Chemical composition of the body

Review of Components of Chemical Composition of the Body

In order to fully understand the mechanisms of human physiology it is important to have an understanding of the chemical composition of the body. This will come in handy when considering the various interactions between cells and structures. We will gloss over the basic chemistry; however, if there are specific questions with regards to chemistry and its effect on biological function feel free to ask on the forum.

Atoms

An **atom** is the smallest unit of matter with unique chemical properties. Atoms are the chemical units of cell structure. They consist of a central nucleus with **protons** and **neutrons** and orbit(s) of **electrons**. A proton carries a +1 positive charge, while a neutron has no charge. Thus the nucleus has a net positive charge. Electrons carry a –1 negative charge and are consequently attracted to the positive nucleus. In general, the number of protons usually equals the number of electrons. Recall that atoms have unique (individual) chemical properties, and thus each type of atom is called a chemical element, or just element.
Atomic number refers to the number of protons in an atom, while atomic weight refers to the number of protons and neutrons in an atom, measured in daltons. It is possible for elements to exist in multiple forms, called **isotopes**; the only difference is the number of neutrons in the nucleus, while protons and electrons always stay the same as the original element.
The human body depends upon four major elements for form and function: Hydrogen (H), Oxygen (O), Carbon (C), and Nitrogen (N).

Bonding

Atoms form molecules when two or more are bonded together.

A_1—bond—A_2 = Molecule: A_1A_2

Covalent bonds are formed when electrons in the outer orbit are shared between two atoms. With this type of bond formed, molecules can rotate around their shared electrons and change shapes. Every atom forms a characteristic number of covalent bonds. The number of bonds depends on the number of electrons in the outer orbit.
For example:

1. Hydrogen (H) has atomic number 1, with 1 electron in its outer orbit. Hydrogen forms 1 bond (single bond) meaning: 1 electron is shared.
2. Oxygen (O) has atomic number 8, with 6 electrons in its outer orbit. Thus Oxygen forms 2 bonds (double bond) meaning: 2 electrons are shared.
3. Nitrogen (N) has atomic number 7, with 5 electrons in its outer orbit. Nitrogen forms 3 bonds (triple bond) meaning: 3 electrons are shared.
4. Carbon (C) has atomic number 6, with 4 electrons in its outer orbit. Carbon forms 4 bonds, meaning: 4 electrons are shared.

In general: # of electrons in outer orbit + Shared electrons = 8 (full octet)
Make note that any electron shared is in attempt to reach a stable state. In most atoms this is an octet, or eight electrons in the outer orbit. Note Hydrogen only has space for 2 electrons in its outer orbit, one present and one shared.
Ions are atoms with a net electric charge due to the gain or loss of one or more electrons. **Ionic bonds** are bonds formed between two oppositely charged ions. **Cations** are ions with a net

positive charge, while **anions** are those with a net negative charge.
Ionic forms of elements are important to the body, as they are able to conduct electricity when dissolved in water. Theses ions are called electrolytes. Single atoms, or atoms that are covalently linked in molecules can undergo ionization. See examples below.

$NaCl \leftrightarrow Na^+ + Cl^-$
$R\text{-}COOH \leftrightarrow R\text{-}COO^- + H^+$
$R\text{-}NH_2 + H^+ \leftrightarrow R\text{-}NH_3$

Where R is any molecule attached to the shown functional group.
An atom with a single electron in its outermost orbital is known as a **free radical**. Free radicals are highly reactive and short-lived. In organism terms, they are responsible for cellular breakdown. Sun damage is a classic example of free radicals acting on skin cells.

Polar bonds are bonds in which the electrons are shared unequally. The unequal sharing gives the atom with the higher share a more negative charge and the one with the lower share of electrons has a slightly more positive charge.

Hydrogen bonds are weak bonds between the hydrogen atom (more positive, lesser share of the electron) in one polar bond and an oxygen or nitrogen atom (more negative, greater share of the electron) in another polar bond.
H--O--H - - - O---H

H
Molecule 1 Molecule 2
Hydrogen bond between hydrogen of one water molecule and the oxygen of another. These bonds are rather weak.

Water

Water is the most common molecule in the human body (~98-99%). Both hydrogen atoms are attached to the single oxygen atom by polar bonds. The oxygen has a slightly negative charge and the hydrogen atoms each have a slightly positive charge. This allows for hydrogen bonds to form between the positive hydrogen atoms and the negative oxygen atoms of neighboring water molecules. The state of water is determined by the weak hydrogen bonds. The bonds remain intact in low temperatures and the water freezes. When the temperature rises the bonds weaken and water becomes a liquid. If the temperature is high enough the bonds will completely break and water becomes a gas.

Solutions

Substances dissolved in a liquid are called **solutes**, while the liquid itself is called the **solvent**. The term **solution** refers to the final product when solutes dissolve in a solvent.
Since water is the most common molecule in the human body, it should be no surprise that water is the most abundant solvent. In the body, a majority of the chemical reactions involve molecules dissolved in water. **Hydrophilic** (water-loving) molecules are molecules that easily dissolve in water. Generally, hydrophilic molecules have polar groups (e.g., OH^-) and/or ionized (e.g., COO^- or NH_2^+) functional groups attached. In contrast, molecules that are not attracted to water are called **hydrophobic** molecules (water-fearing). They are molecules with electrically neutral covalent bonds (e.g., molecules with carbon chains). When non-polar molecules are mixed with water two phases (layers) are formed. A good example is mixing oil and water and then allowing the container to set for a while. There will be two distinct layers visible.
Molecules with a polar/ionized region and one end and a non-polar region at the other end are called **amphipathic**, as the molecule has both hydrophilic and hydrophobic characteristics. If amphipathic molecules are mixed with water, the molecules form clusters with the polar

(hydrophilic) regions at the surface, where they will come into contact with water, and the non-polar (hydrophobic) regions nestled in the center of the cluster away from contact with water. The arrangement will increase the overall solubility in water.

Concentration

With regards to solutions, concentration is the amount of solute present in a unit volume of solution. Concentration values do not reflect the number of molecules present.

Acidity

An **acid** is a molecule that releases protons (hydrogen ions) in solution. Conversely, a **base** is a molecule that can accept a proton. Acids and bases can be further divided into strengths. A **strong acid** is an acid that releases all of its hydrogen ions in solution. Hydrochloric acid (HCl) is an excellent example of a strong acid. **Weak acids** are those which do not completely ionize, or lose their hydrogen ions, in solution. The concentration of free hydrogen ions (protons) is referred to as the acidity of the solution. The unit is **pH** = -log $[H^+]$ where $[H^+]$ is the concentration of free hydrogen ions. pH is a very important concept in biological systems, and certainly holds great weight in the processes of human physiology. Pure water is called a neutral solution, and has a pH value of 7. Alkaline solutions are also known as basic solutions and thus have a lower concentration of hydrogen ions $[H^+]$. The pH of alkaline solutions is greater than 7. Acidic solutions have a high concentration of hydrogen ions $[H^+]$. The pH of acidic solutions is less than 7. Each number on the pH scale indicates a 10-fold change in hydrogen concentration $[H^+]$. Litmus papers are test strips that determine pH based upon color changes in the paper, after the strip is dipped into a solution.

Organic molecules

Organic molecules contain carbon backbones. Every carbon atom will form 4 covalent bonds with other atoms, specifically other carbon atoms as well as hydrogen, nitrogen, oxygen and sulfur atoms. By linking together of many smaller molecules, carbon is able to form very large polymers (macromolecules) many of which are important to human physiology.

Carbohydrates

These important carbon-based molecules are vital to life in that they provide cells with energy. Carbohydrates are composed of carbon, hydrogen and oxygen in a set proportion. Where n is any whole number, the formula is: $C_n(H_2O)_n$.

H— C —OH

Carbohydrates are easily soluble in water due to the polar hydroxyl (OH^-) groups. Most are sweet tasting and are also known by the common name: sugar.
Monosaccharides are the simplest sugars. Glucose ($C_6H_{12}O_6$) is the most abundant, and is called blood sugar because it is the major monosaccharide in blood. The common monosaccharides in the body contain 5 or 6 carbon atoms and are called pentoses and hexoses, respectively.
Disaccharides are carbohydrates composed of two monosaccharides linked together. Sucrose is composed of glucose and fructose. Maltose is composed of glucose and glucose chains. Lactose, milk sugar, is composed of glucose and galactose.
An oxygen atom links together monosaccharides by the removal of a hydrogen atom from one end and a hydroxyl group from the other. The hydroxyl group and the hydrogen combine to form a water molecule. Therefore, hydrolysis of a disaccharide will break the link formed and

disconnect the two monosaccharides.
Polysaccharides are formed when many monosaccharides link together into long chains. Glycogen in animal cells and starch in plant cells are both composed of thousands of glucose molecules linked together.

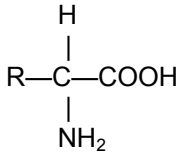
Lipids

Fats to the layman. Lipids are predominantly composed of hydrogen and carbon atoms linked together by neutral covalent bonds. Lipids are non-polar and are consequently are not very soluble in water. There are **four main classes of lipids** to be aware of in learning about human physiology.

1. **Fatty acids** are chains of carbon and hydrogen atoms with a carboxyl group at one end. Generally, they are made of an even number of carbon atoms because they are synthesized by linking together fragments composed of two carbon atoms. If all the carbon atoms are linked by single covalent bonds the chain is called a saturated fatty acid. If the chain is composed of double bonds, the chain is called an unsaturated fatty acid. Furthermore, if only one double bond is present in the chain, then it is a monounsaturated fatty acid, while if there is more than one double bond present it is called a polyunsaturated fatty acid.
2. **Triacylglycerols**, or triglycerides, account for the majority of lipids in the body. They are formed by linking each of the 3 hydroxyl groups of glycerol with the carboxyl groups of three fatty acids, hence the “tri” in the name. When a triacylglycerol is hydrolyzed, the fatty acids are released from the glycerol and the products can be metabolized in order to provide energy for cell functions.
3. Triacylglycerols have a near relative called **phospholipids**. The only difference is that one of the hydroxyl groups of the glycerol is linked to a phosphate. A phospholipid has a non-polar region in the fatty acid, thus the molecule is amphipathic. Phospholipids are very important in building membranes within the body.
4. Finally, **steroids** are composed of 4 interconnected carbon atom rings. They may have a few polar hydroxyl groups attached to the rings. Steroids are not soluble in water due to their polarity. Sex hormones, such as testosterone and estrogen, are examples of steroids, as well as cholesterol and cortisol.

Proteins

In addition to the common four elements of carbon, hydrogen, oxygen and nitrogen, proteins also contain sulfur and other elements in small amounts. Proteins are very large molecules of linked subunits called amino acids. They form very long chains.
Amino acids are composed of an amino (NH_2) and a carboxyl (COOH) group that are linked to a terminal carbon atom. Where R is another functional group or carbon chain, known as the amino acid side chain.



The proteins in living organisms are composed of the same set of 20 amino acids. Each amino acid is distinguished by its side chain (R).
As amino acids are joined together with peptide bonds they are forming a polypeptide, or a sequence of amino acids linked by peptide bonds. A peptide bond occurs when the carboxyl groups of one amino acid forms a polar covalent bond with the amino group of another amino acid. In the formation of this bond one water molecule is releases. The newly formed molecule will then have a free amino group at one end and a free carboxyl group at the other, which allows

for linking additional amino acids.
Glycoproteins are made when monosaccharides are covalently bonded to the side chains of specific amino acids in the protein (polypeptide). The specific amino acids that are singled out in the formation of a glycoprotein are serine and threonine.

Protein Structure

Two things determine the primary structure of a protein.

1. The number of amino acids in the chain
2. Where each specific amino acid occurs in the chain.

It is important to remember that a polypeptide chain is flexible as each amino acid can rotate around its peptide bonds. Therefore, polypeptide chains can be bent into a number of shapes or conformations. The three dimensional conformation of a protein plays an important role in its functioning in the body.

Conformation of proteins is determined by several factors:

1. Hydrogen bonding between neighboring parts of the chain and any water molecules
2. Any ionic bonds between polar and ionized parts along the chain
3. Weak bonds called van der Waals forces between neighboring non-polar regions of the chain
4. Covalent bonds linking side chains of two amino acids

An **alpha helix conformation** is formed when hydrogen bonds form between the hydrogen linked to the nitrogen in one peptide bond and the double bonded oxygen in another. The hydrogen bonds contort the chain into a coil. When hydrogen bonds form between peptide bonds in regions of the polypeptide chain that runs parallel, a straight and extended region forms called a **beta sheet conformation**. The alpha helix and the beta sheet conformations are very common. When ionic bonds form between side chains, and thus interrupt with any repetitive hydrogen bonding, irregular regions called **loop conformations** may occur.
It is worth knowing that **multimeric proteins** are proteins consisting of more than one polypeptide chain. The chains can be similar or different.

Nucleic Acids

Nucleic acids store, transmit and express genetic information. Nucleic acids are composed of subunits called **nucleotides**. Nucleotides contain a phosphate group, a sugar and a ring of carbon and nitrogen atoms. The ring is also known as the base because it can accept hydrogen ions (protons). Nucleotides are linked together by bonds between the phosphate group of one nucleotide and the sugar of the next one. In this fashion, nucleotides form long chains. **DNA** (deoxyribonucleic acid) stores genetic information in the sequence of the nucleotide subunits. **RNA** (ribonucleic acid) uses the information stored in DNA to write the instructions for linking together specific sequences of amino acids in order to form polypeptides per original DNA instructions.
DNA nucleotides contain a five carbon sugar called deoxyribose. DNA has four different nucleotides that correspond to four different bases. The purine bases adenine (A) and guanine (G) are composed of two fused rings of nitrogen and hydrogen. The pyrimidine bases cytosine (C) and thymine (T) which are made of only one ring of nitrogen and hydrogen. Guanine and cytosine pair, while thymine and adenine pair. One purine paired with one pyrimidine.
A DNA molecule looks like a double helix. It consists of two chains of nucleotides coiled around each other held by hydrogen bonds between a purine base on one chain and a pyrimidine base

on the other.
RNA is slightly different than DNA. Specifically, RNA is a single chain of nucleotides, contains the sugar ribose, and the pyrimidine base uracil is present instead of thymine. Uracil can therefore pair with the purine adenine.

Cell structure

Cell Structure

The interior of the cell is divided into the nucleus and the cytoplasm. The nucleus is a spherical or oval shaped structure at the center of the cell. The cytoplasm is the region outside the nucleus that contains cell organelles and cytosol, or cytoplasmic solution. Intracellular fluid is collectively the cytosol and the fluid inside the organelles and nucleus.

Membranes

Membranes are the gateways to the cell. The **plasma membrane**, is the selective barrier surrounding the cell. It provides a barrier to the movement of molecules between the intra and extracellular fluids. Recall that extracellular means outside the cell. The plasma membrane also serves to anchor adjacent cells together and to the extracellular matrix. Various signals and inputs can alter the sensitivity and permeability of membranes.

The Fluid Mosaic Model: membrane structure

Membranes are made of a double layer of lipids, mainly phospholipids, containing embedded proteins. The embedded proteins are important as facilitators in moving molecule through the membrane. The membrane itself is organized into a bimolecular layer, meaning that the non-polar region is organized in the middle (away from water as it is hydrophobic) and the polar regions are oriented toward the outside: the extracellular fluid and the cytosol. Another way to think of it is two rows of pins with their heads to the outside and the needle part to the inside. Heads, needles, needles, heads. Like a sandwich. As the phospholipid molecules are not chemically bound to each other and thus each molecule is free to move independently, the overall bi-layer structure has a flexible fluidity. Cholesterol molecules are also embedded in the plasma membrane and serve to deliver substances to cell organelles by forming vesicles.
The proteins embedded in membrane are categorized into two classes.

1. **Peripheral membrane proteins** are proteins on the membrane surface, mainly the cystolic side where they interact with cytoskeletal elements in order to influence cell shape and motility. These proteins are not amphipathic and are bound to polar regions of the integral proteins.
2. **Integral membrane proteins** span the entire width of the membrane, thus crossing through both the polar and non-polar regions of the structure. These proteins cannot be removed from the membrane without disrupting the lipid bi-layer.

It is important to realize that membrane functions are dependent on the chemical composition and any asymmetries in composition between the two surfaces of the membrane and the specific proteins that are attached to or associated with the membrane. The plasma membrane also has an extracellular surface layer of monosaccharides that are linked to the membrane lipids and proteins. This layer is called the glycocalyx and is important in the intercellular recognition

process.

Membrane Junctions

Integrins are transmembrane proteins that bind to specific proteins in the extracellular matrix and to membrane proteins on adjacent cells. Integrins help to organize cells into tissues. They are also responsible for transmitting signals from the extracellular matrix to the cell interior.
If two cells are adjacent, but separated, they may be junctured by desmosomes. Desmosomes are dense accumulations of protein at the cytoplasmic surface of the plasma membranes of both separate cells. They are infiltrated with protein fibers that extended into either cell. The purpose and function of desmosomes is to hold adjacent cells firmly in place in areas that are subject to stretching, such as skin.
Another type of membrane junction is the tight junction. These junctions are formed by the actual physical joining of the extracellular surfaces of two adjacent plasma membranes. Tight junctions are important in areas where more control over tissue processes is needed, such as the epithelial cells in the intestine that are involved in absorption.
Finally, gap junctions are actual protein channels that link the cytosols of adjacent cells. The drawback to this 'direct link' is that it only permits smaller molecules to pass through.

Cell Organelles

Cell organelles are the little workhouses within the cell. All the functions of life take place in each individual cell. Organelles can be released by breaking the plasma membrane, through homogenization and ultracentrifuging the mixture. The organelles are of different size and density and will settle out at specific rates.
Overview of organelles

1. The **nucleus** is in the center of most cells. Some cells contain multiple nuclei, such as skeletal muscle, while some do not have any, such as red blood cells. The nucleus is the largest membrane-bound organelle. Specifically, it is responsible for storing and transmitting genetic information. The nucleus is surrounded by a selective nuclear envelope. The nuclear envelope is composed of two membranes joined at regular intervals to form circular openings called nuclear pores. The pores allow RNA molecules and proteins modulating DNA expression to move through the pores and into the cytosol. The selection process is controlled by an energy-dependent process that alters the diameter of the pores in response to signals. Inside the nucleus, DNA and proteins associate to form a network of threads called chromatin. The chromatin becomes vital at the time of cell division as it becomes tightly condensed thus forming the rodlike chromosomes with the enmeshed DNA. Inside the nucleus is a filamentous region called the nucleolus. This serves as a site where the RNA and protein components of ribosomes are assembled. The nucleolus is not membrane bound, but rather just a region.
2. **Ribosomes** are the sites where protein molecules are synthesized from amino acids. They are composed of proteins and RNA. Some ribosomes are found bound to granular endoplasmic reticulum, while others are free in the cytoplasm. The proteins synthesized on ribosomes bound to granular endoplasmic reticulum are transferred from the lumen (open space inside endoplasmic reticulum) to the golgi apparatus for secretion outside the cell or distribution to other organelles. The proteins that are synthesized of free ribosomes are released into the cytosol.
3. The **endoplasmic reticulum** (ER) is collectively a network of membranes enclosing a singular continuous space. As mentioned earlier, granular endoplasmic reticulum is associated with ribosomes (giving the exterior surface a rough, or granular appearance). Sometimes granular endoplasmic reticulum is referred to as rough ER. The granular ER is involved in packaging proteins for the golgi apparatus. The agranular, or smooth, ER

lacks ribosomes and is the site of lipid synthesis. In addition, the agranular ER stores and releases calcium ions Ca^{2+} .

4. The **golgi apparatus** is a membranous sac that serves to modify and sort proteins into secretory/transport vesicles. The vesicles are then delivered to other cell organelles and the plasma membrane. Most cells have at least one golgi apparatus, although some may have multiple. The apparatus is usually located near the nucleus.
5. **Endosomes** are membrane-bound tubular and vesicular structures located between the plasma membrane and the golgi apparatus. They serve to sort and direct vesicular traffic by pinching off vesicles or fusing with them.
6. **Mitochondria** are some of the most important structures in the human body. They are they site of various chemical processes involved in the synthesis of energy packets called ATP (adenosine triphosphate). Each mitochondrion is surrounded by two membranes. The outer membrane is smooth, while the inner one is folded into tubule structures called cristae. Mitochondria are unique in that they contain small amounts of DNA containing the genes for the synthesis of some mitochondrial proteins. The DNA is inherited solely from the mother. Cells with greater activity have more mitochondria, while those that are less active have less need for energy producing mitochondria.
7. **Lysosomes** are bound by a single membrane and contain highly acidic fluid. The fluid acts as digesting enzymes for breaking down bacteria and cell debris. They play an important from in the cells of the immune system.
8. **Peroxisomes** are also bound by a single membrane. They consume oxygen and work to drive reactions that remove hydrogen from various molecules in the form of hydrogen peroxide. They are important in maintaining the chemical balances within the cell.
9. The **cytoskeleton** is a filamentous network of proteins that are associated with the processes that maintain and change cell shape and produce cell movements. The cytoskeleton also forms tracks along which cell organelles move propelled by contractile proteins attached to their various surfaces. Like a little highway infrastructure inside the cell. **Three types of filaments make up the cytoskeleton**.
    1. **Microfilaments** are the thinnest and most abundant of the cytoskeleton proteins. They are composed of actin, a contractile protein, and can be assembled and disassembled quickly according to the needs of the cell or organelle structure.
    2. **Intermediate filaments** are slightly larger in diameter and are found most extensively in regions of cells that are going to be subjected to stress. Desmosomes in the skin will contain filaments. Once these filaments are assembled they are not capable of rapid disassembly.
    3. **Microtubules** are hollow tubes composed of a protein called tubulin. They are the thickest and most rigid of the filaments. Microtubules are present in the axons and long dendrite projections of nerve cells. They are capable of rapid assembly and disassembly according to need. Microtubules are structured around a cell region called the centrosome, which surrounds two centrioles composed of 9 sets of fused microtubules. These are important in cell division when the centrosome generates the microtubluar spindle fibers necessary for chromosome separation.

Finally, **cilia** are hair-like motile extensions on the surface of some epithelial cells. They have a central core of 9 sets of fused microtubules. In association with a contractile protein, these microtubules produce movement in cilia. Ciliar movements propel the luminal contents of hollow organs lined with ciliated epithelium.

Movement of molecules across cell membranes

Diffusion

Diffusion is essentially the movement of molecules from a region of higher concentration to a region of lower concentration as a result of thermal motion. Diffusion is an important process in human physiology. Specifically, diffusion is the mechanism of movement of oxygen, nutrients and other molecules across the capillary walls and the movement of other molecules across membranes. The amount of material crossing a surface per unit of time is called flux and depends upon the difference in concentrations between two compartments where movement is potentially going to occur. When diffusion between two compartments is equal, meaning no net movement, the system has reached diffusion equilibrium. Net flux is zero and there are no further changes in concentration. Difference in concentration, temperature, and surface area of diffusion are all positively correlated with direction and magnitude of net flux. While the mass of molecules in solution are negatively correlated with direction and magnitude of net flux. The time that it takes for diffusion to occur increases in proportion to the square of the distance over which molecules diffuse. Diffusion, therefore, is only useful for moving molecules over small distances.

Diffusion through Membranes

The magnitude of net flux can be measured as:

$F= k_pA(C_0 – C_i)$ where,

k_p = permeability constant for a particular molecule at a particular temperature
A = surface area of membrane
C_0 = extracellular concentration of the substance
C_i = intracellular concentration of the substance

Remember that membranes slow down diffusion and molecules will move slowly than through a water layer of equal thickness. i.e. for structural reasons a water layer is easier than a membrane to diffuse through.

Role of Electric Forces on Ion Movement

Membrane potential is the separation of electric charges across a membrane. The separation of charges influences the movement of ions across the membrane. This can act independently of or in conjunction with, or in opposition to, the force generated by concentration differences. Electrochemical gradient refers to these two forces collectively: the force due to charges and the force due to concentration differences.

Diffusion through the Lipid Bi-layer

Non-polar molecules can dissolve in the non-polar fatty acid chains of the membrane phospholipids and therefore non-polar molecules have larger permeability constants than polar molecules.

Diffusion of Ions through Protein Channels

Protein channels formed by integral proteins allow ions to diffuse across the membrane. Different cells have different permeabilities to these ions. The diameter of the channel and the polar groups on the protein subunits forming channel walls determine the permeability of the channels by various ions and molecules.

Regulation of Diffusion through Ion Channels

Channel gating is the opening and closing of ion channels which changes the permeability of a membrane. It is controlled by three modulators:

1. Modulation of allosteric or covalent channel-proteins in ligand-sensitive channels
2. Modulation of channel proteins due to changes due to changes in membrane potential in voltage-gated channels.
3. Modulation of channel proteins due to stretching in mechanosensitive channels.

Several factors and influence a single channel and any one ion can pass through several different channels.

Mediated Transport Systems

There are integral membrane proteins called transporters that mediate movement of molecules that are too polar or too large to move across a membrane by diffusion.
In order to accomplish this, a solute (molecule to be transported) binds to a specific site on a transporter on one surface of the membrane. The transporter then changes shape in order to expose the bound solute to the opposite side of the membrane. The solute then dissociates from the transporter and finds itself on the other side of where it started. Depending on the membrane, and the needs of the cellular environment, there may be many types of transporters present with specific binding sites for particular types of substances. Solute flux magnitude through a mediated transport system is positively correlated with the number of transporters, the rate of conformational change in the transporter protein, and the overall saturation of transporter binding sites which is dependent on the solute concentration and affinity of the transporter. These are important factors to consider in getting large materials through a membrane.

