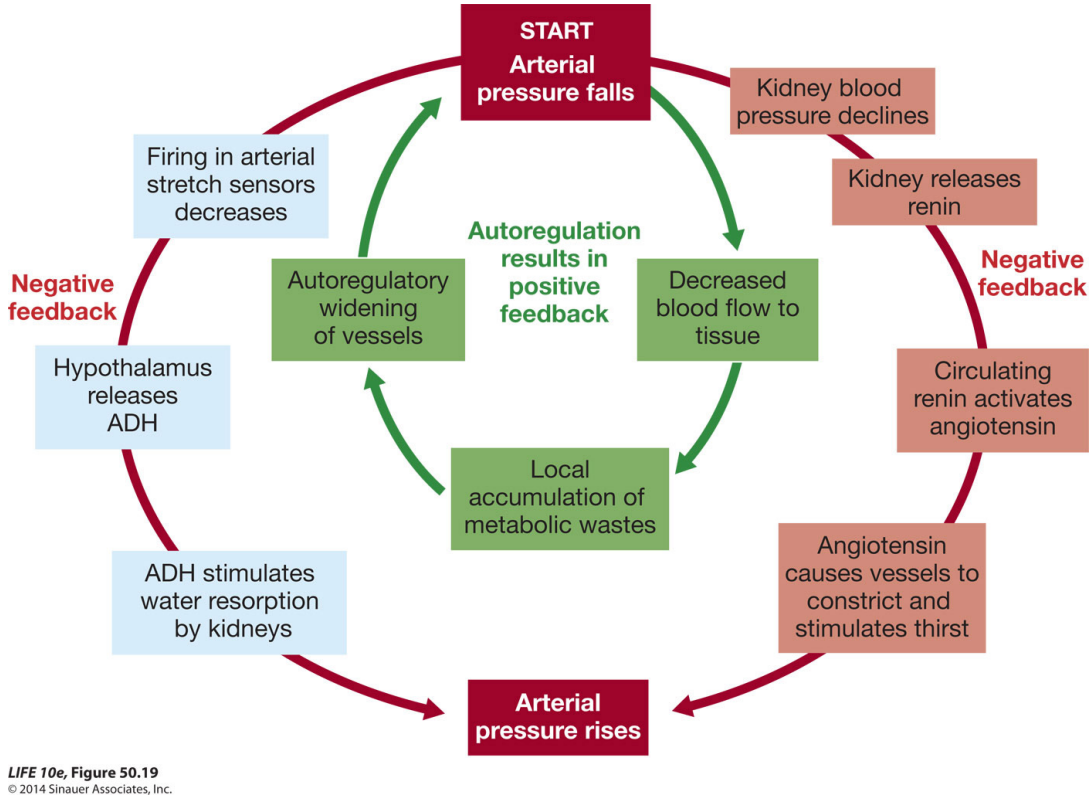
- At rest the cardiac muscle is not at the optimal length for generating maximum contraction. If stretched, the actin/myosin overlap makes it more optimal.
- As a result, anything that increases venous return to the heart will increase pre-load and therefore increase stroke volume.



Regulation of Mean Arterial Pressure:

- As we saw before (on page 12), baroreceptors respond to changes in mean arterial pressure by signaling the ANS to increase or decrease heart rate.
- Hormonal controls can also regulate mean arterial pressure (by influencing TPR). If arterial pressure falls, the following will occur:
    - Positive feedback (further decreases MAP):
        - Decreased blood flow to tissues leads to local accumulation of metabolic waste, leading to autoregulatory widening of vessels. This helps the tissues remove waste, but this actually decreases central blood pressure even more as a consequence of the dilation. Other mechanisms are therefore required to raise central blood pressure.
    - Negative feedback (increases MAP):
        - Kidney activates the RAAS response. The release of renin activates angiotensin. Angiotensin causes peripheral vasoconstriction (arterioles in the body's extremities to constrict), increasing arterial pressure. By reducing blood flow to peripheral tissues, these hormones increase central blood pressure and blood flow to essential organs such as the heart, brain, and kidneys. Angiotensin also causes thirst and the release of aldosterone which causes more water reabsorption from the kidneys, further increasing blood pressure.
        - Stretch receptors in the heart sense the decrease in plasma volume, causing the hypothalamus to release vasopressin (also called ADH, anti-diuretic hormone) via the posterior pituitary. Vasopressin stimulates water reabsorption by kidneys, leading to an increase in arterial pressure.

See the figure on the next page to summarize these responses to low arterial pressure:



LIFE 10e, Figure 50.19

Cardiac Failure

Cardiac failure means the heart fails to pump enough blood. There are several things that can lead to cardiac failure:

- Decreased contractility of the heart
- Acute myocardial infarction (heart attack; which can be caused by coronary thrombosis – blood clot blocking blood flow in a coronary artery [an artery that supplies the heart muscle with blood])
- Chronic diseases: coronary artery disease, hypertension, familial hypertrophic cardiomyopathy (FHC). FHC is caused by a mutation in contractile proteins (autosomal dominant inheritance) – a myofibril structural defect leads to Left Ventricular Hypertrophy which leads to obstruction of septal conduction fibers
- Damaged valves such as narrowing (stenosis) of valves (usually the left atrioventricular [mitral] valve or the aortic valve)
- Shock (septic, hemorrhagic, neurogenic, anaphylactic, cardiogenic)

In both congestive heart failure (CHF) and FHC, there is an imbalance of supply and demand. In CHF, demand is greater than supply and there is usually a pressure overload that the heart must work against to pump blood.

The acute effect of cardiac failure is a reduction in cardiac output (CO). This leads to low arterial pressure and inadequate blood flow to tissues. Local hypoxia and waste accumulation occur as a result. The tissues attempt to compensate with local vasodilation but this leads to a further drop in arterial pressure.

Mechanisms of compensation to cardiac failure:

- Ventricular hypertrophy (enlargement of the ventricles): This is a mechanism to increase blood supply in response to increased demand for blood (or decreased contractility due to damaged heart muscle).
- Sympathetic compensation: Activation of baroreceptors at low blood pressure elevates heart rate and causes peripheral vasoconstriction (constriction of vessels in the body's extremities) increasing venous return. This elevates right atrial pressure (a consequence of the Frank-Starling Law of the heart). Sympathetic stimulation also increases contractility of the heart muscle.

If the critical cardiac output is not reached following these compensatory mechanisms, hormonal responses including release of ADH and the RAAS response will be initiated to increase water reabsorption and raise blood pressure. If this still fails to bring CO back to the critical level (resulting in decompensated heart failure), the resulting systemic congestion and damming of venous blood leads to fluid leakage into extracellular spaces, pulmonary congestion, intravascular clotting, hypoxia, and acidosis. Consequently, the heart muscle may fail due to overstretching, edema (swelling), and hypoxia.

Decompensated heart failure is treated with drugs in an attempt to raise CO back to the critical level. **Digitalis** is a drug extracted from the Digitalis plant. Digitalis slows the calcium ion pumps in myocardial cell membranes, leading to an increase in cytoplasmic calcium concentration, thus improving cardiac contractility. Digitalis is often used as a treatment for congestive heart failure.

The Excretory System

Animals use excretory systems for two reasons: 1) to maintain the volume, concentration, and composition of their extracellular fluids, and 2) to get rid of waste.

Problems Created by the Environment

An animal's environment creates three problems, in regards to salt/water balance, that need to be solved:

1. *Water*: Maintaining an optimal concentration of interstitial fluid (the fluid that bathes tissue)
2. *Ions*: Maintaining an optimal ionic composition of interstitial fluid
3. *Nitrogen waste*: Excreting nitrogenous waste products of metabolism

The solutions to these problems depend on the environment, as shown in the table below:

	Fresh water environment	Salt water environment	Land environment
Water:	Must be excreted	Must be conserved	Must be conserved
Ions:	Must be conserved	Must be excreted	Conserved (but sometimes excreted to detoxify)
Nitrogen waste:	Lost passively in the form of ammonia (NH_3)		Excreted as urea or uric acid

Think about the table above: Why excrete water in fresh water environments? Otherwise the organism would swell up!

However, one important thing to note: There is no active transport of water. Rather, to accomplish osmoregulation, water is moved across membranes via osmosis or hydraulic pressure.

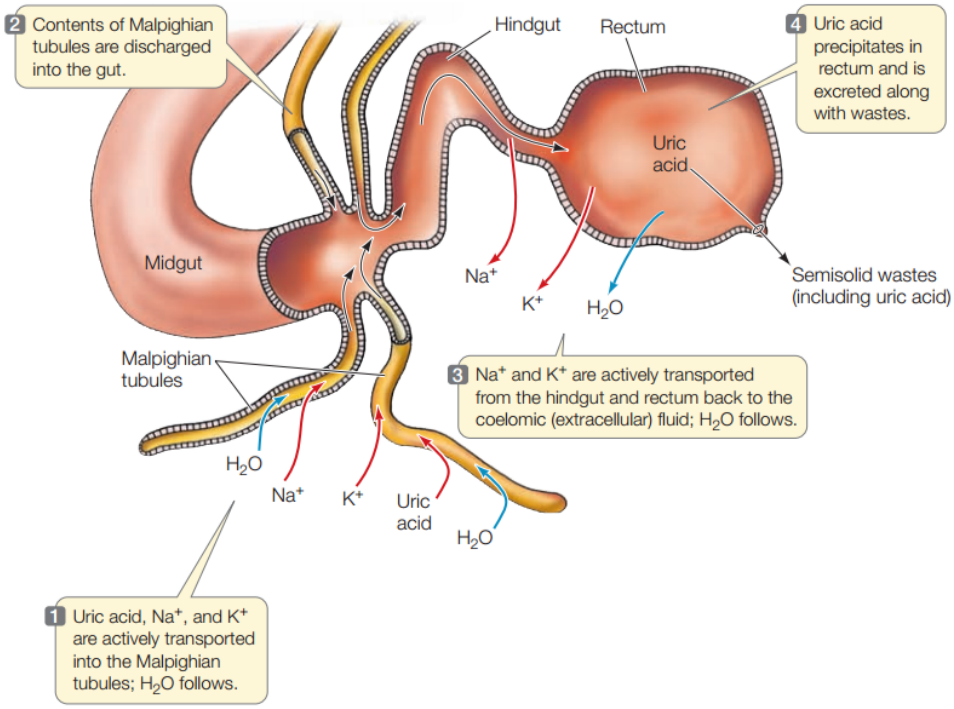
Nitrogen waste removal: **Ammonia** is highly water soluble and inexpensive to produce but is toxic. Fish excrete nitrogenous waste in the form of ammonia since there's enough water around to dilute the ammonia. Mammals remove nitrogen waste in the form of **urea**, which is more expensive to produce but is less toxic and requires less water to dilute. Birds remove nitrogen waste in the form of **uric acid**, which is the most energetically expensive to produce but is the least toxic and is quite insoluble (requiring very little water to remove). Notice some important tradeoffs here: toxicity, water conservation, and energy.

