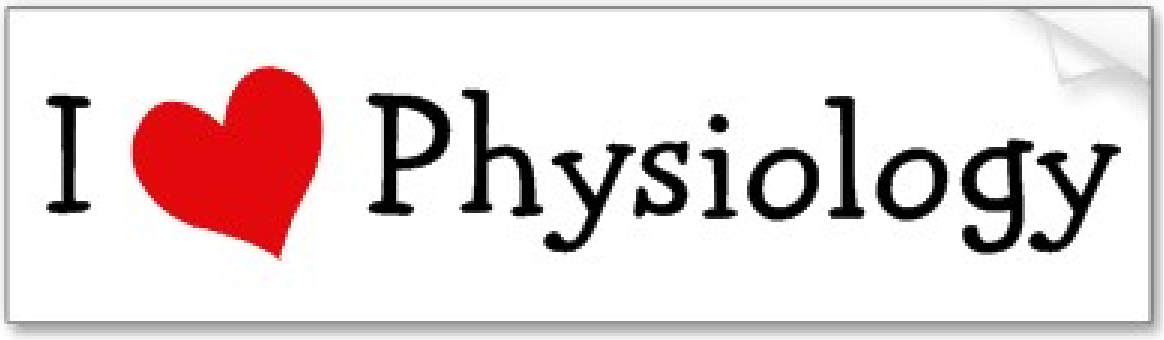


SECTION A

By Catarina Carvalho de Bastos
2012

7. Ion channels

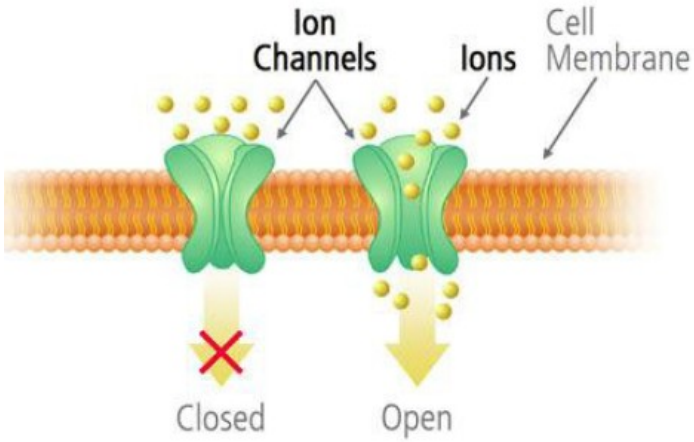
Integral membrane proteins can span the lipid bilayer and form channels that allow ions to diffuse across the membrane.

1. Ion channels show selectivity: this selectivity is based partially on the channel diameter and partially on the charged and polar surfaces of the protein subunits that form the channel walls and electrically attract or repel the ions.
2. Ions channels can exist in an open or closed state. The process of opening and closing ion channels is known as channel gating. A single ion channel may open and close many times each second, suggesting that the channel protein fluctuates between two (or more) conformations. Over an extended period of time, at any given electrochemical gradient, the total number of ions that pass through, a channel opens and how long it stays open.

Five factors can alter the channel protein conformations, producing changes in the opening frequency or duration:

- The binding of specific molecules to channel proteins may directly or indirectly produce either allosteric or covalent change in shape of the channel protein. Such channels are termed ligand-gated channels, and the ligands that influence them are often chemical messengers.
- Changes in membrane potential can cause movement of the charged regions on a channel protein, altering its shape - these are voltage-gated channels
- Physically deforming (stretching) the membrane may affect the conformation of some channel proteins - these are mechanically gated channels.
- Intracellular messenger substances such as: cAMP (e.g. in Ca^{2+} channels in myocardial cells and Cl^- channels in epithelial cells), cGMP (plays a role in muscarinergic effects of acetylcholine and in excitation of the retinal rods), IP3 (e.g. opening of Ca^{2+} channels of intracellular Ca^{2+} stores), small G-proteins (e.g. Ca^{2+} channels of the cell membrane), tyrosine kinases (e.g. Cl^- and K^+ channels during apoptosis), Ca^{2+} (affects, for instance, K^+ channels and degree of activation of rapid Na^+ channels).
- Intracellular metabolites such as ATP (e.g. in K^+ channels in the heart and B cells in pancreatic islets) or H^+ ions (e.g. in K^+ channels in renal epithelial cells).

A particular type of ion may pass through several different types of channels. For example, a membrane may contain ligand-gated potassium (K^+) channels, voltage-gated K^+ channels, and mechanically-gated K^+ channels. Moreover, the same membrane may have several types of voltage-gates K^+ channels, each responding to a different range of membrane voltage, or several types of ligand-gated K^+ channels, each responding to a different chemical messenger.



8.Intercellular communication

Cells receive information from their environment through a class of proteins known as receptors. Molecules that activate (or, in some cases, inhibit) receptors can be classified as hormones, neurotransmitters, cytokines, growth factors but all of these are called receptor ligands.

For several types of intercellular signaling molecules that are unable to permeate the hydrophobic cell membrane due to their hydrophilic nature, the target receptor is expressed on the membrane. When such signaling molecule activates its receptor, the signal is carried into the cell usually by means of a second messenger such as cAMP.

For those intercellular signaling molecules which are able to drops the phospholipids bilayer (lipophilic), there are intracellular receptors, responsible for triggering the biological response

Cells communicate with each other via direct contact (juxtacrine signaling), over short distances (paracrine signaling), or over large distances (endocrine signaling).

- ✓ **Endocrine signals** are produced by endocrine cells and travel through the blood to reach all parts of the body.
- ✓ **Paracrine signals** target only cells in the vicinity of the emitting cell. Neurotransmitters represent an example.
- ✓ **Autocrine signalling** is a form of signaling in which a cell secretes a hormone or chemical messenger that binds to autocrine receptors on the same cell. An example for autocrine signals is found in immune cells.
- ✓ **Juxtacrine signals** are transmitted along cell membranes via protein or lipid components integral to the membrane and are capable of affecting either the emitting cell or cells immediately adjacent.

Some cell-to-cell communication requires direct cell–cell contact.

Intercellular connections - are local specializations of lateral cell membranes between adjacent cells. In general, they serve three functions:

- Increase the cellular attachment - <u>adhering junctions</u>
- Seal the intercellular space - <u>occluding junctions</u>
- Serve for cell-to-cell communication - <u>gap or communicating junctions</u>

Adhering junctions form strong bond between adjacent cells or between basal part of the cell membrane

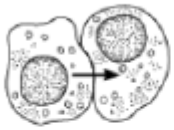
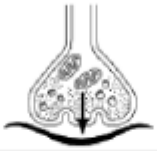
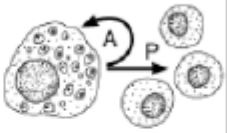
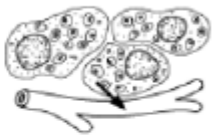
- <u>Spot desmosome</u> (macula adherens) occurs especially in tissues that are subjected to extreme mechanical stress. The intercellular space is 30 nm wide and contains extracellular glycoproteins that promote adhesion of adjacent cells. On both cytoplasmic sides of the macula adherens, there are 20 nm thick electron dense plaques (containing special proteins - desmoplakins I and II), into which tonofilaments insert.
- <u>Belt desmosome</u> (zonula adherens) encircles an epithelial cell completely. In addition, the intercellular space is about half as wide (15 nm). Cytoplasmic plaques are poorly developed.
- <u>Hemidesmosomes</u> = junctions between the plasmalema of basal aspect and lamina basalis.

Occluding junction are sites where plasma membranes are in such close contact that their integral and peripheral proteins are fused. Integral proteins that are shared belong to family occludins and claudins.

They have belt-like structure and encircle epithelial cell completely.

The function of tight junction is to seal the extracellular space between adjacent epithelial cells. They may be “tight” (impermeable), as in the renal distal tubule, or “leaky” (permeable), as in the renal proximal tubule and gallbladder.

Communicating junction or gap junction (nexus): occur between a variety of excitable and non-excitable cells; serve to passage of ions and electrical impulses in the cardiac and smooth muscle. They usually show form of plaques or spot-like regions in which membranes of adjacent cells run in close apposition. Intercellular space is retained and reduced to only 2 to 4 nm. There are numerous bridges in extent of each gap junction formed by a special protein, called connexin

	GAP JUNCTIONS 	SYNAPTIC 	PARACRINE AND AUTOCRINE 	ENDOCRINE 
Message transmission	Directly from cell to cell	Across synaptic cleft	By diffusion in interstitial fluid	By circulating body fluids
Local or general	Local	Local	Locally diffuse	General
Specificity depends on	Anatomic location	Anatomic location and receptors	Receptors	Receptors

9. Second messengers

Second messengers are substance that ester or are generated in the cytoplasm as a result of receptor activation by the first messenger. The second messengers diffuse throughout the cell to serve as chemical relays from the plasma membrane to the biochemical machinery inside the cell. They greatly amplify the strength of the signal.

Types of secondary messenger molecules

There are many basic types of secondary messenger molecules:

- Hydrophobic molecules: water-insoluble molecules, like diacylglycerol, and phosphatidylinositols, which are membrane-associated and diffuse from the plasma membrane into the intermembrane space where they can reach and regulate membrane-associated effector proteins
- Hydrophilic molecules: water-soluble molecules, like cAMP, cGMP, IP_3, and Ca^{2+}, that are located within the cytosol
- Gases: nitric oxide (NO) and carbon monoxide (CO), which can diffuse both through cytosol and across cellular membranes.
- On the other hand, some lipophilic molecules (like steroid hormones) enter the cells themselves.

These intracellular messengers have some properties in common:

- They can be synthesized/released and broken down again in specific reactions by enzymes or ion channels.
- Some (like Ca^{2+}) can be stored in special organelles and quickly released when needed.
- Their production/release and destruction can be localized, enabling the cell to limit space and time of signal activity.

Common mechanism of hydrophilic second messenger systems

There are several different secondary messenger systems (cAMP system, phosphoinositol system, and arachidonic acid system), but they all are quite similar in overall mechanism, though the substances involved in those mechanisms and effects are different.

In all of these cases, a neurotransmitter binds to a membrane-spanning receptor protein molecule. The binding of the neurotransmitter to the receptor changes the receptor and causes it to expose a binding site for a G-protein. The G-protein (named for the GDP and GTP molecules that bind to it) is bound to the inner membrane of the cell and consists of three subunits: alpha, beta and gamma. The G-protein is known as the "transducer."

When the G-protein binds to the receptor, it becomes able to exchange a GDP (guanosine diphosphate) molecule on its alpha subunit for a GTP (guanosine triphosphate) molecule. Once this exchange takes place, the alpha subunit of the G-protein transducer breaks free from the beta and gamma subunits, all parts remaining membrane-bound. The alpha subunit, now free to move along the inner membrane, eventually contacts another membrane-bound protein - the "primary effector."

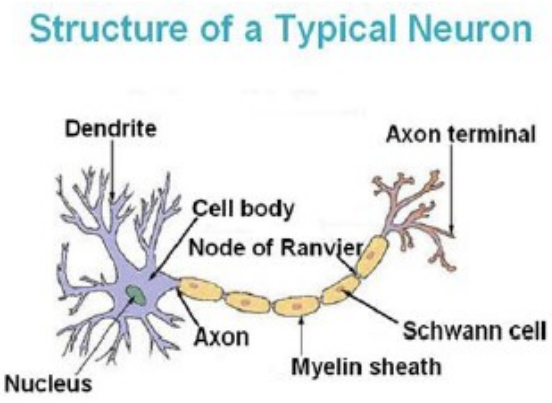
The primary effector then has an action, which creates a signal that can diffuse within the cell. This signal is called the "secondary messenger." (The neurotransmitter is the first messenger.) The secondary messenger may then activate a "secondary effector" whose effects depend on the particular secondary messenger system.

In the case of lipophilic molecules (steroid hormones as well as calcitriol, T3 and T4), once they bind to cytosolic receptor proteins are transported to the cell nucleus, where there is Interaction of the complex hormone-receptor with the HRE (hormone response element of nuclear DNA) ans subsequent influence in transcription → Biological response.

10. Functions of the nerve cell

The nervous tissue consists of two principal types of cells: the nerve cells or neurons, and special supporting cells called neuroglia. Neurons operate by generating electrical signals that move from one part of the cell to another part of the cell or to neighboring cells. Neurons serve as integrators because their output reflects the balance of inputs they receive from thousands or hundreds of thousands of other neurons that impinge upon them. The functional units of nervous tissue are neurons in which two properties of protoplasm are developed to a great degree: irritability (the capacity for response to physical and chemical agents with the initiation of an impulse), and conductivity (the ability to transmit such an impulse from one locality to another).

Functional Morphology



Each neuron consists of three parts: the cell body or perikaryon, the dendrites and the axon or neurite. Terminally, each axon ends in twig like branching or arborizations. The sites of contact between neurons are called synapses.

Dendrites are a series of highly branched outgrowths of the cell body. They and the cell body receive most of the inputs from other. The branching dendrites (some neurons may have as many as 400000) increase the cell's surface area. Thus, dendrites increase a cell's capacity to receive signals from many other neurons. Dendrites contain the same organelles as the cell body proper, except the Golgi network.

The **neuron's cell body** (or soma) contains the nucleus and ribosomes and thus has the genetic information and machinery necessary for protein synthesis. The cell body or perikaryon contains round nucleus with a prominent nucleolus in the centre. By electron microscopy, numerous mitochondria, large Golgi apparatus, lysosomes, microtubules, neurofilaments and inclusions are detectable in the cytoplasm. Free ribosomes and RER are often clustered and form areas known as Nissl bodies. Nissl bodies are considered as morphological indicator of protein synthesis.

The **axon**, sometimes also called a nerve fiber, is a long process that extends from the cell body and carries output to its target cells. Axons range in length from a few microns over a meter. The region where the axon connects to the cell body is known as the initial segment. The initial segment is the trigger zone where, in most neurons, the electrical signals are generated. These signals then propagate away from the cell body along the axon or, sometimes, back along the dendrites. The main axon may have branches, called collaterals.

Each branch ends in an axon terminal, which is responsible for releasing neurotransmitters from the axon. These chemical messengers diffuse across an extracellular gap to the cell opposite the terminal. Different parts of nerve cells serve different functions because of the regional distribution of various membrane-bound channels and pumps.

The axons of many neurons are covered by myelin, which consists of 20 to 200 layers of highly modified plasma membrane wrapped around the axon by nearby supporting cell. In the brain and spinal cord, these myelin-forming cells are the oligodendrocytes. Each oligodendrocyte may branch to form myelin on as many as 40 axons. In the peripheral nervous system, cells called Schwann cells form individual myelin sheaths at regular intervals along the axons. The spaces between adjacent sections of myelin where the axon's plasma membrane is exposed to extracellular fluid are the nodes of Ranvier. The myelin sheath speeds up conduction of the electrical signals along the axon and conserves energy.

To maintain the structure and function of the cell axon, various organelles and other materials must move between the cell body and the axon terminals. This movement, termed axonal transport, depends on a scaffolding of microtubule and specialized types of "motor proteins" known as kinesins and dyneins. Kinesin transport mainly occurs from the cell body toward the axon terminals anterograde), and is important in moving nutrient molecules, enzymes,

mitochondria, neurotransmitter-filled vesicles, and other organelles. Dynein movement is in the other direction (retrograde), carrying recycled membrane vesicles, growth factors, and other chemical signals that can affect the neuron's morphology, biochemistry, and connectivity.

11. Functional morphology of synapses

A synapse is defined as the site of junction of neurons or site of junction between neuron and the effector cell. The synapse itself consists of three distinct parts:

1. A **presynaptic knob** or axonal ending of on neuron, it contains besides mitochondria and neurofilaments a great number of synaptic vesicles, in which transmitters are stored.
2. A **postsynaptic membrane** – is the membrane of the second neuron and/or effector cell.
3. A **synaptic cleft** – is a narrow space, about 20nm, separating above mentioned parts of each synapse.

Types of synapses: Axosomatic, Axodendritic, Acosomatodendritic, Axoaxonal (rare).

There are two types of synapses: electrical and chemical.

At electrical synapses, the plasma membranes of the pre- and postsynaptic cells are joined by gap junctions. These allow the local currents to flow directly across the junction through the connecting channels in either direction from one neuron to the other. This depolarizes the membrane of the second neuron to threshold, continuing the propagation of the action potential.

In chemical synapses, the axon of the presynaptic neuron ends in a slight swelling, the axon terminal, which holds the synaptic vesicles that contain the neurotransmitter. The postsynaptic membrane opposing the axon terminal has a high density of intrinsic and extrinsic membrane proteins that make up a specialized area called the postsynaptic density. The synaptic cleft separates the pre- and postsynaptic neurons and prevents direct propagation of the current from the presynaptic neuron to the postsynaptic cell. Instead, signals are transmitted across the synaptic cleft by means of a chemical messenger – a neurotransmitter – released from the presynaptic axon terminal. Sometimes more than one neurotransmitter may be simultaneously released from an axon, in which case the additional neurotransmitter is called a cotransmitter. These neurotransmitters have different receptors on the postsynaptic cell.

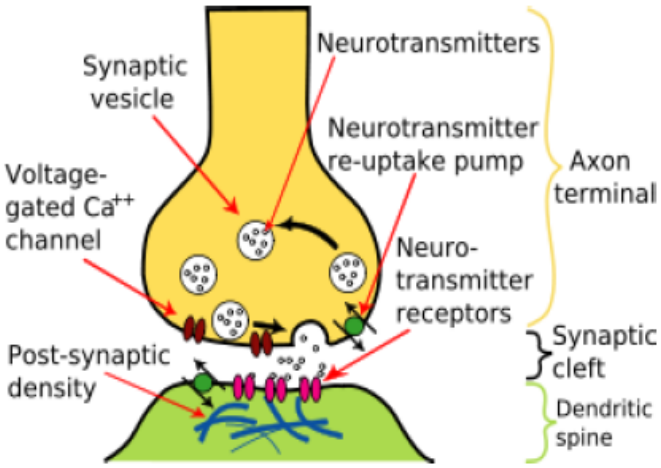
In general, the neurotransmitter is stored on the presynaptic side of the synaptic cleft, whereas receptors for the neurotransmitters are on the postsynaptic side. Therefore, most chemical synapses operate in only one direction.

Mechanisms of neurotransmitter release

Neurotransmitter is stored in small vesicles with lipid bilayer membranes. Neurotransmitter release is initiated when an action potential reaches the terminal of the presynaptic membrane. A key feature of neuron terminals is that in addition to the sodium and potassium channels found elsewhere in the neuron, they also possess voltage-gated calcium channels. Depolarization during the action potential opens these calcium channels, and because the electrochemical gradient favors calcium influx, calcium flows into the axon terminal. Increase in intracellular [Ca2+] activates Ca2+-calmodulin-dependent protein-kinase that phosphorylates synapsin-1; its interaction with the membrane of synaptic vesicles initiates their fusion with the presynaptic membrane and neurotransmitter exocytosis. In addition, calcium stimulates the production of more neurotransmitter-filled vesicles.

Examples of transmitters:

- Acetylcholine (ACh)
- Noradrenaline (norepinephrine, NE)
- Dopamine (DA)
- Serotonine (5-hydroxytryptamine)
- Gamma amino butyric acid (GABA)
- Glutamic acid and Glycine
- some of peptides

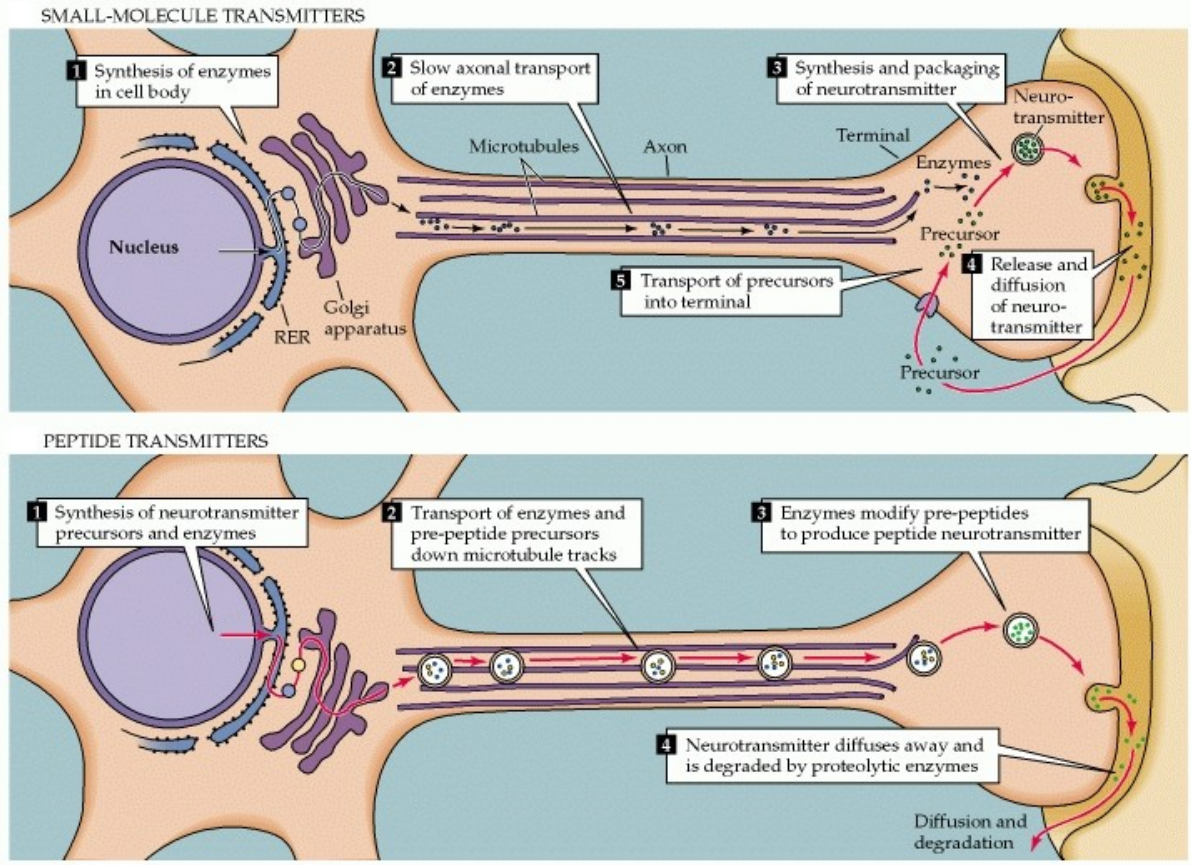


12. Synthesis and break down of neurotransmitters

The **synthesis of small-molecule neurotransmitters** occurs within presynaptic terminals. The enzymes needed for transmitter synthesis are synthesized in the neuronal cell body and transported to the nerve terminal cytoplasm by a mechanism called slow axonal transport. The precursor molecules used by these synthetic enzymes are usually taken into the nerve terminal by transporter proteins found in the plasma membrane of the terminal. The enzymes generate a cytoplasmic pool of neurotransmitter that must then be loaded into synaptic vesicles by transport proteins in the vesicular membrane. For some small-molecule neurotransmitters, the final synthetic steps actually occur inside the synaptic vesicles.

The mechanisms responsible for the synthesis and packaging of peptide transmitters are fundamentally different from those used for the smallmolecule neurotransmitters. Peptide-secreting neurons generally synthesize polypeptides in their cell bodies that are much larger than the final, “mature” peptide. Processing these polypeptides, which are called pre-propeptides (or pre-proproteins), takes place by a sequence of reactions in several intracellular organelles. Pre-propeptides are synthesized in the rough endoplasmic reticulum, where the signal sequence of amino acids - that is, the sequence indicating that the peptide is to be secreted - is removed. The remaining polypeptide, called a propeptide (or proprotein), then traverses the Golgi apparatus and is packaged into vesicles in the trans-Golgi network. The final stages of peptide neurotransmitter processing occur after packaging into vesicles and involve proteolytic cleavage, modification of the ends of the peptide, glycosylation, phosphorylation, and disulfide bond formation.

Neuropeptide synthesis is, therefore, much like the synthesis of proteins secreted from non-neuronal cells (pancreatic enzymes, for instance). A major difference, however, is that the neuronal axon often presents a very long distance between the site of a peptide's synthesis and its ultimate secretion. The peptide-filled vesicles must therefore be transported along the axon to the synaptic terminal. The mechanism responsible for such movement, known as fast axonal transport, carries vesicles at rates up to 400 mm/day along cytoskeletal elements called microtubules (in contrast to the slow axonal transport of the enzymes that synthesize small-molecule transmitters). Peptide-containing vesicles are moved along these microtubule “tracks” by ATP-requiring “motor” proteins such as kinesin.



Degradation

When the neurotransmitter has been secreted into the synaptic cleft, it binds to specific receptors on the postsynaptic cell, thereby generating a postsynaptic electrical signal. The transmitter must then be removed rapidly to enable the postsynaptic cell to engage in another cycle of neurotransmitter release, binding, and signal generation. The mechanisms by which neurotransmitters are removed vary but always involve diffusion in combination with reuptake into nerve terminals or surrounding glial cells, degradation by transmitter-specific enzymes, or in some cases a combination of these mechanisms. For most of the small-molecule neurotransmitters, specific transporter proteins remove the transmitters (or their metabolites) from the synaptic cleft, ultimately delivering them back to the presynaptic terminal for reuse. The majority of polypeptides are degraded by proteases.

The particulars of synthesis, packaging, release and removal differ for each neurotransmitter.

Examples:

- Synthesis of cathecholamines

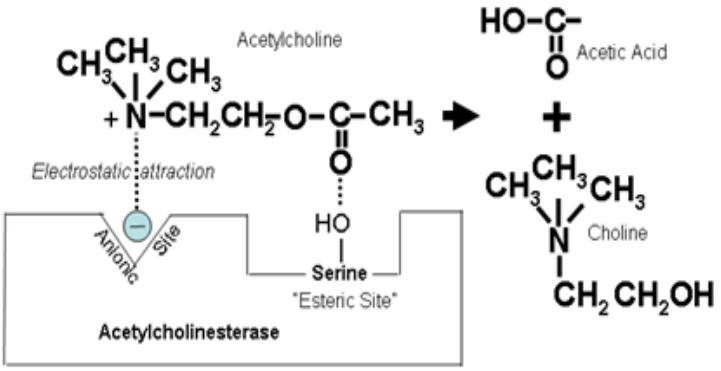
Dopamine is the first catecholamine to be synthesized from steps shown. Norepinephrine and epinephrine, in turn, are derived from further modifications of dopamine. Synthesis of norepinephrine begins in the axoplasm of the terminal nerve endings of adrenergic nerve fibers but is completed inside the secretory vesicles. It is important to note that the enzyme dopamine hydroxylase requires copper as a cofactor. The rate limiting step in the biosynthesis is hydroxylation of tyrosine.

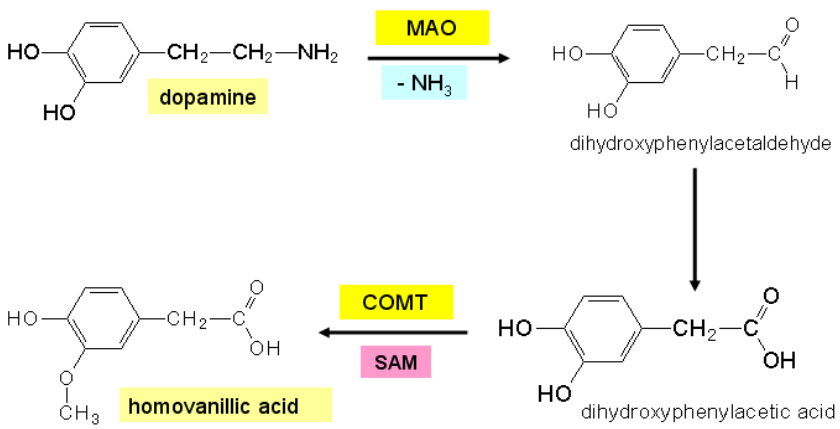
- Synthesis of serotonin

Serotonin is synthesized from the amino acid tryptophan by a short metabolic pathway consisting of two enzymes: tryptophan hydroxylase (TPH) and amino acid decarboxylase (DDC). The TPH-mediated reaction is the rate-limiting step in the pathway.

Degradation and elimination

Neurotransmitter must be broken down once it reaches the post-synaptic cell to prevent further excitatory or inhibitory signal transduction. For example, acetylcholine (ACh), an excitatory neurotransmitter, is broken down by acetylcholinesterase (AChE). Choline is taken up and recycled by the pre-synaptic neuron to synthesize more ACh. Other neurotransmitters such as dopamine are able to diffuse away from their targeted synaptic junctions and are eliminated from the body via the kidneys, or destroyed in the liver. Each neurotransmitter has very specific degradation pathways at regulatory points, which may be the target of the body's own regulatory system or recreational drugs.





13. Proteosynthesis

1. Transcription
2. Post transcriptional modification
3. Translation
4. Post translational modification

The first step in using the genetic information in DNA to synthesize a protein is called transcription and it involves the synthesis of an RNA molecule containing coded information that corresponds to the information in a single gene → messenger RNA (mRNA).

Transcription

The pool of subunits used to synthesize mRNA are free (uncombined) ribonucleotide triphosphates: ATP, GTP, CTP, and UTP. To initiate RNA synthesis, the two strands of the DNA double helix must separate so that the bases in free ribonucleotide triphosphates. The aligned ribonucleotides are joined tohether by the enzyme RNA polymerase, which hydrolyses the nucleotide triphosphates, releasing two of the terminal phosphate groups and joining the remaining phosphate in covalent linkage to the ribose of the adjacent nucleotide. Which of the two DNA strands is used as the template strand for RNA synthesis from a particular gene is determined by a specific sequence of DNA nucleotides called the promoter, which is located near the beginning of the gene on the strand to be transcribed. It is to this promoter region that RNA polymerase binds and initiates transcription.

RNA polymerase moves along the template strand, joining one ribonucleotide at a time to the growing RNA chain. A three-base sequence in RNA that specifies one amino acid is called a codon. Although the entire sequence of nucleotides in the template strand of a gene is transcribed into a complementary sequence of nucleotides known as the primary RNA transcript, only certain segments of most genes actually code for sequences of amino acids. These regions of the gene, known as exons (expression regions), are separated by noncoding sequences of nucleotides known as introns. RNA transcript must undergo splicing.

Translation

After splicing, the mRNA moves through the pores in the nuclear envelope into the cytoplasm. They have specific energy-dependent mechanisms for the selective transport of large molecules such as proteins and RNA.

In the cytoplasm, mRNA binds to a ribosome. Free amino acids do not have the ability to bind by themselves, to the bases in mRNA codons. This process of identification involves the third major class of RNA, known as transfer RNA (tRNA). The key to tRNA's role in protein synthesis is its ability to combine with both a specific amino acid and a codon in ribosome-bound mRNA specific for that amino-acid. This permits tRNA to act as the link between an amino acid and the mRNA codon for that amino acid.

A tRNA molecule is covalently linked to a specific amino acid by an enzyme known as aminoacyl-tRNA synthase. The next step is to link the tRNA, bearing its attached amino acid, to the mRNA codon for that amino acid.. this is achieved by base-pairing between tRNA and mRNA. This tRNA three-letter code sequence is appropriately termed an anticodon.

Protein assembly

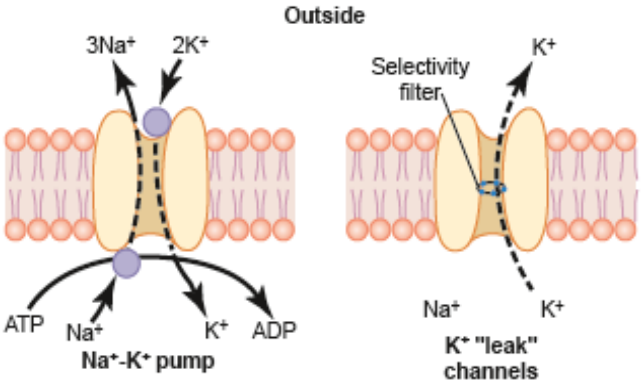
The process of assembling a polypeptide chain based on an mRNA message involves three stages – initiation, elongation, and termination. The initiation of synthesis occurs when a tRNA containing the amino acid methionine binds to the small ribosomal subunit.

The large ribosomal subunit then binds, enclosing the mRNA between the two subunits.

Following the initiation process, the protein chain is elongated by the successive addition of amino acids. When the ribosome reaches a termination sequence in mRNA, the link between the polypeptide chain and the last tRNA is broken, and the completed protein is released from the ribosome.

14. Generation of resting membrane potential

The resting membrane potential of large nerve fibers when not transmitting nerve signals is about -90 millivolts. That is the potential inside the fiber is 90 millivolts more negative that the potential in the extracellular fluid on the outside of the fiber.



The sodium-potassium pump continually pumps sodium ions to the outside of the cell and potassium ions to the inside → more positive charges are pumped to the outside than to the inside (three Na+ ions to the outside for each two K+ ions to the inside), leaving a net deficit of positive ions on the inside; this causes a negative potential inside the cell membrane.

In the nerve membrane there is a channel protein through which potassium and sodium ions can leak, called potassium-sodium "leak" channel. The emphasis is on potassium leakage because, on average, the channels are far more permeable to potassium than to sodium.

Origin of the normal resting membrane potential

Lets make the assumption that the only movement of ions through the membrane is diffusion of potassium ions. Because of the high ratio of potassium ions inside to outside. 35:1, the Nerst potential corresponding to this ratio is -94 millivolts. If potassium ions were the only factor causing the resting potential, the resting potential inside the fiber would be equal to -94 millivolts.

Contribution of sodium diffusion through the nerve membrane

The nerve membrane is slightly permeable to sodium ions, which is caused by the minute diffusion of sodium through the K^+-Na^+ leak channels. The ratio of sodium ions from inside to outside the membrane is 0.1 and this gives a calculated Nerst potential for the inside of the membrane of +61 millivolts. Goldman equation is used to calculate the summed potential. If the membrane is highly permeable to potassium but only slightly permeable to sodium, it is logical that the diffusion of potassium contributes far more to the membrane potential than does the diffusion of sodium. In the normal nerve fiber, the permeability of the membrane to potassium is about 100 times as great as its permeability to sodium. Goldman equation gives a potential inside the membrane of -86 milivolts, which is near potassium potential.

Contribution of the Na^+-K^+ pump

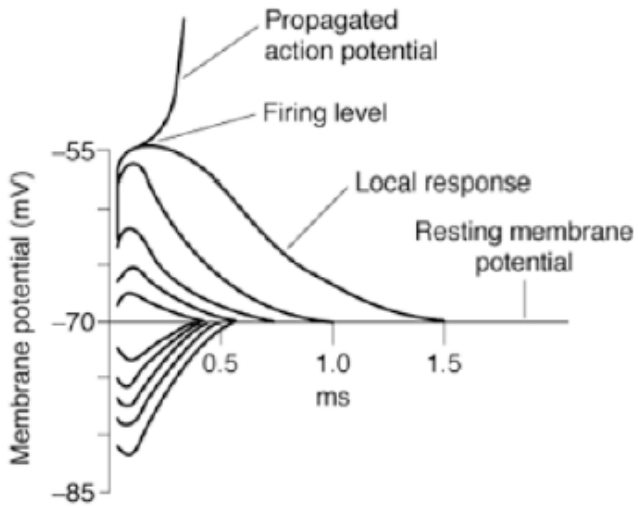
Additional contribution to the resting potential is given by Na^+-K^+ pump. There is continuous pumping of three sodium ions to the outside for each two potassium ions pumped to the inside of the membrane. More sodium ions are being pumped to the outside than potassium to the inside causes continual loss of positive charges from inside the membrane; this creates an additional degree of negativity (about -4 millivolts). The net membrane potential with all these factors operating at the same time is about -90 millivolts.

In summary, the diffusion potentials alone caused by potassium and sodium diffusion would give a membrane potential of about -86 millivolts, almost all of this being determined by potassium diffusion. Then, an additional -4 millivolts is contributed to the membrane potential by the continuously acting electrogenic Na^+-K^+ pump, giving a net membrane potential of -90 millivolts.

15. Local response of membrane potential

At depolarizations less than threshold, the positive feedback cycle cannot get started despite the small initial increase in sodium entry. In such cases, the membrane will return to its resting level as soon as the stimulus is removed, and no action potential will be generated. These weak depolarizations are subthreshold potentials, and the stimuli that cause them are subthreshold stimuli.

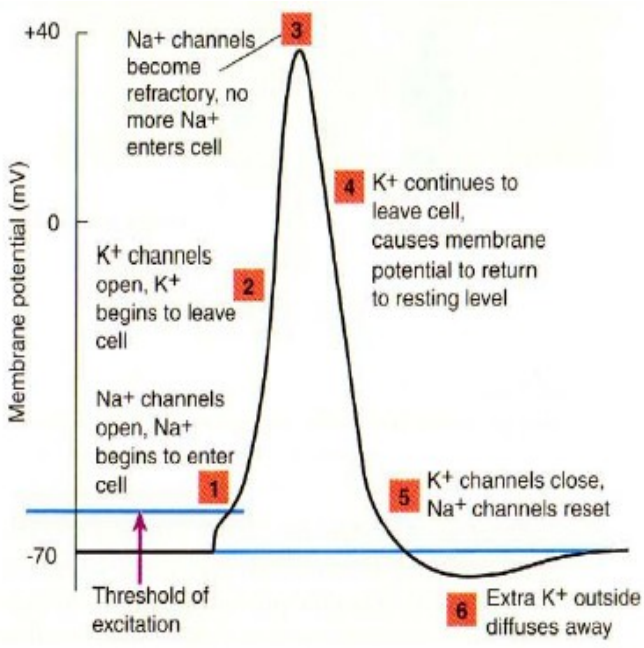
Although the subthreshold stimuli do not produce an action potential, they do have an effect on the membrane potential. This can be demonstrated by placing recording electrodes within a few millimeters of a stimulating electrode and applying subthreshold stimuli of fixed duration. Application of such currents with a cathode leads to a localized depolarizing potential change that rises sharply and decays exponentially with time. Conversely, an anodal current produces a hyperpolarizing potential change of similar duration. These potentials are called electronic potentials.



Electrotonic potentials and local response. The changes in the membrane potential of a neuron following application of stimuli of 0.2, 0.4, 0.6, 0.8, and 1.0 times threshold intensity are shown superimposed on the same time scale. The responses below the horizontal line are those recorded near the anode, and the responses above the line are those recorded near the cathode. The stimulus of threshold intensity was repeated twice. Once it caused a propagated action potential (top line), and once it did not.

16. Action potential

Nerve signals are transmitted by action potential, which are rapid changes in the membrane potential that spread rapidly along the nerve fiber membrane. Each action potential begins with a sudden change from the normal resting negative membrane potential to a positive potential and then ends with an almost equally rapid change back to the negative potential, to conduct a nerve signal, the action potential moves along the nerve fiber until it comes to the fiber's end.

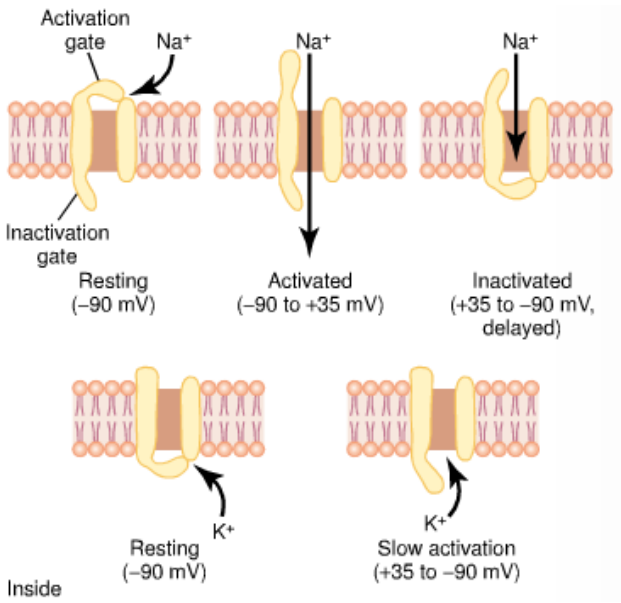


Resting Stage: Resting membrane potential before the action potential begins. The membrane is said to be "polarized" during this stage because of the -90 millivolts negative membrane potential that is present.

Depolarization Stage: The membrane suddenly becomes very permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to diffuse to the interior of the axon. The normal "polarized" state of -90 millivolts is immediately neutralized by the inflowing positively charged sodium ions, with the potential rising rapidly in the positive direction. This is called depolarization.

Repolarization Stage: within a few 10000ths of a second after the membrane becomes highly permeable to sodium ions, the sodium channels begin to close and the potassium channels open more than normal. Then, rapid diffusion of potassium ions to the exterior re-establishes the normal negative resting membrane potential. This is called repolarization.

Voltage-gated sodium and potassium channels



- <u>Activation of sodium channel</u>

When the membrane potential becomes less negative than during the resting state, rising from -90 millivolts toward zero, it finally reaches a voltage – usually somewhere between -70 and -50 millivolts – that causes a sudden conformational change in the activation gate, flipping it all the way to the open position. This is called the activated state; during this state, sodium ions can pour inward through the channel, increasing the sodium permeability of the membrane.

- <u>Inactivation of sodium channel</u>

The same increase in voltage that opens the activation gate also closes the inactivation gate. The inactivation gate, however, closes a few 10000ths os a second after the activation gate opens. Therefore, after the sodium channel has remained open for a few 10000ths of second, the inactivation gate closes, and sodium ions no longer can pour to the inside of the membrane. At this point, the membrane potential begins to recover back toward the resting membrane state, which is the repolarization process. Another important characteristic of the sodium channel

inactivation process is that the inactivation gate will not reopen until the membrane potential returns to or near the original resting membrane potential level.

Voltage-gated potassium channel and its activation

Potassium channel has two states: during the resting state, the gate of the potassium channel is closed, and potassium ions are prevented from passing through this channel to the exterior. When the membrane potential rises from -90 millivolts toward zero, this voltage change causes a conformational opening of the gate and allows increased potassium diffusion outward through the channel. However, because of the slight delay in opening of the potassium channels, for the most part, they open just at the same time that the sodium channels are beginning to close because of inactivation. Thus, the decrease in sodium entry to the cell and the simultaneous increase in potassium exit from the cell combine to speed the repolarization process.

Once threshold is reached, membrane events are no longer dependent upon stimulus strength. Rather, the depolarization generates an action potential because the positive feedback cycle is operating. Action potentials either occur maximally or they do not occur at all. Another way of saying this is that action potentials are all-or-none.

17. Up- and down-regulation of receptors

The number of receptors in a target cell usually does not remain constant from day to day, or even from minute to minute. The receptor proteins themselves are often inactivated or destroyed during the course of their function, and at other times they are reactivated or new ones are manufactured. For instance, increased hormone concentration and increased binding with its target cell receptors sometimes cause the number of active receptors to decrease. This **down-regulation** of the receptors can occur as a result of:

(1) Inactivation of some of the receptor molecules
(2) Inactivation of some of the intracellular protein signaling molecules
(3) Temporary sequestration of the receptor to the inside of the cell
(4) Destruction of the receptors by lysosomes after they are internalized
(5) Decreased production of the receptors decreases the target tissues's responsiveness to the hormone

Some hormones cause **up-regulation** of receptors and intracellular signaling proteins; stimulating hormone induces greater than normal formation of receptor or intracellular signaling molecules. When this occurs, the target tissue becomes progressively more sensitive to the stimulating effects of the hormone.

18. Excitability and refractoriness

Nerve and muscles cells as well as some endocrine, immune, and reproductive cells have plasma membranes capable of producing action potentials. These membranes are called excitable membranes, and their ability to generace action potentials is known as **excitability**.

Refractory periods

During the action potential, a second stimulus, no matter how strong, will not produce a second action potential, and that region of the membrane is then said to be in its absolute refractory period. This occurs during the period when the voltage-gated sodium channels are either already open or have proceeded to the inactivated state during the first action potential. The inactivation gate that has blocked these channels must be removed by repolarizing the membrane and closing the pore before the channels can reopen to the second stimulus.

Following the absolute refractory period, there is an interval during which a second action potential can be produced, but only if the stimulus strength is considerably greater than usual. This is the relative refractory period. During the relative refractory period, some but not all of the voltage-gated sodium channels have returned to a resting state, and some of the potassium channels that repolarized the membranes are still open.

The refractory periods limit the number of action potentials an excitable membrane can produce in a given period of time. Refractory periods contribute to the separation of these action potentials so that individual electrical signals pass down the axon. The refractory periods also are key in determining the direction of action potential propagation.

19. Excitation-contraction coupling

Excitation-contraction coupling is a term that describes the physiological process of converting an electrical stimulus to a mechanical response. The electrical stimulus is usually an action potential and the mechanical response is contraction.

In skeletal muscle:

The skeletal muscle plasma membrane is an excitable membrane capable of generating and propagating action potentials. The electrical activity in the plasma membrane does not directly act upon the contractile proteins, but instead produces a state increased cytosolic calcium concentration, which continues to activate the contractile apparatus long after the electrical activity in the membrane has ceased.

After the release of acetylcholine in the motor plate, fast voltage-gated Na+ channels open, which leads to a firing of an action potential that travels along the sarcolemma and along the T-tubule. In T-tubules, the action potential excites voltage-sensitive channel - dihydropyridine receptor. Their conformation change during action potential induces the opening of a protein embedded in the sarcoplasmic reticulum membrane known as the ryanodine receptor. Calcium is thus released from the SR to the cytosol, activating cross-bridge cycling.

In smooth muscle:

Portions of the sarcoplasmic reticulum are located near the plasma membrane, forming associations similar to the relationship between T-tubules and the SR in skeletal muscle. Action potentials in the plasma membrane can be coupled to the release of sarcoplasmic reticulum calcium at these sites. In addition, second messengers released from the plasma membrane, or generated in the cytosol in response to the binding of extracellular chemical messengers to plasma-membrane receptors, can trigger the release of calcium from the more centrally locates sarcoplasmic reticulum.

There are voltage-sensitive calcium channels in the plasma membranes of smooth muscle cells, as well as calcium channels controlled by extracellular chemical messengers.

In cardiac muscle:

The plasma membrane action potential spreads into the interior of muscle cells via the T-tubules. The action potential in T-tubules opens voltage-sensitive calcium channelsin the T-tubule membrane itself (dihydropyridine). Calcium diffuses from the extracellular fluid through these channels into the cells, causing a small increase in cytosolic calcium concentrationin the region of the immediatly adjacent sarcoplasmic reticulum. This small increase in calcium concentration then causes calcium to bind to calcium receptors on the external surface of the sarcoplasmic reticulum membranes. These calcium sensitive recptors (ryanodine) contain intrinsic calcium channels , and activation of the receptors opens the channels, allowing a large net diffusion of calcium from SR into cytosol (calcium-induced calcium release). It is mainly this calcium that causes the contraction.

20. Molecular mechanism of muscle contraction

In skeletal muscle:

Each of the two myosin heads of a myosin-II molecule bind one ATP molecule in their nucleotide binding pocket. In this state, myosin has only a very weak affinity for actin binding. Cytosolic Ca^{2+} binds to troponin C which then moves tropomyosin and "uncovers" actin. ATP is hydrolysed to ADP + Pi and A-M-ADP-Picomplex is formed.

Pi detaches from the complex, which results in a 40º tilt of the myosin heads. This causes the actin and myosin filaments to slide past each other (first step of the power stroke). The following realease of ADP initiates part two of the power stroke, which ultimately results in the final positioning of the myosin heads. The remaining A-M complex is stable and can again be transformed into a much weaker bond when the myosin heads bind ATP.

Troponin C realeases Ca^{2+} which is pumped back to sarcoplasmic reticulum by Ca^{2+}-ATPase and TnI inhibits actin myosin interactions.

In smooth muscle:

Ca^{2+} binds to calmodulin (CM) -> Ca^{2+}-CM complex binds and activates MLCK (myosin light chain kinase). Ca^{2+}-CM complex also binds with caldesmon (CDM), which then detaches from the actin-tropomyosin complex, thus making it available for filament sliding. Myosin interacts with actin, myosin is phosphorylated and the contraction occurs.

In cardiac muscle:

Ca^{2+} binds to TnC; TnI is removed so actin and myosin can bind. ADP + Pi are freed. Actin filament is pulled about 10 nm towards the sarcomere centre => Contraction.

21. Electrical and mechanical behaviour of skeletal muscle

Electrical behavior

Stimulation of the nerve fibers to a skeletal muscle is the only mechanism by which action potentials are initiated in this type of muscle.

The nerve cell whose axons innervate skeletal muscle fibres are known as motor neurons and their cell bodies are located in either the brainstem on the spinal cord.

A single motor neuron innervates many muscle fibers, but each muscle fiber is controlled by a branch from only one motor neuron. A motor neuron plus the muscle fibers it innervates is called a motor unit. When an action potential occurs in a motor unit are stimulated to contract.

The action potential generated at end-plate is propagated over the surface of the muscle fiberby the same mechanism as in nerve fibers.

Inhibitory potentials do not occur in human skeletal muscle - all neuromuscular junctions are excitatory.

In skeletal muscles, gradation of contraction force is achieved by variable recruitment of motor units and by changing the action potential frequency. A single stimulus always leads to maximum Ca^{2+} release and, thus to a maximum single twitch of skeletal muscle fiber if above threshold. Nonetheless, a single stimulus does not induce maximum shortening of muscle fiber because it is too brief to keep the sliding filament in motion long enough for the end position to be reached.

Muscle shortening continues only if a second stimulus arrives before the muscle has completely relaxed after the first stimulus. This type of stimulus repetition leads to incremental mechanical summation or superposition of the individual contractions.

Mechanical behavior

Muscle is formed by parallel bundles of muscle fibers which are formed by myofibrils. The basic units are called sarcomeres.

- H zone: solely contains myosin filaments.
- A-band: the region where the actin and myosin filaments overlap.
- I-band: the region containing only actin.

Muscle are made up mainly of actin and myosin. Actin is a globular monomer (G-actin) which make a double helix (F-actin)

F-actin has other accessory proteins attached:

- Tropomyosin: smaller double helix, attached to F-actin.
- Troponin: heterodimer bound to one end of tropomyosin.
  Troponin C - binds Ca2+.
  Troponin T - bind to tropomyosin and other troponins.
  Troponin I - inhibits actin-myosin interactions.

Myosin has 2 heavy chains which form a double helix. N-terminal of a heavy chain forms a globular head, which has ATPase activity (ATP + H2O -> ADP + Pi). It also has 4 light chains (MLC).

22. Electrical and mechanical behaviour of smooth muscle

Physical basis for muscle contraction

Smooth muscle does not have the same striated arrangement of actin and myosin filaments as is found in skeletal muscle. Large numbers of actin filaments are attached to so-called dense bodies. Some of these bodies are attached to the cell membrane. Others are dispersed inside the cell. It is mainly through these bonds that the force of contraction is transmitted from one cell to the next.

Interspersed among the actin filaments in the muscle fiber are myosin filaments. The individual contractile unit within a smooth muscle cell shows large numbers of actin filaments radiating from two dense bodies; the ends of these filaments overlap myosin filament a myosin filament located midway between the dense bodies. This contractile unit is similar to the contractile unit of skeletal muscle structure; in fact, the dense bodies of smooth muscle serve the same role as the Z discs in skeletal muscle.

Smooth muscle

Although most skeletal muscles contract and relax rapidly, most smooth muscle contraction is prolonged tonic contraction, lasting hours or even days.

The rapidity of cycling of the myosin cross-bridges in smooth muscle – that is, their attachment to actin, then release from the actin , and reattachment for the next cycle – is much, much slower in smooth muscle than in skeletal muscle; in fact, the frequency is as little as 1/10 to 1/300 that in skeletal muscle. Yet the fraction of time that the cross-bridges remain attached to the actin filaments, which is a major factor that determines the force of contraction, is believed to be greatly increased in smooth muscle. A possible reason for the slow cycling is that the cross-bridge heads have far less ATPase activity than in skeletal muscle, so that degradation of the ATP that energizes the movements of the cross-bridge heads is greatly reduced, with corresponding slowing of the rate of cycling.

Membrane potentials and action potentials in smooth muscle

The quantitative voltage of the membrane potential of smooth muscle depends on the momentary condition of the muscle. In the normal resting state, the intracellular potential is usually about -50 to -60 millivolts.

Action potentials occur in unitary smooth muscle (such as visceral muscle) in the same way that they occur in skeletal muscle. The action potentials of visceral smooth muscle occur in one of two forms:

- Spike potentials – typical spike action potentials, such as those seen in skeletal muscle, occur in most types of unitary smooth muscle. Such action potentials can be elicited in many ways, for example, by electrical stimulation, by the action of hormones on the smooth muscle, by the action of transmitter substances from nerve fibers, by stretch, or as a result of spontaneous generation in the muscle fiber itself.

- Action potentials with plateaus – the onset of this action potential is similar to that of the typical spike potential. However, instead of rapid repolarization is delayed for several hundred to as much as 1000 milliseconds. The importance of the plateau is that it can account for the prolonged contraction that occurs in some types of smooth muscle, such as the ureter, the uterus under some conditions, and certain types of vascular smooth muscle (also, this is the type of action potential seen in cardiac muscle fibers that have a prolonged period of contraction).

23. Electrical and mechanical behaviour of cardiac muscle

Cardiac muscle is striated in the same manner as in typical myofibrils that contain actin and myosin filaments almost identical to those found in skeletal muscle; these filaments lie side by side and slide along one another during contraction in the same manner as occurs in skeletal muscle.

The dark areas crossing the cardiac muscle fibers are called intercalated discs; they are actually cell membranes that separate individual cardiac muscle cells from one another. At each intercalated disc the cell membranes fuse with one another in such a way that they form permeable "communicating" junctions (gap junctions) that allow almost totally free diffusion of ions. Therefore, from a functional point of view, ions move with ease in the intracellular fluid along the longitudinal axes of the cardiac muscle fibers, so that action potentials travel easily from one cardiac muscle cell to the next, past the intercalated discs. Thus cardiac, muscle is a syncytium of many heart muscle cells in which the cardiac cells are so interconnected that when one of these cells becomes excited, the action potential spreads to all of them, spreading from cell to cell.

The heart actually is composed of two syncytiums: the atrial syncytium that constitutes the walls of the two atria, and the ventricular syncytium that constitutes the walls of the two ventricules. The atria are separated from the ventricle by fibrous tissue that surrounds the atrioventriculas (A-V) valvular openings between the atria and ventricles. Normally, potentials are not conducted from the atrial syncytium into the ventricular syncytium directly through this fibrous tissue. Instead, they are conducted only by way of a specialized conductive system called the A-V bundle, a bundle of conductive fibers several millimeters in diameter.

Action potentials in cardiac muscle

The action potential in a ventricular muscle fiber averages about 105 milliovolts, which means that the intracellular potential rises from a very negative value, about -85 millivolt, between beats to a slightly positive value, about +20 millivolts, during each beat. After the initial spike, the membrane remains depolarized for about 0.2 second, exhibiting a plateau, followed at the end of the plateau by abrupt repolarization. The presence of this plateau in the action potential causes ventricular contraction to last as much as 15 times as long in cardiac muscle as in skeletal muscle.

What causes the long action potential and the plateau?

At least two major differences between the membrane properties of cardiac and skeletal muscle account for the prolonged action potential and the plateau in cardiac muscle. First, the action potential of skeletal muscle is caused almost entirely by sudden channels that allow tremendous numbers of sodium ions to enter the skeletal muscle fiber from the extracellular fluid. These channels are called "fast" channels because they remain open for only a few thousandths of a second and then abruptly close. At the end of this closure, repolarization occurs, and the action potential is over within another thousandth of a second or so.

In cardiac muscle, the action potential is caused by opening of two types of channels:

1. The same fast sodium channels as those in skeletal muscle.
2. Another entirely different population of slow calcium channels, which are also called calcium-sodium channels. This second population of channels differs from the fast sodium channels in that they are slower to open and, even more important, remain open for several tenths of a second. During this time, a large quantity of both calcium and sodium ions flows through these channels to the interior of the cardiac muscle fiber, and this maintains a prolonged period of depolarization, causing the plateau in the action potential. Further, the calcium ions that enter during this plateau phase activate the muscle contractile process, while the calcium ions that cause skeletal muscle contraction are derived from the intracellular sarcoplasmic reticulum.

Also, immediately after the onset of the action potential, the permeability of the cardiac muscle membrane for potassium ions decreases about fivefold, an effect that does not occur in skeletal muscle. This decreased potassium permeability may result from the excess calcium influx

through the calcium channels just noted. The decreased potassium permeability greatly decreases the outflux of positively charged potassium ions during the action potential plateau and thereby prevents early return of the action potential voltage to its resting level. When the slow calcium-sodium channels close at the end to 0.2 to 0.3 second and the influx of calcium and sodium ions ceases, the membrane permeability for potassium ion also increases rapidly; this rapid loss of potassium from the fiber immediately returns the membrane potential to its resting level, thus ending the action potential.