Facilitated Diffusion

Facilitated diffusion moves solutes from a region of higher concentration to a region of lower concentration until the concentrations become equalized on both sides of the membrane.

Active Transport

This form of molecule movement requires energy in order to move solute against its electrochemical gradient. Energy is required to either:

1. Alter the affinity of the binding site on different sides of the membrane
2. Alter the rates at which the binding site on the transporters is shifted from one side of the membrane to the other.

Furthermore, there are two ways in which a flow of energy can be coupled to transporters.

1. Primary active transport requires energy is provided by ATPase.

Sodium, potassium—ATPase (Na, K—ATPase) is present in plasma membranes which works by moving 3 Na^+ ions out of a cell and 2 K^+ ions in, resulting in a net transfer of positive charge outside the membrane.
Calcium—ATPase in plasma membranes moves Ca^{2+} ions from the cytosol to the extracellular fluid, while Ca—ATPase in membranes of organelles moves Ca^{2+} from cytosol into the organelle lumen (space).
Hydrogen—ATPase in plasma membranes moves hydrogen ions (H^+ or protons) out of cells.

2. Secondary active transport provides energy from the flow of ions from an area of higher concentration to one of lower concentration. Allosteric modulation modifies the affinity of the binding site. There are technically two types of secondary active transport.
    1. Cotransport occurs if a molecule moves in the same direction as the ion providing the energy. An example is the movement of amino acids using sodium ions.
    2. Countertransport occurs when the molecule moves in the opposite direction as the ion providing the energy. An example is the movement of calcium ions using sodium ions.

In sum, with ions the movement is from high to low concentration, and molecules from low to high.

Osmosis

Osmosis is the net diffusion of water across a membrane. Aquaporins are proteins that form channels in the lipid bi-layer for the polar water molecules to diffuse through. There will be a net diffusion of both compartments leading to diffusion equilibrium with no change in volume in either compartment if the compartments are separated by a membrane that is permeable to both a solute and water. However, if the membrane is only permeable to water (i.e. not to the solute) then diffusion equilibrium will be reached with a net increase in volume of the compartment that had a higher osmolarity to begin with. Osmolarity is the total solute concentration of a solution and is measured in units called osmols. Therefore, water concentration in a solution is negatively correlated with the number of solute particles. Osmotic pressure is the pressure that must be applied to prevent the net flow of water into a solution separated by a membrane. The osmotic pressure increases with increases in osmolarity. Water will then move from regions of lower osmotic pressure to regions of higher osmotic pressure.
When a system reaches equilibrium, the osmolarities of intra- and extracellular fluids are the same. An isotonic solution is a solution which cells will neither swell nor shrink, this is assuming that the cells are placed into a solution of non-penetrating solutes with the same osmolarity as the extracellular fluid. The key thing is that there is no net movement in an isotonic solution. In an hypotonic solution, the solution contains less non-penetrating solutes, and the cells therefore absorb water and the cells swell. Finally, a hypertonic solution is one in which the solution contains more non-penetrating solutes and water moves out of the cells and they shrink. It is important to understand that penetrating solutes do not contribute to the tonicity of the solution.

Endocytosis

Endocytosis is a transportation process that requires energy. The main mechanism is that regions of the plasma membrane fold into the cell which forms small pockets on the inside of the cell. These pockets pinch off into membrane-bound vesicles inside the cell.
Fluid endocytosis refers to when the vesicles formed enclose a small volume of extracellular fluid. However, if certain molecules in the extracellular fluid happen to bind to specific proteins on the plasma membrane and are then carried into the cells with extracellular fluid, the process is then called adsorptive endocytosis. Collectively, these two processes are also called pinocytosis and are demonstrated by most cells.
Some cells will engulf large foreign particles via a process called phagocytosis. This only happens in specialized cells that are relatively few in number and occurrence. The type of particles engulfed include bacteria and cell debris.
Endosomes are usually fused with endocytic vesicles at some point in the process, and the contents of the packets are then passed into organelles such as Lysosomes.
Both pinocytosis and phagocytosis are examples of endocytic processes. The big thing to remember is that the movement of particles is from the outside of the plasma membrane to the

inside.

Exocytosis

In order to move things from the inside of the cell to the outside, membrane-bound vesicles in the cytoplasm will fuse with the plasma membrane and release their contents outside the cell. The bound vesicle material then assimilates into the plasma membrane. In this fashion, portions of the plasma membrane lost during endocytosis can be replaced. Additionally, the process provides a route by which membrane impermeable molecules, such as protein hormones, that are synthesized by cells can be released into the extracellular fluid. Finally, the process of exocytosis is triggered by stimuli that leads to an increase in cystolic calcium concentration which in turn activates proteins required for the vesicle membrane to fuse with the plasma membrane and thus repairing any 'holes' from prior processes.

Epithelial Transport

The luminal (or apical or mucosal) membrane is the plasma membrane surface of an epithelial cell that faces a hollow or fluid filled chamber. The basolateral (or serosal) membrane is the surface of plasma membrane on the opposite side usually adjacent to a network of blood vessels. Substances can cross a layer of epithelial cells via two pathways.

1. The paracellular pathway refers to diffusion between adjacent cells in the epithelium. This pathway is limited to small ions and water because of the presence of tight junctions.
2. The transcellular pathway refers to the movement into an epithelial cell from one side, then diffusion through the cytosol and exit through the opposing membrane.

The transport and permeability characteristics of the luminal and basolateral membranes are not the same due to the presence of different ion channels and transporters. Substances, therefore, are able to move from a region of lower concentration on one side to a higher concentration on the other.

Glands

Gland cells secrete organic molecules synthesized by their own cellular processes and they also secrete salts and water, moving them from one extracellular compartment to another.
The rate of secretion is controlled by chemical or neural signals and work by:

1. Altering the rate of synthesis
2. Altering the rate of exocytosis via calcium channels
3. Altering the pumping rate of transporters and opening rate of ion channels

Two types of glands:

1. Endocrine glands will release their secretions directly into the interstitial fluid surrounding the gland cells. Endocrine glands secrete hormones.
2. Exocrine glands utilize ductworks in order to connect to epithelial surfaces. The secretions flow through the ductworks or onto the surface of the epithelium. Sweat and salivary glands are examples of exocrine function.

Genetic information and protein synthesis

Genetic Code

Genes are sequences of DNA nucleotides that carry and transmit the information specifying amino acid sequences for protein synthesis. Each DNA molecule contains many genes. The genome refers collectively to the total genetic information coded in a cell. With the exception of reproductive cells, all human cells contain 46 DNA molecules in each cell nucleus. Each DNA molecule corresponds to a chromosome. Each chromosome is packaged with proteins called histones. The complex of chromosome and histones are called nucleosomes.
RNA molecules are responsible for transferring information from DNA to the site of protein synthesis. RNA molecules themselves are synthesized according to the information coded in DNA.

transcription translation
DNA -> mRNA -> Protein

Recall that DNA nucleotides are composed of long chains of bases. A triplet code is a sequence of three bases along a single strand of DNA. Each triplet code is 'read' and calls for a specific amino acid. Recall that there are 4 bases in DNA (Guanine, adenine, cytosine, thymine) and 20 amino acids that are linked together in different arrangements to make various proteins. The 4 bases can be arranged into 64 different triplet codes (sequence of three bases). Sixty-one (61) of the codes are matched up to one of the 20 amino acids, a given amino acid can be specified by more than one triplet code, while the remaining three triplet codes act as stop signals and end the protein chain rather than adding an amino acid. As the triplet codes are read, the appropriate amino acid is added to the growing chain, the final result being a protein as determined by the DNA information. The genetic code is universal in all cells.

Protein Synthesis

Transcription: mRNA Synthesis
The first item of business in protein synthesis is the unraveling of the DNA double helix and separation of the two strands of nucleotides. One of the strands will act as a template and will determine the sequence of RNA nucleotides. The template strand is determined by the presence of a specific sequence of DNA nucleotides called the promoter. The sequence is located near the beginning of the gene. RNA polymerase is the enzyme that joins together the aligned ribonucleotides into a strand. When the triplet codes reach a stop sequence or stop signal, the RNA polymerase ends the chain and releases then RNA transcript. As a final touch a series of adenine nucleotides called the poly A tail is added to the end of the transcribed RNA strand. The tail is vital in that it gives the signal necessary to allow the RNA to move out of the nucleus and then bind to ribosomes in the cytoplasm where proteins will be synthesized from the encoded information.
In DNA the three base sequences are called triplet codes, while in RNA the three bases sequences that specify one amino acid are called codons. Therefore, triplet codes and codons are analogous in function. The entire sequence of nucleotides in the entire template strand is transcribed into a primary RNA transcript. Only certain segments of this gene actually code for amino acids. The segments are called exons while the non-coding segments in between exons are called introns. The introns are spliced off of the gene by a spliceosome to form a continuous sequence of exons; the sequence is now called mRNA.

Translation: Polypeptide Synthesis
After the introns are removed, the mRNA moves out into the cytoplasm through the nuclear pores and binds to a ribosome. Each ribosome is composed of proteins and a class of RNA called

ribosomal RNA (rRNA), which is a strand transcribed from the DNA in the nucleolus.
Transfer RNA (tRNA) is the link between an amino acid and its mRNA codon since the clover-leaved shaped molecule of tRNA can combine with both. Transfer RNA is synthesized in the nucleus before it moves out into the cytoplasm. An enzyme called aminoacyl-tRNA synthetase (there are 20 of these, specific to each amino acid) links specific amino acids to tRNA molecules. The tRNA molecule and amino acid are then base paired to mRNA with a three base sequence called the anti-codon. The anti-codon specifies the amino acid.
Protein assembly is a three-stage process:

1. Initiation of the polypeptide chain begins by binding an anti-codon in an amino acid-tRNA complex to the corresponding codon in the mRNA –ribosome complex. This initial binding is driven by enzymes called initiation factors; the activity of these enzymatic factors regulate the rate of protein synthesis. The initiation phase is the slowest of the three phases in the assembly process.
2. Elongation of the polypeptide chain is the second phase. Each amino acid brought to the chain on a tRNA molecule is linked by a peptide bond to the end of the growing protein chain; the free tRNA is then released from the ribosome and will go attach to another amino acid.
3. The ribosome acts as a 'reader' and when it reaches a termination sequence in the mRNA, the link between the polypeptide chain and tRNA is broken. The completed protein is then released from the ribosome and the ribosome is available for the next mRNA strand coming from the nucleus.

As small protein emerge from the ribosome they undergo folding. Larger proteins will fold within the recess of a small, hollow protein chamber called chaperones. If anything is to be added to the protein chain, such as carbohydrate or lipid derivatives, these occur at the chaperone site. Eventually, mRNA molecules are broken down into nucleotides by cytoplasmic enzymes. Mitochondrial DNA does not have introns. Mitochondria each have the complete set of machinery to produce its own proteins, the nuclear DNA supplies the rest.

Regulation of Protein Synthesis

Signals from within or outside the cell can turn on or off the transcription of genes. This regulation is performed through allosteric or covalent modulation of a class of enzymes called transcription factors. A pre-initiation complex at the promoter region forms these factors and activates or represses the initiation process (such as the separation of DNA strands, activation of RNA polymerase).

Protein Secretion
Proteins to be secreted from a cell have a signal sequence that binds to a specific membrane protein on the surface of the granular endoplasmic reticulum and is fed into its lumen, within which the signal sequence is removed and carbohydrate groups are attached (almost all secreted proteins are glycoproteins). Portions of the reticulum bud off, forming vesicles containing the proteins. The vesicles migrate to the golgi apparatus and fuse with the golgi membrane. Within the golgi, groups may be added or removed according to final destinations of the proteins. The proteins are then packaged into vesicles that bud off the surface of the golgi membrane and travel to the plasma membrane, where they fuse and release their contents in the extracellular fluid through a process called exocytosis.

Replication and Expression of Genetic Information
Each cell has 44 autosomes, chromosomes that contain genes that produce the proteins governing cell structure and function, and 2 sex chromosomes containing the genes which determine sex. Each parent contributes half of these (22) autosomes and (1) sex chromosome. Each pair of autosomes has homologous genes coding for the same protein.

Each time a cell divides, all the 46 chromosomes, each corresponding to a DNA molecule, must be replicated and identical copies passed to each of the new daughter cells. Therefore, all cells (except sperms and eggs) have an identical set of DNA (and therefore genes). What makes one cell different from another is the differential expression of various sets of genes.

DNA Replication
DNA is the only molecule in a cell able to duplicate itself without information from some other cell component. During replication, the two strands of double helix separate and each exposed strand acts as a template to which free deoxyribonucleotide triphosphates are base paired. The enzyme DNA polymerase then links the free nucleotides forming a strand complementary to each template strand, forming two identical DNA molecules.
Enzymes that assist in replication are anchored to the DNA just ahead of the site where the strands are separating. So that the enzymes find an anchoring site when the replication process reaches the terminal segment of the DNA molecule, an enzyme called telomerase adds a repeating sequence, called telomere, at the end of the DNA molecule. In the absence of telomerase, each replication results in the shortening of the DNA molecule. Any error in the base sequence during replication is corrected by a mechanism called proofreading.

Cell Division and Cell Cycle

The period between the end of one division and the beginning of the next division is called interphase. A cell spends most of its time in interphase that can be further divided into:
(1) **GI (Gap 1):** Period from end of one division to the S phase.
(2) **S (Synthesis):** Period when DNA replication takes place after G1 phase.
(3) **G2 (Gap 2):** A brief interval between end of S phase and actual cell division.
M phase is the actual cell division consisting of a nuclear division, mitosis, and a cytoplasmic division, cytokinesis.
The two critical checkpoints that control the progress of the cell cycle are the GI - S and the G2 - M boundaries.
Some cells, e.g., stem cells, divide continuously and proceed continuously through successive cell cycles while some cells, e.g., nerve cells rarely divide and spend most of their time in a phase called G_0, which is an arrested G_1 with no entry into the S phase. Go can be a temporary phase and a cell can reenter the active cell cycle upon receipt of suitable signals from proteins called growth factors that control the synthesis of the enzymes, cell division cycle kinases (cdc kinases) and cyclins.
The replication of a DNA molecule results into two identical chains called sister chromatids; joined together at a point called the centromere. Just prior to cell division, there are 46 chromosomes, each consisting of two chromatids. The nuclear membrane breaks, the centromeres of the chromosomes become linked to spindle fibers, composed of microtubules, emerging from the centrosome. The 2 centrioles of the centrosome divide and a pair moves to opposite sides of the cell.
The sister chromatids separate at the centromere and move toward opposite centrioles. Cytokinesis finally divides the cell into two. The spindle fibers dissolve, nuclear membrane reappears and the chromatids uncoil.

Mutation
Any alteration in the DNA nucleotide sequence, produced by factors called mutagens, which break the chemical bonds in DNA and results in loss or incorporation of segments. Also occurs naturally due to errors during replication.
Types of Mutations:
(1) Point mutation - A single base is replaced by a different one. May or may not change an amino acid sequence due to redundancy of genetic code.
(2) Addition/deletion - Whole sections of DNA are added or deleted resulting in misreading of a code or a loss of a set of genes.
A mutation may not have any effect if:

(1) The mutation occurs within an intron segment
(2) The changed amino acid does not influence the structure and function of the polypeptide
(3) The homologous gene is intact and able to produce an intact protein
(4) The amino acid can be obtained from external sources.
Mutation in a sperm or an egg cell does not affect the individual but affects the offspring.
Mutations can contribute by introducing variation, some of which may be competitively better.

DNA Repair Mechanisms
Cells have a number of enzymatic mechanisms that can repair one altered DNA strand based on the template provided by the undamaged strand.

Gene Pool
Alleles are variants of the same gene. One allele of each gene is received from each parent. If both alleles are identical the individual homozygous for that gene, if the two are different the individual is heterozygous. The set of alleles in an individual is called its genotype. The expression of the genotypes into proteins producing a specific structural and functional form is called the phenotype.
Each homologous allele for a gene (except for genes in the sex chromosomes) can be translated into proteins. If only one of the alleles is active and produces a character, it is called a dominant allele. If both the alleles need to be active to produce a specific character, these alleles are called recessive.
Genetic disease can result from the inheritance of mutant genes, which produce abnormal structure or function. Familial hypercholesterolemia, cystic fibrosis, sickle-cell anemia, hemophilia, muscular dystrophy are single gene diseases. Polygenic diseases result from several defective genes, each of which by itself has little effect. Examples are diabetes, hypertension, and cancer.
Chromosomal diseases result from addition or deletion of whole or portions of chromosomes during meiosis. Example is Down's syndrome or trisomy 21 in which the egg has an extra copy of chromosome 21.

Cancer

Cancer is a genetic disorder that is not generally inherited. Arise from mutations in the somatic cells. Results in the failure of the control system that regulates cell division and results into uncontrolled growth.
Dominant cancer-producing genes, called oncogenes, code for abnormal forms of cells surface receptors that bind growth factors and produce a continuous growth signal. Recessive cancer-producing genes, called tumor suppressor genes, fail to produce proteins that inhibit various steps in cell replication.
Abnormal replication of cells forms a tissue mass called tumor. If these cells remain localized it is called a benign tumor, if they invade the surrounding tissue it is called a malignant tumor.
Cancers that develop in epithelial cells are called carcinomas, ones in muscle cells are called sarcomas and ones in white blood cells are called lymphomas. Lung, colon, and breast are the organs most commonly affected. Incidence of cancer increases with age due to the accumulation of defective mutations.
Mutagens that increase the probability of cancerous transformation of a cell are called carcinogens.
Genetic Engineering
Modification of the base sequence of a DNA molecule by addition or deletion of bases. Involves:
(1) Cutting the DNA strands at specific sites, called restriction sites, by bacterial enzymes called restriction nucleases.
(2) Linking the resulting fragments of interest to another DNA molecule using an enzyme called ligase.
The process of transferring DNA from one organism to another is called transfection and the organism into which such a transfer has taken place is called a transgenic organism.

Bacteria can be transfected with human genes to produce large quantities of human proteins. Involves the production of DNA without introns, called complementary DNA (cDNA) by using a viral enzyme called reverse transcriptase on an mRNA template. The requirement for cDNA results from the fact that bacterial DNA does not have introns, nor the mechanism to splice them.

Protein Activity and Cellular Metabolism

Protein Binding Sites

The ability of various molecules and ions to bind to specific sites on the protein surface forms the basis of the wide variety of protein functions. A ligand is any molecule or ion that is bound to the protein surface by either (1) oppositely charged ionic or polar groups or (2) van der Waals forces between nonpolar regions and a binding site is the protein region where a ligand binds. Chemical specificity and affinity are distinct properties of a binding site.

Chemical Specificity
A protein may have several binding sites, each site is specific for a particular or a particular type of ligand. This high chemical specificity is due to the complementary shapes of the ligand and the protein.

Affinity
Affinity is the strength of ligand-protein binding. A binding site could have a **high or low** affinity for a ligand, depending on the **nature of the groups** in both and **proximity** to each other.

Saturation
A single binding site could be occupied or unoccupied and the fraction of sites that are occupied is called saturation. The percent saturation depends on (1) the concentration of unbound ligand and (2) the affinity of the binding site. This saturation will be reflected in the biological activity of the of the protein-ligand complex.

Competition
If there is a competition between two similar ligands for the same binding site, an increase in the concentration of one will inhibit the binding of the other.

Regulation of Binding Sites

Allosteric Modulation
Involves a change in the shape of the functional (active) site by the non-covalent binding of a ligand modulator molecule into a regulatory site. The modulation may take the form of either a turn-off or a turn-on function.
In a multimeric protein, there can be an increase in the affinity for ligand binding due to cooperativity among the functional groups. This process occurs in the binding of oxygen to hemoglobin.

Covalent Modulation
Involves change in the shape of the functional site by the covalent bonding of a chemical group, mostly a phosphate group (PO42-) by a phosphorylation reaction.

Enzymes and Chemical Reactions

Metabolism consists of synthesis (anabolism) and breakdown (catabolism) of organic molecules required for cell structure and function.
Chemical reactions involve: (1) the breaking of chemical bonds in reactant molecules and (2) making of new chemical bonds to form product molecules. Energy is either added or released as heat during chemical reactions.

Determinants of Reaction Rates
Rate of a chemical reaction (number of product molecules formed per unit time) is influenced by:
(1) Reactant concentration - more the reactants, higher is the rate.
(2) Activation energy - energy required by reactant molecules to enter an activated state in which chemical bonds can be broken and formed. Higher the activation energy required, lower is the reaction rate.
(3) Temperature - higher the temperature, higher is the reaction rate because reactant molecules can acquire the required activation energy.
(4) Catalyst - a substance that decreases the required activation energy to increase the reaction rate. Chemical composition of a catalyst is not altered by the reaction and thus a single catalyst molecule can be used over and over again.

Reversibility of a Reaction
Energy released during a reaction determines reversibility of a reaction. Greater the energy released during a reaction, smaller is the probability of product molecules obtaining this energy and undergoing the reverse reaction to reform the reactants. In such a case, ratio of product to reactant concentration will be large and the reaction will tend to be irreversible.
In a reversible chemical reaction, rate of forward reaction decreases and rate of reverse reaction increases as the reaction progresses until the two are equal in a state called the chemical equilibrium, at which point there is no further change in the concentration of reactants and products.

Law of Mass Action
Effect of reactant and product concentration on the direction of net reaction. Increasing the concentration of reactants or decreasing the concentration of products drives the reaction forward and vice versa. This mechanism is important in controlling the direction of metabolic pathways.

Enzymes

Protein catalysts. (A few RNA molecules also possess catalytic activity). In an enzyme-mediated reaction, an enzyme binds to reactants (substrates) to form an enzyme-substrate complex, which breaks down to release products and the enzyme.
The region of the enzyme to which the substrate binds is called the active site, the shape of which determines the chemical specificity of the enzyme.

Cofactors
Substances that bind to enzymes to alter their conformations and make them active. Some cofactors are trace elements. In cases where the cofactor is an organic molecule, it is called a coenzyme. Coenzymes are derived from vitamins.

Regulation of Enzyme-Mediated Reactions
Rate of an enzyme-mediated reaction depends on:
(1) Substrate Concentration: The higher the substrate concentration higher the reaction rate, until enzyme is saturated. Substrate concentration is altered by changes in supply from outside a cell due to changes in diet, rate of absorption from intestine, changes in permeability of plasma

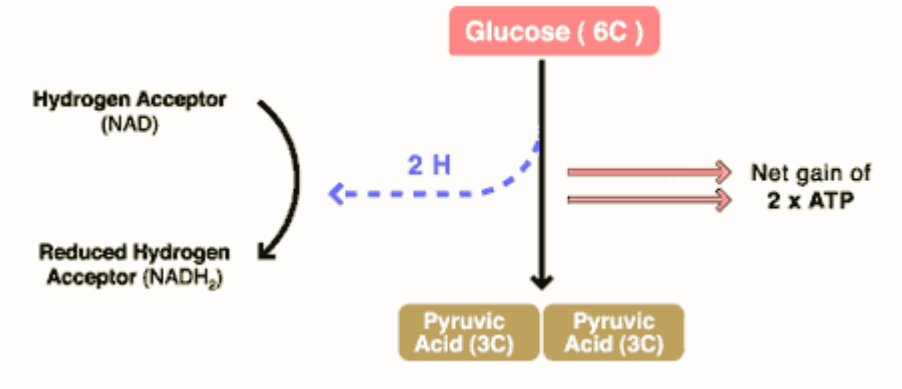
membrane, or changes in intracellular breakdown and synthesis of the substance.
(2) Enzyme Concentration: The higher the enzyme concentration, higher the reaction rate.
(3) Enzyme Activity: The activity of an enzyme can be altered by allosteric or covalent modulation of the binding site affinity. Modulators are products of other chemical reactions or activated by chemical signals.

Multi-enzyme Metabolic Pathways
A sequence of enzyme-mediated reactions. Generally consists of a rate-limiting reaction, the slowest step in the sequence that regulates the rate of the whole pathway. The enzyme controlling this step is strongly regulated, often by end-product inhibition, or inhibition by the final product of the pathway.