Evolution of Excretory Systems

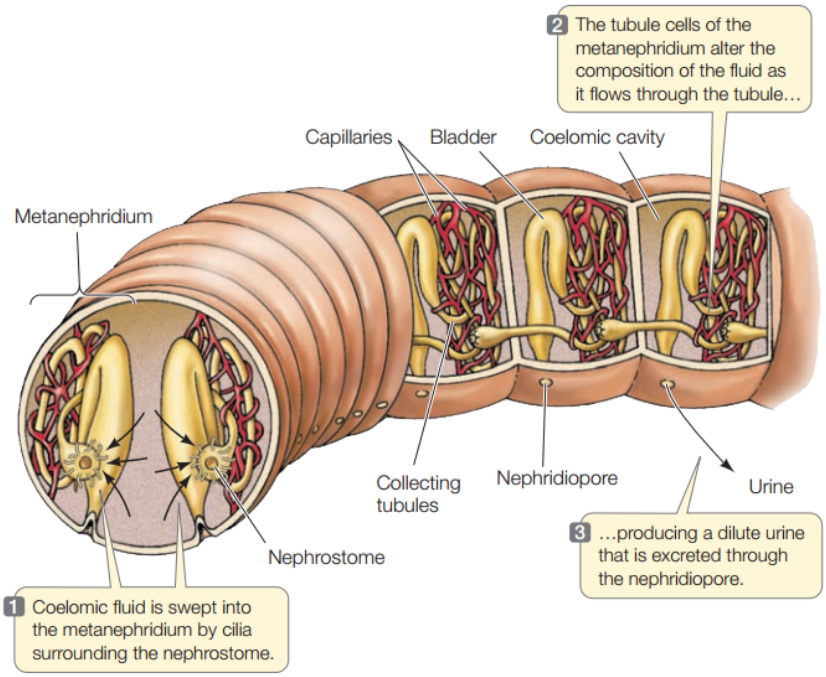
Malpighian tubules of insects:

Insects have several tubules, called **Malpighian tubules**, which empty into the gut. Since insects have an open circulatory system and therefore cannot use blood pressure to filter extracellular fluids into the tubules, an active transport mechanism is required. Cells of the tubules actively transport uric acid, potassium ions, and sodium ions from the extracellular fluid into the tubules. The high concentration of solutes in the tubules causes water to follow osmotically, which flushes the tubule contents toward the gut. At the hindgut and rectum, epithelial cells actively transport sodium and potassium ions from the gut contents back into the extracellular fluid. Water follows the ions and is also pulled out into extracellular fluid. The uric acid concentration becomes very high in the rectum, precipitating into a semisolid-type of matter (with other waste material). The insect excretes this semisolid waste matter. So, in summary: this tubule system uses osmotic gradients to permit excretion of nitrogen-waste (in the form of uric acid) without excessive water loss.

The following diagram illustrates the Malphigian tubules of insects:



Metanephridia of annelids (earthworms):



Annelids (earthworms) are segmented, and each segment has a fluid-filled body cavity called a **coelom**. Unlike insects, annelids have closed circulatory system so they can pump blood under pressure. They use this hydrostatic pressure to cause blood to be *filtered* across thin, permeable capillary walls into the coelom. Now, what happens to the **coelomic fluid** (the fluid that just got filtered across the capillary walls)? Well, each segment of the annelid's body contains a pair of **metanephridia**. The coelomic fluid is swept into the metanephridium by cilia surrounding the **nephrostome** (a funnel-like opening to a metanephridium). As the coelomic fluid goes through the tubules of the metanephridia, the tubule cells use active transport to *reabsorb* certain molecules (e.g. stuff that must be conserved) from the coelomic fluid into the blood and to *secrete* other molecules (e.g. stuff that must be excreted) into the coelomic fluid. The coelomic fluid, by the time it leaves the tubules via the **nephridiopore** (which opens to the outside of the animal), is essentially dilute urine containing nitrogenous wastes and other solutes.

Kidneys of vertebrates:

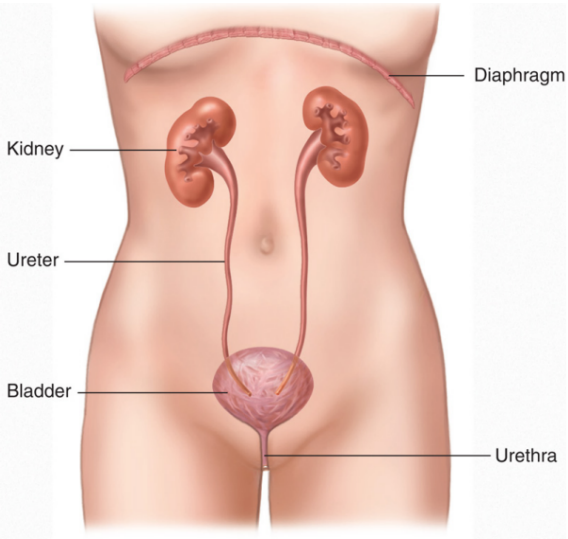
Like in the annelid excretory system we just discussed, vertebrate excretory systems have three basic processes:

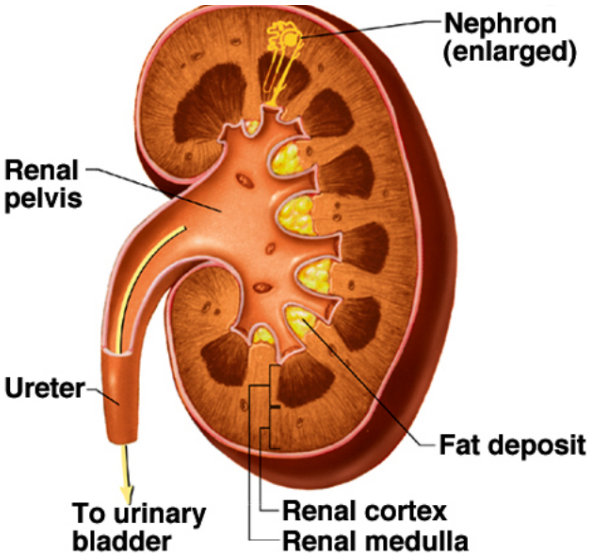
1. **Filtration**: Filtering fluid across thin semipermeable walls (to preserve large molecules such as proteins).
2. **Secretion**: Transport of waste products into the fluid that will eventually become urine.
3. **Reabsorption**: Absorption of things that need to be conserved from the fluid that will eventually become urine back into the body.

Below, we examine the evolution of the vertebrate kidney, by looking at two primitive vertebrate excretory systems that have evolved:

Pronephros Found in cyclostomes (jawless fish)	**Mesonephros** Found in some sharks & amphibians
A paired organ; one nephron filters blood and deposits the filtered blood (the blood filtrate) into the coelom. The blood filtrate then passes through thin ciliated tubules into another nephron where it is processed for solute recovery. This system is the most primitive vertebrate excretory system.	Unlike in pronephros, the glomerulus (a cluster of capillaries responsible for filtration) here is situated in the tubule, rather than in the coelom. As a result, the filtrate goes directly into the tubule system, not into the coelom.

Now, we will look at the human kidney:





It is worth mentioning here that blood flow to the kidney is served by a **renal artery** and is drained by a **renal vein**.

In the human kidney, the **nephron** is the basic functional unit. In the following section, we will take a closer look at the nephron and how functions of the nephron are localized.

Human Renal Function (The Nephron)

The basic structure of the nephron:

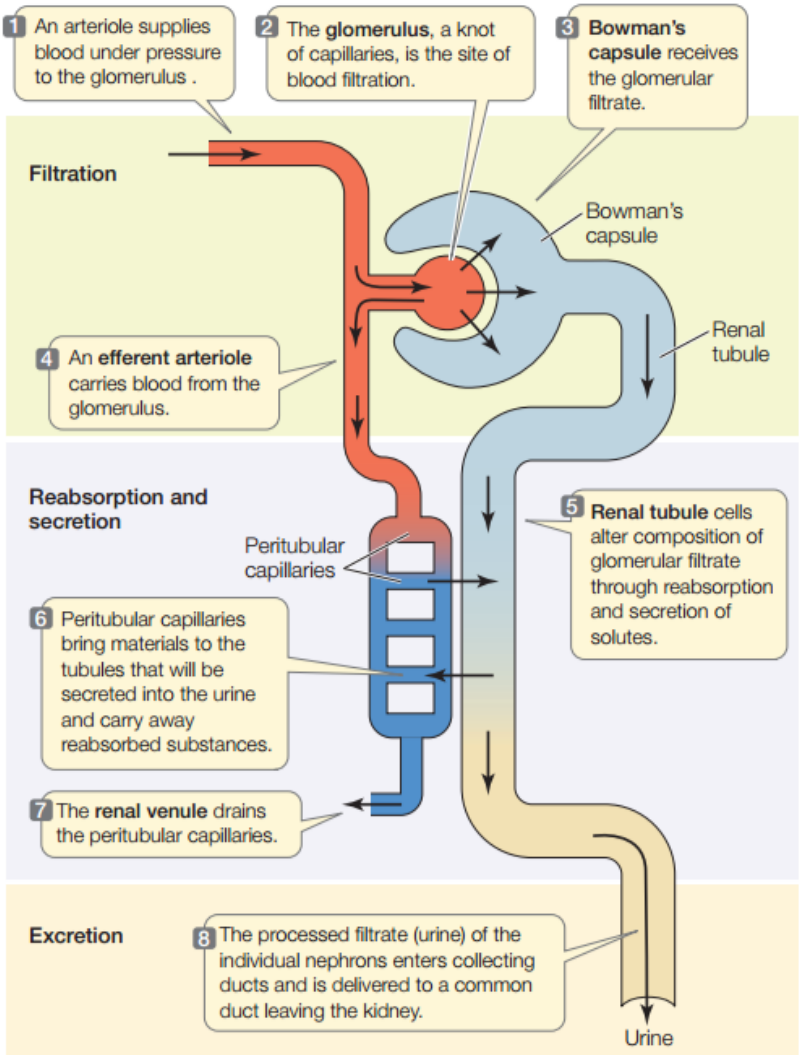
There are 3 things happening in the nephron:

1. **Filtration:** The fluid of the blood is filtered out of the blood vessels and into the renal tubular system. Important components of this process include the:

   -Glomerulus: A cluster of capillaries highly permeable to water, ions, and small molecules. Responsible for **filtration** of blood.