Refractory period of cardiac muscle

Cardiac muscle, like all excitable tissue, is refractory to restimulation during the action potential. The normal refractory period of the ventricle is 0.25 to 0.30 second, which is about the duration of the prolonged plateau action potential. There is an additional relative refractory period of about 0.05 second during which the muscle is more difficult than normal to excite but nevertheless can be excited by a very strong excitatory signal. The refractory period of atrial muscle is much shorter than that for the ventricles (about 0.15 second for the atria compared with 0.25 to 0.30 second for the ventricles).

24. Isometric and isotonic contraction. Length-tension relation.

Isometric and isotonic contraction.

Muscle contraction said to be isometric when the muscle does not shorten during contraction and isotonic when it does shorten but the tension on the muscle remains constant throughout the contraction.

The characteristics of isotonic contraction depend on the load against which the muscle contracts. The isometric system is most often used when comparing the functional characteristics of different muscle types: in muscles which promote long-term support of body (made mainly of slow muscle fibers) the duration of isometric contraction is longer. On the other hand, muscles which are responsible for fast movements (mainly made up of fast fibers) the duration of isometric contraction is much shorter.

Length-tension relation

The spring-like characteristics of the protein titin which is attached to the Z line at one end and the thick filaments at the other, is responsible for most of the passive elastic properties of relaxed muscles. With increased stretch, the passive tension in a relaxed fiber increases. If the stretched fiber is released, it will return to an equilibrium length. The critical point is that the amount of active tension a muscle fiber develops during contraction can also be altered by changing the length of the fiber.

The length at which the fiber develops the greatest isometric active tension is termed the optimal length, l_o.

When a muscle fiber length is 60% of l_o, the fiber develops no tension when stimulated. As the length increases from this point, the isometric tension as each length is increased up to a maximum at l_o. Further lengthening leads to a drop in tension. At lengths of 175% l_o or beyond, the fiber develops no tension when stimulated.

When skeletal muscles are relaxed, the lengths of most fibers are near l_o and thus near the optimal lengths for force generation. The extent to which the relaxed length will change is limited by the muscle's attachment to bones. It rarely exceeds a 30% change from l_o and is often much less.

We can partially explain the relationship between fiber length and the fiber's capacity to develop active tension during contraction in terms of the sliding-filament mechanism. Stretching a relaxed muscle fiber pulls the thin filaments past the thick filaments, changing the amount of overlap between them. Stretching a fiber to 175% of l_o pulls the filaments apart to the point where there is no overlap. At this point, there can be no cross-bridge binding to actin and no development of tension. As the fiber shortens toward l_o, more and more filaments overlap, and the tension developed upon stimulation increases in proportion to the increased number of cross-bridges in the overlap region. Filament overlap is greatest at l_o, allowing the maximal number of cross-bridges to bind to the thin filaments, thereby producing maximal tension. The tension decline at lengths less that l_o is the result of several factors:

- The overlapping sets of thin filaments from opposite ends of the sarcomere may interfere with the cross-bridges' ability to bind and exert force.
- The fact that at very short lengths, the Z lines collide with the ends of the relatively rigid thick filaments, creating an internal resistance to sarcomere shortening.

25. Neuromuscular junction

Each nerve ending makes a junction, called the **neuromuscular junction**, with the muscle fiber near its midpoint. The action potential initiated in the muscle fiber by the nerve signal travels in both directions toward the muscle fiber ends. The nerve fiber forms a complex of branching nerve terminals that invaginate into the surface of the muscle fiber but lie outside the muscle fiber plasma membrane. The entire structure is called the motor end plate. It is covered by one or more Schwann cells that insulate it from the surrounding fluids.

In the axon terminal are many mitochondria that supply adenosine triphosphate (ATP), the energy source that is used for synthesis of an excitatory transmitter acetylcholine. The acetylcholine in turn excites the muscle fiber membrane. Acetylcholine is synthesized in the cytoplasm of the terminal, but it is absorbed rapidly into many small synaptic vesicles. In the synaptic space are large quantities of the enzyme acetylcholinesterase, which destroys acetylcholine a few milliseconds after it has been released from the synaptic vesicles.

When an action potential spreads over the terminal, calcium channels open and allow calcium ions to diffuse from the synaptic space to the interior of the nerve terminal.The calcium ions, in turn, are believed to exert an attractive influence on the acetylcholine vesicles, drawing them to the neural membrane. The vesicles then fuse with the neural membrane and empty thein acetylcholine into the synaptic space by the process of exocytosis.

There are acetylcholine receptors in the muscle fiber membrane; these are acetylcholine-gated ion channels (nicotinic channels). The receptor complex is composed of five subunit proteins, two alpha proteins and one each of beta, delta, and gamma proteins. These protein molecules penetrate all the way through the membrane.

Two acetylcholine molecules attach respectively to the two alpha subunit proteins. This causes a conformational change that opens the channel. The opened acetylcholine channel allow the important positive ions—sodium (Na+), potassium (K+), and calcium (Ca2+)—to move easily through the opening. The principal effect of opening the acetylcholine-gated channels is to allow large numbers of sodium ions to pour to the inside of the fiber, carrying with them large numbers of positive charges. This creates a local positive potential change inside the muscle fiber membrane, called the end plate potential. In turn, this end plate potential initiates an action potential that spreads along the muscle membrane and thus causes muscle contraction.

Destruction of the Released Acetylcholine by Acetylcholinesterase.

The acetylcholine, once released into the synaptic space, continues to activate the acetylcholine receptors as long as the acetylcholine persists in the space. However, it is removed rapidly by two means:

(1) Most of the acetylcholine is destroyed by the enzyme acetylcholinesterase, which is attached to the postsynaptic membrane.

(2) A small amount of acetylcholine diffuses out of the synaptic space and is then no longer available to act on the muscle fiber membrane.

26. Temporal and space summation (summation and recruitment) in skeletal muscle

One of the characteristics of each signal that always must be conveyed is signal intensity. In muscles, the intensity of the stimulus can be conveyed by two ways:

Spatial summation → recruitment

Increasing or decreasing the number of motor units active at any one time changes the amount of force produced by a muscle. The gradual increase in tension results from the recruitment of motor units increasing signal strength which is transmitted by using progressively greater numbers of fibers. The smallest motor neurons in the pool are the only units activated by weak synaptic stimulation. When synaptic input increases, progressively larger motor neurons are recruited: As the synaptic activity driving a motor neuron pool increases, low threshold S units are recruited first, then FR units, and finally, at the highest levels of activity, the FF units. – size principle. The combination of motor units activated by such orderly recruitment optimally matches the physiological properties of different motor unit types with the range of forces required to perform different motor tasks.

Summation

The frequency of the action potentials generated by motor neurons also contributes to the regulation of muscle tension. The increase in force that occurs with increased firing rate reflects the summation of successive muscle contractions: The muscle fibers are activated by the next action potential before they have had time to completely relax, and the forces generated by the temporally overlapping contractions are summed. At the highest firing rates, individual muscle fibers are in a state of "fused tetanus". However, the asynchronous firing of different lower motor neurons provides a steady level of input to the muscle that causes the contraction of a relatively constant number of motor units and averages out the changes in tension due to contractions and relaxations of individual motor units. All this allows the resulting movements to be executed smoothly.

27. Energy production and conservation

A great proportion of the chemical reactions in the cells is concerned with making the energy in food available to the various physiologic systems of the cell. For instance, energy is required for muscle activity, secretion by the glands, and maintenance of membrane potentials by the nerve and muscle fibers, synthesis of substance in the cells, absorption of foods from the gastrointestinal tract, and many other functions.

Coupled Reactions

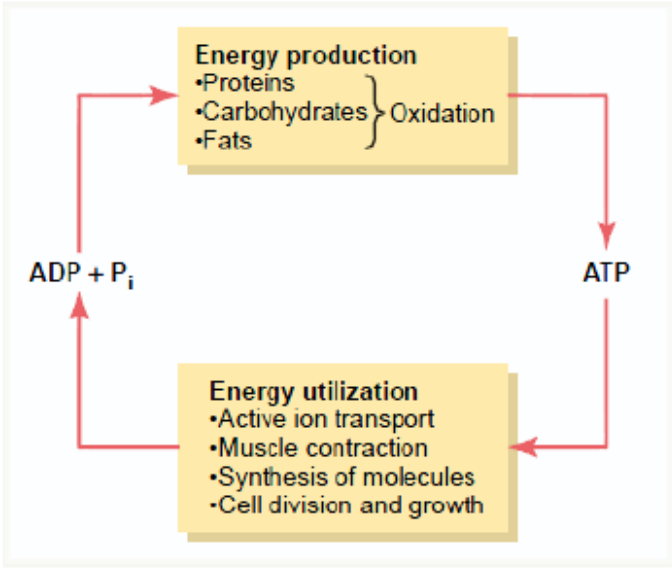
All the energy foods—carbohydrates, fats, and proteins—can be oxidized in the cells, and during this process, large amounts of energy are released. To provide energy needed by the physiologic processes of the cells, the chemical reactions must be "coupled" with the systems responsible for these physiologic functions. This coupling is accomplished by special cellular enzyme and energy transfer systems. ATP is present everywhere in the cytoplasm and nucleoplasm of all cells, and essentially all the physiologic mechanisms that require energy for operation obtain it directly from ATP (or another similar highenergy compound—guanosine triphosphate [GTP]). In turn, the food in the cells is gradually oxidized, and the released energy is used to form new ATP, thus always maintaining a supply of this substance. All these energy transfers take place by means of coupled reactions.

"Free Energy"

The amount of energy liberated by complete oxidation of food is called the free energy of oxidation of the food, and this is generally represented by the symbol DG. Free energy is usually expressed in terms of calories per mole of substance. For instance, the amount of free energy liberated by complete oxidation of 1 mole (180 grams) of glucose is 686,000 calories.

Role of Adenosine Triphosphate in Metabolism

Adenosine triphosphate (ATP) is an essential link between energy-utilizing and energy-producing functions of the body. For this reason, ATP has been called the energy currency of the body, and it can be gained and spent repeatedly.



Energy derived from the oxidation of carbohydrates, proteins, and fats is used to convert adenosine diphosphate (ADP) to ATP, which is then consumed by the various reactions of the body that are necessary for: (1) active transport of molecules across cell membranes; (2) contraction of muscles and performance of mechanical work; (3) various synthetic reactions that create hormones, cell membranes, and many other essential molecules of the body; (4) conduction of nerve impulses; (5) cell division and growth; and (6) many other physiologic functions that are necessary to maintain and propagate life.

ATP is a combination of adenine, ribose, and three phosphate radicals. The last two phosphate radicals are connected with the remainder of the molecule by high-energy bonds.

The amount of free energy in each of these highenergy bonds per mole of ATP is about 7300 calories under standard conditions and about 12,000 calories under the usual conditions of temperature and concentrations of the reactants in the body. Therefore, in the body, removal of each of the last two phosphate radicals liberates about 12,000 calories of energy. After loss of one

phosphate radical from ATP, the compound becomes ADP, and after loss of the second phosphate radical, it becomes adenosine monophosphate (AMP).

ATP production:

a) by aerobic glycolytic pathway – 1 molecule of glucose gives **38** molecules of ATP
b) by anerobic glycolitic pathway – 1 molecule of glucose gives **2** molecules of ATP
c) by oxidation of fatty acids – e.g. 1 molecule of stearic acid gives **146** molecules of ATP
d) by deamination of AA followed by oxidation - In general, the amount of ATP formed for each gram of protein that is oxidized is slightly less than that formed for each gram of glucose oxidized.

Conservation of energy

Storage of carbohydrates

Continual release of energy from glucose when energy is not needed by the cells would be an extremely wasteful process. After absorption into a cell, glucose can be used immediately for release of energy to the cell, or it can be stored in the form of glycogen, which is a large polymer of glucose. All cells of the body are capable of storing at lest some glycogen, but certain cells can store large amounts, especially liver cells and muscle cells. The glycogen molecules can be polymerized to almost any molecular weight, with the average molecular weight being 5 million or greater; most of the glycogen precipitates in the form of solid granules. This conversion of the monosaccharides into glycogen makes it possible to store large quantities of carbohydrates without significantly altering the osmotic pressure of the intracellular fluids. When the glycogen-storing cells (primarily liver and muscle cells) approach saturation with glycogen, the additional glucose is converted into fat in liver and fat cells and is stored as fat in the fat cells.

Storage of lipids

Large quantities of fat are stored in two major tissues of the body, the adipose tissue and the liver. The adipose tissue is usually called fat deposits, or simply tissue fat. The major function of adipose tissue is storage of triglycerides until they are needed to provide energy elsewhere in the body.

Storage of proteins

Once the cells are filled to their limits with stored protein, any additional amino acids in the body fluids are degraded and used for energy or are stored mainly as fat or secondarily as glycogen.

28. Caloric content of food. Direct calorimetry.

Energy Available in Foods

The energy liberated from each gram of carbohydrate as it is oxidized to carbon dioxide and water is 4.1 kcal, and that liberated from fat is 9.3 calories. The energy liberated from metabolism of the average dietary protein as each gram is oxidized to carbon dioxide, water, and urea is 4.35 kcal. . Also, these substances vary in the average percentages that are absorbed from the gastrointestinal tract: about 98 per cent of carbohydrate, 95 per cent of fat, and 92 per cent of protein. Therefore, the average physiologically available energy in each gram of these three foodstuffs is as follows:

1 gram of	Kcal
Carbonhydrate	4
Fat	9
Protein	4

At rest, most of the energy supplied by the diet is converted to heat, since hardly any external mechanical work is being performed. The heat produced is equivalent to the internal energy turnover (e.g., the work performed by the heart and respiratory muscles or expended for active transport or synthesis of substance).

Direct Calorimetry Measures Heat Liberated from the Body

Because a person ordinarily is not performing any external work, the whole-body metabolic rate can be determined by simply measuring the total quantity of heat liberated from the body in a given time. In determining the metabolic rate by direct calorimetry, one measures the quantity of heat liberated from the body in a large, specially constructed calorimeter. The subject is placed in an air chamber that is so well insulated that no heat can leak through the walls of the chamber. Heat formed by the subject's body warms the air of the chamber. However, the air temperature within the chamber is maintained at a constant level by forcing the air through pipes in a cool water bath. The rate of heat gain by the water bath, which can be measured with an accurate thermometer, is equal to the rate at which heat is liberated by the subject's body. Direct calorimetry is physically difficult to perform and is used only for research purposes.

29. Energy balance. Indirect calorimetry

Stability of the body's total mass and composition over long periods requires that energy intake match energy expenditure. Only about 27 per cent of the energy ingested normally reaches the functional systems of the cells, and much of this is eventually converted to heat, which is generated as a result of protein metabolism, muscle activity, and activities of the various organs and tissues of the body. Excess energy intake is stored mainly as fat, whereas a deficit of energy intake causes loss of total body mass until energy expenditure eventually equals energy intake or death occurs. If the caloric content of the food ingested is less than the energy output – ie, if the balance is negative – endogenous stores are utilized. Glycogen, body protein, and fat are catabolized, and the individual loses weight. Deficits of energy stores, for example, rapidly activate multiple mechanisms that cause hunger and drive a person to seek food. If the caloric value of the food intake exceeds energy loss due to heat and work and the food is properly digested and absorbed – ie, if the balance is positive – energy is stored, and the individual gains weight.

To balance basal output so that the energy-consuming tasks essential for life can be performed, the average adult must take in about 2000 kcal/d. Caloric requirements above the basal level depend on the individual's activity.

Indirect Calorimetry—The "Energy Equivalent" of Oxygen

Because more than 95 per cent of the energy expended in the body is derived from reactions of oxygen with the different foods, the whole-body metabolic rate can also be calculated with a high degree of accuracy from the rate of oxygen utilization. When 1 liter of oxygen is metabolized with glucose, 5.01 kcal of energy are released; when metabolized with starches, 5.06 kcal are released; with fat, 4.70 kcal; and with protein, 4.60 kcal.

Using these figures, it is striking how nearly equivalent are the quantities of energy liberated per liter of oxygen, regardless of the type of food being metabolized. For the average diet, the quantity of energy liberated per liter of oxygen used in the body averages about 4.825 kcal. This is called the energy equivalent of oxygen; using this energy equivalent, one can calculate with a high degree of precision the rate of heat liberation in the body from the quantity of oxygen used in a given period of time. If a person metabolizes only carbohydrates during the period of the metabolic rate determination, the calculated quantity of energy liberated, based on the value for the average energy equivalent of oxygen (4.825 kcal/L), would be about 4 per cent too little. Conversely, if the person obtains most energy from fat, the calculated value would be about 4 per cent too great.

30. Physiological role of calcium

Calcium is the most abundant mineral in the human body. Our bones and teeth are mostly comprised of calcium. Of all the calcium in the human body, 99% of it is contained in the bones and teeth. The remaining 1% is found throughout the body in blood, muscle, and in the fluid between cells.

Calcium circulates in the bloodstream and between the cells either as the free ions (50%), bound to albumin (40%) or in form of chelates with oxalate, succinate, citrate… (10%). The physiological value of calcium in blood ranges between 2.0 and 2.7 mmol/l.

The non-skeletal calcium plays several vital roles biological functions in the human body: it is needed for muscle contraction, fertilization, blood vessel contraction and expansion, secretion of hormones and for the process of sending messages through the nervous system (action potentials). Because these functions are so vital, the body maintains a constant level of this fluid based calcium by taking calcium from the bones when needed.

Many enzymes require calcium ions as a cofactor; those of the blood-clotting cascade being notable examples. Extracellular calcium is also important for maintaining the potential difference across excitable cell membranes (for example, neuromuscular excitation - hypocalcemia increases/hypercalcemia decreases the excitability of muscles), as well as proper bone formation.

ECC in skeletal muscle & myocardium: Ca^{2+} binds to troponin C on the thin filaments, causing a conformational change in troponin that moves tropomyosin out of the way; the cross-bridge cycle beings.

EEC in smooth muscle: Ca^{2+} binds to calmodulin. The Ca^{2+}-calmodulin complex binds to and activate myosin light-chain kinase. When activated, myosin light-chain phosphorylates myosin and allows it to bind to actin. Contraction then occurs.

In neuromuscular junction: Ca^{2+} triggers a marked increase in exocytosis of ACh containing vesicles.

Blood coagulation: Activation of Factor X.

In myocardial contractility: Related to the intracellular Ca^{2+} concentration. The magnitude of the tension that develops is proportional to the intracellular $[Ca^{2+}]$.

Cell adhesion: Tight junction - interactions with cadherins.

Decrease in extracellular Ca^{2+} causes typical spasm in muscles of extremities.

31. Vitamins – overview

Required Daily Amounts of Vitamins

Vitamin	Amount
A	5000 IU
Thiamine	1.5 mg
Riboflavin	1.8 mg
Niacin	20 mg
Ascorbic acid	45 mg
D	400 IU
E	15 IU
K	70 µg
Folic acid	0.4 mg
B_{12}	3 µg
Pyridoxine	2 mg
Pantothenic acid	Unknown

Daily Requirements of Vitamins

A vitamin is an organic compound needed in small quantities for normal metabolism that cannot be manufactured in the cells of the body. Lack of vitamins in the diet can cause important metabolic deficits. The requirements vary considerably, depending on such factors as body size, rate of growth, amount of exercise, and pregnancy.

Storage of Vitamins in the Body

Vitamins are stored to a slight extent in all cells. Some vitamins are stored to a major extent in the liver. For instance, the quantity of vitamin A stored in the liver may be sufficient to maintain a person for 5 to 10 months without any intake of vitamin A. The quantity of vitamin D stored in the liver is usually sufficient to maintain a person for 2 to 4 months without any additional intake of vitamin D.

Absence of vitamin C, one of the water-soluble vitamins, can cause symptoms within a few weeks and can cause death from scurvy in 20 to 30 weeks. Vitamin A, D, E and K are not soluble in water.

Vitamin A

Vitamin A occurs in animal tissues as retinol. Vitamin A is needed to form the visual pigments and, therefore, to prevent night blindness. Vitamin A is also necessary for normal growth of most cells of the body and especially for normal growth and proliferation of the different types of epithelial cells. Main food sources are liver, butter, egg yolk, coloured vegetables and fruits.

Thiamine (Vitamin B1)

Thiamine operates in the metabolic systems of the body principally as thiamine pyrophosphate; this compound functions as a cocarboxylase, operating mainly in conjunction with a protein decarboxylase for decarboxylation of pyruvic acid and other α-keto acids. Thiamine deficiency (beriberi) causes decreased utilization of pyruvic acid and some amino acids by the tissues, but increased utilization of fats. Thus, thiamine is specifically needed for the final metabolism of carbohydrates and many amino acids.

Niacin (Vitamin B3)

Niacin, also called nicotinic acid, functions in the body as coenzymes in the form of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes are hydrogen acceptors; they combine with hydrogen atoms as they are removed from food substrates by many types of dehydrogenases. Its mainly found in meat and liver.

Riboflavin (Vitamin B2)

Riboflavin normally combines in the tissues with phosphoric acid to form two coenzymes, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). They operate as hydrogen carriers in important oxidative systems of the mitochondria. It is found in eggs, milk liver, yeast and cereals.

Cobalamin (Vitamin B12)

Vitamin B12 performs several metabolic functions, acting as a hydrogen acceptor coenzyme. Its most important function is to act as a coenzyme for reducing ribonucleotides to deoxyribonucleotides, a step that is necessary in the replication of genes. This could explain the major functions of vitamin B12: promotion of growth and of red blood cell formation and maturation. It is only found in animal products.

Folic Acid (Vitamin B11)

Folic acid functions as a carrier of hydroxymethyl and formyl groups. Perhaps it's most important use in the body is in the synthesis of purines and thymine, which are required for formation of DNA. Therefore, folic acid, like vitamin B12, is required for replication of the cellular genes. This may explain one of the most important functions of folic acid—to promote growth.
Main food sources are leafy vegetables and liver.

Pyridoxine (Vitamin B6)

Pyridoxine exists in the form of pyridoxal phosphate in the cells and functions as a coenzyme for many chemical reactions related to amino acid and protein metabolism. Its most important role is that of coenzyme in the transamination process for the synthesis of amino acids. As a result, pyridoxine plays many key roles in metabolism, especially protein metabolism. Main food sources are meat, liver, cereal germs and yeast.

Pantothenic Acid (Vitamin B5)

Pantothenic acid mainly is incorporated in the body into coenzyme A (CoA), which has many metabolic roles in the cells. Two of these are conversion of decarboxylated pyruvic acid into acetyl-CoA before its entry into the citric acid cycle; and degradation of fatty acid molecules into multiple molecules of acetyl-CoA. Thus, lack of pantothenic acid can lead to depressed metabolism of both carbohydrates and fats. Main food sources are liver, milk and eggs.

Ascorbic Acid (Vitamin C)

Ascorbic acid is essential for activating the enzyme prolyl hydroxylase, which promotes the hydroxylation step in the formation of hydroxyproline, an integral constituent of collagen. Without ascorbic acid, the collagen fibers that are formed in virtually all tissues of the body are defective and weak. Therefore, this vitamin is essential for the growth and strength of the fibers in subcutaneous tissue, cartilage, bone, and teeth. Main food sources are fresh fruits, vegetables and potatoes.

Vitamin D

Vitamin D increases calcium absorption from the gastrointestinal tract and helps control calcium deposition in the bone. The mechanism by which vitamin D increases calcium absorption is mainly to promote active transport of calcium through the epithelium of the ileum. In particular, it increases the formation of a calcium binding protein in the intestinal epithelial cells that aids in calcium absorption. Main food sources are butter, fish, oil and eggs. It is partly formed in skin.

Vitamin E

Vitamin E is a name for a group of natural antioxidants. Deficiency of vitamin E prevents normal growth and sometimes causes degeneration of the renal tubular cells and the muscle cells. Vitamin E is believed to play a protective role in the prevention of oxidation of unsaturated fats. Main food sources are plant oils, nuts, seeds and germ oil.

Vitamin K

Vitamin K is necessary for the formation by the liver of prothrombin, Factor VII (proconvertin), Factor IX, and Factor X, all of which are important in blood coagulation. Therefore, when vitamin K deficiency occurs, blood clotting is retarded. Main food sources are vegetables and liver. It is partly formed by intestinal bacteria.

32. Hypovitaminoses and hypervitaminoses

Hypovitaminoses

Avitaminosis is any disease caused by chronic or long-term vitamin deficiency or caused by a defect in metabolic conversion, such as tryptophan to niacin. They are designated by the same letter as the vitamin.

Avitaminosis includes:

- Vitamin A deficiency causes xerophthalmia or night blindness.
- Thiamine (Vit B1) deficiency causes Beriberi.
- Niacin (Vit B3) deficiency causes Pellagra (classically described by "the four D's": diarrhea, dermatitis, dementia and death. It is exarcebated by diets lacking tryptophan which can be converted in limited quantities to niacin).
- Vitamin B12 deficiency leads to megaloblastic anemia.
- Vitamin C deficiency leads to scurvy.

Deficiency of ascorbic acid for 20 to 30 weeks, which occurred frequently during long ship voyages in the past, causes scurvy. One of the most important effects of scurvy is failure of wounds to heal. This is caused by failure of the cells to deposit collagen fibrils and intercellular cement substances. As a result, healing of a wound may require several months instead of the several days ordinarily necessary. Lack of ascorbic acid also causes cessation of bone growth. The cells of the growing epiphyses continue to proliferate, but no new collagen is laid down between the cells, and the bones fracture easily at the point of growth because of failure to ossify. Also, when an already ossified bone fractures in a person with ascorbic acid deficiency, the osteoblasts cannot form new bone matrix. Consequently, the fractured bone does not heal. The blood vessel walls become extremely fragile in scurvy because of (1) failure of the endothelial cells to be cemented together properly and (2) failure to form the collagen fibrils normally present in vessel walls. The capillaries are especially likely to rupture, and as a result, many small petechial hemorrhages occur throughout the body. The hemorrhages beneath the skin cause purpuric blotches, sometimes over the entire body. In extreme scurvy, the muscle cells sometimes fragment; lesions of the gums occur, with loosening of the teeth; infections of the mouth develop; and vomiting of blood, bloody stools, and cerebral hemorrhage can all occur. Finally, high fever often develops before death.

Ascorbic acid deficiency weakens collagen fibers throughout the body. Without ascorbic acid, the collagen fibers that are formed in virtually all tissues of the body are defective and weak as it is essential for the growth and strength of the fibers in subcutaneous tissue, cartilage, bone, and teeth.

- Vitamin D deficiency causes rickets.

Rickets occurs mainly in children. It results from calcium or phosphate deficiency in the extracellular fluid, usually caused by lack of vitamin D. If the child is adequately exposed to sunlight, the 7-dehydrocholesterol in the skin becomes activated by the ultraviolet rays and forms vitamin D3, which prevents rickets by promoting calcium and phosphate absorption from the intestines, as discussed earlier in the chapter. Children who remain indoors through the winter in general do not receive adequate quantities of vitamin D without some supplementation in the diet. Rickets tends to occur especially in the spring months because vitamin D formed during the preceding summer is stored in the liver and available for use during the early winter months. Also, calcium and phosphate absorption from the bones can prevent clinical signs of rickets for the first few months of vitamin D deficiency.

- Vitamin K deficiency causes impaired coagulation (vitamin K is necessary for the formation of prothrombin, factor VII, factor IX and factor X in liver).
- Vitamin E deficienty – In the absence of vitamin E, the quantity of unsaturated fats in the cells becomes diinishe, causing abnormal structure and function of such cellualr organelles as the mitochondria, the lysosomes, and even the cell membrane.

Hypervitaminoses

Vitamin poisoning, hypervitaminosis or vitamin overdose refers to a condition of high storage levels of vitamins, which can lead to toxic symptoms. The medical names of the different conditions are derived from the vitamin involved: an excess of vitamin A, for example, is called hypervitaminosis A. Generally, toxic levels of vitamins are achieved through high supplement intake and not from dietary sources. Toxicities of fat-soluble vitamins result also can be caused by a large intake of highly fortified foods, but foods rarely deliver dangerous levels of water-soluble vitamins.

- Hypervitaminosis A is characterized by anorexia, headache, hepatosplenomegaly, irritability, scaly dermatitis, patchy loss of hair, bone pain, and hyperostosis.
- Hypervitaminosis D is associated with weight loss, calcification of many soft tissues, and eventual renal failure.
- Hypervitaminosis K is characterized by gastrointestinal disturbance and anemia.

Large doses of water-soluble vitamins have been thought to be less likely to cause problems because they can be rapidly cleared from the body.

34. Principles of balanced nutrition

- Diet should provide.
- Sufficient amount of energy.
- Right proportion of lipids, carbohydrates and proteins.
- Minerals and vitamins.
- Biological value of proteins: Measure of the proportion of absorbed protein from a food which becomes incorporated into the proteins of the organism's body.
- An adult male (70kg) would require:

carbohydrates	400 g	6.8 MJ	55 %
protein	100 g	1.7 MJ	15 %
fat	100 g	3.9 MJ	30 %
Total		12.4 MJ	

- Caloric value of the diet should approximate the ratio of energy expenditure
  - o Insufficient caloric intake: fat and protein stores of the body are catabolized.
  - o Excessive intake over a long period of time: obesity.

Man (70 kg)	kcal/m2/h	
rest	40	(lying awake)
light activity	70	(clerical work)
moderate activity	120	(walking, housework)
heavy activity	300-600	(bicycling, running)

- Food restriction is believed to extend the life span maybe due to protection from damage caused by radicals.

Most foods contain a mix of some or all of the nutrient classes, together with other substances such as toxins or various sorts. Some nutrients can be stored internally (e.g. the fat soluble vitamins), while others are required more or less continuously. Poor health can be caused by a lack of required nutrients or, in extreme cases, too much of a required nutrient. For example, both salt and water (both absolutely required) will cause illness or even death in too large amounts.

In general, eating a wide variety of fresh, whole (unprocessed), foods have proven favorable compared to monotonous diets based on processed foods. In particular, the consumption of whole-plant foods slows digestion and allows better absorption, and a more favorable balance of essential nutrients per kcal, resulting in better management of cell growth, maintenance, and mitosis (cell division), as well as better regulation of appetite and blood sugar. Regularly scheduled meals (every few hours) have also proven more wholesome than infrequent or haphazard ones.

Regulation of food intake

Several neuronal centers of the hypothalamus participate in the control of food intake.The lateral nuclei of the hypothalamus serve as a feeding center, and stimulation of this area causes an animal to eat voraciously (hyperphagia). The lateral hypothalamic feeding center operates by exciting the motor drives to search for food. The ventromedial nuclei of the hypothalamus serve as the satiety center. This center is believed to give a sense of nutritional satisfaction that inhibits the

feeding center. Electrical stimulation of this region can cause complete satiety, and even in the presence
of highly appetizing food, the animal refuses to eat (aphagia). The paraventricular, dorsomedial, and arcuate nucleiof the hypothalamus also play a major role in regulating food intake. For example, lesions of the paraventricular nuclei often cause excessive eating, whereas lesions of the dorsomedial nuclei usually depress eating behavior. These nuclei of the hypothalamus also influence the secretion of several hormones that are important in regulating energy balance and metabolism, including those from the thyroid and adrenal glands, as well as the pancreatic islet cells. The hypothalamus receives neural signals from the gastrointestinal tract that provide sensory information about stomach filling, chemical signals from nutrients in the blood (glucose, amino acids, and fatty acids) that signify satiety, signals from gastrointestinal hormones, signals from hormones released by adipose tissue, and signals from the cerebral cortex (sight, smell, and taste) that influence feeding behavior.

Neurons and neurotransmitters in the hypothalamus that stimulace or inhibit feeding
(1) propopiomelanocortin (POMC) neurons.
(2) neurons that produce the orexigenicsubstances neuropeptide Y (NPY).
Activation of the POMC neurons decreases food intake and increases energy expenditure, whereas activation of the NPY-AGRP neurons increases food intake and reduces energy expenditure.
Defective signaling of the melanocortin pathway is associated with extreme obesity. In contrast, excessive activation of the melanocortin system reduces appetite – Anorexia.

Factors that regulate quantity of food intake

Regulation of the quantity of food intake can be divided into short-term regulation, which is concerned primarily with preventing overeating at each meal, and long-term regulation, which is concerned primarily with maintenance of normal quantities of energy stores in the body.

- ✓ Short-term regulation of food intake

Gastrointestinal Filling Inhibits Feeding: When the gastrointestinal tract becomes distended, especially the stomach and the duodenum, stretch inhibitory signals are transmitted mainly by way of the vagi to suppress the feeding center.

Gastrointestinal Hormonal Factors Suppress Feeding: Cholecystokinin is released mainly in response to fat entering the duodenum and has a direct effect on the feeding centers to reduce subsequent eating. Thus, eating a meal stimulates the release of several gastrointestinal hormones that may induce satiety and reduce further intake of food.

Ghrelin—a Gastrointestinal Hormone—Increases Feeding: Blood levels of ghrelin rise during fasting, peak just before eating, and then fall rapidly after a meal, suggesting a possible role in stimulating feeding.

Oral Receptors Meter Food Intake: Various “oral factors” related to feeding, such as chewing, salivation, swallowing, and tasting, “meter” the food as it passes through the mouth, and after a certain amount has passed, the hypothalamic feeding center becomes inhibited.

- ✓ Long-term regulation of food intake

Decrease in blood glucose concentration cause hunger. the same effect for blood amino acid concentration and blood concentration of breakdown products of lipids.

Temperature Regulation and Food Intake: When an animal is exposed to cold, it tends to increase feeding; when it is exposed to heat, it tends to decrease its caloric intake. This is caused by interaction within the hypothalamus between the temperature-regulating system and the food intake–regulating system.

Feedback Signals from Adipose Tissue Regulate Food Intake

Hypothalamus senses energy storage through the actions of leptin, a peptide hormone released from adipocytes.When the amount of adipose tissue increases (signaling excess energy storage), the adipocytes produce increased amounts of leptin. Stimulation of leptin receptors in these hypothalamic nuclei initiates multiple actions that decrease fat storage, including (1) decreased production in the hypothalamus of appetite stimulators; (2) activation of POMC neurons; (3) increased production in the hypothalamus of substances, such as corticotropin-releasing hormone, that decrease food intake; (4) increased sympathetic nerve activity (through neural projections from the hypothalamus to the vasomotor centers), which increases metabolic rate and energy expenditure; and (5) decreased insulin secretion by the pancreatic beta cells, which decreases energy storage.

33. Basal Metabolism

Even when a person is at complete rest, considerable energy is required to perform all the chemical reactions of the body. This minimum level of energy required to exist is called **the basal metabolic rate (BMR)** and accounts for about 50 to 70 per cent of the daily energy expenditure in most sedentary individuals. Because the level of physical activity is highly variable among different individuals, measurement of the BMR provides a useful means of comparing one person's metabolic rate with that of another.

The usual method for determining BMR is to measure the rate of oxygen utilization over a given period of time under the following conditions:

1. The person must not have eaten food for at least 12 hours.
2. The BMR is determined after a night of restful sleep.
3. No strenuous activity is performed for at least 1 hour before the test.
4. All psychic and physical factors that cause excitement must be eliminated.
5. The temperature of the air must be comfortable and between 20° and 25°C.
6. No physical activity is permitted during the test.

The BMR normally averages about 65 to 70 kcal per hour in an average 70-kilogram man (=6300 – 7350 kJ/day). Although much of the BMR is accounted for by essential activities of the central nervous system, heart, kidneys, and other organs, the variations in BMR among different individuals are related mainly to differences in the amount of skeletal muscle and body size. Skeletal muscle, even under resting conditions, accounts for 20 to 30 per cent of the BMR. For this reason, BMR is usually corrected for differences in body size by expressing it as kcal per hour per square meter of body surface area, calculated from height and weight. Much of the decline in BMR with increasing age is probably related to loss of muscle mass and replacement of muscle with adipose tissue, which has a lower rate of metabolism. Likewise, slightly lower BMRs in women, compared with men, are due partly to their lower percentage of muscle mass and higher percentage
of adipose tissue.

Factors affecting BMR:

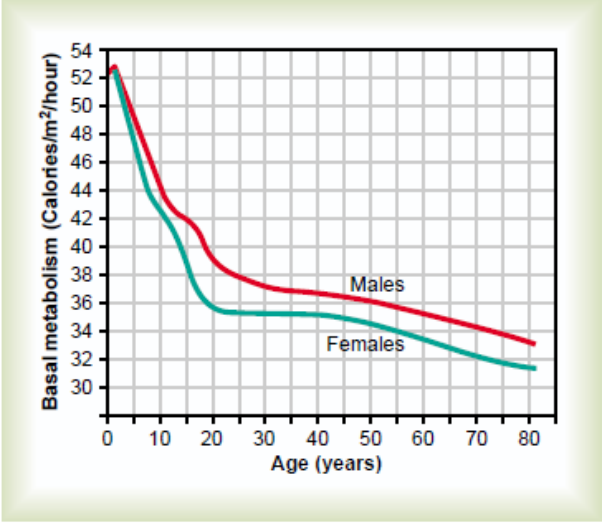
- Surface area

Standard value for BMR: 167 kJ/ m^2/h x surface in m^2 (men) and 150 kJ/ m^2/h x surface in m^2 (women).

Using Harris-Benedict formula:

BMR man: 66.5 + (13.8 x b.w.) + 5 x height (cm) - 6.8 x age
BMR woman: 66.5 + (9.5 x b.w.) + 1.8 x height (cm) - 4.7 x age

- Sex
- Age: Newborns have low BMR which increases during childhood and puberty. Decreasing BMR in old age.
- Hormones:
  - Catecholamines
  - Thyroid hormones
  - Insulin
  - Growth hormone
- Body temperature: BMR increases by 10% every increase in 1◦C
- Climate: higher temperatures are related to lower BMR and lower temperatures to higher BMR.
- Nutritional status: fasting and undernutrition decrease BMR.



35. Glycaemia

Glycemia means the presence, or the level, of glucose in one's blood. Normally, in mammals the
body maintains the blood glucose level at a reference range between about 3.6 and 5.8 mmol/L.

Hypoglycemia: Medical term for a state produced by a lower than normal level of blood glucose. The most common forms of moderate and severe hypoglycemia occur as a complication of treatment of diabetes mellitus with insulin or oral medications.

Hyperglycemia: High blood sugar is a condition in which an excessive amount of glucose circulates in the blood plasma. This is generally a blood glucose level higher than 10 mmol/L, but symptoms may not start to become noticeable until even higher values such as 15-20 mmol/L. However, chronic levels exceeding 7 mmol/L can produce organ damage.

Absorption carbohydrate

Glucose is the body‘s major energy source during the absorptive state. Much of the absorbed glucose enters cells and is catabolized to carbon dioxide and water, providing energy for ATP formation. Since skeletal muscle makes up the majority of body mass, it is the major consumer of glucose, even at rest. Skeletal muscle not only catabolizes glucose during the absorptive phase, but also converts some of the glucose to the polysaccharide glycogen, which is then stored in the muscle for future use.

Adipose tissue cells (adipocytes) also catabolize glucose for energy, but the most important fate of glucose in adipocytes during the absorptive phase is its transformation to fat (triacylglycerides).

Another large fraction of the absorbed glucose enters the liver cells. This is a very important point: during the absorptive period, there is net uptake of glucose by the liver. It is ether stored as glycogen, or transformed to α-glycerol phosphate and fatty acids.

Postabsorptive state

No glucose is being absorbed from the intestinal tract, yet the plasma glucose concentration must be maintained because the brain normally utilizes only glucose for energy. If plasma glucose concentration decreases too much, alteration of neural activity can occur, ranging from subtle impairment of mental function to seizures, coma, and even death.
The events that maintain plasma glucose concentration fall into two categories:

(1) reactions that provide sources of blood glucose.
(2) cellular utilization of fat for energy, thus sparing glucose.

1. Glycogenolysis, the hydrolysis of glycogen stres to monomers of glucose-6-phosphate, occurs in the liver and skeletal muscle. In the liver, glucose-6-phosphate is enzymatically converted to glucose, which then enters the blood. The amount of glucose available from this source, however, can supply the body’s needs for only several hours before hepatic glycogen is nearly depleted.
Glycogenolysis also occurs in skeletal muscle, which contains approximately the same amount of glycogen as the liver. Unlike liver, however, muscle lacks the enzyme necessary to form glucose from the glucose-6-phosphate formed during glycogenolysis. Instead, the glucose-6-phosphate undergoes glycolysis within muscle to yield ATP, pyruvate, and lactate. Some of the lactate enters the blood, circulates to the liver, and is converted into glucose, which can then leave the liver cells to enter the blood. Thus, muscle glycogen contributes to the blood glucose indirectly via the liver.
2. the catabolism of triacylglycerides yields glycerol and fatty acids, a process termed lipolysis. The glycerol and fatty acids then enter the blood by diffusion. The glycerol reaching the liver is converted to glucose.
3. a few hours into the postabsorptive period, protein becomes the major source of blood glucose. Large quantities of protein in muscle and other tissues can be catabolized without serious cellular malfunction. The kidneys can also perform gluconeogenesis, but mainly during a prolonged fast.

Glucose Sparing (Fat utilization)

Most organs and tissues markedly reduce their glucose catabolism and increase their fat utilization, the latter becoming the major energy source. This metabolic adjustment, termed glucose sparing, „spares" the glucose produced by the liver for the nervous system's use.

Endocrine and Neural control of the absorptive and postabsorptive states

Insulin and glucagon are peptide hormones secreted by the islets of Langerhans, clusters of endocrine cells in the pancreas. The beta cells (or B cells) are the source of insulin, and the alpha cells of glucagon.

✓ Insulin

Insulin is the most important controller of organic metabolism. Its secretion, and thus plasma concentration, is increased during the absorptive state and decreased during the postabsorptive state.

The metabolic effects of insulin are exerted mainly on muscle cells (both cardiac and skeletal), adipose tissue cells, and liver cells.

Like all peptide hormones, insulin induces its effects by binding to specific receptors on the plasma membranes on its target cells. In muscle cells and adipose tissue cells, an increased insulin concentration stimulates cytoplasmic vesicles that contain a particular type of glucose transporter (GLUT4) in their membrane to fuse with the plasma membrane. The increased number of plasma membrane glucose transporters resulting from this fusion then causes a greater rate of glucose movement from the extracellular fluid into the cells by facilitated diffusion.

Of great significance is that the cells of the brain express a different subtype of GLUT, one which has very high affinity for glucose and whose activity is not insulin-dependent. This ensures that even if plasma insulin levels are very low (as in prolonged fasting), cells of the brain can continue to take up glucose from the blood and maintain CNS function.

Insulin favors glycogen formation and storage by

(1) increasing glucose transport into the cell

(2) stimulating the key enzyme (glycogen synthase) that catalyzes the rate-limiting step in glycogen synthesis

(3) inhibiting the key enzyme (glycogen phosphorylase) that catalyses glycogen catabolism.

Control of insulin secretion

The major controlling factor for insulin secretion is the plasma glucose concentration. An increase in plasma glucose concentration, as occurs after a meal, acts on the B cells of the islets of Langerhans to stimulate insulin secretion, whereas a decrease in plasma glucose removes the stimulus for insulin secretion.

The insulin stimulates the entry of glucose into muscle and adipose tissue, as well as net uptake, rather that net output, of glucose by the liver. These effects eventually reduce the blood concentration of glucose to its pre-meal level, thereby removing the stimulus for insulin secretion and causing it to return to its previous level.

✓ Glucagon

Glucagon is the peptide hormone produced by the alpha cells of the pancreatic islets. The major physiological effects of glucagon occur within the liver and oppose those of insulin. It:

(1) increases glycogen breakdown

(2) increases gluconeogenesis

The overall results are to increase the plasma concentrations of glucose which are important for the postabsorptive period, and to prevent hypoglycemia.

The major stimulus for glucagon secretion at these times is hypoglycemia. The adaptive value of such a reflex is clear: a decreasing plasma glucose concentration induces an increase in the release of glucagon, which, by its effects on metabolism, serves to restore normal blood glucose concentration by glycogenolysis and gluconeogenesis while at the same time supplying (if the fast is prolonged) fatty acids and ketones for the cell utilization. Conversely, an increased

plasma glucose concentration inhibits glucagon's secretion, thereby helping to return the plasma glucose concentration toward normal.

Epinephrine and sympathetic nerves to liver and adipose tissue

Epinephrine stimulates:

(1) glycogenolysis in both the liver, and skeletal muscle
(2) gluconeogenesis in the liver
(3) lipolysis in adipocytes

Enhanced sympathetic nervous system activity exerts effects on organic metabolism specifically, increased plasma concentration of glucose.

Hypoglycemia leads to increases in both epinephrine secretion and sympathetic nerve activity to the liver and adipose tissue. This is the same stimulus that leads to increased glucagon secretion. When the plasma glucose concentration decreases, glucose receptors in the central nervous system (and, possibly, the liver) initiate the reflexes that lead to increased activity in the sympathetic pathways to the adrenal medulla, liver, and adipose tissue. The adaptive value of the response is the same as that for the glucagon response to hypoglycemia: blood glucose returns toward normal, and fatty acids are supplied for cell utilization.

Cortisol

Cortisol, the major glucocorticoid produced by the adrenal cortex, plays an essential permissive role in the adjustments to fasting. The presence of cortisol in the blood maintains the concentrations of the key liver and adipose tissue enzymes required for gluconeogenesis. Cortisol actually reduces the sensitivity of target cells to insulin, which helps to maintain plasma glucose levels during fasting.

Diabetes Mellitus

Diabetes can be due to a deficiency of insulin, or to a decreased responsiveness to insulin. Thus, diabetes is not one but several diseases with different causes. Classification of these diseases rests on how much insulin a person's pancreas is secreting.

In type I diabetes mellitus (T1DM), insulin is completely or almost completely absent from the islets of Langerhans and the plasma. Therefore, therapy with insulin is essential. In type II diabetes mellitus (T2DM), insulin is usually present in plasma at nearly normal or even above-normal levels, but cellular sensitivity to insulin is lower than normal.

T1MD is due to the total or near-total autoimmune destruction of the pancreatic beta cells by the body's own white blood cells. Because of insulin deficiency, untreated patients with T1DM always have elevated glucose concentrations in their blood. The increase in glucose occurs because:

(1) glucose fails to enter insulin's target cells normally
(2) the liver continuously makes glucose by glycogenolysis and gluconeogenesis, and secretes the glucose into the blood.

Another result of the insulin deficiency is pronounced lipolysis with subsequent elevation of plasma glycerol and fatty acids.

Some of the problems are due to the effects that extremely elevaed plasma glucose concentration produces on renal function. The elevated plasma glucose of diabetes increases the filtered load of glucose beyond the maximum tubular reabsorptive capacity, and therefore large amounts of glucose are excreted. Also ketones may appear in urine.

36. Acid-base balance

Precise control of extracellular fluid H^+ concentration involves much more than simple elimination of H^+ by the kidneys. There are also multiple acid-base buffering mechanisms involving the blood, cells, and lungs that are essential in maintaining normal H^+ concentrations in both the extracellular and the intracellular fluid. Precise H^+ regulation is essential because the activities of almost all enzyme systems in the body are influenced by H^+ concentration. Therefore, changes in hydrogen concentration alter virtually all cell and body functions. The term alkalosis refers to excess removal of H^+ from the body fluids, in contrast to the excess addition of H^+, which is referred to as acidosis. The normal pH of arterial blood is 7.4, whereas the pH of venous blood and interstitial fluids is about 7.35 because of the extra amounts of carbon dioxide (CO_2) released from the tissues to form H_2CO_3 in these fluids

Because the normal pH of arterial blood is 7.4, a person is considered to have acidosis when the pH falls below this value and to have alkalosis when the pH rises above 7.4. The lower limit of pH at which a person can live more than a few hours is about 6.8, and the upper limit is about 8.0. The pH of urine can range from 4.5 to 8.0, depending on the acid-base status of the extracellular fluid. As discussed later, the kidneys play a major role in correcting abnormalities of extracellular fluid H^+ concentration by excreting acids or bases at variable rates. There are three primary systems that regulate the H^+ concentration in the body fluids to prevent acidosis or alkalosis:

(1) the chemical acid-base buffer systems of the body fluids, which immediately combine with acid or base to prevent excessive changes in H^+ concentration;

(2) the respiratory center, which regulates the removal of CO_2 (and, therefore, H_2CO_3) from the extracellular fluid;

(3) the kidneys, which can excrete either acid or alkaline urine, thereby readjusting the extracellular fluid H^+ concentration toward normal during acidosis or alkalosis. When there is a change in H^+ concentration, the buffer systems of the body fluids react within a fraction of a second to minimize these changes.

Buffer systems do not eliminate H^+ from or add them to the body but only keep them tied up until balance can be reestablished. The second line of defense, the respiratory system, also acts within a few minutes to eliminate CO_2 and, therefore, H_2CO_3 from the body.

These first two lines of defense keep the H^+ concentration from changing too much until the more slowly responding third line of defense, the kidneys, can eliminate the excess acid or base from the body. Although the kidneys are relatively slow to respond compared with the other defenses, over a period of hours to several days, they are by far the most powerful of the acid-base regulatory systems.

Bicarbonate buffer base

$$\uparrow H^+ + HCO_3^- \longrightarrow H_2CO_3 \longrightarrow CO_2 + H_2O$$

$$CO_2 + H_2O \longrightarrow H_2CO_3 \longrightarrow \uparrow HCO_3^- + H^+$$

When a strong acid such is added to the bicarbonate buffer solution, the increased H^+ released is buffered by HCO^{3-}. As a result, more H_2CO_3 is formed, causing increased CO_2 and H_2O production. The excess CO_2 greatly stimulates respiration, which eliminates the CO_2 from the extracellular fluid. The opposite reactions take place when a strong base is added to the bicarbonate buffer solution.

The net result, therefore, is a tendency for the CO_2 levels in the blood to decrease, but the decreased CO_2 in the blood inhibits respiration and decreases the rate of CO_2 expiration. The rise in blood HCO^{3-} that occurs is compensated for by increased renal excretion of HCO^{3-}.

Henderson-Hasselbalch equation

$$pH = 6.1 + \log \frac{HCO_3^-}{0.03 \times Pco_2}$$

One can calculate the pH of a solution if the molar concentration of HCO^{3-} and the PCO_2 are known. From the Henderson-Hasselbalch equation, it is apparent that an increase in HCO^{3-} concentration causes the pH to rise, shifting the acid-base

balance toward alkalosis. An increase in PCO_2 causes the pH to decrease, shifting the acid-base balance toward acidosis. Normal physiologic acid-base homeostasis results from the coordinated efforts of both the lungs and the kidneys, and acid-base disorders occur when one or both of these control mechanisms are impaired, thus altering either the bicarbonate concentration or the PCO_2 of extracellular fluid. Acidosis caused by a primary decrease in bicarbonate concentration is termed metabolic acidosis, whereas alkalosis caused by a primary increase in bicarbonate concentration is called metabolic alkalosis. Acidosis caused by an increase in PCO_2 is called respiratory acidosis, whereas alkalosis caused by a decrease in PCO_2 is termed respiratory alkalosis.

Phosphate buffer system

$$H_2PO_4^- \rightleftharpoons HPO_4^{2-} + H^+$$

Although the phosphate buffer system is not important as an extracellular fluid buffer, it plays a major role in buffering renal tubular fluid and intracellular fluids.

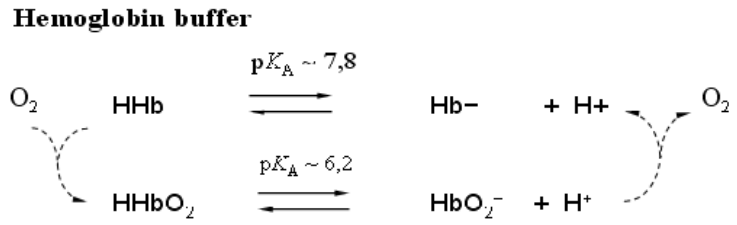
In contrast to its rather insignificant role as an extracellular buffer, the phosphate buffer is especially important in the tubular fluids of the kidneys, for two reasons:

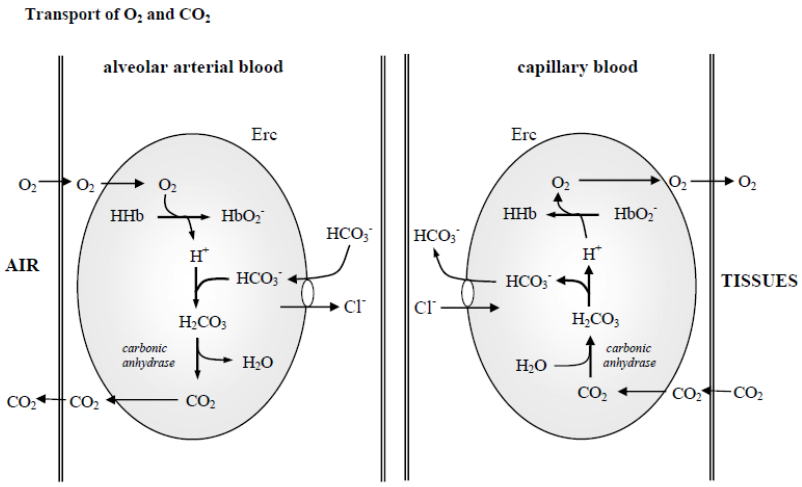
(1) phosphate usually becomes greatly concentrated in the tubules, thereby increasing the buffering power of the phosphate system

(2) the tubular fluid usually has a considerably lower pH than the extracellular fluid does, bringing the operating range of the buffer closer to the pK (6.8) of the system. The phosphate buffer system is also important in buffering intracellular fluid because the concentration of phosphate in this fluid is many times that in the extracellular fluid. Also, the pH of intracellular fluid is lower than that of extracellular fluid and therefore is usually closer to the pK of the phosphate buffer system compared with the extracellular fluid.

Proteins: important intracellular buffers

In the red blood cell, hemoglobin (Hb) is an important buffer. Except for the red blood cells, the slowness with which H^+ and HCO^{3-} move through the cell membranes often delays for several hours the maximum ability of the intracellular proteins to buffer extracellular acid-base abnormalities.



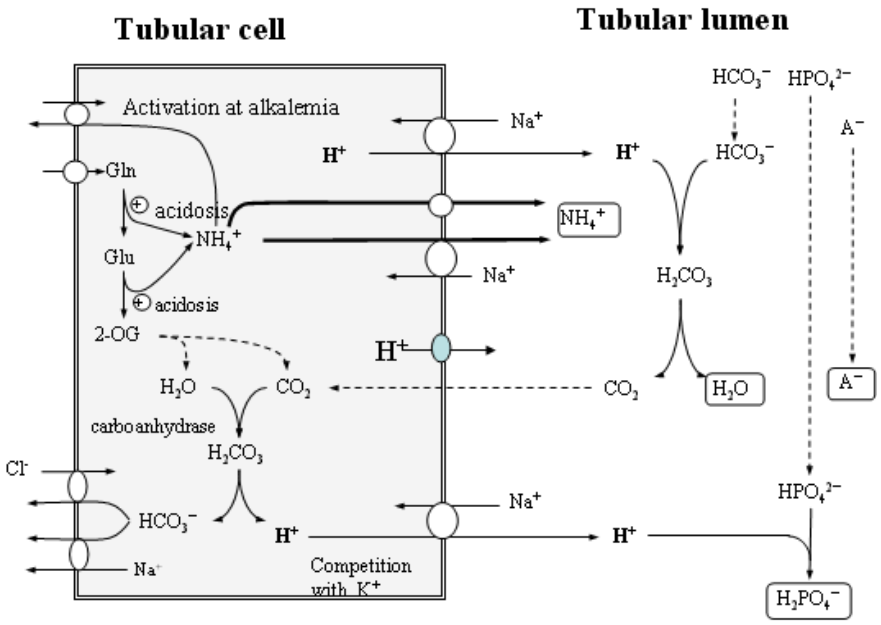


Respiratory Regulation of Acid-Base Balance

The second line of defense against acid-base disturbances is control of extracellular fluid CO_2 concentration by the lungs. An increase in ventilation eliminates CO_2 from extracellular fluid, which, by mass action, reduces the H^+ concentration. Conversely, decreased ventilation increases CO_2, thus also increasing H^+ concentration in the extracellular fluid.

The kidneys control acid-base balance by excreting either acidic or basic urine. Excreting acidic urine reduces the amount of acid in extracellular fluid, whereas excreting basic urine removes base from the extracellular fluid.

When there is a reduction in the extracellular fluid H^+ concentration (alkalosis), the kidneys fail to reabsorb all the filtered bicarbonate, thereby increasing the excretion of bicarbonate. Because HCO^{3-} normally buffers hydrogen in the extracellular fluid, the loss of bicarbonate is the same as adding H^+ to the extracellular fluid. Therefore, in alkalosis, the removal of HCO^{3-} raises the extracellular fluid H^+ concentration back toward normal. In acidosis, the kidneys do not excrete bicarbonate into the urine but reabsorb all the filtered bicarbonate and produce new bicarbonate, which is added back to the extracellular fluid. This reduces the extracellular fluid H^+ concentration back toward normal. Thus, the kidneys regulate extracellular fluid H^+ concentration through three fundamental mechanisms: secretion of H^+, reabsorption of filtered HCO^{3-} and production of new HCO^{3-}.