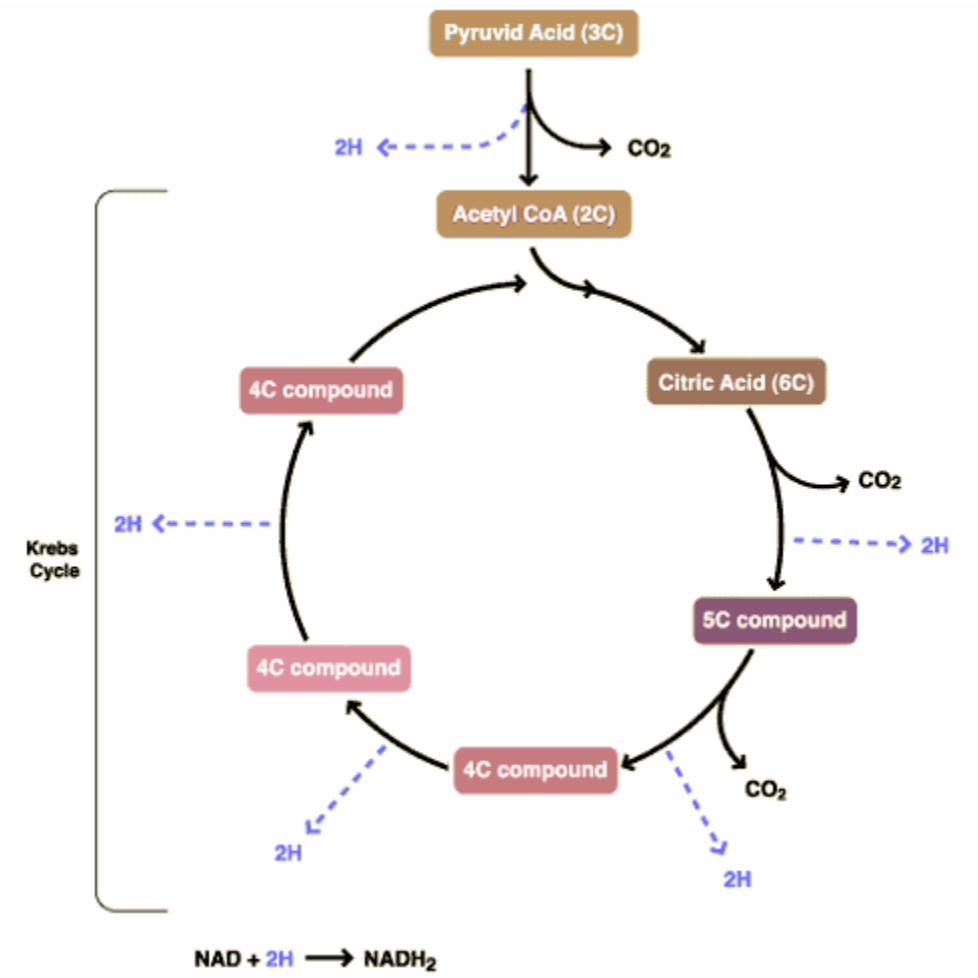
ATP
Adenosine triphosphate is the primary molecule to which energy is transferred during the breakdown of fuel molecules, carbohydrates and fats. (A cell cannot use heat energy to perform its functions). ATP is then hydrolyzed to release energy which can be used by the energy requiring processes in cells such as (1) production of force and movement, (2) active transport across membranes and (2) synthesis of organic molecules used in cell structures and functions. ATP is an energy transfer molecule and NOT an energy storage molecule. It transfers energy from fuel molecules to cells in small amounts

Metabolic Pathways

Glycolysis
Partially catabolizes carbohydrates, primarily glucose. Converts a 6 C glucose into two 3 C pyruvate. Produces a net gain of 2 ATP by a process called substrate-level phosphorylation. The reactions do not use oxygen and take place in cytosol. If oxygen is present (aerobic conditions), the pyruvate enters Krebs cycle. In absence of oxygen (anaerobic conditions), pyruvate is converted to lactate. Glycolysis occurs in cells lacking mitochondria, e.g., erythrocytes and in certain skeletal muscle cells during intense muscle activity. Other monosaccharides, e.g., fructose and galactose can also be catabolized by glycolysis. In some organisms, e.g., yeast, pyruvate is converted into CO^2 and alcohol by a process called fermentation.

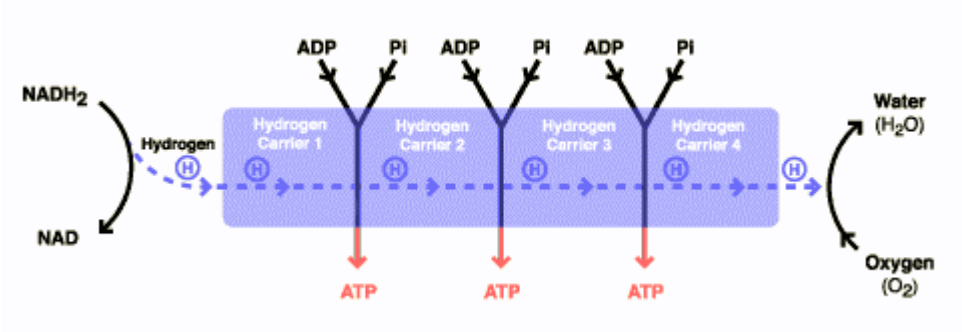


Krebs Cycle
Also called the citric acid cycle or tricarboxylic cycle. Utilizes molecules produced during carbohydrate, protein or fat breakdown and produces CO^2. hydrogen bound to coenzymes and 1 ATP. The reactions occur in the mitochondrial matrix and utilize oxygen. The primary molecule entering the cycle is acetyl coenzyme A (acetyl CoA) derived from pyruvate, fatty acids or amino acids. Total ATP production is 2 since 2 pyruvate molecules are entering the cycle from glycolysis.



Oxidative Phosphorylation

Oxidative phosphorylation uses the hydrogen attached to the coenzymes from Krebs cycle and oxygen to produce water and 34 ATP molecules, releasing hydrogen-free form of the coenzymes in the process. Occurring in the inner mitochondrial membrane mediated by cytochromes, the process is also called an electron transport chain.



Carbohydrate Synthesis

Glycogen Storage - Glucose is stored in skeletal muscles and liver in the form of glycogen, a polysaccharide. Enzymes for glycogen synthesis and breakdown are located in cytosol. Whether glucose enters the catabolic pathway to form pyruvate or the anabolic pathway to form glycogen is controlled at a single point, working under a feedback mechanism operated by hormones that

modulate enzymes.

Glucose Synthesis - Glucose is synthesized in liver and kidneys from intermediates derived from catabolism of glycerol and some amino acids, by a process called gluconeogenesis. The major substrate in this process is pyruvate and 6 ATP molecules are consumed to produce 1 molecule of glucose.

Fat Metabolism

Fat Catabolism - A substantial amount of energy is derived from catabolism of fatty acids that takes place in mitochondrial matrix, by a series of reactions called beta-oxidation. Acetyl CoA is produced, which can then enter Krebs cycle. The catabolism of an 18 C saturated fatty acid yields 146 ATP.

Fat Synthesis - Fat accounts for a major portion of energy stored in the body. Acetyl CoA molecules come together to form long, even numbered C chains and these fatty acids combine with glycerols to form triacylglycerols, in the smooth endoplasmic reticulum.
Majority of body fat is stored in cells called adipocytes, the entire cytoplasm of which is filled with a single fat droplet. Adipocytes synthesize and store triacylglycerols during food uptake and cluster to form adipose tissue, most of which underlies the skin.

Protein and Amino Acid Metabolism

Amino Acid Catabolism - Protein catabolism requires proteases to break the peptide bonds and release smaller peptides or amino acids. Amino acids can be catabolized either to form ATP or to provide intermediates for a variety of other molecules.
The amino group of amino acid is either removed by oxidative deamination to produce a keto acid and NH_3 or transferred to a keto acid by transamination. The keto acid can enter the glycolytic pathway or the synthetic pathways for glucose and fat. The N from the amino group can be used to synthesize important N containing molecules such as purines and pyrimidines.
The toxic NH_3 passes into blood through plasma membrane and goes to liver where it is linked with CO_2 to form the relatively nontoxic urea, which is excreted by the kidneys.

Amino acid Synthesis - Keto acids, e.g., pyruvic acid can be transaminated to form amino acids. This process can only form 11 of the 20 amino acids and the remaining 9, which must be obtained from food, are called essential amino acids.
Total free amino acid pools in the body are derived from:
(1) Ingested protein degraded to amino acids during digestion,
(2) Synthesis of nonessential amino acids from keto acids
(3) Breakdown of body proteins.
These are the pools from which proteins can be synthesized.

Essential Nutrients
Essential nutrients are substances that are required for the optimal function of body but cannot be synthesized at all or can be synthesized only in inadequate amounts by the body. They must be continually supplied in food.
Water is an essential nutrient because far more is lost in urine, from skin and respiratory tract than can be synthesized by the body.
Mineral elements, 9 essential amino acids, two fatty acids - linoleic and linolenic acids, inositol, choline, and carnitine are essential nutrients.

Vitamins
Vitamins are a group of 14 organic essential nutrients, required in small amounts. Plants and bacteria have enzymes to synthesize vitamins and these are primary sources of vitamins.

Excess water-soluble vitamins are excreted through urine while fat-soluble ones are stored in fat tissue.

Homeostatic Mechanisms and Cellular Communication

Homeostatic Mechanisms and Cellular Communication

Homeostasis is the relatively stable conditions of the internal environment that result from compensatory regulatory responses performed by homeostatic control systems. The set point of a single variable is frequently controlled by multiple systems. Such redundancy allows fine-tuning. Steady state is the state of a system at which a particular variable remains constant by a continuous input of energy (unlike an equilibrium state) and the steady state of this variable is called the set point.
In face of a continuing perturbation, homeostatic responses do not return the regulated variable completely to its original value and this difference is called the error signal. It serves as a signal to maintain the homeostatic response. More precise the homeostatic mechanisms are, smaller is the error signal required to drive the system and lower is the fluctuation in the set point of the variable.
A negative feedback system is one in which an increase or decrease in the variable being regulated brings about responses that move the variable in the direction opposite to the direction of the change.
A positive feedback system is one in which a disturbance sets off a chain of events that increase the disturbance even further. Such a system displaces a system away from its normal set point. Such resetting may be adaptive and could be a part of the body's defenses. Set points may also change on a rhythmical basis.
Feed forward Regulation anticipates changes in a variable, improves the speed of homeostatic response and minimizes amount of deviation from the set point. Such regulation muse external detectors or learning

Components of Homeostatic Control Systems

Reflexes
A reflex is a specific, involuntary, unpremeditated response to a particular stimulus. A stimulus being a detectable change in the internal or external environment. The pathway meditating a reflex is called a reflex arc.
A receptor detects the stimulus and produces a signal that is relayed through a pathway called the **afferent pathway** to the integrating center, which receives signals from many receptors. The output of the integrating center reflects the net effect of the total afferent input. The output is sent through a pathway called the **efferent pathway** to an effector, the activity of which constitutes the response of the system.

Local Homeostatic Responses
A homeostatic response, the entire sequence of which occurs only in the area of the stimulus, providing the body with mechanisms for local self-regulation.

Intercellular Chemical Messengers
Three types.

(1) A **hormone** that enable the hormone-secreting cell to communicate with the cell acted upon by it, the target cell, with blood acting as the delivery medium
(2) A **neurotransmitter** that is released by a nerve cell and diffuses through the extracellular fluid to act upon a second nerve cell or an effector cell
(3) A **paracrine/autocrine agent** that participates in local communication between cells. They do not enter the bloodstream and may be released as a result of stimuli resulting from local chemical changes or neurotransmitters and hormones.
Paracrine agents are synthesized by cells and are released into extracellular fluid upon receipt of an appropriate stimulus. They diffuse to neighboring cells, some of which are their target cells.
Autocrine agents are local chemical messengers that are released into the extracellular fluid and act upon the same cells that secreted them.
The same chemical may act as any of three types of chemical messengers. Example: Eicosanoids, prostaglandins, thromboxanes.

Processes Related to Homeostasis

Acclimatization
Acclimatization is the improved functioning of an existing homeostatic mechanism in response to a particular stress. If it does not involve any genetic change and is completely reversible, it is also a physiological acclimatization while one that is induced during the critical development period of a structure or function may be irreversible and is called developmental acclimatization.

Biological Rhythms

Feedforward systems operate without detectors. They activate homeostatic mechanisms and anticipate when a change is likely to occur. The rhythms are internally driven but entrained (timing is set) by environmental cues. These cues can also phase-shift (reset the timing) a rhythm. In absence of cues, a rhythm free-runs and shows a different periodicity.
A circadian rhythm is one that cycles every 24 hours. The suprachiasmatic nucleus in the brain and the pineal gland, which secretes melatonin, are the principal pacemakers (time clocks) of circadian rhythms.

Apoptosis
Apoptosis is the ability of cells to self-destruct by autodigestion with endogenous enzymes. The plasma membrane is kept intact and digested contents are not released, instead phagocytic cells engulf the whole cell. Apoptosis eliminates undesirable cells. Cells are prevented from self-destruction by chemical signals. Abnormal inhibition of such signals may lead to cancer, while a very high rate of apoptosis leads to degenerative diseases, e.g., osteoporosis.

Aging
Loss in the capacity of (1) homeostatic control systems to respond to environmental changes and (2) cells to divide. Genes have a role in aging evidenced by diseases, e.g., Werner's syndrome - premature aging due to mutation of a single gene.

Balance in the Homeostasis of Chemicals
Many homeostatic systems work to add and remove different chemicals in the body such that a constant pool is available for different metabolic pathways. Total body balance and the pool concentration of a chemical is determined by:
(1) Addition of a substance to the pool from (a) gastrointestinal tract or lungs, (b) synthesized within the body or (c) released from storage deposits
(2) Removal of a substance from the pool through (a) loss in urine, feces, expired air, body surface etc. and (b) accumulation in storage deposits.
Three possible states of boy balance are:
(1) If loss > gain and total amount of a molecule in the body decreases, it is called a **negative**

balance
(2) If gain > loss and total amount of a molecule in the body increases, it is called **positive balance**
(3) If gain = loss and total amount of a molecule in the body is constant, it is called **stable balance**.

Chemical Control of Cells

Receptors
Receptors are glycoproteins that bind specific messengers. Present on plasma membranes of target cells. The binding initiates events leading to response of the cell. The same receptor-messenger combination may produce different responses in different cell types. A single cell may contain different receptors that upon binding with a messenger lead to different responses. Antagonists are drugs that compete with messengers for the receptors and slow down the response of the cell. Agonists are drugs that combine with the receptor and mimic the messenger to increase the response of the cell.

Regulation of Receptors
Affinity of some receptors increases in the absence of messengers, increasing responsiveness of the cell to the messenger. This is called up-regulation.
Down- and up-regulation are made possible by continuous synthesis and degradation of receptors. Binding of a messenger to a receptor can take the messenger-receptor complex inside the cell via endocytosis. Similarly, receptors can be synthesized inside the cell and made available to the plasma membrane.

Signal Transduction Pathways
Combination of messenger with receptor causes a change in conformation of the receptor, an event called receptor activation. This can lead to changes in (1) permeability, transport properties, or electrical state of the plasma membrane, (2) metabolism of the cell, (3) secretory activity of the cell, (4) rate of proliferation and differentiation of the cell and (5) contractile activity of the cell. Mechanisms by which receptor activation leads to final response of the cell are called signal transduction pathways. The different types of pathways are:
(1) Pathways with Intracellular Receptors
(2) Pathways with extracellular receptors
(3) Receptors that function as ion channels
(4) Receptors that -function as enzymes
(5) Receptors that interact with cytoplasmic JAK proteins
(6) Receptors that interact with G proteins
(7) Receptors that act as transcription factors
If there are two chemical messengers involved in the signal transduction pathway, the one that binds to a specific receptor on the plasma membrane is called the first messenger and the one that is enzymatically generated as a result of receptor activation and enters the cytoplasm is called the second messenger. Ca^{2+} frequently acts as a second messenger.
The transduction pathways stop when the concentration of the first messenger decreases due to its metabolism and diffusion. Receptors either become chemically altered, decreasing their affinity for the first messenger or they are removed when the messenger-receptor complex is taken up inside the cell by endocytosis.

Neural Control Mechanisms

Neural Control Mechanisms

Nerve cells called neurons generate electric signals that pass from one end of the cell to another and release chemical messengers called neurotransmitters to communicate with other cells

Structure

A neuron has: (1) a cell body containing the cell organelles, (2) dendrites, branched outgrowths from the cell body that receive inputs over its vast surface area, (3) an axon, a single long process that extends from the cell body to its target cells, (4) an axon terminal which releases neurotransmitters that diffuse through extracellular space to trigger cells opposite the terminal.
A nerve fiber is a single axon while a nerve is a bundle of axons bound together by connective tissue.
Axons of some neurons are covered by myelin, a layer of plasma membranes with supporting cells that are called glial cells in CNS and Schwann cells in the peripheral nervous system. The spaces between adjacent sections of myelin where the axon is exposed to extracellular fluid are called nodes of Ranvier. Myelin speeds up conduction of electric signals.

Glial Cells
Glial cells physically and metabolically support neurons. Oligodendroglia form the myelin covering of CNS axons. Astroglia regulate the composition of extracellular fluid in CNS. Microglia perform immune functions.

Functional Classes of Neurons
3 types:
(1) **Afferent neurons** that have sensory receptors at their ends and convey signals from tissues and organs into CNS
(2) **Efferent neurons** that transmit signals from CNS to effector cells
(3) **Interneurons** that connect neurons within CNS.
The junction between two neurons, where one neuron alters the activity of another (via a neurotransmitter) is called a synapse. A neuron conducting signals toward a synapse is called a presynaptic neuron while a neuron conducting signals away from a synapse is a postsynaptic neuron.

Neural Growth and Regeneration
Development of neurons is guided by neurotropic (neurogrowth) factors. Neurons outside the CNS can repair themselves but neurons within the CNS cannot.

Membrane Potentials
The difference in the amount of charge between two points is called potential difference and its unit of measurement is volt. This difference tends to make the charge low, producing an electric current. The material through which it is flowing obstructs the current and this is called resistance. Ohm's law gives the relationship

$$I = E/R$$

Where: I = electric current
E = electric potential
R = resistance

Materials with high resistance are called insulators, and those with low resistance are called conductors. Water with dissolved ions (electrolytes) is a good conductor while lipids are insulators. Intra- and extracellular fluids have numerous ions and are therefore conductors while the plasma membrane separating them is an insulator.

Resting Membrane Potential
Potential difference across the plasma membrane of a cell under resting conditions with inside of

the cell being negatively charged with respect to outside. Magnitude of the potential is determined by (1) differences in specific ion concentrations in intra- and extracellular fluids, and (2) differences in membrane permeabilities to different ions as a function of the number of open ion channels for these ions.
Na^+ and K^+ play the most important roles in generating the resting membrane potential. Nat is greater outside while K^+ is greater inside the cell. K^+ moves out of the cell and Na^+ moves into the cell down their concentration gradients but intracellular concentration of these two ions are kept constant by an active transport system that pumps Na^+ out of the cell and K^+ into it. However, the pump brings out 3 Na^+ for every 2 K^+ it pumps in, making inside of the cell negative.

Graded and Action Potentials
Graded potentials are changes in membrane potential confined to a small region of plasma membrane. Magnitude of these potentials is related to the magnitude of the initiating stimulus. They initiate a signal.
Action potentials are large, rapid alterations in the membrane potential. Membranes capable of producing action potentials are called excitable membranes. Examples are membranes in nerve and muscle cells.

Ionic Basis of Action Potential
During an action potential, voltage gated Na^+ channels open and allow a large influx of Na^+ ions into the cell, making inside of the cell less negative and this is called depolarization. The membrane starts returning rapidly to the resting membrane potential because Na^+ channels close, voltage gated K^+ channels open, K^+ moves out and this is called repolarization. However, so much K^+ moves out that inside of the cell becomes more negative than the original resting membrane potential and this is called hyperpolarization. In some cells, Ca^{2+} channels serve the same function as Na^+ channels. Local anesthetics block the Na^+ channels and prevent an action potential.

Threshold and All-or-None Response
The potential at which a membrane is depolarized to generate an action potential is called the threshold potential and stimulus that is strong enough to depolarize the membrane is called threshold stimulus.
A stimulus of more than threshold magnitude also elicits an action potential of the same amplitude as that caused by a threshold stimulus. This is because once the threshold is reached membrane events are no longer dependent upon the stimulus strength. Therefore, action potentials occur maximally or do not occur at all and this is called an all-or-none response. This is why a single action potential cannot convey information about the magnitude of the stimulus that initiated it

Refractory Periods
The period after an action potential when a second stimulus will, not produce a second action potential is called absolute refractory period. It occurs because once the voltage gated Na^+ channels close, the membrane needs to repolarize before the channels can open once again. Following the absolute refractory period, there is an interval during which a second action potential can be produced only is the stimulus strength is greater than usual. This is called relative refractory period and is a result of hyperpolarization.

Initiation of Action Potential
The initial depolarization in afferent neurons is achieved by either a graded potential called receptor potential in the receptors or by a spontaneous change in the neuron membrane potential called pacemaker potential.

Action Potential Propagation
Since a neuron is a long cell, it gets depolarized part by part and not all at once. Area of the membrane that gets depolarized has a difference in potential with the adjacent area of the

membrane that is still at resting potential causing a local current. This current then depolarizes the adjacent resting membrane and a new action potential is generated there and so on. Because depolarization of an area is followed by a refractory period, the action potential moves unidirectionally.
Velocity of action potential propagation is positively correlated with fiber diameter because a larger fiber offers less resistance
Myelin sheath, being an insulator prevents the flow of ions between intra- and extracellular compartments. Therefore, action potentials occur only at the non-insulated nodes of Ranvier and this jump of action potentials from one node to another is called saltatory conduction. By preventing leakage of charge, myelin increases the speed of propagation, enabling axons to be thinner.

Synapses

A synapse is a junction between two neurons, where the electrical activity in the presynaptic neuron influences the electrical activity in the postsynaptic neuron. The influence can be either excitatory or inhibitory.
If many presynaptic cells affect a single postsynaptic cell it is called convergence and allows information from many sources to influence the activity of one cell. If a single presynaptic cell affects many postsynaptic cells it is called divergence and allows one information source to affect multiple pathways.

Functional Anatomy of Synapses
At electric synapses, the pre- and postsynaptic cells are joined by gap junctions, allowing action potentials to flow directly across the junction. Such synapses are rare.
At chemical synapses, axon of the presynaptic neuron ends in a swelling called the axon terminal and an extracellular space called the synaptic cleft separates the preand post- synaptic neurons, preventing direct propagation of current between them. Signals are transmitted across the synaptic cleft by a chemical messenger - a neurotransmitter - released from the presynaptic axon terminal and bound by receptors at the postsynaptic cell. Most chemical synapses operate in only direction.
Neurotransmitters in axon terminals are stored in membrane bound synaptic vesicles that are docked at the synaptic membrane. When an action potential depolarizes the axon terminal, voltage gated Ca^{2+} channels in the membrane open, and Ca^{2+} diffuses from extracellular space into the axon terminal. The Ca^{2+} induce reactions that allow the vesicles to fuse with the plasma membrane and liberate their contents into the synaptic cleft by exocytosis.

Excitatory Chemical Synapses
The activated receptor on the postsynaptic membrane opens Na^{+} channels. There is a net movement of Na^{+} ions into the cell, resulting in depolarization. This potential change in the postsynaptic neuron is called an excitatory postsynaptic potential (EPSP). It is a graded potential.

Inhibitory Chemical Synapses
The activated receptor on the postsynaptic membrane opens Cl^{-} channels. There is a net movement of Cl^{-} ions into the cell, resulting in hyperpolarization. The potential change in the postsynaptic neuron is called an inhibitory postsynaptic potential (IPSP). It is a graded potential.

Activation of the Postsynaptic Cell
In most neurons, one EPSP is not enough to cross the threshold in the postsynaptic neuron and only the combined effects of many excitatory synapses can initiate an action potential. If a number of EPSPs arriving at different times create a depolarization it is called a temporal summation. If a number of EPSPs arriving at different locations create a depolarization, it is called a spatial summation. IPSPs also show similar summations but the effect is a hyperpolarization.

Neurotransmitters and Neuromodulators

Neuromodulators modify the postsynaptic cell's response to neurotransmitters or change the presynaptic cell's synthesis, release or metabolism of the neurotransmitter.

Acetylcholine (Ach)
Major neurotransmitter. Fibers that release ACh are called cholinergic fibers. Acetylcholine is degraded by the enzyme, acetylcholinesterase.

Biogenic Amines
Biogenic amines are neurotransmitters containing an amino group. Catecholamines such as dopamine, norepinephrine and epinephrine, serotonin. Nerve fibers that release epinephrine and norepinephrine are called adrenergic and noradrenergic fibers respectively.

Amino Acid Neurotransmitters
Amino acid neurotransmitters are the most prevalent neurotransmitters in CNS. Glutamate, aspartate GABA (gamma aminobutyric acid), glycine,

Neuropeptides
Neuropeptides are composed of two or more amino acids. Neurons releasing neuropeptides are called **peptidergic**. Beta-endorphin, dynorphin, enkephalins.
Nitric oxide, ATP, adenine also act as neurotransmitters.
Neuroeffector Communication
Many neurons of peripheral nervous system end at neuroeffector junctions on muscle and gland cells. Neurotransmitters released by these efferent neurons then activate the target cell.

Structure of the Nervous System

A group of nerve fibers traveling together in the CNS is called a pathway or tract and if it joins the left and the right halves, it is called a commissure.
Information in CNS passes along two types of pathways:
(1) Long neural pathways in which neurons with long axons carry information directly between brain and spinal cord or between different regions of brain. There is no alteration in the transmitted information.
(2) Multineuronal or multisynaptic pathway. Made up of many neurons or synapses. New information can be integrated into the transmitted information.
Cell bodies of neurons having similar function cluster together and such clusters are called ganglia in the peripheral nervous system and nuclei in the CNS.

CNS: Spinal Cord

The spinal cord lies within the vertebral column. The central gray matter is composed of interneurons, cell bodies, dendrites and glial cells. This is surrounded by white matter composed of myelinated axons of interneurons. The fiber tracts either descend to relay information from the brain or ascend to relay information to the brain or transmit information across different levels of the spinal cord.
Afferent fibers enter from the peripheral system enter on dorsal side of the cord via dorsal roots and form the dorsal root ganglia. Efferent fibers leave the cord on the ventral side via ventral roots. Dorsal and ventral roots from the same level combine to form a spinal nerve outside the cord, one on each side. 31 pairs of spinal nerves are designated by 4 levels of exit - cervical (8), thoracic (12), lumbar (5), and sacral (5).