   -**Bowman's capsule:** receives the filtrate (the filtered blood). In the Bowman's capsule, **podocytes**, cells containing foot projections, wrap around glomerular capillaries and leave slits between them. Blood is filtered through these slits.

2. **Reabsorption and Secretion:** After passing through Bowman's capsule, the filtrate travels through tube-like structures called **Renal tubules.** Cells in the renal tubules remove specific ions, nutrients, and water from the filtrate and return them to the blood (**reabsorption**). Cells in the renal tubules also add substances that need to be excreted directly to the filtrate (**secretion**).



3. **Excretion:** The processed filtrate enters the **Collecting duct**, the final part of the nephron. Urine gets concentrated here, after which it exits the kidney and the body.

Let's briefly discuss the components of renal circulation:

- **Afferent arteriole**: Supplies blood under pressure to the glomerulus.
- **Efferent arteriole**: Carries blood away from the glomerulus.
- **Peritubular capillaries**: Bring materials to the renal tubules that will be secreted into the filtrate and carry away substances reabsorbed from the filtrate.
- **Renal venule**: Drains the peritubular capillaries.

At this point, I hope that you can appreciate that one major role of excretory systems is to "keep as much of the good stuff as possible; get rid of as much of the bad stuff as possible." As you can see, accomplishing this is no easy matter – hence why we have evolved such an elaborate system.

Calculations of renal function:

First, before we delve into any calculations, let's define a few variables:

- **[Px] = Concentration of substance x in plasma**
- **[Ux] = Concentration of substance x in urine**
- **V = Flow rate of urine**

Now, let's discuss some basic renal calculations:

1) Concentration ability: How well does the kidney concentrate substance x?

$$\text{Concentration ability} = [Ux] / [Px]$$

2) Renal clearance factor (RCF): How much blood plasma can be cleared of substance x per unit time?

$$RCF = ([Ux] / [Px])*V$$

3) Glomerular filtration rate (GFR): How much plasma passes from the circulation into the Bowman's capsule per unit time?

- To calculate this, we must find a substance that is neither secreted nor reabsorbed by the renal tubules. One such substance is inulin. Thus, RCF of inulin = GFR.

$$GFR = \text{RCF of inulin}$$

4) **Rate of nephron entry**: The rate at which substance x enters the nephron.

$$\text{Rate of nephron entry} = [Px]*GFR$$

5) Rate of excretion: The rate at which substance x leaves the kidney and is excreted into urine.

$$\text{Rate of excretion} = [Ux]*V$$

6) Rate of secretion/reabsorption: Rate at which substance x is secreted or reabsorbed (represents an exchange between renal tubule and peritubular capillaries).

$$\text{Rate of secretion or reabsorption} = [Px]*GFR - [Ux]*V$$

- If negative, then it's the rate of secretion
- If positive, then it's the rate of reabsorption
- If zero, then there's no secretion or reabsorption (like inulin)

Think about why the above equation is true: When [Px]*GFR (rate of nephron entry) is very large but [Ux]*V (rate of excretion) is very small, that means lots of substance X is entering the nephron but very little of substance X is leaving the nephron. Where does

that substance X go? It must've been reabsorbed! On the other hand, when [Ux]*V (rate of excretion) is very large but [Px]*GFR (rate of nephron entry) is very small, that means not a lot of substance X enters the nephron but a lot of substance X is being excreted. Why is so much substance X being excreted even though so little entered the nephron in the first place? Because large amounts of substance X are secreted into the filtrate from the peritubular capillaries so when the filtrate reaches the end of the nephron, there's actually a ton of substance X!

The Loop of Henle:

The glomerular filtrate, upon reaching Bowman's capsule, is similar in composition to blood plasma except large things (proteins, cells, etc.) have been excluded from entering the filtrate. Now, let's discuss the specifics of what happens to the filtrate after it leaves the Bowman's capsule:

1) **Proximal convoluted tubule** (PCT): The destination of the filtrate after Bowman's capsule, the PCT is responsible for most of the reabsorption of water and solutes from the filtrate. Sodium ions are actively transported out of the tubule (with chloride following) and other solutes, such as glucose and amino acids, are also actively transported out. However, the osmolarity of the fluid flowing through the PCT has not changed at all, even after all the reabsorption that occurs (this is because solutes are transported out and water osmotically follows the ions as they are reabsorbed). The PCT is clearly not sufficient to concentrate the urine.

2) **The Loop of Henle**: Uses a **countercurrent multiplier** mechanism to concentrate the urine.

a) **Descending limb**: The first part of the loop of Henle and the next stop for the filtrate going through the renal tubules. The descending limb is permeable to water but impermeable to ions. As the filtrate moves down this limb, water is reabsorbed (water moves out of the tubules). At the bottom of this limb, the filtrate ends up being very concentrated as a result. Why was water able to continuously move out of this limb? Because high osmolarity was established in the interstitial fluid by the ascending limb, as we will now see.

b) **Ascending limb**: After the descending limb comes the ascending limb. Unlike the descending limb, the ascending limb is impermeable to water but permeable to ions. In the first part of the ascending limb, called the **thin ascending limb**, sodium ions and chloride ions passively move out of the tubule into interstitial fluid (since, remember, the filtrate at this point has very high osmolarity so sodium ions and chloride ions can easily move out of tubule fluid). Once the filtrate reaches the upper part of the ascending limb, called the **thick ascending limb,** sodium ions and chloride ions are actively pumped out into the interstitial fluid (but water can't follow). Net result: sodium and chloride ions moving out of ascending limb make the interstitial fluid very high in osmolarity and that's why, in the descending limb, water is able to passively be reabsorbed.

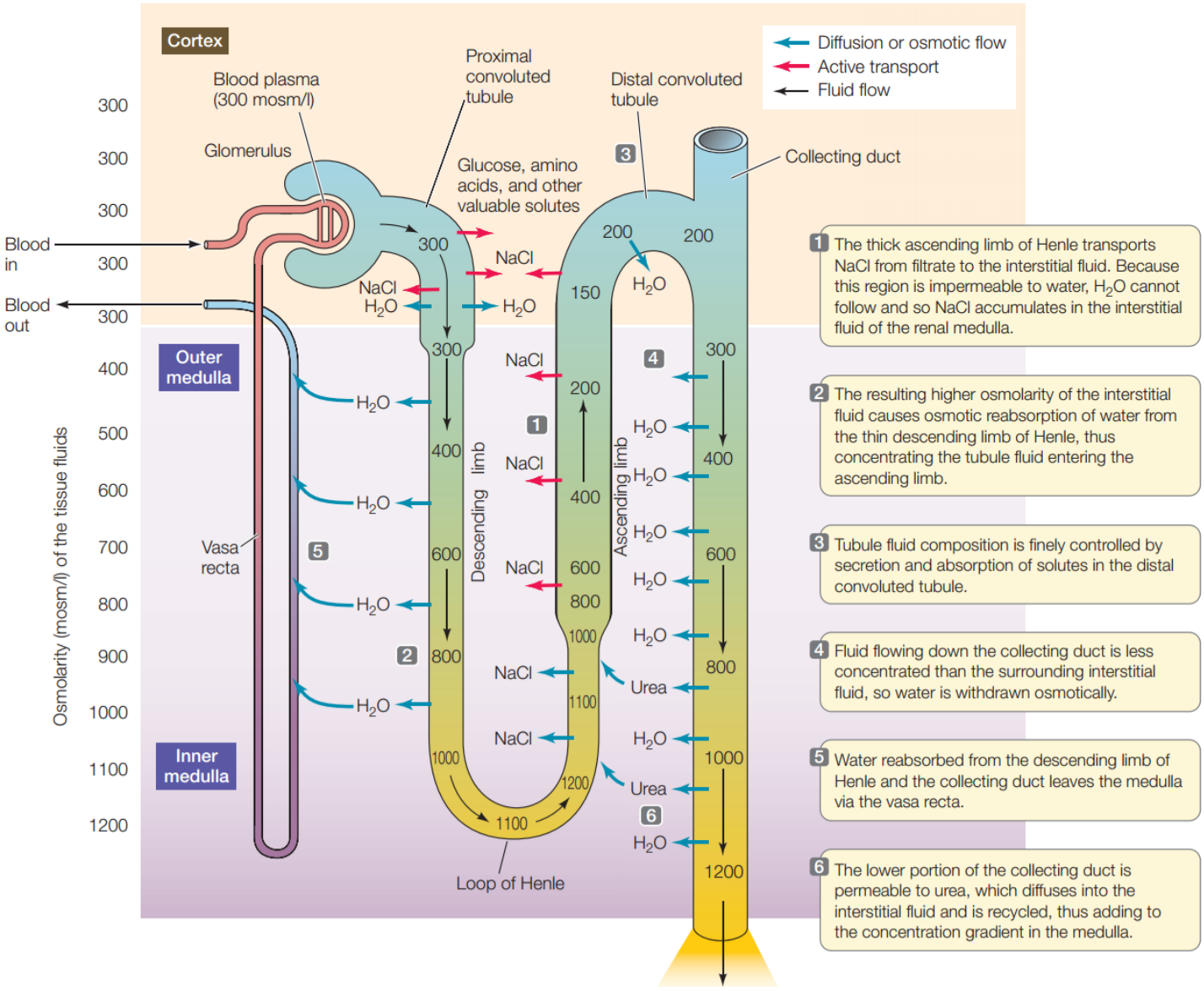
(This process is confusing so please refer to the diagram on the next page for a better visualization)

3) **Distal convoluted tubule** (DCT): Comes after the loop of Henle. Here, the composition of filtrate is fine-tuned via active secretion or reabsorption of solutes such as K^+.