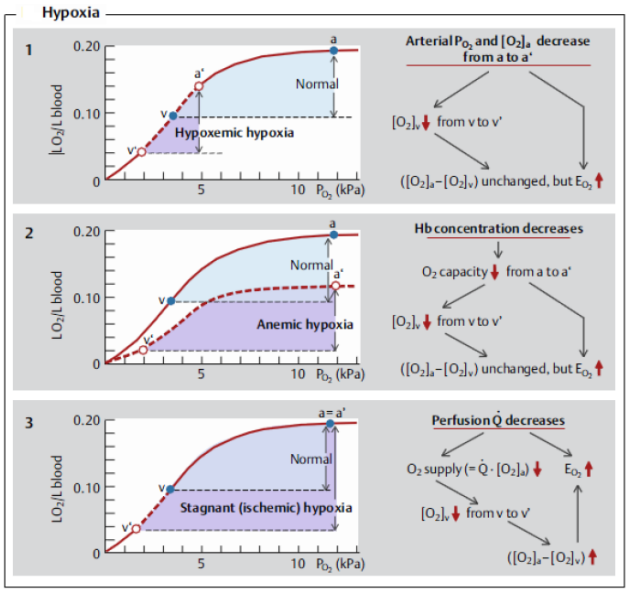
37. Hypoxia and ischemia

Hypoxia

Hypoxia is defined as a deficiency of oxygen at the tissue level. There are many potential causes of hypoxia, but they can be classed in four general categories:

- Hypoxic hypoxia (also termed hypoxemia), in which the arterial PO2 is reduced.
- Anemic or carbon monoxide hypoxia, in which the arterial PO2, is normal but the total oxygen content of the blood is reduced because of inadequate numbers of erythrocytes, deficient or abnormal hemoglobin, or competition for the hemoglobin molecule by carbon monoxide.
- Ischemic hypoxia, (also called hypoperfusion hypoxia), in which blood flow to the tissues is too low.
- Histotoxic hypoxia, in which the quantity of oxygen reaching the tissues is normal, but the cell is unable to utilize the oxygen because a toxic agent – cyanide, for example – has interfered with the cell's metabolic machinery.

The primary causes of hypoxic hypoxia in disease are listed in the table. Exposure to the reduce PO2 of high altitude also causes hypoxic hypoxia but is, of course, not a disease.



Causes of a decreased arterial PO2 (Hypoxic hypoxia) in disease
1. Hyperventilation may be caused (a) by a defect anywhere along the respiratory control pathway, from the medulla through the respiratory muscles; (b) by severe thoracic cage abnormalities, and (c) by major obstruction of the upper airway. The hypoxemia of hypoventilation is always accompanied by an increased arterial PO2.
2. Diffusion impairment results from thickening of the alveolar membranes or a decrease in their surface area. In turn, it causes blood PO2, and alveolar PO2 to fail to equilibrate. Often it is apparent only during exercise. Arterial PCO_2 is either normal, since carbon dioxide diffuses more readily than oxygen, or reduced if the hypoxemia reflexly stimulates ventilation.
3. A shunt is (a) an anatomic abnormality of the cardiovascular system that causes mixed venous blood to bypass ventilated alveoli in passing from the right side of the heart to the left side, or (b) an interpulmonary defect in which mixed venous blood perfuses unventilated alveoli (ventilation-perfusion=0). Arterial PCO_2 generally does not rise since the effect of the shunt on arterial PCO_2 is counterbalanced by the increased ventilation reflexly stimulated by the hypoxemia.
4. Ventilation-perfusion inequality is by far the most common cause of hypoxemia. It occurs in chronic obstructive lung diseases and many other lung diseases. Arterial PCO_2 may be normal or increased, depending upon how much ventilation is reflexly stimulated.

Ischemia

Rather than hypoxia, ischemia is an absolute or relative shortage of the blood supply to an organ, i.e. a shortage of oxygen, glucose and other blood-borne fuels. A relative shortage means the mismatch of blood supply (oxygen/fuel delivery) and blood request for adequate metabolism of tissue. Ischemia results in tissue damage because of a lack of oxygen and nutrient. Ultimately, this can cause severe damage because of the potential for a build-up of metabolic wastes.

- Cardiac ischemia may be asymptomatic or may cause chest pain, known as angina pectoris.

- Bowel ischemia: both large and small bowel can be affected by ischemia.
- Brain ischemia: is insufficient blood flow to the brain, and can be acute (ie, rapid) or chronic (ie, long-lasting).
- Cutaneous ischemia: Reduced blood flow to the skin layers may result in mottling or uneven, patchy discoloration of the skin.

Restoration of blood flow after a period of ischemia can actually be more damaging than the ischemia. Reintroduction of oxygen causes a greater production of damaging free radicals as well as allowing, via removal of the extracellular acidotic conditions, influx of calcium and thus calcium overloading. Overall this result in reperfusion injury which can result in potentially fatal cardiac arrhythmias, also necrosis can be greatly accelerated. Low doses of hydrogen sulfide (H_2S) have been found to protect against regional myocardial ischemia–reperfusion injury.

38. Heat production and heat loss

Heat production

Heat production by the metabolic systems is increased by promoting shivering, sympathetic excitation of heat production, and thyroxine secretion.

Shivering thermogenesis

Located in the hypothalamus is an area called the primary motor center for shivering. This area is normally inhibited by signals from the heat center but is excited by cold signals from the skin and spinal cord. Therefore, this center becomes activated when the body temperature falls even a fraction of a degree below a critical temperature level. It then transmits signals that cause shivering through the brain stem, into the spinal cord, and finally to the anterior motor neurons. These signals are nonrhythmical and do not cause the actual muscle shaking. Instead, they increase the tone of the skeletal muscles throughout the body by facilitating the activity of the anterior motor neurons.When the tone rises above a certain critical level, shivering begins. This probably results from feedback oscillation of the muscle spindle stretch reflex mechanism.

Non-shivering thermogenesis

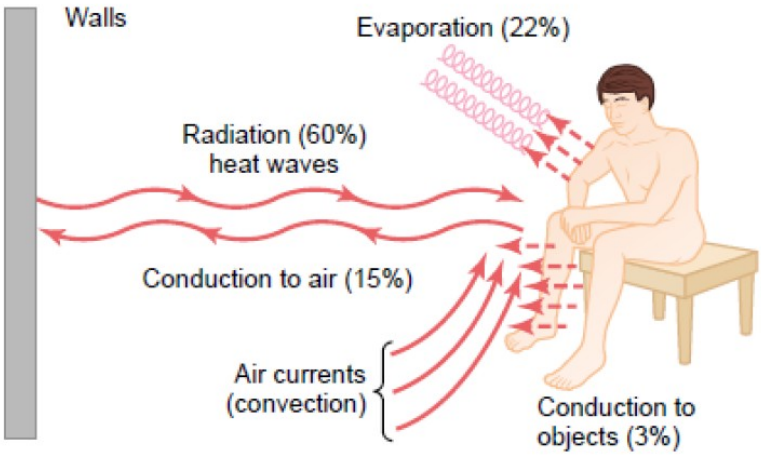
Although physical work and the thermogenic effect of food cause liberation of heat, these mechanisms are not aimed primarily at regulation of body temperature. Shivering provides a regulated means of producing heat by increasing muscle activity in response to cold stress. Another mechanism, nonshivering thermogenesis, can also produce heat in response to cold stress. This type of thermogenesis is stimulated by sympathetic nervous system activation, which releases norepinephrine and epinephrine, which in turn increase metabolic activity and heat generation. In certain types of fat tissue, called brown fat, sympathetic nervous stimulation causes liberation of large amounts of heat.This type of fat contains large numbers of mitochondria and many small globules of fat instead of one large fat globule. In these cells, the process of oxidative phosphorylation in the mitochondria is mainly “uncoupled.” That is, when the cells are stimulated by the sympathetic nerves, the mitochondria produce a large amount of heat but almost no ATP, so that almost all the released oxidative energy immediately becomes heat.

Increased Thyroxine Output as a Long-Term Cause of Increased Heat Production.

Cooling increases production of the neurosecretory hormone thyrotropin-releasing hormone by the hypothalamus. This hormone is carried by way of pituitary gland, where it stimulates secretion of thyroidstimulating hormone. Thyroid-stimulating hormone in turn stimulates increased output of thyroxine by the thyroid gland. The increased tyroxine increases the rate of cellular metabolism throughout the body. This increase in metabolism does not occur immediately but requires several weeks’ exposure to cold to make the thyroid gland hypertrophy and reach its new level of thyroxine secretion.

Heat loss

The skin, the subcutaneous tissues, and especially the fat of the subcutaneous tissues act together as a heat insulator for the body. The fat is important because it conducts heat only one third as readily as other tissues.



Heat loss occurs by the physical processes of radiation, conduction, convection, and evaporation.

1. Radiation - The amount of heat lost by radiation from the skin is chiefly determined by the temperature of the radiator (fourth power of its absolute temperature). Heat net–radiates from the

body surface to objects or individuals when they are cooler than the skin, and net–radiates to the body from objects (sun) that are warmer than the skin. Heat radiates from the body into the environment when no radiating object is present (night sky). Heat radiation does not require the aid of any vehicle and is hardly affected by the air temperature (air itself is a poor radiator).

2. Conduction and convection – These processes involve the transfer of heat from the skin to cooler air or a cooler object (e.g. sitting on rock) in contact with the body (conduction). The amount of heat lost by conduction to air increases greatly when the warmed air moves away from the body by natural convection (heated air rises) or forced convection (wind).

3. Evaporation - The first two mechanisms alone are unable to maintain adequate temperature homeostasis at high environmental temperatures or during strenuous physical activity. Evaporation is the means by which the body copes with the additional heat. The water lost by evaporation reaches the skin surface by diffusion (insensible perspiration) and by neuron-activated sweat glands. About 2428 kJ (580 kcal) of heat are lost for each liter of water evaporating and thereby cooling the skin. At temperatures above 36 °C or so, heat loss occurs by evaporation only. At even higher environmental temperatures, heat is absorbed by radiation and conduction/convection. The body must lose larger amounts of heat by evaporation to make up for this. The surrounding air must be relatively dry in order for heat loss by evaporation to occur. Humid air retards evaporation. When the air is extremely humid, the average person cannot tolerate temperatures above 33ºC, even under resting conditions.

39. Hormone-receptor complex

Hormones are messenger substances that convey information signals relevant to cell function.

Types of hormone

1. Peptide hormones and glycoprotein hormones are hydrophilic hormones stored in secretory granules and released by exocytosis as required. Multiple hormones can be produced from a single gene (e.g., POMC gene) by variable splicing and posttranslational modification.

2. Steroid hormones and calcitriol are chemically related lipophilic hormones metabolized from cholesterol. They are not stored, but are synthesized as needed.

3. Tyrosine derivatives include (a) the hydrophilic catecholamines dopamine, epinephrine and norepinephrine and (b) lipophilic thyroid hormones (T3, T4).

The lipophilic hormones are transported in the blood while bound to plasma proteins. Corticosteroids are carried bound to globulin and albumin, testosterone and estrogen to sex hormone-binding globulin and T3 and T4 to albumin and two other plasma proteins.

The first step of a hormone's action is to bind to specific receptors at the target cell. Receptors for some hormones are located on the target cell membrane, whereas other hormone receptors are located in the cytoplasm or the nucleus. When the hormone combines with its receptor, this usually initiates a cascade of reactions in the cell, with each stage becoming more powerfully activated so that even small concentrations of the hormone can have a large effect. Each receptor is usually highly specific for a single hormone; this determines the type of hormone that will act on a particular tissue. The locations for the different types of hormone receptors are generally the following:

1. In or on the surface of the cell membrane. The membrane receptors are specific mostly for the protein, peptide, and catecholamine hormones.

2. In the cell cytoplasm. The primary receptors for the different steroid hormones are found mainly in the cytoplasm.

3. In the cell nucleus. The receptors for the thyroid hormones are found in the nucleus and are believed to be located in direct association with one or more of the chromosomes.

Intracellular signaling after hormone receptor activation

Almost without exception, a hormone affects its target tissues by first forming a hormone-receptor complex. This alters the function of the receptor itself, and the activated receptor initiates the hormonal effects.

Ion-channel-linked receptors

Neurotransmitter substances, such as acetylcholine and norepinephrine, combine with receptors in the postsynaptic membrane. This almost always causes a change in the structure of the receptor, usually opening or closing a channel for one or more ions. Some of these ion channel–linked receptors open (or close) channels for sodium ions, others for potassium ions, others for calcium ions, and so forth. The altered movement of these ions through the channels causes the subsequent effects on the postsynaptic cells.

G protein-linked hormone recptors

Many hormones activate receptors that indirectly regulate the activity of target proteins (e.g., enzymes or ion channels) by coupling with groups of cell membrane proteins called heterotrimeric GTP-binding proteins. Some parts of the receptor that proteide into the cell cytoplasm (especially the cytoplasmic tail of the receptor) are coupled to G proteins that include three (i.e., trimeric) parts—the a, b, and g subunits. When the ligand (hormone) binds to the extracellular part of the receptor, a conformational change occurs in the receptor that activates the G proteins and induces intracellular signals that either (1) open or close cell membrane ion channels or (2) change the activity of an enzyme in the cytoplasm of the cell. The trimeric G proteins are named for their ability to bind guanosine nucleotides. In their inactive state, the a, b, and g subunits of G proteins form a complex that binds guanosine diphosphate (GDP) on the a

subunit. When the receptor is activated, it undergoes a conformational change that causes the GDP-bound trimeric G protein to associate with the cytoplasmic part of the receptor and to exchange GDP for guanosine triphosphate (GTP). Displacement of GDP by GTP causes the a subunit to dissociate from the trimeric complex and to associate with other intracellular signaling proteins; these proteins, in turn, alter the activity of ion channels or intracellular enzymes such as adenylyl cyclase or phospholipase C, which alters cell function. The signaling event is rapidly terminated when the hormone is removed and the a subunit inactivates itself by converting its bound GTP to GDP; then the a subunit once again combines with the b and g subunits to form an inactive.

Enzyme-linked hormone receptors

Some receptors, when activated, function directly as enzymes or are closely associated with enzymes that they activate. These enzyme-linked receptors are proteins that pass through the membrane only once When the hormone binds to the extracellular part of the receptor, an enzyme immediately inside the cell membrane is activated (or occasionally inactivated). Although many enzyme-linked receptors have intrinsic enzyme activity, others rely on enzymes that are closely associated with the receptor to produce changes in cell function.

Intracellular Hormone receptors and activation of genes

Several hormones, including adrenal and gonadal steroid hormones, thyroid hormones, retinoid hormones, and vitamin D, bind with protein receptors inside the cell rather than in the cell membrane. Because these hormones are lipid soluble, they readily cross the cell membrane and interact with receptors in the cytoplasm or nucleus. The activated hormonereceptor complex then binds with a specific regulatory (promoter) sequence of the DNA called the hormone response element, and in this manner either activates or represses transcription of specific genes and formation of messenger RNA (mRNA).

40. Physiological applications of law of Laplace

In medicine it is often referred to as the Law of Laplace, and it is used in the context of respiratory physiology, in particular alveoli in the lung, where a single alveolus is modeled as being a perfect sphere. The Law of Laplace describes the relationship bwteen pressure (P), surface pension (T), and the readius (r) of an alveolus.

$$P = 2T/r$$

There is an inverse relationship between surface tension and alveolar radius. It follows from this that a small alveolus will experience a greater inward force than a large alveolus, if their surface tensions are equal. In that case, if both alveoli are connected to the same airway, the air would flow from the smaller alveoli to the big one. The small alveolus will be more likely to collapse.

This explains why the presence of surfactant lining the alveoli is of vital importance. Surfactant reduces the surface tension on all alveoli, but its effect is greater on small alveoli than on large alveoli. Thus, surfactant compensates for the size differences between alveoli, and ensures that smaller alveoli do not collapse.

The Law of Laplace also explains various phenomena encountered in the pathology of vascular or gastrointestinal walls. The "surface tension" in this case represents the muscular tension on the wall of the vessel. For example, if an aneurysm forms in a blood vessel wall, the radius of the vessel has increased. This means that the inward force on the vessel decreases, and therefore the aneurysm will continue to expand until it ruptures. A similar logic applies to the formation of diverticuli in the gut.

Also, the Laplace law explain why during the ejection phase of the systole of the heart, the pressure inside the left ventricle initially continues to rise even though the aortic valve is opened.

$P = \frac{T \times h}{r}$ where h is the thickness of the ventricular wall

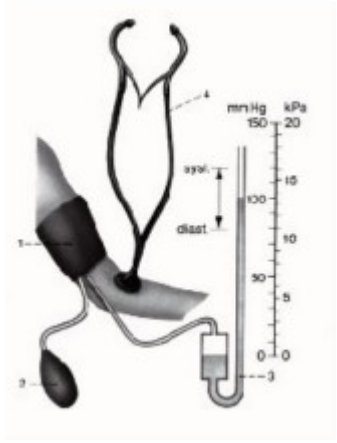
When the aortic valve pens and the ventricular wall contracts, the radius of the ventricle diminishes and the thickness of the wall increases, resulting in the incresed pressure.

41. Invasive assessment of blood pressure

Arterial blood pressure (BP) is most accurately measured invasively through an arterial line. Invasive arterial pressure measurement with intravascular cannulae involves direct measurement of arterial pressure by placing a cannula needle in an artery (usually radial, femoral, dorsalis pedis or brachial). The cannula must be connected to a sterile, fluid-filled system, which is connected to an electronic pressure transducer. The advantage of this system is that pressure is constantly monitored beat-by-beat, and a waveform (a graph of pressure against time) can be displayed. . Cannulation for invasive vascular pressure monitoring is infrequently associated with complications such as thrombosis, infection, and bleeding. It is generally reserved for patients where rapid variations in arterial pressure are anticipated. Invasive vascular pressure monitors are pressure monitoring systems designed to acquire pressure information for display and processing. There are a variety of invasive vascular pressure monitors for trauma, critical care, and operating room applications. These include single pressure, dual pressure, and multi-parameter (i.e. pressure/temperature). The monitors can be used for measurement and follow-up of arterial, central venous, pulmonary arterial, left atrial, right atrial, femoral arterial, umbilical venous, umbilical arterial, and intracranial pressures.

42. Non-invasive assessment of blood pressure

Riva Rocci (auscultatory) method



- Using sphygmomanometer - Cuff wrapped around the arm;
- Stethoscope is placed over the brachial artery at the ant cubital fossa;
- Cuff is inflated until the pressure is well above expected systolic pressure;
- The artery is occluded by the cuff and there will be no pulse sound;
- The pressure in the cuff is lowered using the valve;
- At the point where systole pressure exceeds the cuff, a sharp sound can be heard as blood forces its way through the vessel – this first sound is systole;
- As the cuff pressure is lowered further, the sounds become louder, then dull and weaker and gradually fades to a point – this last sound is diastole;

These sounds (kortikoff sounds) can be heard due to turbulent flow in the brachial artery, because when the artery is narrowed, the velocity of flow through the constriction exceeds the critical velocity - turbulent flow.

Oscillometric method

Involves the observation of oscillations in the sphygmomanometer cuff pressure which are caused by the oscillations of blood flow, i.e. the pulse. The electronic version of this method is sometimes used in long-term measurements and general practice. It uses a sphygmomanometer cuff like the auscultatory method, but with an electronic pressure sensor (transducer) to observe cuff pressure oscillations, electronics to automatically interpret them, and automatic inflation and deflation of the cuff. The pressure sensor should be calibrated periodically to maintain accuracy.

Oscillometric measurement requires less skill than the auscultatory technique, and may be suitable for use by untrained staff and for automated patient home monitoring.

The cuff is inflated to a pressure initially in excess of the systolic arterial pressure, and then reduces to below diastolic pressure over a period of about 30 seconds. When blood flow is zero (cuff pressure exceeding systolic pressure) or unimpeded (cuff pressure below diastolic pressure), cuff pressure will be essentially constant. When blood flow is present, but restricted, the cuff pressure, which is monitored by the pressure sensor, will vary periodically in synchrony with the cyclic expansion and contraction of the brachial artery, i.e., it will oscillate. The values of systolic and diastolic pressure are computed, not actually measured from the raw data, using an algorithm; the computed results are displayed.

Oscillometric monitors may produce inaccurate readings in patients with heart and circulation problems, that include arterial sclerosis, arrhythmia, preeclampsia, pulsus alternans, and pulsus paradoxus.

The term NIBP, for Non-Invasive Blood Pressure, is often used to describe oscillometric monitoring equipment.

Palpation

- Inflate arm cuff until radial pulse is no longer detectable;
- Let pressure fall and determine the pressure at which the radial pulse first becomes palpable => systolic pressure;
- Due to difficulty in measuring – pressures are usually 2-3 mmHg lower than measured in riva rocci method.

Note: When arterial pressure is measured using a sphygmomanometer (i.e. blood pressure cuff) on the upper arm, the systolic and diastolic pressures that are measured represent the pressure within the brachial artery, which is slightly different than the pressure found in the aorta or the pressure found in other distributing arteries. As the aortic pressure pulse travels down the aorta

and into distributing arteries, there are characteristic changes in the systolic and diastolic pressures, as well as in the mean pressure. The systolic pressure rises and the diastolic pressure falls, therefore the pulse pressure increases, as the pressure pulse travels away from the aorta. This occurs because of reflective waves from vessel branching, and from decreased arterial compliance (increased vessel stiffness) as the pressure pulse waves travels from the aorta into systemic arteries. There is only a small decline in mean arterial pressure as the pressure pulse travels down distributing arteries due to the relatively low resistance of large distributing arteries.

Finapres (method of Prof. Jan Peñáz)

The Finapres non-invasive blood pressure (BP) monitor uses the method of Peñáz to indirectly record the arterial waveform.

Volume clamp with physiocal technology

The volume-clamp method was first introduced by Czech physiologist Prof. J Peñáz in 1967. With this method, finger arterial pressure is measured using a finger cuff in combination with an infrared plethysmograph, which consists of an infrared light source and detector. The infrared light is absorbed by the blood, and the pulsation of arterial diameter during a heart beat causes a pulsation in the light detector signal.

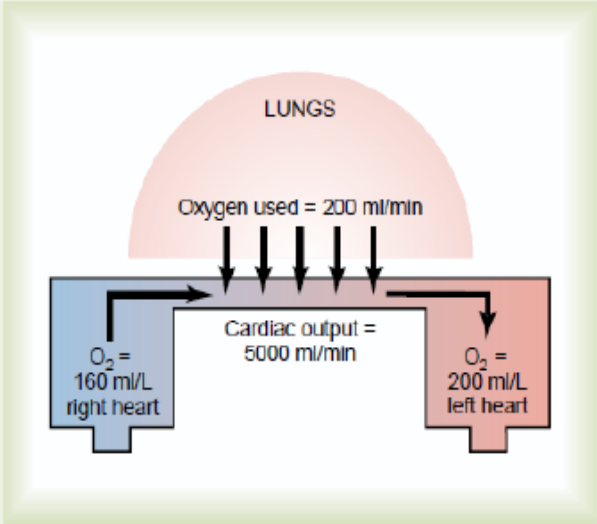
43. Measurement of cardiac output

Cardiac Output is the volume of blood being pumped by the heart, in particular by a left or right ventricle in the time interval of one minute.

$$CO = \text{Stroke Volume} \times \text{Heart Rate}$$

In the human, except in rare instances, cardiac output is measured by indirect methods that do not require surgery. Two of the methods commonly used are the oxygen Fick method and the indicator dilution method.

Oxygen Fick Principle



The Fick principle is explained by the figure to the right. This figure shows that 200 ml of oxygen are being absorbed from the lungs into the pulmonary blood each minute. It also shows that the blood entering the right heart has an oxygen concentration of 160 ml per liter of blood, whereas that leaving the left heart has an oxygen concentration of 200 ml per liter of blood. From this data, one can calculate that each liter of blood passing through the lungs absorbs 40 ml of oxygen. Because the total quantity of oxygen absorbed into the blood from the lungs each minute is 200 ml, dividing 200 by 40 calculates a total of five 1-liter portions of blood that must pass through the pulmonary circulation each minute to absorb this amount of oxygen. Therefore, the quantity of blood flowing through the lungs each minute is 5 liters, which is also a measure of the cardiac output. Thus, the cardiac output can be calculated by the following formula:

$$CO = \frac{VO_2}{(ca - cv)} \times 100$$

Where
VO_2 is the amount of O_2 absorbed by the lungs (ml/min)
Ca is the oxygen content of arterial blood
Cv is the oxygen content of venous blood
(ca – cv) is also known as the arteriovenous oxygen difference.

In applying this Fick procedure for measuring cardiac output in the human being venous blood is usually obtained through a catheter inserted up the brachial vein of the forearm, through the subclavian vein, down to the right atrium, and, finally, into the right ventricle or pulmonary artery. And systemic arterial blood can then be obtained from any systemic artery in the body. The rate of oxygen absorption by the lungs is measured by the rate of disappearance of oxygen from the respired air, using any type of oxygen meter.

Indicator Dilution Method

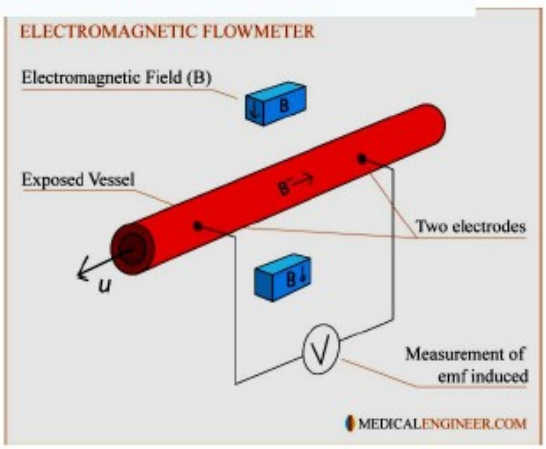
The method measures the concentration of a dye at different points in the circulation, usually from an intravenous injection and then at a downstream sampling site, usually in a systemic artery.

A small amount of indicator, such as a dye, is injected into a large systemic vein or, preferably, into right atrium. This passes through the right side of the heart, then through the blood vessels of the lungs, through the left side of the heart and, finally, into the systemic arterial system. The concentration of the dye is recorded as the dye passes though one of the peripheral arteries.

$$CO = \frac{\text{amount of indicator injected (mol)}}{\text{Average concentration in arterial blood after a single circulation through the heart (mol/l)}}$$

44. Measurement of blood flow

Electromagnetic Flowmeter



This Method is based on the principle of generattion of electromotive force in blood that is moving through a magnetic field. A blood vessel is placed between the poles of a strong magnet, and electrodes are placed on the two wires of the vessel perpendicular to the magnetic lines of force.

When blood flows through the vessel, an electrical voltage proportional to the rate of the blood flow is generated between the two electrodes, and this is recorded using an appropriate voltmeter or electronic recording apparatus.

A special advantage of the electromagnetic flowmeter is that it can record changes in flow in less than 1/100 of a second, allowing accurate recording of pulsatile changes in flow as well as steady flow.

Ultrasonic Doppler Flowmeter

A microscopic piezoelectric crystal is mounted at one end of the device. This crystal, when energized with an appropriate electronic apparatus, transmits ultrasound at a frequency of several hundred thousand cycles per second downstream along the flowing blood. A portion of the sound is reflected by the red blood cells in the flowing blood. The reflected sound waves then travel backward from the blood cells toward the crystal. These reflected waves have a lower frequency than the transmitted wave because the red blood cells are moving away from the transmitter crystal. This is called Doppler effect.

Reflected wave is received back onto the crystal and amplified greatly by the electronic apparatus. the electronic apparatus determines the frequency difference between the transmitted wave and the reflected wave, thus determining the velocity of blood flow.

45. Phonocardiography

A **Phonocardiogram** or PCG is a plot of high fidelity recording of the sounds and murmurs made by the heart with the help of the machine called phonocardiograph. The sounds are thought to result from vibrations created by closure of the heart valves.

First heart sound - contraction of the ventricles first causes sudden backflow of blood against the A-V valves (the tricuspid and mitral valves), causing them to close and bulge toward the atria until the chordae tendineae abruptly stop the back bulging. The elastic tautness of the chordae tendineae and of the valves then causes the back surging blood to bounce forward again into each respective ventricle.This causes the blood and the ventricular walls, as well as the taut valves, to vibrate and causes vibrating turbulence in the blood. The vibrations travel through the adjacent tissues to the chest wall, where they can be recorded by the microphone.

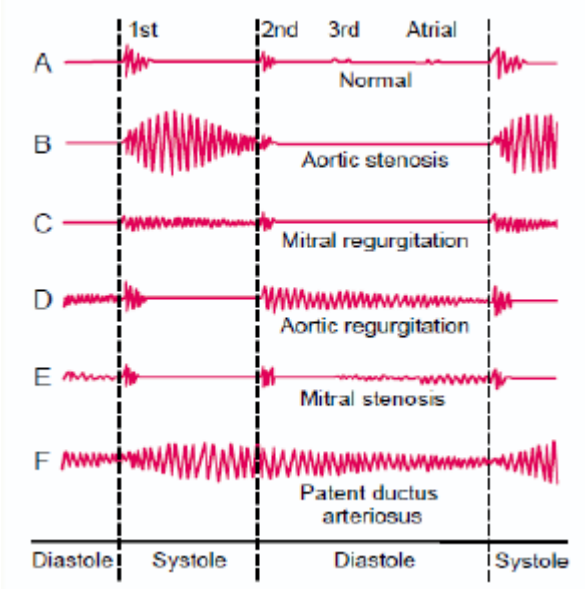
Second heart sound - results from sudden closure of the semilunar valves at the end of systole. When the semilunar valves close, they bulge backward toward the ventricles, and their elastic stretch recoils the blood back into the arteries, which causes a short period of reverberation of blood back and forth between the walls of the arteries and the semilunar valves, as well as between these valves and the ventricular walls.

The duration of each of the heart sounds is slightly more than 0.10 second—the first sound about 0.14 second and the second about 0.11 second.

Third heart sound - is heard at the beginning of the middle third of diastole. A logical but unproved explanation of this sound is oscillation of blood back and forth between the walls of the ventricles initiated by inrushing blood from the atria.

Atrial heart sound (fourth heart sound) - This sound occurs when the atria contract, and presumably, it is caused by the inrush of blood into the ventricles, which initiates vibrations similar to those of the third heart sound.

The ability to quantitate the sounds made by the heart provides information not readily available from more sophisticated tests, and provides vital information about the effects of certain cardiac drugs upon the heart. It is also an effective method for tracking the progress of the patient's disease.



49. Cardiac contractility, ejection fraction, heart failure

Contractility – is the intrinsic ability of cardiac muscle to develop a force at a given muscle length. – is also called inotropism. – is related to the intracellular Ca^{2+} concentration. – can be estimated by the ejection fraction (stoke volume/ end-diastolic volume), which is normally 0.55 (55%). – Positive inotropic agents produce an increase in contractility. – Negative inotropic agents produce a decrease in contractility.

Factors that increase contractility (positive inotropism)

a. *Increases heart rate*

– When more action potentials occur per unit time, more Ca^{2+} enters the myocardial cells during the action potential plateaus, more Ca^{2+} is released from the SR, and greater tension is produced during contraction.

a. *Sympathetic stimulation (cathecholamines) via β1 receptors*

– increases the force of contraction by two mechanisms:

(1) It increases the inward Ca^{2+} current during the platue of each cardiac action potential.

(2) It increases the activity of the Ca^{2+} pump of the SR (by phosphorylation of phospholamban); as a result more Ca^{2+} is available for release in subsequent beats.

c. *Cardiac glycosides (digitialis)*

– increase the force of contraction by inhibiting Na^+, K^+-ATPase in the myocardial cell membrane.

– As a result of this inhibition, the intracellular [Na^+], diminishing the Na^+ gradient across the cell membrane.

– Na^+-Ca^{2+} exchange (a mechanism that extrudes Ca^{2+} from the cell) depends on the size of the Na^+ gradient and thus is diminished, producing increase in intracellular [Ca^{2+}].

Factors that decrease contractility (negative inotropism) .

– *Parasympathetic stimulation* (ACh) via muscarinic receptors decrease the force of contraction in the atria by decreasing the inward Ca^{2+} current during the platue of the cardiac action potential.

Ejection fraction is the fraction of the end-diastolic volume (EDV) that is ejected with each beat.

$$\text{Ejection fraction (EF)} = \frac{\text{SV x 100}}{\text{EDV}}$$

Heart failure

The term “cardiac failure” means simply failure of the heart to pump enough blood to satisfy the needs of the body. It can be acute and associated with sudden death, or chronic. The failure may involve primarily the right ventricle, but much more commonly it involves the larger, thicker left ventricle or both ventricles.

In acute heart failure cardiac output falls precariously low. So, many of the circulatory reflexes are immediately activated.The best known of these is the baroreceptor reflex, which is activated by diminished arterial pressure. It is probable that the chemoreceptor reflex, the central nervous system ischemic response, and even reflexes that originate in the damaged heart also contribute to activating the sympathetic nervous system and parasympathetic nervous signals to the heart become reciprocally inhibited at the same time.

Strong sympathetic stimulation has two major effects on the circulation: first on the heart itself, and second on the peripheral vasculature. If all the ventricular musculature is diffusely damaged but is still functional, sympathetic stimulation strengthens this damaged musculature. If part of the muscle is nonfunctional and part of it is still normal, the normal muscle is strongly stimulated by sympathetic stimulation, in this way partially compensating for the nonfunctional muscle. Thus, the heart, one way or another, becomes a stronger pump. After sympathetic compensation about twofold elevation of the very low cardiac output curve. Sympathetic stimulation also increases venous return because it increases the tone of most of the blood

vessels of the circulation, especially the veins, raising the mean systemic filling pressure to 12 to 14 mm Hg, almost 100 per cent above normal. This increased filling pressure greatly increases the tendency for blood to flow from the veins back into the heart. Therefore, the damaged heart becomes primed with more inflowing blood than usual, and the right atrial pressure rises still further, which helps the heart to pump still larger quantities of blood.

In chronic heart failure (congestive heart failure), cardiac output is initially inadequate during exercise but adequate at rest. As the disease progresses, the output at rest also becomes inadequate. There are two types of failure, systolic and diastolic. In systolic failure, stroke volume is reduced because ventricular contraction is weak. This causes an increase in the end-systolic ventricular volume, so that the ejection fraction – the fraction of the blood in the ventricles that is ejected during systole – falls from 65% to as low as 20%. The initial response to failure is activation of the genes that cause cardiac myocytes to hypertrophy, and thicken of the ventricular wall (cardiac remodeling). The incomplete filling of the arterial system leads to increased discharge of the sympathetic nervous system and increased secretion of renin and aldosterone, so Na+ and water is retained. The responses are initially compensatory, but eventually the failure worsens and the ventricles dilate. In diastolic failure, the ejection fraction is initially maintained but the elasticity of the myocardium is reduced so filling during diastole is reduced. This leads to inadequate stroke volume and the same cardiac remodeling and Na+ and water retention that occur in systolic failure. It should be noted that the inadequate cardiac output in failure may be relative rather than absolute.

Recovery of myocardium after myocardium after myocardial infacrtion

After a heart becomes suddenly damaged as a result of myocardial infarction, the natural reparative processes of the body begin immediately to help restore normal cardiac function. For instance, a new collateral blood supply begins to penetrate the peripheral portions of the infarcted area of the heart, often causing much of the heart muscle in the fringe areas to become functional again. Also, the undamaged portion of the heart musculature hypertrophies, in this way offsetting much of the cardiac damage. The degree of recovery depends on the type of cardiac damage, and it varies from no recovery to almost complete recovery.

Treatment

Treatment of congestive heart failure is aimed at improving cardiac contractility, treating the symptoms, and decreasing the load on the heart. Currently, the most effective treatment in general use is inhibition of the production of angiotensin II with angiotensin-converting enzyme inhibitors. Blocking the production of angiotensin II or its effects also reduces the circulating aldosterone level and decreases blood pressure, reducing the afterload against which the heart pumps. Digitalis derivatives such as dioxin have classically been used to treat congestive heart failure because of their ability to increase intracellular Ca^{2+} and hence exert a positive inotropic effect, but they are now used in a secondary role to treat systolic dysfunction and slow the ventricular rate in patients with atrial fibrillation.

50. Cardiac catheterization

Cardiac catheterization (heart cath) is the insertion of a catheter into a chamber or vessel of the heart. This is done for both investigational and interventional purposes. Coronary catheterization is a subset of this technique, involving the catheterization of the coronary arteries.

Procedure

Local anaesthetic is injected into the skin to numb the area. A small puncture is then made with a needle in either the femoral artery in the groin or the radial artery in the wrist, before a guidewire is inserted into the arterial puncture. A plastic sheath (with a stiffer plastic introducer inside it) is then threaded over the wire and pushed into the artery (Seldinger technique). The wire is then removed and the side-port of the sheath is aspirated to ensure arterial blood flows back. It is then flushed with saline.

Catheters are inserted using a long guidewire and moved towards the heart. Once in position above the aortic valve the guidewire is then removed. The catheter is then engaged with the origin of the coronary artery (either left main stem or right coronary artery) and x-ray opaque iodine-based contrast is injected to make the coronary vessels show up on the x-ray fluoroscopy image.

When the necessary procedures are complete, the catheter is removed. Firm pressure is applied to the site to prevent bleeding. If the femoral artery was used, the patient will probably be asked to lie flat for several hours to prevent bleeding or the development of a hematoma.

A cardiac catheterization is a general term for a group of procedures that are performed using this method, such as coronary angiography, as well as left ventrical angiography. Once the catheter is in place, it can be used to perform a number of procedures including angioplasty, angiography, balloon septostomy, and an Electrophysiology study.

<u>Indications for investigational use</u>

This technique has several goals:

- Confirm the presence of a suspected heart ailment
- Quantify the severity of the disease and its effect on the heart
- Seek out the cause of a symptom such as shortness of breath or signs of cardiac insufficiency
- Make a patient assessment prior to heart surgery

<u>Investigative techniques used with cardiac catheterization</u>

A probe that is opaque to X-rays is inserted into the left or right chambers of the heart for the following reasons:

- To measure intracardiac and intravascular blood pressures
- To take tissue samples for biopsy
- To inject various agents for measuring blood flow in the heart; also to detect and quantify the presence of an intracardiac shunt
- To inject contrast agents in order to study the shape of the heart vessels and chambers and how they change as the heart beats

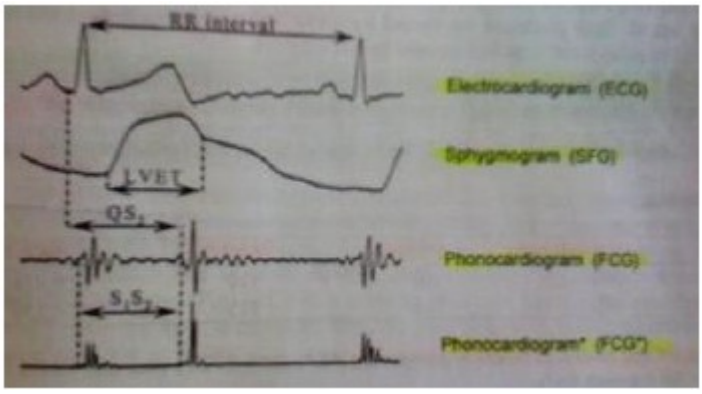
51. Polygraphic methods

A polygraph (or “lie detector”) is an instrument that measures and records several physiological indices such as blood pressure, pulse, respiration, breathing rhythms/ratios, and skin conductivity while the subject is asked and answers a series of questions, in the belief that deceptive answers will produce physiological responses that can be differentiated from those associated with non-deceptive answers.

Polygraphs are in some countries used as an interrogation tool. Within the US federal government, a polygraph examination is also referred to as a psycho physiological detection of deception (PDD) examination.

This method was in the past used in clinical practice, nowadays it is replaced by other methods. In practicals, it will help us to demonstrate interrelationships of particular processes of cardiac action.

(Masaryk Uni. Phys. Prac.): Evaluation Systolic Time Interval using Polygraph Recording 3 parameters will be registered simultaneously; electrical activity of the heart by means of electrocardiography (ECG; I. lead), pulse wave on a. carotis by means of infrared sensor, sfygmography (SFG) and heart sounds by means of phonocardiography (FCG).



Measured parameters (from figure):

- RR interval: cardiac cycle duration (time between two successive R on ECG recording)
- LVET: Ejection phase duration (time from the onset of the sphygmographic curve to the dicrotic incisure, it corresponds to the time interval between the opening and closure of the aortic valves)
- QS2: electromechanical systole – time from electrical activation of septum to closure of aortic valve (time from Q ton ECG recording to the 2nd heart sound on FCG or FCG* recording) S1S2: duration of mechanical systole (time between 1st and 2nd heart sound on FCG or FCG* recording)

Calculated parameters:

- S2S1: mechanical diastole duration (S2S1= RR interval - S1S2)
- PEP: preejection period – time from electrical activation of septum to opening of seminlunar valves (PEP = QS2 – LVET)
- IVC: isovolumic contraction duration (IVC = S1S2 – LVET)
- EML: electromechanical latency – time from electrical activation of septum to closing of atrioventricular valves and beginning of systole of ventricles (EML=QS2 - S1S2)

Indexes

$\Delta P/\Delta t$ = average speed of pressure increase in isovolumic phase of systole PEP/LVET = it is index of cardiac contractility.

Systolic intervals depend on the heart rate. In order to compare various recordings the interval must be corrected. The easiest and most often used correction is done according to Bazett's formula:

Ic = Im /√RR , where Ic is corrected interval, Im is measured interval in milliseconds and RR is cycle length in . seconds.

52. Electromyography

Electromyography (EMG) is a technique for evaluating and recording the electrical activity produced by skeletal muscles. EMG is performed using an instrument called an electromyograph, to produce a record called an electromyogram. An electromyograph detects the electrical potential generated by muscle cells when these cells are electrically or neurologically activated. The signals can be analyzed to detect medical abnormalities, activation level, and recruitment order or to analyze the biomechanics of human or animal movement.

Procedure

There are two kinds of EMG in widespread use: surface EMG and intramuscular (needle and fine-wire) EMG.

1. To perform intramuscular EMG, a needle electrode or a needle containing two fine-wire electrodes is inserted through the skin into the muscle tissue. A trained professional observes the electrical activity while inserting the electrode. The insertional activity provides valuable information about the state of the muscle and its innervating nerve. Normal muscles at rest make certain, normal electrical sounds when the needle is inserted into them. Then the electrical activity when the muscle is at rest is studied. Abnormal spontaneous activity might indicate some nerve and/or muscle damage. Then the patient is asked to contract the muscle smoothly. The shape, size, and frequency of the resulting motor unit potentials are judged. Then the electrode is retracted a few millimeters, and again the activity is analyzed until at least 10–20 units have been collected. Each electrode track gives only a very local picture of the activity of the whole muscle. Because skeletal muscles differ in the inner structure, the electrode has to be placed at various locations to obtain an accurate study.

2. Intramuscular EMG may be considered too invasive or unnecessary in some cases. Instead, a surface electrode may be used to monitor the general picture of muscle activation, as opposed to the activity of only a few fibers as observed using an intramuscular EMG. This technique is used in a number of settings; for example, in the physiotherapy clinic, muscle activation is monitored using surface EMG and patients have an auditory or visual stimulus to help them know when they are activating the muscle (biofeedback).

A motor unit is defined as one motor neuron and all of the muscle fibers it innervates. When a motor unit fires, the impulse is carried down the motor neuron to the muscle. The area where the nerve contacts the muscle is called the neuromuscular junction, or the motor end plate. After the action potential is transmitted across the neuromuscular junction, an action potential is elicited in all of the innervated muscle fibers of that particular motor unit. The sum of all this electrical activity is known as a motor unit action potential (MUAP). This electrophysiologic activity from multiple motor units is the signal typically evaluated during an EMG. The composition of the motor unit, the number of muscle fibers per motor unit, the metabolic type of muscle fibers and many other factors affect the shape of the motor unit potentials in the myogram.

Normal results

Muscle tissue at rest is normally electrically inactive. After the electrical activity caused by the irritation of needle insertion subsides, the electromyograph should detect no abnormal spontaneous activity (i.e., a muscle at rest should be electrically silent, with the exception of the area of the neuromuscular junction, which is, under normal circumstances, very spontaneously active). When the muscle is voluntarily contracted, action potentials begin to appear. As the strength of the muscle contraction is increased, more and more muscle fibers produce action potentials. When the muscle is fully contracted, there should appear a disorderly group of action potentials of varying rates and amplitudes (a complete recruitment and interference pattern).

53. Registration of membrane potential and currents

Electrodes for Active Biosignals

Polarisable (electrodes produce variable own contact potential via an electrochemical reaction) or non-polarisable (constant own contact potential)

- Polarisable: the measured biopotential will be inaccurate as the electrode voltage is variable e.g. movement of electrode or patient, humidity (sweating), chemical composition of ambient medium, tec. Most polarisable electrodes are made of noble metals. In the case of concentration polarisation, the concentration of ions changes around electrodes due to electrochemical processes. In case of chemical polarisation, Gates are liberated on the surface on the electrodes.
- Non-polarisable electrode: accurate measurement of biopotential. In practice, the silver-chloride (Ag-AgCl) electrode is most often used.

- Macro or Microelectrodes: latter used for biopotentials from individual cells. Small tip diameter (0.5 µm) and made of metal (polarisable) or glass (non-polarisable). The glass microelectrode is a capillary with an open end filled with an electrolyte of standard concentration.
- Superficial or needle electrodes: superficial electrodes are metallic plates of different shape and size. Good electric contact is ensure by a conducting gel. Their shape is often dish-like. Needle electrodes are used for recording of biopotentials or long-term recording of heart or brain potentials.

Ion currents in cell membrane

Patch-clamp method

The conductance of the cell membrane is by the type and number of ion channels that are momentarily open. Patch-clamp techniques permit the direct measurement of ionic currents through single ion channels.

During patch-clamp recording, the opening of a glass electrode is placed over a cell membrane in such a way that the opening covers only a small part of the membrane (patch) containing only one or a small number of ion channels.

In single channel recording, the membrane potential is kept at a preset value (voltage clamp). this permits the measurement of ionic current in a single channel.

55. Lung ventilation, volumes, measurement

Ventilation is defined as the exchange of air between the atmosphere and alveoli. Air moves from a region of high pressure to one of low pressure.

$$F = \Delta P/R \leftrightarrow F = (Palv - Patm)$$

Flow (F) is proportional to the pressure difference (ΔP) between two points and inversely proportional to the resistance(R).

When Palv is less than Patm, the driving force for air flow is negative, indicating that air flow is inward (inspiration). When Palv is greater than Patm, the driving force for air flow is positive, indicating that air flow is outward (expiration). These alveolar pressure changes are caused by changes in the dimensions of the chest wall and lungs.

This is explained by Boyle's law:

$$P1V1=P2V2$$

An increase in the volume of a container decreases in the container volume increases the pressure.

Lungs are passive elastic structures, and their volume, therefore, depends upon:

(1) the difference in pressure – termed the transpulmonary pressure (Ptp) – between the inside and the outside of the lungs.

(2) how stretchable the lungs are.

The pressure inside the lungs is the air pressure inside the alveoli (Palv), and the pressure outside the lungs is the pressure of the intrapleural fluid surrounding the lungs (Pip).

$$\text{Transpulmonary pressure} = Palv - Pip$$

The muscles of the chest wall and the diaphragm contract and cause the chest wall to expand during inspiration. As the chest wall expands, it lowers Pip according to Boyle's law. Since Palv-Pip (=Ptp) becomes more positive as a result, the lungs expand. As this occurs, Palv becomes more negative compared to Patm and air flows inward. Therefore, we normally increase the transmural pressure of the lungs (Ptp) to fill it with air by actively decreasing the pressure surrounding the lungs (Pip) relative to the pressure inside the lungs (Palv). When the respiratory muscles relax, elastic recoil of the lungs drives passive expiration back to the starting point.

Pulmonary volumes, capacities and their measurement

A simple method for studying pulmonary ventilation is to record the volume movement of air into and out of the lungs, a process called spirometry. It consists of a drum inverted over a chamber of water, with the drum counterbalanced by a weight. In the drum is a breathing gas, usually air or oxygen; a tube connects the mouth with the gas chamber.When one breathes into and out of the chamber, the drum rises and falls, and an appropriate recording is made on a moving sheet of paper.

Pulmonary Volumes

1. The tidal volume is the volume of air inspired or expired with each normal breath; it amounts to about 500 milliliters in the adult male.

2. The inspiratory reserve volume is the extra volume of air that can be inspired over and above the normal tidal volume when the person inspires with full force; it is usually equal to about 3000 milliliters.

3. The expiratory reserve volume is the maximum extra volume of air that can be expired by forceful expiration after the end of a normal tidal expiration; this normally amounts to about 1100 milliliters.

4. The residual volume is the volume of air remaining in the lungs after the most forceful expiration; this volume averages about 1200 milliliters.

Pulmonary Capacities

In describing events in the pulmonary cycle, it is sometimes desirable to consider two or more of the volumes together

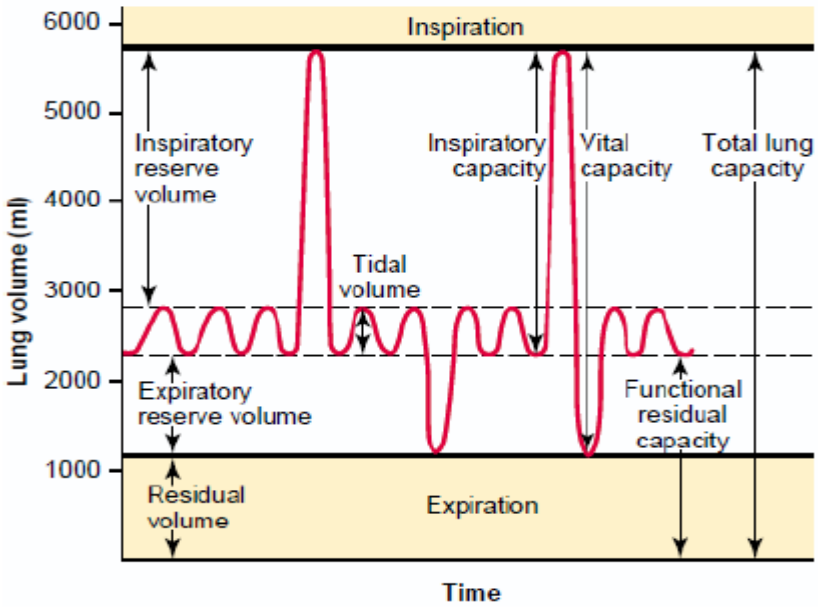
1. The inspiratory capacity equals the tidal volume plus the inspiratory reserve volume. This is the amount of air (about 3500 milliliters) a person can breathe in, beginning at the normal expiratory level and distending the lungs to the maximum amount.

2. The functional residual capacity equals the expiratory reserve volume plus the residual volume. This is the amount of air that remains in the lungs at the end of normal expiration (about 2300 milliliters).

3. The vital capacity equals the inspiratory reserve volume plus the tidal volume plus the expiratory reserve volume. This is the maximum amount of air a person can expel from the lungs after first filling the lungs to their maximum extent and then expiring to the maximum extent (about 4600 milliliters).

4. The total lung capacity is the maximum volume to which the lungs can be expanded with the greatest possible effort (about 5800 milliliters); it is equal to the vital capacity plus the residual volume.

All pulmonary volumes and capacities are about 20 to 25 per cent less in women than in men, and they are greater in large and athletic people than in small and asthenic people.

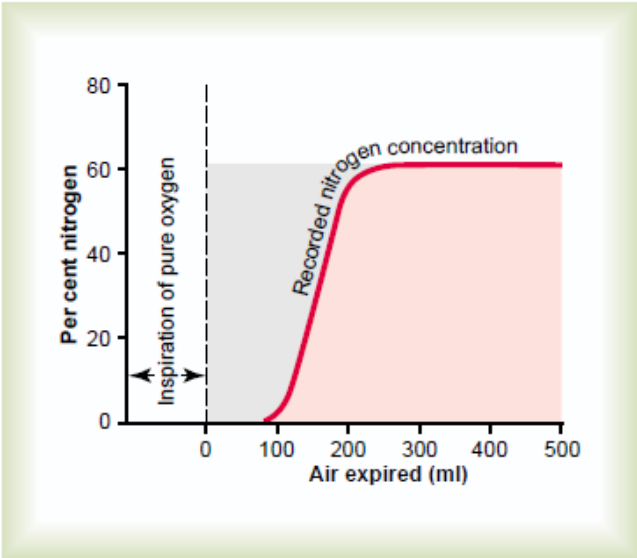


56. Dead space, measurement

Gas exchange areas but simply fills respiratory passages where gas exchange does not occur, such as the nose, pharynx, and trachea.This air is called **dead space air** because it is not useful for gas exchange. On expiration, the air in the dead space is expired first, before any of the air from the alveoli reaches the atmosphere. Therefore, the dead space is very disadvantageous for removing the expiratory gases from the lungs.

Measurement of the Dead Space Volume.

A simple method for measuring dead space volume is demonstrated by the graph. In making this measurement, the subject suddenly takes a deep breath of oxygen.This oxygen also mixes with the alveolar air but does not completely replace this air. Then the person expires through a rapidly recording nitrogen meter, which makes the record shown in the figure. The first portion of the expired air comes from the dead space regions of the respiratory passageways, where the air has been completely replaced by oxygen. Therefore, in the early part of the record, only oxygen appears, and the nitrogen concentration is zero. Then, when alveolar air begins to reach the nitrogen meter, the nitrogen concentration rises rapidly, because alveolar air containing large amounts of nitrogen begins to mix with the dead space air. After still more air has been expired, all the dead space air has been washed from the passages, and only alveolar air remains.Therefore, the recorded nitrogen concentration reaches a plateau level equal to its concentration in the alveoli.The gray area represents the air that has no nitrogen in it; this area is a measure of the volume of dead space air. For exact quantification, the following equation is used:



$$VD = \frac{\text{grey area} \times VE}{\text{pink area} + \text{grey area}}$$

where VD is dead space air and VE is the total volume of expired air. Let us assume, for instance, that the gray area on the graph is 30 square centimeters, the pink area is 70 square centimeters, and the total volume expired is 500 milliliters. The dead space would be

$$\frac{30 \times 500}{30 + 70}, \text{ or } 150 \text{ ml}$$

Normal Dead Space Volume

The normal dead space air in a young adult man is about 150 milliliters.This increases slightly with age.

Anatomic Versus Physiologic Dead Space

The method just described for measuring the dead space measures the volume of all the space of the respiratory system other than the alveoli and their other closely related gas exchange areas; this space is called the anatomic dead space. On occasion, some of the alveoli themselves are nonfunctional or only partially functional because of absent or poor blood flow through the adjacent pulmonary capillaries.Therefore, from a functional point of view, these alveoli must also be considered dead space. When the alveolar dead space is included in the total measurement of dead space, this is called the physiologic dead space, in contradistinction to the anatomic dead space. In a normal person, the anatomic and physiologic dead spaces are nearly equal because all alveoli are functional in the normal lung, but in a person with partially functional or nonfunctional

alveoli in some parts of the lungs, the physiologic dead space may be as much as 10 times the volume of the anatomic dead space, or 1 to 2 liters.

The physiological dead space is measured in the clinical pulmonary function laboratory by making appropriate blood and expiratory gas measurements and using the following equation, called the Bohr equation:

$$\frac{Vdphys}{VT} = \frac{PaCO_2 - PECO_2}{PaCO_2}$$

in which VDphys is the physiologic dead space, VT is the tidal volume, $PaCO_2$ is the partial pressure of carbon dioxide in the arterial blood, and $PECO_2$ is the average partial pressure of carbon dioxide in the entire expired air.

When the physiologic dead space is great, much of the work of ventilation is wasted effort because so much of the ventilating air never reaches the blood.

57. Resistance of airways, measurement

The volume of air that flows into or out of the alveoli per unti time is directly proportional to the pressure difference between the atmosphere and alveoli and is inversely proportional to the resistance to flow of the airways.

The factors that determine airway resistance are analogous to those determining vascular resistance in the circulatory system: tube length, tube radius, and interactions between moving molecules. The most impostant factor by far is the radius of the tube – airway resistance is inversely proportional to the fourth power of the aieway radii.

Poiseuille's law:

$$R = \frac{8nl}{\pi R4}$$

Physical, neural, and chemical factors affect airway radii and therefore resistance. One important physical factor is the transpulmonary pressure, which exerts a distending force on the airways. Transpulmonary pressure increases during inspiration, airway radius becomes larger and airway resistance lower as the lungs expand during inspiration. The opposite occurs during expiration.

A second physical factor holding the airways open is the elastic connective tissue fibers that link the outside of the airways to the surrounding alveolar tissue. These fibers are pulled upon as the lungs expand during inspiration, and in turn they help pull the airways open even more than between breaths – lateral traction.