CNS: Brain

Brainstem: Consists of midbrain, pons and medulla oblongata. Contains the reticular formation, a bundle of axons that is involved in motor functions, cardiovascular and respiratory control, etc.
Cerebellum: An important center for coordinating movements and for controlling balance and posture.
Forebrain: The larger component of forebrain, the cerebrum consists of the right and left cerebral hemispheres that have an outer shell of gray matter the cerebral cortex. Each hemisphere is divided into 4 lobes: frontal, parietal, occipital and temporal. The cortex is the most complex integrating area. The central core of the brain is formed by the diencephalon consisting of the thalamus - a collection of several large nuclei, and the hypothalamus - the master command center for neural and endocrine coordination.

Peripheral Nervous System

Transmits signals between the CNS and receptors/effectors. Consists of 12paairs of cranial nerves that connect with the brain and 31 pairs of spinal nerves that connect with the spinal cord. The efferent system is further divided into a somatic and an autonomic system.

Somatic Nervous System

Innervates skeletal muscles. Consists of myelinated axons without any synapses. Activity of these neurons leads to excitation (contraction) of skeletal muscles and therefore they are called motor neurons. They are never inhibitory.

Autonomic nervous system

Innervates smooth and cardiac muscles. Parallel chains, each with two neurons, connect the CNS and effector cells. The synapse between these two neurons is called the autonomic ganglion, the nerve fibers between the CNS and the ganglion are called pre-ganglionic fibers and those between the ganglion and the effector cells are called post-ganglionic fibers.
Further divided into **sympathetic** (fight or flight) and **parasympathetic** (rest and relax) components.
Sympathetic ganglia lie close to the spinal cord while parasympathetic ganglia lie close to the organs. Sympathetic system is arranged to act as a single unit while parasympathetic system is arranged such that the parts can act independently. Sympathetic system is involved in responses to stress. Many organs and glands receive dual innervation from both sympathetic and parasympathetic fibers. The two systems generally have opposite effects and work together to regulate a response. Most autonomic responses usually occur without conscious control.

Blood Supply, Blood-Brain Barrier and Cerebrospinal Fluid

Neural tissue of the CNS is covered by 3 membranes called meninges - the outermost **dura mater**, the middle **arachnoid** and the inner **pia mater**. The space between the pia and the arachnoid, the subarachnoid space, is filled with **cerebrospinal fluid (CSF)**. It acts as a shock absorber for neural tissue.
The brain is highly dependent on a continuous supply of glucose and oxygen via blood. It has little stored glycogen.

Exchange of substances between blood and extracellular fluid in CNS is highly restricted via a complex group of blood-brain barrier mechanisms. The CSF and the extracellular fluid in the brain

are in diffusion equilibrium with each other but maintain a difference with the blood.

Sensory systems

The Sensory Systems

A sensory system is a part of nervous system consisting of sensory receptors that receive stimuli from internal and external environment, neural pathways that conduct this information to brain and parts of brain that processes this information. The information is called sensory information and it may or may not lead to conscious awareness. If it does, it can be called sensation.

Receptors
Specialized endings of afferent neurons or separate cells that affect ends of afferent neurons. They collect information about external and internal environment in various energy forms-and energy that activates a receptor is called a stimulus. Stimulus energy is first transformed into graded or receptor potentials and the process by which a stimulus is transformed into an electrical response is called stimulus transduction.
Each receptor is specific to a certain type of stimulus, which is called its adequate stimulus. Specificity also exists in the range of stimulus energies that the receptor responds to. However, a receptor can be activated by a nonspecific stimulus if its intensity is sufficiently high.

Receptor Potential
Gating of ion channels in specialized receptor membranes allows a change in ion fluxes across the membrane, generating a graded receptor potential. The graded potential initiates an action potential, frequency and NOT magnitude of which is determined by magnitude of the graded potential. Magnitude of the receptor potential is determined by stimulus strength, summation of receptor potentials, and receptor sensitivity. The decrease in sensitivity with a constant stimulus is called adaptation.

Neural Pathways in Sensory Systems
A single afferent neuron with all its receptor endings makes a sensory unit. When stimulated, this is the portion of body that leads to activity in a particular afferent neuron is called the receptive field of that neuron.
Afferent neurons enter the CNS, diverge and synapse upon many interneurons. These afferent neurons are called sensory or ascending pathways and specific ascending pathways if they carry information about a single type of stimulus. The ascending pathways reach the cerebral cortex on the side opposite to where their sensory receptors are located.
Specific ascending pathways that transmit information from somatic receptors and taste buds go to somatosensory cortex (parietal lobe), the ones from eyes go to visual cortex (occipital lobe), and the ones from ears go to auditory cortex (temporal lobe).
Olfaction is NOT represented in cerebral cortex.
Nonspecific ascending pathways consist of polymodal neurons and are activated by sensory units of several types. These pathways are important in alertness and arousal.
Cortical association areas, lying outside primary cortical sensory areas, participate in more complex analysis of incoming information such as comparison, memory, language, motivation, emotion etc.

Primary Sensory Coding

Sensory systems code 4 aspects of a stimulus:
(1) **Stimulus Type (modality)**. All receptors of a single afferent neuron are sensitive to the same type of stimulus.
(2) **Stimulus Intensity.** An increased stimulus results in a larger receptor potential,, leading to a higher frequency of action potential. Stronger stimuli also affect a larger area and recruit a larger number of receptors.
(3) **Stimulus Location.** Coded by site of the stimulated receptor. The precision of location, called **acuity**, is negatively correlated with the amount of convergence in ascending pathways, size of the receptive field and overlap with adjacent receptive fields. Response is highest at the center of receptive field since receptor density is the highest there. Using lateral inhibition, a process by which information from neurons at the edge of a stimulus is inhibited, acuity can be increased.
(4) **Stimulus Duration**. **Rapid adapting receptors** respond rapidly at the onset of stimulus but slow down or stop firing during the remainder of stimulus (they adapt quickly). They are important in signaling rapid change. Slow adapting receptors maintain their response at or near the initial level of firing through the duration of stimulus and are important in signaling slow changes.

Somatic Sensation
Sensations from skin, muscles, bone are initiated by somatic receptors. Receptors for visceral sensations are similar.

Touch-Pressure
Mechanoreceptors in the skin are of 2 types, rapid and slow adapting ones.

Posture and Movement
Muscle-spindle stretch receptors, occurring in skeletal muscles respond to the absolute magnitude and the rate of muscle stretch. Mechanoreceptors in joints, tendons, ligaments and skin also participate.

Temperature
Thermoreceptors are of two types, one that responds to an increase and the other that responds to a decrease in temperature.

Pain
Nociceptors respond to intense mechanical deformation, excessive heat etc. which cause tissue damage and many chemicals that are released by damaged cells or cells of immune system.
If the initial stimulus of pain leads to an increased sensitivity to subsequent painful stimuli it is called hyperalgesia. If descending pathways inhibit the transmission of pain stimuli, it leads to a suppression of pain and this is called stimulation-produced analgesia.
If both visceral and somatic afferent converge on the same interneuron, excitation of one can lead to excitation of the other, leading to the pain being felt at a site different from the actual injured part. This is called referred pain.
Stimulating non-pain afferent fibers can inhibit neurons in the pain pathway and this therapy is called transcutaneous electric nerve stimulation (TENS). Rubbing on a painful area and acupuncture work for the same reason.

Vision

Optics
Receptors in eye are sensitive to only the visible light of electromagnetic spectrum. Lens and cornea focus impinging light rays into an image at fovea centralis area of retina. Light passing from air into cornea is bent and the curved surface of cornea plays the major role in focusing. Changes in lens shape make adjustments (accommodation) for distance. Lens shape is controlled by zonular fibers that are in turn controlled by the smooth ciliary muscle. To focus on distant objects, the lens is pulled into a flattened oval shape. For near vision, the pull is removed

to make the lens more spherical and provide additional bending for light rays.
Cells of the lens lose their organelles and are therefore transparent. The lens become progressively opaque as newer cells replace older ones, which accumulate in the lens. This is called cataract.
If the lens loses its elasticity (due to age) and cannot assume a spherical shape, it leads to loss of near vision and this is called presbyopia.
If images of far objects focus at a point in front of retina, the eye is nearsighted or myopic and far vision is poor. If images of near objects focus at a point behind retina, the eye is farsighted or hyperopic and near vision is poor. If the lens or cornea is not smooth, it is called astigmatism.
The lens separates an anterior chamber filled with aqueous humor and a posterior chamber filled with vitreous humor. If aqueous humor is formed faster than it is removed, it results in an increased pressure within the eye. This can cause irreversible blindness with the death of optic nerves and it is called glaucoma.
The pigmented, opaque iris that has a central hole, the pupil, controls amount of light entering the eye. The iris has smooth muscles, innervated by autonomic nerves. Stimulation of the sympathetic nerves dilates the pupil to let in mare light when light is poor and stimulation of the parasympathetic nerves constricts the pupil to allow in less light when light is bright.

Photoreceptor Cells

Rods - sensitive and responding to low light and cones - less sensitive and responding to bright light. There are three kinds of cones containing red-, green-, or blue sensitive pigment.
Photoreceptors contain photopigments, which absorb light. There are 4 photopigments, rhodopsin in the rods and one in each of the 3 cone types. Each photopigment contains an integral membrane protein, opsin, which binds a light sensitive chromatophore molecule. The chromatophore - retinal (a derivative of vitamin A) is the same in all the 4 photopigments. The opsin is different in each type of photopigment, absorbing light at different wavelengths of the spectrum.
Light activates retinal, causing it to change shape and triggering a hyperpolarization in the bipolar cells, which synapse with the photoreceptor cells. After its activation, retinal changes back to its resting shape by light-independent mechanisms and the photoreceptor cell is depolarized

Neural Pathways
Photoreceptor cells synapse with neurons called bipolar cells which, in turn, synapse with ganglion cells that produce the first action potentials in the chain. Axons from ganglion cells form the optic nerve, which crosses over to the opposite side of the optic chiasm.

Sound Transmission in the Ear

Outer Ear (Pinna/Auricle) - Directs and amplifies sound waves.

External Auditory Canal –the ear canal leading from the outside to the middle ear cavity
Tympanic membrane (Eardrum) - Vibrates at the frequency of sound waves.
Middle Ear Cavity - Filled with air. Has a movable chain of 3 bones, the malleus, incus and stapes that couple and amplifies the vibrations in the tympanic membrane to the
Oval window- a membrane covered opening separating the middle ear and the
Inner Ear (cochlea)
Scala vestibuli - Filled with fluid
Cochlear duct - Lined by the basilar membrane upon which sits the organ of Corti containing the receptor cells.

Organ of Corti
Receptor cells of the organ of Corti, the hair cells, are mechanoreceptors that have hairlike stereocilia. Vibration of the basilar membrane. with which the hair cells are attached. stimulates

the hair cells and the pressure waves are transformed into receptor potentials.

Neural Pathways
Afferent neurons from the hair cells form the cochlear nerve.

Hearing
Entire audible range extends from 20 to 20,000 Hz.

Vestibular System
A series of fluid filled tubes in the inner ear that connect with each other and the cochlear duct containing hair cells that detect changes in motion
2 Parts:

Semicircular Canals
Detect angular acceleration during rotation of the head along the three axes.

Utricle and Saccule
Provide information about linear acceleration and changes in head position relative to gravity.

Vestibular Information
Information from hair cells in the vestibular apparatus is transmitted to the parietal lobe and is integrated with information from other parts of body, leading to sense of posture and movement. Unexpected inputs from the vestibular system leads to vertigo or motion sickness.

Chemical Tastes

Taste
Taste buds found on the tongue respond to 4 basic modalities, sweet, sour, salty and bitter. Each groups has a distinct transductional system. Organized into independent pathways but a single receptor cell may respond to more than one taste category in various degrees.
Smell
Odor is related to chemical structure of a substance. Olfactory receptor cells lie in the olfactory epithelium in upper part of nasal cavity. These cells have several long, non-motile cilia, which contain binding sites for olfactory stimuli. Each cell contains one type of receptor. Axons of olfactory receptor cells of same specificity synapse together. Information is passed into the olfactory cortex in the limbic system.

Principles of Hormonal Control Systems

Principles of Hormonal Control Systems

Hormones are chemical messengers that enter the blood directly upon their secretion from endocrine glands. A single gland or cell may secrete multiple hormones and multiple glands may secrete the same single hormone.

Three broad classes of hormones:

1. **Amine Hormones** - Derivative of the amino acid tyrosine.
    a. **Thyroid Hormones** - Thyroid gland is located in the lower neck, wrapped around the trachea. Consists of follicles that secrete the two iodine containing hormones

thyroxine (T4) and triiodothyronine (T3). These thyroid hormones (TH) regulate oxygen consumption, growth and brain development. T4 is secreted in larger amounts but is mostly converted to T3, the more active form.

b. **Adrenal Medullary Hormones** - There are 2 adrenal glands, one on top of each kidney. Each gland has 2 endocrine parts, an inner adrenal medulla and a surrounding adrenal cortex. The medulla secretes epinephrine (E) and norepinephrine (NE) which are catecholamines. These hormones exert actions similar to those of sympathetic nerves. More epinephrine than norepinephrine is secreted.

2. **Peptide Hormones** - The majority of hormones. Initially synthesized as larger preprohormones that are then cleaved to prohormones in the ER. The prohormone is then cleaved to the active hormone in the golgi. These hormones may also serve as neurotransmitters. Calcitonin, a peptide hormone secreted by parafollicular cells of thyroid gland, participates in the regulation of blood Ca^{2+} level.

3. **Steroid Hormones**- Produced by the adrenal cortex and the gonads.
   a. **Adrenal Cortex Hormones**

      Aldosterone participates in mineral balance (mineralocorticoid) by controlling the handling of Na+, K+, and H+ ions by the kidney.
      Cortisol and corticosterone affects the metabolism of glucose (glucocorticoid) and other organic nutrients. Cortisol also affects stress responses and regulation of the immune system.
      Adrenal androgens are less potent than the other androgen, testosterone. Play some role at puberty and some in the adult female.

   b. **Hormones of the Gonads** - Testosterone is the major androgen secreted by the testes. The major female hormone, estradiol, secreted by the ovaries, is derived from androgens.

Hormone Transport in Blood
Water-soluble hormones are transported dissolved in blood plasma while others circulate in blood, bound to plasma proteins. The free hormone diffuses across capillary walls to encounter its target cells.

Hormone Metabolism and Excretion
Concentration of a hormone in plasma depends upon its rate of secretion and rate of removal. Hormones are either excreted by kidneys or metabolized in blood or the target cells.

Mechanisms of Hormone Action
Hormones reach all tissues via blood but only cells that have receptors to bind the hormone act as target cells for the hormone.
A low concentration of hormone is compensated for by an increase in the number of receptors - up-regulation while a high concentration of hormones leads to a decrease in the number of receptors - down-regulation.
A hormone can reduce the number of receptors available for a second hormone, resulting in decreased effectiveness of the second hormone (antagonism). A hormone can also induce an increase in the number of receptors for a second hormone, increasing the latter's effectiveness

(permissiveness).

Events Elicited by Hormone-Receptor Binding
Receptors for peptide hormones and catecholamines are present on the extracellular surface of the plasma membrane while those for steroid and thyroid hormones are mainly present on the intracellular surface of the membrane.
Hormone-receptor binding influences (1) ion channels, (2) enzyme activity that is part of the receptor, (3) activity of JAK kinases, (4) G proteins and second messengers. Genes could also be activated or inhibited, causing a change in the synthesis rate of proteins coded for by these genes

Control of Hormone Secretion

Control by Plasma Concentrations of Specific Substances
Plasma concentrations of specific ions or nutrients may control the secretion of a hormone and the hormone may in turn control the concentration of its regulators in a negative feedback manner.

Control by Neurons
Secretion of some hormones may be under the control of autonomic or central nervous system

Control by Other Hormones
Hormones called tropic hormones may control the secretion of other hormones.

Control System Involving the Hypothalamus and Pituitary
Pituitary gland (hypophysis) lies below the hypothalamus and is connected to it by the infundibulum. The pituitary has 2 lobes:
(1) Posterior pituitary (**neurohypophysis**) - A neural extension of the hypothalamus. Posterior pituitary hormones are actually produced in the hypothalamus but are stored in the posterior pituitary. The hormones (a) oxytocin stimulates contraction of smooth muscles in breasts and uterus of females and (b) vasopressin (antidiuretic hormone or ADH) participates in control of water excretion and regulates blood pressure.
(2) Anterior pituitary (**adenohypophysis**) - Connected to hypothalamus by blood vessels called hypothalamo-pituitary portal vessels. Hypothalamic hormones called hypophysiotropic hormones control the secretion of anterior pituitary hormones (all peptides), which in turn control the secretion of other hormones from other endocrine glands. The adaptive value of such a chain of control is that it allows more precise feedback control.
Thyroid stimulating hormone (TSH, thyrotropin) induces secretion of T4 and T3 from the thyroid. Adrenocorticotropic hormone (ACTH) stimulates secretion of cortisol by the adrenal cortex. The gonadotropins, Follicle stimulating hormone (FSH) and lutenizing hormone (LH) stimulate secretion of estradiol and progesterone from ovaries and testosterone from testes, as well as regulate the growth and development of ova and sperm. Growth hormone (GH) stimulates the liver to secrete a growth hormone called insulin-like growth factor I (IGF-I), and exerts direct effects on metabolism. Prolactin does not exert control over the secretion of another hormone but stimulates development of mammary glands and milk production in females.

Hypophysiotropic Hormones
These hormones are secreted by neurons in response to action potentials. Each of these hormones is named after the anterior pituitary hormone that it controls. Corticotropin releasing hormone (CRH) stimulates the secretion of ACTH. Growth hormone releasing hormone (GHRH) stimulates the secretion of GH. Thyrotropin releasing hormone (TRH) stimulates the secretion of TSH or thyrotropin. Gonadotropin releasing hormone (GnRH) stimulates the secretion of gonadotropins (FSH and LH). Somatostatin (SS) inhibits secretion of GH. Prolactin-inhibiting hormone (PIH) inhibits secretion of prolactin.

Feedback Control of the Hypothalamus and Anterior Pituitary
If the last hormone in a chain of control can exert a negative feedback on the hypophysio-pituitary system, it is called long-loop negative feedback. If an anterior pituitary hormone exerts a negative feedback effect on the hypothalamus, it is called short-loop negative feedback. Seen for pituitary hormones that do not influence other endocrine glands.

Candidate Hormones
Candidate hormones do not fit the classical description of hormones because:
(1) Their functions are not conclusively documented, e.g., melatonin produced by the pineal gland probably plays an important part in circadian rhythms and sleep.
(2) They act as agents but it is not certain if they reach the
target cells via paracrine/autocrine blood, e.g., growth factors

Endocrine Disorders
(1) Hyposecretion - If a gland is secreting too little hormone because it itself is unable to function normally, the disorder is called primary hyposecretion. Causes could be genetic lack of an enzyme, dietary deficiency of a precursor, infection etc.
If a gland is secreting too little hormone because there is too little tropic hormone to stimulate it, the disorder is called secondary hyposecretion.
(2) Hypersecretion - Primary hypersecretion is a gland itself secreting too much hormone while secondary hypersecretion is the excessive stimulation of a gland by its tropic hormone.
(3) Hyporesponsiveness - Target cells do not respond to the hormone due to a deficiency of receptors, a defect in the signal transduction mechanism or a deficiency of an enzyme that catalyzes the activation of the hormone. In diabetes mellitus, the target cells of the hormone insulin are hyporesponsive.
(4) Hyperresponsiveness - Hypersecretion of thyroid hormones can lead to hyperresponsiveness to epinephrine and a consequent increase in heart rate.

Muscle

Muscle

Muscle cells are specialized to generate force and movement. There are three types of muscle tissue: (1) skeletal muscle, (2) smooth muscle, and (3) cardiac muscle.

Skeletal Muscle
Attached to the bone and moves them by contraction. The contraction is initiated by neural impulses and is under voluntary control.

Structure
A muscle consists of a number of muscle fibers bound together by connective tissue and it is attached to a bone by collagen bundles called tendons. A single muscle fiber is a multinucleated cell and is formed from myoblasts during development. After infancy, new fibers are formed only from undifferentiated satellite cells and any compensation for lost muscles in adulthood occurs mostly through an increase in the size of fibers.
Skeletal muscle cells have longitudinal bundles called myofibrils in the cytoplasm. Each myofibril consists of a repeating unit called sarcomere. Each sarcomere has a band of thick filaments in the middle called the A band, and they are flanked on both sides by thin filaments. One end of the thin filaments is anchored to the Z line in the I band which separates adjacent sarcomeres and the other end partially overlap the thick filaments. Due to the banded pattern provided by thin and thick filaments, skeletal muscle is also called striated muscle.

Central region of the sarcomere where there is no overlap between thin and thick filaments is called the H zone. A band called the M line, in center of the H zone, link the center regions of thick filaments. Titin protein fibers from the Z line are linked to the M line and the thick filaments. Space between overlapping thick and thin filaments is bridged by projections called cross bridges from the thick filaments. In a cross section, each thick filament is surrounded by a hexagonal array of six thin filaments and each thin filament is surrounded by a triangular array of three thick filaments. Thick filaments contain the contractile protein, myosin. Thin filaments contain the contractile protein, actin and two other proteins, troponin and tropomyosin.

Molecular Mechanisms of Contraction
Each actin molecule contains a binding site for myosin. Each myosin molecule contains a binding site for actin and one for ATP.

Sliding-Filament Mechanism
Muscle contraction is produced by cross bridge cycles. A cycle has 4 steps:
(1) Energizing of myosin cross bridge
A + M•ATP —> A + M*•ADP•Pi (ATP is energizer here)
(2) Attachment of cross bridge to a thin filament
A + M*•ADP•Pi —> A•M*•ADP•Pi
(3) Movement of cross bridge, producing tension
A•M*•ADP•Pi —> A•M + ADP + Pi
(4) Detachment of cross bridge from thin filament
A•M + ATP —> A + M•ATP (ATP is modulator here)
Movement of the cross bridges make the overlapping thick and thin filaments slide past each other (they do not change in length) to produce a contraction.

Roles of Troponin, Tropomyosin and Calcium
In a resting muscle fiber, the protein tropomyosin, held by troponin, covers the myosin-binding sites on actin and prevents cross bridges from making contact with actin.
An action potential releases Ca^{2+} from the sarcoplasmic reticulum of the cell and increases cytosolic concentration of a Ca^{2+} in the muscle fiber. When Ca^{2+} binds to troponin, it removes tropomyosin from the myosin-binding site and makes it possible for cross bridges to attach with actin.

Sarcoplasmic Reticulum
The sarcoplasmic reticulum is homologous to endoplasmic reticulum. Forms a sleeve around each myofibril. Has enlarged regions called lateral sacs that store Ca^{2+}, and a tubular structure called transverse (T) tubule. Depolarization of the plasma membrane leads to depolarization of the T-tubule and opens the Ca^{2+} channels of the lateral sacs. To end contraction, Ca^{2+} is pumped back into the lateral sacs by active transport proteins called Ca-ATP-ases.

Neuromuscular Junction
Nerve cells that innervate skeletal muscle fibers are called motor (somatic efferent) neurons. These neurons have cell bodies in the CNS and large, myelinated axons that can propagate action potentials at high velocities. At a muscle, the axon gives branches to many muscle fibers but each fiber gets only one branch. A motor neuron and the fibers it innervates are together called a motor unit. The region of muscle-fiber plasma membrane lying directly under the axon is called the motor end plate and the junction is called the neuromuscular junction.
Axon terminals of a motor neuron contain vesicles filled with acetylcholine (ACh). An action potential opens Ca^{2+} channels in the nerve plasma membrane and Ca^{2+} diffuses in to enable these vesicles to fuse with the plasma membrane and release ACh in the extracellular space. ACh opens ion channels in the motor end plate and produces a depolarization called end plate potential (EPP).
The enzyme acetylcholinesterase on the motor end plate breaks down ACh to close the ion channels and return the plate to resting potential.

Mechanics of a Single Fiber Contraction
Force exerted on an object by a contracting muscle is called muscle tension, and the force exerted on the muscle by the object (weight) is called load. These are opposing forces and whether exertion of force leads to fiber shortening depends on relative magnitudes of tension and load. For fibers to shorten and move a load, tension must be greater than load.
When a muscle develops tension but does not shorten, the contraction is called isometric (constant length). Seen when muscle supports a load in constant position or attempts to move a supported load that is greater than the tension. During such a contraction, the bound cross bridges do not move.
A contraction in which the muscle shortens while load remains constant is called isotonic (constant tension). In such a contraction, the cross bridges bound to actin move, shortening the fibers. Before an isotonic shortening, there is a period of isometric contraction during which tension increases.
A lengthening (eccentric) contraction occurs when a load on a muscle is greater than the tension and the load lengthens the muscle. Not an active process but a result of external force on the muscle. In a lengthening contraction, cross bridges are pulled toward the Z line.

Twitch Contraction
Mechanical response of a single muscle fiber to a single action potential. Following the action potential, there is a latent period, before the tension in muscle fiber increases. Time interval from beginning of tension development and peak tension is called contraction time.
Latent period is longer in an isotonic twitch than in an isometric twitch while duration of contraction is longer in an isometric twitch than in an isotonic twitch. Latent period is positively correlated while velocity of shortening, duration of twitch and distance shortened are negatively correlated with load.

Frequency-Tension Relation
Increase in muscle tension from successive action potentials is called summation and a maintained contraction in response to repetitive stimulation is called tetanus. If a tetanus oscillates, it is called unfused tetanus while a tetanus without oscillations is called fused tetanus.