4) **Collecting duct**: By the time the tubular fluid reaches the collecting duct, the major solute present is urea (since most other solutes were reabsorbed earlier on). As the tubule fluid flows down the collecting duct, it loses water osmotically to the interstitial fluid (remember from before that high osmolarity was established in the interstitial fluid). As water is withdrawn from the collecting duct, some urea also passively leaks out into the interstitial fluid, adding to its osmotic potential. This urea diffuses back into the loop of Henle and

is returned to the collecting duct. The recycling of urea contributes significantly to the osmolarity of the interstitial fluid and therefore the ability of the kidney to concentrate the urine in the collecting duct.

Take a look at the diagram below illustrating how urine gets concentrated. Note how the osmolarity of the interstitial fluid as well as the tubular fluid increases as we approach the inner **medulla** (the inner region of the kidney containing the bottom of the loop of Henle) from the **cortex** (the outer region of the kidney containing the glomeruli and convoluted tubules). This concentration gradient allows for effective concentration of urine. Another thing to note: The peritubular capillaries surrounding the loop of Henle are known as **vasa recta**. The arrangement of the vasa recta helps *maintain* the concentration gradient of interstitial fluid; it is arranged in such a way so that the established concentration gradient is not simply washed out when blood flows through.

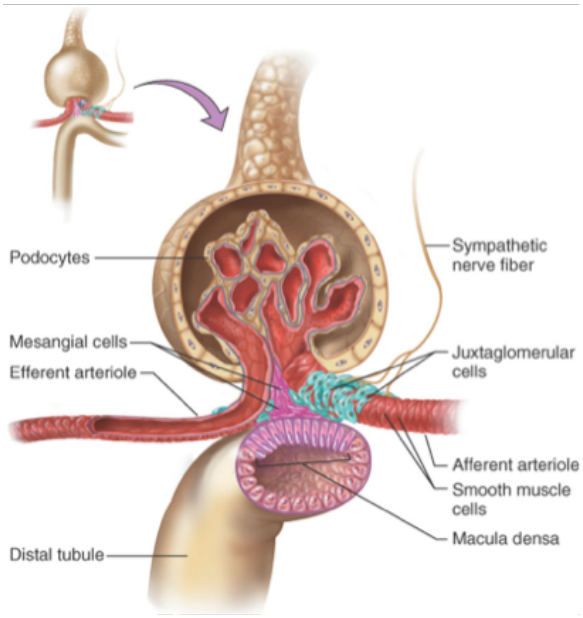


Desert animals generally have much longer loops of Henle because they need to conserve water as much as possible. Concentrating urine more (by establishing an extremely large concentration gradient, which requires a long loop of Henle) allows for more water to be conserved.

Regulation of Renal Function

Filtering blood is an essential feature of vertebrate excretory systems, and kidneys attempt to keep this function going by maintaining a constant glomerular filtration rate (GFR). Without regulation, the GFR would increase with increased blood pressure and decrease with decreased blood pressure. The body will therefore maintain the GFR through:

1. **Myogenic response**: When blood pressure rises, smooth muscle in the afferent arterioles constrict, reducing blood flow into the glomerulus.
2. **Renin-angiotensin-aldosterone system (RAAS)**:
   a. When GFR decreases, the filtrate goes through the nephron slowly so more reabsorption can occur. Hence, the concentration of solutes (i.e. NaCl) in the tubular fluid goes down. The macula densa cells in the distal convoluted tubule sense this drop in concentration and signal renal afferent arterioles to dilate (increasing GFR) and to release **renin** (The cells that secrete renin are called juxtaglomerular cells). Notice that the distal convoluted tubule is located in close proximity to the glomerulus and renal afferent arteriole allowing this process to occur (see figure to the right).



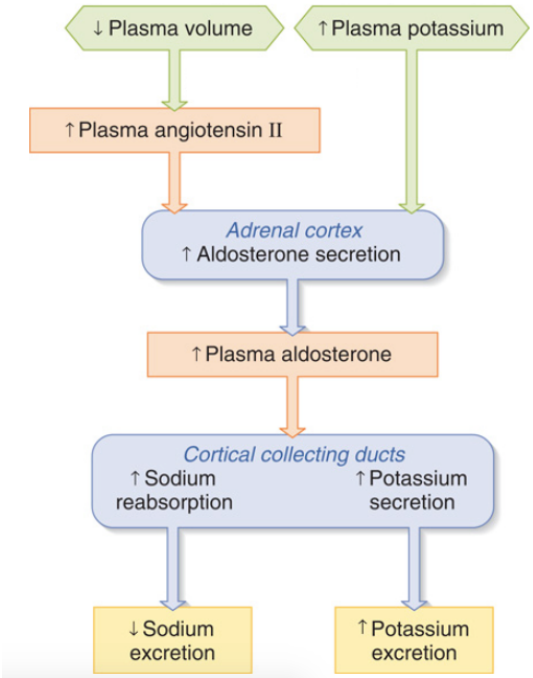
   b. The enzyme renin, through proteolytic activity, converts the circulating protein, **angiotensinogen**, into an active hormone called **angiotensin I**.
   c. Angiotensin I circulates and is converted by an enzyme in the lungs, called **angiotensin converting enzyme (ACE)**, into **angiotensin II**.
   d. Angiotensin II does several things that help increase GFR back to normal:
      i. It constricts efferent renal arterioles, which leads to an increase in blood pressure in the glomerulus. *(Constriction of "afferent" arterioles decreases pressure in the glomerulus because these arterioles enter the glomerulus; constriction of "efferent" arterioles increases pressure in the glomerulus because these arterioles exit the glomerulus).*
      ii. It constricts peripheral blood vessels throughout the body – which leads to an elevation in central blood pressure.
      iii. It stimulates thirst – so we drink more water, increasing our blood volume (and therefore our blood pressure).
      iv. It stimulates the outer part of the adrenal gland (adrenal cortex) to release the steroid hormone: **aldosterone**. Aldosterone stimulates sodium ion reabsorption in the distal convoluted tubule and in the collecting duct. Aldosterone also stimulates the secretion of potassium ions into the filtrate, but more sodium is reabsorbed than potassium is secreted (3 Na^+ reabsorbed per 2 K^+ secreted) so there is a net flow of solute out the filtrate. Water gets reabsorbed as well as it passively follows the Na^+ that leaves. Hence, due to the water reabsorption, blood volume (and therefore blood pressure) increases but blood osmolarity remains unchanged (although sodium entered the bloodstream, so did water, therefore there's no net change in blood osmolarity).

Summary: Low blood pressure (low GFR) -> RAAS activation -> elevate blood pressure. *(As an aside, certain drugs, called ACE inhibitors, block ACE's activity of making angiotensin II. Such drugs lower blood pressure and are often prescribed for treatment of hypertension & congestive heart failure)*

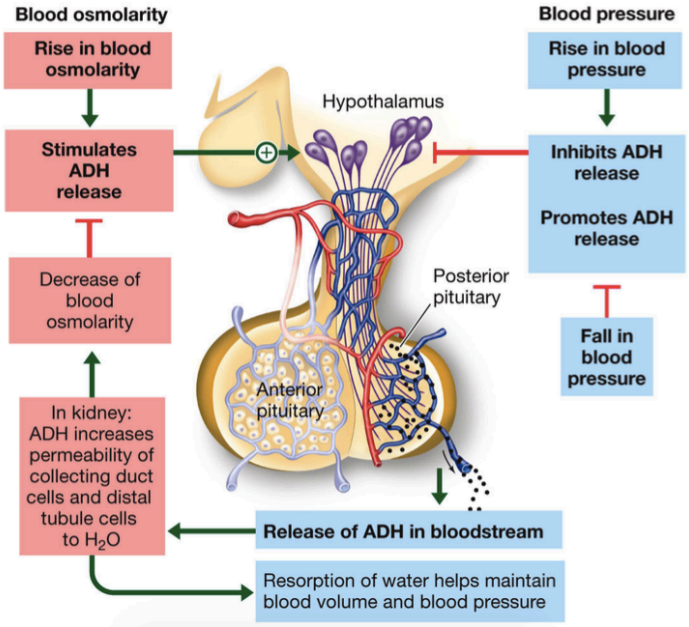
3. **Vasopressin**: When plasma osmolarity increases or blood pressure decreases, the hypothalamus increases production of **antidiuretic hormone** (**ADH**; also called vasopressin), which is released into circulation by the posterior pituitary. ADH increases expression of aquaporins (water channel proteins) in collecting duct cells and also increases insertion of these proteins into the collecting duct cell membranes. This results in an increase in permeability of the collecting duct to water, allowing more water to be reabsorbed. More water reabsorbed = more blood volume = higher blood pressure. And, unlike aldosterone, the reabsorption of water here results in lower blood osmolarity (because no ions get reabsorbed with the water)

We discussed two hormones that affect blood volume via water reabsorption: aldosterone and ADH. Let's look at some additional features of these two hormones:

Aldosterone secretion and its effects:



ADH secretion and its effects:



As mentioned on the previous page, aldosterone stimulates secretion of K^+ from the blood into the filtrate. High K+ levels in the blood can cause the adrenal gland to secrete aldosterone. Thus, there are two ways that the adrenal cortex is signaled to secrete aldosterone: 1) an increase in angiotensin II levels in the blood, and 2) an increase in K^+ levels in the blood.

As an aside, alcohol is a diuretic; it inhibits the secretion of ADH, resulting in more fluid loss through urination (less water gets reabsorbed in the collecting duct). Excessive consumption of alcohol can lead to dehydration because of too much fluid loss.