The increase in intrapleural pressure compresses the small conducting airways and decreases their radii. Therefore, because of increased airway resistance, there is a limit to how much one can increase the air flow rate during a forced expiration. The harder one pushes, the greater the compression of the airways.

A variety of neuroendocrine and paracrine factors can influence airway smooth muscleand thereby airway resistance.

Epinephrine relaxes airway smooth muscle whereas the leukotrienes produced in the lungs during inflammation contract the muscle.

Under abnormal circumstances, changes in these factors may cause serious increases in airway resistance.

Asthma

Intermittent episodes in which airway smooth muscle contracts strongly, markedly increasing airway resistance. The basic defect in asthma is chronic inflammation of the airways, the causes of which vary from person to person and include, amog others, allergy, viral infections, and sensitivity to environmental factors. The underlying inflammation makes the airway smooth muscle hyperresponsive and causes it to contact strongly when, the person exercises or is exposed to cigarette smoke, environmental pollutants, viruses, allergens, normally released bronchoconstrictor chemicals.

Chronic Obstructive Pulmonary Disease

The term chronic obstructive pulmonary disease refers to

(1) emphysema

(2) chronic bronchitis

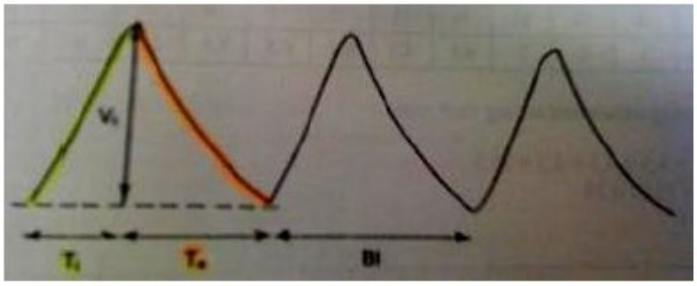
(3) a combination of the two

They cause severe difficulties not only in ventilation but in oxygenation of the blood.

58. Pneumography and pneumotachography

Pneumography is a method of recording the respiratory movements. Sensor – respiratory belt - works on piezoelectric principle (mechanical stimuli – increase or decrease of chest circumference are converted to electrical signal). The signal is then amplified and recorded.

- Duration of inspiration (Ti)
- Duration of expiration (Te)
- Respiratory intervals (BI =breathing interval)
- Amplitude Vt



Pneumography –recording, the way of evaluation

Pneumotachography

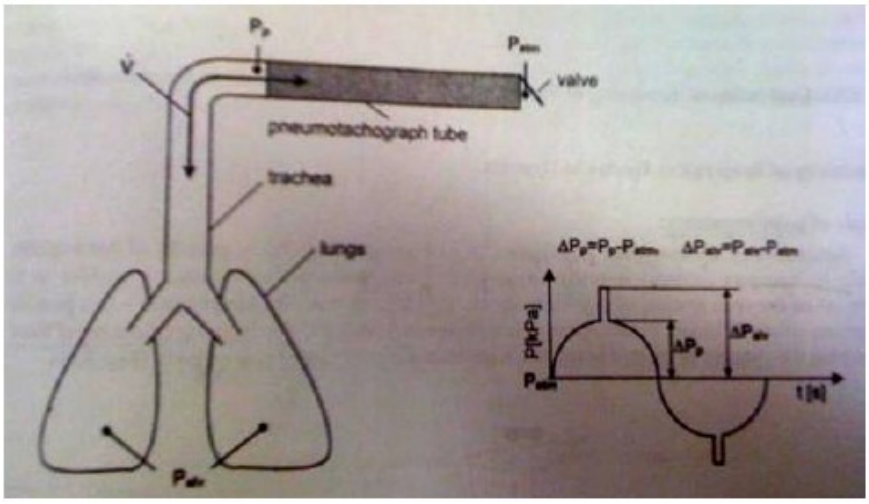
The pneumotachograph is an instrument consisting of parallel tubes of equal diameter that ensure laminar flow during breathing. One of the tubes has two side-branches near its both ends that are connected to a differential manometer by rubber tubing. The differential manometer measures the difference in air pressure of the inspired air or expired air. The pressure at the end of the pneumotachograph corresponds approximately to atmospheric pressure and is taken as zero.

Pressure in the alveoli is estimated by closing the outer end of the pneumotachograph by a special device (valve) for a fraction of second during normal breathing. The alveolar and airway pressure equilibrate at this moment and the alveolar pressure is recorded. Estimation of airway resistance is important for diagnosis of bronchial asthma where it is increased.

During breathing through the pneumotachograph, two resistances are connected in series: that of the pneumotachograph (Rp) and the airway resistance (Ra). If the alveolar pressure (Palv), pressure at proximal end of the pneumotachograph (Pp), and resistance of the pneumotachograph (Rp) are known, then:

The formula for calculation of airway resistance is:

$$R_a = Rp \times (\Delta Palv/\Delta Pp - 1)$$



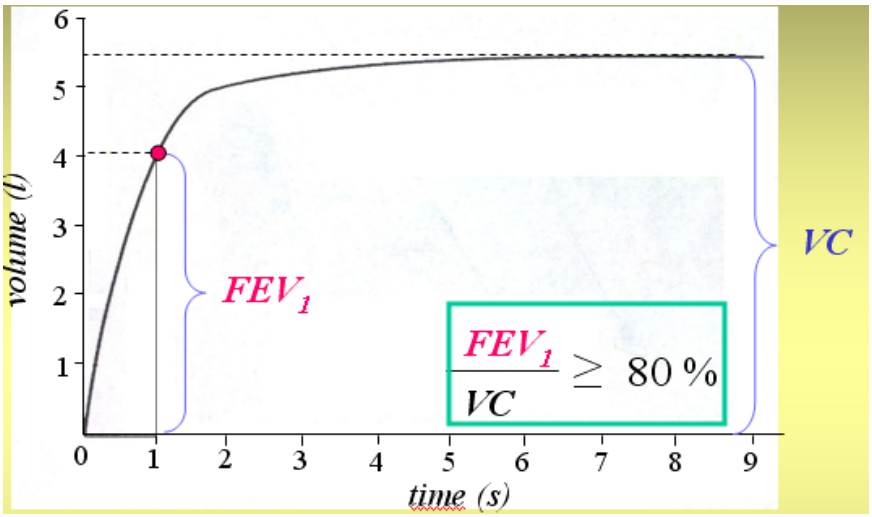
59. Maximum respiratory flow – volume curve (spirogram)

The measurement of dynamic volumes is an useful tool the access the function of the lungs.

Forced vital capacity

Is the maximal volume of air a person can expire after a maximal expiration. Under these conditions, the person is expiring the resting tidal volume and inspiratory reserve volume just inspired, plus the expiratory reserve volume.

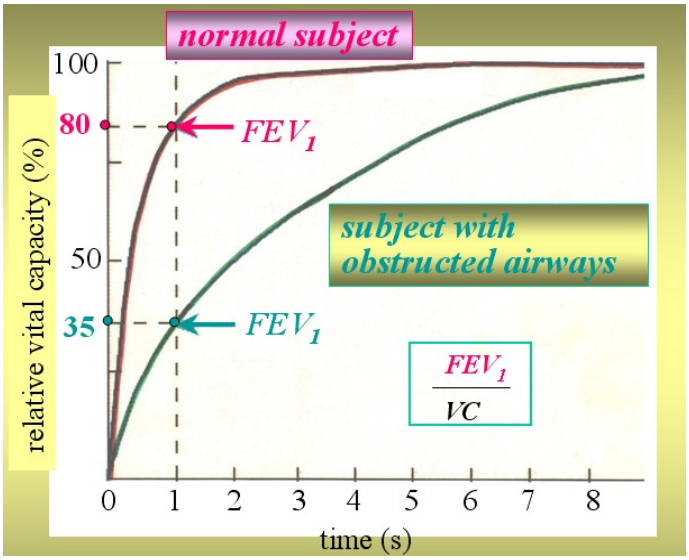
A variant on this method is the forced expiratory volume in 1s, (FEV1), in which the person takes a maximal inspiration and then exhales maximally as fast as possible. The important value is the fraction of the total "forced" vital capacity expired 1s. normal individual can expire approximately 80% of the vital capacity in one second.



This ratio enables to distinguish restrictive disorders (pulmonary fibrosis,…) from obstructive disorders with increased airway resistance (asthma bronchial).

For example, people with obstructive lung diseases (increased airway resistance) typically have FEV1 that is less than 80% of the vital capacity because it is difficult for them to expire air rapidly through the narrowed airways.

In contrast, restrictive lung diseases are characterized by normal airway resistance but impaired respiratory movement because of anormalities in the lung tissue, the pleura, the chest wall, or the neuromuscular machinery. Restrictive lung diseases are thos characterized by a reduced vital capacity but a normal ration of FEV2/VC.



61. Clearance

The rates at which different substances are “cleared” from the plasma provide a useful way of quantitating the effectiveness with which the kidneys excrete various substances. By definition, the renal clearance of a substance is the volume of plasma that is completely cleared of the substance by the kidneys per unit time.

However, renal clearance provides a useful way of quantifying the excretory function of the kidneys and, can be used to quantify the rate at which blood flows through the kidneys as well as the basic functions of the kidneys: glomerular filtration, tubular reabsorption, and tubular secretion. necessary to supply the amount of substance excreted in the urine per unit time.
Stated mathematically,

$$C_s \times P_s = U_s \times V \leftrightarrow C_s = \frac{U_s \times V}{P_s}$$

where Cs is the clearance rate of a substance s, Ps is the plasma concentration of the substance, Us is the urine concentration of that substance, and V is the urine flow rate. Thus, renal clearance of a substance is calculated from the urinary excretion rate (Us \ V) of that substance divided by its plasma concentration.

Inulin Clearance Can Be Used to Estimate GFR

If a substance is freely filtered (filtered as freely as water) and is not reabsorbed or secreted by the renal tubules, then the rate at which that substance is excreted in the urine (Us \ V) is equal to the filtration rate of the substance by the kidneys (GFR x Ps). Thus,

$$GFR \times P_s = U_s \times V$$

of the substance as follows:

$$GFR = \frac{U_s \times V}{P_s} = C_s$$

A substance that fits these criteria is inulin. Inulin, which is not produced in the body, and must be administered intravenously to a patient to measure GFR. Inulin is not the only substance that can be used for determining GFR. Other substances that have been used clinically to estimate GFR include radioactive iothalamate and creatinine.

Creatinine Clearance and Plasma Creatinine Concentration Can Be Used to Estimate GFR

Creatinine is a by-product of muscle metabolism and is cleared from the body fluids almost entirely by glomerular filtration. Therefore, the clearance of creatinine can also be used to assess GFR. Because measurement of creatinine clearance does not require intravenous infusion into the patient, this method is much more widely used than inulin clearance for estimating GFR clinically. However, creatinine clearance is not a perfect marker of GFR because a small amount of it is secreted by the tubules, so that the amount of creatinine excreted slightly exceeds the amount filtered. There is normally a slight error in measuring plasma creatinine that leads to an overestimate of the plasma creatinine concentration, and fortuitously, these two errors tend to cancel each other. Therefore, creatinine clearance provides a reasonable estimate of GFR. An approximation of changes in GFR, however, can be obtained by simply measuring plasma creatinine concentration (PCr), which is inversely proportional to GFR If GFR suddenly decreases by 50%, the kidneys will transiently filter and excrete only half as much creatinine, causing accumulation of creatinine in the body fluids and raising plasma concentration.

62. Cardiovascular response to Valsalva manouvre

The integrity of the baroreceptor mechanism can be tested with the **Valsalva maneuver** (i.e. expiring against a closed epiglottis).

It is performed by forcible exhalation against a closed airway, usually done by closing one's mouth and pinching one's nose shut.

Physiological response:

- ✓ Expiring against a closed glottis causes an increase in intrathoracic pressure, which decreases venous return.
- ✓ The decrease in venous return causes a decrease in cardiac output and arterial pressure.
- ✓ If the baroreceptor reflex is intact, the decrease in arterial pressure is sensed by the baroreceptors, leading to an increase in sympathetic outflow to the heart and blood vessels. In the test, an increase in heart rate would be noted.
- ✓ When the person stops the maneuver, there is a rebound increase in venous return, cardiac output, and arterial pressure. The increase in arterial pressure is sensed by the baroreceptors, which direct a decrease in heart rate.

Recordings of blood pressure (systolic) and pulse rate during a normal response to Valsalva's maneuver is studied; deviation from this response pattern signifies either abnormal heart function or abnormal autonomic nervous control of the heart.

The maneuver can sometimes be used to diagnose heart abnormalities, especially when used in conjunction with echocardiogram.

63. Examination of baroreflex sensitivity

By far the best known of the nervous mechanisms for arterial pressure control is the baroreceptor reflex. Basically, this reflex is initiated by stretch receptors, called either baroreceptors or pressoreceptors, located at specific points in the walls of several large systemic arteries. A rise in arterial pressure stretches the baroreceptors and causes them to transmit signals into the central nervous system. “Feedback” signals are then sent back through the autonomic nervous system to the circulation to reduce arterial pressure downward toward the normal level. A few baroreceptors are located in the wall of almost every large artery of the thoracic and neck regions; baroreceptors are extremely abundant in (1) the wall of each internal carotid artery slightly above the carotid bifurcation, an area known as the carotid sinus, and (2) the wall of the aortic arch. Signals from the “carotid baroreceptors” are transmitted through very small Hering’s nerves to the glossopharyngeal nerves in the high neck, and then to the tractus solitarius in the medullary area of the brain stem. Signals from the “aortic baroreceptors” in the arch of the aorta are transmitted through the vagus nerves also to the same tractus solitarius of the medulla. The barorecptors are highly activated in values around the normal blood pressure. Even a slight change in pressure causes a strong change in the baroreflex signal to readjust arterial pressure back toward normal. Thus, the baroreceptor feedback mechanism functions most effectively in the pressure range where it is most needed. The baroreceptors respond extremely rapidly to changes in arterial pressure; in fact, the rate of impulse firing increases in the fraction of a second during each systole and decreases again during diastole. Furthermore, the baroreceptors respond much more to a rapidly changing pressure than to a stationary pressure.

Circulatory Reflex Initiated by the Baroreceptors

After the baroreceptor signals have entered the tractus solitarius of the medulla, secondary signals inhibit the vasoconstrictor center of the medulla and excite the vagal parasympathetic center. The net effects are (1) vasodilation of the veins and arterioles throughout the peripheral circulatory system and (2) decreased heart rate and strength of heart contraction. Therefore, excitation of the baroreceptors by high pressure in the arteries reflexly causes the arterial pressure to decrease. Conversely, low pressure has opposite effects, reflexly causing the pressure to rise back toward normal.

Function of the Baroreceptors During Changes in Body Posture.

The ability of the baroreceptors to maintain relatively constant arterial pressure in the upper body is important when a person stands up after having been lying down. Immediately on standing, the arterial pressure in the head and upper part of the body tends to fall, and marked reduction of this pressure could cause loss of consciousness. However, the falling pressure at the baroreceptors elicits an immediate reflex, resulting in strong sympathetic discharge throughout the body. This minimizes the decrease in pressure in the head and upper body.

65. Special methods of ECG and blood pressure examination (24-hour-monitoring, late potentials, invasive electrophysiological studies)

24-hour-monitoring (Holter Monitoring)

Holter Monitoring: to detect irregular heart rhythms, patients wear a Walkman-size recording box attached to their chest by five adhesive electrode patches for 24-48 hours.

Event Recorder: Patients carry a pager-sized event recording box so they can make a one- to two-minute recording of their heart rhythm when they actually experience symptoms. This is useful for patients with relatively infrequent and brief symptoms.

Late potentials (Signal-averaged electrocardiography (SAECG))

A resting electrocardiogram (ECG) is recorded in the supine position using an ECG machine equipped with SAECG software. Unlike standard basal ECG recording, which requires only a few seconds, SAECG recording requires a few minutes (usually about 7-10 minutes), as the machine must record multiple subsequent QRS potentials to remove interference due to skeletal muscle and to obtain a statistically significant average trace.

Results SAECG recording yields a single, averaged QRS potential, usually printed in a much larger scale than standard ECGs, upon which the SAECG software performs calculations to reveal small variations (typically 1-25 mV) in the final portion of the QRS complex (the so-called "late potentials", or more accurately, "late ventricular potentials"). These can be immediately interpreted by comparing results with cut-off values. Late potentials are taken to represent delayed and fragmented depolarisation of the ventricular myocardium, which may be the substrate for a micro-re-entry mechanism, implying a higher risk of potentially dangerous ventricular tachyarrhythmias. This has been used for the risk stratification of sudden cardiac death in people who have had a myocardial infarction, as well as in people with known coronary heart disease, cardiomyopathies, or unexplained syncope.

Invasive electrophysiological studies

The procedure involves inserting a catheter – a narrow, flexible tube – attached to electricity monitoring electrodes, into a blood vessel, often through a site in the groin or neck, and winding the catheter wire up into the heart. The journey from entry point to heart muscle is navigated by images created by a fluoroscope, an x-ray-like machine that provides continuous, “live” images of the catheter and heart muscle. Once the catheter reaches the heart, electrodes at its tip gather data and a variety of electrical measurements are made. These data pinpoint the location of the faulty electrical site. During this “electrical mapping,” the cardiac arrhythmia specialist may investigate, through pacing (the use of tiny electrical impulses), some of the very arrhythmias that are the crux of the problem.

Once the damaged site or sites are confirmed, the specialist may administer different medications or electrical impulses to determine their ability to halt the arrhythmia and restore normal heart rhythm. Based on this data, as well as information garnered before the study, sometimes the specialist will proceed to place an implantable cardioverter device (ICD) or a pacemaker or will perform radiofrequency ablation. In any case, the information proves useful for diagnosis and treatment.

66. Examination methods in endocrinology (historical and biological methods, RIA, enzyme-imuno-analysis)

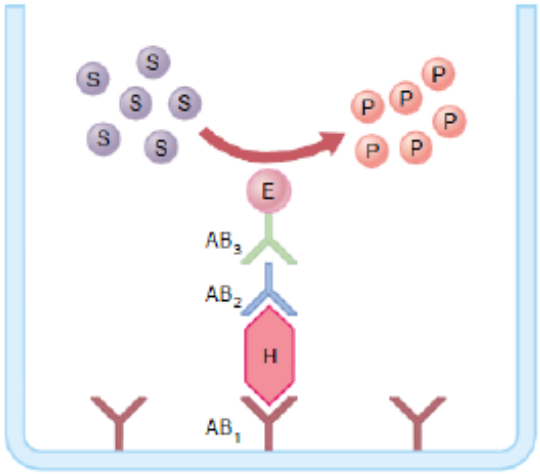
Radioimmunoassay (RIA)

It is a method of clinical biochemistry and haematology. It is used for determination of low concentrated substances, e.g. hormones in blood.

To perform a radioimmunoassay, a known quantity of an antigen is made radioactive, frequently by labeling it with gamma-radioactive isotopes of iodine attached to tyrosine. This radiolabeled antigen is then mixed with a known amount of antibody for that antigen, and as a result, the two chemically bind to one another. Then, a sample of serum from a patient containing an unknown quantity of that same antigen is added. This causes the unlabeled (or "cold") antigen from the serum to compete with the radiolabeled antigen ("hot") for antibody binding sites. As the concentration of "cold" antigen is increased, more of it binds to the antibody, displacing the radiolabeled variant, and reducing the ratio of antibody-bound radiolabeled antigen to free radiolabeled antigen. The bound antigens are then separated from the unbound ones, and the radioactivity of the free antigen remaining in the supernatant is measured. Using known standards, a binding curve can then be generated which allows the amount of antigen in the patient's serum to be derived.

In RIA, mainly β-emitters are used (tritium, iodine-125, iron-59 etc.), because the detector can be very close to the radioactive sample.

Enzyme immunoassay (EIA)



Basic principles of the enzyme-linked immunosorbent assay (ELISA) for measuring the concentration of a hormone (H). AB_1 and AB_2 are antibodies that recognize the hormone at different binding sites, and AB_3 is an antibody that recognizes AB_2. E is an enzyme linked to AB_3 that catalyzes the formation of a colored fluorescent product (P) from a substrate (S). The amount of the product is measured using optical methods and is proportional to the amount of hormone in the well if there are excess antibodies in the well.

Also known as Enzyme-Linked Immunosorbent Assay (ELISA) can be used to measure almost any protein, including hormones. This test combines the specificity of antibodies with the sensitivity of simple enzyme assays. The figure on the right shows the basic elements of this method, which is often performed on plastic plates that each have 96 small wells. Each well is coated with an antibody (AB_1) that is specific for the hormone being assayed. Samples or standards are added to each of the wells, followed by a second antibody (AB_2) that is also specific for the hormone but binds to a different site of the hormone molecule. A third antibody (AB_3) is added that recognizes AB_2 and is coupled to an enzyme that converts a suitable substrate to a product that can be easily detected by colorimetric or fluorescent optical methods.

In contrast to competitive radioimmunoassay methods, ELISA methods use excess antibodies so that all hormone molecules are captured in antibody-hormone complexes. Therefore, the amount of hormone present in the sample or in the standard is proportional to the amount of product formed.

69. Respiratory quotient

“Respiratory Quotient” is the ratio of CO_2 production to O2 utilization and can be used to estimate fat and carbohydrate utilization.

When carbohydrates are metabolized with oxygen, exactly one carbon dioxide molecule is formed for each molecule of oxygen consumed. This ratio of carbon dioxide output to oxygen usage is called the respiratory quotient, so the respiratory quotient for carbohydrates is 1.0.

When fat is oxidized in the body’s cells, an average of 70 carbon dioxide molecules are formed for each 100 molecules of oxygen consumed. The respiratory quotient for the metabolism of fat averages 0.70.When proteins are oxidized by the cells, the average respiratory quotient is 0.80. The reason that the respiratory quotients for fats and proteins are lower than that for carbohydrates is that a large share of the oxygen metabolized with these foods is required to combine with the excess hydrogen atoms present in their molecules, so that less carbon dioxide is formed in relation to the oxygen used.

Using of the respiratory quotient to determine the relative utilization of different foods by the body: First, one knows that the output of carbon dioxide by the lungs divided by the uptake of oxygen during the same period is called the respiratory exchange ratio. Over a period of 1 hour or more, the respiratory exchange ratio exactly equals the average respiratory quotient of the metabolic reactions throughout the body. If a person has a respiratory quotient of 1.0, he or she is metabolizing almost entirely carbohydrates, because the respiratory quotients for both fat and protein metabolism are considerably less than 1.0. Likewise, when the respiratory quotient is about 0.70, the body is metabolizing almost entirely fats, to the exclusion of carbohydrates and proteins. And, finally, if we ignore the normally small amount of protein metabolism, respiratory quotients between 0.70 and 1.0 describe the approximate ratios of carbohydrate to fat metabolism. To be more exact, one can first determine the protein utilization by measuring nitrogen excretion and then, using the appropriate mathematical formula, calculate almost exactly the utilization of the three foodstuffs.

Some of the important findings from studies of respiratory quotients are the following:

1. Immediately after a meal, almost all the food that is metabolized is carbohydrates, so that the respiratory quotient at that time approaches 1.0.
2. About 8 to 10 hours after a meal, the body has already used up most of its readily available carbohydrates, and the respiratory quotient approaches that for fat metabolism, about 0.70.
3. In untreated diabetes mellitus, little carbohydrate can be used by the body’s cells under any conditions, because insulin is required for this. Therefore, when diabetes is severe, most of the time the respiratory quotient remains near that for fat metabolism, 0.70.

70. Cardiopulmonary response to exercise

Cardiovascular system in exercise

A key requirement of cardiovascular function in exercise is to deliver the required oxygen and other nutrients to the exercising muscles. For this purpose, the muscle blood flow increases drastically during exercise. Although, two points can be made about blood flow in a working muscle:

(1) The actual contractile process itself temporarily decreases muscle blood flow because the contracting skeletal muscle compresses the intramuscular blood vessels; therefore, strong tonic muscle contractions can cause rapid muscle fatigue because of lack of delivery of enough oxygen and other nutrients during the continuous contraction.

(2) The blood flow to muscles during exercise increases markedly.

ml/100 g Muscle/min	
Resting blood flow	3.6
Blood flow during maximal exercise	90

Almost one half this increase in flow results from intramuscular vasodilation caused by the direct effects of increased muscle metabolism The remaining increase results from multiple factors, the most important of which is probably the moderate increase in arterial blood pressure that occurs in exercise, usually about a 30 per cent increase. The increase in pressure not only forces more blood through the blood vessels but also stretches the walls of the arterioles and further reduces the vascular resistance.

Work Output, Oxygen Consumption, and Cardiac Output During Exercise.

It is not surprising that all these are directly related to one another, as shown by the linear functions, because the muscle work output increases oxygen consumption, and oxygen consumption in turn dilates the muscle blood vessels, thus increasing venous return and cardiac output (by Frank-Starling principle).

Effect of Training on Heart Hypertrophy and on Cardiac Output.

Not only do the skeletal muscles hypertrophy during athletic training but the heart does also. However, heart enlargement and increased pumping capacity occur almost entirely in the endurance types, not in the sprint types, of athletic training. Even though the heart of the marathoner is considerably larger than that of the normal person, resting cardiac output is almost exactly the same as that in the normal person. However, this normal cardiac output is achieved by a large stroke volume at a reduced heart rate Thus, the heart-pumping effectiveness of each heartbeat is 40 to 50 per cent greater in the highly trained athlete than in the untrained person, but there is a corresponding decrease in heart rate at rest.

Relation of Cardiovascular Performance to V.O2 Max.

During maximal exercise the cardiac output is about 90 per cent of the maximum that the person can achieve. This is in contrast to about 65 per cent of maximum for pulmonary ventilation. Therefore, one can readily see that the cardiovascular system is normally much more limiting on $V.O_2$ Max than is the respiratory system, because oxygen utilization by the body can never be more than the rate at which the cardiovascular system can transport oxygen to the tissues.

Respiratory system in exercise

Oxygen Consumption and Pulmonary Ventilation in Exercise.

Normal oxygen consumption for a young man at rest is about 250 ml/min. However, under maximal conditions, this can be increased to approximately the following average levels:

ml/min	
Untrained average male	3600
Athletically trained average male	4000

Male marathon runner	5100

Both oxygen consumption and total pulmonary ventilation increase between the resting state and maximal intensity of exercise in the well-trained athlete.

Limits of Pulmonary Ventilation

The maximal breathing capacity is about 50 per cent greater than the actual pulmonary ventilation during maximal exercise. This provides an element of safety for athletes, giving them extra ventilation that can be called on in such conditions as (1) exercise at high altitudes, (2) exercise under very hot conditions, and (3) abnormalities in the respiratory system.

Oxygen Diffusing Capacity of Athletes.

The oxygen diffusing capacity is a measure of the rate at which oxygen can diffuse from the pulmonary alveoli into the blood. There is an increase in diffusing capacity between the resting state and the state of maximal exercise. This results mainly from the fact that blood flow through many of the pulmonary capillaries is sluggish or even dormant in the resting state, whereas in maximal exercise, increased blood flow through the lungs causes all the pulmonary capillaries to be perfused at their maximal rates, thus providing a far greater surface area through which oxygen can diffuse into the pulmonary capillary blood.

Blood Gases During Exercise.

Because of the great usage of oxygen by the muscles in exercise, one would expect the oxygen pressure of the arterial blood to decrease markedly during strenuous athletics and the carbon dioxide pressure of the venous blood to increase far above normal. However, this normally is not the case. Both of these values remain nearly normal, demonstrating the extreme ability of the respiratory system to provide adequate aeration of the blood even during heavy exercise. This demonstrates another important point: The blood gases do not always have to become abnormal for respiration to be stimulated in exercise. Instead, respiration is stimulated mainly by neurogenic mechanisms during exercise. Part of this stimulation results from direct stimulation of the respiratory center by the same nervous signals that are transmitted from the brain to the muscles to cause the exercise. An additional part is believed to result from sensory signals transmitted into the respiratory center from the contracting muscles and moving joints. All this extra nervous stimulation of respiration is normally sufficient to provide almost exactly the necessary increase in pulmonary ventilation required to keep the blood respiratory gases—the oxygen and the carbon dioxide— very near to normal.

71. Autocrine, paracrine, endocrine regulation

Autocrines are secreted by cells into the extracellular fluid and affect the function of the same cells that produced them by binding to cell surface receptors.

Paracrines are secreted by cells and released, once given the appropriate stimulus, into the extracellular fluid : they then diffuse to the neighbouring cells of a different type. Paracrine agents are generally inactivated locally by existing enzymes so that they do not enter the bloodstream in large quantities.

Frequently a messenger may serve both paracrine and autocrine functions simultaneously.

Inputs that control hormone secretion

Hormone secretion is mainly under the control of three types of inputs to endocrine cells:

(1) changes in the plasma concentrations of mineral ions or organic nutrients
(2) neurotransmitters released from neurons impinging on the endocrine cell
(3) another hormone or neurohormone (or in some cases, a paracrine/autocrine agent) acting on the endocrine cell

Control by plasma concentrations of mineral ions or organic nutrients

There are multiple hormones whose secretion is directly controlled, at least in part, by the plasma concentrations of specific mineral ions or organic nutrients. A major function of the hormone is to regulate, through negative feedback, the plasma concentration of the ion or nutrient controlling its secretion.

Control by neurons

The adrenal medulla behaves like, a sympathetic ganglion and thus is stimulated by sympathetic preganglionic fibers.

Both parasympathetic and sympathetic inputs to other glands may occur, come inhibitory and some stimulatory.

Control by other hormones

In many cases, the secretion os a particular hormone is directly controlled by the blood concentration of another hormone. A hormone that stimulates the secretion of another hormone if often referred to as tropic hormone. The tropic hormones usually stimulate not only secretion but also the growth of the stimulated gland.

Negative Feedback Prevents Overactivity of Hormone Systems.

Although the plasma concentrations of many hormones fluctuate in response to various stimuli that occur throughout the day, all hormones studied so far appear to be closely controlled. In most instances, this control is exerted through negative feedback mechanisms that ensure a proper level of hormone activity at the target tissue. After a stimulus causes release of the hormone, conditions or products resulting from the action of the hormone tend to suppress its further release. In other words, the hormone (or one of its products) has a negative feedback effect to prevent oversecretion of the hormone or overactivity at the target tissue. The controlled variable is often not the secretory rate of the hormone itself but the degree of activity of the target tissue.Therefore, only when the target tissue activity rises to an appropriate level will feedback signals to the endocrine gland become powerful enough to slow further secretion of the hormone.
Feedback regulation of hormones can occur at all levels, including gene transcription and translation steps involved in the synthesis of hormones and steps involved in processing hormones or releasing stored hormones.

Surges of Hormones Can Occur with Positive Feedback.

In a few instances, positive feedback occurs when the biological action of the hormone causes additional secretion of the hormone. One example of this is the surge of luteinizing hormone (LH) that occurs as a result of the stimulatory effect of estrogen on the anterior pituitary before ovulation. The secreted LH then acts on the ovaries to stimulate additional secretion of

estrogen, which in turn causes more secretion of LH. Eventually, LH reaches an appropriate concentration, and typical negative feedback control of hormone secretion is then exerted.

72. Chemical characteristics of hormones

There are three general classes of hormones:

1. Proteins and polypeptides, including hormones secreted by the anterior and posterior pituitary gland, the pancreas (insulin and glucagon), the parathyroid gland (parathyroid hormone), and many others.

2. Steroids secreted by the adrenal cortex (cortisol and aldosterone), the ovaries (estrogen and progesterone), the testes (testosterone), and the placenta (estrogen and progesterone). The chemical structure of steroid hormones is similar to that of cholesterol, and in most instances they are synthesized from cholesterol itself.They are lipid soluble.

3. Derivatives of the amino acid tyrosine, secreted by the thyroid (thyroxine and triiodothyronine) and the adrenal medullae (epinephrine and norepinephrine). There are no known polysaccharides or nucleic acid hormones.

Water-soluble hormones (peptides and catecholamines) are dissolved in the plasma and transported from their sites of synthesis to target tissues, where they diffuse out of the capillaries, into the interstitial fluid, and ultimately to target cells. Steroid and thyroid hormones, in contrast, circulate in the blood mainly bound to plasma proteins. However, protein-bound hormones cannot easily diffuse across the capillaries and gain access to their target cells and are therefore biologically inactive until they dissociate from plasma proteins. The relatively large amounts of hormones bound to proteins serve as reservoirs, replenishing the concentration of free hormones when they are bound to target receptors or lost from the circulation. Binding of hormones to plasma proteins greatly slows their clearance from the plasma.

Most of the peptide hormones and catecholamines are water soluble and circulate freely in the blood. They are usually degraded by enzymes in the blood and tissues and rapidly excreted by the kidneys and liver, thus remaining in the blood for only a short time. For example, the half-life of angiotensin II circulating in the blood is less than a minute. Hormones that are bound to plasma proteins are cleared from the blood at much slower rates and may remain in the circulation for several hours or even days.The half-life of adrenal steroids in the circulation, for example, ranges between 20 and 100 minutes, whereas the half-life of the protein-bound thyroid hormones may be as long as 1 to 6 days.

73. Sympathetic alpha- and beta-receptors

There are two major types of adrenergic receptors, alpha receptors and beta receptors. (The beta receptors in turn are divided into beta1 and beta2 receptors because certain chemicals affect only certain beta receptors. Also, there is a division of alpha receptors into alpha1 and alpha2 receptors.) Norepinephrine and epinephrine, both of which are secreted into the blood by the adrenal medulla, have slightly different effects in exciting the alpha and beta receptors. Norepinephrine excites mainly alpha receptors but excites the beta receptors to a lesser extent as well. Conversely, epinephrine excites both types of receptors approximately equally. Therefore, the relative effects of norepinephrine and epinephrine on different effector organs are determined by the types of receptors in the organs. If they are all beta receptors, epinephrine will be the more effective excitant. Certain alpha functions are excitatory, whereas others are inhibitory. Likewise, certain beta functions are excitatory and others are inhibitory. Therefore, alpha and beta receptors are not necessarily associated with excitation or inhibition but simply with the affinity of the hormone for the receptors in the given effector organ. A synthetic hormone chemically similar to epinephrine and norepinephrine, isopropyl norepinephrine, has an extremely strong action on beta receptors but essentially no action on alpha receptors.

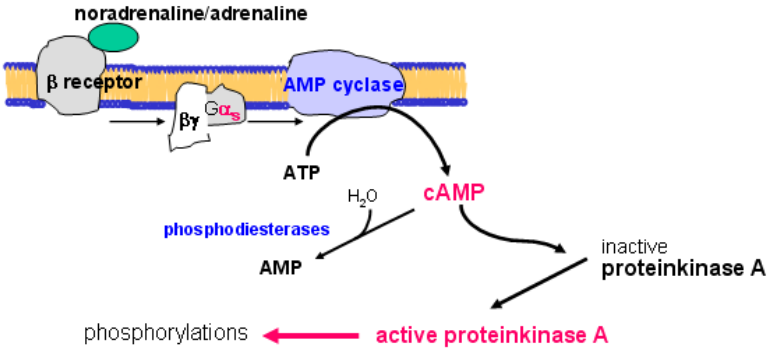
β-Adrenergic receptors

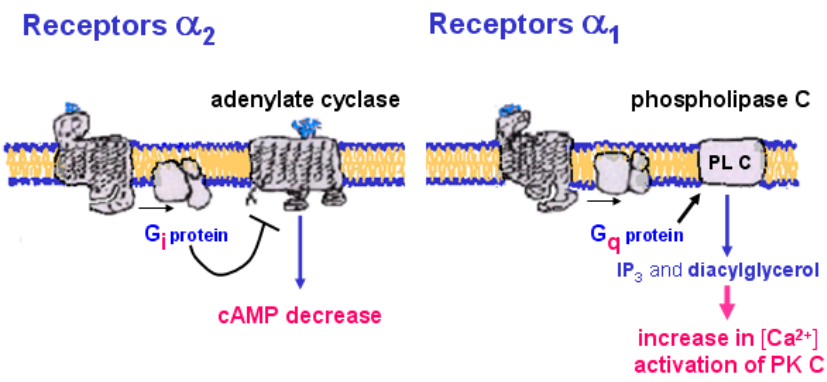
After binding an agonist, all types of β-receptors activate Gs proteins so that adenylate cyclase is stimulated, cAMP concentration increases, and proteinkinase A is activated. Particular types differ namely in their location and affinity to various catecholamines:

β1 are present in the membranes of cardiomyocytes,
β2 in the smooth muscles and blood vessels of the bronchial stem,
β3 in the adipose tissue.

α2-Adrenergic receptors

The effect is quite opposite to that of β-receptors, binding of catecholamines results in the interaction with Gi protein, decrease in adenylate cyclase activity and in cAMP concentration.
α1-Adrenergic receptors activate Gq proteins and initiate the phosphatidylinositol cascade by stimulation of phospholipase C resulting in an increase of intracellular Ca2+ concentration and activation of proteinkinase C.





74. Sex differentiation

Genetic sex is defined by the chromosome, XY in males and XX in females.

Gonadal sex is defined by the presence of testes in males and ovaries in females.

Phenotypic sex is defined by the characteristics of the internal genital tract and the external genitalia.

Male phenotype

The testes of gonodal males secrete antimüllerian hormone and testosterone.

Testosterone stimulates the growth and differentiation of the wolffian ducts, which develop into male internal genital tract.

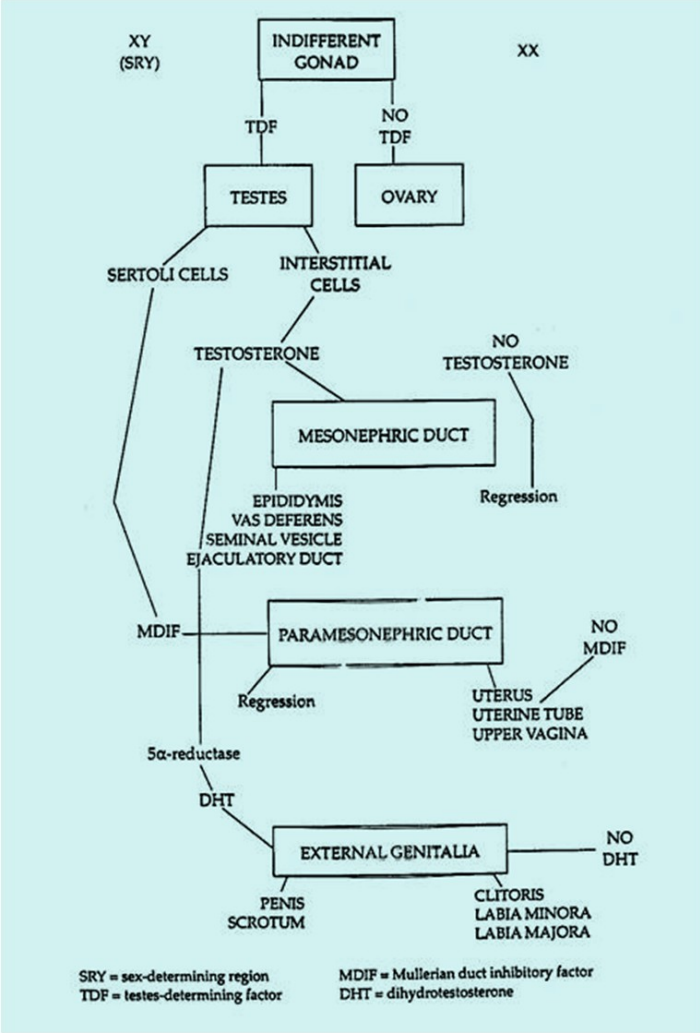
Antimüllerian hormone causes atrophy of the müllerian ducts (which would have become the female internal genital tract).

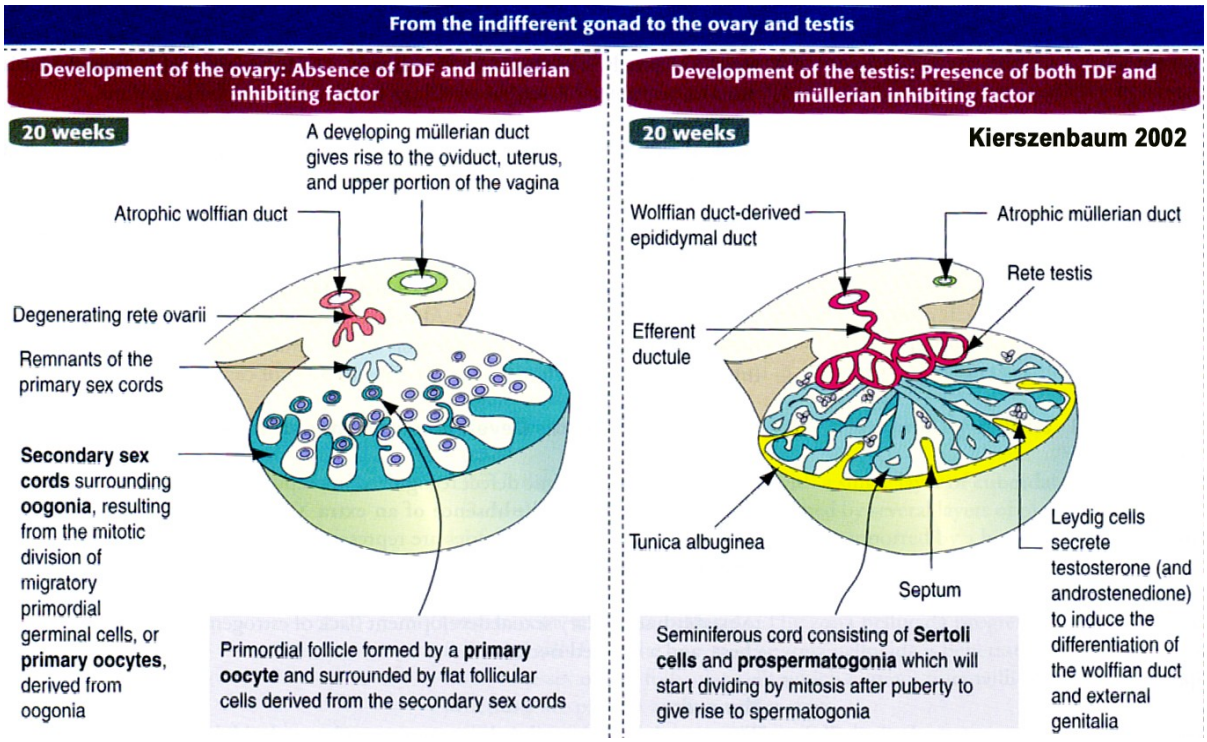
Female phenotype

The ovaries of gonodal females secrete estrogen, but not antimüllerian hormone or testosterone.

Without testosterone, wolffian ducts do not differentiate.

Without antimüllerian hormone, the müllerian ducts are not suppressed and therefore develop into the female internal genital tract.





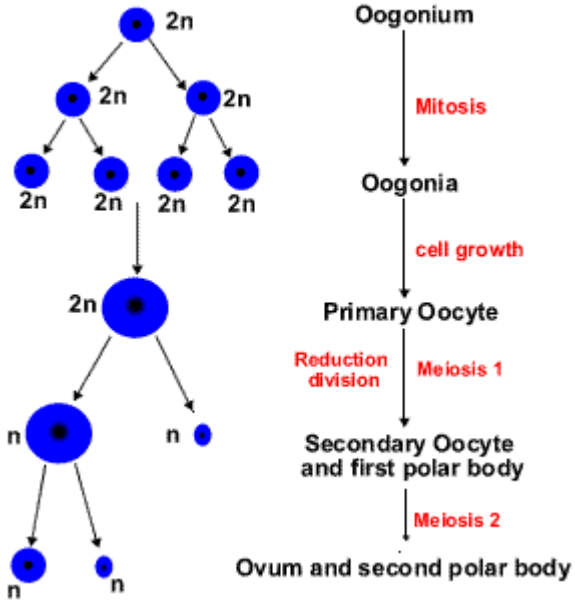
75. Oogenosis

The ovaries contain an estimated total of 2 to 4 million eggs, and no new ones appear after birth. Only a few, perhaps 400, will be ovulated during a woman's lifetime. All the others degenerate at some point in their development so that few, if any, remain by the time a women reaches approximately 50 years of age. One result of this developmental pattern is that the eggs ovulated near age 50 are 35 to 40 years older than those ovulated just after puberty. It is possible that certain defects more common among children born to older women are the result of aging changes in the egg.

During early in-utero development, the primitive germ-cells, or oogonia, undergo numerous mitotic divisions. Around the 7th month after conception, the fetal oogonia cease dividing.

During fetal life, all the oogonia develop into primary oocytes which then begin a first meiotic division by replicating their DNA. They do not, however, complete the division in th fetus. Accordingly, all the eggs present at birth are primary oocytes containing 46 chromosomes, each with two chromatids. The cells are said to be in a state of meiotic arrest. This state continues until puberty and the onset of renewed activity in the ovaries. Only those primary oocytes destined for ovulation will ever complete the first meiotic division, for it occurs just before the egg is ovulated. Each daughter cell receives 23 chromosomes, each with two chromatids. In this division, however, one of the two daughter cells, the secondary oocyte, retains virtually all the cytoplasm. The other, termed the first polar body, is very small and nonfunctional. Thus, the primary oocyte, which is already as large as the egg will be, passes on to the secondary oocyte just half of its chromosomes but almost all of its nutrient-rich cytoplasm.

The second meiotic division occurs in a fallopian tube afer ovulation, but only if the secondary oocyte is fertilized – that is, penetrated by a sperm. As a result of this second meiotic division, the daughter cells each receive 23 chromosomes, each a single chromatid. Once again, one daughter cell, now termed an ovum, retains nearly all the cytoplasm. The other daughter cell, the second polar body, is very small and nonfunctional. The net result of oogenesis is that each primary oocyte can produce only one ovum.



76. Hormonal contraception

Hormonal Suppression of Fertility—"The Pill."

It has long been known that administration of either estrogen or progesterone, if given in appropriate quantities during the first half of the monthly cycle, can inhibit ovulation. The reason for this is that appropriate administration of either of these hormones can prevent the preovulatory surge of LH secretion by the pituitary gland, which is essential in causing ovulation. Why the administration of estrogen or progesterone prevents the preovulatory surge of LH secretion is not fully understood. However, experimental work has suggested that immediately before the surge occurs, there is probably a sudden depression of estrogen secretion by the ovarian follicles, and this might be the necessary signal that causes the subsequent feedback effect on the anterior pituitary that leads to the LH surge.The administration of sex hormones (estrogens or progesterone) could prevent the initial ovarian hormonal depression that might be the initiating signal for ovulation. The problem in devising methods for the hormonal suppression of ovulation has been in developing appropriate combinations of estrogens and progestins that suppress ovulation but do not cause other, unwanted effects. For instance, too much of either hormone can cause abnormal menstrual bleeding patterns. However, use of certain synthetic progestins in place of progesterone, especially the 19-norsteroids, along with small amounts of estrogens usually prevents ovulation yet allows an almost normal pattern of menstruation. Therefore, almost all "pills" used for the control of fertility consist of some combination of synthetic estrogens and synthetic progestins.The main reason for using synthetic estrogens and progestins is that the natural hormones are almost entirely destroyed by the liver within a short time after they are absorbed from the gastrointestinal tract into the portal circulation. However, many of the synthetic hormones can resist this destructive propensity of the liver, thus allowing oral administration. Two of the most commonly used synthetic estrogens are ethinyl estradiol and mestranol. Among the most commonly used progestins are norethindrone, norethynodrel, ethynodiol, and norgestrel. The drug is usually begun in the early stages of the monthly cycle and continued beyond the time that ovulation would normally occur. Then the drug is stopped, allowing menstruation to occur and a new cycle to begin.

There are two main types of hormonal contraceptive formulations: combined methods which contain both an estrogen and a progestin, and progestin-only methods which contain only progesterone or one of its synthetic analogues (progestins). Combined methods work by suppressing ovulation; while progestin-only methods reduce the frequency of ovulation, most of them rely heavily on secondary mechanisms such as changes in cervical mucus.

Combined

The most popular form of hormonal contraception is the combined oral contraceptive pill. It is taken once a day, most commonly for 21 days followed by a seven-day break. The contraceptive patch is applied to the skin and worn continuously. A combined injectable contraceptive is a shot given once per month.

Progestin-only

The progestin only pill (POP) is taken once per day within the same three-hour window. For women not using ongoing hormonal contraception, progestin-only pills may be taken after intercourse as emergency contraception. Two types of progestin-only contraceptive implants are available. Both are inserted under the skin of the upper arm.

77. Spermatogenesis

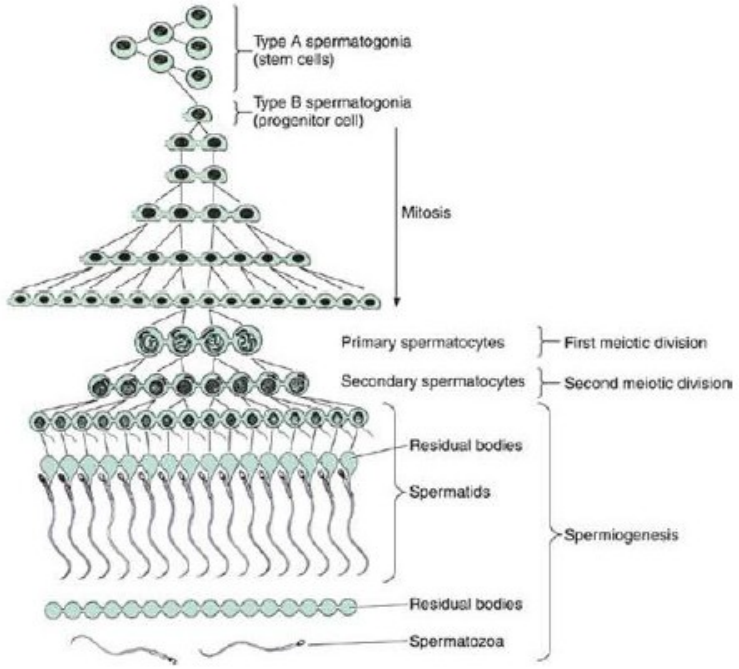
Maturation process of male gametes is called spermatogenesis. It includes the series of events by which spermatogonia are transformed into haploid spermatids. These are then gradually developed into mature sperms by the process known as spermiogenesis (histological differentiation of spermatids). Seminiferous tubules of the testis are the site where both differentiation events occur.

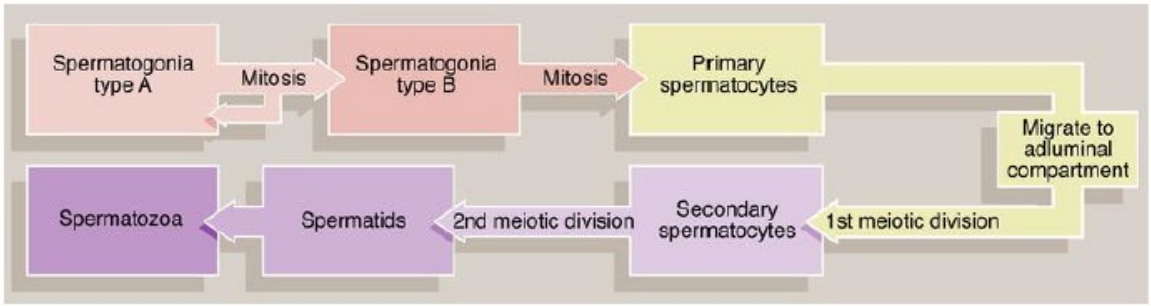
Spermatogenesis

It begins with a primitive germ cell, the spermatogonium. At sexual maturity, spermatogonia begin dividing by mitosis, producing successive generations of cells. The newly formed cells can follow one or two paths: they can continue dividing as stem cells, also called type A spermatogonia, or they can differentiate during progressive mitotic cycles to become type B spermatogonia. Type B spermatogonia are progenitor cells that will differentiate into primary spermatocytes (44 + XY and 4N of DNA). . From this first meiotic division arise smaller cells called secondary spermatocytes. Division of each secondary spermatocytes results in two cells that contain 23 chromosomes, the spermatids.

Spermiogenesis

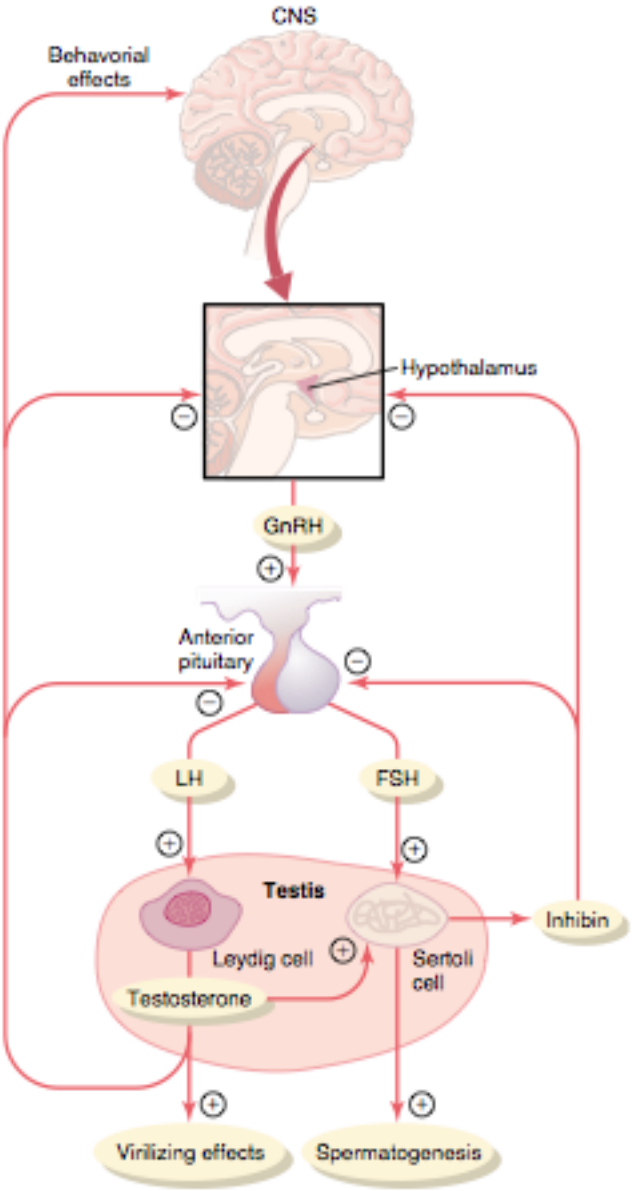
It is the final stage of production of spermatozoids. During spermiogenesis the spermatids are transformed into spermatozoa.





78. Puberty and menopause

In males



Puberty and Regulation of Its Onset

During childhood the hypothalamus does not secrete significant amounts of GnRH. One of the reasons for this is that, during childhood, the slightest secretion of any sex steroid hormones exerts a strong inhibitory effect on hypothalamic secretion of GnRH. Yet, for reasons still not understood, at the time of puberty, the secretion of hypothalamic GnRH breaks through the childhood inhibition, and adult sexual life begins.

Male Adult Sexual Life and Male Climacteric.

After puberty, gonadotropic hormones are produced by the male pituitary gland for the remainder of life, and at least some spermatogenesis usually continues until death. Most men, however, begin to exhibit slowly decreasing sexual functions in their late 40s or 50s, This decline in sexual function is related to decrease in testosterone secretion. The decrease in male sexual function is called the male climacteric. Occasionally the male climacteric is associated with symptoms of hot flashes, suffocation, and psychic disorders similar to the menopausal symptoms of the female. These symptoms can be abrogated by administration of testosterone,

Control of Male Sexual Functions by Hormones from the Hypothalamus and Anterior Pituitary Gland

A major share of the control of sexual functions in both the male and the female begins with secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus. This hormone in turn stimulates the anterior pituitary gland to secrete two other hormones called gonadotropic hormones: (1) luteinizing hormone (LH) and (2) follicle-stimulating hormone (FSH). In turn, LH is the primary stimulus for the secretion of testosterone by the testes, and FSH mainly stimulates spermatogenesis.

GnRH and Its Effect in Increasing the Secretion of LH and FSH

GnRH is a peptide secreted by neurons whose cell bodies are located in the arcuate nuclei of the hypothalamus. The endings of these neurons terminate mainly in the median eminence of the hypothalamus, where they release GnRH into the hypothalamic-hypophysial portal vascular system. Then the GnRH is transported to the anterior pituitary gland in the hypophysial portal blood and stimulates the release of the two gonadotropins, LH and FSH.

GnRH is secreted intermittently a few minutes at a time once every 1 to 3 hours.

The secretion of LH by the anterior pituitary gland is also cyclical, with LH following fairly faithfully the pulsatile release of GnRH. Conversely, FSH secretion increases and decreases only slightly with each fluctuation of GnRH secretion; instead, it changes more slowly over a period of many hours in response to longer-term changes in GnRH.

Gonadotropic Hormones: LH and FSH

Both of the gonadotropic hormones, LH and FSH, are secreted by the same cells, called gonadotropes, in the anterior pituitary gland. In the absence of GnRH secretion from the hypothalamus, the gonadotropes in the pituitary gland secrete almost no LH or FSH.