Length-Tension Relation
Passive tension in a relaxed fiber increases with increased stretch due to the elongation of titin filaments. Magnitude of active tension during contraction depends on the passive tension of a fiber because the potential for cross bridge formation is different at different overlaps between actin and myosin filaments. The length at which the fiber develops the greatest active tension is called optimal length, l_0. In a relaxed state, the length of most fibers is near l_0.

Skeletal Muscle Energy Metabolism
Muscle glycogen is the major fuel at initial stages of exercise and is followed by utilization of blood glucose and fatty acids.
A muscle fiber generates ATP by:
(1) Phosphorylation of ADP by creatine phosphate. Source of ATP during the initial phase of contraction. Followed by the slower pathways of:
(2) Oxidative phosphorylation in mitochondria
(3) Glycolysis in cytosol. This pathway provides a majority of the energy and lactic acid is produced.
At the end of muscle activity, creatine phosphate and glycogen levels are restored by energy-dependent processes, leading to a continued elevated level of oxygen consumption, called oxygen debt, even after exercise is over.

Muscle Fatigue
Decline in muscle tension as a result of previous contractile activity. A fatigued muscle also has decreased shortening velocity and slower rate of relaxation. Onset and rate of fatigue depend on

type of skeletal muscle and duration of contractile activity. If a fatigued muscle is allowed to rest, it recovers. Rate of recovery depends on duration and intensity of previous exercise. Fatigue is not due to low ATP since a fatigued muscle still has quite high concentration of ATP. Fatigue may be an adaptation to prevent rigor that will result from very low ATP level.
High frequency fatigue accompanying high intensity, short duration exercise is due to failure in the conduction of action potential in the T tubule. Recovery from such fatigue is rapid. Low frequency fatigue seen with low intensity, long duration exercise is due to the build up of lactic acid, which changes the conformation of muscle proteins. Recovery from such fatigue is slow.

Types of Skeletal Muscle Fibers
(1) **Fast fibers** contain myosin with high ATPase activity and therefore have high shortening velocity. Fatigue rapidly.
(2) **Slow fibers** contain myosin with low ATPase activity and therefore have low shortening velocity. Fatigue slowly.
(3) **Oxidative fibers** have numerous mitochondria and therefore a high capacity of oxidative phosphorylation. ATP production is dependent on blood borne oxygen and fuel.
Also contain an oxygen binding protein called myoglobin, which increases rate of oxygen diffusion into the fiber. This protein gives the fibers a red color and therefore these fibers are also called red muscle fibers.
Glycolytic fibers have few mitochondria but a high concentration of glycolytic enzymes and glycogen. Have a pale color and therefore are also called white muscle fibers. Larger and have more thick and thin filaments and therefore can develop more tension. Fatigue rapidly.
Three types of skeletal fibers: (I) Slow-oxidative fibers, (2) Fast-oxidative fibers and (3) Fast-glycolytic fibers. Most muscles contain all three kinds of fibers.

Whole Muscle Contraction

Control of Muscle Tension
Total tension a muscle can develop depends on
(1) Amount of tension developed by each fiber and
(2) Number of fibers contracting at any time, which in turn depends on
(a) Number of fibers in each motor unit (motor unit size) and
(b) Number of active motor units. Increasing the number of active motor units in a muscle, called recruitment, is achieved by increasing excitatory input to the motor neurons. Finer control of muscle tension is possible in muscles with small motor unit size.

Muscle Adaptation to Exercise
Increased amount of contractile activity (exercise) increases size (hypertrophy) of muscle fibers and capacity for ATP production. Low intensity exercise affects oxidative fibers, increasing the number of mitochondria and capillaries. High intensity exercise affects glycolytic fibers, increasing their diameter by an increased synthesis of actin and myosin filaments, and an increased synthesis of glycolytic enzymes.

Lever Action of Muscles and Bones
A contracting muscle exerts a pulling force and moves the bones. If this leads to a limb bending at a joint, it is called flexion while if it leads to a limb straightening from a joint, it is called extension. Groups of muscles producing opposite movements at a joint are called antagonists.

Skeletal Muscle Disease
Poliomyelitis leads to paralysis of skeletal muscles due to destruction of motor neurons by a virus. Muscular dystrophy is progressive degeneration of skeletal and cardiac muscle fibers due to a low amount of the protein dystrophin that maintains the structural integrity of plasma membrane during stretching. It is a sex-linked recessive disease. Myasthenia gravis leads to muscle fatigue due to low number of ACh receptors on the motor end plate.

Smooth Muscle
Lack the banded structure of skeletal muscles. Controlled by the autonomic nervous system and is not under voluntary control.

Structure
A smooth muscle fiber is a spindle-shaped, uninucleate cell. Has the capacity to divide throughout life. The thick and thin filaments are not regularly aligned in into sarcomeres but are oriented diagonally to the long axis of the cell. Thin filaments are attached to plasma membrane or to cytoplasmic structures called dense bodies. Concentration of myosin is low and that of actin is high.

Contraction
Thin filaments do not have troponin. As cytosolic Ca2+ concentration increases,
(1) Calcium binds to calmodulin, a protein
(2) Calcium-calmodulin complex binds to the enzyme, myosin light-chain kinase and activates it
(3) The active kinase uses ATP to phosphorylate the myosin cross bridges
(4) The phosphorylated cross bridges bind to actin
(5) Myosin is dephosphorylated by myosin light-chain phosphatase
ATPase activity is low and therefore cross bridge cycling and muscle shortening is slow. Dissociation of dephosphorylated cross bridges is slow and therefore the muscle can maintain tension with very low ATP consumption. Does not undergo fatigue during prolonged periods of activity. Range of muscle lengths over which tension can be developed is greater.

Sources of Cytosolic Calcium
(1) Sarcoplasmic reticulum - Does not have T-tubules.
(2) Extracellular calcium - Opening of Ca^{2+} channels in the plasma membrane.
Rate of Ca^{2+} removal is slower with the result that a twitch lasts longer. Concentration of Ca^{2+} in response to a single action potential is only sufficient enough to activate a proportion of cross bridges. Therefore, tension in smooth muscle can be graded by varying cytosolic Ca^{2+} concentration. A low-level tension is always maintained, even in absence of external stimuli, and this is called smooth-muscle tone.

Membrane Activation
Plasma membrane of smooth muscles receives both excitatory and inhibitory inputs and the contractile state of the muscle depends on the relative intensity of both.
Some smooth muscle fibers generate action potentials spontaneously in the absence of any input. The potential change occurring during such spontaneous depolarization is called pacemaker potential.
Smooth muscles do not have motor end plates. The postganglionic autonomic neuron divides into branches in the smooth muscle fibers, and each branch has a series of swollen regions called varicosities, which contain vesicles filled with neurotransmitter that is released when an action potential arrives. The same neurotransmitter can produce an excitation in one fiber and inhibition in the other. Varicosities from a single axon may innervate several fibers and a single fiber may receive varicosities from both sympathetic and parasympathetic neurons.
Smooth muscle plasma membrane also binds hormones and respond to them. Paracrine agents, acidity, oxygen concentration, osmolarity, ion composition can also influence smooth muscle tension, providing a response mechanism to local factors.

Types of Smooth Muscle

(1) Single-unit Smooth Muscle
All the fibers undergo synchronous activity because adjacent fibers arc linked by gap junction d action potential occurring anywhere is propagated to all other cells. The whole muscle responds to stimulation as a single unit. Some of the fibers may be pacemaker cells and they can control

the contraction of the entire muscle a majority of which may consist of non-pacemaker cells. The nerve terminals therefore need to be restricted only to the pacemaker cells.
(2) Multi-unit Smooth Muscle
Each fiber responds independently of its neighboring fibers because there are no connecting gap junctions.

Control of body movement

Control of Body Movement

Motor Control Hierarchy
A motor program is the pattern of neural activities required to perform a movement is created and transmitted via neurons that are organized in a hierarchical manner. The program is continuously updated. Learning and skill can develop if the program is repeated frequently enough.

Voluntary and Involuntary Actions
Voluntary movement is accompanied by a conscious awareness of the action while involuntary movement is not. All motor behaviors lie in a continuum and have both components in different degrees.

Local Control of Motor Neurons
Important in keeping the motor program updated by gathering information from local levels through afferent fibers.

Interneurons
Interneurons are synapses that integrate inputs from both higher centers and peripheral receptors.

Local Afferent Input
Afferent inputs to local interneurons bring information about tension of muscles, movement of joints etc. that in turn influence movements.

Length-Monitoring Systems
Changes in muscle length and rate of these changes are monitored by stretch receptors located within structures called muscle spindles that are present in modified muscle fibers called intrafusal fibers. (Rest of the fibers responsible for the force of a muscle are called extrafusal fibers.) Stretching a muscle fires these receptors while contraction of the muscle slows the firing of these receptors.
Afferent fibers from these receptors can take 4 pathways:

1. Some fibers go back directly to motor neurons of the same muscle without interposition of any interneurons and these arcs are called monosynaptic stretch reflex arcs.
2. Some fibers end on interneurons that inhibit the antagonistic muscles and this is called reciprocal innervation.
3. Some fibers activate motor neurons of synergistic muscles.
4. Some fibers continue to the brainstem.

Alpha-Gamma Coactivation
The larger motor neurons that control the extrafusal fibers are called alpha motor neurons and the

smaller- motor neurons that control the intrafusal fibers are called gamma motor neurons. These neurons are excited or coactivated at the same time to get continuous information about muscle length.

Tension-Monitoring Systems
Receptors located in the tendons called Golgi tendon organs monitor the tension on a muscle.

Withdrawal Reflex
If a stimulus activates flexor motor neurons and inhibits extensor motor neurons, moving the body away from the stimulus, it is called a withdrawal reflex. The effect is produced on the same side of the body where the stimulus arose (ipsilateral side) and an opposite effect may be produced on the other side (contralateral side) to compensate for any lost support due to the withdrawal. This is crossed-extensor reflex.

Muscle Tone
Passive resistance of skeletal muscle to stretch due to some degree of alpha motor neuron activity and the viscoelastic properties of the muscle. Abnormally 1ight muscle tone called hypertonia can result in brief spasms, prolonged cramps or constant rigidity.

Maintenance of Upright Posture and Balance
Coordinated muscular activities support the skeleton and the upright posture. The afferent pathways of postural reflexes come from: (1) the eyes, (2) the vestibular apparatus (3) the somatic receptors. There are brain centers that coordinate this information and compare it with an internal representation of the body's geometry. The efferent pathways are the alpha motor neurons to the skeletal muscles.

Walking
Requires the coordination of many muscles. Extensor muscles are activated on one side to support the body's weight and the contralateral extensors are inhibited by reciprocal inhibition to allow the nonsupporting limb to flex and swing forward.

Consciousness and behavior

Consciousness and Behavior

States of Consciousness
Defined either by (1) behavior - ranging from attentive and alert to coma and (2) electrical pattern of brain activity, recorded as an electroencephalogram (EEG).

Electroencephalogram
The electric potential difference between two points on the scalp. The amplitude indicates degree of synchronous activity and frequency indicates responsiveness (low frequency = sleep to high frequency = alert).

Wakeful State
The high frequency, low amplitude wave pattern of an awake relaxed adult is called the alpha rhythm. As people become more attentive, the wave pattern becomes low amplitude, high frequency oscillations called the beta rhythm. This transformation is called EEG arousal.

Sleep
Has 2 phases:

(1) The longer **NREM (non-rapid eye movement) sleep**, which shows a high amplitude-low frequency wage pattern. Growth hormone and gonadotropic hormones are released. Blood pressure, heart and respiratory rates decrease.
(2) **REM (rapid eye movement) sleep**, which shows a wave pattern similar to the awake state - the reason it is also called paradoxical sleep. Skeletal muscle tension is decreased during this phase except that in the eye and the respiratory muscles. Blood pressure, heart and respiratory rates increase.

Neural Substrates of States of Consciousness
Periods of sleep and wakefulness show a circadian or daily rhythm, the clock timing of which depends on the suprachiasmatic nucleus. Aminergic neurons that release norepinephrine or serotonin are dominant during wakefulness while cholinergic neurons are dominant during REM sleep. NREM sleep is intermediate to these two states.

Coma and Brain Death
Coma is a severe decrease in mental function due to structural, physiological or metabolic impairment of the brain. A person in coma is characterized by a sustained loss of capacity for arousal even in response to vigorous stimulation. There is no outward behavioral expression of any mental function and sleep-wake cycles disappear. Brain death is irreversible coma without drug intoxication. There should not be any functioning neural tissue above the spinal cord.

Conscious Experiences
Sensory awareness and awareness about mental representations

Directed Attention
Avoidance of irrelevant stimuli and focusing on relevant stimuli is called directed attention. Preattentive processing of information directs attention toward meaningful stimuli before we focus on them. Focusing is possible without making any behavioral response. If it is followed by orientation toward the stimulus source, it is called orienting response. If the behavioral response to the stimulus progressively decreases as it is found to be irrelevant, it is called habituation.

Neural Mechanisms for Directed Attention
Directing attention to an object involves 3 neurological processes:

1. Disengaging attention from present focus,
2. Moving attention to new focus
3. Engaging attention to new focus Brainstem plays an important role in the orienting response. The locus ceruleus, a-nucleus in the brainstem, directs the information to particular areas in the brain. Cerebral cortex is involved in the perception of the stimulus.

Motivation and Emotion

Motivation
Motivation is responsible for goal-directed behavior. Motivation leads to hormonal, autonomic or behavioral responses. Behavior related directly to homeostasis is called primary motivated behavior. If relation between the behavior and the goal is indirect, it is secondary motivated behavior and this is influenced by factors called incentives such as habit, learning etc. Motivations may be shaped by rewards (positive reinforcers) or punishments (negative reinforcers). The mesolimbic dopamine pathway is involved in the motivation process.

Emotion
An individual's assessment of the environment and their disposition to it. Amygdala, a cluster of nuclei on the temporal lobe, are central to emotional states.

Altered States of Consciousness

Schizophrenia
Information is not properly regulated in the brain. Motor control is abnormal. Dopamine pathways are overactive.

Mood Disorders: Depressions and Bipolar Disorders
Mood is sustained inner emotion that affects the person's perception of the world. Depressive disorders are indicated by loss of energy, interest and anxiety. Bipolar disorders are swings between depression and mania -an abnormally elated mood. Can be treated by electroconvulsive therapy (ECT) in which pulses of electric current are used to activate a large number of neurons and alter neurotransmitter function to down-regulate some postsynaptic receptors.

Psychoactive Substances, Dependence and Tolerance
Psychoactive substances exert their actions by altering neurotransmitter-receptor interactions. Psychological dependence is a craving for a substance and an inability to stop. Physical dependence requires one to take the substance to avoid withdrawal physiological symptoms occurring with cessation of substance use. Tolerance to a substance occurs when increasing doses of a substance are required to achieve the desired effect. Cross-tolerance is development of tolerance to one substance due to use of another.

Learning and Memory
Learning is the acquisition and storage of information as a consequence of experience. Measured y an increase in likelihood of a particular behavior in response to a stimulus. Rewards and punishment influence learning.

Memory
Permanent stored form of learned information. Processes that mediate between learning and memory are called memory encoding. Two types: (1) Declarative memory is knowledge of one's past experience or the world. Limbic system is important for this type of memory. (2) Non-declarative memory is memory for performance of skilled behaviors. Sensorimotor cortex, basal ganglia, and cerebellum are important for this type of memory.

Working Memory
Working memory is the primary or short-term memory that registers and retains information for a very short time. Makes possible a temporary impression of one's present environment in a readily accessible form. Focusing attention is important for memory-based skills.

Cerebral Dominance and Language
In the majority of population, the left cerebral hemisphere is specialized to produce language. Distinct areas are specialized for different language skills. During development, assignment of language functions can take place in either hemisphere but it progressively shifts to the left. Although language skills emerge spontaneously in all children, they must be exposed to language during a critical period. Verbal memory is associated with the left hemisphere and nonverbal memory is associated with the right.

Circulation

Circulation

BLOOD
Composed of a liquid, plasma, suspended with the cells erythrocytes (red blood cells) leukocytes (white blood cells) and platelets (cell fragments). Hematocrit is the percentage of blood volume occupied by the erythrocytes.

Plasma
Consists of a number of inorganic and organic substances - nutrients, metabolic wastes, hormones dissolved in water. Also contains bilirubin, - a product of hemoglobin breakdown, the proteins, albumin- synthesized by liver and the most abundant ones, globulins and fibrinogen - functioning in clotting. Plasma from which all proteins have been removed is called serum.

Blood Cells

(1) Erythrocytes
Carry oxygen and carbon dioxide by binding them with iron in hemoglobin. Have a high surface-to-volume ratio. Plasma membrane has surface proteins and polysaccharides that confer blood group. Reticulocytes, produced in the soft interior of bones, called bone marrow, lose their cell organelles and enter the circulation as erythrocytes. Degraded at end of their lives in liver and spleen. Iron, folic acid and vitamin B12 are important constituents.
Iron - Homeostatic control of iron balance resides in intestinal epithelium. Iron is stored in liver as ferritin. Iron released from degraded erythrocytes is carried to bone marrow by plasma protein transferrin, and incorporated into new erythrocytes.
Regulation of Erythrocyte Production - Erythrocyte production is stimulated by a hormone called erythropoietin, secreted mainly by kidneys.
Anemia- A decrease in the ability of blood to carry oxygen due to (1) a decrease in total number of erythrocytes or (2) a lower concentration of hemoglobin per erythrocyte or
(3) a combination of both.
Sickle cell anemia results in abnormal shape of hemoglobin due to a genetic mutation. Results in a blockage of capillaries.
Polycythemia is an excess of erythrocytes that results in a lower flow of blood in capillaries.

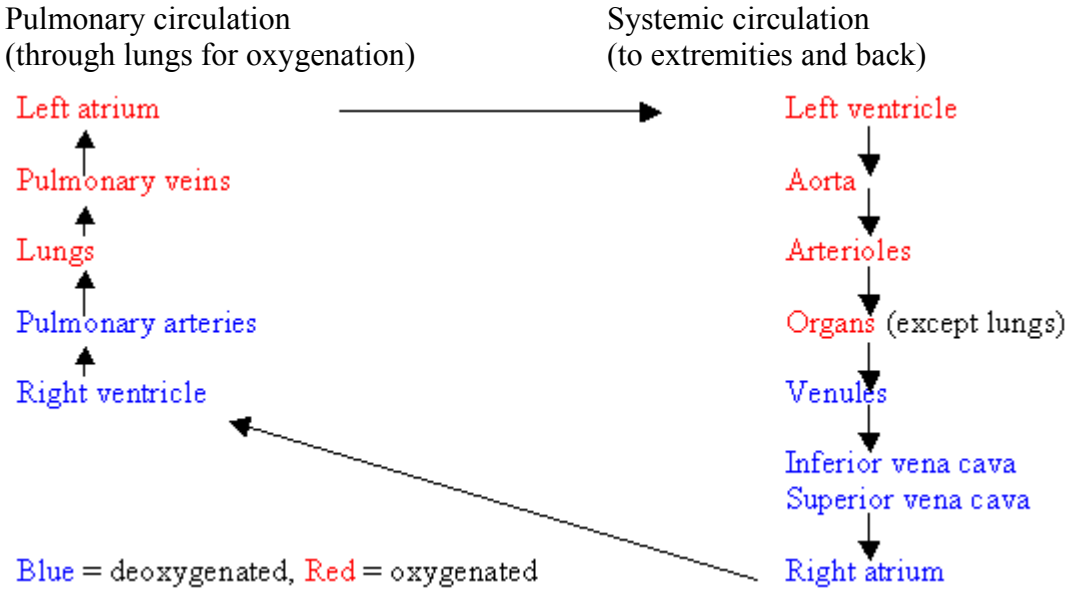
(2) Leukocytes
Consists of 3 types of polymorphonuclear granulocytes (have multilobed nuclei and granules) - (a) eosinophils, (b) basophils and (c) neutrophils (most abundant), monocytes and lymphocytes. All leukocytes are produced in bone marrow. Participate in body defense.

Platelets
Platelets are colorless cell fragments that enter circulation when cytoplasmic portions of bone marrow cells called megakaryocytes are pinched off. Their primary function is in the blood clotting process.

Regulation of Blood Cell Production
In children, marrow of most bones produces blood cells while in adults only bones of upper body produce blood cells. All blood cells are descended from single population of bone marrow cells called pluripotent hematopoietic stem cells. These cells can divide into either (1) pluripotent stem cells or (2) lymphoid stem cells that gives rise to lymphocytes or (3) myeloid stem cells that gives rise to all other types of blood cells. Division and differentiation of these cells are regulated by protein hormones and paracrine agents, collectively called hematopoietic growth factors (HGFs).

Design of Cardiovascular System
Rapid flow blood in one direction is called bulk flow, produced by pumping action of the heart.

The high branching of blood vessels ensures the proximity of all cells to some capillaries. Nutrients and metabolic end products move between capillary blood and interstitial fluid by diffusion.
The heart is longitudinally divided into 2 halves: left and right, and each half contains two chambers: the upper atrium and the lower ventricle. The atrium on each side is connected to the ventricle on that side but there is no connection between the two atria or the two ventricles. Blood is pumped out of heart through one set of vessels and returns to heart via another set. Vessels carrying blood away from heart are called arteries while those carrying blood toward heart are called veins.



Pressure, Flow, and Resistance
Blood flows from a region of high to a region of low pressure and rate of blood flow (F) is given
$F=\Delta p/R$
where:
Δp is the difference in pressure between two points
R is resistance to flow
R, in turn, is determined by viscosity of blood and length & radius of blood vessels.
Under most physiological conditions, changing the radius of blood vessels controls flow of blood. (i.e. vasoconstriction, vasodilation)

Heart Anatomy

The heart is a muscle enclosed in a sac called pericardium. Walls of the heart are composed of cardiac muscle cells, called myocardium. A thin layer of cells called endothelial cells lines the inner surface. Located between the atrium and ventricle on each side are the atrioventricular (AV) valves, right AV valve is called the tricuspid valve, and the left AV valve is called the mitral valve. The valve at the opening of right ventricle into pulmonary artery is called pulmonary valve, the valve where left ventricle enters aorta is called aortic valve and these two valves are also called semilunar valves. These valves will only allow blood to flow in one direction and their opening and closing is a passive process resulting from pressure differences across the valves.

Cardiac Muscle
Cardiac muscle cells are striated and desmosomes and gap junctions at structures called intercalated disks join adjacent cells. Some cells do not function in contraction but they do form the conducting system, which initiates the heartbeat and spreads it throughout the heart

These muscle cells are obviously vital and they are innervated with a rich supply of sympathetic fibers that release norepinephrine and parasympathetic fibers that release acetylcholine.
Blood supply to cardiac muscle cells is supplied and drained by coronary arteries, and coronary veins, respectively. Blood being pumped through the chambers does not exchange substances with the cells of the heart muscle.

Heartbeat Coordination

Sequence of Excitation
A group of nerve cells, called the sinoatrial (SA) node in right atrium depolarizes first. The discharge rate of the SA node determines heart rate. Depolarization quickly spreads to left atrium and the two atria contract simultaneously. The action potential then spreads to ventricles, after a small delay, through the atrioventricular (AV) node, located at base of the right atrium. The delay in the action potential allows atrial contraction to be completed before the ventricle contracts. The potential then spreads to the ventricles via the bundle of His (atrioventricular bundle) and the Purkinje fibers and both ventricles contract simultaneously. Capacity of the SA node for spontaneous, rhythmical self-excitation is a result of gradual depolarization, called the pacemaker potential, of the cells as a result of Na^+ channels opening once again during the repolarization phase of the previous potential.

Electrocardiogram
Electrical events in the heart can be indirectly recorded at the surface of the skin from the currents generated in the extracellular fluids. An EKG (ECG) recording should consist of 3 deflections: (1) P wave - the atrial depolarization, (2) QRS complex - the ventricular depolarization and (3) T wave - the ventricular repolarization.
The long refractory period of heart muscle cells limits re-excitation of cardiac nerve cells, thus inhibiting tetanus.
Mechanical Events of the Cardiac Cycle
The cardiac cycle is divided into two phases:
(1) Systole is the phase of ventricular contraction and blood ejection. During the first part of the systole phase, the ventricles contract while all valves are still closed and therefore no blood is ejected. This period is called isovolumetric ventricular contraction. The volume of blood ejected from each ventricle is called stroke volume (SV). The amount of blood remaining after ejection is called end-systolic volume (ESV).
(2) Diastole is the phase when the ventricules relax and blood fills into the chambers. During the first part of diastole, the ventricles relax while all valves are still closed and this period is called isovolumetric ventricular relaxation. The amount of blood in ventricle at the end of diastole is called end-diastolic volume (EDV).
SV = EDV - ESV

Cardiac Output
To find the volume of blood pumped by each ventricle per minute:
CO = HR x SV Cardiac output equals heart rate multiplied by stroke volume.

Control of Heart Rate
SA node is innervated by the autonomic nervous system. Activity in parasympathetic nerves releases Ach, which close Na^+ channels and decreases the slope of pacemaker potential, causing heart rate to decrease. Activity in sympathetic nerves releases norepinephrine, which then opens Na^+ channels and increases the slope of pacemaker potential, causing heart rate to increase.

Control of Stroke Volume
A more forceful contraction of the ventricle can cause a greater emptying of the ventricle, thus increasing stroke volume.
EDV & SV: Frank Starling Mechanism

The greater the EDV results in a greater stretching of ventricular muscles, thus producing a more forceful contraction. Cardiac muscle is normally not at its optimal length (l_o), so additional stretching increases force of contraction. In sum, as the end systolic volume decreases, the overall stroke volume increases.
Sympathetic nerves release norepinephrine, which can increase myocardial contractility by increasing calcium infusion.