Regulation of Acid/Base Balance

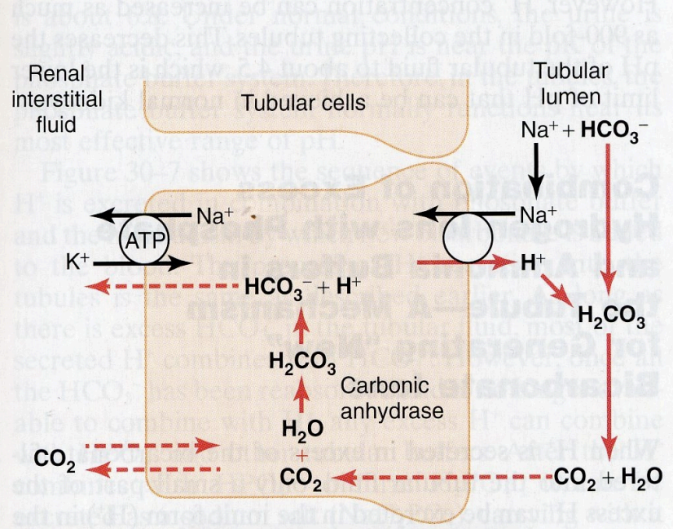
There are three ways acid/base balance is achieved, each having different time scales:

1. Buffering (seconds)
2. Elimination of acid by the respiratory system (minutes)
3. Elimination of acid by the kidney (hours)

Recall the bicarbonate buffer system: $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$. Bicarbonate is the major buffer for the extracellular fluid, but its pKa is about 6.1 (which is a bit off from physiological pH). But, its big advantage is that both [CO_2] and [HCO_3^-] can be controlled physiologically. The respiratory system can eliminate CO_2; the renal system can reabsorb HCO_3^- (and eliminate H^+).

How the renal system reabsorbs bicarbonate:

1. HCO_3^- is filtered from the blood to the filtrate.
2. The tubular fluid is acidified by the active secretion of H^+ (in exchange for Na^+).
3. H^+ combines with HCO_3^-, resulting in the formation of H_2CO_3 in the filtrate.
4. H_2CO_3 dissociates into CO_2 and H_2O, and the CO_2 diffuses into tubule cells.
5. Carbonic anhydrase in the tubule cells facilitates the hydration of the CO_2 to H_2CO_3, which dissociates into H^+ and HCO_3^-.
6. H^+ is pumped into the renal tubule (H^+ is essentially recycled throughout this process), and HCO_3^- returns to the interstitial fluid.



Net result: HCO_3^- is reabsorbed out of the filtrate and into the interstitial fluid.

Other mechanisms for H^+ secretion and HCO_3^- reabsorption:

Phosphate ions and ammonia (NH_3) both act as buffers and can increase the capacity for hydrogen ions to be excreted. Phosphate ions are filtered in the kidney and can accept H^+ ions transported into the tubular fluid (resulting in the production of $H_2PO_4^-$, which will be excreted). Ammonia secreted into the filtrate also can accept H^+ ions transported into the tubular fluid (resulting in the production of ammonium ions, NH_4^+, which will be excreted).

A new supply of bicarbonate ions can also be made. New bicarbonate can be made by the breakdown of glutamine to bicarbonate and ammonium (NH_4^+) ions in renal tubule cells. The bicarbonate will be returned to the blood, while the ammonium will be excreted.

Acid/base imbalance is the result of one of the following four conditions:

- **Respiratory alkalosis** = Too little CO_2. Kidneys will try to compensate by decreasing [HCO_3^-].
- **Respiratory acidosis** = Too much CO_2. Kidneys will try to compensate by increasing [HCO_3^-].
- **Metabolic alkalosis** = Too much HCO_3^-. Hypoventilation will occur as a means of compensating.
- **Metabolic acidosis** = Too little HCO_3^-. Hyperventilation will occur as a means of compensating.

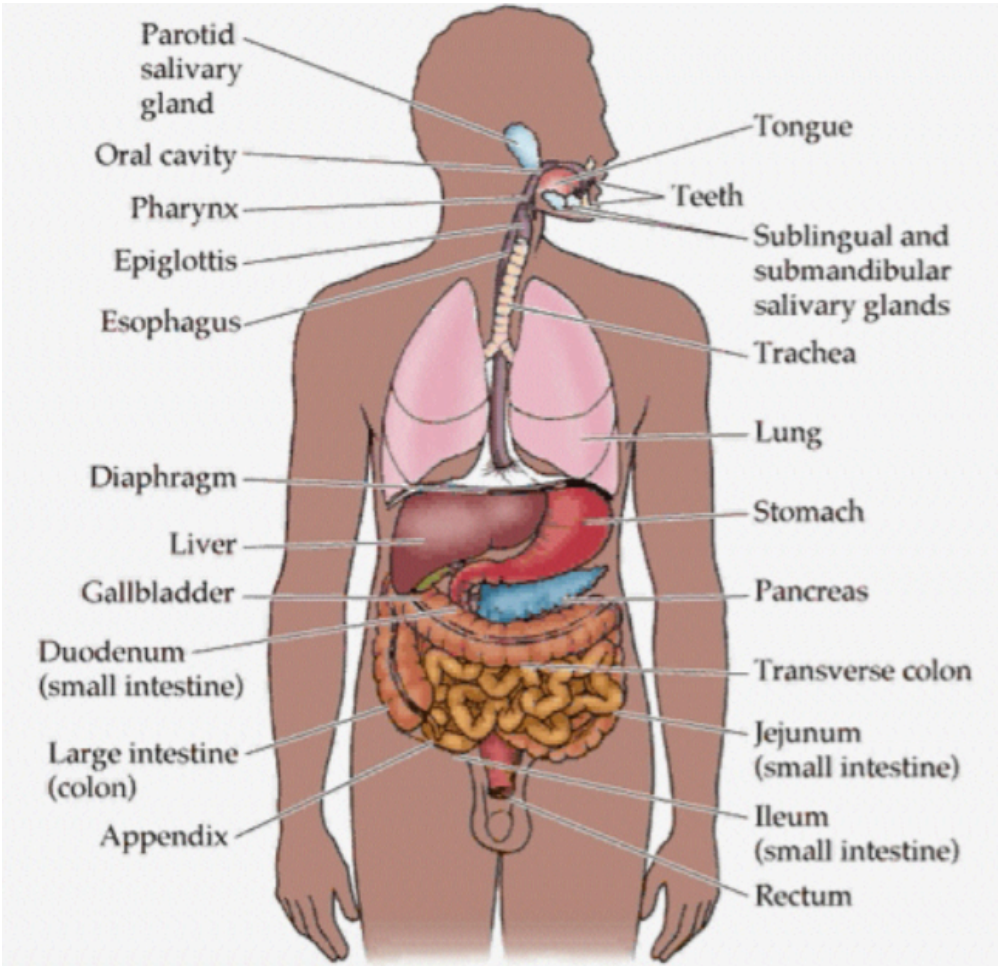
Note the interplay between the respiratory system and the renal system in maintaining acid/base balance. The normal pCO_2 value is 40 mm Hg and the normal HCO_3^- concentration is 24 mEq/L.

The Digestive System

Our digestive system is responsible for several major tasks. One is to move food through our gastrointestinal tract, which spans from the mouth (where food is ingested) to the anus (where food is evacuated). Another function is to secrete digestive chemicals sequentially and at such a rate that the breakdown of food is complete and the absorption of nutrients is maximal. Finally, the digestive system helps us store fuel reserves whenever possible and to preserve glucose for the brain.

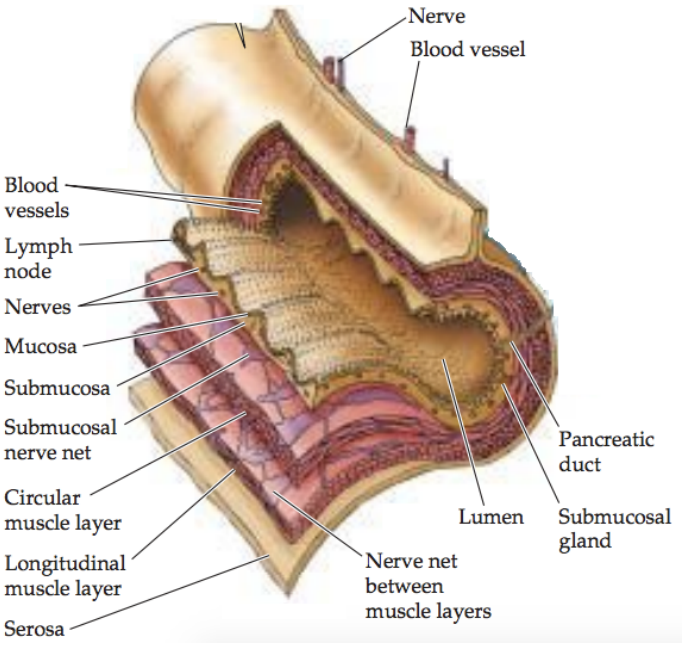
Anatomy of the Gastrointestinal Tract

Let's first look at the gross anatomy of the gastrointestinal (GI) tract:



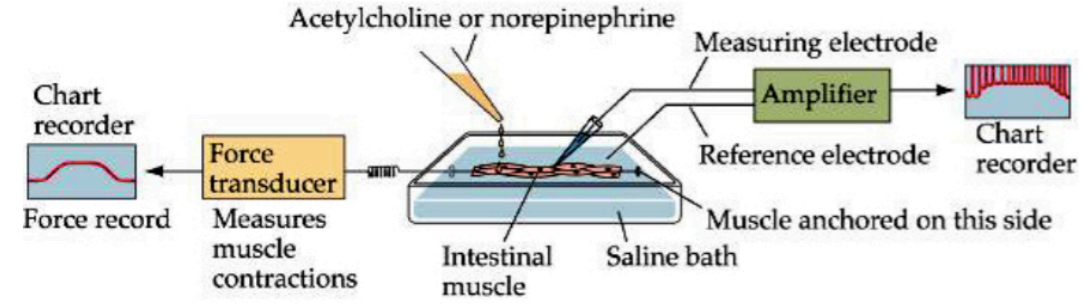
As you can see, the digestive system consists of a tubular gut running from the mouth to the anus as well as several accessory structures, which secrete digestive chemicals. Let's now take a closer look at the tubular gut and discuss its cellular anatomy. The gut consists of several concentric layers:

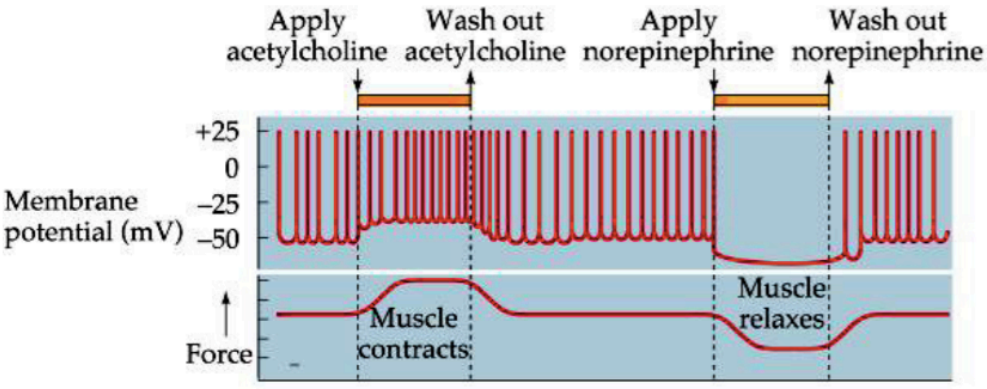
1. **Serosa**: The outermost layer, which is a layer of epithelium that is continuous with the peritoneum. The peritoneum is a thin, strong, two-layered membrane that lines the walls of the abdominal cavity and covers the abdominal organs.
2. **Muscularis**: Two layers of smooth muscle. The inner layer is a circular layer of smooth muscle, responsible for constricting the gut, while the outer layer is a longitudinal layer of smooth muscle, responsible for shortening the gut lengthwise. Between these two layers is the Myenteric plexus, which is a nerve network that controls the smooth muscles.
3. **Submucosa**: A layer of loose connective tissue supporting blood vessels, lymphatics, and secretory glands. The blood and lymph vessels in the submucosa carry absorbed nutrients to the rest of the body. A nerve network, called Meissner's plexus, is also found in the submucosa. This nerve network has sensory functions and controls secretions.
4. **Mucosa**: The inner layer of the gut. Some epithelial cells of the mucosa have secretory roles while others function in absorption of nutrients. The cells that function in absorption have projections called microvilli, which increase the surface area over which absorption can take place.



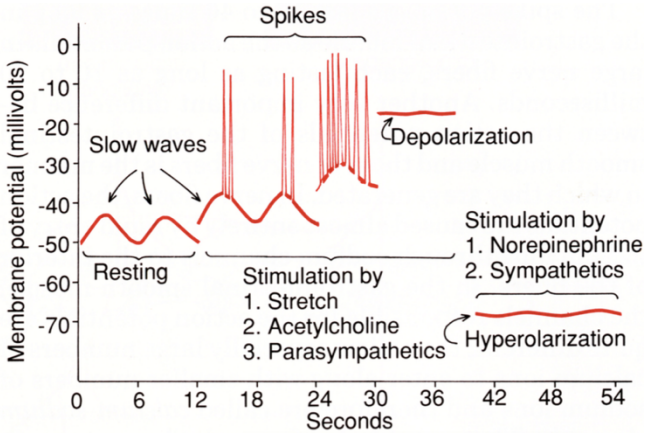
Gut Smooth Muscle

Smooth muscle cells are uninuclear and have the same excitable membranes and contractile mechanism as skeletal muscle, though they are not striated. These cells are electrically coupled through gap junctions and therefore can contract simultaneously. Smooth muscles of the gut are innervated by the autonomic nervous system. As shown in the following experiment, gut smooth muscles are depolarized by acetylcholine and hyperpolarized by norepinephrine.





The membrane potential of gut smooth muscle cells oscillates in a basic electrical rhythm. This rhythm is modified by stretch (stretching causes depolarization) and by the neurotransmitters of the autonomic nervous system. See the figure to the right.

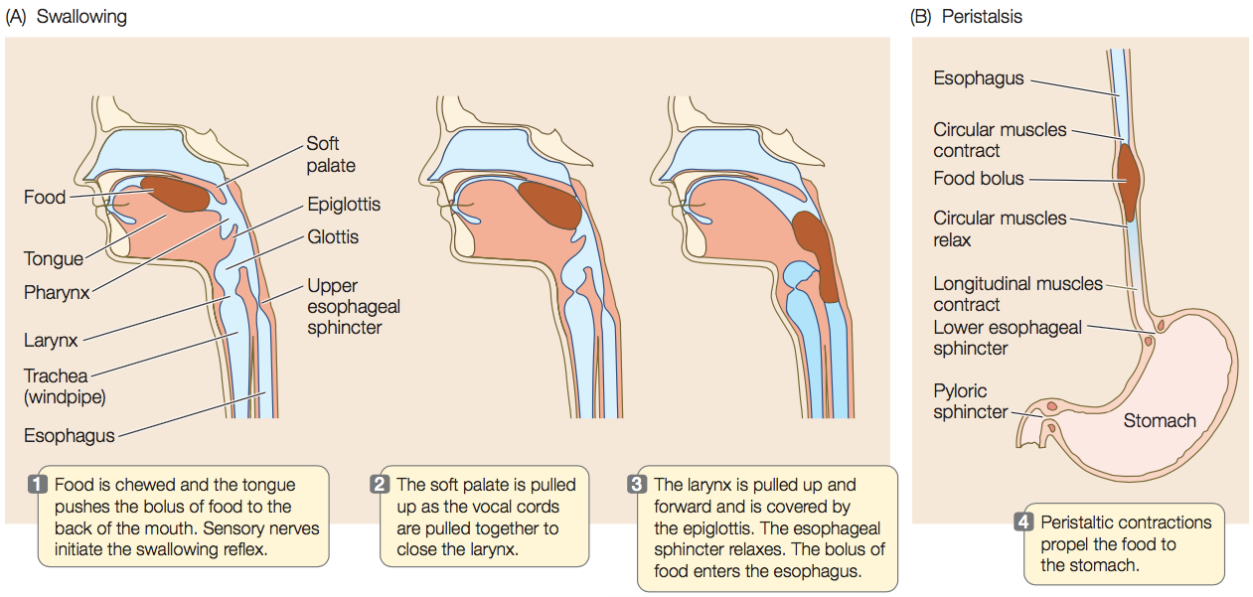


Food Movement Through the GI Tract

Swallowing

Transport of a food bolus from the mouth through the *esophagus* (food tube) into the stomach begins with swallowing, which is a central nervous system reflex. This reflex is initiated when sensory nerves are stimulated by the presence of the food bolus at the back of the mouth. In swallowing, the *soft palate* (the soft tissue making up the back of the roof of the mouth) is elevated to close the *nasopharynx*, the part of the throat that joins with the nasal cavity. Additionally, to prevent food from entering the *trachea* (windpipe), the vocal cords close the *larynx* (voice box), and a flap of tissue called the *epiglottis* covers the entrance to the larynx. When the food bolus enters the esophagus, waves of muscular contraction, called **peristalsis**, begins. Peristalsis is partially due to the sensitivity of smooth muscles to being stretched; when a bolus of food reaches a smooth muscle region of the esophagus and stretches it, the muscle responds by contracting, thus pushing the food toward the stomach.

Why doesn't the contraction of the esophageal smooth muscle push the food back toward the mouth? Because the myenteric plexus coordinates the muscles so that contraction is always preceded by an **anticipatory wave of relaxation**. When a region of the gut smooth muscle contracts, the circular smooth muscle just beyond it relaxes while the longitudinal smooth muscle contracts, pushing the food into that area. The resulting stretch causes that circular smooth muscle to contract while the next region relaxes. In this way peristalsis moves food down the gut from the mouth to the anus.



Stomach and Intestinal Motility

Anticipatory waved of relaxation open the *esophageal valve*, a sphincter (ring of circular smooth muscle) at the junction of the esophagus and stomach. In the upper regions of the stomach, peristalsis breaks down into mixing waves, which help mix the ingested food with stomach juices to form **chyme**. In the *pylorus*, the part of the stomach that connects the stomach to the *duodenum* (the first part of the small intestine), peristalsis resumes. Anticipatory waves of relaxation open up the *pyloric valve* (another sphincter), which allows entry of the chyme into the duodenum.

In the small intestine, peristalsis continues to move the food through. The small intestine consists of three parts: the *duodenum*, the *jejunum*, and the *ileum*. At the end of the small intestine (in the ileum), anticipatory relaxation opens up the *ileocecal valve*, a sphincter which allows entry into the large intestine (colon). In the large intestine, mixing motions, called haustrations, mix and compress the digested food while moving it along. Mass motions (bowel movements) move the contents of the colon into the lower S-shaped *sigmoid colon* and then into the *rectum*.

The expulsion of waste material from the rectum, or defecation, occurs via relaxation of the muscles of the anal sphincter. We have voluntary control over the external anal sphincter whereas the internal anal sphincter is under involuntary reflex control.

Control of Gut Motility

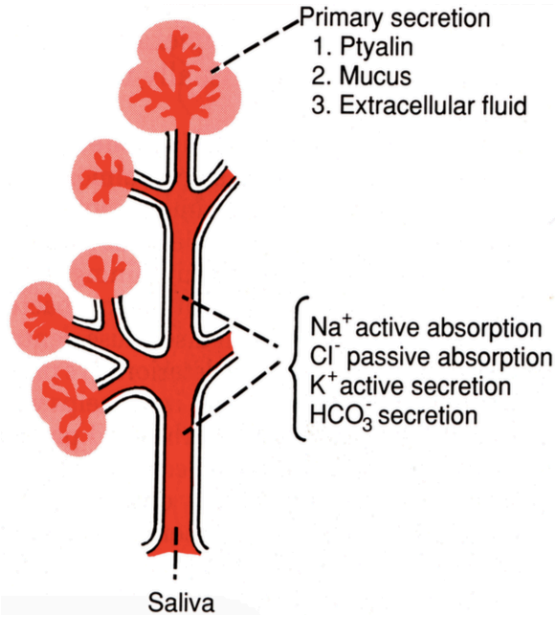
Gut motility is controlled by several things:

1. **Gastro-enteric reflex**: Mechanical distension in the stomach (from the presence of food) is sensed by the *enteric nervous system*, an autonomic system of nerves that helps govern the functioning of our GI tract, and leads to an increase in peristalsis in the small intestine.
2. **Cephalic reflexes**: Reflexes which arise from the sight, smell, thought, or taste of food. These reflexes lead to stomach contractions and promote gastric motility.
3. **Hormonal controls**:
    a. Positive hormonal controls: **Gastrin**, released by cells in the stomach, stimulates stomach contractions.
    b. Negative hormonal controls: **Cholecystokinin** (**CCK**), **secretin**, and **gastric inhibitory peptide** (**GIP**), all inhibit gastric contraction and therefore delay gastric emptying.