LH and FSH are glycoproteins. They exert their effects on their target tissues in the testes mainly by activating the cyclic adenosine monophosphate second messenger system, which in turn activates specific enzyme systems in the respective target cells.

Testosterone—Regulation of Its Production by LH.

Testosterone is secreted by the interstitial cells of Leydig in the testes, but only when they are stimulated by LH from the anterior pituitary gland. Furthermore, the quantity of testosterone secreted increases approximately in direct proportion to the amount of LH available.

Mature Leydig cells are normally found in a child's testes for a few weeks after birth but then disappear until after the age of about 10 years. However, secretion of LH at puberty causes testicular interstitial cells to evolve into functioning Leydig cells.

Inhibition of Anterior Pituitary Secretion of LH and FSH by Testosterone—Negative Feedback Control of Testosterone Secretion.

The testosterone secreted by the testes in response to LH has the reciprocal effect of inhibiting anterior pituitary secretion of LH. Most of this inhibition probably results from a direct effect of testosterone on the hypothalamus to decrease the secretion of GnRH. This in turn causes a corresponding decrease in secretion of both LH and FSH by the anterior pituitary, and the decrease in LH reduces the secretion of testosterone by the testes. Thus, whenever secretion of testosterone becomes too great, this automatic negative feedback effect, operating through the hypothalamus and anterior pituitary gland, reduces the testosterone secretion back toward the desired operating level. Conversely, too little testosterone allows the hypothalamus to secrete large amounts of GnRH, with a corresponding increase in anterior pituitary LH and FSH secretion and consequent increase in testicular testosterone secretion.

Regulation of Spermatogenesis by FSH and Testosterone

FSH binds with specific FSH receptors attached to the Sertoli cells in the seminiferous tubules. This causes these cells to grow and secrete various spermatogenic substances. Simultaneously, testosterone (and dihydrotestosterone) diffusing into the seminiferous tubules from the Leydig cells in the interstitial spaces also has a strong tropic effect on spermatogenesis. Thus, to initiate spermatogenesis, both FSH and testosterone are necessary.

Negative Feedback Control of Seminiferous Tubule Activity— Role of the Hormone Inhibin.

When the seminiferous tubules fail to produce sperm, secretion of FSH by the anterior pituitary gland increases markedly. Conversely, when spermatogenesis proceeds too rapidly, pituitary secretion of FSH diminishes. The cause of this negative feedback effect on the anterior pituitary is believed to be secretion by the Sertoli cells of still another hormone called inhibin. This hormone has a strong direct effect on the anterior pituitary gland to inhibit the secretion of FSH and possibly a slight effect on the hypothalamus to inhibit secretion of GnRH.

In females

Puberty and Menarche

Puberty means the onset of adult sexual life, and menarche means the beginning of the cycle of menstruation. The period of puberty is caused by a gradual increase in gonadotropic hormone secretion by the pituitary, beginning in about the eighth year of life, and usually culminating in the onset of puberty and menstruation between ages 11 and 16 years in girls (average, 13 years).

In the female, as in the male, the infantile pituitary gland and ovaries are capable of full function if appropriately stimulated. However, as is also true in the male, the hypothalamus does not secrete significant quantities of GnRH during childhood.

The figure 81-10 shows (1) the increasing levels of estrogen secretion at puberty, (2) the cyclical variation during the monthly sexual cycle, (3) the further increase in estrogen secretion during the first few years of reproductive life, (4) the progressive decrease in estrogen secretion toward the end of reproductive life, and, finally, (5) almost no estrogen or progesterone secretion beyond menopause.

Menopause

At age 40 to 50 years, the sexual cycle usually becomes irregular, and ovulation often fails to occur. After a few months to a few years, the cycle ceases altogether. The period during which the cycle ceases and the female sex hormones diminish to almost none is called menopause.

The cause of menopause is "burning out" of the ovaries. At about age 45 years, only a few primordial follicles remain to be stimulated by FSH and LH and the production of estrogens by the ovaries decreases as the number of primordial follicles approaches zero. When estrogen production falls below a critical value, the estrogens can no longer inhibit the production of the gonadotropins FSH and LH. Instead, the gonadotropins FSH and LH (mainly FSH) are produced after menopause in large and continuous quantities, but as the remaining primordial follicles become atretic, the production of estrogens by the ovaries falls virtually to zero.

At the time of menopause, a woman must readjust her life from one that has been physiologically stimulated by estrogen and progesterone production to one devoid of these hormones. The loss of estrogens often causes marked physiological changes in the function of the body, including (1) "hot flushes" characterized by extreme flushing of the skin, (2) psychic sensations of dyspnea, (3) irritability, (4) fatigue, (5) anxiety, (6) occasionally various psychotic states, and (7) decreased strength and calcification of bones throughout the body.

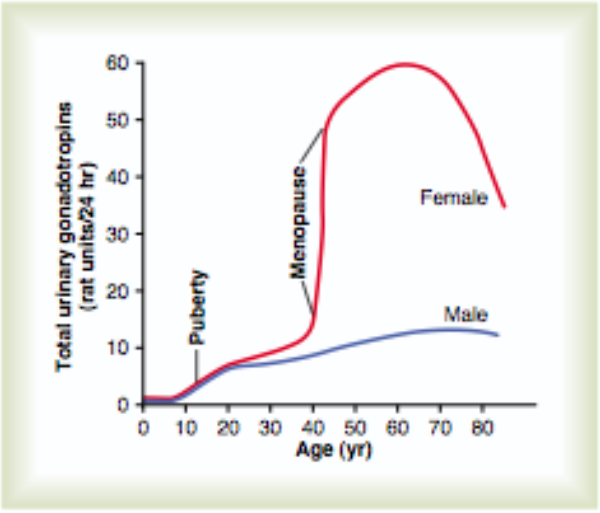


Figure 81–9

Total rates of secretion of gonadotropic hormones throughout the sexual lives of female and male human beings, showing an especially abrupt increase in gonadotropic hormones at menopause in the female.

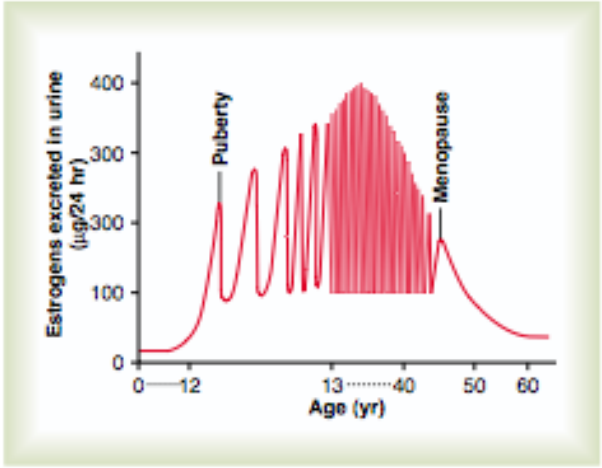


Figure 81–10

Estrogen secretion throughout the sexual life of the female human being.

79. Physiological significance of positive and negative feed-back

Negative Feedback Nature of Most Control Systems

In the regulation of carbon dioxide concentration, a high concentration of carbon dioxide in the extracellular fluid increases pulmonary ventilation. This, in turn, decreases the extracellular fluid carbon dioxide concentration because the lungs expire greater amounts of carbon dioxide from the body. In other words, the high concentration of carbon dioxide initiates events that decrease the concentration toward normal, which is negative to the initiating stimulus. Conversely, if the carbon dioxide concentration falls too low, this causes feedback to increase the concentration. This response also is negative to the initiating stimulus.

In the arterial pressure–regulating mechanisms, a high pressure causes a series of reactions that promote a lowered pressure, or a low pressure causes a series of reactions that promote an elevated pressure. In both instances, these effects are negative with respect to the initiating stimulus.

Therefore, in general, if some factor becomes excessive or deficient, a control system initiates negative feedback, which consists of a series of changes that return the factor toward a certain mean value, thus maintaining homeostasis.

Positive Feedback Can Sometimes Cause Vicious Cycles and Death

Why do essentially all control systems of the body operate by negative feedback rather than positive feedback? Positive feedback does not lead to stability but to instability and often death.

One example: the heart of a healthy human being pumps about 5 liters of blood per minute. If the person has suddenly bled 2 liters, the amount of blood in the body is decreased to such a low level that not enough blood is available for the heart to pump effectively. As a result, the arterial pressure falls, and the flow of blood to the heart muscle through the coronary vessels diminishes. This results in weakening of the heart, further diminished pumping, a further decrease in coronary blood flow, and still more weakness of the heart; the cycle repeats itself again and again until death occurs. Note that each cycle in the feedback results in further weakening of the heart. In other words, the initiating stimulus causes more of the same, which is positive feedback.

Positive feedback is better known as a “vicious cycle” but a mild degree of positive feedback can be overcome by the negative feedback control mechanisms of the body, and the vicious cycle fails to develop. For instance, if the person in the before mentioned example had bled only 1 liter instead of 2 liters, the normal negative feedback mechanisms for controlling cardiac output and arterial pressure would overbalance the positive feedback and the person would recover.

Positive Feedback Can Sometimes Be Useful.

In some instances, the body uses positive feedback to its advantage. Blood clotting is an example of a valuable use of positive feedback. When a blood vessel is ruptured and a clot begins to form, multiple enzymes called clotting factors are activated within the clot itself. Some of these enzymes act on other unactivated enzymes of the immediately adjacent blood, thus causing more blood clotting. This process continues until the hole in the vessel is plugged and bleeding no longer occurs. On occasion, this mechanism can get out of hand and cause the formation of unwanted clots. In fact, this is what initiates most acute heart attacks, which are caused by a clot beginning on the inside surface of an atherosclerotic plaque in a coronary artery and then growing until the artery is blocked.

Childbirth is another instance in which positive feedback plays a valuable role. When uterine contractions become strong enough for the baby’s head to begin pushing through the cervix, stretch of the cervix sends signals through the uterine muscle back to the body of the uterus, causing even more powerful contractions. Thus, the uterine contractions stretch the cervix, and the cervical stretch causes stronger contractions. When this process becomes powerful enough, the baby is born.

Another important use of positive feedback is for the generation of nerve signals. That is, when the membrane of a nerve fiber is stimulated, this causes slight leakage of sodium ions through sodium channels in the nerve membrane to the fiber’s interior. The sodium ions entering the fiber then change the membrane potential, which in turn causes more opening of channels, more change of potential, still more opening of channels, and so forth. Thus, a slight leak becomes

an explosion of sodium entering the interior of the nerve fiber, which creates the nerve action potential. This action potential in turn causes electrical current to flow along both the outside and the inside of the fiber and initiates additional action potentials. This process continues again and again until the nerve signal goes all the way to the end of the fiber.

81. Homeostasis

Homeostasis

The term homeostasis is used by physiologists to mean maintenance of nearly constant conditions in the internal environment. Essentially all organs and tissues of the body perform functions that help maintain these constant conditions. Nearly every organ and tissue of the human body contributes to homeostasis, sometimes in multiple ways, and usually in concert with each other. For instance, the lungs provide oxygen to the extracellular fluid to replenish the oxygen used by the cells, the kidneys maintain constant ion concentrations, and the gastrointestinal system provides nutrients.

Homeostasis must be described differently for each variable as they can vary differently from each other. For example, arterial oxygen level is tightly controlled and demonstrates very little variability. On the other end, blood glucose may vary considerably over the course of one day.

Even just one nonhomeostatic variable, among the many that can be described, can have life-threatening consequences. Typically, though, if one system becomes dramatically out of balance, other systems in the body become nonhomeostatic as a consequence. Certain kinds of disease, in fact can be defined as the loss of homeaostasis in one or more systems in the body. When homeostasis is maintained, we refer to physiology; when it is not, we refer to pathophysiology.

Homeostasis denotes the relatively stable internal environmental conditions that result from the compensating regulatory responses performed by homeostatic control system.

Temperature

Thermoregulation is an important aspect of human homeostasis. The control center for body temperature and central thermosensors are located in the hypothalamus. Additional thermosensors are located in the spinal cord and skin. Temperature may enter a circle of positive feedback, when temperature reaches extremes of 45°C (113°F), at which cellular proteins denature, causing the active site in proteins to change, thus causing metabolism stop and ultimately death.

Iron

Is an essential element for human beings. The control of this necessary but potentially toxic substance is an important part of many aspects of human health and disease. When the body levels of iron are too low, then hepcidin in the duodenal epithelium is decreased. This causes an increase in ferroportin activity, stimulating iron uptake in the digestive system. An iron surplus will stimulate the reverse of this process. In individual cells, an iron deficiency causes responsive element binding protein (IRE-BP) to bind to iron responsive elements (IRE) on mRNAs for transferrin receptors, resulting in increased production of transferrin receptors. These receptors increase binding of transferrin to cells, and therefore stimulating iron uptake.

Sugar

Blood glucose is regulated with two hormones, insulin and glucagon, both released from the pancreas. . When blood sugar levels become too high, insulin is released from the pancreas. Glucose, or sugar, is stored in body cells as glycogen, lowering the blood sugar levels. On the other hand, when blood sugar levels become too low, glucagon is released. It promotes the release of glycogen, converted back into glucose. This increases blood sugar levels.

Osmoregulation

Osmoregulation is the active regulation of the osmotic pressure of bodily fluids to maintain the homeostasis of the body's water content; that is it keeps the body's fluids from becoming too dilute or too concentrated. The cell’s plasma membrane contains mechanosensors that stimulate balancing ion flow accompanied by water.

Pressure

The renin-angiotensin system (RAS) is a hormone system that helps regulate long-term blood pressure and extracellular volume in the body.

Calcium

When blood calcium becomes too low, calcium-sensing receptors in the parathyroid gland become activated. This results in the release of PTH, which acts to increase blood calcium, e.g. by release from bones.

82. Regulation of constant pH

The pH of different cellular compartments, body fluids, and organs is usually tightly regulated in a process called acid-base homeostasis.

The pH of blood is usually slightly basic with a value of pH 7.4. This value is often referred to as physiological pH in biology and medicine.

Maintanance of constant pH in body

System / Organ	What is altered?	How quickly?
Buffers in ECF/ICF	pH	sec / min
Lungs	pCO_2	hours
Liver	way of NH$_3$ detoxication	days
Kidney	NH_4^+ / $H_2PO_4^-$ excretion HCO_3^- resorption	days

Buffer bases in (arterial) plasma

Buffer base	mmol/l
HCO_3^-	24
Protein-His	17*
HPO_4^{2-}	1
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Total	42

* Molarity of negative charge = binding sites for H$^+$

Buffers

- ✓ Prevent a change in pH when H+ ions are added to or removed from a solution.
- ✓ Are most effective within 1.0 pH unit of the pK of the buffer (i.e., in the linear portion of the titration curve).

Extracellular buffers.

a. The major extracellular buffer is HCO_3^- which is produced from CO_2 and H_2O – the pK of the CO_2/HCO_3^- buffer pair is 6.1.

b. Phosphate is a minor extracellular buffer. – The pK of the H_2PO^-/HPO^{2-} buffer pair is 6.8

a. Organic phosphates [e.g., AMP, ADP, ATP, 2,3-diphosphoglycerate (DPG)].

b. Proteins

- Imidazole and α-amino groups on proteins have pKs that are within the physiological pH range.
- Hemoglobin is a major intracellular buffer.
- In the physiological pH range, deoxyhemoglobin is a better buffer than oxyhemoglobin.

Respiratory control in maintaning acid-base status

The respiratory system regulates acid base balance by controlling the rate of CO_2 removal. Increase of $[H^+]$ in arteries at metabolic disturbances, or ↑ of pCO_2 in CNS activates medullary respiratory center that stimulates increased ventilation promoting elimination of CO_2. Conversely, the peripheral chemoreceptors reflexely suppres respiratory activity in response to a fall in arterial H^+ concentration resulting from non-respiratory causes.

Contribution of liver to maintenance of acid base balance

Two ways of NH_3 elimination in the liver

- urea synthesis (connected with release of $2H^+$ - acidifying process)
- glutamin synthesis (without release of H^+)

Higher synthesis of glutamin is stimulated at acidosis, synthesis of urea is potentiated at alkalosis.

Kidneys function in maintaning acid-base balance.

- H^+ excretion
- HCO_3^- excretion, resorption
- ammonia secretion

Urinary buffers

H^+ transporters in tubular cells and collecting duct can secrete H^+ against the concentration gradient until the tubular fluid becomes 800 times more acidic than plasma. At this point, further secretion stops, because the gradient becomes too great for the secretory process to continue.

The corresponding pH value is 4,5.

H^+ ions are buffered by:

HPO_4^- (filtered from blood)

NH_3 secreted from tubular cells

If more buffer base is available in the urine, more H^+ can be secreted before the limiting gradient is reached.

83. Kidney in regulation of homeostasis

The kidneys “clear” unwanted substances from the filtrate (and therefore from the blood) by excreting them in the urine while returning substances that are needed back to the blood. The kidneys serve multiple functions, including the following:

1) Excretion of metabolic waste products and foreign chemicals
2) Regulation of water and electrolyte balances
3) Regulation of body fluid osmolality and electrolyte concentrations
4) Regulation of arterial pressure
5) Regulation of acid-base balance
6) Secretion, metabolism, and excretion of hormones
7) Gluconeogenesis

Excretion of Metabolic Waste Products, Foreign Chemicals, Drugs, and Hormone Metabolites

The kidneys are the primary means for eliminating waste products of metabolism that are no longer needed by the body. These products include urea (from the metabolism of amino acids), creatinine (from muscle creatine), uric acid (from nucleic acids), end products of hemoglobin breakdown (such as bilirubin), and metabolites of various hormones. These waste products must be eliminated from the body as rapidly as they are produced. The kidneys also eliminate most toxins and other foreign substances that are either produced by the body or ingested, such as pesticides, drugs, and food additives.

Regulation of Water and Electrolyte Balances

For maintenance of homeostasis, excretion of water and electrolytes must precisely match intake. If intake exceeds excretion, the amount of that substance in the body will increase. If intake is less than excretion, the amount of that substance in the body will decrease.

Intake of water and many electrolytes is governed mainly by a person’s eating and drinking habits, requiring the kidneys to adjust their excretion rates to match the intake of various substances.

Regulation of Arterial Pressure

The kidneys play a dominant role in long-term regulation of arterial pressure by excreting variable amounts of sodium and water. The kidneys also contribute to short-term arterial pressure regulation by secreting vasoactive factors or substances, such as renin, that lead to the formation of vasoactive products (e.g., angiotensin II).

Regulation of Acid-Base Balance

The kidneys contribute to acid-base regulation, along with the lungs and body fluid buffers, by excreting acids and by regulating the body fluid buffer stores. The kidneys are the only means of eliminating from the body certain types of acids, such as sulfuric acid and phosphoric acid, generated by the metabolism of proteins.

Regulation of Erythrocyte Production.

The kidneys secrete erythropoietin, which stimulates the production of red blood cells. One important stimulus for erythropoietin secretion by the kidneys is hypoxia. The kidneys normally account for almost all the erythropoietin secreted into the circulation.

Regulation of 1,25–Dihydroxyvitamin D3 Production

The kidneys produce the active form of vitamin D, 1,25- dihydroxyvitamin D3 (calcitriol), by hydroxylating this vitamin at the “number 1” position. Calcitriol is essential for normal calcium deposition in bone and calcium reabsorption by the gastrointestinal tract. Calcitriol plays an important role in calcium and phosphate regulation.

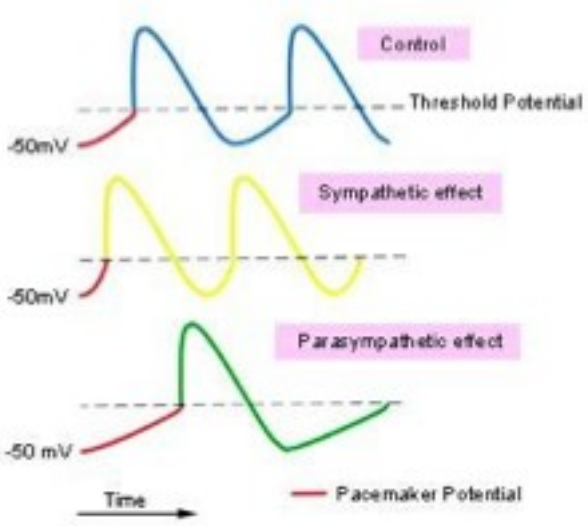
Glucose Synthesis

The kidneys synthesize glucose from amino acids and other precursors during prolonged fasting, a process referred to as gluconeogenesis. The kidneys’ capacity to add glucose to the

blood during prolonged periods of fasting rivals that of the liver. With chronic kidney disease or acute failure of the kidneys, these homeostatic functions are disrupted, and severe abnormalities of body fluid volumes and composition rapidly occur.

With complete renal failure, enough potassium, acids, fluid, and other substances accumulate in the body to cause death within a few days, unless clinical interventions such as hemodialysis are initiated to restore, at least partially, the body fluid and electrolyte balances.

84. Regulation of cardiac output



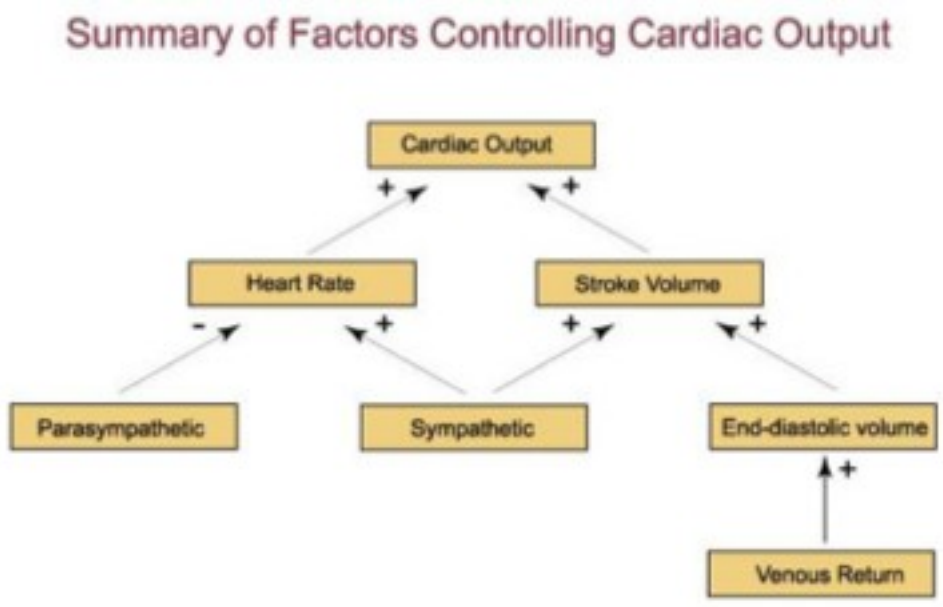
The following factors, among others, directly affect the cardiac output: (1) the basic level of body metabolism, (2) whether the person is exercising, (3) the person's age, and (4) size of the body.
For young, healthy men, resting cardiac output averages about 5.6 L/min. For women, this value is about 4.9 L/min.

Control of Heart Rate

The SA node of the heart is inervated by both sympathetic and parasympathetic nerve fibers. Under conditions of rest the parasympathetic fibers release acetylcholine, which acts to slow the pacemaker potential of the SA node and thus reduce heart rate. Under conditions of physical or emotional activity sympathetic nerve fibers release norepinephrine, which acts to speed up the pacemaker potential of the SA node thus increasing heart rate. Sympathetic nervous system activity also causes the release of epinephrine from the adrenal medulla. Epinephrine enters the blood stream, and is delivered to the heart where it binds with SA node receptors. Binding of epinephrine leads to further increase in heart rate.

Control of Stroke Volume

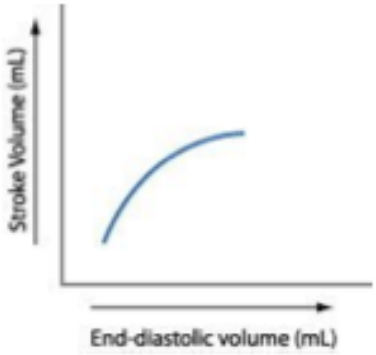
Under conditions of rest, the heart does not fill to its maximum capacity. If the heart were to fill more per beat then it could pump out more blood per beat, thus increasing stroke volume. Also, the ventricles of the heart empty only about 50% of their volume during systole. If the heart were to contract more strongly then the heart could pump out more blood per beat. In other words, a stronger contraction would lead to a larger stroke volume. During periods of exercise, the stroke volume increases because of both these mechanisms; the heart fills up with more blood and the heart contracts more strongly.



Stroke volume is increased by 2 mechanisms:
1. increase in end-diastolic volume
2. increase in sympathetic system activity

End-diastolic Volume

An increase in venous return of blood to the heart will result in greater filling of the ventricles during diastole. Consequently the volume of blood in the ventricles at the end of diastole, called end-diastolic volume, will be increased. A larger end-diastolic volume will stretch the heart. Stretching the muscles of the heart optimizes the length-strength relationship of the cardiac muscle fibers, resulting in stronger contractility and greater stroke volume.



Starling's Law

Starling's Law describes the relationship between end-diastolic volume and stroke volume. It states that the heart will pump out whatever volume is delivered to it. If the end-diastolic volume doubles then stroke volume will double.

An Increase in Sympathetic Activity Increases Stroke Volume

The cardiac muscle cells of the ventricular myocardium are richly inervated by sympathetic nerve fibers. Release of norepinephrine by these fibers causes an increase in the strength of myocardiall contraction, thus increasing stroke volume. Norepinephrine is thought to increase the intracellular concentration of calcium in myocardial cells, thus facilitating faster actin/myosin cross bridging. Also, a general sympathetic response by the body will induce the release of epinephrine from the adrenal medulla. Epinephrine, like norepinephrine will stimulate an increase in the strength of myocardial contraction and thus increase stroke volume.

85. Regulation of blood circulation upon orthostasis

The following changes occur when an individual from a supine to a standing position:

1. When a person stands, a significant volume of blood pools in the lower extremities because of the high compliance of the veins (muscular activity would prevent this pooling).
2. As a result of venous pooling and increased local venous pressure, Pc in the legs increases and fluid is filtered into the interstitium. If net filtration of fluid exceeds the ability of the lymphatics to return it tp the circulation, edema will occur.
3. Blood volume and venous return decrease. As a result of the decrease in venous return, both stroke volume and cardiac output decrease (Frank-Starling law).
4. Initially, arterial pressure decreases because of the reduction in cardiac output. If cerebral blood pressure becomes low enough, faiting may occur.
5. Compensatory mechanisms will attempt to increase blood pressure to normal. The carotid sinus baroreceptors respond to the decrease in arterial pressure by decreasing the firing rate of the carotid sinus nerves. A coordinated response from the vasomotor center then increases sympathetic outflow to the heart and blood vessels and decreases parasympathetic outflow to the heart. As a result, heart rate and TPR increase, and blood pressure increases toward normal.
6. Orthostatic hypotension (fainting or lightheadedness of standing) may occur in individuals whose baroreceptor reflex mechanism is impaired (e.g. individuals trated with sympatholitic agents).

Summary of Responses to Standing

Arterial blood pressure	↓ initially, then corrects
Heart rate	↑
Cardiac output	↓
Stroke volume	↓
TPR	↑
Central venous pressure	↓

TPR - total peripheral resistance.

86. Regulation of ventilation

Respiratory Center

The respiratory center is composed of several groups of neurons located bilaterally in the medulla oblongata and pons of the brain stem, as shown in Figure 41–1. It is divided into three major collections of neurons: (1) a dorsal respiratory group, located in the dorsal portion of the medulla, which mainly causes inspiration; (2) a ventral respiratory group, located in the ventrolateral part of the medulla, which mainly causes expiration; and (3) the pneumotaxic center, located dorsally in the superior portion of the pons, which mainly controls rate and depth of breathing. The dorsal respiratory group of neurons plays the most fundamental role in the control of respiration.

Dorsal Respiratory Group of Neurons—Its Control of Inspiration and of Respiratory Rhythm

Most of its neurons are located within the nucleus of the tractus solitarius. The nucleus of the tractus solitarius is the sensory termination of both the vagal and the glossopharyngeal nerves, which transmit sensory signals into the respiratory center from (1) peripheral chemoreceptors, (2) baroreceptors, and (3) several types of receptors in the lungs.

Inspiratory “Ramp” Signal.

The nervous signal that is transmitted to the inspiratory muscles, mainly the diaphragm, is not an instantaneous burst of action. potentials. Instead, in normal respiration, it begins weakly and increases steadily in a ramp manner for about 2 seconds. Then it ceases abruptly for approximately the next 3 seconds, which turns off the excitation of the diaphragm and allows elastic recoil of the lungs and the chest wall to cause expiration. Next, the inspiratory signal begins again for another cycle; this cycle repeats again and again, with expiration occurring in between.

Ventral Respiratory Group of Neurons—Functions in Both Inspiration and Expiration

Located in each side of the medulla, is the ventral respiratory group of neurons, found in the nucleus ambiguus rostrally and the nucleus retroambiguus caudally. The function of this neuronal group differs from that of the dorsal respiratory group in several important ways:

1. The neurons of the ventral respiratory group remain almost totally inactive during normal quiet respiration.
2. There is no evidence that the ventral respiratory neurons participate in the basic rhythmical oscillation that controls respiration.
3. When the respiratory drive for increased pulmonary ventilation becomes greater than normal, respiratory signals spill over into the ventral respiratory neurons from the basic oscillating mechanism of the dorsal respiratory area. As a consequence, the ventral respiratory area contributes extra respiratory drive as well.
4. Electrical stimulation of a few of the neurons in the ventral group causes inspiration, whereas stimulation of others causes expiration. Therefore, these neurons contribute to both inspiration and expiration. They are especially important in providing the powerful expiratory signals to the abdominal muscles during very heavy expiration. Thus, this area operates more or less as an overdrive mechanism when high levels of pulmonary ventilation are required, especially during heavy exercise.

Control of Overall Respiratory Center Activity

Chemical Control of Respiration

The ultimate goal of respiration is to maintain proper concentrations of oxygen, carbon dioxide, and hydrogen ions in the tissues. It is fortunate, therefore, that respiratory activity is highly responsive to changes in each of these.

Excess carbon dioxide or excess hydrogen ions in the blood mainly act directly on the respiratory center itself, causing greatly increased strength of both the inspiratory and the expiratory motor signals to the respiratory muscles.

Oxygen, in contrast, does not have a significant direct effect on the respiratory center of the brain in controlling respiration. Instead, it acts almost entirely on peripheral chemoreceptors

located in the carotid and aortic bodies, and these in turn transmit appropriate nervous signals to the respiratory center for control of respiration.

Direct Chemical Control of Respiratory Center Activity by Carbon Dioxide and Hydrogen Ions

Blood carbon dioxide concentration or hydrogen ion concentration have an effect in an additional neuronal area, a chemosensitive area, located bilaterally, lying only 0.2 millimeter beneath the ventral surface of the medulla. This area is highly sensitive to changes in either blood PCO_2 or hydrogen ion concentration, and it in turn excites the other portions of the respiratory center.

Excitation of the Chemosensitive Neurons by Hydrogen Ions Is Likely the Primary Stimulus

The sensor neurons in the chemosensitive area are especially excited by hydrogen ions; in fact, it is believed that hydrogen ions may be the only important direct stimulus for these neurons. However, hydrogen ions do not easily cross the blood-brain barrier. For this reason, changes in hydrogen ion concentration in the blood have considerably less effect in stimulating the chemosensitive neurons than do changes in blood carbon dioxide, even though carbon dioxide is believed to stimulate these neurons secondarily by changing the hydrogen ion concentration.

Carbon Dioxide Stimulates the Chemosensitive Area

Although carbon dioxide has little direct effect in stimulating the neurons in the chemosensitive area, it does have a potent indirect effect. It does this by reacting with the water of the tissues to form carbonic acid, which dissociates into hydrogen and bicarbonate ions; the hydrogen ions then have a potent direct stimulatory effect on respiration. Why does blood carbon dioxide have a more potent effect in stimulating the chemosensitive neurons than do blood hydrogen ions? The answer is that the bloodbrain barrier is not very permeable to hydrogen ions, but carbon dioxide passes through this barrier almost as if the barrier did not exist. Consequently, whenever the blood PCO_2 increases, so does the PCO_2 of both the interstitial fluid of the medulla and the cerebrospinal fluid. In both these fluids, the carbon dioxide immediately reacts with the water to form new hydrogen ions. Thus, paradoxically, more hydrogen ions are released into the respiratory chemosensitive sensory area of the medulla when the blood carbon dioxide concentration increases than when the blood hydrogen ion concentration increases.

Decreased Stimulatory Effect of Carbon Dioxide After the First 1 to 2 Days.

Excitation of the respiratory center by carbon dioxide is great the first few hours after the blood carbon dioxide first increases, but then it gradually declines over the next 1 to 2 days, decreasing to about one fifth the initial effect. Part of this decline results from renal readjustment of the hydrogen ion concentration in the circulating blood back toward normal after the carbon dioxide first increases the hydrogen concentration. The kidneys achieve this by increasing the blood bicarbonate, which binds with the hydrogen ions in the blood and cerebrospinal fluid to reduce their concentrations. But even more important, over a period of hours, the bicarbonate ions also slowly diffuse through the blood-brain and blood– cerebrospinal fluid barriers and combine directly with the hydrogen ions adjacent to the respiratory neurons as well, thus reducing the hydrogen ions back to near normal. A change in blood carbon dioxide concentration therefore has a potent acute effect on controlling respiratory drive but only a weak chronic effect after a few days' adaptation.

Peripheral Chemoreceptor System for Control of Respiratory Activity—Role of Oxygen in Respiratory Control

In addition to control of respiratory activity by the respiratory center itself, still another mechanism is available for controlling respiration. This is the peripheral chemoreceptor system. Special nervous chemical receptors, called chemoreceptors, are located in several areas outside the brain. They are especially important for detecting changes in oxygen in the blood, although they also respond to a lesser extent to changes in carbon dioxide and hydrogen ion concentrations. The chemoreceptors transmit nervous signals to the respiratory center in the brain to help regulate respiratory activity.

Most of the chemoreceptors are in the carotid bodies. However, a few are also in the aortic bodies, and a very few are located elsewhere in association with other arteries of the thoracic and abdominal regions.

The carotid bodies are located bilaterally in the bifurcations of the common carotid arteries. Their afferent nerve fibers pass through Hering's nerves to the glossopharyngeal nerves and then to the dorsal respiratory area of the medulla. The aortic bodies are located along the arch of the aorta; their afferent nerve fibers pass through the vagi, also to the dorsal medullary respiratory area.

Stimulation of the Chemoreceptors by Decreased Arterial Oxygen.

When the oxygen concentration in the arterial blood falls below normal, the chemoreceptors become strongly stimulated. The impulse rate is particularly sensitive to changes in arterial Po2 in the range of 60 down to 30 mm Hg, a range in which hemoglobin saturation with oxygen decreases rapidly.

Effect of Carbon Dioxide and Hydrogen Ion Concentration on Chemoreceptor Activity.

An increase in either carbon dioxide concentration or hydrogen ion concentration also excites the chemoreceptors and, in this way, indirectly increases respiratory activity. Yet there is one difference between the peripheral and central effects of carbon dioxide: the stimulation by way of the peripheral chemoreceptors occurs as much as five times as rapidly as central stimulation, so that the peripheral chemoreceptors might be especially important in increasing the rapidity of response to carbon dioxide at the onset of exercise.

Basic Mechanism of Stimulation of the Chemoreceptors by Oxygen Deficiency.

The exact means by which low Po2 excites the nerve endings in the carotid and aortic bodies is still unknown. However, these bodies have multiple highly characteristic glandular-like cells, called glomus cells, that synapse directly or indirectly with the nerve endings.

Effect of Low Arterial PO2 to Stimulate Alveolar Ventilation When Arterial Carbon Dioxide and Hydrogen Ion Concentrations Remain Normal

There is almost no effect on ventilation as long as the arterial Po2 remains greater than 100 mm Hg. But at pressures lower than 100 mm Hg, ventilation approximately doubles when the arterial Po2 falls to 60 mm Hg and can increase as much as fivefold at very low Po2s. Under these conditions, low arterial Po2 obviously drives the ventilatory process quite strongly.

87. Regulation of gastric and pancreatic secretion

Stimulation of Gastric Acid Secretion

Parietal Cells of the Oxyntic Glands Are the Only Cells That Secrete Hydrochloric Acid

The parietal cells, located deep in the oxyntic glands of the main body of the stomach, are the only cells that secrete hydrochloric acid. The acidity of the fluid secreted by these cells can be very great, with pH as low as 0.8. However, secretion of this acid is under continuous control by both endocrine and nervous signals. Furthermore, the parietal cells operate in close association with another type of cell called enterochromaffin-like cells (ECL cells), the primary function of which is to secrete histamine.

The ECL cells lie in the deep recesses of the oxyntic glands and therefore release histamine in direct contact with the parietal cells of the glands. The rate of formation and secretion of hydrochloric acid by the parietal cells is directly related to the amount of histamine secreted by the ECL cells. In turn, the ECL cells can be stimulated to secrete histamine in several different ways: (1) Probably the most potent mechanism for stimulating histamine secretion is by the hormonal substance gastrin, which is formed almost entirely in the antral portion of the stomach mucosa in response to proteins in the foods being digested. (2) In addition, the ECL cells can be stimulated by (a) acetylcholine released from stomach vagal nerve endings and (b) probably also by hormonal substances secreted by the enteric nervous system of the stomach wall.

Stimulation of Acid Secretion by Gastrin

Gastrin is itself a hormone secreted by gastrin cells, also called G cells. These cells are located in the pyloric glands in the distal end of the stomach. When meats or other protein-containing foods reach the antral end of the stomach, some of the proteins from these foods have a special stimulatory effect on the gastrin cells in the pyloric glands to cause release of gastrin into the digestive juices of the stomach. The vigorous mixing of the gastric juices transports the gastrin rapidly to the ECL cells in the body of the stomach, causing release of histamine directly into the deep oxyntic glands. The histamine then acts quickly to stimulate gastric hydrochloric acid secretion.

Phases of Gastric Secretion

Gastric secretion is said to occur in three “phases”: a cephalic phase, a gastric phase, and an intestinal phase.

Cephalic Phase

The cephalic phase of gastric secretion occurs even before food enters the stomach, especially while it is being eaten. It results from the sight, smell, thought, or taste of food, and the greater the appetite, the more intense is the stimulation. Neurogenic signals that cause the cephalic phase of gastric secretion origi- nate in the cerebral cortex and in the appetite centers of the amygdala and hypothalamus. They are trans- mitted through the dorsal motor nuclei of the vagi and thence through the vagus nerves to the stomach. This phase of secretion normally accounts for about 20 per cent of the gastric secretion associated with eating a meal.

Gastric Phase

Once food enters the stomach, it excites (1) long vagovagal reflexes from the stomach to the brain and back to the stomach, (2) local enteric reflexes, and (3) the gastrin mechanism, all of which in turn cause secretion of gastric juice during several hours while food remains in the stomach. The gastric phase of secretion accounts for about 70 per cent of the total gastric secretion.

Intestinal Phase

The presence of food in the upper portion of the small intestine, particularly in the duodenum, will continue to cause stomach secretion of small amounts of gastric juice, probably partly because of small amounts of gastrin released by the duodenal mucosa.

Regulation of Pepsinogen Secretion

Regulation of pepsinogen secretion by the peptic cells in the oxyntic glands is much less complex than regulation of acid secretion; it occurs in response to two types of signals: (1) stimulation of the peptic cells by acetylcholine released from the vagus nerves or from the gastric enteric nervous plexus, and (2) stimulation of peptic cell secretion in response to acid in the stomach. The acid probably does not stimulate the peptic cells directly but instead elicits additional enteric nervous reflexes that support the original nervous signals to the peptic cells. Therefore, the rate of secretion of pepsinogen, the precursor of the enzyme pepsin that causes protein digestion, is strongly influenced by the amount of acid in the stomach.

Regulation of Pancreatic Secretion

Basic Stimuli That Cause Pancreatic Secretion

Three basic stimuli are important in causing pancreatic secretion:

1. Acetylcholine, which is released from the parasympathetic vagus nerve endings and from other cholinergic nerves in the enteric nervous system
2. Cholecystokinin, which is secreted by the duodenal and upper jejunal mucosa when food enters the small intestine
3. Secretin, which is also secreted by the duodenal and jejunal mucosa when highly acid food enters the small intestine

The first two of these stimuli, acetylcholine and cholecystokinin, stimulate the acinar cells of the pancreas, causing production of large quantities of pancreatic digestive enzymes but relatively small quantities of water and electrolytes to go with the enzymes. Without the water, most of the enzymes remain temporarily stored in the acini and ducts until more fluid secretion comes along to wash them into the duodenum. Secretin, in contrast to the first two basic stimuli, stimulates secretion of large quantities of water solution of sodium bicarbonate by the pancre- atic ductal epithelium.

Multiplicative Effects of Different Stimuli

When all the different stimuli of pancreatic secretion occur at once, the total secretion is far greater than the sum of the secretions caused by each one separately. Therefore, the various stimuli are said to “multiply,” or “potentiate,” one another. Thus, pancreatic secretion normally results from the combined effects of the multiple basic stimuli, not from one alone.

Phases of Pancreatic Secretion

Pancreatic secretion occurs in three phases, the same as for gastric secretion: the cephalic phase, the gastric phase, and the intestinal phase. Their characteristics are as follows.

❖Cephalic and Gastric Phases

During the cephalic phase of pancreatic secretion, the same nervous signals from the brain that cause secretion in the stomach also cause acetylcholine release by the vagal nerve endings in the pancreas. This causes moderate amounts of enzymes to be secreted into the pancreatic acini. But little of the secretion flows immediately through the pancreatic ducts into the intestine because only small amounts of water and electrolytes are secreted along with the enzymes. But, again, only small amounts reach the duo- denum because of continued lack of significant fluid secretion.

❖Intestinal Phase

After chyme leaves the stomach and enters the small intestine, pancreatic secretion becomes copious, mainly in response to the hormone secretin.

Secretin Stimulates Secretion of Copious Quantities of Bicarbonate Ions—Neutralization of Acidic Stomach Chyme

Secretin present in an inactive form, prosecretin, in so-called S cells in the mucosa of the duodenum and jejunum. When acid chyme with pH less than 4.5 to 5.0 enters the duodenum from the stomach, it causes duodenal mucosal release and activation of secretin, which is then

absorbed into the blood. The one truly potent constituent of chyme that causes this secretin release is the hydrochloric acid from the stomach.

Secretin in turn causes the pancreas to secrete large quantities of fluid containing a high concentration of bicarbonate ion but a low concentration of chloride ion. The secretin mechanism is especially important for two reasons: First, secretin begins to be released from the mucosa of the small intestine when the pH of the duodenal contents falls below 4.5 to 5.0, and its release increases greatly as the pH falls to 3.0. This immediately causes copious secre- tion of pancreatic juice containing abundant amounts of sodium bicarbonate. The net result is then the following reaction in the duodenum:

Then the carbonic acid immediately dissociates into carbon dioxide and water. The carbon dioxide is absorbed into the blood and expired through the lungs, thus leaving a neutral solution of sodium chloride in the duodenum. In this way, the acid contents emptied into the duodenum from the stomach become neutralized, so that further peptic digestive activity by the gastric juices in the duodenum is immediately blocked. Because the mucosa of the small intestine cannot withstand the digestive action of acid gastric juice, this is an essential protective mechanism to prevent development of duodenal ulcers.

Bicarbonate ion secretion by the pancreas provides an appropriate pH for action of the pancreatic digestive enzymes, which function optimally in a slightly alkaline or neutral medium, at a pH of 7.0 to 8.0. Fortunately, the pH of the sodium bicarbonate secretion averages 8.0.

Cholecystokinin—Its Contribution to Control of Diges- tive Enzyme Secretion by the Pancreas.

The presence of food in the upper small intestine also causes a second hormone, cholecystokinin, to be released from yet another group of cells, the I cells, in the mucosa of the duodenum and upper jejunum. This release of cholecystokinin results especially from the presence of proteoses and peptones (products of partial protein digestion) and long-chain fatty acids in the chyme coming from the stomach.

Cholecystokinin, like secretin, passes by way of the blood to the pancreas but instead of causing sodium bicarbonate secretion causes mainly secretion of still much more pancreatic digestive enzymes by the acinar cells. This effect is similar to that caused by vagal stimulation but even more pronounced.

The differences between the pancreatic stimulatory effects of secretin and cholecystokinin:

(1) intense sodium bicarbonate secretion in response to acid in the duodenum, stimulated by secretin, (2) a dual effect in response to soap (a fat), and (3) intense digestive enzyme secretion (when peptones enter the duodenum) stimulated by cholecystokinin.

88. Thermoregulation

Humans are capable of maintaining their body temperatures within very narrow limits despite wide fluctuations in ambient temperature and are termed homeothermic. The relatively constant and high body temperature frees biochemical reactions from fluctuating with the external temperature. However, the maintenance of a relatively high body temperature (approximately 37ºC in normal persons) imposes a requirement for precise regulatory mechanisms, since further elevations of temperature cause nerve malfunction and protein denaturation.

Regulation of Body Temperature—Role of the Hypothalamus

The temperature of the body is regulated almost entirely by nervous feedback mechanisms, and almost all these operate through temperature-regulating centers located in the hypothalamus. For these feed-back mechanisms to operate, there must also be temperature detectors to determine when the body temperature becomes either too high or too low.

Role of the Anterior Hypothalamic-Preoptic Area in Thermostatic Detection of Temperature

The anterior hypothalamic preoptic area has been found to contain large numbers of heat-sensitive neurons as well as about one third as many cold-sensitive neurons. These neurons are believed to function as temperature sensors for controlling body temperature. The heat-sensitive neurons increase their firing rate in response to a 10°C increase in body temperature. The cold-sensitive neurons, by contrast, increase their firing rate when the body temperature falls.

When the preoptic area is heated, the skin all over the body immediately breaks out in a profuse sweat, while the skin blood vessels over the entire body become greatly dilated. This is an immediate reaction to cause the body to lose heat, thereby helping to return the body temperature toward the normal level. In addition, any excess body heat production is inhibited. Therefore, it is clear that the hypothalamic-preoptic area has the capability to serve as a thermostatic body temperature control center.

Detection of Temperature by Receptors in the Skin and Deep Body Tissues

Although the signals generated by the temperature receptors of the hypothalamus are extremely power-ful in controlling body temperature, receptors in other parts of the body play additional roles in temperature regulation. This is especially true of temperature receptors in the skin and in a few specific deep tissues of the body.

The skin is endowed with both cold and warmth receptors. There are far more cold receptors than warmth receptors—in fact, 10 times as many in many parts of the skin. Therefore, peripheral detection of temperature mainly concerns detecting cool and cold instead of warm temperatures.
When the skin is chilled over the entire body, immediate reflex effects are invoked and begin to increase the temperature of the body in several ways: (1) by providing a strong stimulus to cause shivering, with a resultant increase in the rate of body heat production; (2) by inhibiting the process of sweating, if this is already occurring; and (3) by promoting skin vasoconstriction to diminish loss of body heat from the skin.

Deep body temperature receptors are found mainly in the spinal cord, in the abdominal viscera, and in or around the great veins in the upper abdomen and thorax. These deep receptors function differently from the skin receptors because they are exposed to the body core temperature rather than the body surface temperature. Yet, like the skin temperature receptors, they detect mainly cold rather than warmth. It is probable that both the skin and the deep body receptors are concerned with preventing hypothermia—that is, preventing low body temperature.

Posterior Hypothalamus Integrates the Central and Peripheral Temperature Sensory Signals

Even though many temperature sensory signals arise in peripheral receptors, these signals contribute to body temperature control mainly through the hypothalamus. The area of the hypothalamus that they stimulate is located bilaterally in the posterior hypothalamus approximately at the level of the mammillary bodies. The temperature sensory signals from the anterior hypothalamic-preoptic area are also trans- mitted into this posterior hypothalamic area. Here the signals from the preoptic area and the signals from elsewhere in the body are combined and integrated to control the heat-producing and heat-conserving reactions of the body.

Neuronal Effector Mechanisms That Decrease or Increase Body Temperature

When the hypothalamic temperature centers detect that the body temperature is either too high or too low, they institute appropriate temperature-decreasing or temperature-increasing procedures.

Temperature-Decreasing Mechanisms When the Body Is Too Hot

The temperature control system uses three important mechanisms to reduce body heat when the body temperature becomes too great:

1. Vasodilation of skin blood vessels. In almost all areas of the body, the skin blood vessels become intensely dilated. This is caused by inhibition of the sympathetic centers in the posterior hypothalamus that cause vasoconstriction. Full vasodilation can increase the rate of heat transfer to the skin.

2. Sweating. The effect of increased body temperature to cause sweating is a sharp increase in the rate of evaporative heat loss resulting from sweating when the body core temperature rises above the critical level of 37°C.

3. Decrease in heat production. The mechanisms that cause excess heat production, such as shivering and chemical thermogenesis, are strongly inhibited.

Temperature-Increasing Mechanisms When the Body Is Too Cold

When the body is too cold, the temperature control system institutes exactly opposite procedures. They are:

1. Skin vasoconstriction throughout the body. This is caused by stimulation of the posterior hypothalamic sympathetic centers.

2. Piloerection. Sympathetic stimulation causes the arrector pili muscles attached to the hair follicles to contract, which brings the hairs to an upright stance. This is not important in human beings, but in lower animals, upright projection of the hairs allows them to entrap a thick layer of “insulator air” next to the skin, so that transfer of heat to the surroundings is greatly depressed.

3. Increase in thermogenesis (heat production). Heat production by the metabolic systems is increased by promoting shivering, sympathetic excitation of heat production, and thyroxine secretion. These methods of increasing heat require additional explanation, which follows.

Hypothalamic Stimulation of Shivering

Located in the dorsomedial portion of the posterior hypothalamus near the wall of the third ventricle is an area called the primary motor center for shivering. This area is normally inhibited by signals from the heat center in the anterior hypothalamic-preoptic area but is excited by cold signals from the skin and spinal cord. Therefore, as shown by a sudden increase in “heat production”, this center becomes activated when the body temperature falls even a fraction of a degree below a critical temperature level. It then transmits signals that cause shivering through the spinal cord, and finally to the anterior motor neurons. These signals are non-rhythmical and do not cause the actual muscle shaking. Instead, they increase the tone of the skeletal muscles throughout the body by facilitating the activity of the anterior motor neurons. When the tone rises above a certain critical level, shivering begins. This probably results from feedback oscillation of the muscle spindle stretch reflex mechanism. During maximum shivering, body heat production can rise to four to five times normal.

Sympathetic “Chemical” Excitation of Heat Production

An increase in either sympathetic stimulation or circulating norepinephrine and epinephrine in the blood can cause an immediate increase in the rate of cellular metabolism. This effect is called chemical thermogenesis. It results at least partially from the ability of norepinephrine and epinephrine to uncouple oxidative phosphorylation.

Acclimatization greatly affects the intensity of chemical thermogenesis;

In adult human beings, who have almost no brown fat, it is rare for chemical thermogenesis to increase the rate of heat production more than 10 to 15 per cent. However, in infants, who do have a small amount of brown fat in the interscapular space, chemical thermogenesis can increase the rate of heat production 100 per cent, which is probably an important factor in maintaining normal body temperature in neonates.

Increased Thyroxine Output as a Long-Term Cause of Increased Heat Production

Cooling the anterior hypothalamic- preoptic area also increases production of the neurosecretory hormone thyrotropin-releasing hormone by the hypothalamus. This hormone is carried by way of the hypothalamic portal veins to the anterior pituitary gland, where it stimulates secretion of thyroid- stimulating hormone.

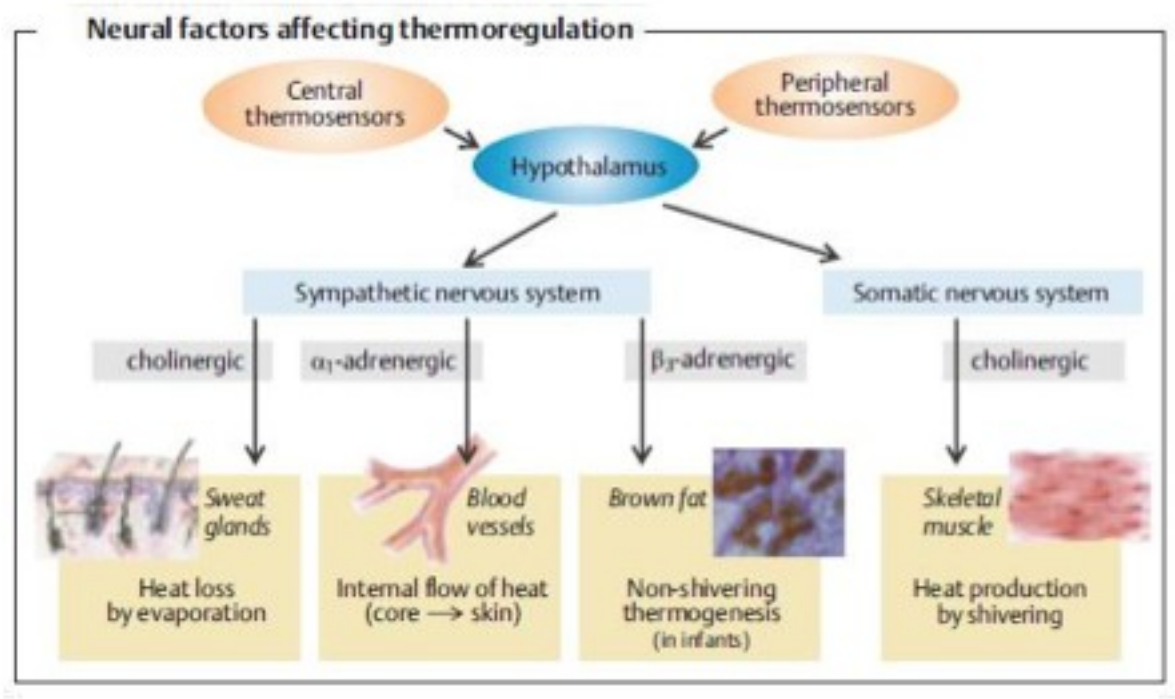
Thyroid-stimulating hormone in turn stimulates increased output of thyroxine by the thyroid gland. The increased thyroxine increases the rate of cellular metabolism throughout the body, which is yet another mechanism of chemical thermogenesis. This increase in metabolism does not occur immediately but requires several weeks' exp sure to cold to make the thyroid gland hypertrophy.

Concept of a "Set-Point" for Temperature Control

It is clear that at a critical body core temperature of about 37.1°C, drastic changes occur in the rates of both heat loss and heat production. At temperatures above this level, the rate of heat loss is greater than that of heat production, so the body temperature falls and approaches the 37.1°C level. At temperatures below this level, the rate of heat production is greater than that of heat loss, so the body temperature rises and again approaches the 37.1°C level. This crucial temperature level is called the "set-point" of the temperature control mechanism. That is, all the temperature control mechanisms continually attempt to bring the body temperature back to this set-point level.

Local Skin Temperature Reflexes

When a person places a foot under a hot lamp and leaves it there for a short time, local vasodilation and mild local sweating occur. Conversely, placing the foot in cold water causes local vasoconstriction and local cessation of sweating. These reactions are caused by local effects of temperature directly on the blood vessels and also by local cord reflexes conducted from skin receptors to the spinal cord and back to the same skin area and the sweat glands. The intensity of these local effects is, in addition, controlled by the central brain temperature controller, so that their overall effect is proportional to the hypothalamic heat control signal times the local signal. Such reflexes can help prevent excessive heat exchange from locally cooled or heated portions of the body.



90. Regulation of renal functions

The determinants of GFR that are most variable and subject to physiologic control include the glomerular hydrostatic pressure and the glomerular capillary colloid osmotic pressure. These variables, in turn, are influenced by the sympathetic nervous system, hormones and autacoids (vasoactive substances that are released in the kidneys and act locally), and other feedback controls that are intrinsic to the kidneys.

Sympathetic Nervous System Activation Decreases GFR

Essentially all the blood vessels of the kidneys, including the afferent and the efferent arterioles, are richly innervated by sympathetic nerve fibers. Strong activation of the renal sympathetic nerves can constrict the renal arterioles and decrease renal blood flow and GFR. Moderate or mild sympathetic stimulation has little influence on renal blood flow and GFR. For example, reflex activation of the sympathetic nervous system resulting from moderate decreases in pressure at the carotid sinus baroreceptors or cardiopulmonary receptors has little influence on renal blood flow or GFR.

Hormonal and Autacoid Control of Renal Circulation

There are several hormones and autacoids that can influence GFR and renal blood flow.

Norepinephrine, Epinephrine, and Endothelin Constrict Renal Blood Vessels and Decrease GFR

Hormones that constrict afferent and efferent arterioles, causing reductions in GFR and renal blood flow, include norepinephrine and epinephrine released from the adrenal medulla. In general, blood levels of these hormones parallel the activity of the sympathetic nervous system; thus, norepinephrine and epinephrine have little influence on renal hemodynamics except under extreme conditions, such as severe hemorrhage.