Vascular System

Arteries
Arteries are large, elastic tubes lined at the interior by endothelial cells. Arterial walls have connective tissue and smooth muscles. During systole, contraction of ventricles ejects blood into arteries, distending the arterial walls. During diastole, the walls recoil passively and more blood is driven out. There is always some blood in the arteries to keep them semi-inflated. Maximum arterial pressure reached during systole is called systolic pressure (SP), and minimum arterial pressure reached during diastole is called diastolic pressure (DPI) and difference between SP and DP is called pulse pressure (PP). Average pressure driving blood into tissues is called mean arterial pressure (MAP).

Arterioles
Contain smooth muscles, which can relax to increase vessel radios (vasodilation) or contract to decrease vessel radius (vasoconstriction), and control blood flow through an organ, can be calculated with:
F_{organ} = MAP / $Resistance_{organ}$

Local Controls
Local controls are mechanisms independent of hormones and nerves. Hyperemia occurs when blood flow in an organ increases by arteriolar dilation in response to an increase in metabolic activity that causes local changes such as decrease in O^2, increase in CO^2 and H^+.

Extrinsic Controls
Sympathetic nerves provide a rich supply of impulses to arterioles. Release norepinephrine and cause vasoconstriction
Hormones such as vasopressin (from posterior pituitary) and angiotension II (from liver) constrict arterioles.

Capillaries
Capillaries permeate every tissue in the body to provide front line access to cells in order to exchange nutrients and metabolic end products.

Anatomy of the Capillary Network
A capillary is a thin walled tube of endothelial cells one layer thick resting on a basement membrane without any surrounding muscle or elastic tissue. The endothelial cells are separated from each other by narrow, water-filled spaces called intercellular clefts.

Velocity of Capillary Blood Flow
Blood velocity decreases as blood passes through the huge cross sectional area of a capillary.

Diffusion and Exchange across Capillary Wall
There are three basic mechanisms by which substances move across capillary walls to enter or leave the interstitial fluid:
(1) Diffusion is the only important means by which net movement of nutrients, oxygen and metabolic end products can occur. Intercellular clefts allow the passage of polar molecules. Brain

capillaries, however, are tight with no intercellular clefts. Liver capillaries are leaky with large clefts for movement of substances. The transcapillary diffusion gradient is setup by utilization or production of a substance.
(2) Vesicle transport allows for the passage of molecules via endo- and exocytosis.
(3) Bulk flow enables protein-free plasma to move from capillaries to the interstitial fluid due to hydrostatic pressure. This is opposed by an osmotic force, resulting from differences in protein concentration that tends to move interstitial fluid into the capillaries. Bulk flow also serves to function in distributing extracellular fluid.
The net filtration pressure (NFP) can be calculated by:

$$NFP = P_c - P_{IF} - \pi_P + \pi_{IF}$$

Where:
P_c = capillary hydrostatic pressure (favoring fluid movement out of capillary)
P_{IF} = interstitial fluid hydrostatic pressure (favoring fluid movement into capillary)
π_P = the osmotic force due to plasma protein concentration (favoring fluid movement into capillary)
π_{IF} = the osmotic force due to interstitial fluid protein concentration (favoring fluid movement out of capillary)
These four factors are called Starling forces.

Veins

Veins are thin walled, low resistance vessels that carry blood from the tissues to the heart.

Determinants of Venous Pressure
Total blood volume is the important determinant of venous pressure. At any given time, most of the blood is in veins. Walls of veins are more elastic and thus can accommodate large volumes of blood with relatively small increase in pressure. The walls contain smooth muscle innervated by sympathetic neurons which release norepinephrine and constricts vessels which increases pressure and drives more blood.
During skeletal muscle contraction, veins in the muscle are compressed, which reduces their diameter and increases pressure. This is called skeletal muscle pump. When the diaphragm descends during inspiration, there is an increased pressure in intraabdominal veins and a decreased pressure in intrathoracic veins, increasing venous pressure. This is called the respiratory pump. Venous valves prevent backflow of blood in veins.

Lymphatic System
The lymphatic system is a network of small organs (lymph nodes) and tubes (lymphatic vessels) through which flows lymph. Lymph is a fluid derived from interstitial fluid. Lymphatic capillaries are composed of a single layer of endothelial cells resting on a basement membrane. Their water channels are permeable to all interstitial fluid components, including protein. Interstitial fluid enters these capillaries by bulk flow and the fluid flows through lymph nodes and ends in two lymphatic ducts that drain into subclavian veins in the lower neck. Lymphatic vessels carry interstitial fluid back to the cardiovascular system and compensates for net filtration out of blood capillaries. Additionally, the lymphatic system provides a pathway by which fat absorbed in gastrointestinal tract reaches the blood. Infections causing blockage of lymphatic system leads to accumulation of interstitial fluid, called edema.

Mechanism of Lymph Flow
Lymph is propelled by the rhythmical contractions of smooth muscle lining the walls of lymphatic vessels. The contractions are triggered by stretching of the walls when lymph enters the system. Lymphatic vessels have valves to produce a one-way flow. The vessels are innervated by sympathetic neurons and are also influenced by the skeletal muscle pump and the respiratory pump.

Regulation of Systemic Arterial Pressure
Mean arterial pressure is determined by cardiac output and total peripheral resistance (TPR). TPR is the sum of resistances to flow offered by all systemic blood vessels.
MAP = CO x TPR
Arteriolar resistance is the main determinant of TPR. Any deviation in MAP elicits homeostatic reflexes so that CO or TPR is changed to minimize the deviation.

Baroreceptor Reflexes

Arterial Baroreceptors
These are the short-term regulators of MAP. Pressure receptors are present in the carotid sinus at the neck, the aortic arch (aortic arch baroreceptors), pulmonary vessels, wall of the heart and large systemic veins. Afferent neurons, the firing rate of which is positively correlated to MAP, from these receptors travel to the brainstem.

Medullary Cardiovascular Center
This is the primary integrating center for baroreceptor reflexes in the brainstem medulla oblongata. When arterial baroreceptors decrease their discharge as a result of less MAP, sympathetic outflow increases, increasing heart rate, ventricular contractility, and vasoconstriction. Also elicits an increased secretion of Angiotensin II and vasopressin, which constrict arterioles.

Blood Volume
Long term regulation of MAP is dependent upon blood volume. An increase in MAP decreases blood volume by increasing excretion of salt and water by kidneys, consequently bringing down MAP.

Hemorrhage and Other Causes of Hypotension
Hypotension is low blood pressure due to low blood volume. SV, CO, MAP decrease as a direct result of hemorrhage and arterial baroreceptor reflexes work to restore them to normal. HR and TPR increase as reflex responses due to increases in sympathetic outflow. Interstitial fluid is moved into the vascular system due to reduced capillary pressure. In the long term, fluid ingestion and kidney excretion are altered, erythropoiesis is stimulated to replace blood volume. Loss of large quantities of cell-free extracellular fluid through sweating, vomiting, diarrhea etc. also invoke similar symptoms and responses. Hypotension can cause fainting. Hypotension can be an indicator of insufficiencies of the autonomic nervous system.

Shock
Tissue or organ damage due to reduced blood flow is called shock.
(1) Hypovolemic shock is caused by a decrease in blood volume due to hemorrhage or loss of fluid
(2) Low-resistance shock is due to a decrease in TPR due to excessive release of vasodilators, as in allergy and infection
(3) Cardiogenic shock due to a decrease in CO (cardiac output), as in a heart attack.

Upright Posture
There is a decrease in the effective circulating blood volume during transition from a horizontal to a vertical position. In a horizontal position, all blood vessels are at the same level and almost all pressure is due to cardiac output. In a vertical position, there is an additional pressure at every point, equal to weight of the blood column from the heart to that point. This results in distension of blood vessels due to pooling of blood and increased capillary filtration in lower parts of the body. Effect of gravity can be offset by contraction of skeletal muscles in the legs.

Exercise
As CO increases, there is an increased blood flow to muscles and skin (to dissipate heat). CO is

increased by a large increase in HR - caused by increased activity in the SA node, and a small increase in SV - caused by an increased ventricular contractility mediated by sympathetic activity. There is also an increase in EDV and the Frank Starling mechanism comes into play. Venous return is promoted by:
(1) increased activity in skeletal muscle pump
(2) increased activity in respiratory pump inspiration (due to increased depth and frequency of inspiration)
Control mechanisms for these cardiovascular changes involve feedforward regulation, active hyperemia, resetting of arterial baroreceptors.

Maximal Oxygen Consumption and Training
Oxygen consumption increases in proportion to magnitude of exercise until a point maximal oxygen consumption (V_{02}max). After V_{02}max is reached, any further increase in work can be only briefly sustained by anaerobic metabolism. V_{02}max is limited by:
(1) CO,
(2) ability of respiratory system's to deliver oxygen to blood
(3) ability of muscles to use oxygen.
Normally, V_{02}max is determined by cardiac output.

Hypertension
Increased arterial pressure, generally due to an increased TPR resulting from reduced arteriolar radius. Renal hypertension results from increased secretion of renin, which generates angiotensin II - a vasoconstrictor. Hypertension results in an increase in muscle mass of the left ventricle (left ventricular hypertrophy) since it has to pump against an increased arterial pressure. This could decrease contractility leading to heart failure.

Heart Failure
In heart failure, the heart fails to pump an adequate CO. In diastolic dysfunction, the wall of the ventricle has reduced compliance and has a reduced ability to fill adequately resulting in reduced EDV and therefore a reduced SV. Systolic dysfunction results from myocardial damage and results in a decrease in cardiac contractility and a lower SV. Adaptive reflexes to counter the reduced CO results in (1) fluid retention and can cause edema - one in the lung can impair gas exchange, and (2) increased TPR makes it harder for the heart to pump.

Coronary Artery Disease and Heart Attacks
In coronary artery disease, changes in the coronary arteries cause insufficient blood flow (ischemia) to heart, resulting in damage to myocardium (myocardial infarction or heart attack). Chest pains associated with this are called angina pectoris. Ventricular fibrillation triggers abnormal impulse conduction by damaged myocardial cells resulting in uncoordinated ventricular contractions. Major cause of coronary artery disease is atherosclerosis - a thickening of the arterial wall due to:
(1) Abnormal smooth muscle
(2) Cholesterol deposits
(3) Dense layers of connective tissue. The thickened wall reduces blood flow and also releases vasoconstrictors. Atherosclerosis of a cerebral artery can lead to localized brain damage - a stroke or reversible neurologic deficits called transient ischemic attacks (TIAs). Coronary thrombosis is total occlusion of a blood vessel by a blood clot.

Hemostasis - Prevention of Blood Loss
Hemostasis is the stoppage of bleeding from small vessels. Venous bleeding leads to a less rapid blood loss because veins have lower blood pressure. Accumulation of blood in a tissue as a result of bleeding is called hematoma. When a blood vessel is severed, it constricts and the opposite endothelial surfaces of the vessel sticks together to slow the outflow. It is followed by other processes including clotting.

Formation of a Platelet Plug
Injury to a vessel exposes the underlying connective tissue collagen, and platelets bind to the collagen via an intermediary called von Willebrand factor (vWF) - a plasma protein secreted by endothelial cells and platelets. Binding of platelets to collagen triggers the release of secretions from platelets that change the shape and surface proteins of platelets (platelet activation), causing them to stick together (platelet aggregation) and creating a platelet plug. The platelet plug acts as a primary sealer. The plug does not expand away from the damaged endothelium because intact endothelium synthesize and release prostacyclin (prostaglandin 12, PGI2) that inhibits platelet aggregation.

Blood Coagulation: Clot Formation
Blood is transformed into a solid gel, called a clot or thrombus, that consists mainly of the protein fibrin. It supports and reinforces the platelet plug. Plasma protein prothrombin is converted to the enzyme thrombin, which then catalyzes the formation of fibrin from fibrinogen. Platelets are essential to clot formation since they provide the surface on which many of the reactions occur. Vitamin K is required as a precursor to produce prothrombin and other clotting factors. Plasma calcium is also required for this process.

Anticlotting Systems
The fibrinolytic (thrombolytic) system removes the clot after the vessel is repaired. Plasminogen activators activate a plasma proenzyme, plasminogen to the enzyme plasmin that digests fibrin to dissolve the clot.

Common Anticlotting Drugs
Aspirin, Heparin, Streptokinase

Respiration

Respiration

Organization of the Respiratory System
Each lung is composed of air sacs called alveoli - the sites of gas exchange with blood. Airways are tubes through which air flows between external environment and alveoli. A respiratory cycle consists of an inspiration (inhalation) movement of air from the external environment into alveoli, and an expiration (exhalation) - movement of air from alveoli to external environment.

Airways and Blood Vessels
During inspiration, air passes through nose/mouth, pharynx (throat) and larynx. These constitute the upper airways. Airways beyond the larynx are divided into 2 zones:
(1) The conducting zone where there is no gas exchange. This consists of the tracheal tube, which branches into two bronchi, one of which enters each lung and makes further branching. Walls of trachea and bronchi contain cartilage for support. The first branches without cartilage are called terminal bronchioles.
(2) The respiratory zone where gas exchange occurs. Consists of respiratory bronchioles with alveoli attached to them.
Epithelial surfaces of airways up to respiratory bronchioles have cells that secrete mucus to trap particulate matter in air, which is then moved by cilia present on these cells and swallowed. Macrophages, which engulf pathogens, are also present.

Alveoli: The Site of Gas Exchange

Alveoli are hollow sacs having open ends continuous with lumens of airways. Inner walls lined by a single layer of flat epithelial cells called type I alveolar cells, interspersed by thicker, specialized cells called type II alveolar cells. Alveolar walls contain capillaries and a small interstitial space with interstitial fluid and connective tissue. Blood within an alveolar wall capillary is separated from air within alveolus by a very thin barrier. There are also pores in the walls that permit flow of air. The extensive surface area and the thin barrier permit rapid exchange of large quantities of oxygen and carbon dioxide by diffusion.

Lungs and the Thoracic Wall

Lungs are situated in thorax - the body compartment between neck and abdomen. Thorax is a closed compartment, bound at the neck by muscles and separated from the abdomen by a sheet of skeletal muscle, the diaphragm. Wall of thorax is composed of ribs, breastbone (sternum) and intercostal muscles between ribs.

A closed sac, the pleural sac, consisting of a thin sheet of cells, called pleura, surrounds each lung. The pleural surface coating the lung (visceral pleura) is attached to lung by connective tissue. The outer layer (parietal pleura) is attached to the thoracic wall and diaphragm. A thin layer of intrapleural fluid separates the two layers of pleura. Changes in hydrostatic pressure of the intrapleural fluid - the intrapleural pressure (P_{ip}) or the intrathoracic pressure cause lungs and thoracic wall to move in and together during breathing.

Ventilation and Lung Mechanics

Ventilation is exchange of air between atmosphere and alveoli. Air moves by bulk flow, from a high pressure to a low pressure region. Flow rate can be found with:

$F = (P_{atm} - P_{alv})/R$

where, P_{atm}, is the atmospheric pressure and P_{alv} is the alveolar pressure.

During ventilation, air is moved in and out of lungs by changing alveolar pressure through changes in lung dimensions.

Volume of lungs depends on (1) difference in pressure between inside and outside of lungs, called transpulmonary pressure and (2) stretchability of the lungs, called lung compliance. Muscles used in respiration are attached to chest wall. When they contract or relax, they change the chest dimensions, which in turn changes transpulmonary pressure, which in turn changes lung volume, which in turn changes alveolar pressure, causing air to flow in or out of lungs.

Stable Balance between Breaths

Transpulmonary pressure = $P_{alv} - P_{ip}$

P_{alv} is zero, which means it is same as atmospheric pressure. P_{ip} is negative, or less than atmospheric pressure because the elastic recoil of the lung inwards and the elastic recoil of chest wall outwards increases volume of intrapleural space between them and decreases the pressure within.. Therefore, transpulmonary pressure is greater than zero and this pressure puts an expanding force equal to the force of elastic recoil of lung and keeps it from collapsing. Volume of lungs is kept stable and there is air inside lungs. By a similar phenomenon, the pressure difference across chest (P_{atm}- P_{ip}) directed inward keeps the elastic chest wall from moving outward excessively.

Inspiration

Inspiration is initiated by neurally induced contractions. The diaphragm moves down and intercostal, muscles moves rib cage out. The size of the thorax increases and P_{ip} drops even further. This increases transpulmonary pressure, thus expanding the lungs. This increases size of alveoli, decreasing pressure within them. When $P_{atm} < P_{alv}$, it causes a bulk flow of air from the external environment through airways and into the lungs. When $P_{atm} = P_{alv}$, air flow ceases.

Expiration

The diaphragm and intercostal muscles relax during expiration. The chest recoils, becoming smaller. P_{ip} increases, thus decreasing transpulmonary pressure. Lungs recoil, compressing air in alveoli and increasing P_{alv}. Air passively flows out from alveoli to the external environment. Under

certain conditions, air can also be expired actively by contracting a set of intercostal and abdominal muscles that decrease thoracic dimensions.

Lung Compliance
Lung compliance is a measure of elasticity or the magnitude of change in lung volume (ΔVL) that can be produced by a given change in transpulmonary pressure.
$CL = \Delta VL / \Delta (P_{alv} - P_{ip})$
When lung compliance is low, Pip must be made lower to achieve lung expansion. This requires more vigorous contractions of diaphragm and intercostal muscles.

Determinants of Lung Compliance
Since the surface of alveolar cells is moist, surface tension between water molecules resists stretching of lung tissue. Type II alveolar cells secrete a substance called pulmonary surfactant that decreases surface tension and increases lung compliance. Respiratory distress syndrome of newborns is a result of low lung compliance.

Airway Resistance
Resistance is determined mainly by radius. Transpulmonary pressure exerts a distending force and keeps airways from collapsing, makes them larger during expiration and smaller during inspiration.
Asthma is a disease in which airway smooth muscle contracts and increases airway resistance.
Chronic Obstructive Pulmonary Disease (COPD) is chronic bronchitis or the production of excessive mucus in bronchi that obstructs the airways.
Heimliech Maneuver
This maneuver is the manual application of an upward pressure applied to the abdomen of a person, who is choking on an object caught in the airways. This maneuver can force the diaphragm to move up, reducing thoracic size and increasing alveolar pressure. The forceful expiration that is produced can expel the lodged object.

Lung Volumes and Capacities
Tidal volume is the volume of air entering lungs during a single inspiration or leaving the lungs in a single expiration. Maximal amount of air that can be increased ABOVE this value during the deepest inspiration is called inspiratory reserve volume. After expiration of a resting tidal volume, volume of air still remaining in lungs is called functional residual capacity. Additional volume of air that can be expired (by active contraction of expiratory muscles) after expiration of resting tidal volume is called expiratory reserve volume. Air still remaining in lungs after a maximal expiration is called residual volume. Vital capacity is maximal volume of air that can be expired after a maximal inspiration.

Alveolar Ventilation
Minute ventilation = Tidal volume x Respiratory rate
Units: (ml/min) = (ml/breath) x (breaths/minute)
Anatomic dead space is space within the airways that does not permit gas exchange with blood.
Total volume of fresh air entering the alveoli per minute is called alveolar ventilation.
Ventilation = (Tidal volume - anatomic dead space) x respiratory rate
Units: (ml/min) = (ml/breath) – (ml/breath) x (breaths/min)
Since a fixed volume of each tidal volume goes to dead space, increased depth of breathing is more effective in elevating alveolar ventilation than increased breathing rate.
The volume of inspired air that is not used for gas exchange as a result of reaching alveoli with no blood supply is called alveolar dead space. The sum of anatomic and alveolar dead space is called physiologic dead space.

Gas Exchange in Alveoli and Tissues
In steady state, volume of oxygen consumed by body cells per unit time is equal to volume of

oxygen added to blood in lungs, and volume of carbon dioxide produced by cells is. identical to rate at which it is expired.
The ratio of CO_2 produced / O_2 consumed is called respiratory quotient (RQ), which depends on type of nutrients being used for energy.

Alveolar Gas Pressures
Alveolar P_{02} is lower than atmospheric P_{02} because oxygen in alveolar air keeps entering pulmonary capillaries. Alveolar Pool is higher than atmospheric P_{CO2} because carbon dioxide enters alveoli from pulmonary capillaries. P_{02} is positively correlated with (1) P_{O2}, of atmospheric air, (2) rate of alveolar ventilation and inversely correlated with
(3) rate of oxygen consumption. P_{CO2} is inversely correlated with (1) rate of alveolar ventilation and (2) positively correlated with rate of oxygen consumption.
Hypoventilation is an increase in the ratio of carbon dioxide production to alveolar ventilation while hyperventilation is a decrease in this ratio.

Alveolar-Blood Gas Exchange
Blood entering pulmonary capillaries is systemic venous blood having a high P_{CO2} and a low P_{02}. Differences in partial pressures of oxygen and carbon dioxide on two sides of alveolar-capillary membrane result in net diffusion of oxygen from alveoli to blood and of carbon dioxide from blood to alveoli. With this diffusion, capillary blood P_{02} rises and its P_{CO2} falls and net diffusion of these gases ceases when capillary partial pressures become equal to those in alveoli.
In diffuse interstitial fibrosis, alveolar walls thicken with connective tissue reducing gas exchange.
Ventilation-perfusion inequality can result from:
(1) ventilated alveoli with no blood supply
(2) blood flow through alveoli with no ventilation, reducing gas exchange.

Gas Exchange in Tissues
Metabolic reactions within cells consume oxygen and produce carbon dioxide. Intracellular P_{O2} is lower and P_{CO2} is higher than in blood. As a result, there is a net diffusion of oxygen from blood into cells, and a net diffusion of carbon dioxide from cells into blood.

Transport of Oxygen in Blood
Oxygen is carried in 2 forms:
(1) dissolved in plasma
(2) reversibly combined with hemoglobin (Hb) molecules in erythrocytes. Each Hb molecule is a globin protein with four iron containing hemegroups attached to it. Each heme group binds one molecule of oxygen. Hb exist in two forms: deoxyhemoglobin (Hb) and oxyhemoglobin (HbO_2). Fraction of all Hb in form of $Hb0_2$ is called percent Hb saturation.

$$\text{Percent saturation} = \frac{O_2 \text{ bound to Hb} \times 100}{\text{Maximal capacity of Hb to bind } O_2}$$

(Oxygen carrying capacity)

Effect of P_{02} on Hemoglobin Saturation
Raising blood P_{O2} increases combination of oxygen with Hb and binding of one oxygen molecule to Hb increases the affinity of the remaining sites on the same molecule. Therefore, extent to which oxygen combines with Hb increases rapidly as P_{O2} increases and this relationship between the two variables is called the oxygen-hemoglobin dissociation curve. The plateau of the curve at higher P_{O2} provides a safety factor for oxygen supply at low alveolar P_{O2}.
Diffusion gradient favoring oxygen movement from alveoli to blood is maintained because oxygen binds to Hb and keeps the plasma P_{O2}, low and only dissolved oxygen contributes to P_{O2}. In tissues the procedure is reversed.
Carbon Monoxide and Oxygen Carriage
CO competes for the oxygen binding sites on Hb and also decreases the unbinding of oxygen from Hb.
Effects of Blood P_{C02}, H^+ concentration, Temperature and DPG on Hb Saturation

The more active a tissue is, the greater is its PCO_2, H+ concentration and temperature. CO_2, H+ ions and DPG (2, 3-diphosphoglycerate) combine with Hb and modify it allosterically, thereby shifting the dissociation curve to the right. This shift causes Hb to release more oxygen to the tissues.

Transport of Carbon Dioxide in Blood
Some fraction of carbon dioxide is dissolved and carried in blood. Some reacts reversibly with Hb to form carbamino Hb.
$CO2 + Hb \leftrightarrow HbC0_2$
Some carbon dioxide is converted to bicarbonate.

$$CO_2 + H_2O \leftrightarrow \underset{\text{Carbonic anhydrase}}{H_2CO_3} \leftrightarrow HCO_{3-} + H^+$$

The enzyme, carbonic anyhydrase, is present in erythrocytes where the reaction takes place after which the bicarbonate moves out into the plasma.

Transport of H^+ ions between Tissues and Lungs
If a person is hypoventilating, arterial H^+ concentration rises due to increased P_{CO2} and this is called respiratory acidosis. Hyperventilation lowers H^+ and this is called respiratory alkalosis. Deoxyhemoglobin has a higher affinity for H^+ ions than oxy-hemoglobin and binds most of H^+ produced. In the lungs, when deoxyhemoglobin is converted to oxyhemoglobin, H^+ ions are released.

Control of Respiration
Diaphragm and intercostal muscles are skeletal muscles and therefore breathing depends upon cyclical excitation of these muscles. Control of this neural activity resides in neurons called medullary inspiratory neurons in medulla oblongata. These neurons receive inputs from apneustic and pneumotaxics center in pons. Negative feedback from pulmonary stretch receptors is also involved in controlling respiration (Hering Breur reflex).

Control of Ventilation by P_{O2}, P_{CO2}, and H^+ Concentration

Control by P_{02} and P_{C02}
Peripheral chemoreceptors called carotid bodies and aortic bodies are in close contact with arterial blood and are stimulated by a steep decrease in arterial P_{O2} and an increase in H^+ concentration. They give inputs to medulla.
Control by H^+ not due to CO_2
Lactic acid in exercising muscles can cause metabolic acidosis or metabolic alkalosis, changing H^+ concentration and stimulating peripheral chemoreceptors.