Secretions of the GI Tract

Salivation

Salivation is under neural control and is a reflex response to the smell, taste, touch, or thought of food. There are three major salivary glands: parotid, submandibular, and sublingual. The glands are structured as branching ducts ending in clusters of acinar cells. These acinar cells secrete mucus, extracellular fluid, and **amylase** (ptyalin), which breaks down starch. Additionally, bicarbonate buffer is present in saliva – K^+ ions and bicarbonate ions (HCO_3^-) are secreted into the salivary ducts in exchange for NaCl.

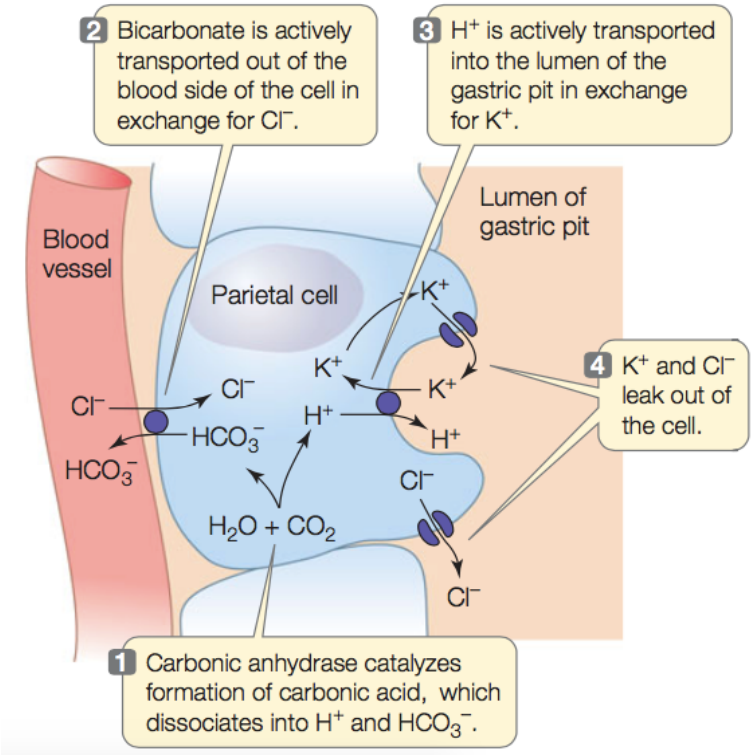


Stomach Secretions

Deep infoldings in the walls of the stomach called gastric pits are lined with three types of exocrine secretory cells:

1. **Chief cells**: produce **pepsinogen**, the precursor to **pepsin**, a proteolytic enzyme that begins the digestion of proteins.
2. **Parietal cells**: produce **hydrochloric acid** (**HCl**), which establishes the acidity of the gastric environment. This acidity kills most ingested microbes and also converts pepsinogen into its active form: pepsin.
3. **Mucus-producing cells**: produce **mucus**, which provides a protective coating for the walls of the stomach so that pepsin and HCl do not damage them.

How do parietal cells of the stomach produce HCl? The enzyme **carbonic anhydrase** in these cells catalyzes the hydration of CO_2 to H_2CO_3, which dissociates into H^+ and bicarbonate ion (HCO_3^-). An **antiporter** transport protein pumps out HCO_3^- in exchange for Cl^- on the blood side of the gastric pits, and an antiporter on the stomach lumen side pumps H^+ out into the stomach lumen in exchange for K^+. However, this K^+ can leak out again down its concentration gradient. Thus, the inward transport of K^+ acts like an endless conveyer belt moving H^+ out into the stomach lumen. As H^+ is moved out into the stomach lumen, Cl^- passively follows the H^+. See the diagram on the right for an illustration of this entire process.



Control of Gastric Secretions: The stomach secretions are under neural and hormonal control:

1. **Neural control:** Both the enteric nervous system and the vagus nerve (a cranial nerve that parasympathetically innervates various components of the digestive system) regulate gastric secretions. Cephalic reflexes (which, as mentioned previously, arise from the sight, smell, thought, or taste of food) increase neural activity that results in increased stomach secretions.
2. **Hormonal control:**

   Negative: Hormones released by the duodenum, including secretin and CCK and GIP, inhibit secretion of HCl (to prevent acid accumulation in the environment of the small intestine). Somatostatin (released by the pancreas in response to low pH in the stomach) also inhibits HCl secretion.

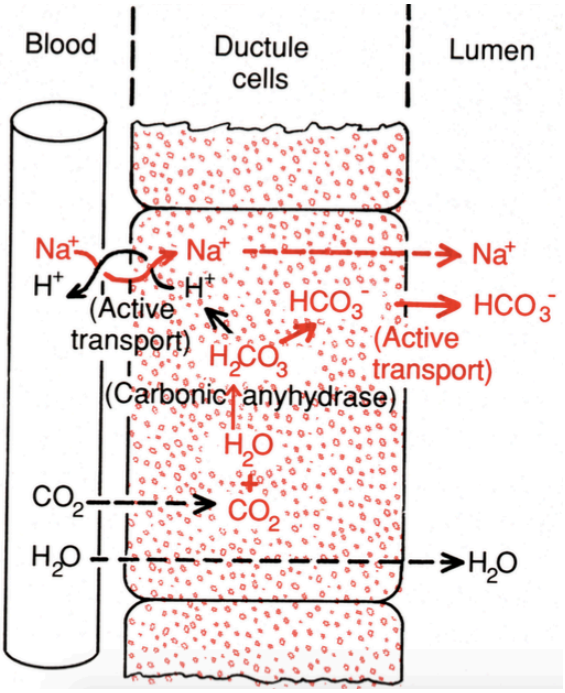
   Positive: Gastrin, released into the bloodstream by cells in the stomach, stimulates secretion of pepsinogen and HCl. Other chemical signals, including histamine and acetylcholine, also stimulate secretion of HCl. Histamine acts by inserting the H^+/K^+ antiporter into parietal cell membranes.

   In fact, gastrin and acetylcholine work by stimulating the release of histamine while somatostatin works by inhibiting the release of histamine.

The secretions of the stomach are highly corrosive to living tissues and can result in **ulcers**—places where the mucosal lining of the stomach is damaged. It was initially believed that HCl secretion was the primary cause of ulcers, and a stressful lifestyle can result in ulcers by increasing gastric HCl secretion. However, we now know that ulcers are caused by a bacterium, *Helicobacter pylori*, and that antibiotics can be used to cure ulcers.

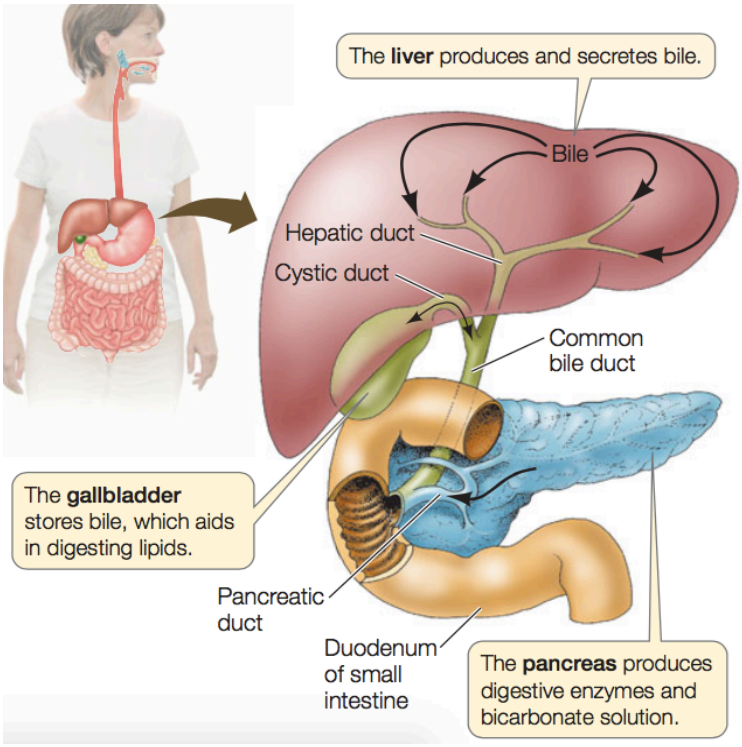
Pancreatic and Liver Secretions

The pancreas consists of three types of cells: endocrine cells, acinar cells, and duct cells. The endocrine cells, which we will discuss later, produce hormones that primarily function in regulating blood glucose levels. The acinar cells produce digestive enzymes in inactive (zymogen) form. One such zymogen is **trypsinogen**, which eventually is cleaved into the active enzyme, **trypsin**, by **enterokinase** (a duodenal enzyme) upon entering the duodenum. The duct cells of the pancreas secrete **bicarbonate** into the duodenum. The bicarbonate solution helps neutralize the acidic pH of chyme as chyme enters the small intestine.



Pancreatic secretions are under hormonal control; CCK stimulates the release of digestive zymogens while secretin stimulates the production of bicarbonate. The figure to the right shows the production of bicarbonate: The enzyme carbonic anhydrase in duct cells catalyzes the hydration of CO_2 to H_2CO_3, which dissociates into H^+ and bicarbonate ion (HCO_3^-). An antiporter transport protein pumps H^+ out into the blood in exchange for Na^+, and an antiporter on the lumen side pumps out HCO_3^-, and Na^+ passively follows.

The liver produces **bile**, which is stored in the gall bladder, and released through the **common bile duct**. The common bile duct eventually joins with the pancreatic duct, and leads into the duodenum via the **sphincter of Oddi**. Bile is synthesized from cholesterol and functions in emulsifying fats in the small intestine; that is, it breaks lipid aggregates into smaller particles, called micelles, which increases the surface area for which lipases (fat-digesting enzymes), secreted by pancreatic acinar cells, can act on the fats. CCK stimulates bile release.