Another vasoconstrictor, endothelin, is a peptide that can be released by damaged vascular endothelial cells of the kidneys as well as by other tissues. The physiologic role of this autacoid is not completely understood. However, endothelin may contribute to hemostasis (minimizing blood loss) when a blood vessel is severed, which damages the endothelium and releases this powerful vasoconstrictor. Plasma endothelin levels also are increased in certain disease states associated with vascular injury, such as toxemia of pregnancy, acute renal failure, and chronic uremia, and may contribute to renal vasoconstriction and decreased GFR in some of these pathophysiologic conditions.

Angiotensin II Constricts Efferent Arterioles.

A powerful renal vasoconstrictor, angiotensin II, can be considered a circulating hormone as well as a locally produced autacoid because it is formed in the kidneys as well as in the systemic circulation. Because angiotensin II preferentially constricts efferent arterioles, increased angiotensin II levels raise glomerular hydrostatic pressure while reducing renal blood flow. It should be kept in mind that increased angiotensin II formation usually occurs in circumstances associ- ated with decreased arterial pressure or volume depletion, which tend to decrease GFR. In these circumstances, the increased level of angiotensin II, by constricting efferent arterioles, helps prevent decreases in glomerular hydrostatic pressure and GFR; at the same time, though, the reduction in renal blood flow caused by efferent arteriolar constriction contributes to decreased flow through the peritubular capillaries, which in turn increases reabsorption of sodium and water.
Thus, increased angiotensin II levels that occur with a low-sodium diet or volume depletion help preserve GFR and maintain normal excretion of metabolic waste products such as urea and creatinine that depend on glomerular filtration for their excretion; at the same time, the angiotensin II–induced constriction of efferent arterioles increases tubular reabsorption of sodium and water, which helps restore blood volume and blood pressure.

Endothelial-Derived Nitric Oxide Decreases Renal Vascular Resistance and Increases GFR.

An autacoid that decreases renal vascular resistance and is released by the vascular endothelium throughout the body is endothelial-derived nitric oxide. A basal level of nitric oxide production appears to be important for maintaining vasodilation of the kidneys. This allows the

kidneys to excrete normal amounts of sodium and water. Therefore, administration of drugs that inhibit this normal formation of nitric oxide increases renal vascular resistance and decreases GFR and urinary sodium excretion, eventually causing high blood pressure.

Prostaglandins and Bradykinin Tend to Increase GFR.

Hormones and autacoids that cause vasodilation and increased renal blood flow and GFR include the prostaglandins (PGE2 and PGI2) and bradykinin. Although these vasodilators do not appear to be of major importance in regulating renal blood flow or GFR in normal conditions, they may dampen the renal vasoconstrictor effects of the sympathetic nerves or angiotensin II, especially their effects to constrict the afferent arterioles.

Autoregulation of GFR and Renal Blood Flow

Feedback mechanisms intrinsic to the kidneys normally keep the renal blood flow and GFR relatively constant, despite marked changes in arterial blood pressure. These mechanisms still function in blood-perfused kidneys that have been removed from the body, independent of systemic influences. This relative constancy of GFR and renal blood flow is referred to as autoregulation.

The primary function of blood flow autoregulation in most tissues other than the kidneys is to maintain the delivery of oxygen and nutrients at a normal level and to remove the waste products of metabolism, despite changes in the arterial pressure. In the kidneys, the normal blood flow is much higher than that required for these functions. The major function of autoregulation in the kidneys is to maintain a relatively constant GFR and to allow precise control of renal excretion of water and solutes.

The GFR normally remains autoregulated (that is, remains relatively constant), despite considerable arterial pressure fluctuations that occur during a person's usual activities. For instance, a decrease in arterial pressure to as low as 75 mm Hg or an increase to as high as 160 mm Hg changes GFR only a few percentage points. In general, renal blood flow is auto-regulated in parallel with GFR, but GFR is more efficiently autoregulated under certain conditions.

92. Sympathetic nervous system (overview)

Part of the autonomic nervous system The vegetative or autonomic nervous system supplies the internal organs and their coverings.

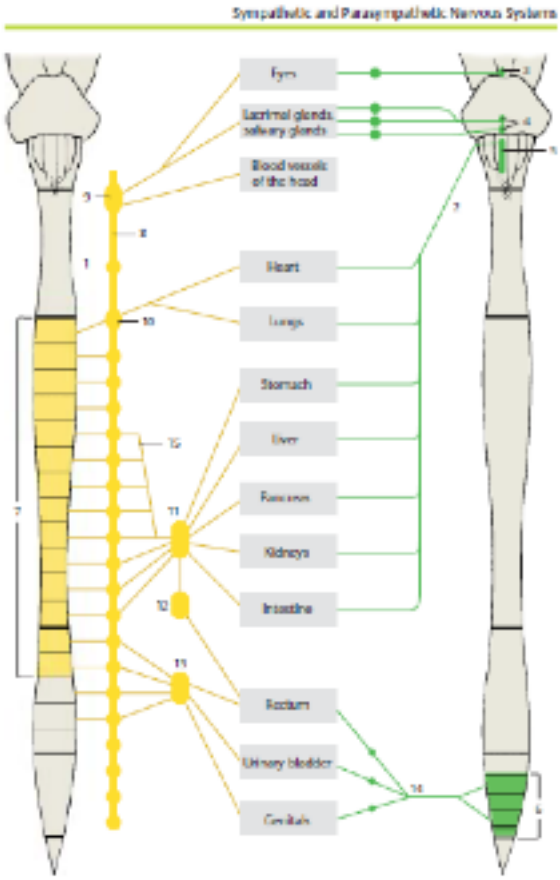
The main function of the autonomic nervous system is to stabilize the internal environment of the organism and to regulate the function of the organs in accordance with the changing requirements of the surroundings. This regulation is achieved by interaction of two antagonistic parts of the autonomic system, the sympathetic nervous system (yellow, below) and the parasympathetic nervous system (green below). The sympathetic nervous system is stimulated by increased physical activity, resulting in elevated blood pressure, accelerated heart rate and respiratory rate, dilated pupils, raised hair, and increased perspiration. At the same time, the peristaltic activity of the gastrointestinal tract is suppressed and secretion by intestinal glands is reduced.

The sympathetic nervous system is responsible for increased performance under stress and in states of emergency.

We distinguish between a peripheral and a central autonomic nervous system. The sympathetic neurons occupy the lateral horn in the thoracic and upper lumbar segments of the spinal cord.

Sympathetic Nervous System

The sympathetic neurons in the thoracic and lumbar lateral horn send their axons via the communicating branches to the sympathetic trunk. The latter consists of a chain of sympathetic ganglia which lie on each side of the vertebral column, in front of the transverse processes of each vertebra, and extend from the base of the skull to the coccyx. They are interconnected by interganglionic branches.



There are three ganglia in the cervical segment, namely, the superior cervical ganglion, the variable middle cervical ganglion, and the stellate ganglion (cervicothoracic ganglion). The thoracic segment contains 10 – 11 ganglia, the lumbar segment usually four, and the sacral segment also four ganglia. The chain is completed by the small unpaired ganglion which lies in the middle in front of the coccyx. The sacral ganglia receive their preganglionic fibers via interganglionic branches from spinal cord levels T12 – L2.

From the thoracic and lumbar sympathetic trunk ganglia, nerves extend to ganglia that lie within dense nervous plexuses on both sides of the abdominal aorta. The upper group of ganglia are the celiac ganglia to which the greater splanchnic nerve extends from the fifth to the ninth sympathetic trunk ganglia. Below it lies the superior mesenteric ganglion and the inferior mesenteric ganglion. The superior hypogastric plexus and the inferior hypogastric plexus expand in the pelvis.

The middle cervical ganglion may be absent, and the inferior cervical ganglion has in most cases fused with the first thoracic ganglion to form the stellate ganglion. Its postganglionic fibers form plexuses around the subclavian artery and around the vertebral artery. Fiber bundles connecting the stellate ganglion with the middle cervical ganglion extend across the subclavian artery and form the subclavian ansa. Nerves from the cervical ganglia and nerves from the upper thoracic ganglia extend to the heart and to the hila of the lungs, where they participate together with the parasympathetic fibers of the vagus nerve in the formation of the cardiac plexus.

93. Parasympathetic nervous system (overview)

Part of the autonomic nervous system The vegetative or autonomic nervous system supplies the internal organs and their coverings.

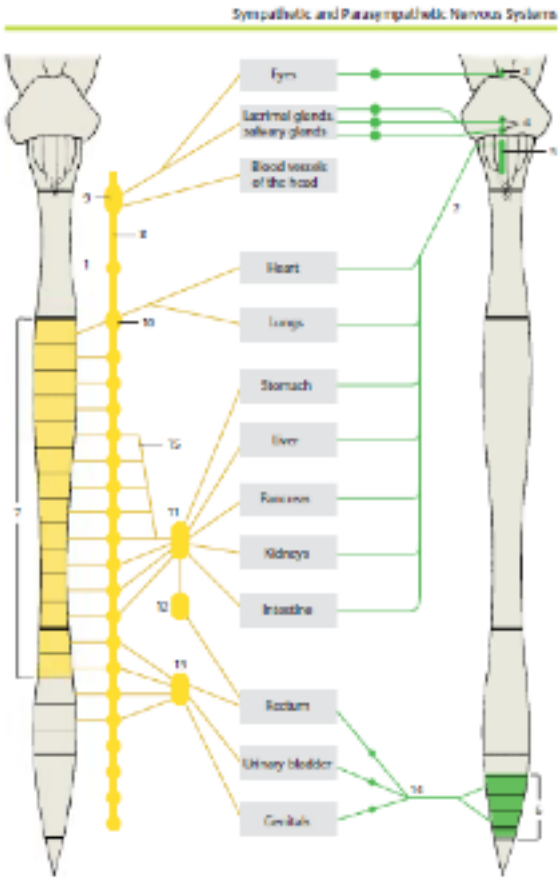
The main function of the autonomic nervous system is to stabilize the internal environment of the organism and to regulate the function of the organs in accordance with the changing requirements of the surroundings. This regulation is achieved by interaction of two antagonistic parts of the autonomic system, the sympathetic nervous system (yellow, below) and the parasympathetic nervous system (green below. When the parasympathetic system predominates, it increases peristaltic activity and intestinal secretion, stimulates defecation and urination, and reduces the heart rate and respiratory rate, while the pupils constrict.

We distinguish between a peripheral and a central autonomic nervous system.

Parasympathetic neurons form nuclei in the brain stem:

- The Edinger-Westphal nucleus (3)
- The salivatory nuclei (4)
- The dorsal nucleus of the vagus nerve (5)

The sacral spinal cord also contains parasympathetic neurons (6).



Parasympathetic Nervous System

The fibers of the central parasympathetic neurons run within various cranial nerves to the parasympathetic ganglia in the head region where they synapse; the postganglionic fibers extend to the effector organs. The vagus nerve, which is the principal nerve of the parasympathetic nervous system, descends together with the large cerebral vessels (neurovascular trunk of the neck); after passing through the superior thoracic aperture, it divides into plexuses in the regions of the thoracic and abdominal viscera.

The cells lying in the intermediolateral nucleus and intermediomedial nucleus of the sacral spinal cord send their axons through the third and fourth sacral root to the pudendal nerve; from here the fibers pass as pelvic nerves into the inferior hypogastric plexus and to the pelvic organs (urinary bladder, rectum, and genitals). Synapses with postganglionic neurons are formed in the inferior hypogastric plexus or in small ganglia of the various organ plexuses. As is the case with the sympathetic nervous system, the peripheral supply is provided by two neurons: the first neuron (preganglionic neuron) in the spinal cord, and the second neuron (postganglionic neuron) in the ganglia.

94. Adaptation to extreme environmental conditions

The term adaption denotes a characteristic that favors survival in specific environments. Homeostatic control systems are inherited biological adaptions. An individual's ability to respond to a particular environmental stress(load) is not fixed, however, but it can be enhanced, with no change in genetic endowment by prolonged exposure to that stress. This type of adaptation – the improved functioning of an already existing homeostatic system – is known as acclimatization.

The precise anatomical and physiological changes that bring about increased capacity to withstand change during acclimatization are highly varied. Typically, they involve an increase in the number, size, or sensitivity of one or more of the cell types in the homeostatic control system that mediate the basic response.

Adaptions are usually completely reversible (desadaptation) after finishing the loading. However, at the critical period for development of a structure or response, it is termed a development acclimatization and may be irreversible.

Maladaptation is a damage due to high reaction of adaptation processes.

Adaptation structural changes

Size of cell:

- ↑ hypertrophy (exercise – skeletal and heart muscle, prolongation of sarcomeres during stratching)
- ↓ atrophy (incativity, denervation – neurology, after poliomyelitis not damaged neurons innervated denervated muscles – greater motor units). Cells can be activated but a limited period, but a programmed death can develop – apoptosis

Number of cells:

- ↑ hyperplasia
- ↓ aplasia

- Adaptation to high altitude – hypoxia
  - ✓ Difusing capacity of the lungs 3x
  - ↑ lung volume, ↑ depth of respiration = ventilation ↑ nº of alveoli + sucking effect – volume of blood
  - ↑ volume of capillaries – area
  - ↑ Pulmonary pressure – hypertrophy of the right ventricle = ↑ perfusion
  - ↑ hematocrit to 55%, Hb 200 g/l, ↑ volume of eruthrocytes by 30%

Renal hypoxia – erythropoitin - ↑ erythropoesis and maturation of erythrocytes

- ↑ vascularization – activation of angiogenesis by hypoxia – vascular endothelial growth factor (VEGF), fibroblast, angiogenin.
- ↑ ability of the tissue cells to use O2 despite ↓ pO2 - ↑ nº of oxidative enzymes. ↑ expression of enzymes in mitochondria - ↑ extraction of O2

  - ✓ Chronic mountain sickness – too high adaptation changes – maldaptation
- Too high hematocrit - ↑ viscosity of blood
- Too high pulmonary pressure
- Right heart congestive heart failure
- Decreased systemic blood pressure

  - ✓ Acclimatization of the sweating mechanism to heat
- Sweting: the epithelial cells produce the percursor fluid – NaCl as in plasma, following NaCl reabsorption dependent on rate of sweating – at high rate of sweating the amount of reabsorbed NaCl only slightly increases = concentration of NaCl in sweat is increased and its loss is high
- After acclimatization:

-↑ secretion of aldosterone

-↓ concentration of NaCl in sweat

Diving reflex

Upon initiation of the reflex, three changes happen to the body, in this order:

1. Bradycardia is the first response to submersion. Immediately upon facial contact with cold water, the human heart rate slows down ten to twenty-five percent. Slowing the heart rate lessens the need for bloodstream oxygen, leaving more to be used by other organs.

2. Next, peripheral vasoconstriction sets in. When under high pressure induced by deep diving, capillaries in the extremities start closing off, stopping blood circulation to those areas. Note that vasoconstriction usually applies to arterioles, but in this case is completely an effect of the capillaries. Toes and fingers close off first, then hands and feet, and ultimately arms and legs stop allowing blood circulation, leaving more blood for use by the heart and brain. Human musculature accounts for only 12% of the body's total oxygen storage, and the body's muscles tend to suffer cramping during this phase.

3. Finally is the blood shift that occurs only during very deep dives. Organ and circulatory walls allow plasma/water to pass freely throughout the thoracic cavity, so its pressure stays constant and the organs aren't crushed. In this stage, the lungs' alveoli fill up with blood plasma, which is reabsorbed when the animal leaves the pressurized environment. This stage of the diving reflex has been observed in humans (such as world champion freediver Martin Štěpánek) during extremely deep (over 90 m or 300 ft) freedives.

95. Adaptation to exercise

Effect of Athletic Training on Muscles and Muscle Performance

Importance of Maximal Resistance Training

Muscles that function under no load, even if they are exercised for hours on end, increase little in strength. At the other extreme, muscles that contract at more than 50 per cent maximal force of contraction will develop strength rapidly even if the contractions are performed only a few times each day.

The approximate percentage increase in strength that can be achieved in a previously untrained young person by this resistive training program is about 30 per cent during the first 6 to 8 weeks but almost plateaus after that time. Along with this increase in strength is an approximately equal percentage increase in muscle mass, which is called muscle hypertrophy. In old age, many people become so sedentary that their muscles atrophy tremendously.

Muscle Hypertrophy.

With training, the muscles can become hypertrophied perhaps an additional 30 to 60 per cent. Most of this hypertrophy results from increased diameter of the muscle fibers rather than increased numbers of fibers, but this probably is not entirely true, because a very few greatly enlarged muscle fibers are believed to split down the middle along their entire length to form entirely new fibers. The changes that occur inside the hypertrophied muscle fibers themselves include (1) increased numbers of myofibrils, proportionate to the degree of hypertrophy; (2) increase in mitochondrial enzymes; (3) increase in the components of the phosphagen metabolic system, including both ATP and phosphocreatine; (4) increase in stored glycogen; and (5) increase in stored triglyceride (fat). Because of all these changes, the capabilities of both the anaerobic and the aerobic metabolic system are increased.

Cardiovascular response

1. The central command (anticipation of exercise)
- originates in the motor cortex or from reflexes initiated in muscle proprioceptors when exercise is anticipated.
- initiates the following changes:

a. Sympathetic outflow to the heart and blood vessels in increased. As a result, heart rate and contractility (stroke volume) are increased, and unstressed volume is decreased.

b. Cardiac output is increased, primarily as a result of the increased heart rate, and, to a lesser extent, the increased stroke volume.

c. Venous return is increased as a result of muscular activity. Increased venous return provides more blood for each stroke volume (Frank-Starling law).

d. Arteriolar resistance in the skin, splanchnic regions, kidneys, and inactive muscles is increased. Accordingly, blood flow to these organs is decreased.

2. Increased metabolic activity of skeletal muscle
- Vasodilator metabolites (lactate, K^+, and adenosine) accumulate because of increased metabolism of the exercising muscle.
- These metabolites cause arteriolar dilation in the active skeletal muscle, thus increasing skeletal blood flow (active hyperemia).
- As a result of the increased blood flow, O_2 delivery to the muscle is increased. The number of perfused capillaries is increased so that the diffusion distance for O_2 is decreased.
- This vasodilation accounts for the overall decrease in TPR that occurs with exercise. Note that activation of the sympathetic nervous system alone (by the central command) would cause an increase in TPR.

Respiratory response

1. During exercise, there is an increase in ventilatory rate that matches the increase in O_2 consumption and CO_2 production by the body. The stimulus for the increased ventilation rate is not

completely understood. However, joint and muscle receptors are activated during movement and cause an increase in breathing rate at the beginning of exercise.
2. The mean values for arterial PO_2 and PCO_2 do not change during exercise.
- Arterial pH does not change during moderate exercise because of lactic acidosis.
3. On the other hand, venous PCO_2 increases during exercise because the excess CO_2 produced by the exercising muscle is carried to the lungs in venous blood.
4. Pulmonary blood flow increases because cardiac output increases during exercise. As a result, more pulmonary capillaries are perfused, and more gas exchange occurs. The distribution of V/Q ratios throughout the lung is more even during exercise than when at rest, and there is a resulting decrease in the physiologic dead space.

<u>Sources of ATP during muscular work:</u>

- In the first 10 sec – ATP itself creatine phosphate currently present in muscle cell
- After 30 sec – mainly anaerobic glycolysis. glucose → 2 lactate + 2 ATP
- After 10 min – aerobic oxidation of glucose. glucose → 2 acetyl-CoA → 38 ATP
- After 2 hours – aerobic oxidation of FA
  Stearic acid → 9 acetyl-CoA → 146 ATP
  Palmitic acid → 129 ATP

96. Integration of nervous and hormonal regulation

Nerve impulses and hormonal signals serve to control and regulate the metabolism and internal balance (blood pressure, pH, water and electrolyte balance, temperature, etc.), physical growth and maturation, reproductive functions, sexual response, and responses to the social environment. The signals received by sensors (= sensory receptors) in the inner organs, musculoskeletal system, skin and the sensory organs, as well as psychological factors, skeletal muscles and other factors also play a part in regulation and control. The signals are used by many feedback mechanisms in the body.

Hypothalamus Controls Pituitary Secretion

Almost all secretion by the pituitary is controlled by either hormonal or nervous signals from the hypothalamus. Secretion from the posterior pituitary is controlled by nerve signals that originate in the hypothalamus and terminate in the posterior pituitary. In contrast, secretion by the anterior pituitary is controlled by hormones called hypothalamic releasing and hypothalamic inhibitory hormones (or factors) secreted within the hypothalamus itself and then conducted, to the anterior pituitary through minute blood vessels called hypothalamic-hypophysial portal vessels. In the anterior pituitary, these releasing and inhibitory hormones act on the glandular cells to control their secretion. The hypothalamus receives signals from many sources in the nervous system.

Hypothalamic-Hypophysial Portal Blood Vessels of the Anterior Pituitary Gland

The anterior pituitary is a highly vascular gland with extensive capillary sinuses among the glandular cells. Almost all the blood that enters these sinuses passes first through another capillary bed in the lower hypothalamus. The blood then flows through small hypothalamic-hypophysial portal blood vessels into the anterior pituitary sinuses. Small arteries penetrate into the substance of the median eminence and then additional small vessels return to its surface, coalescing to form the hypothalamic-hypophysial portal blood vessels. These pass downward along the pituitary stalk to supply blood to the anterior pituitary sinuses.

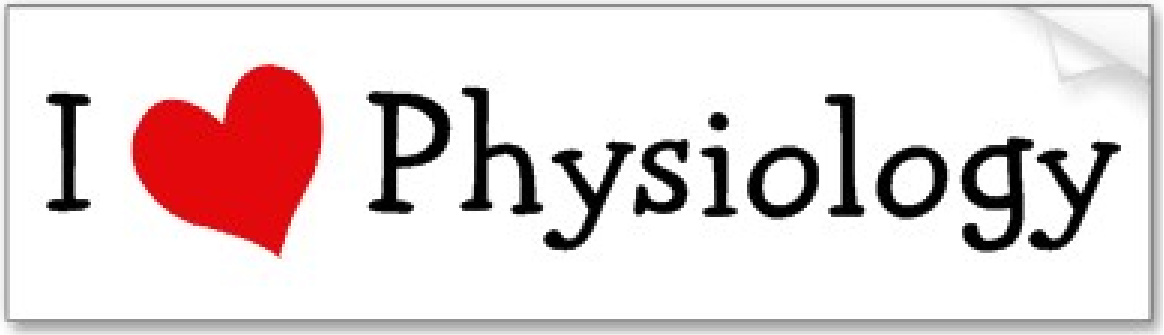
Hypothalamic Releasing and Inhibitory Hormones Are Secreted into the Median Eminence.

Special neurons in the hypothalamus synthesize and secrete the hypothalamic releasing and inhibitory hormones that control secretion of the anterior pituitary hormones.These neurons originate in various parts of the hypothalamus and send their nerve fibers to the median eminence and tuber cinereum, an extension of hypothalamic tissue into the pituitary stalk. The endings of these fibers are different from most endings in the central nervous system, in that thein function is not to transmit signals from one neuron to another but rather to secrete the hypothalamic releasing and inhibitory hormones into the tissue fluids. These hormones are immediately absorbed into the hypothalamic-hypophysial portal system and carried directly to the sinuses of the anterior pituitary gland.

Hypothalamic Releasing and Inhibitory Hormones Control Anterior Pituitary Secretion.

The function of the releasing and inhibitory hormones is to control secretion of the anterior pituitary hormones. For most of the anterior pituitary hormones, it is the releasing hormones that are important, but for prolactin, a hypothalamic inhibitory hormone probably exerts more control. The major hypothalamic releasing and inhibitory hormones are the following:

1. Thyrotropin-releasing hormone (TRH), which causes release of thyroid-stimulating hormone
2. Corticotropin-releasing hormone (CRH), which causes release of adrenocorticotropin
3. Growth hormone–releasing hormone (GHRH), which causes release of growth hormone, and growth hormone inhibitory hormone (GHIH), also called somatostatin, which inhibits release of growth hormone
4. Gonadotropin-releasing hormone (GnRH), which causes release of the two gonadotropic hormones, luteinizing hormone and follicle-stimulating hormone
5. Prolactin inhibitory hormone (PIH), which cause inhibition of prolactin secretion



SECTION B

1. Blood composition – values

The blood volume of an adult correlates with his or her body mass and amounts to aprox. 4-4.5 l in women and 4.5-5l in men. The functions of blood include the transport of various molecules (O_2, CO_2, nutrients metabolites, vitamins, electrolytes, etc), heat (regulation of body temperature) and transmission of signals (hormones) as well as buffering and immune defense.

The blood consists of a suspension of special cells in liquid called plasma. In an adult man, the blood is about 1/12th of the body weight and this corresponds to 5-6 liters. Blood consists of 55 % plasma, and 45 % by cells or cells fragments called formed elements.

Plasma

Cells free serum or plasma, can be obtained by centrifugation. The plasma is a slightly alkaline fluid, with a typical yellowish color. It consists of 90 % water and 10% dry matter. Nine parts of it are made up by organic substances, whereas one part is made up by minerals. These organic substances are composed of glycides (glucose), lipids (cholesterol, triglycerides, phospholipids, lecithin, fats), proteins (globulins, albumins, fibrinogen), glycoproteins, hormones (gonadotropins, erythropoietin, thrombopoietin), amino acids and vitamins. The mineral substances are dissolved in ionic form, which is dissociated into positive and negative ions.

The hematocrit is defined as the percentage of blood volume that is erythrocytes. It is measured by centrifuging a sample of blood. The erythrocytes are forced to the bottom of the centriguge tube, the plasma remains on top, and the leukocytes and platelets form a very thin layer between them the normal hematocrit is approximately 45% in men, and 42% in women.

Blood cells:

- Red blood cells – erythrocytes — 4-6 millions/1µl of blood
- White blood cells – leukocytes — 5000 – 9000/ 1µl
- Platelets – thrombocytes — 150000 – 250000/ 1µl

Erythrocytes

- 4 – 6 million/µl
- Shape: biconcave disc
- Lifespan: 120 days

Leukocytes

Granulocytes:	Agranulocytes
- neutrophils - eosinophils - basophils	- lymphocytes - monocytes

Neutrophil granulocytes
- 71% of all white blood cells
- ø 10-12 µm

Eosinophil granulocytes
- 1-4% of all white blood cells
- ø 12-14 µm

Basophil granulocytes
- up to 1% of all white blood cells
- ø up to 10 µm

Lymphocytes (20% of all white blood cells)
- T-lymphocytes
- B-lymphocytes

Monocytes (5% of all blood cells)
- ø 15-20 µm

Thrombocytes
- 150000-300000/1µl
- thrombocytes X thrombocytopenia
- are not cells, but cytoplasmatic fragments fo a large cell
- shape: flattened discoid plate
- size: 2-4 µm

Arterial blood
PO2 = 100 mm Hg
PCO_2 = 40 mm Hg

Venous blood
PO2 = 40 mm Hg
PCO_2 = 45 mm Hg
Hemoglobin: 2.15-2.65 mmol/l

2. Red blood cell. Haemolysis.

Red Blood Cells (Erythrocytes)

The major function of red blood cells, also known as erythrocytes, is to transport hemoglobin, which in turn carries oxygen from the lungs to the tissues. The red blood cells have other functions besides transport of hemoglobin. For instance, they contain a large quantity of carbonic anhydrase, an enzyme that catalyzes the reversible reaction between carbon dioxide (CO_2) and water to form carbonic acid (H_2CO_3), increasing the rate of this reaction.The rapidity of this reaction makes it possible for the water of the blood to transport enormous quantities of CO_2 in the form of bicarbonate ion (HCO_3 –) from the tissues to the lungs, where it is reconverted to CO_2 and expelled into the atmosphere as a body waste product. The hemoglobin in the cells is an excellent acid-base buffer (as is true of most proteins), so that the red blood cells are responsible for most of the acid-base buffering power of whole blood.

Shape and Size of Red Blood Cells.

Normal red blood cells, are biconcave discs having a mean diameter of about 7.8 micrometers. The shapes of red blood cells can change remarkably as the cells squeeze through capillaries.Actually, the red blood cell can be deformed into almost any shape. Furthermore, because the normal cell has a great excess of cell membrane for the quantity of material inside, deformation does not stretch the membrane greatly and, consequently, does not rupture the cell, as would be the case with many other cells.

Concentration of Red Blood Cells in the Blood

Normal values are aprox. 4 – 6 million/µl. Persons living at high altitudes have greater numbers of red blood cells.

Life Span and Destruction of Red Blood Cells

When red blood cells are delivered from the bone marrow into the circulatory system, they normally circulate an average of 120 days before being destroyed. Even though mature red cells do not have a nucleus, mitochondria, or endoplasmic reticulum, they do have cytoplasmic enzymes that are capable of metabolizing glucose and forming small amounts of adenosine triphosphate.These enzymes also (1) maintain permiability of the cell membrane, (2) maintain membrane transport of ions, (3) keep the iron of the cells' hemoglobin in the ferrous form rather than ferric form, and (4) prevent oxidation of the proteins in the red cells. Even so, the metabolic systems of old red cells become progressively less active and more fragile, presumably because their life processes wear out. Once the red cell membrane becomes fragile, the cell ruptures during passage through some tight spot of the circulation. Many of the red cells self-destruct in the spleen, where they squeeze through the red pulp of the spleen.There, the spaces between the structural trabeculae of the red pulp, through which most of the cells must pass, are only 3 micrometers wide, in comparison with the 8-micrometer diameter of the red cell. When the spleen is removed, the number of old abnormal red cells circulating in the blood increases considerably.

Destruction of Hemoglobin.

When red blood cells burst and release their hemoglobin, the hemoglobin is phagocytized almost immediately by macrophages in many parts of the body, but especially by the Kupffer cells of the liver and macrophages of the spleen and bone marrow. During the next few hours to days, the macrophages release iron from the hemoglobin and pass it back into the blood, to be carried by transferrin either to the bone marrow for the production of new red blood cells or to the liver and other tissues for storage in the form of ferritin. The porphyrin portmon of the hemoglobin molecule is converted by the macrophages, through a series of stages, into the bile pigment bilirubin, which is released into the blood and later removed from the body by secretion through the liver into the bile.

3. Haemoglobin and its derivatives

Hemoglobin

- is a globular protein of four subunits. The tetramer can be envisioned as being composed of two identical dimmers, (αβ)1, (αβ)2
- each subunit contains a heme proton, which is a complex of protophyrin IX and ferrous iron (Fe2+).
- each subunit is a polypeptide chain.

Formation of Hemoglobin

Synthesis of hemoglobin begins in the proerythroblasts and continues even into the reticulocyte stage of the red blood cells.Therefore, when reticulocytes leave the bone marrow and pass into the blood stream, they continue to form minute quantities of hemoglobin for another day or so until they become mature erythrocytes. First, succinyl-CoA, formed in the Krebs metabolic cycle, binds with glycine to form a pyrrole molecule. In turn, four pyrroles combine to form protoporphyrin IX, which then combines with iron to form the heme molecule. Finally, each heme molecule combines with a long polypeptide chain, a globin synthesized by ribosomes, forming a subunit of hemoglobin called a hemoglobin chain; four of these in turn bind together loosely to form the whole hemoglobin molecule. There are several slight variations in the different subunit hemoglobin chains, depending on the amino acid composition of the polypeptide portion. The different types of chains are designated alpha chains, beta chains, gamma chains, and delta chains. The most common form of hemoglobin in the adult human being, hemoglobin A, is a combination of two alpha chains and two beta chains. each of the four chains can bind loosely with one molecule of oxygen, making a total of four molecules of oxygen (or eight oxygen atoms) that can be transported by each hemoglobin molecule.

Hemoglobin: the oxygen dissociation curve for hemoglobin is in shape, indicating that the subunits cooperate in binding oxygen. Cooperative binding of oxygen by the four subunits of hemoglobin means that the binding of an oxygen molecule at one heme groups in the same hemoglobin molecule. This effect is referred to as heme-heme interaction. Although it is more difficult for the first oxygen molecule to bind to hemoglobin, the subsequent binding of oxygen occurs with high affinity.

Shift of the oxygen-dissociation curve: Hemoglobin from which 2,3-BPG has been removed has a high affinity for oxygen. However, the oresence of 2,3-BPG significantly reduces the affinity of hemoglobin for oxygen, shifting the oxygen-dissociation curve to the right.

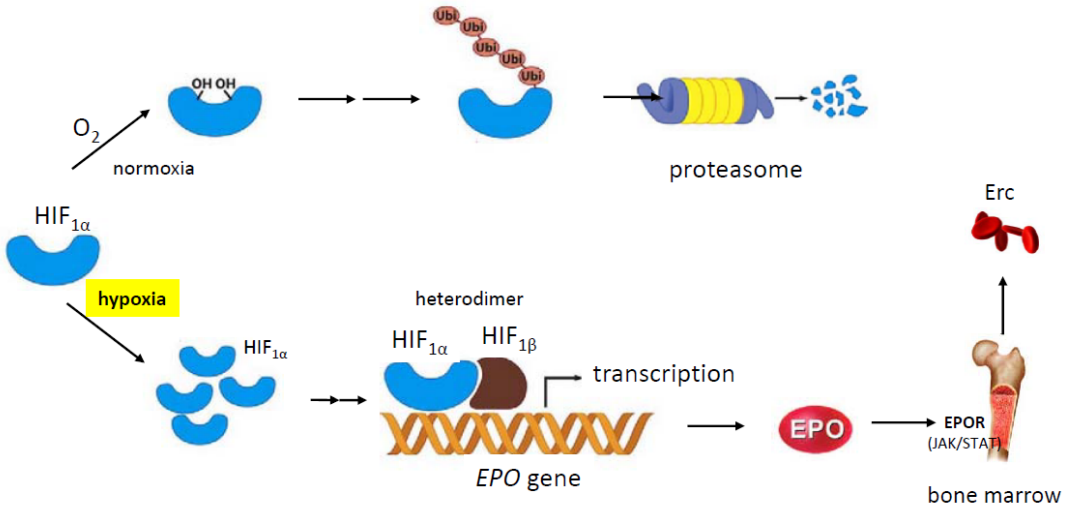
Minor hemoglobins

Each of these oxygen-carrying proteins is a tetramer composed of two α-globulin-like polypeptides and two β-globulin-like polypeptides. Certain hemoglobins, such as HbF, are normally synthesized only during fetal development, whereas others, such as HbA2, are synthesized in the adult, although at low levels compared with HbA. HbA can also become modified by the covalent addition of a hexose. For example, addition of glucose forms the glucosylated hemoglobin derivative, HbA1c.

Fetal hemoglobin

- in fetal hemoglobin, the β chains are replaced by γ chains.
- the O2 affinity of fetal hemoglobin is higher than the O2 affinity of adult hemoglobin because 2,3-BPG binds less avidity.
- because the O2 affinity of fetal hemoglobin is higher than the O2 affinity of adult hemoglobin, O2 movement from mother to fetus is facilitated.

4. Erytropoesis



- receptors with tyrosine kinase activity in bone marrow increase the conversion of stem cells into red blood cell percursors.

Erythropoesis
- Proerythroblast
- Basophilic erythroblast
- Polychromatophilic erythroblast
- Ortochromatic erythroblast
- Reticulocyte

Process - during repeated mitoses:
- cell size decreases from 20 micrometers to 8 micrometers in diameter
- condensation of nuclear chromatin, nucleoli disappear, nucleus will be extruded - enucleation
- hemoglobin production
- transformation of cytoplasm staining – from basophilia (caused by ribosomes) to acidophilia (caused by hemoglobin production)

<u>Proerythroblast</u>
- ø15 – 20 μm
- basophilic cytoplasm forms iregular, „ear-shaped“ projections from the surface of the cell
- spherical nucleus contains 2 – 3 nucleoli

<u>Basophilic erythroblast</u>
- ø 16 μm
- basophilic cytoplasm
- condensation of nuclear chromatin begins
- absence of nucleoli

<u>Polychromatophilic erythroblast</u>
- ø 12 μm
- production of hemoglobin begins and causes irregular staining of cytoplasm – partly basophilic, partly acidophilic
- condensed chromatin

<u>Ortochromatophilic erythroblast</u>
- ø 9 – 10 μm
- acidophilic cytoplasm with hemoglobin

- pycnotic nucleus in excentric position before enucleation

Reticulocyte
- ø 8 μm
- acidophilic cytoplasm with hemoglobin
- without nucleus, but with the rests of some organelles – substantia reticulofilamentosa

5. Suspension stability of RBC (sedimentation rate)

Erythrocyte Sedimentation Rate (E.S.R.)

Estimation of E.S.R. is a non-specific laboratory method providing us with information on many physiological and pathological processes in organism. Only in case of two diseases – temporal arthritis and rheumatic polymyalgia – estimation of E.S.R. represents important diagnostic criterion. Taking in consideration its low sensitivity, E.S.R. cannot be used as screening test in asymptomatic persons. On the other hand, marked increase in sedimentation rate (above 100mm/h) is always cause by pathological process – infection, tumors or cancer diseases.

The ESR is governed by the balance between pro-sedimentation factors, mainly fibrinogen, and those factors resisting sedimentation, namely the negative charge of the erythrocytes (zeta potential). When an inflammatory process is present, the high proportion of fibrinogen in the blood causes red blood cells to stick to each other. The red cells form stacks called 'rouleaux' which settle faster. Rouleaux formation can also occur in association with some lymphoproliferative disorders in which one or more immunoglobulins are secreted in high amounts. Rouleaux formation can, however, be a normal physiological finding in horses, cats and pigs.

The ESR is increased by any cause or focus of inflammation. The ESR is increased in pregnancy or rheumatoid arthritis, and decreased in polycythemia, sickle cell anemia, hereditary spherocytosis, and congestive heart failure. The basal ESR is slightly higher in females.

Principle of method (Fahreus-Westergreen)

Red blood cells membranes are negatively charged. They float in the plasma although they are specifically heavier (they are driven away from each other). Any factor decreasing or impairing their surface charge causes their aggregation. . Anti-coagulated blood is sucked up into a vertical glass tube fixed in a stand in such a way that it cannot flow out. After 1, 2 (or even 24) hours, the height of the plasma column above the sedimenting red cells is measured. When working with blood which has a high E.S.R. the readings are made each 15 or 30 min during two hours.

Physiological (average) values:
Men: 2-8 mm/h, women: 7-12 mm/h, newborns: 2mm/h, infants: 4-8 mm/h

6. Cellular immunity

T cells constitute a family that has two major functional subsets, termed cytotoxic T cells and helper T cells. There may also be a third subset, called suppressor T cells, which have been hypothesized to inhibit the function of both B cells and cytotoxic T cells.

Another way to categorized T cells is not by function but rather by the presence of certain proteins, called CD4 and CD8. Cytotoxic T cells have CD4 and helper T cells express CD4.

Cytotoxic T cells are “attack” cells. Following activation, they travel to the location of their target, bind to them via antigen on these targets, and directly kill their targets via secreted chemicals. Responses mediated by cytotoxic T cells are directed against the body’s own cells that have become cancerous or infected with viruses (or certain bacteria and parasites that, like viruses, take up residence inside host cells). Cytotoxic Tcells must enter the blood and seek out the targets.

Helper T cells assist in the activation and function of both B cells and cytotoxic T cells.
Helper T cells first combine with antigen and then undergo activation. Once activated, they secrete cytokines that act on B cells and cytotoxic T cells that have also bound antigen. B cells and cytotoxic T cells cannot function adequately unless they are stimulated by cytokines from helper T cells.

T-Cell receptors

T-cell receptors for antigens are two-chained proteins that, like immunoglobulins, have specific regions that differ from one T-cell clone to another. However, T-cell receptors remain embedded in the T-cell membrane. Multiple DNA rearrangements occur during T-cell maturation, leading to millions of distinct T cells clones – distinct in that the cells of any given clone possess receptors of a single specificity. For T cells, this maturation occurs during their residence in the thymus.

The T-cell receptor cannot combine with antigen unless the antigen is first complexed with certain of the body’s own plasma membrane proteins. The T-cell receptor then combines with the entire complex of antigen and body (“self”) protein.

T cells can bind antigen only when the antigen appears on the plasma membrane of a host cell complexed with the cell’s MHC proteins. Cells bearing these complexes, therefore function as antigen-presenting cells (APCs).

Presentation to Helper T Cells

Helper T cells require class II MHC proteins to function. Only macrophages, B cells, and therefore can function as APCs for helper T cells.

The function of the macrophage as an APC for helper T cells is easier to visualize since the macrophage forms a link between nonspecific and specific immune defenses. After a microbe or noncellular antigen has been phagocytized by a macrophage in nonspecific response, it is partially broken down into smaller peptide fragments by the macrophage’s proteolytic enzymes. The resulting digested fragments actually fit into a deep groove in the center of the MHC protein. The fragment-MHC complex is then transported to the cell surface, where it is displayed in the plasma membrane. It is to this entire complex on the cell surface of the macrophage (or macrophage-like cell) that a specific helper T cell binds).

It is not the intact antigen but rather the peptide fragments, termed antigenic determinants or epitopes, of the antigen that are complexed to the MHC proteins and presented to the T cell.
Binding between helper T-cell receptor and an antigen bound to class II MHC proteins on an APC is the essential antigen-specific even in helper T-cell activation. However, this binding by itself will not result in T-cell activation. In addition, nonspecific interactions occur between other (nonspecific) pair of proteins on the surfaces of the attached helper T cell and APC, and these provide a necessary costimulus for T-cell activation.

Finally, the antigenic binding of the APC to the T cell, along with the costimulus, causes the APC to secrete large amounts of the cytokines interleukin I (IL-I) and tumor necrosis factor (TNF), which act as paracrine agents on the attached helper T cell to provide yet another important stimulus for activation.

Thus, the APC participates in the activation of a helper T cell in three ways:

(1) antigen presentation
(2) provision of a costimulus in the form of a matching nonantigenic plasma membrane protein
(3) secretion of IL-I, TNF and other cytokines

The activated helper T cell itself now secretes various cytokines that have both autocrine effects on the helper T cell and paracrine effects on adjacent B cells and any nearby cytotoxic T cells, NK cells, and still other cell types.

Presentation to Cytotoxic T Cells

Because class I MHC proteins are synthesized by virtually all nucleated cells, any such cell can act as an APC for a cytotoxic T cell. The major function of cytotoxic T cells is the destruction of any of the body's own cells that have become cancerous or infected with viruses. The key point is that the antigens that complex with class I MHC proteins arise within body cells. They are "endogenous" antigens, synthesized by a body cell.

In the case of viruses, once a virus has taken up residence inside a host cell, the viral nucleic acid causes the host cell. A cancerous cell has had one or more of its genes altered by chemicals, radiation, or other factors. The altered genes, called oncogenes, code for proteins that are not normally found in the body. Such proteins act as antigens.

In both virus-infected cells and cancerous cells, some of the endogenously produced antigenic proteins are hydrolyzed by cytosolic enzymes (in proteosomes) into peptide fragments, which are transported into the endoplasmatic reticulum. There they are complexed with the host cell's class I MHC proteins and then shuttled by exocitosis to the plasma membrane surface, where a cytotoxic T cell specific for the complex can bind to it.

7. Humoural immunity

Formation of Antibodies by Plasma Cells

B-Cell receptors

Before exposure to a specific antigen, the clones of B lymphocytes remain dormant in the lymphoid tissue. On entry of a foreign antigen, macrophages in the lymphoid tissue phagocytize the antigen and then present it to adjacent B lymphocytes. In addition, the antigen is presented to T cells at the same time, and activated helper T cells are formed. These helper cells also contribute to extreme activation of the B lymphocytes. Once B cells are activated by antigen and helper T cell cytokines they proliferate and differentiate (lymphoblast -> plasmablasts) into plasma cells. The cytoplasm expands and the rough endoplasmic reticulum proliferates. The plasmablasts then begin to divide and secrete antibodies. The plasma cells derived from a particular B cell can secrete only one particular antibody. Each B cell always displays on its plasma membrane copies of the particular antibody its plasma cell progeny can produce. This surface protein (glycoprotein, to be more accurate) act as the receptor for the antigen specific to it.

B-cell receptors and plasma cell antibodies constitute the family of proteins known as immunoglobulins. The receptors themselves, even though they are identical to the antibodies to be secreted by the plasma cell derived from the activated B cell, are technically not antibodies since only secreted immunoglobulins are termed antibodes. The antibodies are secreted into the lymph and carried to the circulating blood.This process continues for several days or weeks until finally exhaustion and death of the plasma cells occur.

Formation of “Memory” Cells—Difference Between Primary Response and Secondary Response.

A few of the lymphoblasts formed by activation of a clone of B lymphocytes do not go on to form plasma cells but instead form moderate numbers of new B lymphocytes similar to those of the original clone. In other words, the B cell population of the specifically activated clone becomes greatly enhanced, and the new B lymphocytes are added to the original lymphocytes of the same clone.They also circulate throughout the body to populate all the lymphoid tissue; immunologically, however, they remain dormant until activated once again by a new quantity of the same antigen. These lymphocytes are called memory cells. Subsequent exposure to the same antigen will cause a much more rapid and much more potent antibody response this second time around, because there are many more memory cells than there were original B lymphocytes of the specific clone.

Nature of the Antibodies

The antibodies are gamma globulins called immunoglobulins (abbreviated as Ig). All the immunoglobulins are composed of combinations of light and heavy polypeptide chains. Most are a combination of two light and two heavy chains. The end of each light and heavy chain is called the variable portion; the remainder of each chain is called the constant portion.The variable portion is different for each specificity of antibody, and it is this portion that attaches specifically to a particular type of antigen.The constant portion of the antibody determines other properties of the antibody, establishing such factors as diffusivity of the antibody in the tissues, adherence of the antibody to specific structures within the tissues, attachment to the complement complex, the ease with which the antibodies pass through membranes, and other biological properties of the antibody.

Classes of Antibodies.

There are five general classes of antibodies, respectively named IgM, IgG, IgA, IgD, and IgE. Ig stands for immunoglobulin, and the other five respective letters designate the respective classes.

Mechanisms of Action of Antibodies

Antibodies act mainly in two ways to protect the body against invading agents: (1) by direct attack on the invader and (2) by activation of the “complement system” that then has multiple means of its own for destroying the invader.

Direct Action of Antibodies on Invading Agents.

Because of the bivalent nature of the antibodies and the multiple antigen sites on most invading agents, the antibodies can inactivate the invading agent in one of several ways, as follows: 1. Agglutination, in which multiple large particles with antigens on their surfaces, such as bacteria or red cells, are bound together into a lump 2. Precipitation, in which the molecular complex of soluble antigen (such as tetanus toxin) and antibody becomes so large that it is rendered insoluble and precipitates 3. Neutralization, in which the antibodies cover the toxic sites of the antigenic agent; 4. Lysis, in which some potent antibodies are occasionally capable of directly attacking membranes of cellular agents and thereby cause rupture of the agent. These direct actions of antibodies attacking the antigenic invaders often are not strong enough to play a major role in protecting the body against the invader. Most of the protection comes through the amplifying effects of the complement system.

8. Histocompatibility (MHC)

The self plasma membrane proteins that must be complexed with the antigen in order for T-cell recognition to occur konstitute a group of proteins coded for by genes found on a single chromosome and known collectively as the major histocompatibility komplex (MHC). The proteins are therefore called MHC proteins. Since no two persons other than indentical twins have the same MHC genes, no two individuals have the same MHC proteins on the plasma membranes of their cells. MHC proteins are, in essence, cellular „identity tags“ – that is, genetic markers of biological self.

The MHC proteins are often termed „restriction elements“ since the ability of a T cell's receptor to recognize an antigen is restricted to situations in which the antigen is first complexed with an MHC protein. There are two classes of MHC proteins: I and II. Class I MHC proteins are found on the surface of virtually all cell sof a person's body excerpt erythrocytes. Class II MHC proteins are found only on the surface of macrophages, B cells and macrophage-like cells.

The different subsets of T cells do not all have the same MHC requirements: cytotoxic T cells require antigen to be associated with class I MHC proteins, whereas helper T cells require class II MHC proteins.

CD4 binds Class II proteins and CD8 binds Class I proteins.

MHC restriction of the lymphocytes receptors	
CELL TYPE	MHC RESTRICTION
B	Do not interact with MHC proteins
Helper T	Class II, found only on macrophages, macrophages-like cells, and B cells
Cytotoxic T	Class I, found on all nucleated cells of the body
NK	Interaction with MHC proteins not required for activation

10. Blood groups antigens (ABO group, Rh group)

O-A-B Blood Types

A and B Antigens—Agglutinogens

Two antigens—type A and type B—occur on the surfaces of the red blood cells in a large proportion of human beings. It is these antigens (also called agglutinogens because they often cause blood cell agglutination) that cause most blood transfusion reactions. Because of the way these agglutinogens are inherited, people may have neither of them on their cells, they may have one, or they may have both simultaneously.

Major O-A-B Blood Types

In transfusing blood from one person to another, the bloods of donors and recipients are normally classified into four major O-A-B blood types, depending on the presence or absence of the two agglutinogens, the A and B agglutinogens. When neither A nor B agglutinogen is present, the blood is type O. When only type A agglutinogen is present, the blood is type A. When only type B agglutinogen is present, the blood is type B. When both A and B agglutinogens are present, the blood is type AB.

Genetic Determination of the Agglutinogens.

Two genes, one on each of two paired chromosomes, determine the O-A-B blood type. These genes can be any one of three types but only one type on each of the two chromosomes: type O, type A, or type B. The type O gene is either functionless or almost functionless, so that it causes no significant type O agglutinogen on the cells. Conversely, the type A and type B genes do cause strong agglutinogens on the cells.

The six possible combinations of genes are OO, OA, OB, AA, BB, and AB. These combinations of genes are known as the genotypes, and each person is one of the six genotypes.

A person with genotype OO produces no agglutinogens, and therefore the blood type is O. A person with genotype OA or AA produces type A agglutinogens and therefore has blood type A. Genotypes OB and BB give type B blood, and genotype AB gives type AB blood.

Human ABO Blood Groups					
Genetic Possibilities					
Blood group	Percent	Antigen on RBC	Homozygous	Heterozigous	Antibody in blood
A	41%	A	AA	AO	Anti-B
B	9%	Blood group	BB	BO	Anti-A
AB	3%	A and B	-	AB	Neither anti-A nor anti-B
O	47%	Neither A nor B	OO	-	Both anti-A and anti-B

Agglutinins

When type A agglutinogen is not present in a person's red blood cells, antibodies known as anti-A agglutinins develop in the plasma. Also, when type B agglutinogen is not present in the red blood cells, antibodies known as anti-B agglutinins develop in the plasma.

Type O blood, although containing no agglutinogens, does contain both anti-A and anti-B agglutinins; type A blood contains type A agglutinogens and anti-B agglutinins; type B blood contains type B agglutinogens and anti-A agglutinins. Finally, type AB blood contains both A and B agglutinogens but no agglutinins.

Immediately after birth, the quantity of agglutinins in the plasma is almost zero. Two to 8 months after birth, an infant begins to produce agglutinins—anti-A agglutinins when type A agglutinogens are not present in the cells, and anti-B agglutinins when type B agglutinogens are not in the cells.

Origin of Agglutinins in the Plasma

The agglutinins are gamma globulins, as are almost all antibodies, and they are produced by the same bone marrow and lymph gland cells that produce antibodies to any other antigens. Most of them are IgM and IgG immunoglobulin molecules.

Agglutination Process In Transfusion Reactions

When bloods are mismatched so that anti-A or anti-B plasma agglutinins are mixed with red blood cells that contain A or B agglutinogens, respectively, the red cells agglutinate as a result of the agglutinins' attaching themselves to the red blood cells. Because the agglutinins have several binding sites, a single agglutinin can attach to two or more red blood cells at the same time, thereby causing the cells to be bound together by the agglutinin. This causes the cells to clump, which is the process of "agglutination."

Rh Blood Types

Rh Antigens—"Rh-Positive" and "Rh-Negative" People.

There are six common types of Rh antigens, each of which is called an Rh factor. These types are desig- nated C, D, E, c, d, and e.A person who has a C antigen does not have the c antigen, but the person missing the C antigen always has the c antigen. The same is true for the D-d and E-e antigens. Also, because of the manner of inheritance of these factors, each person has one of each of the three pairs of antigens.

The type D antigen is widely prevalent in the population and considerably more antigenic than the other Rh antigens. Anyone who has this type of antigen is said to be Rh positive, whereas a person who does not have type D antigen is said to be Rh negative.

About 85 per cent of all white people are Rh positive and 15 per cent, Rh negative.

Erythroblastosis Fetalis ("Hemolytic Disease of the Newborn")

Erythroblastosis fetalis is a disease of the fetus and newborn child characterized by agglutination and phagocytosis of the fetus's red blood cells. In most instances of erythroblastosis fetalis, the mother is Rh negative and the father Rh positive. The baby has inherited the Rh-positive antigen from the father, and the mother develops anti-Rh agglutinins from exposure to the fetus's Rh antigen. In turn, the mother's agglutinins diffuse through the placenta into the fetus and cause red blood cell agglutination.

Incidence of the Disease

An Rh-negative mother having her first Rh-positive child usually does not develop sufficient anti-Rh agglutinins to cause any harm. However, about 3 per cent of second Rh-positive babies exhibit some signs of erythroblastosis fetalis; about 10 per cent of third babies exhibit the disease; and the incidence rises progressively with subsequent pregnancies.

Effect of the Mother's Antibodies on the Fetus

After anti-Rh antibodies have formed in the mother, they diffuse slowly through the placental membrane into the fetus's blood. There they cause agglutination of the fetus's blood. The agglutinated red blood cells subsequently hemolyze, releasing hemoglobin into the blood. The fetus's macrophages then convert the hemoglobin into bilirubin, which causes the baby's skin to become yellow (jaundiced). The antibodies can also attack and damage other cells of the body.

11. Function of platelets

Platelets have many functional characteristics of whole cells, even though they do not have nuclei and cannot reproduce. In their cytoplasm are such active factors as (1) actin and myosin molecules, which are contractile proteins similar to those found in muscle cells, and still another contractile protein, thrombosthenin, that can cause the platelets to contract; (2) residuals of both the endoplasmic reticulum and the Golgi apparatus that synthesize various enzymes and especially store large quantities of calcium ions; (3) mitochondria and enzyme systems that are capable of forming adenosine triphosphate (ATP) and adenosine diphosphate (ADP); (4) enzyme systems that synthesize prostaglandins, which are local hormones that cause many vascular and other local tissue reactions; (5) an important protein called fibrin-stabilizing factor; and (6) a growth factor that causes vascular endothelial cells, vascular smooth muscle cells, and fibroblasts to multiply and grow, thus causing cellular growth that eventually helps repair damaged vascular walls.

The cell membrane of the platelets is also important. On its surface is a coat of glycoproteins that repulses adherence to normal endothelium and yet causes adherence to injured areas of the vessel wall, especially to injured endothelial cells and even more so to any exposed collagen from deep within the vessel wall. In addition, the platelet membrane contains large amounts of phospholipids that activate multiple stages in the blood-clotting process.

Thus, the platelet is an active structure. It has a half-life in the blood of 8 to 12 days, so that over several weeks its functional processes run out. Then it is eliminated from the circulation mainly by the tissue macrophage system. More than one half of the platelets are removed by macrophages in the spleen, where the blood passes through a latticework of tight trabeculae.

12. Hemostasis

The term hemostasis means prevention of blood loss. Whenever a vessel is severed or ruptured, hemostasis is achieved by several mechanisms: (1) vascular constriction, (2) formation of a platelet plug, (3) formation of a blood clot as a result of blood coagulation, and (4) eventual growth of fibrous tissue into the blood clot to close the hole in the vessel permanently.

Vascular Constriction

Immediately after a blood vessel has been cut or ruptured, the trauma to the vessel wall itself causes the smooth muscle in the wall to contract; this instantaneously reduces the flow of blood from the ruptured vessel. The contraction results from (1) local myogenic spasm, (2) local autacoid factors from the traumatized tissues and blood platelets, and (3) nervous reflexes. The nervous reflexes are initiated by pain nerve impulses or other sensory impulses that originate from the traumatized vessel or nearby tissues. However, even more vaso-constriction probably results from local myogenic contraction of the blood vessels initiated by direct damage to the vascular wall. And, for the smaller vessels, the platelets are responsible for much of the vasoconstriction by releasing a vasoconstrictor substance, thromboxane A2.

The more severely a vessel is traumatized, the greater the degree of vascular spasm. The spasm can last for many minutes or even hours, during which time the processes of platelet plugging and blood coagulation can take place.

Formation of the Platelet Plug

If the cut in the blood vessel is very small the cut is often sealed by a platelet plug.

Mechanism of the Platelet Plug

When platelets come in contact with a damaged vascular surface, especially with collagen fibers in the vascular wall, the platelets themselves immediately change their own characteristics drastically. They begin to swell; they assume irregular forms with numerous irradiating pseudopods protruding from their surfaces; their contractile proteins contract forcefully and cause the release of granules that contain multiple active factors; they become sticky so that they adhere to collagen in the tissues and to a protein called von Willebrand factor that leaks into the traumatized tissue from the plasma; they secrete large quantities of ADP; and their enzymes form thromboxane A2. The ADP and thromboxane in turn act on nearby platelets to activate them as well, and the stickiness of these additional platelets causes them to adhere to the original activated platelets.