Control of Ventilation during Exercise
Blood P_{CO2}, P_{O2}, and H^+ concentration due to CO_2 do no change much during exercise due to compensatory hyperventilation. Change in H^+ concentration due to lactic acid, input from mechanoreceptors in joints and muscles, increase in body temperature, increase in plasma epinephrine, etc. play important roles in stimulating ventilation.

Other Ventilatory Responses
Protective reflexes such as cough and sneeze reflexes, protecting the respiratory system from irritants. Receptors for sneeze located in nose or pharynx, while those for cough are located in the larynx, trachea and bronchi. The reflexes are characterized by a deep inspiration followed by a violent expiration.
Voluntary control of breathing is accomplished by descending pathways from the cerebral cortex. Cannot be maintained when involuntary stimuli are very high.
Reflex from J receptors, which are located in lungs, are stimulated by increase in lung interstitial pressure due to occlusion of a pulmonary vessel (pulmonary embolus), left ventricle failure etc.

Reflex effect is tachypnea (rapid breathing).

Hypoxia
Deficiency of oxygen at tissue level. There are four types:
(1) Hypoxic hypoxia (hypoxemia) which is characterized by reduced arterial P_{O2}.
(2) Anemic hypoxia occurs when total oxygen content of blood is reduced due to inadequate number of erythrocytes, deficient or abnormal Hb, or binding of CO to Hb. Arterial P_{O2} remains normal.
(3) Ischemic hypoxia (hypoperfusion hypoxia) occurs when blood flow to tissues is low.
(4) Histotoxic hypoxia occurs when tissue is unable to utilize the oxygen due to interference from a toxic agent. However, the quantity of oxygen reaching the tissue is normal.
Retention of carbon dioxide and increased arterial P_{CO2}, is called hypercapnea.

Emphysema
Disease characterized by increased airway resistance, decreased surface area for ventilation due to alveolar fusion, and ventilation-perfusion inequalities.

Nonrespiratory Functions of the Lungs
Lungs (1) concentrate a large number of biologically active substances in the bloodstream and also remove them, (2) produce and add new substances to blood and (3) trap and dissolve small blood clots.

Kidneys and regulation of water and inorganic ions

Renal Functions
Kidneys remove/add substances from/to the plasma.
(1) Regulate water concentration, inorganic ion composition, and volume of internal environment by controlling their excretion.
(2) Excrete metabolic wastes, including urea, uric acid, and creatinine into urine
(3) Excrete foreign chemicals in urine
(4) Synthesize glucose from amino acids and other precursors (gluconeogenesis).
(5) Secrete the hormones, erythropoietin, renin, and 1, 25-dihydroxyvitamin D_3.

Structure of Kidneys and Urinary System
The two kidneys lie near the back of the abdominal wall. Urine flows from kidneys through ureters into bladder, from which it is eliminated through the urethra. The outer part of kidney is called renal cortex and the inner part is called renal medulla. Each kidney is made up of subunits called nephrons and each nephron consists of (1) an initial filtering component called renal corpuscle located in the cortex and (2) a tubule located in the medulla that extends out from renal corpuscle. The renal corpuscle forms a filtrate that is free of cells and proteins, and as it flows through the tubule, substances are added to it or removed from it and the final exiting fluid is called urine.
Each renal corpuscle contains a tuft of capillary loops called glomerulus, which protrudes into a fluid filled space called Bowman's space. Blood enters the glomerulus by an afferent arteriole and leaves it by an efferent arteriole. Protein free fluid from glomerulus enters Bowman's space and is drained by the proximal tubule which leads to the descending limb of loop of Henle, from where the fluid goes to the ascending limb and then to the distal convoluted tubule. The fluid then flows into the collecting duct system, comprised of the connecting tubule, followed by the cortical collecting duct and the medullary collecting duct. Medullary collecting ducts from numerous nephrons merge and drain into the renal pelvis, which is continuous with the ureter. The tubules are also connected to another set of blood vessels called peritubular capillaries.

The part of ascending limb passing between the afferent and efferent arterioles has a patch of cells called macula densa and wall of the afferent arteriole at this point has cells called juxtaglomerular (JG) cells, which secrete the hormone renin. These two types of cells comprise the juxtaglomerular apparatus (JGA).

Basic Renal Processes

Filtration of plasma from glomerular capillaries into Bowman's space is called glomerular filtration and the filtrate is called glomerular filtrate. During its passage through tubules, substances move from tubules to peritubular capillaries, a process called tubular reabsorption and substances move from peritubular capillaries to tubules, a process called tubular secretion.

$A_E = A_F + A_S - A_{RA}$

A_E = Amount excreted

A_F = Amount filtered

A_S = Amount secreted

A_{RA} = Amount reabsorbed

For a given substance, a particular combination of all these processes applies.

Glomerular Filtration

Glomerular filtrate contains all plasma substances in same concentrations as plasma except proteins and molecules bound to these proteins. It is a bulk flow process.

Net glomerular filtration pressure = $P_{GC} - P_{BS} - \pi_{GC}$

Where:

P_{GC} is glomerular capillary hydrostatic pressure favoring filtration from capillary to Bowman's space

P_{BS} is Bowman's space hydrostatic pressure favoring movement from Bowman's space to capillaries

π_{GC} is osmotic pressure resulting from presence of protein in glomerular capillary plasma and no protein in Bowman's space

Normally, net filtration pressure is positive.

Glomerular Filtration Rate (GFR) - Volume of liquid filtered from glomeruli into the Bowman's capsule per unit time. GFR is determined by net filtration pressure, permeability of the corpuscular membranes and surface area available for filtration. GFR is subject to physiological regulation by neural and hormonal inputs to afferent and efferent arterioles. Constriction of afferent arterioles decreases P_{GC} while constriction of efferent arterioles increases it. Mesangial cells, which are modified smooth muscle cells are involved in this constriction process.

Filtered load is the total amount of any nonprotein substance filtered into Bowman's space. It is given by multiplying GFR with the plasma concentration of the substance. If the quantity of a substance excreted in urine is less than filtered load, tubular reabsorption has occurred, if it is more then tubular secretion has occurred.

Tubular Reabsorption

Waste products are reabsorbed incompletely so that they are mostly excreted in the urine, while useful products are reabsorbed completely so that they are mostly not excreted.

Reabsorption by Diffusion

Reabsorption by mediated transport is responsible for reabsorption of many substances, e.g., glucose molecules are coupled to the reabsorption of sodium. The limit to which these mediated transport systems can move materials per unit time is called transport maximum (T_m). This limit is a result of saturation of binding sites on membrane transport proteins. In people with diabetes mellitus, plasma glucose concentration is so high that the filtered load of glucose exceeds the glucose T_m. and therefore, glucose appears in urine (glucosuria).

Tubular Secretion

Tubular secretion is responsible for moving substances, e.g., H^+ and K^+ ions, from peritubular capillaries into tubular lumen by diffusion or transcellular mediated transport. Some of the

movements are coupled to reabsorption of Na^+ ions.

Metabolism by Tubules
Tubule cells can synthesize glucose, ammonia, etc. and add it to blood as needed. It can catabolize peptides etc. and remove them from the body.

Regulation
Hormones and neurotransmitters regulate channels and transporters. In order to excrete waste products, GFR must be large resulting in large filtered loads of substances. The primary role of proximal tubule and loop of Henle is to reabsorb large quantities of substances. Such extensive reabsorption ensures that distal segments receive small amounts of substances, and that their quantities in urine can be fine-tuned and regulated. Most homeostatic controls are therefore exerted on distal segments.

Renal Clearance
Renal clearance is the measure of the volume of plasma from which a substance is completely removed by kidneys per unit time.
Clearance of substance S = $\frac{\text{Mass of S excreted per unit time}}{\text{Plasma concentration of S}}$

$C_S = \frac{U_S V}{P_S}$

Where:
C_S = clearance of S
U_S = urine concentration of S
V = urine volume per unit time
P_S = plasma concentration of S
C_S of a substance equals GFR if it is filtered but not reabsorbed, secreted or metabolized.

Micturition
Urine flow through ureters to bladder is propelled by contractions of ureter wall smooth muscle. Urine is stored in bladder and ejected during urination, or micturition. The bladder is a chamber with walls made of smooth muscle called detrusor muscle, contraction of which produces urination. Part of the muscle at the base of bladder, where urethra begins, functions as a sphincter called the internal urethral sphincter. Below this sphincter is a ring of skeletal muscle called the external urethral sphincter, which surrounds the urethra.
The detrusor muscle receives parasympathetic input, while the internal sphincter receives sympathetic input and the external sphincter receives motor input. While the bladder is filling, there is little parasympathetic input to the detrusor muscle but there are strong sympathetic and motor inputs to the sphincters. While filling occurs, the detrusor muscle is relaxed, and sphincters are closed. As bladder fills, stretch receptors stimulate the parasympathetic fibers, resulting in contraction of the detrusor muscle. Sympathetic and motor inputs to sphincters are inhibited and sphincters open to produce urination. There is voluntary control over the external sphincter.

Total Body Balance of Sodium and Water
Water is gained from:
(1) Ingestion
(2) Oxidation of organic nutrients.
Water is lost from
(1) Skin via sweat glands
(2) Respiratory passageways
(3) Gastrointestinal tract
(4) Urinary tract. Water and salt balance is primarily a result of regulation through urinary loss.

Basic Renal Processes for Sodium and Water
Sodium and water filter freely from glomerular capillaries to the Bowman's space. They undergo

considerable reabsorption in the proximal tubule but the major hormonal controls on reabsorption are exerted in the collecting ducts. They are not secreted into the tubules.

Primary Active Sodium Reabsorption
Sodium moves out of lumen into the epithelium by diffusion or by ion channels or by cotransport with glucose (which is also being reabsorbed) or countertransport with H^+ ions (which are being secreted). Na, K-ATPase, transports sodium out of the epithelium into the interstitial fluid.

Coupling of Water Reabsorption
The removal of sodium lowers the osmolarity of lumen and raises that of the interstitial fluid. This causes a net diffusion of water from the lumen into the interstitial fluid through the epithelium. Water permeability of the proximal tubule is high but only that of collecting ducts is under the control of vasopressin (ADH). ADH stimulates insertion of aquaporin channels, increasing water permeability. Low ADH leads to water diuresis or diabetes insipidus. Increased urine flow due to increased solute excretion is called osmotic diuresis.

The Countercurrent Multiplier System
Fluid from proximal tubule has same osmolarity as plasma since it absorbs sodium and water equally. In the ascending limb, sodium, but not water, is actively reabsorbed from the lumen, making the interstitial fluid of the medulla hyperosmotic. Due to this hyperosmocity, there is passive diffusion of water from the lumen into the interstitial fluid in the descending limb. Fluid in the distal tubule becomes progressively dilute as sodium is transported out and then in the cortical and medullary ducts, water diffuses out of the tubule into the hyperosmotic interstitial fluid and urine is concentrated.

Renal Sodium Regulation
Since sodium is the major extracellular solute, changes in total body sodium result in changes in volume of extracellular fluid, changing plasma volume and therefore blood pressure, which is detected by the baroreceptors.
Sodium excreted = Sodium filtered - Sodium reabsorbed

Control of GFR
Lower total body sodium can decrease GFR by vasoconstriction, resulting in lower pressure in renal arteries.

Control of Reabsorption
The control of reabsorption is more important for long-term regulation.
Aldosterone and Renin-Angiotensin System
Aldosterone stimulates sodium reabsorption by cortical collecting ducts (and large intestine, sweat and salivary glands). Secretion of aldosterone is controlled by angiotensin II, which is produced from angiotensinogen in a reaction, the rate limiting step of which is controlled by renin from JG cells. These cells act as internal baroreceptors as well as receive sympathetic inputs from external baroreceptors. Angiotensin II is also a vasoconstrictor itself.

Renal Water Regulation
Water excreted = Water filtered - Water reabsorbed
Water excretion is regulated mainly at the level of reabsorption by vasopressin.

Baroreceptor Control of Vasopressin Secretion
The secretion of vasopressin can be triggered by decreased extracellular volume but the baroreceptor reflex plays a relatively lesser role because it has a higher threshold.

Osmoreceptor Control of Vasopressin Secretion
Changes in total body water with which there is no change in total body sodium are regulated by reflexes that alter water excretion without altering sodium excretion. Receptors that control

vasopressin secretion mainly due to water gain or loss are the osmoreceptors in hypothalamus.

Thirst
Stimulated by lower extracellular volume, higher plasma osmolarity, angiotensin II and the brain centers for thirst are located in hypothalamus.

Potassium Regulation
Potassium is filtered in the renal corpuscle and most of it absorbed in the tubules. Any changes in potassium excretion, however, are mainly due to changes in potassium secretion by cortical collecting ducts. This secretion is associated with reabsorption of sodium by Na, K-ATPase. Aldosterone-secreting cells are sensitive to potassium concentration of their extracellular fluid and an increased potassium concentration stimulates aldosterone production, thereby increasing potassium secretion and its excretion from the body.

Calcium Regulation
In addition to gastrointestinal tract and kidneys, which determine net intake and excretion of calcium, calcium can be redistributed between extracellular fluid and bone.

Kidneys
Calcium is filtered in renal corpuscle and most of it is reabsorbed. There is no tubular secretion of calcium. Therefore, Calcium excreted = Calcium filtered - Calcium absorbed Control of calcium excretion is exerted mainly on reabsorption.

Gastrointestinal Tract
Calcium absorption in the GI tract is under hormonal control and is a major means for control of calcium balance.

Hormonal Controls

Parathyroid Hormone
Parathyroid hormones are produced by parathyroid glands in neck that are controlled directly by extracellular calcium concentration. It increases movement of calcium from bone tissue into extracellular fluid, increases renal tubular calcium reabsorption and stimulating production of 1, 25-dihydroxy-vitamin D^3.

1, 25-dihydroxyvitamin D^3
1, 25-dihydroxy-vitamin $D^{3\ is}$ derived from vitamin D in the liver and kidneys, this hormone increases intestinal absorption of calcium.

Calcitonin
Parafollicular cells of thyroid gland secrete calcitonin; it decreases plasma calcium concentration by reducing bone resorption.

Hydrogen Ion Regulation
H^+ ion can be redistributed in the body by binding it reversibly with a buffer such as bicarbonates, phosphates, proteins and Hb.

Respiratory Mechanisms
Ventilation is altered by reflex mechanisms in order to compensate for H^+ ion imbalance.

Renal Mechanisms
Kidneys compensate for H^+ ion imbalance by altering plasma HCO_{3-} ion concentration. A lowering of plasma H^+ ion concentration results in excretion of large quantities of HCO_{3-}ions while a rise in H^+ ion concentration results in production of HCO_{3-} ions and their addition to plasma by tubular cells.

Bicarbonate Handling
HCO_3 is filtered at renal corpuscle and undergoes reabsorption in the tubule. It is also secreted in the collecting ducts. Therefore:
HCO_3 excreted = HCO_3 filtered + HCO_3 secreted - HCO_3 reabsorbed
Inside the cell, CO^2 and H_2O combine to form H_2C0_3, which dissociates to yield H^+ and HCO_3 ions. HCO_3 moves to the interstitial fluid by diffusion while H^+ ion is secreted into the lumen by an active process involving H-ATPase pumps. The secreted H^+ ion combines with filtered HCO_3 in the lumen and generates CO_2 and H_2O, which diffuse into the cell and the whole process is repeated. If an excess of H+ ions is secreted, it combines with nonbicarbonate buffer, usually HPO_4^{2-}, in the lumen and is excreted. In such a case, the HCO_3 generated within the cell and entering the plasma is a net gain of HCO_3 .

Digestion and Absorption of Food

The Digestion and Absorption of Food

The gastrointestinal (GI) system includes the gastrointestinal tract (mouth, pharynx, esophagus, stomach, small intestine, large intestine) and accessory organs (salivary gland, liver, gallbladder, pancreas) that secrete substances into the tract via connecting ducts.
GI system breaks down particles of ingested food into molecular forms by enzymes (digestion) that are then transferred to the internal environment (absorption).

Functions of GI organs
The GI tract begins at the mouth, where digestion begins with chewing. Saliva containing mucus and the enzyme amylase is secreted from 3 pairs of salivary glands, located in the head. Mucus moistens the food and amylase partially digests polysaccharides (starches). Food then reaches the stomach through the pharynx and esophagus.
The stomach is the sac that stores and digests food macromolecules into a solution called chyme. Glands lining the stomach secrete hydrochloric acid that dissolves food particles and protein-digesting enzymes, called pepsin.
Final stages of digestion and most of the nutrient absorption occurs in next portion of the tract: the small intestine. The small intestine is divided into 3 segments - duodenum, jejunum, and ileum.
The pancreas is a gland located behind the stomach. From its exocrine portion it secretes (1) digestive enzymes and (2) a fluid rich in HCO_3 ions to neutralize the acid from stomach. The liver secretes bile. Bile contains HCO_3 ions and bile salts to solubilize fats. Bile reaches the gall bladder through hepatic ducts and is stored in the gall bladder between meals. During a meal, bile is secreted from the gland by smooth muscle contraction and reaches the duodenum portion of the small intestine by the common bile duct.
Monosaccharides, amino acids and mineral salts are absorbed by transporter-mediated processes while fatty acid water diffuse passively.
Undigested material is passed to large intestine, where it is temporarily stored and concentrated by reabsorption of salts and water. Finally, contractions of rectum, the last part of large intestine, expel the feces through the anus.

Structure of GI Tract Wall
The luminar surface is covered by a single layer of epithelium containing exocrine and endocrine cells. The exocrine cells disintegrate and discharge into the lumen, releasing their enzymes. The epithelia with an underlying layer of connective tissue (lamnia propia) and muscle (muscularis mucosa) are called mucosa. Below the mucosa is a layer of inner circular and outer longitudinal

smooth muscle called muscularis externa, which provides the forces for moving and mixing the GI contents. The outermost layer of the tube is made up of connective tissue called serosa. The luminar surface of the tube is highly convoluted into projections called villi and microvilli; both of which increase total surface area for absorption. The center of each villus has a single blunt-ended lymphatic vessel called lacteal. Venous drainage from the intestine transports absorbed materials to the liver for processing via the hepatic portal vein.

Digestion and Absorption

Carbohydrate
Digestion begins in the mouth by salivary amylase and completed in the small intestine by pancreatic amylase. Monosaccharides, such as glucose, galactose and fructose, are produced by the breakdown of polysaccharides and are transported to the intestinal epithelium by facilitated diffusion or active transport. Facilitated diffusion moves the sugars to the bloodstream.

Protein
Proteins are broken down to peptide fragments by pepsin in the stomach, and by pancreatic trypsin and chemotrypsin in the small intestine. The fragments are then digested to free amino acids by carboxypeptidase from the pancreas and aminopeptidase from the intestinal epithelium. Free amino acids enter the epithelium by secondary active transport and leave it by facilitated diffusion. Small amounts of intact proteins can enter interstitial fluid by endo- and exocytosis.

Fat
Fat digestion occurs by pancreatic lipase in small intestine. A monoglyceride and two fatty acids are produced in the digestive process. Large lipid droplets are first broken down into smaller droplets, by a process called emulsification. Emulsification is driven by mechanical disruption (by contractile activity of GI tract) and emulsifying agents (amphipathic bile salts). Pancreatic colipase binds the water-soluble lipase to the lipid substrate.
Digested products and bile salts form amphipathic micelles. These micelles keep the insoluble products in soluble aggregates from which small amounts are released and absorbed by epithelial cells via diffusion. Free fatty acids and monoglycerides then recombine into triacylglycerols at the smooth ER, are processed further in the Golgi and enter the interstitial fluid as droplets called chylomicrons, which are then taken up by the lacteals in the intestine.

Vitamins
Fat-soluble vitamins are absorbed and stored along with fats. Most water-soluble vitamins are absorbed by diffusion or mediated transport. Vitamin B_{12}, because of its large size and charged nature, first binds to a protein, called intrinsic factor, which is secreted by the stomach epithelium, and is then absorbed by endocytosis.

Water
The stomach absorbs some water but most is absorbed at small intestine by diffusion.

Regulation of GI Processes

Control mechanisms of the GI system regulate conditions in the lumen of the tract. Reflexes are initiated by:
(1) Distension of wall by volume of luminal contents
(2) Chyme osmolarity
(3) Chyme pH
(4) Chyme concentrations of specific products.

Neural Regulation of the GI tract

Impulses to the GI muscles and exocrine glands are supplied by enteric nervous system, the local nervous system of GI tract, which allows local, short reflexes, independent of CNS. Long reflexes through the CNS are possible via sympathetic and parasympathetic nerves, which also innervate the GI tract.

Hormonal Regulation
Endocrine cells are scattered throughout GI epithelia and surface of these cells is exposed to the lumen. Chemical substances in the chyme stimulate them to release hormones into blood.
Phases of GI control
Each phase is named according to where the receptor for a reflex is located. These phases do not occur in temporal sequence.
1. The cephalic phase is initiated when sight, smell, taste, chewing, and emotional states stimulate receptors in the head. Reflexes mediated by sympathetic and parasympathetic fibers activate secretory and contractile activity.
2. The gastric phase is initiated by distension, acidity, and the presence of amino acids and peptides in the stomach. This phase is mediated by short and long reflexes and activates the secretion of gastrin.
3. The intestinal phase is initiated by distension, acidity, osmolarity of digestive products in intestine and is mediated by GI hormones and short and long neural reflexes.

Mouth, Pharynx, and Esophagus

Chewing is controlled by somatic nerves to the skeletal muscles and the reflex activation of mechanoreceptors on the palate, gums and tongue.
Autonomic nerves in response to chemoreceptors and pressure receptors in mouth stimulate saliva secretion.
Swallowing is mediated by pressure receptors on walls of pharynx, which send impulses to the swallowing center in the medulla oblongata. The center activates muscles in the pharynx and esophagus. Multiple responses occur in a temporal sequence. The palate is elevated to prevent food from entering the nasal cavity, respiration is inhibited and the epiglottis covers the glottis to prevent food from entering trachea (windpipe). The upper esophageal sphincter opens and food enters the esophagus and moves toward the stomach by muscle contractions called peristaltic waves. Food then moves to the stomach when the lower esophageal sphincter opens. A less efficient, or faulty, lower esophageal sphincter results in the reflux of gastric contents into the esophagus (gastro-esophageal reflux), this reversal results in heartburn and over time contributes to ulceration of esophagus.
Epithelium lining the stomach invaginates into the mucosa, forming tubular glands. Parietal (oxyntic) cells secrete acid and intrinsic factor and chief cells secrete pepsinogen. Also scattered throughout are enterochromaffin-like (ECL) cells, which secrete histamine, and other cells that secrete somatostatin. The antrum, a lower portion of the stomach, secretes gastrin.
Increased protein content in a meal stimulates release of gastrin and histamine, which in turn stimulates HCl secretion. Somatostatin inhibits acid secretion by inhibiting the release of gastrin and histamine. Enterogastones in the duodenum also inhibit gastric acid secretion.
The precursor pepsinogen, which is produced by chief cells, is converted to pepsin by the acid in the stomach.
The stomach produces peristaltic waves in response to the arrival of food. The pyloric sphincter between the stomach and duodenum opens to release small amounts of chyme into the duodenum with each wave. These waves are generated by pacemaker cells in the longitudinal smooth muscle layer and are spread out by gap junctions. Gastrin, distension of stomach etc. stimulate gastric motility while distension of duodenum inhibits it.

Pancreatic Secretions
Inactive trypsinogen is secreted by pancreas and is later converted by the intestinal enzyme enterokinase to active trypsin, which digests proteins. Pancreatic amylase and lipase are secreted in active forms. The pancreas also secretes bicarbonate ions.

Secretion of pancreatic enzymes is stimulated by cholecystokinin (CCK), the secretion of which is triggered by the detected presence of fatty acids and amino acids in the small intestine. The secretion of bicarbonate ions is stimulated by secretin, which is triggered by acidity in small intestine.

Bile Secretion
Bile contains bile salts, which solubilize fats, and bicarbonate ions, which in turn are used to neutralize stomach acids. Bile salts, secreted by hepatocytes (liver cells) enter the GI tract and are reabsorbed by transporters in the intestine and are returned to the liver via the portal vein. This recycling pathway is called the entero-hepatic circulation.
The sphincter of Oddi controls the entry of the bile duct into the duodenum. When the sphincter is closed, secreted bile is shunted into the gallbladder. The presence of fat in the intestine releases CCK, which relaxes the sphincter to discharge bile salts into the duodenum.

Small Intestine
The most common motion of the small intestine is stationary contraction and relaxation, called segmentation. Segmentation results in little net movement. The chyme is mixed and brought into contact with the intestine wall and then moved slowly toward the large intestine. The movements are initiated by pacemaker cells in the smooth muscle layer.
After most of the materials are absorbed, segmentation is replaced by peristaltic activity called migrating motility complex, which moves any undigested material to the large intestine. The candidate intestinal hormone, motilin, initiates migrating motility.

Large Intestine
The large intestine consists of 3 parts: the cecum, colon and rectum. The primary function is to store and concentrate fecal material for elimination. Chyme enters the cecum through the ileocecal sphincter, which relaxes and opens as a result of the gastroileal reflex.
Na^+ is absorbed along with water. K^+ and HCO_{3-} ions are secreted into the lumen. Undigested polysaccharides (fiber) are metabolized to short-chain fatty acids by the residing bacteria and these are then absorbed by diffusion. A small amount of vitamin K is also produced and absorbed. Bacterial metabolism produces a mixture of gases, called flatus.