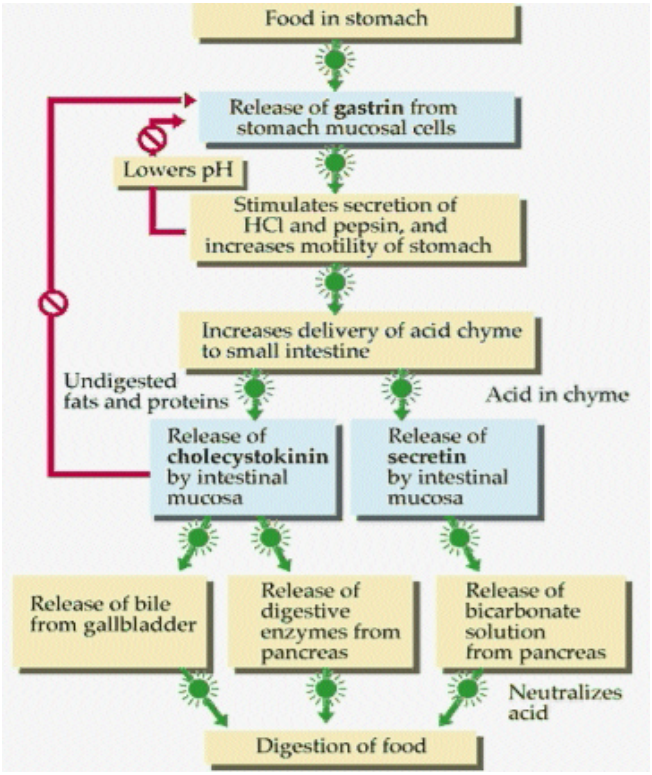


Small Intestine Secretions

The small intestine is structured as a series of hills and valleys. The hills are **villi**, finger-like projections that function in absorption of nutrients. The valleys, known as **crypts of Lieberkühn**, function in secretion of intestinal juice. This intestinal juice primarily resembles extracellular fluid but also contains enteropeptidase, which converts trypsinogen into trypsin. The intestinal epithelium, which covers the villi and crypts, contains numerous membrane projections, called **microvilli**, that form a **brush-border**. Enzymes produced by intestinal epithelial cells, including dipeptidases, disaccharidases, and lipases, are embedded within this brush-border and are known as **brush-border enzymes.** Thus the final steps of digestion are carried out on the brush border to avoid osmotic shock.

Review of Hormones that Regulate Digestive Secretions

Before we move on to talk about absorption, let's summarize how three main hormones: Gastrin, CCK, and secretin, regulate digestive secretions:



- Gastrin, released in response to the presence of food in the stomach, stimulates the secretion of HCl and pepsin in the stomach. Gastrin is inhibited as the pH of the stomach gets lower.
- CCK, released in response to chyme entering the duodenum, inhibits the secretion of HCl by the stomach, stimulates the release of bile from the gallbladder, and stimulates the release of digestive enzymes from the pancreas.
- Secretin, released in response to chyme entering the duodenum, stimulates the release of bicarbonate solution from the pancreas.

The flow chart to the left summarizes this hormonal control of digestive secretions

Absorption

Digestion is the breakdown of complex proteins, carbohydrates, and fats by hydrolysis and is catalyzed by digestive enzymes working in the lumen of the GI tract and on the brush border. Once the nutrients are reduced to their smaller components, they must be absorbed into the body from the GI tract. This process is **Absorption.**

Proteins

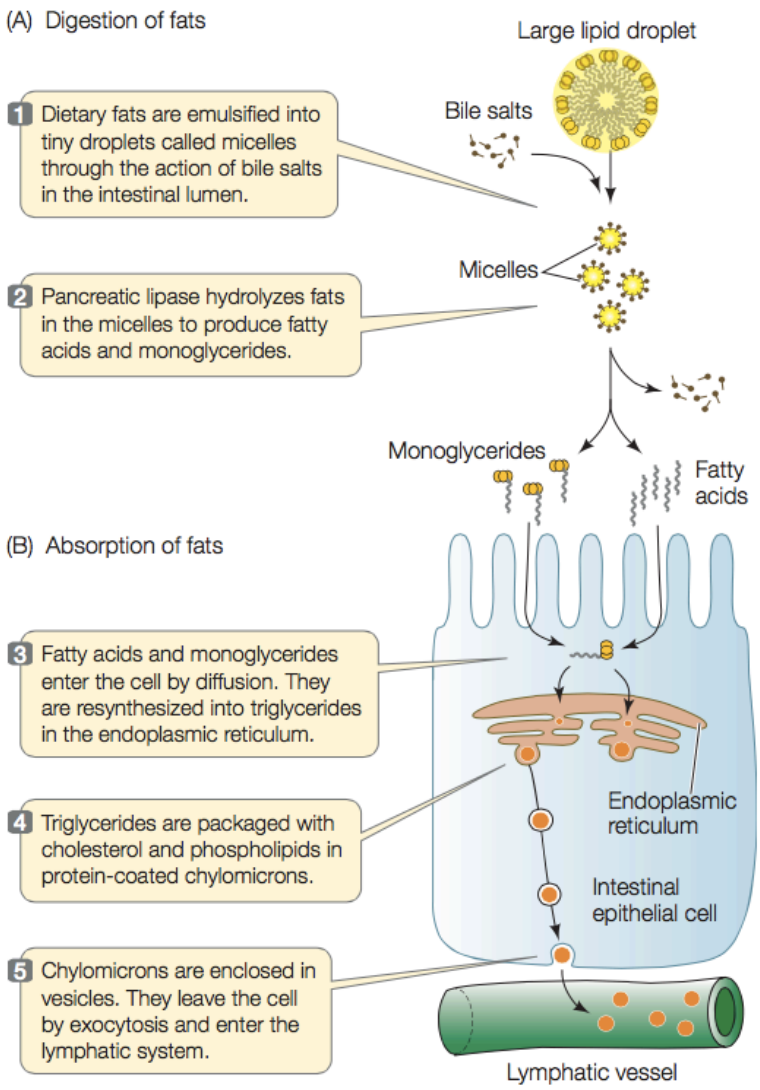
After proteins are digested into tri- and di-peptides and amino acids, these breakdown products are transported across the intestinal epithelial membrane by transporters (symporters) that mainly work by sodium co-transport (in other words, they "hitchhike" with sodium absorption).

Carbohydrates

Complex carbohydrates are digested into monosaccharides. The monosaccharides glucose and galactose are absorbed by sodium cotransport (requiring active transport of sodium to create a concentration gradient). The monosaccharide fructose is absorbed by facilitated diffusion (passively). This mechanism works for fructose because once fructose enters the cell it is converted to glucose. Thus the concentration of fructose in the cell is always low and the concentration gradient is maintained.

Fats

As mentioned previously, bile breaks lipid aggregates into smaller particles, called micelles, which increases the surface area for which pancreatic lipases can act on the fats. The lipases digest the fats into free fatty acids and monoglycerides which, being lipid-soluble, can simply pass through the plasma membranes of the microvilli. In the intestinal epithelial cells, these molecules are reassembled into triglycerides, combined with cholesterol and phospholipids, and coated with protein to form water-soluble **chylomicrons**. Chlylomicrons do not enter the blood directly; rather, they pass into lymph vessels called lacteals that are inside each villus. They then flow through the lymphatic system, entering the bloodstream through the thoracic ducts at the base of the neck. See the diagram on the next page for an illustration of the digestion and absorption of fats.



Management of Fuel Supply

Cells need a variable, yet constant, supply of energy, but food intake is episodic; therefore, there must be some means to manage fuel supplies over time. Most cells can use glucose, fats, ketones, and amino acids as fuel, but nervous tissue (e.g. the brain) requires glucose. Glucose enters cells via diffusion, so blood glucose levels must be monitored and maintained.

Absorptive period

During the absorptive period (when food is in the gut), the management strategy is to burn glucose for energy and direct surplus nutrients into storage.

Postabsorptive period

During the postabsorptive period (4-12 hours after a meal), the management strategy is to maintain a constant blood glucose level for the brain and to shift the metabolism of other cells to use other fuel reserves such as fats.

Storing glucose

An enzyme (hexokinase or glucokinase) phosphorylates glucose after glucose enters the cell. When glucose is phosphorylated, it is trapped within the cell and cannot leave through the glucose transporter. This is irreversible in most cells, but in a few cells such as liver cells, a glucose phosphatase can dephosphorylate glucose so it can diffuse out. Since glucose can enter and exit liver cells, the liver is ideal for storing glucose when there's excess glucose and for releasing glucose back into the blood when there's not enough glucose going around.

Glucose is stored as **glycogen** (a polymer of glucose) in the liver via a process that converts glucose into glycogen (**glycogenesis**). When the liver is replete with glycogen, additional glucose is converted through glycolysis to acetyl-CoA which is used to synthesize triglycerides (fats). When the liver needs to release glucose into the blood, **glycogenolysis** (the breakdown of glycogen into glucose) occurs. Also, as another means of making glucose, the liver is capable of **gluconeogenesis**: forming glucose from substrates such as amino acids, glycerol, pyruvate, or lactate. For example, the **Cori Cycle** is a pathway by which the liver converts pyruvate and lactate released by muscle into glucose.

Fat metabolism

Chylomicrons deliver dietary triglycerides, phospholipids, and cholesterol to the tissues of the body via the circulatory system. In tissues, lipoprotein lipases break down chylomicrons so fats can be absorbed. The liver stores fats and releases free fatty acids and lipoproteins into the bloodstream (so that other tissues, such as adipose tissue, may use or store them). **Lipoproteins** are assemblies of triglycerides, phospholipids, and cholesterol, with a protein coat. There are several classes of lipoproteins: VLDL (very low density lipoprotein), LDL (low density lipoprotein), and HDL (high density lipoprotein). HDLs collect fat molecules from tissues and take them back to the liver. On the other hand, LDLs deliver fat molecules around the body. LDLs are sometimes considered "bad cholesterol" because they can deliver fats to the walls of arteries, blocking them.

Hormonal control of fuel supply

Insulin is the major control hormone; insulin promotes glucose uptake and metabolism (resulting in a decrease in blood glucose level) during the absorptive phase. In most cells (excluding nervous tissue), the major glucose transporter is sequestered intracellularly and is only inserted into the cell membrane when insulin is present. Additionally, insulin activates the enzyme responsible for the first step of glucose metabolism: the phosphorylation of glucose. Further, insulin activates the enzymes of glycogenesis, and also promotes the synthesis and storage of triglycerides in adipose tissue (insulin inhibits hormone sensitive lipase, which is responsible for mobilizing stored fats in adipose tissue).

A lack of insulin decreases glucose uptake (resulting in an increase in blood glucose level) and shifts cells to metabolize other fuel reserves during the postabsorptive phase. The hormones, **glucagon** and **epinephrine**, also play a role during the postabsorptive phase; both activate the enzyme, glycogen phosphorylase, which catalyzes the rate-limiting step in glycogenolysis.