Therefore, at the site of any opening in a blood vessel wall, the damaged vascular wall activates successively increasing numbers of platelets that themselves attract more and more additional platelets, thus forming a platelet plug. This is at first a loose plug, but it is usually successful in blocking blood loss if the vascular opening is small. Then, during the subsequent process of blood coagulation, fibrin threads form. These attach tightly to the platelets, thus constructing an unyielding plug.

Importance of the Platelet Mechanism for Closing Vascular Holes

The platelet-plugging mechanism is extremely important for closing minute ruptures in very small blood vessels that occur many thousands of times daily. Indeed, multiple small holes through the endothelial cells themselves are often closed by platelets actually fusing with the endothelial cells to form additional endothelial cell membrane.

Blood Coagulation in the Ruptured Vessel

The third mechanism for hemostasis is formation of the blood clot. The clot begins to develop in 15 to 20 seconds if the trauma to the vascular wall has been severe, and in 1 to 2 minutes if the trauma has been minor. Activator substances from the traumatized vascular wall, from platelets, and from blood proteins adhering to the traumatized vascular wall initiate the clotting process. Within 3 to 6 minutes after rupture of a vessel, if the vessel opening is not too large, the entire opening or broken end of the vessel is filled with clot. After 20 minutes to an hour, the clot retracts; this closes the vessel still further. Platelets also play an important role in this clot retraction.

Mechanism of Blood Coagulation

Whether blood will coagulate depends on the balance between procogulants and anticoagulants. In the blood stream, the anticoagulants normally predominate, so that the blood does not coagulate while it is circulating in the blood vessels. But when a vessel is ruptured, procoagulants from the area of tissue damage become “activated” and override the anticoagulants, and then a clot does develop.

General Mechanism

Clotting takes place in three essential steps: (1) In response to rupture of the vessel or damage to the blood itself, a complex cascade of chemical reactions occurs in the blood involving more than a dozen blood coagulation factors. The net result is formation of a complex of activated substances collectively called prothrombin activator. (2) The prothrombin activator catalyzes conversion of prothrombin into thrombin. (3) The thrombin acts as an enzyme to convert fibrinogen into fibrin fibers that enmesh platelets, blood cells, and plasma to form the clot.

Initiation of Coagulation: Formation of Prothrombin Activator

These mechanisms are set into play by (1) trauma to the vascular wall and adjacent tissues, (2) trauma to the blood, or (3) contact of the blood with damaged endothelial cells or with collagen and other tissue elements outside the blood vessel. In each instance, this leads to the formation of prothrombin activator. Prothrombin activator is generally considered to be formed in two ways, although, in reality, the two ways interact constantly with each other: (1) by the extrinsic pathway that begins with trauma to the vascular wall and surrounding tissues and (2) by the intrinsic pathway that begins in the blood itself.

In both the extrinsic and the intrinsic pathways, a series of different plasma proteins called blood- clotting factors play major roles. Most of these are inactive forms of proteolytic enzymes. When converted to the active forms, their enzymatic actions cause the successive, cascading reactions of the clotting process.

Most of the clotting factors are designated by Roman numerals. To indicate the activated form of the factor, a small letter “a” is added after the Roman numeral, such as Factor VIIIa to indicate the activated state of Factor VIII.

Extrinsic Pathway for Initiating Clotting

The extrinsic pathway for initiating the formation of prothrombin activator begins with a traumatized vascular wall or traumatized extravascular tissues that come in contact with the blood. This leads to the following steps:

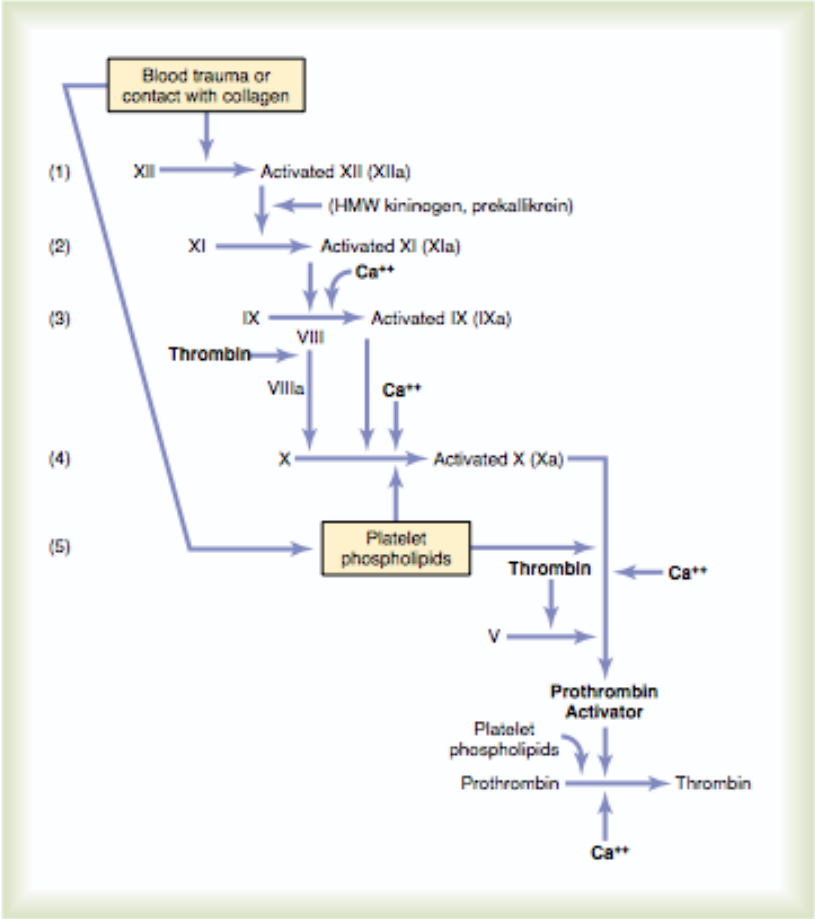
1. Release of tissue factor - Traumatized tissue releases a complex of several factors called tissue factor or tissue thromboplastin. This factor is composed especially of phospholipids from the membranes of the tissue plus a lipoprotein complex that functions mainly as a proteolytic enzyme.

2. Activation of Factor X—role of Factor VII and tissue factor. The lipoprotein complex of tissue factor further complexes with blood coagulation Factor VII and, in the presence of calcium ions, acts enzymatically on Factor X to form activated Factor X (Xa).

3. Effect of activated Factor X (Xa) to form prothrombin activator—role of Factor V. The activated Factor X combines immediately with tissue phospholipids as well as with Factor V to form the complex called prothrombin activator. Within a few seconds, in the presence of calcium ions (Ca2+), this splits prothrombin to form thrombin, and the clotting process proceeds. At first, the Factor V in the prothrombin activator complex is inactive, but once clotting begins and thrombin begins to form, the proteolytic action of thrombin activates Factor V. This then becomes an additional strong accelerator of prothrombin activation. Thus, in the final prothrombin activator complex, activated Factor X is the actual protease that causes splitting of prothrombin to form thrombin; activated Factor V greatly accelerates this protease activity, and platelet phospholipids act as a vehicle that further accelerates the process. Note especially the positive feedback effect of thrombin, acting through Factor V, to accelerate the entire process once it begins.

Intrinsic Pathway for Initiating Clotting

The second mechanism for initiating formation of prothrombin activator, and therefore for initiating clotting, begins with trauma to the blood itself or exposure of the blood to collagen from a



traumatized blood vessel wall. Then the process continues through the series of cascading reactions.

1. Blood trauma causes (1) activation of Factor XII and (2) release of platelet phospholipids.
2. Activation of Factor XI. The activated Factor XII acts enzymatically on Factor XI to activate this factor as well. This reaction also requires HMW (high-molecular-weight) kininogen and is accelerated by prekallikrein.
3. Activation of Factor IX by activated Factor XI.
4. Activation of Factor X—role of Factor VIII. The activated Factor IX, acting in concert with activated Factor VIII and with the platelet phospholipids and factor 3 from the traumatized platelets, activates Factor X.
5. Action of activated Factor X to form prothrombin activator—role of Factor V. This step in the intrinsic pathway is the same as the last step in the extrinsic pathway. That is, activated Factor X combines with Factor V and platelet or tissue phospholipids to form the complex called prothrombin activator. The prothrombin activator in turn initiates within seconds the cleavage of prothrombin to form thrombin, thereby setting into motion the final clotting process, as described earlier.

Conversion of Prothrombin to Thrombin

The prothrombin activator, in the presence of sufficient amounts of ionic Ca2+, causes conversion of prothrombin to thrombin. The thrombin causes polymerization of fibrinogen molecules into fibrin fibers.

Platelets also play an important role in the conversion of prothrombin to thrombin because much of the prothrombin first attaches to prothrombin receptors on the platelets already bound to the damaged tissue.

Prothrombin is formed continually by the liver, and it is continually being used throughout the body for blood clotting. If the liver fails to produce prothrombin, in a day or so prothrombin concentration in the plasma falls too low to provide normal blood coagulation.

Vitamin K is required by the liver for normal formation of prothrombin as well as for formation of a few other clotting factors. Therefore, either lack of vitamin K or the presence of liver disease that prevents normal prothrombin formation can decrease the prothrombin level so low that a bleeding tendency results.

Conversion of Fibrinogen to Fibrin— Formation of the Clot

Fibrinogen is formed in the liver, and liver disease can decrease the concentration of circulating fibrinogen.

Action of Thrombin on Fibrinogen to Form Fibrin

Thrombin is a protein enzyme with weak proteolytic capabilities. It acts on fibrinogen to remove four low-molecular- weight peptides from each molecule of fibrinogen, forming one molecule of fibrin monomer that has the automatic capability to polymerize with other fibrin monomer molecules to form fibrin fibers which polymerize into long fibrin fibers that constitute the reticulum of the blood clot.

Fibrin-stabilizing factor is present in small amounts in normal plasma globulins but is also released from platelets entrapped in the clot. Before fibrin-stabilizing factor can have an effect on the fibrin fibers, it must itself be activated. The same thrombin that causes fibrin formation also

activates the fibrin-stabilizing factor. Then this activated substance operates as an enzyme to cause covalent bonds between more and more of the fibrin monomer molecules, as well as multiple cross- linkages between adjacent fibrin fibers, thus adding tremendously to the three-dimensional strength of the fibrin meshwork.

Blood Clot.

The clot is composed of a meshwork of fibrin fibers running in all directions and entrapping blood cells, platelets, and plasma. The fibrin fibers also adhere to damaged surfaces of blood vessels; therefore, the blood clot becomes adherent to any vascular opening and thereby prevents further blood loss.

Clot Retraction—Serum

Within a few minutes after a clot is formed, it begins to contract and usually expresses most of the fluid from the clot. The fluid expressed is called serum because all its fibrinogen and most of the other clotting factors have been removed; in this way, serum differs from plasma. Serum cannot clot because it lacks these factors.

Platelets are necessary for clot retraction to occur. Furthermore, platelets entrapped in the clot continue to release procoagulant substances, one of the most important of which is fibrin-stabilizing factor, which causes more and more cross-linking bonds between adjacent fibrin fibers. In addition, the platelets themselves contribute directly to clot contraction by activating platelet thrombosthenin, actin, and myosin molecules, which are all contractile proteins in the platelets and cause strong contraction of the platelet spicules attached to the fibrin. This also helps compress the fibrin meshwork into a smaller mass. The contraction is activated and accelerated by thrombin as well as by calcium ions released from calcium stores in the mitochondria, endoplasmic reticulum, and Golgi apparatus of the platelets.

As the clot retracts, the edges of the broken blood vessel are pulled together, thus contributing still further to the ultimate state of hemostasis.

13. Anticlotting mechanism

Prevention of Blood Clotting in the Normal Vascular System— Intravascular Anticoagulants
Endothelial Surface Factors

Probably the most important factors for preventing clotting in the normal vascular system are (1) the smoothness of the endothelial cell surface, which prevents contact activation of the intrinsic clotting system; (2) a layer of glycocalyx on the endothelium, which repels clotting factors and platelets, thereby preventing activation of clotting; and (3) a protein bound with the endothelial membrane, thrombomodulin, which binds thrombin. Not only does the binding of thrombin with thrombomodulin slow the clotting process by removing thrombin, but the thrombomodulin-thrombin complex also activates a plasma protein, protein C, that acts as an anticoagulant by inactivating activated Factors V and VIII.

When the endothelial wall is damaged, its smoothness and its glycocalyx-thrombomodulin layer are lost, which activates both Factor XII and the platelets, thus setting off the intrinsic pathway of clotting. If Factor XII and platelets come in contact with the subendothelial collagen, the activation is even more powerful.

Antithrombin Action of Fibrin and Antithrombin III

Among the most important anticoagulants in the blood itself are those that remove thrombin from the blood. The most powerful of these are (1) the fibrin fibers that themselves are formed during the process of clotting and (2) an alpha-globulin called antithrombin III or antithrombin-heparin cofactor.

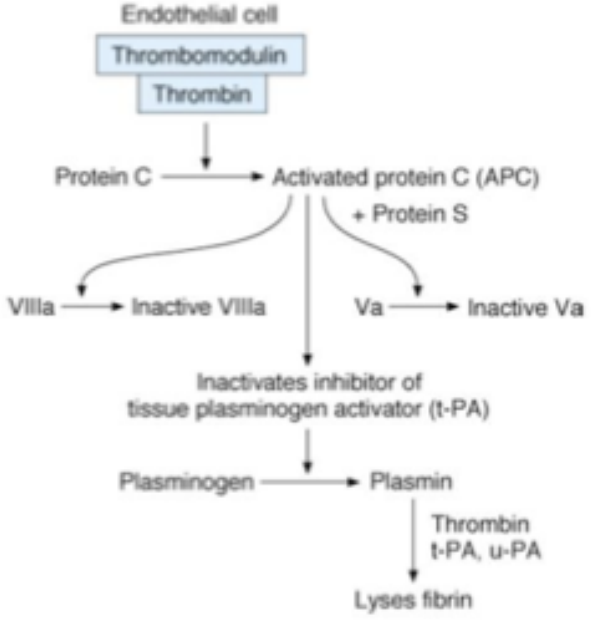
The thrombin that does not adsorb to the fibrin fibers soon combines with antithrombin III, which further blocks the effect of the thrombin on the fibrinogen and then also inactivates the thrombin .

Heparin

Heparin is another powerful anticoagulant, but its concentration in the blood is normally low, so that only under special physiologic conditions does it have significant anticoagulant effects. By itself, it has little or no anticoagulant properties, but when it combines with antithrombin III, the effectiveness of antithrombin III for removing thrombin increases, and thus it acts as an anticoagulant. Therefore, in the presence of excess heparin, removal of free thrombin from the circulating blood by antithrombin III is almost instantaneous.

The complex of heparin and antithrombin III removes several other activated coagulation factors in addition to thrombin, further enhancing the effectiveness of anticoagulation. The others include activated Factors XII, XI, X, and IX.

Heparin is produced by many different cells of the body, but especially large quantities are formed by the basophilic mast cells located in the pericapillary connective tissue throughout the body. These cells continually secrete small quantities of heparin that diffuse into the circulatory system. The basophil cells of the blood, which are functionally almost identical to the mast cells, release small quantities of heparin into the plasma.



Lysis of Blood Clots—Plasmin

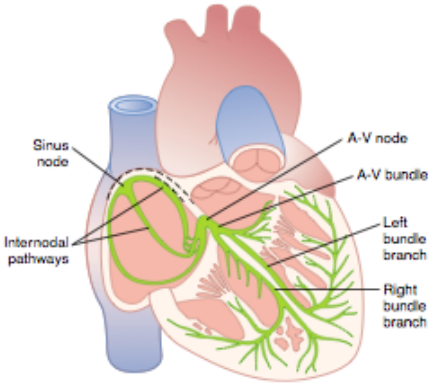
The plasma proteins contain a plasminogen (or profibrinolysin) that, when activated, becomes a substance called plasmin (or fibrinolysin). Plasmin is a proteolytic enzyme that resembles trypsin, the most important proteolytic digestive enzyme of pancreatic secretion. Plasmin digests fibrin fibers and some other protein coagulants such as fibrinogen, Factor V, Factor VIII, prothrombin, and Factor XII. Therefore, whenever plasmin is formed, it can cause lysis of a clot by

destroying many of the clotting factors, thereby sometimes even causing hypocoagulability of the blood.

Activation of Plasminogen to Form Plasmin: Then Lysis of Clots.

When a clot is formed, a large amount of plasminogen is trapped in the clot along with other plasma proteins. This will not become plasmin or cause lysis of the clot until it is activated. The injured tissues and vascular endothelium very slowly release a powerful activator called tissue plasminogen activator (t-PA) that, after the clot has stopped the bleeding, eventually converts plasminogen to plasmin, which in turn removes the remaining unnecessary blood clot. In fact, many small blood vessels in which blood flow has been blocked by clots are reopened by this mechanism.

14. Conduction system of the heart



Specialized Excitatory and Conductive System of the Heart

Sinus (Sinoatrial) Node

It is located in the superior posterolateral wall of the right atrium immediately below and slightly lateral to the opening of the superior vena cava. The sinus nodal fibers connect directly with the atrial muscle fibers, so that any action potential that begins in the sinus node spreads immediately into the atrial muscle wall.

Automatic Electrical Rhythmicity of the Sinus Fibers

Some cardiac fibers have the capability of self-excitation. For this reason, the sinus node ordinarily controls the rate of beat of the entire heart. Note (figure to the right) that the "resting membrane potential" of the sinus nodal fiber between discharges has a negativity of about - 55 to -60 millivolts, in comparison with -85 to -90 millivolts for the ventricular muscle fiber. The cause of this lesser negativity is that the cell membranes of the sinus fibers are naturally leaky to sodium and calcium ions, and positive charges of the entering sodium and calcium ions neutralize much of the intracellular negativity.

That cardiac muscle has three types of membrane ion channels that play important roles in causing the voltage changes of the action potential. They are (1) fast sodium channels, (2) slow sodiumcalcium channels, and (3) potassium channels. Opening of the fast sodium channels for a few 10,000ths of a second is responsible for the rapid upstroke spike of the action potential observed in ventricular muscle, because of rapid influx of positive sodium ions to the interior of the fiber. Then the "plateau" of the ventricular action potential is caused primarily by slower opening of the slow sodium-calcium channels, which lasts for about 0.3 second. Finally, opening of potassium channels allows diffusion of large amounts of positive potassium ions in the outward direction through the fiber membrane and returns the membrane potential to its resting level.

But there is a difference in the function of these channels in the sinus nodal fiber because the "resting" potential is much less negative—only -55 millivolts in the nodal fiber instead of the -90 millivolts in the ventricular muscle fiber. At this level of -55 millivolts, the fast sodium channels mainly have already become "inactivated," which means that they have become blocked. The cause of this is that any time the membrane potential remains less negative than about -55 millivolts for more than a few milliseconds, the inactivation gates on the inside of the cell membrane that close the fast sodium channels become closed and remain so. Therefore, only the slow sodium-calcium channels can open (i.e., can become "activated") and thereby cause the action potential. As a result, the atrial nodal action potential is slower to develop than the action potential of the ventricular muscle.

Self-Excitation of Sinus Nodal Fibers

Because of the high sodium ion concentration in the extracellular fluid outside the nodal fiber, as well as a moderate number of already open sodium channels, positive sodium ions from outside the fibers normally tend to leak to the inside. Therefore, between heartbeats, influx of positively charged sodium ions causes a slow rise in the resting membrane potential in the positive direction. Thus, the "resting" potential gradually rises between each two heartbeats. When the potential reaches a threshold voltage of about -40 millivolts, the sodium-calcium channels become "activated," thus causing the action potential. Therefore, basically, the inherent leakiness of the sinus nodal fibers to sodium and calcium ions causes their self-excitation.

Why does this leakiness to sodium and calcium ions not cause the sinus nodal fibers to remain depolarized all the time?

The answer is that two events occur during the course of the action potential to prevent this. First, the sodium-calcium channels become inactivated (i.e., they close) within about 100 to 150 milliseconds after opening, and second, at about the same time, greatly increased numbers of potassium channels open. Therefore, influx of positive calcium and sodium ions through the sodium-calcium channels ceases, while at the same time large quantities of positive potassium ions diffuse out of the fiber. Both of these effects reduce

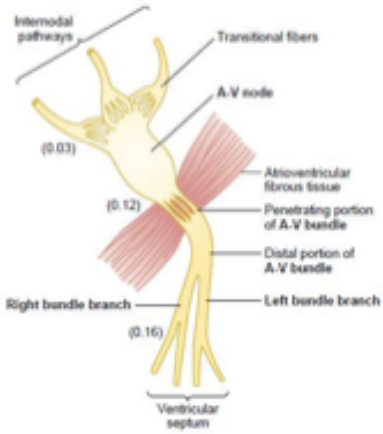
the intracellular potential back to its negative resting level and therefore terminate the action potential. Furthermore, the potassium channels remain open for another few tenths of a second, temporarily continuing movement of positive charges out of the cell, with resultant excess negativity inside the fiber; this is called hyperpolarization.

Last, we must explain why this new state of hyperpolarization is not maintained forever. The reason is that during the next few tenths of a second after the action potential is over, progressively more and more potassium channels close. The inward-leaking sodium and calcium ions once again overbalance the outward flux of potassium ions, and this causes the “resting” potential to drift upward once more, finally reaching the threshold level for discharge at a potential of about -40 millivolts. Then the entire process begins again.

15. Cardiac automaticity

Automatic Electrical Rhythmicity of the Sinus Fibers

Some cardiac fibers have the capability of self-excitation, a process that can cause automatic rhythmical discharge and contraction. This is especially true of the fibers of the heart's specialized conducting system, including the fibers of the sinus node. For this reason, the sinus node ordinarily controls the rate of beat of the entire heart.



Mechanism of Sinus Nodal Rhythmicity

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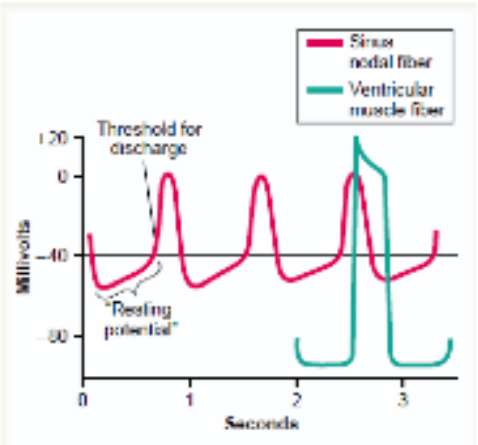


Self-Excitation of Sinus Nodal Fibers

See question 14.

16. Spread and retreat of excitation wavefront

Internodal Pathways and Transmission of the Cardiac Impulse Through the Atria

The ends of the sinus nodal fibers connect directly with surrounding atrial muscle fibers. Therefore, action potentials originating in the sinus node travel outward into these atrial muscle fibers. In this way, the action potential spreads through the entire atrial muscle mass and, eventually, to the A-V node. The velocity of conduction in most atrial muscle is about 0.3 m/sec, but conduction is more rapid, about 1 m/sec, in several small bands of atrial fibers. One of these, called the anterior interatrial band, passes through the anterior walls of the atria to the left atrium. In addition, three other small bands curve through the anterior, lateral, and posterior atrial walls and terminate in the A-V node; these are called, respectively, the anterior, middle, and posterior internodal pathways. The cause of more rapid velocity of conduction in these bands is the presence of specialized conduction fibers. These fibers are similar to even more rapidly conducting "Purkinje fibers" of the ventricles

Atrioventricular Node, and Delay of Impulse Conduction from the Atria to the Ventricles

The atrial conductive system is organized so that the cardiac impulse does not travel from the atria into the ventricles too rapidly; this delay allows time for the atria to empty their blood into the ventricles before ventricular contraction begins. It is primarily the A-V node and its adjacent conductive fibers that delay this transmission into the ventricles.

The A-V node is located in the posterior wall of the right atrium immediately behind the tricuspid valve. The impulse, after traveling through the internodal pathways, reaches the A-V node about 0.03 second after its origin in the sinus node. Then there is a delay of another 0.09 second in the A-V node itself before the impulse enters the penetrating portion of the A-V bundle, where it passes into the ventricles. A final delay of another 0.04 second occurs mainly in this penetrating A-V bundle, which is composed of multiple small fascicles passing through the fibrous tissue separating the atria from the ventricles.

Thus, the total delay in the A-V nodal and A-V bundle system is about 0.13 second. This, in addition to the initial conduction delay of 0.03 second from the sinus node to the A-V node, makes a total delay of 0.16 second before the excitatory signal finally reaches the contracting muscle of the ventricles.

Rapid Transmission in the Ventricular Purkinje System

Special Purkinje fibers lead from the A-V node through the A-V bundle into the ventricles. Except for the initial portion of these fibers where they penetrate the A-V fibrous barrier, they have functional characteristics that are quite the opposite of those of the A-V nodal fibers. They are very large fibers, even larger than the normal ventricular muscle fibers, and they transmit action potentials at a velocity of 1.5 to 4.0 m/sec, a velocity about 6 times that in the usual ventricular muscle and 150 times that in some of the A-V nodal fibers. This allows almost instantaneous transmission of the cardiac impulse throughout the entire remainder of the ventricular muscle.

The rapid transmission of action potentials by Purkinje fibers is believed to be caused by a very high level of permeability of the gap junctions at the intercalated discs between the successive cells that make up the Purkinje fibers. Therefore, ions are transmitted easily from one cell to the next, thus enhancing the velocity of transmission. The Purkinje fibers also have very few myofibrils, which means that they contract little or not at all during the course of impulse transmission.

One-Way Conduction Through the A-V Bundle

A special characteristic of the A-V bundle is the inability, of action potentials to travel backward from the ventricles to the atria. This prevents re-entry of cardiac impulses by this route from the ventricles to the atria, allowing only forward conduction from the atria to the ventricles.

Furthermore, it should be recalled that everywhere, except at the A-V bundle, the atrial muscle is separated from the ventricular muscle by a continuous fibrous barrier. This barrier normally acts as an insulator to prevent passage of the cardiac impulse between atrial and ventricular muscle through any other route besides forward conduction through the A-V bundle itself. (In rare instances, an abnormal muscle bridge does penetrate the fibrous barrier elsewhere

besides at the A-V bundle. Under such conditions, the cardiac impulse can re-enter the atria from the ventricles and cause a serious cardiac arrhythmia.)

Distribution of the Purkinje Fibers in the Ventricles—The Left and Right Bundle Branches

After penetrating the fibrous tissue between the atrial and ventricular muscle, the distal portion of the A-V bundle passes downward in the ventricular septum for 5 to 15 millimeters toward the apex of the heart. Then the bundle divides into left and right bundle branches that lie beneath the endocardium on the two respective sides of the ventricular septum. Each branch spreads downward toward the apex of the ventricle, progressively dividing into smaller branches. These branches in turn course sidewise around each ventricular chamber and back toward the base of the heart. The ends of the Purkinje fibers penetrate about one third the way into the muscle mass and finally become continuous with the cardiac muscle fibers.

From the time the cardiac impulse enters the bundle branches in the ventricular septum until it reaches the terminations of the Purkinje fibers, the total elapsed time averages only 0.03 second. Therefore, once the cardiac impulse enters the ventricular Purkinje conductive system, it spreads almost immediately to the entire ventricular muscle mass.

Transmission of the Cardiac Impulse in the Ventricular Muscle

Once the impulse reaches the ends of the Purkinje fibers, it is transmitted through the ventricular muscle mass by the ventricular muscle fibers themselves. The velocity of transmission is now only 0.3 to 0.5 m/sec, one sixth that in the Purkinje fibers.

The cardiac muscle wraps around the heart in a double spiral, with fibrous septa between the spiraling layers; therefore, the cardiac impulse does not neces-sarily travel directly outward toward the surface of the heart but instead angulates toward the surface along the directions of the spirals. Because of this, transmission from the endocardial surface to the epicardial surface of the ventricle requires as much as another 0.03 second, approximately equal to the time required for transmission through the entire ventricular portion of the Purkinje system. Thus, the total time for transmission of the cardiac impulse from the initial bundle branches to the last of the ventricular muscle fibers in the normal heart is about 0.06 second.

17. Electric vector of the heart. Vectocardiography.

Use of Vectors to Represent Electrical Potentials

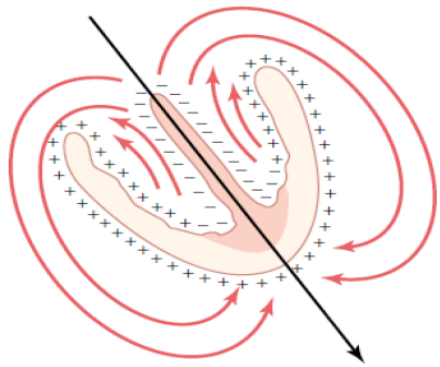
A vector is an arrow that points in the direction of the electrical potential generated by the current flow, with the arrowhead in the positive direction. Also, by convention, the length of the arrow is drawn proportional to the voltage of the potential.

Electrical current flows between the depolarized areas inside the heart and the nondepolarized areas on the outside of the heart. Some current also flows inside the heart chambers directly from the depolarized areas toward the still polarized areas. Overall, considerably more current flows downward from the base of the ventricles toward the apex than in the upward direction.

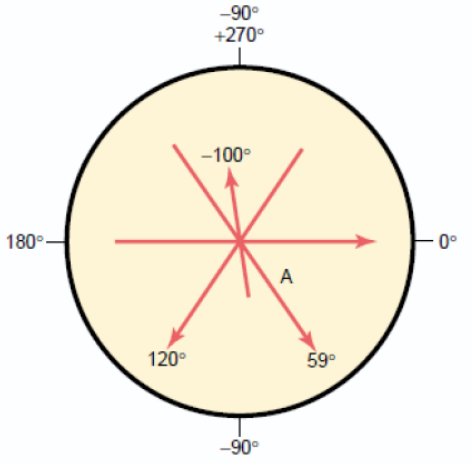
Therefore, the summated vector of the generated potential at this particular instant, called the instantaneous mean vector, is represented by the long black arrow drawn through the center of the ventricles in a direction from base toward apex.

In a normal heart, the average direction of the vector during spread of the depolarization wave through the ventricles, called the mean QRS vector, is about +59 degrees, which is shown by vector A drawn through the center of figure on the right in the +59-degree direction.

This means that during most of the depolarization wave, the apex of the heart remains positive with respect to the base of the heart.



Mean vector through the partially depolarized ventricles.



Vectocardigram

The so-called vectorcardiogram depicts these changes at different times during the cardiac cycle

18. Specific features of cardiac metabolism

Under resting conditions, cardiac muscle normally consumes fatty acids to supply most of its energy instead of carbohydrates (about 70 per cent of the energy is derived from fatty acids). However, as is also true of other tissues, under anaerobic or ischemic conditions, cardiac metabolism must call on anaerobic glycolysis mechanisms for energy. Unfortunately, glycolysis consumes tremendous quantities of the blood glucose and at the same time forms large amounts of lactic acid in the cardiac tissue, which is probably one of the causes of cardiac pain in cardiac ischemic conditions.

As is true in other tissues, more than 95 per cent of the metabolic energy liberated from foods is used to form ATP in the mitochondria. This ATP in turn acts as the conveyer of energy for cardiac muscular contraction and other cellular functions. In severe coronary ischemia, the ATP degrades first to adenosine diphosphate, then to adenosine monophosphate and adenosine. Because the cardiac muscle cell membrane is slightly permeable to adenosine, much of this can diffuse from the muscle cells into the circulating blood.

The released adenosine is believed to be one of the substances that causes dilation of the coronary arterioles during coronary hypoxia. However, loss of adenosine also has a serious cellular consequence. Within as little as 30 minutes of severe coronary ischemia, as occurs after a myocardial infarct, about one half of the adenine base can be lost from the affected cardiac muscle cells. Furthermore, this loss can be replaced by new synthesis of adenine at a rate of only 2 per cent per hour. Therefore, once a serious bout of coronary ischemia has persisted for 30 or more minutes, relief of the ischemia may be too late to save the lives of the cardiac cells. This almost certainly is one of the major causes of cardiac cellular death during myocardial ischemia.

19. Heart as a pump

Excitation-Contraction Coupling—Function of Calcium Ions and the Transverse Tubules

The term "excitation-contraction coupling" refers to the mechanism by which the action potential causes the myofibrils of muscle to contract. There are differences in this mechanism in cardiac muscle that have important effects on the characteristics of cardiac muscle contraction. As is true for skeletal muscle, when an action potential passes over the cardiac muscle membrane, the action potential spreads to the interior of the cardiac muscle fiber along the membranes of the transverse (T) tubules. The T tubule action potentials in turn act on the membranes of the longitudinal sarcoplasmic tubules to cause release of calcium ions into the muscle sarcoplasm from the sarcoplasmic reticulum. In another few thousandths of a second, these calcium ions diffuse into the myofibrils and catalyze the chemical reactions that promote sliding of the actin and myosin filaments along one another; this produces the muscle contraction. Thus far, this mechanism of excitation-contraction coupling is the same as that for skeletal muscle, but there is a second effect that is quite different. In addition to the calcium ions that are released into the sarcoplasm from the cisternae of the sarcoplasmic reticulum, a large quantity of extra calcium ions also diffuses into the sarcoplasm from the T tubules themselves at the time of the action potential. Indeed, without this extra calcium from the T tubules, the strength of cardiac muscle contraction would be reduced considerably because the sarcoplasmic reticulum of cardiac muscle is less well developed than that of skeletal muscle and does not store enough calcium to provide full contraction. The strength of contraction of cardiac muscle depends to a great extent on the concentration of calcium ions in the extracellular fluids. The reason for this is that the openings of the T tubules pass directly through the cardiac muscle cell membrane into the extracellular spaces surrounding the cells, allowing the same extracellular fluid that is in the cardiac muscle interstitium to percolate through the T tubules as well. Consequently, the quantity of calcium ions in the T tubule system—that is, the availability of calcium ions to cause cardiac muscle contraction—depends to a great extent on the extracellular fluid calcium ion concentration. At the end of the plateau of the cardiac action potential, the influx of calcium ions to the interior of the muscle fiber is suddenly cut off, and the calcium ions in the sarcoplasm are rapidly pumped back out of the muscle fibers into both the sarcoplasmic reticulum and the T tubule–extracellular fluid space. As a result, the contraction ceases until a new action potential comes along.

The Cardiac Cycle

The cardiac events that occur from the beginning of one heartbeat to the beginning of the next are called the cardiac cycle. Each cycle is initiated by spontaneous generation of an action potential in the sinus node. This node is located in the superior lateral wall of the right atrium near the opening of the superior vena cava, and the action potential travels from here rapidly through both atria and then through the A-V bundle into the ventricles. Because of this special arrangement of the conducting system from the atria into the ventricles, there is a delay of more than 0.1 second during passage of the cardiac impulse from the atria into the ventricles.This allows the atria to contract ahead of ventricular contraction, thereby pumping blood into the ventricles before the strong ventricular contraction begins.Thus, the atria act as primer pumps for the ventricles, and the ventricles in turn provide the major source of power for moving blood through the body's vascular system.

Diastole and Systole

The cardiac cycle consists of a period of relaxation called diastole, during which the heart fills with blood, followed by a period of contraction called systole.

Function of the Atria as Primer Pumps

Blood normally flows continually from the great veins into the atria; about 80 per cent of the blood flows directly through the atria into the ventricles even before the atria contract. Then, atrial contraction usually causes an additional 20 per cent filling of the ventricles. Therefore, the atria simply function as primer pumps that increase the ventricular pumping effectiveness as much as 20 per cent. However, the heart can continue to operate under most conditions even without this extra 20 per cent effectiveness because it normally has the capability of pumping 300 to 400 per

cent more blood than is required by the resting body.Therefore, when the atria fail to function, the difference is unlikely to be noticed unless a person exercises; then acute signs of heart failure occasionally develop, especially shortness of breath.

Function of the Ventricles as Pumps

Filling of the Ventricles. During ventricular systole, large amounts of blood accumulate in the right and left atria because of the closed A-V valves. Therefore, as soon as systole is over and the ventricular pressures fall again to their low diastolic values, the moderately increased pressures that have developed in the atria during ventricular systole immediately push the A-V valves open and allow blood to flow rapidly into the ventricles, as shown by the rise of the left ventricular volume curve.This is called the period of rapid filling of the ventricles. The period of rapid filling lasts for about the first third of diastole. During the middle third of diastole, only a small amount of blood normally flows into the ventricles; this is blood that continues to empty into the atria from the veins and passes through the atria directly into the ventricles. During the last third of diastole, the atria contract and give an additional thrust to the inflow of blood into the ventricles; this accounts for about 20 per cent of the filling of the ventricles during each heart cycle.

20. Differences between left and right heart

The difference between the two ventricles has to do with their related functions Since the left ventricle has to pump blood much further (all the way around the body, including right up to the top of the head and all the way to the toes) it has to do more work than the right does (which only has to pump blood as far as the lungs and back to the heart). So the muscular walls of the left ventricle are much thicker to produce the necessary force required for the more strenuous job it has to do. Another difference is seen in the valves. The valves between the ventricles and the atria are called the atrioventricular valves. The one between the right atria and ventricle has three parts, or cusps, and is called the tricuspid valve. The one in the left side of the heart between the left atria and ventricle has two cusps and is called the bicuspid (or the mitral valve). To sum it all up: The right ventricle pumps blood to both lungs, and the left ventricle pumps blood to all the other body tissues.

Signs of:

- Left-sided failure

Common respiratory signs are tachypnea (increased rate of breathing) and increased work of breathing (non-specific signs of respiratory distress). Rales or crackles, heard initially in the lung bases, and when severe, throughout the lung fields suggest the development of pulmonary edema (fluid in the alveoli).

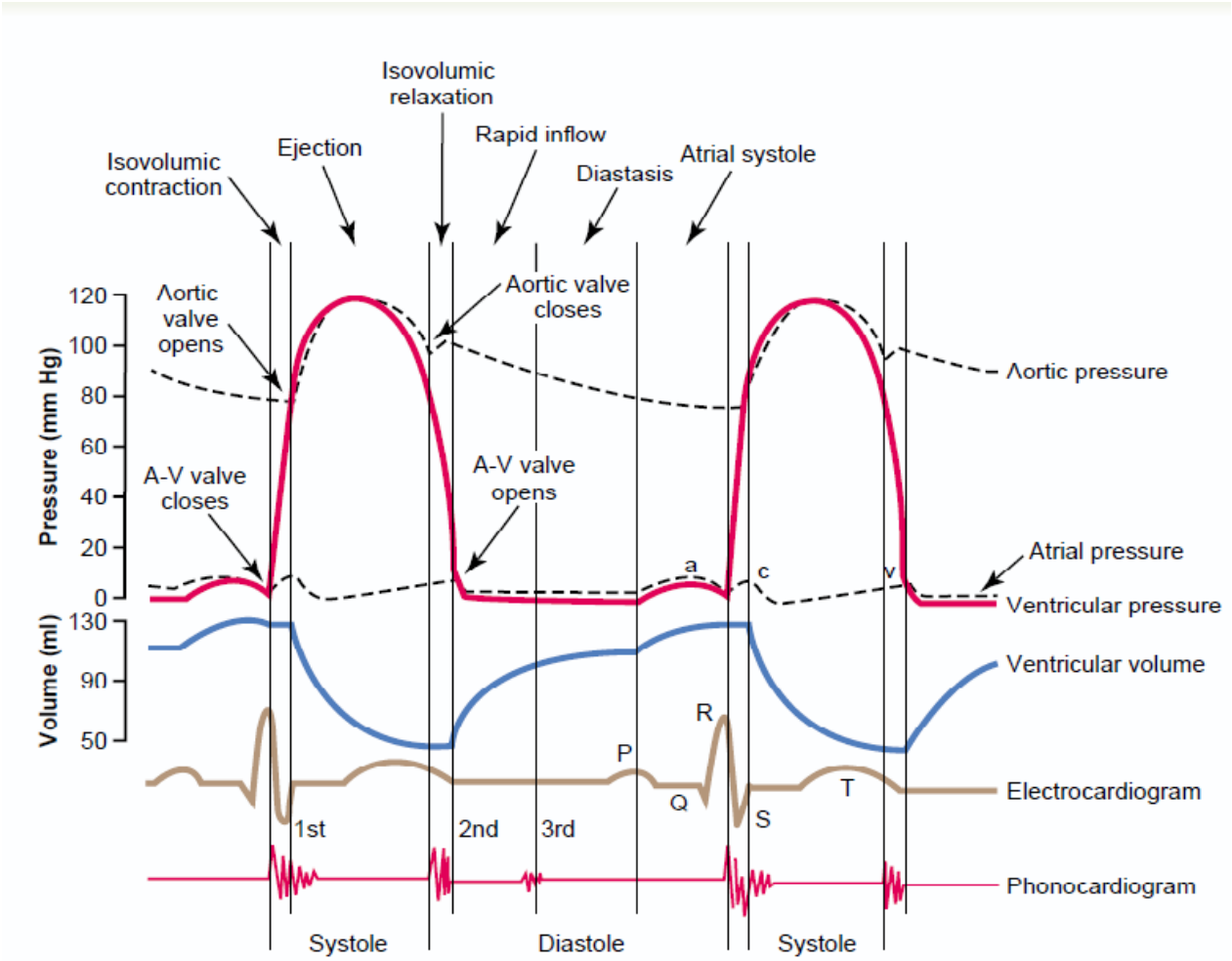
- Right-sided failure

Physical examination can reveal pitting peripheral edema, ascites, and hepatomegaly. Jugular venous pressure is frequently assessed as a marker of fluid status, which can be accentuated by the hepatojugular reflux. If the right ventriclar pressure is increased, a parasternal heave may be present, signifying the compensatory increase in contraction strength.

21. Determinants of cardiac performance: preload, afterload, inotropy

Concepts of Preload and Afterload

In assessing the contractile properties of muscle, it is important to specify the degree of tension on the muscle when it begins to contract, which is called the preload, and to specify the load against which the muscle exerts its contractile force, which is called the afterload. For cardiac contraction, the preload is usually considered to be the end-diastolic pressure when the ventricle



has become filled. The afterload of the ventricle is the pressure in the artery leading from the ventricle. (Sometimes the afterload is loosely considered to be the resistence in the circulation rather than the pressure.) The importance of the concepts of preload and afterload is that in many abnormal functional states of the heart or circulation, the pressure during filling of the ventricle (the preload), the arterial pressure against which the ventricle must contract (the afterload), or both are severely altered from normal.

Inotropism

Preload or afterload-independent changes in myocardial contraction force are referred to as contractility or inotropism. It increases in response to norepinephrine (NE) and epinephrine (E) as well as to increases in heart rate (β1-adrenoceptor-mediated, positive inotropic effect and frequency inotropism, respectively. This causes a number of effects, particularly, an increase in isovolumic pressure peaks. The heart can therefore pump against increased pressure levels and/or eject larger SVs (at the expense of the ESV).

While changes in the preload only affect the force of contraction, changes in contractility also affect the velocity of contraction. The steepest increase in isovolumic pressure per unit time (maximum dP/dt) is therefore used as a measure of contractility in clinical practice. dP/dt is increased E and NE and decreased by bradycardia or heart failure.

22. Cardiac reserve. Heart failure.

Cardiac Reserve

The maximum percentage that the cardiac output can increase above normal is called the cardiac reserve. Thus, in the healthy young adult, the cardiac reserve is 300 to 400 per cent. In athletically trained persons, it is occasionally 500 to 600 per cent. But in heart failure, there is no cardiac reserve. Any factor that prevents the heart from pumping blood satisfactorily will decrease the cardiac reserve. This can result from ischemic heart disease, primary myocardial disease, vitamin deficiency that affects cardiac muscle, physical damage to the myocardium, valvular heart disease, and many other factors.

Diagnosis of Low Cardiac Reserve—Exercise Test.

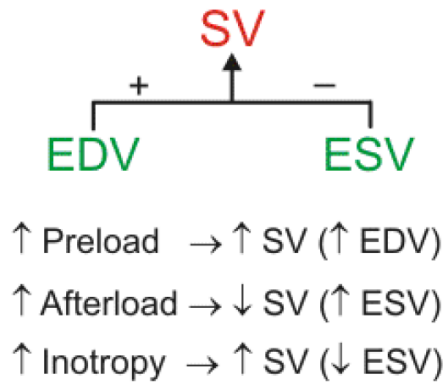
As long as persons with low cardiac reserve remain in a state of rest, they usually will not know that they have heart disease. However, a diagnosis of low cardiac reserve usually can be easily made by requiring the person to exercise either on a treadmill or by walking up and down steps, either of which requires greatly increased cardiac output. The increased load on the heart rapidly uses up the small amount of reserve that is available, and the cardiac output soon fails to rise high enough to sustain the body's new level of activity.

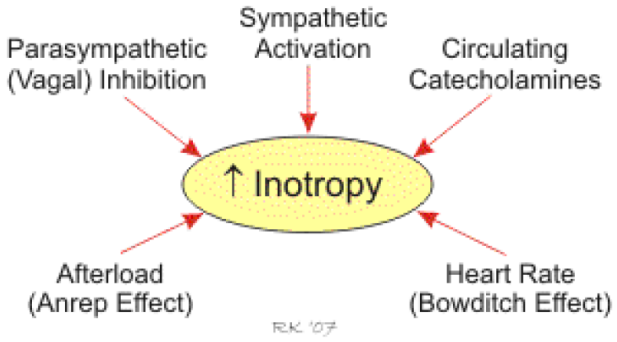
The acute effects are as follows:

1. Immediate and sometimes extreme shortness of breath (dyspnea) resulting from failure of the heart to pump sufficient blood to the tissues, thereby causing tissue ischemia and creating a sensation of air hunger

2. Extreme muscle fatigue resulting from Muscle ischemia, thus limiting the person's ability to continue with the exercise

3. Excessive increase in heart rate because the nervous reflexes to the heart overreact in an attempt to overcome the inadequate cardiac output. Exercise tests are part of the armamentarium of the cardiologist. These tests take the place of cardiac output measurements that cannot be made with ease in most clinical settings.





Note - In the human heart, an abrupt increase in afterload can cause a small increase in inotropy (Anrep effect) by a mechanism that is not fully understood.

Note #2 - Sympathetic inv, has a positive inotropic affect on ventricles, however parasympathetic inv, has a very little – inotropic affect on ventricles but more significant affect on the atria.

Heart failure

The term "cardiac failure" means simply failure of the heart to pump enough blood to satisfy the needs of the body. It can be acute and associated with sudden death, or chronic. The failure may involve primarily the right ventricle, but much more commonly it involves the larger, thicker left ventricle or both ventricles.

In acute heart failure cardiac output falls precariously low. So, many of the circulatory reflexes are immediately activated.The best known of these is the baroreceptor reflex, which is activated by diminished arterial pressure. It is probable that the chemoreceptor reflex, the central nervous system ischemic response, and even reflexes that originate in the damaged heart also contribute to activating the sympathetic nervous system and parasympathetic nervous signals to the heart become reciprocally inhibited at the same time.

Strong sympathetic stimulation has two major effects on the circulation: first on the heart itself, and second on the peripheral vasculature. If all the ventricular musculature is diffusely damaged but is still functional, sympathetic stimulation strengthens this damaged musculature. If part of the muscle is nonfunctional and part of it is still normal, the normal muscle is strongly stimulated by sympathetic stimulation, in this way partially compensating for the nonfunctional muscle. Thus, the heart, one way or another, becomes a stronger pump. After sympathetic compensation about twofold elevation of the very low cardiac output curve. Sympathetic stimulation also increases venous return because it increases the tone of most of the blood vessels of the circulation, especially the veins, raising the mean systemic filling pressure to 12 to 14 mm Hg, almost 100 per cent above normal. This increased filling pressure greatly increases the tendency for blood to flow from the veins back into the heart. Therefore, the damaged heart becomes primed with more inflowing blood than usual, and the right atrial pressure rises still further, which helps the heart to pump still larger quantities of blood.

In chronic heart failure (congestive heart failure), cardiac output is initially inadequate during exercise but adequate at rest. As the disease progresses, the output at rest also becomes inadequate. There are two types of failure, systolic and diastolic. In systolic failure, stroke volume is reduced because ventricular contraction is weak. This causes an increase in the end-systolic ventricular volume, so that the ejection fraction – the fraction of the blood in the ventricles that is ejected during systole – falls from 65% to as low as 20%. The initial response to failure is activation of the genes that cause cardiac myocytes to hypertrophy, and thicken of the ventricular wall (cardiac remodeling). The incomplete filling of the arterial system leads to increased discharge of the sympathetic nervous system and increased secretion of renin and aldosterone, so Na+ and water is retained. The responses are initially compensatory, but eventually the failure worsens and the ventricles dilate. In diastolic failure, the ejection fraction is initially maintained but the elasticity of the myocardium is reduced so filling during diastole is reduced. This leads to inadequate stroke volume and the same cardiac remodeling and Na+ and water retention that occur in systolic failure. It should be noted that the inadequate cardiac output in failure may be relative rather than absolute.

Recovery of myocardium after myocardial infacrtion

After a heart becomes suddenly damaged as a result of myocardial infarction, the natural reparative processes of the body begin immediately to help restore normal cardiac function. For instance, a new collateral blood supply begins to penetrate the peripheral portions of the infarcted area of the heart, often causing much of the heart muscle in the fringe areas to become functional again. Also, the undamaged portion of the heart musculature hypertrophies, in this way offsetting much of the cardiac damage. The degree of recovery depends on the type of cardiac damage, and it varies from no recovery to almost complete recovery.

Treatment

Treatment of congestive heart failure is aimed at improving cardiac contractility, treating the symptoms, and decreasing the load on the heart. Currently, the most effective treatment in general use is inhibition of the production of angiotensin II with angiotensin-converting enzyme inhibitors. Blocking the production of angiotensin II or its effects also reduces the circulating aldosterone level and decreases blood pressure, reducing the afterload against which the heart pumps. Digitalis derivatives such as dioxin have classically been used to treat congestive heart failure because of their ability to increase intracellular Ca2+ and hence exert a positive inotropic effect, but they are now used in a secondary role to treat systolic dysfunction and slow the ventricular rate in patients with atrial fibrillation.

23. Cardiac cycle. Phases. Pressure-volume loop.

The Cardiac Cycle

The cardiac events that occur from the beginning of one heartbeat to the beginning of the next are called the cardiac cycle. Each cycle is initiated by spontaneous generation of an action potential in the sinus node which travels from here rapidly through both atria and then through the A-V bundle into the ventricles.

Diastole and Systole

The cardiac cycle consists of a period of relaxation called diastole, during which the heart fills with blood, followed by a period of contraction called systole.

Function of the Atria as Primer Pumps

Blood normally flows continually from the great veins into the atria. Then, atria contract pumping the residual blood into the ventricles. Therefore, the atria simply function as primer pumps that increase the ventricular pumping effectiveness as much as 20 per cent. However, the heart can continue to operate under most conditions even without this extra 20 per cent effectiveness because it normally has the capability of pumping 300 to 400 per cent more blood than is required by the resting body. Therefore, when the atria fail to function, the difference is unlikely to be noticed unless a person exercises; then acute signs of heart failure occasionally develop, especially shortness of breath.

Pressure Changes in the Atria—The a, c, and v Waves

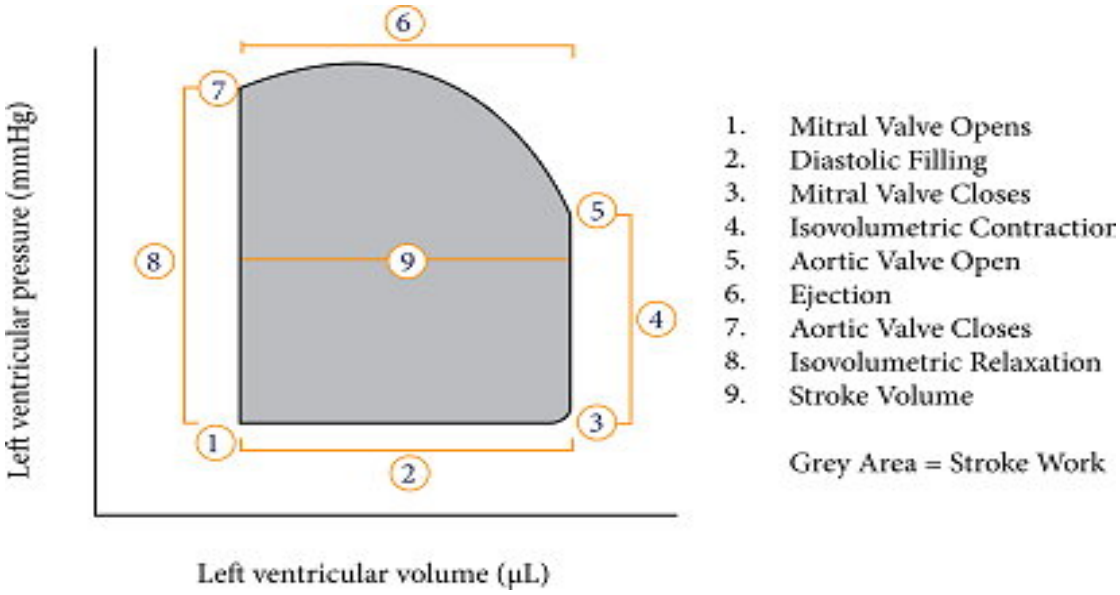
In the atrial pressure curve three minor pressure elevations, called the a, c, and v atrial pressure waves, are noted. The a wave is caused by atrial contraction. Ordinarily, the right atrial pressure increases 4 to 6 mm Hg during atrial contraction, and the left atrial pressure increases about 7 to 8 mm Hg. The c wave occurs when the ventricles begin to contract; it is caused partly by slight backflow of blood into the atria at the onset of ventricular contraction but mainly by bulging of the A-V valves backward toward the atria because of increasing pressure in the ventricles. The v wave occurs toward the end of ventricular contraction; it results from slow flow of blood into the atria from the veins while the A-V valves are closed during ventricular contraction. Then, when ventricular contraction is over, the A-V valves open, allowing this stored atrial blood to flow rapidly into the ventricles and causing the v wave to disappear.

Function of the Ventricles as Pumps

Filling of the Ventricles. During ventricular systole, large amounts of blood accumulate in the right and left atria because of the closed A-V valves. Therefore, as soon as systole is over and the ventricular pressures fall again to their low diastolic values, the moderately increased pressures that have developed in the atria during ventricular systole immediately push the A-V valves open and allow blood to flow rapidly into the ventricles.This is called the period of rapid filling of the ventricles. The period of rapid filling lasts for about the first third of diastole. During the middle third of diastole, only a small amount of blood normally flows into the ventricles; this is blood that continues to empty into the atria from the veins and passes through the atria directly into the ventricles. During the last third of diastole, the atria contract and give an additional thrust to the inflow of blood into the ventricles; this accounts for about 20 per cent of the filling of the ventricles during each heart cycle.

Emptying of the Ventricles During Systole Period of Isovolumic (Isometric) Contraction.

Immediately after ventricular contraction begins, the ventricular pressure rises abruptly causing the A-V valves to close. Then an additional 0.02 to 0.03 second is required for the ventricle to build up sufficient pressure to push the semilunar (aortic and pulmonary) valves open against the pressures in the aorta and pulmonary artery.Therefore, during this period, contraction is occurring in the ventricles, but there is no emptying. This is called the period of isovolumic or isometric contraction, meaning that tension is increasing in the muscle but little or no shortening of the muscle fibers is occurring.



Period of Ejection

When the left ventricular pressure rises slightly above 80 mm Hg (and the right ventricular pressure slightly above 8 mm Hg), the ventricular pressures push the semilunar valves open. Immediately, blood begins to pour out of the ventricles, with about 70 per cent of the blood emptying occurring during the first third of the period of ejection and the remaining 30 per cent emptying during the next two thirds. Therefore, the first third is called the period of rapid ejection, and the last two thirds, the period of slow ejection.

Period of Isovolumic (Isometric) Relaxation

At the end of systole, ventricular relaxation begins suddenly, allowing both the right and left intraventricular pressures to decrease rapidly. The elevated pressures in the distended large arteries that have just been filled with blood from the contracted ventricles immediately push blood back toward the ventricles, which snaps the aortic and pulmonary valves closed. For another 0.03 to 0.06 second, the ventricular muscle continues to relax, even though the ventricular volume does not change, giving rise to the period of isovolumic or isometric relaxation. During this period, the intraventricular pressures decrease rapidly back to their low diastolic levels. Then the A-V valves open to begin a new cycle of ventricular pumping.