Motility and Defecation
Regular contractions of the circular smooth muscle produce a slow rhythmic segmentation movement. The undigested material moves slowly in order to provide resident bacteria time to grow and multiply. Following a meal, there is a wave of intense contraction, called mass movement. The internal anal sphincter is made of smooth muscle and closes the anus, while the external anal sphincter is made of skeletal muscle and is under voluntary control. Both sphincters regulate the anal opening and closing. Mass movement of fecal material into the anus initiates the defecation reflex, which is mediated by mechanoreceptors. The two sphincters open to expel the feces. If defecation is delayed, rectal contents are driven back into colon by reverse peristalsis until the next mass movement.

Pathophysiology of the GI Tract Ulcers
Ulcers are eroded areas of gastric surface and breaks in the mucosal barrier, which expose the underlying tissue to corrosive action of acid and pepsin. Damage to underlying blood vessels may cause bleeding.

Vomiting
The vomit reflex results in the forceful expulsion of toxic gastric contents. This reflex is coordinated by the vomiting center in the medulla oblongata. Various mechano- and chemo-receptors in the stomach and elsewhere can trigger this reflex. Increased salivation, sweating, heart rate, pallor etc. accompany the reflex. Abdominal muscles contract to raise abdominal pressure while the lower esophageal sphincter opens and gastric contents are forced into the esophagus (retching). If the upper esophageal sphincter opens, contents are then expelled from

the mouth (vomiting). Excessive vomiting can lead to loss of water and salts, which will ultimately result in dehydration.

Gallstones
Excessive secretion of water insoluble cholesterol in bile results in formation of crystals, called gallstones, which can close the opening of gallbladder or the bile duct. If a stone prevents bile from entering the intestine fat digestion and absorption decreases. If a stone blocks the entry of the pancreatic duct, it prevents pancreatic enzymes from entering the intestine, thus preventing the digestion of other nutrients. A blocked bile duct inhibits further secretion of bile, resulting in accumulation of bilirubin in tissues, producing a yellowish coloration called jaundice. Jaundice is common in newborns and is rectified by sunlight exposure.

Lactose Intolerance
Lactose intolerance results from a lack of the enzyme lactase which digests lactose, the sugar in milk. The lack of lactase results in the incomplete digestion of lactose to glucose and galactose.

Constipation and Diarrhea
Constipation is the absence of defecation due to decreased motility of the large intestine. This results in excess absorption of water from feces, making it hard to expel.
Dietary fiber, which is not digested in small intestine, can produce distension and increase motility.
Diarrhea results from decreased fluid absorption, or increased fluid secretion resulting in increased luminal fluid, which in turn, causes distension and increased motility. Diarrhea results in decreased blood volume, loss of water and other nutrients.

Regulation of Organic Metabolism, Growth and Energy Balance

Regulation of Organic Metabolism, Growth and Energy Balance

Events of Absorptive and Post-absorptive States
Absorptive state is the period during which ingested nutrients enter blood and some of these nutrients supply the energy need of the body while the remainder is stored. Post-absorptive state is the period during which the GI tract is empty of nutrients and body stores must supply required energy.

Absorptive State

Carbohydrates and proteins are absorbed primarily as monosaccharides and amino acids, respectively, into the blood while fat is absorbed as triacylglycerols into the lymph.

Absorbed Carbohydrates
During the absorptive state, glucose is the major energy source and some of it is converted to glycogen and stored in skeletal muscle and liver. In adipose tissue, glucose is transformed and stored as fat.
Absorbed Triacylglycerols
Fatty acids of plasma chylomicrons are released within adipose tissue capillaries and form triacylglycerols.
Absorbed Amino Acids
Most amino acids enter cells and are used to synthesize proteins and any excess amino acids

are converted to carbohydrate or fat.

Postabsorptive State

In this state, the net synthesis of glycogen, fat, and protein ceases, and net catabolism of these substances begins. Plasma glucose level is maintained by:

1. Glycogenolysis, which is the hydrolysis of glycogen stores in liver and skeletal muscles.
2. Lipolysis, catabolism of triacylglycerols into glycerol and fatty acids in adipose tissues. Any glycerol reaching the liver is converted to glucose.
3. Protein is catabolized to glucose.

Such new synthesis of glucose is called gluconeogenesis.

Glucose Sparing (Fat Utilization)

Glucose sparing means the reduction of glucose catabolism and increase in fat utilization by most tissues. This spares glucose for the brain and thus protein breakdown is minimized.

Endocrine and Neural Control

Insulin

A peptide hormone secreted by beta (B) cells of islets of Langerhans, in the pancreas. Its secretion is increased during the absorptive state and decreased during the post-absorptive state. Insulin targets are muscular, adipose and liver-tissues. The main roles of insulin are to stimulate the movement of glucose from extracellular fluid into cells by facilitated diffusion, stimulate glycogen synthesis and inhibit glycogen catabolism.

Control of Insulin Secretion

Insulin is controlled by an increase in plasma glucose or amino acid concentration, and the hormone glucose dependent insulinotropic peptide (GIP), which is secreted in the GI tract to stimulate insulin secretion. Parasympathetic fibers stimulate insulin secretion.

Glucagon

Glucagon is a peptide hormone secreted by alpha (A) cells of the pancreas. Its target is the liver tissue and its actions are opposed to that of insulin. Glucagon increases glycogen breakdown and gluconeogenesis to increase the plasma concentration of glucose during the post-absorptive state or when plasma glucose is low (hypoglycemia). Sympathetic nerves stimulate glucagon secretion. On a side note, cortisol and growth hormone also have effects similar to that of glucagon.

Diabetes Mellitus

Diabetes mellitus results from a deficiency of insulin or hyporesponsiveness (slowed response) to insulin.

In insulin dependent diabetes mellitus (IDDM) or type 1 diabetes, insulin is very low or absent as a result of destruction of beta cells. Large amounts of glucose are excreted as the plasma glucose level is very high and the filtered load of glucose exceeds the maximum tubular reabsorptive capacity. Treatment must involve administration of insulin.

In noninsulin-dependent diabetes mellitus (NIDDM) or type 2 diabetes, plasma insulin level is normal but there is target-cell hyporesponsiveness to insulin, termed insulin resistance, which is also related to obesity.

Hypoglycemia

A low plasma glucose level will result from an excess of insulin (beta cells) or deficiency of glucagon (alpha cells).

Regulation of Plasma Cholesterol
The two sources of cholesterol are diet and synthesis by the liver. The liver also excretes cholesterol by adding it to bile. The homeostatic control that keeps the plasma cholesterol constant mainly involves hepatic synthesis.
The ingestion of saturated fatty acids (animal fats) raises plasma cholesterol while unsaturated fatty acids (vegetable fats) lowers it. Low-density lipoproteins (LDL) deliver cholesterol to cells throughout body while high-density lipoproteins (HDL) removes excess cholesterol from blood and tissue and delivers it to the liver for excretion. The ratio of LDL to HDL is important and the lower the ratio, the lower the deposition of extra cholesterol in the blood vessels.

Control of Growth

1. Environmental Factors
Adequacy of nutrient supply is a vital factor in growth.

2. Hormonal Influences

Growth Hormone and Insulin-Like Growth Factors
GH, secreted by anterior pituitary, is the single most important hormone for postnatal growth. An excess of GH produces gigantism, whereas a deficiency produces dwarfism. When excess GH produces bone thickening without lengthening and overgrowth of other organs, it is called acromegaly.
GH exerts its effect on growth by promoting secretion of IGF-I from liver and other tissues. IGF-I promotes cell division, and stimulates protein synthesis by promoting the uptake of amino acids by cells.

Thyroid Hormone
TH is important for controlling metabolism and plays a permissive role in the normal development and maintenance of the nervous system. A decrease in TH during infancy leads to mental retardation, called endemic cretinism.

Insulin
Insulin is an anabolic (building) hormone and inhibits protein degradation. It also promotes cell division and differentiation because it is required for production of IGF-I.

Sex Hormones
Sex hormones stimulate the secretion of GH and IGF-I. Testosterone exerts an anabolic effect by stimulating protein synthesis.

Cortisol
Cortisol exerts antigrowth effects by stimulating protein catabolism (breakdown).

Concepts of Energy Expenditure
The breakdown of organic molecules liberates the energy stored in their bonds. The energy produced is used by cells to perform biological work - muscle contraction (external work) and active transport, molecular synthesis (internal work).
Energy that is liberated (ΔE) during breakdown of an organic molecule can either appear as heat (H) or be used to perform work (W).
$\Delta E=H+W$
Energy for work must first be incorporated into ATP. Heat cannot be converted to work but is used to maintain body temperature and thus homeostasis.

Metabolic Rate

Metabolic rate is the total energy expenditure per unit time. Basal metabolic rate (BMR) is the metabolic rate under certain standardized conditions (subject is at mental and physical rest in a room at a comfortable temperature and has not eaten for 12 hours). Most of the activity contributing to basal metabolic rate is from the activity of the heart, liver, kidney and brain.

Thyroid Hormones
Thyroid hormones are the most important determinant of BMR. They can increase BMR by increasing oxygen consumption and heat-production in most body tissues, which is termed a calorigenic effect, by reducing ATP production.
Epinephrine
Epinephrine increases metabolic rate by calorigenic effect. Epinephrine stimulates the catabolism of glycogen and triacylglycerols.
Food-Induced Thermogenesis
Ingestion of food raises body temperature and protein has the greatest effect in producing temperature changes.

Muscle Activity
Muscle activity increases muscle contraction, e.g., during exercise or shivering, which in turn increases the metabolic rate.

Regulation of Total-Body Energy Stores
Energy stored = Energy from food intake - (Internal heat produced + External work)
The body weight of adults is regulated around a set point by reflexively adjusting caloric intake and/or energy expenditure.

Control of Food Intake
A hormone, leptin, synthesized by adipose tissue, is released in proportion to the amount of fat in adipose tissue. The hormone acts on the hypothalamus to cause a reduction in food intake by inhibiting the release of a neuropeptide that stimulates eating. It also stimulates metabolic rate and therefore controls changes in energy expenditure. Leptin is important in long-term control. In short-term, various satiety signals such as insulin, body temperature, presence of food in GI tract act on the hypothalamus to regulate the duration and frequency of meals..

Overweight and Obesity
Overweight is a term to describe an increased amount of fat in the body and obesity is the state of being excessively overweight. The body mass index (BMI) is an index of weight and is calculated by dividing a person's weight by the square of their height. Low calorie diets have limited effectiveness to control weight since it results in a drop in metabolic rate, preventing further weight loss. Exercise, however, lowers the set point around which total body stores of fat are regulated. Exercise is an effective method, over time, in managing weight and body fat stores.

Eating Disorders
Anorexia nervosa is the pathological fear of gaining weight and consequent reduction of food intake. This disorder leads to low blood pressure, low body temperature and altered secretion of many hormones and a severe case may lead to death. Bulimia is recurrent episodes of binge eating associated with self-induced vomiting, laxatives, diuretics, dieting or exercise in order to rid the body of ingested food.

Regulation of Body Temperature
The ability to maintain body temperatures within narrow limits is called homeothermy. The total heat content of the body is net difference between heat production and heat loss. In steady state, heat production equals heat loss.

Mechanisms of Heat Loss or Gain
The body surface can lose heat by radiation, conduction, convection and by the evaporation of water.

Temperature-Regulating Reflexes
Changes in body temperature are detected by two types of thermoreceptors, ones in the skin (peripheral thermoreceptors) and ones in hypothalamus, spinal cord etc. (central thermoreceptors). Central thermoreceptors provide the essential negative feedback for maintenance of core body temperature while peripheral thermoreceptors provide feedforward information.
The hypothalamus serves as the overall integrator of reflexes and sends outputs via sympathetic nerves to sweat glands, skin arterioles, and adrenal medulla and via motor neurons to skeletal muscles.
Control of Heat Production
Changes in muscle activity constitute the major control of heat production and a decrease in core body temperature leads to an increase in skeletal muscle contraction, which then leads to shivering (rhythmical muscle contractions). No external work is performed by shivering and all liberated energy appears as internal heat, called shivering thermogenesis. Voluntary muscle contractions are also used to produce heat.
Control of Heat Loss by Radiation and Conduction
The skin's effectiveness as an insulator is subject to physiological control by a change in blood flow to the skin cells. As more blood reaches the skin from the core the closer the two temperatures become. Blood vessels reduce the insulating capacity of skin by carrying heat to the surface to be lost to the external environment. Vasoconstrictor sympathetic nerves, firing of which is increased in response to cold and decreased in response to heat, control these vessels. Behavioral mechanisms, such as curling up into a ball when cold, reduce the surface area exposed to the environment, thus decreasing heat loss by radiation and conduction.
Control of Heat Loss by Evaporation
Water loss through skin, sweat and respiratory tract can also contribute to heat loss.
Integration of Effector Mechanisms
The range of environmental temperatures over which body temperature can be maintained by vasoconstriction or vasodilation alone is called the thermoneutral zone. Below and above this zone, the body must increase its heat production and increase heat loss respectively.

Temperature Acclimatization
Changes in sweating onset, volume and composition determine adaptation to high temperatures. Sodium loss through sweat is reduced by its increased reabsorption due to aldosterone secretion.

Fever and Hyperthermia
Fever is the elevation of body temperature due to a resetting of the thermostat in the hypothalamus. Body temperature is always maintained during a fever. Fevers are caused by infection or stress. The raising of the body thermostat results in the overall sensation of feeling cold. Vasoconstriction and shivering occur to drive up body temperature. When the thermostat is reset and the fever breaks, it leads to person feeling hot, vasodilation and sweating occurs. Sometimes this process is referred to as fever and chills.
The thermostat is reset by chemical messengers, called endogenous pyrogen (EP), which consists of interleukin 1 (IL-1) and IL6. Both of which are released from macrophages, acting upon hypothalamus. Excessive and potentially damaging fever is prevented and temperature is brought back to normal.
Increased body temperature stimulates defensive responses to infection. An elevation in body temperature not due to infection is called hyperthermia. Exercise and retention of heat is a common cause.

Heat Exhaustion and Heat Stroke

Heat exhaustion is a state of collapse due to hypotension from: (1) depletion of plasma volume secondary to sweating, resulting in decreased cardiac output and (2) extreme dilation of skin blood vessels resulting in decreased peripheral resistance. It is a safety device to force cessation of work in a hot environment when heat loss mechanisms are overtaxed, preventing a large rise in body temperature.
Heat Stroke is a complete breakdown of heat-regulating systems so that the body temperature keeps going up. It is characterized by collapse, delirium, seizures, and unconsciousness. Heat stroke occurs due to overexertion in hot environments. It works in a positive feedback manner, raising body temperature, increasing metabolism and producing still further heat.

Human Reproduction

Terminology and Concepts

Primary reproductive organs are called gonads - testes in the male and ovaries in the female. Gonads (1) produce reproductive cells called gametes - spermatozoa in males and ova in females, the process being called gametogenesis, and (2) secrete steroid hormones called sex hormones - testosterone in male, estradiol and progesterone in females.
Testosterone belongs to a class of hormones that have masculinizing actions called androgens and estradiol belongs to a class of hormones called estrogens. Androgens are not unique to males and estrogens are not unique to females.
GnRH stimulates the release of pituitary gonadotropins - FSH and LH, which act upon the gonads to stimulate the development of sperm and ova and secretion of sex hormones. The sex hormones exert a negative feedback on the secretion of GnRH, LH and FSH.
Accessory reproductive organs consist of ducts through which sperm and ova are transported and the glands emptying into these ducts. Secondary sexual characteristics comprise the external differences between males and females.

Gametogenesis
Developing gametes are called germ cells and the first stage in their development is proliferation of primordial germ cells by mitosis or cell division in which each daughter cell receives a full set of chromosomes identical to those of the original cell. In females, this mitotic activity occurs only during embryonic development while in males it begins at puberty and continues throughout life. Although this is currently an area of research and new things are coming to light with regards to mitotic activity in female gonads. The second stage of development occurs by meiosis or cell division in which each daughter cell receives half of the chromosomes of the original cell.

Male Reproductive Physiology

Testes are suspended in sacs called scrotum. Spermatogenesis or sperm formation occurs in seminiferous tubules in the testes. Walls of these tubules are composed of developing germ cells, sertoli cells and leydig cells that lie between the tubules secrete testosterone. Seminiferous tubules empty into a duct called epididymis, which leads to the vas deferens. Ducts from the two glands - the seminal vesicles join the vas deferens to form two ejaculatory ducts, which then enter the prostrate gland and the paired bulbourethral glands before joining the urethra. Prostrate glands and seminal vesicles secrete a fluid in which sperm cells are suspended, and this fluid together with the sperm cells is called semen. The glandular secretions contain nutrients, buffers that protect the sperm from vaginal acidity, chemicals that increase sperm motility and mucus for lubrication.

Spermatogenesis
Undifferentiated germ cell, termed spermatogonia, divide by mitosis and differentiate to produce primary spermatocytes, which grow and undergo first meiotic division to form secondary spermatocytes, which undergo second meiotic division to form spermatids. Spermatids then develop into spermatozoa.
The head of a sperm consists of DNA nucleus and a tip, which is covered by the acrosome, a vesicle containing many enzymes that play an important role in sperm's penetration of egg. Most of the tail is a flagellum that propels the sperm.
Leydig cells secrete testosterone and sertoli cells divide the tubules into separate compartments with separate environments where different stages of spermatogenesis can take place. They also secrete androgen binding protein, which binds testosterone and act as intermediaries between germ cells and hormones.

Sperm Transport
The vas deferens and epididymis store the sperm until ejaculation. Sperms are non-motile at this time. During passage through epididymis, they are concentrated by fluid absorption.

Erection
Penis consists of vascular compartments and arteries supplying them are normally constricted so that there is little blood in them, and penis is flaccid. Sexual excitation in higher brain centers, stimulation of mechanoreceptors in penis, inhibition of sympathetic fibers and release of nitric oxide dilate these arteries, cause these compartments to become engorged with blood at a high pressure, making the penis elongated and rigid. Erectile dysfunction is inability to achieve erection due to various physiological and/or psychological causes. Viagra, and related products, block the breakdown of cGMP; a messenger involved in relaxation of arterial smooth muscle, which promotes erection.

Ejaculation
Stimulation of sympathetic nerves contracts the smooth muscles lining the ducts and discharges semen through urethra. The sphincter at the base of urinary bladder is closed so that sperm cannot enter bladder nor can urine be expelled. Heart rate and blood pressure increases and skeletal muscles contract throughout the body and this event is called orgasm.

Hormonal Control of Male Reproductive Functions

Control of Testes
FSH acts on sertoli cells to stimulate spermatogenesis. LH acts on leydig cells to stimulate testosterone secretion.

Testosterone:

1. Stimulates spermatogenesis.
2. Induces differentiation of male accessory reproductive organs and maintains their function.
3. Induces male secondary sex characteristics
4. Stimulates protein anabolism, bone growth, erythropoietin secretion
5. Required for sex drive and may enhance aggressive behavior.

Female Reproductive Physiology

Production of female gamete, the egg, followed by its release from ovary is called ovulation. Ovulation is cyclical and predictable. These cycles are called menstrual cycles in humans. Cyclical changes in hormone secretion by ovaries cause changes in the entire female reproductive tract, including the uterus, which is made ready to receive and nourish the gamete.

There is no menstruation during pregnancy.
The ovaries end close to the uterine tubes (oviducts or fallopian tubes), which are attached to the uterus. The uterus is a hollow, thick walled, muscular organ that houses the fetus during pregnancy and is the source of bleeding during menstruation. The lower portion of uterus is called cervix, and the canal leading from the cervix to the outside is the vagina. These are the structures of the female internal genitalia.

Ovarian Function

Oogenesis

Primitive germ cells, called oogonia undergo mitosis and develop into primary oocytes (with 46 chromosomes) and remain at a state of meiotic arrest (they begin the first meiotic development but do not complete it). All the germ cells in a female are at this developmental stage at birth. Although this is an area currently being studied further.
At puberty, primary oocytes destined for ovulation complete meiosis, each daughter cell receiving 23 chromosomes. One of the two daughter cells retains all the cytoplasm and is called the secondary oocyte while the other, called the first polar body, is nonfunctional. The second meiotic division occurs in uterine tube after ovulation, ONLY IF the secondary oocyte is fertilized. Again, one daughter cell retains all the cytoplasm and is called ovum while the other cell, called the second polar body, is nonfunctional and is later absorbed by the body.

Control of Ovarian Function

Three Phases:
1. Follicular Phase of Ovary (corresponding to the Proliferative Phase of the Uterus)
FSH and LH increase during follicular phase because estrogen concentration is low and therefore negative feedback on these pituitary hormones is low. FSH and LH stimulate primary follicles (containing primary oocytes) to grow and stimulate their theca cells to produce estrogen.
Estrogen leads to a thickening of the uterine epithelium, the endometrium.
Estrogen begins to exert a negative feedback on FSH. As FSH goes down, all the follicles cannot be maintained and all but one follicle degenerates. The one dominant follicle (Graafian follicle) survives because (a) it is hyperresponsive to FSH and can maintain itself even under low FSH, and (b) it also becomes sensitive to LH.
In the meanwhile, LH does not drop but shoots up (LH surge) because increased estrogen exerts a positive feedback effect on the LH releasing mechanism of pituitary.
LH surge leads to release of the primary oocyte (ovulation).
2. Luteal Phase of Ovary (corresponding to Secretory Phase of the Uterus) The now empty follicle, corpus luteum, starts secreting estrogen and progesterone. These hormones exert a negative feedback on secretion from LH and FSII, preventing new follicles from maturing.
Progesterone converts the endometrium into a secretory tissue full of glycogen and blood vessels, ready to receive a fertilized egg.
3. Beginning of new cycle (corresponding to Menstrual Phase of the Uterus)
(If the egg is not fertilized) If fertilization does not occur, the corpus luteum degenerates and estrogen and progesterone levels recede. The lack of estrogen and progesterone leads to the collapse of the vascular endometrium, which in turn leads to menstruation.

Pregnancy

Egg and Sperm Transport

At ovulation, the egg enters the uterine tube. Sperm enters the uterus during intercourse and moves into the uterine tube through its own rhythmic propulsions. Most of the sperm cells die in the acidic vaginal environment and/or due to the exhaustion of their energy supply.

Fertilization
The sperm binds to the egg by complementary surface proteins. The binding triggers the acrosome reaction in the sperm and its enzymes digest the egg membrane. The sperm then passes into the cytoplasm of the egg.
The fertilized egg (zygote) releases enzymes that harden the egg membrane and inactivate the sperm binding sites to prevent additional sperms from fusing.

Implantation and Placentation
The zygote undergoes mitotic cell divisions (without cell growth) called cleavage, becoming a blastocyst, which embeds in the endometrium, in a process called implantation.
If the zygote divides into two completely separate masses, it results in identical (monozygotic) twins. Fraternal twins result from two ovulated eggs being fertilized.
The outer layer of the blastocyst, the trophoblast gives rise to the fetal part of the placenta while the inner cell mass develops into the embryo proper.
Fetal blood and maternal blood both flow through the placenta (without mixing), exchanging gases, nutrients, hormones, and wastes through a structure called the placenta. The placenta is a combination of fetal and maternal tissues. Blood vessels enter and leave the placenta through the umbilical cord, which is connected, to the baby at the site of the belly button.
The fetus is surrounded by a space called the amniotic cavity filled with a fluid called amniotic fluid, providing a buffer to mechanical and other disturbances. A number of genetic disorders can be diagnosed by sampling this amniotic fluid (amniocentesis) for the presence or absence of certain chemicals.

Hormonal Changes during Pregnancy
The uterus is maintained during pregnancy by progesterone and estrogen that initially comes from the corpus luteum, which in turn is maintained by the hormone, chorionic gonadotropin that is produced by the trophoblast. Corpus luteum later regresses and the placenta itself produces the required estrogen and progesterone. High levels of these hormones inhibit secretion of GnRH and gonadotropins, thus eliminating menstrual cycles during pregnancy.

Parturition
A normal pregnancy lasts for 38 weeks from the day of ovulation and conception. Delivery occurs by rhythmical contractions of the uterus, stimulated by oxytocin. The cervix dilates and the infant moves out through the vagina.

Lactation
Lactation is the secretion of milk by the mammary glands, or breasts. Estrogen and progesterone secretion at the onset of puberty leads to breast enlargement due to the development of the duct system. During pregnancy, estrogen stimulates the secretion of prolactin and placental lactogen, which stimulate the development of the glands (alveoli) in the breasts.
However, milk secretion is inhibited by estrogen and progesterone during pregnancy. A decline in the levels of these two hormones as a result of placental removal during childbirth removes the inhibitory effect. Milk secretion is maintained by prolactin release as a result of afferent input from nipple receptors to hypothalamus during suckling which also inhibits dopamine secretion.
Milk ejection from the alveoli to the ducts is stimulated by the action of oxytocin, released as a result of the suckling reflex. Suckling also inhibits the hypothalamo-pituitary-ovarian hormone chain, which in effect blocking ovulation.

Contraception
Oral contraceptives are made of synthetic progesterone and estrogen combinations that inhibit pituitary gonadotropin release and thereby prevent ovulation.
Postcoital contraceptives include progesterone antagonists that prevent progesterone from binding to uterine wall, leading to erosion of the endometrium.

Puberty

Puberty is the period during which reproductive organs mature and reproduction becomes possible. This process is initiated by secretion of adrenal androgens which is stimulated by ACTH. In females, the first menstrual period is called menarche.

Menopause
Menopause is the cessation of menstrual periods with age, as a result of a decrease in the number of ovarian follicles and their hyporesponsiveness to gonadotropins. Plasma estrogen levels decrease resulting in high gonadotropin secretion. A decrease in bone mass called osteoporosis occurs as well as hot flashes or the sudden dilation of arterioles, increase in body temperature, and sweating.