End-Diastolic Volume, End-Systolic Volume, and Stroke Volume Output

During diastole, normal filling of the ventricles increases the volume of each ventricle to about 110 to 120 milliliters. This volume is called the end-diastolic volume. Then, as the ventricles empty during systole, the volume decreases about 70 milliliters, which is called the stroke volume output.The remaining volume in each ventricle, about 40 to 50 milliliters, is called the end-systolic volume. The fraction of the end-diastolic volume that is ejected is called the ejection fraction—usually equal to about 60 per cent. When the heart contracts strongly, the end-systolic volume can be decreased to as little as 10 to 20 milliliters. Conversely, when large amounts of blood flow into the ventricles during diastole, the ventricular enddiastolic volumes can become as great as 150 to 180 milliliters in the healthy heart. By both increasing the end-diastolic volume and decreasing the end-systolic volume, the stroke volume output can be increased to more than double normal.

Function of the Valves Atrioventricular Valves

The A-V valves (the tricuspid and mitral valves) prevent backflow of blood from the ventricles to the atria during systole, and the semilunar valves (the aortic and pulmonary artery valves) prevent backflow from the aorta and pulmonary arteries into the ventricles during diastole. These valves, close and open passively. That is, they close when a backward pressure gradient pushes blood backward, and they open when a forward pressure gradient forces blood in the forward direction.

Function of the Papillary Muscles

Papillary muscles attach to the the A-V valves by the chordae tendineae. The papillary muscles contract when the ventricular walls contract, but contrary to what might be expected, they do not help the valves to close. Instead, they pull the valves inward toward the ventricles to prevent their bulging too far backward toward the atria during ventricular contraction. If a chorda tendinea becomes ruptured or if one of the papillary muscles becomes paralyzed, the valve bulges far backward during ventricular contraction, sometimes so far that it leaks severely and results in severe or even lethal cardiac incapacity.

Aortic and Pulmonary Artery Valves

The aortic and pulmonary artery semilunar valves function quite differently from the A-V valves. First, the high pressures in the arteries at the end of systole cause the semilunar valves to snap to the closed position, in contrast to the much softer closure of the A-V valves. Second, because of smaller openings, the velocity of blood ejection through the aortic and pulmonary valves is far greater than that through the much larger A-V valves.

24. Stroke volume and cardiac output

Stroke volume

- is the volume ejected from the ventricle on each beat.
- Is expressed by the following equation:

$$\text{Stroke volume} = \text{End-diastolic volume} - \text{End-systolic volume}$$

Ejection fraction

- is the fraction of the end-diastolic volume in each stroke volume
- is normally 0.55 or 55%
- is expressed by the following equation:

$$\text{Ejection fraction} = \frac{\text{Stroke volume}}{\text{End-diastolic volume}}$$

Cardiac output

- is expressed by the following equation:

$$\text{Cardiac output} = \text{Stroke volume} \times \text{Heart rate}$$

Stroke work

-is the work the heart performs on each beat
- is equal to force x distance, where force is aortic pressure and distance is stroke volume
- is expressed by the following equation:

$$\text{Stroke work} = \text{Aortic pressure} \times \text{Stroke volume}$$

-Fatty acids are the primary energy source for stroke work

Work Output of the Heart

The stroke work output of the heart is the amount of energy that the heart converts to work during each heartbeat while pumping blood into the arteries. Minute work output is the total amount of energy converted to work in 1 minute; this is equal to the stroke work output times the heart rate per minute.

Work output of the heart is in two forms. First, by far the major proportion is used to move the blood from the low-pressure veins to the high-pressure arteries. This is called volume-pressure work or external work. Second, a minor proportion of the energy is used to accelerate the blood to its velocity of ejection through the aortic and pulmonary valves. This is the kinetic energy of blood flow component of the work output.

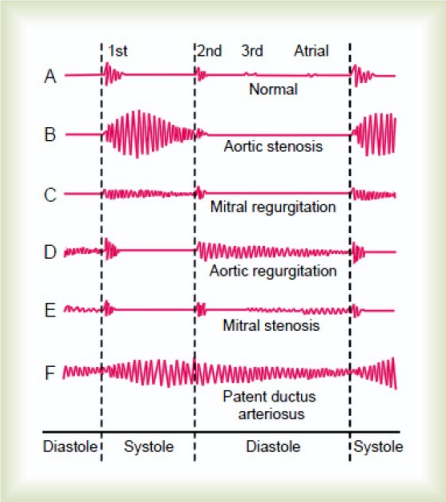
Right ventricular external work output is normally about one sixth the work output of the left ventricle because of the sixfold difference in systolic pressures that the two ventricles pump. The additional work output of each ventricle required to create kinetic energy of blood flow is proportional to the mass of blood ejected times the square of velocity of ejection.

Ordinarily, the work output of the left ventricle required to create kinetic energy of blood flow is only about 1 per cent of the total work output of the ventricle and therefore is ignored in the calculation of the total stroke work output. But in certain abnormal conditions, such as aortic stenosis, in which blood flows with great velocity through the stenosed valve, more than 50 per cent of the total work output may be required to create kinetic energy of blood flow.

25. Heart sounds. Diagnostic significance

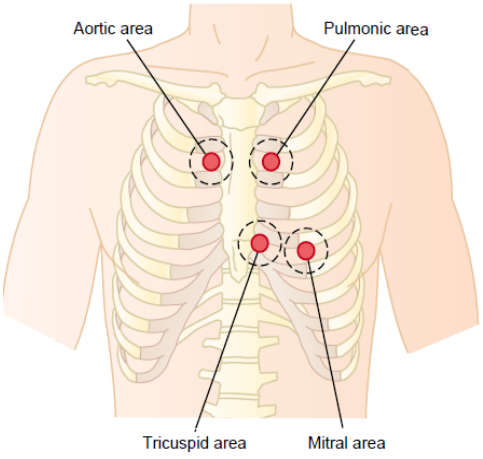
Normal Heart Sounds

Listening with a stethoscope to a normal heart, one hears two sounds. The first heart sound is associated with closure of the atrioventricular (A-V) valves at the beginning of systole, and the second heart sound is associated with closure of the semilunar (aortic and pulmonary) valves at the end of systole.



Causes of the First and Second Heart Sounds

The cause of the first heart sound is vibration of the taut valves immediately after closure, along with vibration of the adjacent walls of the heart and major vessels around the heart. That is, in generating the first heart sound, contraction of the ventricles first causes sudden backflow of blood against the A-V valves (the tricuspid and mitral valves), causing them to close and bulge toward the atria until the chordae tendineae abruptly stop the back bulging. The elastic tautness of the chordae tendineae and of the valves then causes the back surging blood to bounce forward again into each respective ventricle.This causes the blood and the ventricular walls, as well as the taut valves, to vibrate and causes vibrating turbulence in the blood. The second heart sound results from sudden closure of the semilunar valves at the end of systole. When the semilunar valves close, they bulge backward toward the ventricles, and their elastic stretch recoils the blood back into the arteries, which causes a short period of reverberation of blood back and forth between the walls of the arteries and the semilunar valves, as well as between these valves and the ventricular walls.



Duration of the First and Second Heart Sounds

The duration of each of the heart sounds is slightly more than 0.10 second—the first sound about 0.14 second, and the second about 0.11 second. The reason for the shorter second sound is that the semilunar valves are more taut than the A-V valves, so that they vibrate for a shorter time than do the A-V valves.

Third Heart Sound

Occasionally a weak, rumbling third heart sound is heard at the beginning of the middle third of diastole. A logical but unproved explanation of this sound is oscillation of blood back and forth between the walls of the ventricles initiated by inrushing blood from the atria. The reason the third heart sound does not occur until the middle third of diastole is believed to be that in the early part of diastole, the ventricles are not filled sufficiently to create even the small amount of elastic tension necessary for reverberation.

Atrial Heart Sound (Fourth Heart Sound)

An atrial heart sound can sometimes be recorded in the phonocardiogram, but it can almost never be heard with a stethoscope because of its weakness. This sound occurs when the atria contract, and presumably, it is caused by the inrush of blood into the ventricles, which initiates vibrations similar to those of the third heart sound.

Chest Surface Areas for Auscultation of Normal Heart Sounds

Listening to the sounds of the body, usually with the aid of a stethoscope, is called auscultation. The figure shows the areas of the chest wall from which the different heart valvular sounds can best be distinguished. The areas for listening to the different heart sounds are not

directly over the valves themselves. The aortic area is upward along the aorta because of sound transmission up the aorta, and the pulmonic area is upward along the pulmonary artery. The tricuspid area is over the right ventricle, and the mitral area is over the apex of the left ventricle, which is the portion of the heart nearest the surface of the chest; the heart is rotated so that the remainder of the left ventricle lies more posteriorly.

Heart Murmurs Caused by Valvular Lesions

Many abnormal heart sounds, known as “heart murmurs,” occur when there are abnormalities of the valves, as follows.

26. Autoregulation of cardiac contraction: Starling principle

Regulation of Heart Pumping

When a person is at rest, the heart pumps only 4 to 6 liters of blood each minute. During severe exercise, the heart may be required to pump four to seven times this amount. The basic means by which the volume pumped by the heart is regulated are (1) intrinsic cardiac regulation of pumping in response to changes in volume of blood flowing into the heart and (2) control of heart rate and strength of heart pumping by the autonomic nervous system.

Intrinsic Regulation of Heart Pumping—The Frank-Starling Mechanism

The amount of blood pumped by the heart each minute is determined almost entirely by the rate of blood flow into the heart from the veins, which is called venous return. That is, each peripheral tissue of the body controls its own local blood flow, and all the local tissue flows combine and return by way of the veins to the right atrium. The heart, in turn, automatically pumps this incoming blood into the arteries, so that it can flow around the circuit again. This intrinsic ability of the heart to adapt to increasing volumes of inflowing blood is called the Frank-Starling mechanism of the heart. Basically, the Frank-Starling mechanism means that the greater the heart muscle is stretched during filling, the greater is the force of contraction and the greater the quantity of blood pumped into the aorta. Or, stated another way:Within physiologic limits, the heart pumps all the blood that returns to it by the way of the veins.

What Is the Explanation of the Frank-Starling Mechanism?

When an extra amount of blood flows into the ventricles, the cardiac muscle itself is stretched to greater length. This in turn causes the muscle to contract with increased force because the actin and myosin filaments are brought to a more nearly optimal degree of overlap for force generation. Therefore, the ventricle, because of its increased pumping, automatically pumps the extra blood into the arteries. This ability of stretched muscle, up to an optimal length, to contract with increased work output is characteristic of all striated muscle, and is not simply a characteristic of cardiac muscle. In addition to the important effect of lengthening the heart muscle, still another factor increases heart pumping when its volume is increased. Stretch of the right atrial wall directly increases the heart rate by 10 to 20 per cent; this, too, helps increase the amount of blood pumped each minute, although its contribution is much less than that of the Frank-Starling mechanism.

28. Heart rate

Heart rate is the number of heartbeats per unit of time - typically expressed as beats per minute (bpm) - which can vary as the body's need for oxygen changes, such as during exercise or sleep. The measurement of heart rate is used by medical professionals to assist in the diagnosis and tracking of medical conditions. It is also used by individuals, such as athletes, who are interested in monitoring their heart rate to gain maximum efficiency from their training. The R wave to R wave interval (RR interval) is the inverse of the heart rate.

Heart rate is measured by finding the pulse of the body. This pulse rate can be measured at any point on the body where an artery's pulsation is transmitted to the surface - often as it is compressed against an underlying structure like bone - by pressuring it with the index and middle finger. The thumb should not be used for measuring another person's heart rate, as its strong pulse may interfere with discriminating the site of pulsation.

Possible points for measuring the heart rate are:

1. The ventral aspect of the wrist on the side of the thumb (radial artery)
2. The ulnar artery
3. The neck (carotid artery),
4. The inside of the elbow, or under the biceps muscle (brachial artery)
5. The groin (femoral artery)
6. Behind the medial malleolus on the feet (posterior tibial artery)
7. Middle of dorsum of the foot (dorsalis pedis).
8. Behind the knee (popliteal artery)
9. Over the abdomen (abdominal aorta)
10. The chest (apex of heart), which can be felt with one's hand or fingers. However, it is possible to auscultate the heart using a stethoscope.
11. The temple
12. The lateral edge of the mandible

A more precise method of determining pulse involves the use of an electrocardiograph, or ECG (also abbreviated EKG).

Resting heart rate (HRrest)

It’s a person's heart rate when they are at rest: awake but lying down, and not having immediately exerted themselves. Typical healthy resting heart rate in adults is 60–80 bpm, with rates below 60 bpm referred to as bradycardia and rates above 100 bpm referred to as tachycardia. Note however that conditioned athletes often have resting heart rates below 60 bpm. Tour de France cyclist Lance Armstrong has a resting HR around 32 bpm.

Rate of Heartbeat as Determined from the Electrocardiogram

The rate of heartbeat can be determined easily from an electrocardiogram because the heart rate is the reciprocal of the time interval between two successive heartbeats. If the interval between two beats as determined from the time calibration lines is 1 second, the heart rate is 60 beats per minute. The normal interval between two successive QRS complexes in the adult person is about 0.83 second. This is a heart rate of 60/0.83 times per minute, or 72 beats per minute.

29. Arrhythmias

Tachycardia

The term “tachycardia” means fast heart rate, usually defined in an adult person as faster than 100 beats per minute. The general causes of tachycardia include increased body temperature, stimulation of the heart by the sympathetic nerves, or toxic conditions of the heart. The heart rate increases about 10 beats per minute for each degree Fahrenheit (18 beats per degree Celsius) increase in body temperature, up to a body temperature of about 105°F (40.5°C); beyond this, the heart rate may decrease because of progressive debility of the heart muscle as a result of the fever. Fever causes tachycardia because increased temperature increases the rate of metabolism of the sinus node, which in turn directly increases its excitability and rate of rhythm.

Many factors can cause the sympathetic nervous system to excite the heart. For instance, when a patient loses blood and passes into a state of shock or semishock, sympathetic reflex stimulation of the heart often increases the heart rate to 150 to 180 beats per minute.

Bradycardia The term “bradycardia” means a slow heart rate, usually defined as fewer than 60 beats per minute.

Bradycardia in Athletes. The athlete’s heart is larger and considerably stronger than that of a normal person, which allows the athlete’s heart to pump a large stroke volume output per beat even during periods of rest. When the athlete is at rest, excessive quantities of blood pumped into the arterial tree with each beat initiate feedback circulatory reflexes or other effects to cause bradycardia.

Vagal Stimulation as a Cause of Bradycardia

Any circulatory reflex that stimulates the vagus nerves causes release of acetylcholine at the vagal endings in the heart, thus giving a parasympathetic effect.

Sinus Arrhythmia

The heart rate increases and decreases no more than 5 per cent during quiet respiration. Then, during deep respiration, the heart rate increases and decreases with each respiratory cycle by as much as 30 per cent. Sinus arrhythmia can result from any one of many circulatory conditions that alter the strengths of the sympathetic and parasympathetic nerve signals to the heart sinus node. In the “respiratory” type of sinus arrhythmia, this results mainly from “spillover” of signals from the medullary respiratory center into the adjacent vasomotor center during inspiratory and expiratory cycles of respiration.The spillover signals cause alternate increase and decrease in the number of impulses transmitted through the sympathetic and vagus nerves to the heart.

Abnormal Rhythms That Result from Block of Heart Signals Within the Intracardiac Conduction Pathways

Sinoatrial Block

In rare instances, the impulse from the sinus node is blocked before it enters the atrial muscle. This phenomenon resultans standingstill of the atria. However, the ventricles pick up a new rhythm, the impulse usually originating spontaneously in the atrioventricular (A-V) node, so that the rate of the ventricular QRS-T complex is slowed but not otherwise altered.

Atrioventricular Block

The only means by which impulses ordinarily can pass from the atria into the ventricles is through the A-V bundle, also known as the bundle of His. Conditions that can either decrease the rate of impulse conduction in this bundle or block the impulse entirely are as follows: 1. Ischemia of the A-V node or A-V bundle fibers often delays or blocks conduction from the atria to the ventricles. Coronary insufficiency can cause ischemia of the A-V node and bundle in the same way that it can cause ischemia of the myocardium. 2. Compression of the A-V bundle by scar tissue or by calcified portions of the heart can depress or block conduction from the atria to the ventricles. 3. Inflammation of the A-V node or A-V bunde can depress conductivity from the atria to the

ventricles. 4. Extreme stimulation of the heart by the vagus nerves in rare instances blocks impulse conduction through the A-V node.

Incomplete Atrioventricular Heart Block

- *Prolonged P-R (or P-Q) Interval—First Degree Block.*

The usual lapse of time between beginning of the P wave and beginning of the QRS complex is about 0.16 second when the heart is beating at a normal rate. In general, when the P-R interval increases to greater than 0.20 second, the P-R interval is said to be prolonged - first degree incomplete heart block. It is defined as a delay of conduction from the atria to the ventricles but not actual blockage of conduction.

- *Second Degree Block*

When conduction through the A-V bundle is slowed enough to increase the P-R interval to 0.25 to 0.45 second, the action potential sometimes is strong enough to pass through the bundle into the ventricles and sometimes is not strong enough. In this instance, there will be an atrial P wave but no QRS-T wave, and it is said that there are “dropped beats” of the ventricles. This condition is called second degree heart block.

At times, every other beat of the ventricles is dropped, so that a “2:1 rhythm” develops, with the atria beating twice for every single beat of the ventricles.At other times, rhythms of 3:2 or 3:1 also develop.

Complete A-V Block (Third Degree Block)

When the condition causing poor conduction in the A-V node or A-V bundle becomes severe, complete block of the impulse from the atria into the ventricles occurs. In this instance, the ventricles spontaneously establish their own signal, usually originating in the A-V node or A-V bundle. Note that the rate of rhythm of the atria in this electrocardiogram is about 100 beats per minute, whereas the rate of ventricular beat is less than 40 per minute.

Stokes-Adams Syndrome—Ventricular Escape

In some patients with A-V block, the total block comes and goes; that is, impulses are conducted from the atria into the ventricles for a period of time and then suddenly impulses are not conducted. The duration of block may be a few seconds, a few minutes, a few hours, or even weeks or longer before conduction returns. This condition occurs in hearts with borderline ischemia of the conductive system. Each time A-V conduction ceases, the ventricles often do not start their own beating until after a delay of 5 to 30 seconds. This results from the phenomenon called overdrive suppression. This means that ventricular excitability is at first in a suppressed state because the ventricles have been driven by the atria at a rate greater than their natural rate of rhythm. However, after a few seconds, some part of the Purkinje system beyond the block, usually in the distal part of the A-V node beyond the blocked point in the node, or in the A-V bundle, begins discharging rhythmically at a rate of 15 to 40 times per minute and acting as the pacemaker of the ventricles. This is called ventricular escape. Because the brain cannot remain active for more than 4 to 7 seconds without blood supply, most patients faint a few seconds after complete block occurs because the heart does not pump any blood for 5 to 30 seconds, until the ventricles “escape.” After escape, however, the slowly beating ventricles usually pump enough blood to allow rapid recovery from the faint and then to sustain the person. These periodic fainting spells are known as the Stokes-Adams syndrome.

Premature Contractions

A premature contraction is a contraction of the heart before the time that normal contraction would have been expected.This condition is also called extrasystole, premature beat, or ectopic beat.

Causes of Premature Contractions. Most premature contractions result from ectopic foci in the heart, which emit abnormal impulses at odd times during the cardiac rhythm.

Premature Atrial Contractions

There is an ectopic origin of the beat in the atria near the A-V node. Also, the interval between the premature contraction and the next succeeding contraction is slightly prolonged,

which is called a compensatory pause. One of the reasons for this is that the premature contraction originated in the atrium some distance from the sinus node, and the impulse had to travel through a considerable amount of atrial muscle before it discharged the sinus node. Consequently, the sinus node discharged late in the premature cycle, and this made the succeeding sinus node discharge also late in appearing. Premature atrial contractions occur frequently in otherwise healthy people. Indeed, they often occur in athletes whose hearts are in very healthy condition.

Pulse Deficit

When the heart contracts ahead of schedule, the ventricles will not have filled with blood normally, and the stroke volume output during that contraction is depressed or almost absent. Therefore, the pulse wave passing to the peripheral arteries after a premature contraction may be so weak that it cannot be felt in the radial artery. Thus, a deficit in the number of radial pulses occurs when compared with the actual number of contractions of the heart.

A-V Nodal or A-V Bundle Premature Contractions

premature contraction that originated in the A-V node or in the A-V bundle. The P wave is missing from the electrocardiographic record of the premature contraction. Instead, the P wave is superimposed onto the QRS-T complex because the cardiac impulse traveled backward into the atria at the same time that it traveled forward into the ventricles; this P wave slightly distorts the QRS-T complex, but the P wave itself cannot be discerned as such.

Premature Ventricular Contractions

Premature ventricular contractions (PVCs) alternating with normal contractions. PVCs cause specific effects in the electrocardiogram, as follows: 1. The QRS complex is usually considerably prolonged. The reason is that the impulse is conducted mainly through slowly conducting muscle of the ventricles rather than through the Purkinje system. 2. The QRS complex has a high voltage for the following reasons: when the normal impulse passes through the heart, it passes through both ventricles nearly simultaneously; consequently, in the normal heart, the depolarization waves of the two sides of the heart—mainly of opposite polarity to each other—partially neutralize each other in the electrocardiogram.When a PVC occurs, the impulse almost always travels in only one direction, so that there is no such neutralization effect, and one entire side or end of the ventricles is depolarized ahead of the other; this causes large electrical potentials, 3. After almost all PVCs, the T wave has an electrical potential polarity exactly opposite to that of the QRS complex, because the slow conduction of the impulse through the cardiac muscle causes the muscle fibers that depolarize first also to repolarize first.

Paroxysmal Tachycardia

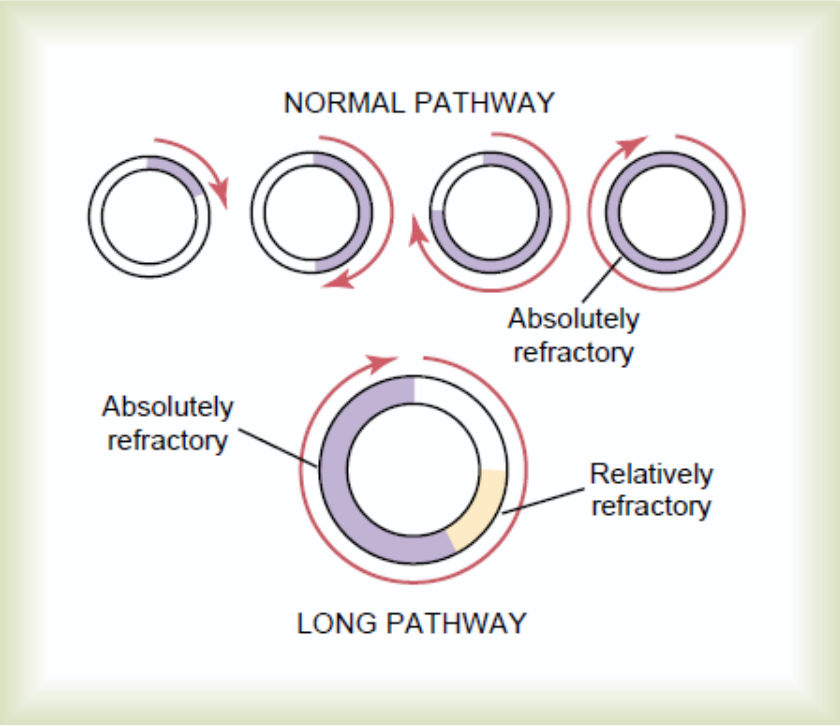
Some abnormalities in different portions of the heart, including the atria, the Purkinje system, or the ventricles, can occasionally cause rapid rhythmical discharge of impulses that spread in all directions throughout the heart. This is believed to be caused most frequently by re-entrant circus movement feedback pathways that set up local repeated self–re-excitation. Because of the rapid rhythm in the irritable focus, this focus becomes the pacemaker of the heart. The term “paroxysmal” means that the heart rate becomes rapid in paroxysms, with the paroxysm beginning suddenly and lasting for a few seconds, a few minutes, a few hours, or much longer. Then the paroxysm usually ends as suddenly as it began, with the pacemaker of the heart instantly shifting back to the sinus node.

30. Mechanism of re-entry

Phenomenon of Re-entry—"Circus Movements" as the Basis for Ventricular Fibrillation

When the normal cardiac impulse in the normal heart has traveled through the extent of the ventricles, it has no place to go because all the ventricular muscle is refractory and cannot conduct the impulse farther. Therefore, that impulse dies, and the heart awaits a new action potential to begin in the atrial sinus node. Under some circumstances, however, this normal sequence of events does not occur. Therefore, let us explain more fully the background conditions that can initiate re-entry and lead to "circus movements," which in turn cause ventricular fibrillation. Figure 13–14 shows several small cardiac muscle strips cut in the form of circles. If such a strip is stimulated at the 12 o'clock position so that the impulse travers in only one direction, the impulse spreads progressively around the circle until it returns to the 12 o'clock position. If the originally stimulated muscle fibers are still in a refractory state, the impulse then dies out because refractory muscle cannot transmit a second impulse. But there are three different conditions that can cause this impulse to continue to travel around the circle, that is, to cause "re-entry" of the impulse into muscle that has already been excited. This is called a "circus movement." First, if the pathway around the circle is too long, by the time the impulse returns to the 12 o'clock position, the originally stimulated muscle will no longer be refractory and the impulse will continue around the circle again and again. Second, if the length of the pathway remains constant but the velocity of conduction becomes decreased enough, an increased interval of time will elapse before the impulse returns to the 12 o'clock position. By this time, the originally stimulated muscle might be out of the refractory state, and the impulse can continue around the circle again and again. Third, the refractory period of the muscle might become greatly shortened. In this case, the impulse could also continue around and around the circle.

All these conditions occur in different pathological states of the human heart, as follows: (1) A long pathway typically occurs in dilated hearts. (2) Decreased rate of conduction frequently results from (a) blockage of the Purkinje system, (b) ischemia of the muscle, (c) high blood potassium levels, or (d) many other factors. (3) A shortened refractory period commonly occurs in response to various drugs, such as epinephrine, or after repetitive electrical stimulation. Thus, in many cardiac disturbances, re-entry can cause abnormal patterns of cardiac contraction or abnormal cardiac rhythms that ignore the pace-setting effects of the sinus node.



31. Athlete´s heart

An Athletic Heart is known in sports medicine as a non-pathological condition of a sportsman's heart. The heart enlarges through (extreme) physical training (aerobic exercise, especially endurance sports) and the resting pulse lowers.

A larger heart results in higher cardiac output, or, in other words, more blood is being pumped out with each beat. With high cardiac output, the heart can allow itself to beat less, thus the bradycardia occurs.

Among the differences between untrained individuals and trained athletes it that the athletes have lower heart rates, greater end-systolic volumes, and greater stroke volumes in rest. Therefore, they can potentially achieve a given increase in cardiac output by further increase in stroke volume without increasing their heart rate to as great a degree as an untrained individual.

When one is diagnosed with Athlete's Heart, there are usually three characteristics that accompany the condition:

- ✓ Bradycardia is a slower than normal heartbeat around 40-60 beats per minute.
- ✓ Cardiomegaly is the state of an enlarged heart.
- ✓ Cardiac hypertrophy is the thickening of the muscular wall of the heart, specifically the left ventricle

32. Coronary circulation

Physiologic Anatomy of the Coronary Blood Supply

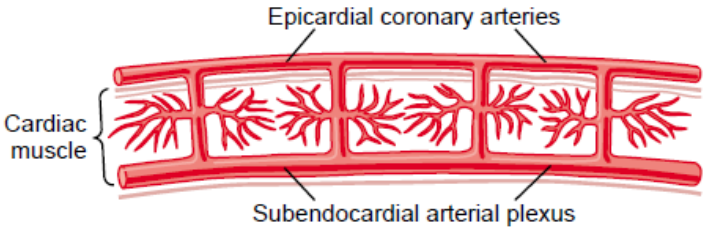
The main coronary arteries lie on the surface of the heart and smaller arteries then penetrate from the surface into the cardiac muscle mass. It is almost entirely through these arteries that the heart receives its nutritive blood supply. Only the inner 1/10 millimeter of the endocardial surface can obtain significant nutrition directly from the blood inside the cardiac chambers, so that this source of muscle nutrition is minuscule. The left coronary artery supplies mainly the anterior and left lateral portions of the left ventricle, whereas the right coronary artery supplies most of the right ventricle as well as the posterior part of the left ventricle in 80 to 90 per cent of people. Most of the coronary venous blood flow from the left ventricular muscle returns to the right atrium of the heart by way of the coronary sinus—which is about 75 per cent of the total coronary blood flow. And most of the coronary venous blood from the right ventricular muscle returns through small anterior cardiac veins that flow directly into the right atrium, not by way of the coronary sinus. A very small amount of coronary venous blood also flows back into the heart through very minute thebesian veins, which empty directly into all chambers of the heart.

Normal Coronary Blood Flow

The resting coronary blood flow in the human being averages about 225 ml/min, which is about 4 to 5 per cent of the total cardiac output. During strenuous exercise, the heart in the young adult increases its cardiac output fourfold to sevenfold, and it pumps this blood against a higher than normal arterial pressure. Consequently, the work output of the heart under severe conditions may increase sixfold to ninefold. At the same time, the coronary blood flow increases threefold to fourfold to supply the extra nutrients needed by the heart. This increase is not as much as the increase in workload, which means that the ratio of energy expenditure by the heart to coronary blood flow increases. Thus, the “efficiency” of cardiac utilization of energy increases to make up for the relative deficiency of coronary blood supply.

Phasic Changes in Coronary Blood Flow During Systole and Diastole—Effect of Cardiac Muscle Compression

The coronary capillary blood flow in the left ventricle muscle falls to a low value during systole, which is opposite to flow in vascular beds elsewhere in the body. The reason for this is strong compression of the left ventricular muscle around the intramuscular vessels during systolic contraction. During diastole, the cardiac muscle relaxes and no longer obstructs blood flow through the left ventricular muscle capillaries, so that blood flows rapidly during all of diastole. Blood flow through the coronary capillaries of the right ventricle also undergoes phasic changes during the cardiac cycle, but because the force of contraction of the right ventricular muscle is far less than that of the left ventricular muscle, the inverse phasic changes are only partial in contrast to those in the left ventricular muscle.



Epicardial Versus Subendocardial Coronary Blood Flow—Effect of Intramyocardial Pressure.

Smaller, intramuscular arteries derived from the epicardial arteries penetrate the muscle, supplying the needed nutrients. Lying immediately beneath the endocardium is a plexus of subendocardial arteries. During systole, blood flow through the subendocardial plexus of the left ventricle, where the intramuscular coronary vessels are compressed greatly by ventricular muscle contraction, tends to be reduced. But the extra vessels of the subendocardial plexus normally compensate for this. Later Control of Coronary Blood Flow

Local Muscle Metabolism Is the Primary Controller of Coronary Flow

Blood flow through the coronary system is regulated mostly by local arteriolar vasodilation in response to cardiac muscle need for nutrition. That is, whenever the vigor of cardiac contraction

is increased, regardless of cause, the rate of coronary blood flow also increases. Conversely, decreased heart activity is accompanied by decreased coronary flow. Oxygen Demand as a Major

Factor in Local Coronary Blood Flow Regulation

Blood flow in the coronaries usually is regulated almost exactly in proportion to the need of the cardiac musculature for oxygen. Normally, about 70 per cent of the oxygen in the coronary arterial blood is removed as the blood flows through the heart muscle. Because not much oxygen is left, very little additional oxygen can be supplied to the heart musculature unless the coronary blood flow increases. Fortunately, the coronary blood flow does increase almost in direct proportion to any additional metabolic consumption of oxygen by the heart. However, the exact means by which increased oxygen consumption causes coronary dilation has not been determined.

Nervous Control of Coronary Blood Flow

Stimulation of the autonomic nerves to the heart can affect coronary blood flow both directly and indirectly. The direct effects result from action of the nervous transmitter substances acetylcholine from the vagus nerves and norepinephrine and epinephrine from the sympathetic nerves on the coronary vessels themselves. The indirect effects result from secondary changes in coronary blood flow caused by increased or decreased activity of the heart. The indirect effects, which are mostly opposite to the direct effects, play a far more important role in normal control of coronary blood flow. Thus, sympathetic stimulation, which releases norepinephrine and epinephrine, increases both heart rate and heart contractility as well as increases the rate of metabolism of the heart. In turn, the increased metabolism of the heart sets off local blood flow regulatory mechanisms for dilating the coronary vessels, and the blood flow increases approximately in proportion to the metabolic needs of the heart muscle. In contrast, vagal stimulation, with its release of acetylcholine, slows the heart and has a slight depressive effect on heart contractility. These effects in turn decrease cardiac oxygen consumption and, therefore, indirectly constrict the coronary arteries.

Direct Effects of Nervous Stimuli on the Coronary Vasculature

The distribution of parasympathetic (vagal) nerve fibers to the ventricular coronary system is not very great. However, the acetylcholine released by parasympathetic stimulation has a direct effect to dilate the coronary arteries. The sympathetic transmitter substances norepinephrine and epinephrine can have either vascular constrictor or vascular dilator effects, depending on the presence or absence of constrictor or dilator receptors in the blood vessel walls.The constrictor receptors are called alpha receptors and the dilator receptors are called beta receptors. Both alpha and beta receptors exist in the coronary vessels. In general, the epicardial coronary vessels have a preponderance of alpha receptors, whereas the intramuscular arteries may have a preponderance of beta receptors. Therefore, sympathetic stimulation can, at least theoretically, cause slight overall coronary constriction or dilation, but usually constriction.

33. Coronary reserve. Ischaemic heart disease

Myocardial O2 consumption

Is defined as Qcor (coronary blood flow) times the arteriovenous O2 concentration difference, (Ca–Cv)O2. The myocardial (Ca–Cv)O2 is relatively high (0.12 L/L blood), and oxygen extraction at rest ([Ca–Cv]O2/CaO2 = 0.12/0.21) is almost 60% and, thus, not able to rise much further. Therefore, an increase in Qcor is practically the only way to increase myocardial VO2 when the O2 demand rises.

Adaptation of the myocardial O2 supply

According to need is therefore primarily achieved by adjusting vascular resistance. The (distal) coronary vessel resistance can normally be reduced to about 1/4 the resting value (coronary reserve). The coronary blood flow Qcor (approx. 250 mL/min at rest) can therefore be increased as much as 4–5 fold. In other words, approx. 4 to 5 times more O2 can be supplied during maximum physical exertion.

Ischemic heart disease

Ischemic heart disease, is a disease characterized by reduced blood supply to the heart muscle, usually due to coronary artery disease (atherosclerosis of the coronary arteries). Ischaemic heart disease may present with any of the following problems:

– Angina pectoris (chest pain on exertion, in cold weather or emotional situations)

– Acute chest pain: acute coronary syndrome, unstable angina or myocardial infarction ("heart attack", severe chest pain unrelieved by rest associated with evidence of acute heart damage)

– Heart failure (difficulty in breathing or swelling of the extremities due to weakness of the heart muscle)

Stable angina

In "stable" angina, chest pain with typical features occurring at predictable levels of exertion, various forms of cardiac stress tests may be used to induce both symptoms and detect changes by way of electrocardiography (using an ECG), echocardiography (using ultrasound of the heart) or scintigraphy (using uptake of radionuclide by the heart muscle). If part of the heart seems to receive an insufficient blood supply, coronary angiography may be used to identify stenosis of the coronary arteries and suitability for angioplasty or bypass surgery.

ECGs show elevation of the "ST segment", which in the context of severe typical chest pain is strongly indicative of an acute myocardial infarction (MI); this is termed a STEMI (ST-elevation MI), and is treated as an emergency with either urgent coronary angiography and percutaneous coronary intervention (angioplasty with or without stent insertion) or with thrombolysis ("clot buster" medication), whichever is available.

In the absence of ST-segment elevation, heart damage is detected by cardiac markers (blood tests that identify heart muscle damage).

Pathogenesis

The disease process underlying most ischemic heart disease is atherosclerosis of the coronary arteries. The arteries become "furred up" by fat-rich deposits in the vessel wall (plaques). Stable angina is due to inability to supply the myocardium (heart muscle) with sufficient blood in situations of increased demand for oxygen, such as exsertion.

Unstable angina, STEMI and NSTEMI are attributed to "plaque rupture", where one of the plaques gets weakened, develops a tear, and forms an adherent blood clot that either obstructs blood flow or floats further down the blood vessel, causing obstruction there.

Treatment

In stable IHD, antianginal drugs may be used to reduce the rate of occurrence and severity of angina attacks.

Treatment of coronary artery disease includes addressing "modifiable" risk factors. This includes suppression of cholesterol (usually with statins), even in those with statistically normal

cholesterol levels, control of blood pressure, blood sugars (if diabetic), regular exercise and a healthy diet. Smokers are encouraged to stop smoking.

34. Cardiovascular system – general principles

Functional Parts of the Circulation

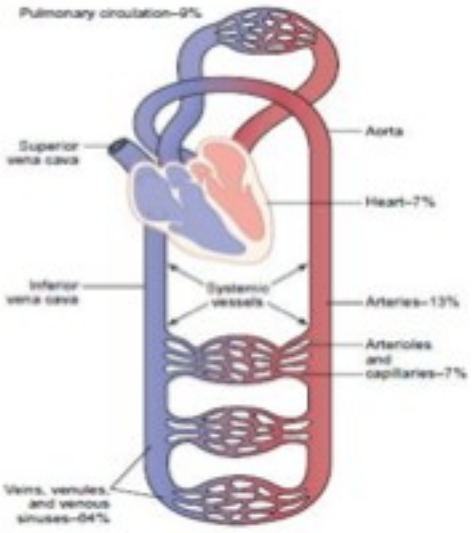
The function of the arteries is to transport blood under high pressure to the tissues. For this reason, the arteries have strong vascular walls, and blood flows at a high velocity in the arteries.

The arterioles are the last small branches of the arterial system; they act as control conduits through which blood is released into the capillaries. The arteriole has a strong muscular wall that can close the arteriole completely or can, by relaxing, dilate it severalfold, thus having the capability of vastly altering blood flow in each tissue bed in response to the need of the tissue.

The function of the capillaries is to exchange fluid, nutrients, electrolytes, hormones, and other substances between the blood and the interstitial fluid.

The venules collect blood from the capillaries, and they gradually coalesce into progressively larger veins.

The veins function as conduits for transport of blood from the venules back to the heart; equally important, they serve as a major reservoir of extra blood.



Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.

Volumes of Blood in the Different Parts of the Circulation

About 84 per cent of the entire blood volume of the body is in the systemic circulation, and 16 per cent in heart and lungs. Of the 84 per cent in the systemic circulation, 64 per cent is in the veins, 13 per cent in the arteries, and 7 per cent in the systemic arterioles and capillaries. The heart contains 7 per cent of the blood, and the pulmonary vessels, 9 per cent.

Pressures in the Various Portions of the Circulation

Because the heart pumps blood continually into the aorta, the mean pressure in the aorta is high, averaging about 100 mm Hg. Also, because heart pumping is pulsatile, the arterial pressure alternates between a systolic pressure level of 120 mm Hg and a diastolic pressure level of 80 mm Hg.

As the blood flows through the systemic circulation, its mean pressure falls progressively to about 0 mm Hg by the time it reaches the termination of the venae cavae where they empty into the right atrium of the heart.

The pressure in the systemic capillaries varies from as high as 35 mm Hg near the arteriolar ends to as low as 10 mm Hg near the venous ends, but their average “functional” pressure in most vascular beds is about 17 mm Hg.

In the pulmonary arteries, the pressure is pulsatile, just as in the aorta, but the pressure level is far less: pulmonary artery systolic pressure averages about 25 mm Hg and diastolic pressure 8 mm Hg, with a mean pulmonary arterial pressure of only 16 mm Hg. The mean pulmonary capillary pressure averages only 7 mm Hg. Yet the total blood flow through the lungs each minute is the same as through the systemic circulation.

The low pressures of the pulmonary system are in accord with the needs of the lungs, because all that is required is to expose the blood in the pulmonary capillaries to oxygen and other gases in the pulmonary alveoli.

Basic Theory of Circulatory Function

There are three basic principles that underlie all functions of the system.

1. The rate of blood flow to each tissue of the body is almost always precisely controlled in relation to the tissue need.

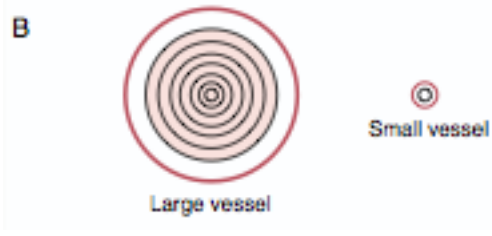
2. The cardiac output is controlled mainly by the sum of all the local tissue flows.

3. In general the arterial pressure is controlled independently of either local blood flow control or cardiac output control

35. Significance of Poiseuille-Hagen formula for blood flow

The conductance of the vessel increases in proportion to the fourth power of the diameter.

Poiseuille's Law.



The cause of this great increase in conductance when the diameter increases can be explained by referring to figure, which shows cross sections of a large and a small vessel. The concentric rings inside the vessels indicate that the velocity of flow in each ring is different from that in the adjacent rings because of laminar flow, which was discussed earlier in the chapter. That is, the blood in the ring touching the wall of the vessel is barely flowing because of its adherence to the vascular endothelium. The next ring of blood toward the center of the vessel slips past the first ring and, therefore, flows more rapidly. The third, fourth, fifth, and sixth rings likewise flow at progressively increasing velocities. Thus, the blood that is near the wall of the vessel flows extremely slowly, whereas that in the middle of the vessel flows extremely rapidly.In the small vessel, essentially all the blood is near the wall, so that the extremely rapidly flowing central stream of blood simply does not exist. By integrating the velocities of all the concentric rings of flowing blood and multiplying them by the areas of the rings, one can derive the following formula, known as Poiseuille's law:

$$F = \frac{\pi \Delta P r^4}{8 \eta l}$$

in which F is the rate of blood flow, ΔP is the pressure difference between the ends of the vessel, r is the radius of the vessel, l is length of the vessel, and η is viscosity of the blood. Note particularly in this equation that the rate of blood flow is directly proportional to the fourth power of the radius of the vessel, which demonstrates once again that the diameter of a blood vessel (which is equal to twice the radius) plays by far the greatest role of all factors in determining the rate of blood flow through a vessel.

Importance of the Vessel Diameter "Fourth Power Law" in Determining Arteriolar Resistance

In the systemic circulation, about two thirds of the total systemic resistance to blood flow is arteriolar resistance in the small arterioles. The internal diameters of the arterioles range from as little as 4 micrometers to as great as 25 micrometers. However, their strong vascular walls allow the internal diameters to change tremendously, often as much as fourfold. From the fourth power law discussed above that relates blood flow to diameter of the vessel, one can see that a fourfold increase in vessel diameter can increase the flow as much as 256-fold. Thus, this fourth power law makes it possible for the arterioles, responding with only small changes in diameter to nervous signals or local tissue chemical signals, either to turn off almost completely the blood flow to the tissue or at the other extreme to cause a vast increase in flow.

36. Vascular resistance

Resistance to Blood Flow in Series and Parallel Vascular Circuits

Blood pumped by the heart flows from the high pressure part of the systemic circulation (i.e., aorta) to the low pressure side (i.e., vena cava) through many miles of blood vessels arranged in series and in parallel. The arteries, arterioles, capillaries, venules, and veins are collectively arranged in series. When blood vessels are arranged in series, flow through each blood vessel is the same and the total resistance to blood flow (Rtotal) is equal to the sum of the resistances of each vessel:

$$R_{total} = R_1 + R_2 + R_3 + R_4 \ldots$$

The total peripheral vascular resistance is therefore equal to the sum of resistances of the arteries, arterioles, capillaries, venules, and veins. Blood vessels branch extensively to form parallel circuits that supply blood to the many organs and tissues of the body. This parallel arrangement permits each tissue to regulate its own blood flow, to a great extent, independently of flow to other tissues.

For blood vessels arranged in parallel, the total resistance to blood flow is expressed as:

$$\frac{1}{R_{total}} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_4} \ldots$$

It is obvious that for a given pressure gradient, far greater amounts of blood will flow through this parallel system than through any of the individual blood vessels. Therefore, the total resistance is far less than the resistance of any single blood vessel. Flow through each of the parallel vessels is determined by the pressure gradient and its own resistance, not the resistance of the other parallel blood vessels. However, increasing the resistance of any of the blood vessels increases the total vascular resistance.

It may seem paradoxical that adding more blood vessels to a circuit reduces the total vascular resistance. Many parallel blood vessels, however, make it easier for blood to flow through the circuit because each parallel vessel provides another pathway, or conductance, for blood flow. The total conductance (Ctotal) for blood flow is the sum of the conductance of each parallel pathway:

$$C_{total} = C_1 + C_2 + C_3 + C_4 \ldots$$

For example, brain, kidney, muscle, gastrointestinal, skin, and coronary circulations are arranged in parallel, and each tissue contributes to the overall conductance of the systemic circulation. Blood flow through each tissue is a fraction of the total blood flow (cardiac output) and is determined by the resistance (the reciprocal of conductance) for blood flow in the tissue, as well as the pressure gradient. Therefore, amputation of a limb or surgical removal of a kidney also removes a parallel circuit and reduces the total vascular conductance and total blood flow (i.e., cardiac output) while increasing total peripheral vascular resistance.

Effect of Blood Hematocrit and Blood Viscosity on Vascular Resistance and Blood Flow

Note especially that another of the important factors in Poiseuille's equation is the viscosity of the blood. The greater the viscosity, the less the flow in a vessel if all other factors are constant. But what makes the blood so viscous? It is mainly the large numbers of suspended red cells in the blood, each of which exerts frictional drag against adjacent cells and against the wall of the blood vessel.

Effect of Hematocrit on Blood Viscosity

The viscosity of blood increases drastically as the hematocrit increases. The viscosity of whole blood at normal hematocrit is about 3; this means that three times as much pressure is required to force whole blood as to force water through the same blood vessel. When the

hematocrit rises to 60 or 70, which it often does in polycythemia, the blood viscosity can become as great as 10 times that of water, and its flow through blood vessels is greatly retarded.

Other factors that affect blood viscosity are the plasma protein concentration and types of proteins in the plasma, but these effects are so much less than the effect of hematocrit that they are not significant.

Effects of Pressure on Vascular Resistance and Tissue Blood Flow

An increase in arterial pressure not only increases the force that pushes blood through the vessels but also distends the vessels at the same time, which decreases vascular resistance. Thus, greater pressure increases the flow in both of these ways. Therefore, for most tissues, blood flow at 100 mm Hg arterial pressure is usually four to six times as great as blood flow at 50 mm Hg instead of two times as would be true if there were no effect of increasing pressure to increase vascular diameter.

37. Blood pressure. Hypertension

The contraction of the ventricles ejects blood into the pulmonary and systemic arteries during systole. If a precisely equal quantity of blood were to flow simultaneously out of the arteries, the total volume of blood in the arteries would remain constant, and arterial presuure would not change. Such is not the case, however. A volume of blood equal to only about one-third the stroke volume leaves the arteries during systole. The rest of the stroke volume remains in the arteries during systole, distending them and raising the arterial pressure. When ventricular contraction ends, the stretched arterial walls recoil passively, like a stretched rubber band being released, and blood continues to be driven into the arterioles during diastole. As blood leaves the arteries, the arterial volume and therefore the arterial pressure slowly fall, but the next ventricular contraction occurs while there is still adequate blood in the arteries to stretch them partially. Therefore, the arterial pressure does not fall to zero.

The maximum arterial pressure reached during peak ventricular ejection is called systolic pressure (SP). The minimum arterial pressure occurs just before ventricular ejection begins and is called diastolic pressure (DP). Arterial pressure is generally recorded as systolic/diastolic.

The difference betwen systolic and diastolic pressure is called the pulse pressure. It can be felt as a pulsation or throb in the arteries of the wrist or neck with each heartbeat. During diastole, nothing is felt over the artery, but the rapid rise in pressure as the next systole pushes out the artery wall, and it is this expansion of the vessel that produces the detactable throb.

The most importnat factors determining the magnitude of the pulse pressure are

(1) stroke volume
(2) speed of ejection of the stroke volume
(3) arterial compliance

Specifically, the pulse pressure that ventricular ejection produces is greater if the volume of blood ejected increases, if the speed at which it is ejected increases, or if the arteries are less compliant.

It is evident that arterial pressure is continuously changing throughout the cardiac cycle. The average pressure (mean arterial pressure, MAP) in the cycle is not merely the value halfway because diastole lasts longer than systole. The true mean arterial pressure can be obtained by complex methods, but for most purposes it is approximately equal to the diastolic pressure plus one-third of the pulse pressure (SP-DP), largely because diastole lasts about twice as long as systole:

$$MAP = DP + 1/3\ (SP-DP)$$

The MAP is the most important of the pressures described because it is the pressure driving blood into the tissues averaged over the entire cardiac cycle.

Hypertension

Refers to arterial pressure being abnormally high, as opposed to hypotension, when it is abnormally low. Theoretically, hypertension could result from an increase in cardiac output or in total peripheral resistance, or both. In reality, however, the major abnormality in most cases of well-established hypertension is incresed total peripheral resistance caused by abnormally reduced arteriolar radius.

The cause of the hypertension is increased release of renin from the kidneys, with subsquent increased generation of the potent vasoconstrictor angiotensin II.

Much evidence suggests that excessive sodium retention is a contributing factor in genetic predisposed persons. Obesity and sedentary lifestyle are definite risk factors, and weight reduction and exercise are frequently effective in causing some reduction of blood pressure in people with hypertension. Cigarette smoking, too, is a definite rick factor.

Hypertension causes a variety of problems. One of the organs most affected is the heart. Because the left ventricle in a hypertensive person must chronically pump against an increased arterial pressure (afterload), it develops an adaptative increase in muscle mass (left ventricluar hypertrophy). Changes in the organization and properties of myocardial cells occur, and these result in diminished contractile function and heart failure.

38. Arterial elasticity – significance

Vascular Distensibility

A valuable characteristic of the vascular system is that all blood vessels are distensible. When the pressure in blood vessels is increased, this dilates the blood vessels and therefore decreases their resistance. The result is increased blood flow not only because of increased pressure but also because of decreased resistance, usually giving at least twice as much flow increase for each increase in pressure as one might expect.

Vascular distensibility also plays other important roles in circulatory function. For example, the distensible nature of the arteries allows them to accommodate the pulsatile output of the heart and to average out the pressure pulsations. This provides smooth, continuous flow of blood through the very small blood vessels of the tissues.

The most distensible by far of all the vessels are the veins. Even slight increases in venous pressure cause the veins to store 0.5 to 1.0 liter of extra blood. Therefore, the veins provide a reservoir function for storing large quantities of extra blood that can be called into use whenever required elsewhere in the circulation.

Units of Vascular Distensibility

Vascular distensibility normally is expressed as the fractional increase in volume for each millimeter of mercury rise in pressure, in accordance with the following formula:

$$\text{Vascular distensibility} = \frac{\text{Increase in volume}}{\text{Increase in pressure} \times \text{Original volume}}$$

Difference in Distensibility of the Arteries and the Veins

Anatomically, the walls of the arteries are far stronger than those of the veins. Consequently, the arteries, on average, are about eight times less distensible than the veins. That is, a given increase in pressure causes about eight times as much increase in blood in a vein as in an artery of comparable size.

In the pulmonary circulation, the pulmonary vein distensibilities are similar to those of the systemic circulation. But, the pulmonary arteries normally operate under pressures about one sixth of those in the systemic arterial system, and their distensibilities are correspondingly greater, about six times the distensibility of systemic arteries.

Vascular Compliance (or Vascular Capacitance)

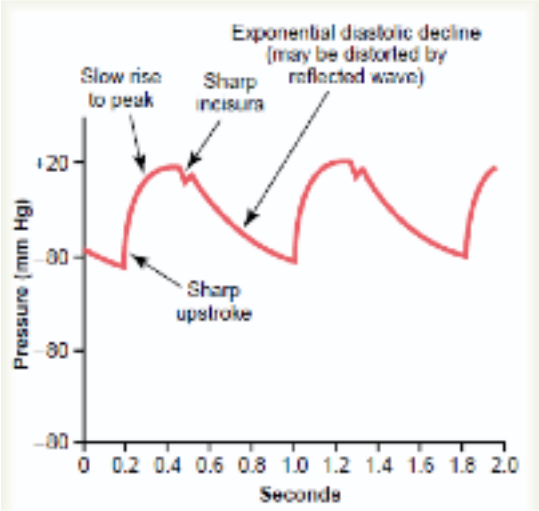
In hemodynamic studies, it usually is much more important to know the total quantity of blood that can be stored in a given portion of the circulation for each millimeter of mercury pressure rise than to know the distensibilities of the individual vessels. This value is called the compliance or capacitance of the respective vascular bed; that is,

$$\text{Vascular compliance} = \frac{\text{Increase in volume}}{\text{Increase in pressure}}$$

Compliance and distensibility are quite different. A highly distensible vessel that has a slight volume may have far less compliance than a much less distensible vessel that has a large volume because compliance is equal to distensibility times volume.

The compliance of a systemic vein is about 24 times that of its corresponding artery because it is about 8 times as distensible and it has a volume about 3 times as great (8 x 3 = 24).

39. Arterial pulse wave



A typical record of the pressure pulsations at the root of the aorta is shown in figure to the right. In the healthy young adult, the pressure at the top of each pulse, called the systolic pressure, is about 120 mm Hg. At the lowest point of each pulse, called the diastolic pressure, it is about 80 mm Hg. The difference between these two pressures, about 40 mm Hg, is called the pulse pressure.

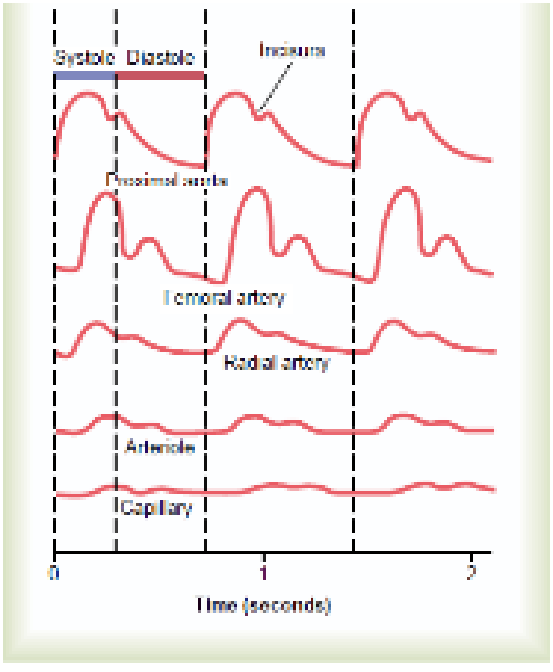
Two major factors affect the pulse pressure: (1) the stroke volume output of the heart and (2) the compliance (total distensibility) of the arterial tree.

In general, the greater the stroke volume output, the greater the amount of blood that must be accommodated in the arterial tree with each heartbeat, and, therefore, the greater the pressure rise and fall during systole and diastole, thus causing a greater pulse pressure. Conversely, the less the compliance of the arterial system, the greater the rise in pressure for a given stroke volume of blood pumped into the arteries.

The pulse pressure in old age sometimes rises to as much as twice normal, because the arteries have become hardened with arteriosclerosis and therefore are relatively noncompliant.

Transmission of Pressure Pulses to the Peripheral Arteries

The velocity of pressure pulse transmission in the normal aorta is 3 to 5 m/sec; in the large arterial branches, 7 to 10 m/sec; and in the small arteries, 15 to 35 m/sec. In general, the greater the compliance of each vascular segment, the slower the velocity, which explains the slow transmission in the aorta and the much faster transmission in the much less compliant small distal arteries.



Note especially in the three lower curves that the intensity of pulsation becomes progressively less in the smaller arteries, the arterioles, and, especially, the capillaries. In fact, only when the aortic pulsations are extremely large or the arterioles are greatly dilated can pulsations be observed in the capillaries.

This progressive diminution of the pulsations in the periphery is called damping of the pressure pulses. The cause of this is twofold: (1) resistance to blood movement in the vessels and (2) compliance of the vessels. The resistance damps the pulsations because a small amount of blood must flow forward at the pulse wave front to distend the next segment of the vessel; the greater the resistance, the more difficult it is for this to occur. The compliance damps the pulsations because the more compliant a vessel, the greater the quantity of blood required at the pulse wave front to cause an increase in pressure. Therefore, in effect, the degree of damping is almost directly proportional to the product of resistance times compliance.

40. Physiological role of endothelium

The endothelium is the thin layer of cells that line the interior surface of blood vessels, forming an interface between circulating blood in the lumen and the rest of the vessel wall. Endothelial cells line the entire circulatory system, from the heart to the smallest capillary. These cells reduce turbulence of the flow of blood allowing the fluid to be pumped farther.

The endothelium normally provides a non-thrombogenic surface because it contains heparan sulphate which acts as a cofactor for activating antithrombin III, a protease that cleaves several factors in the coagulation cascade.

Endothelial cells are involved in many aspects of vascular biology, including:

a) Vasoconstriction and vasodilation, and hence the control of blood pressure
b) Blood clotting (thrombosis & fibrinolysis)
c) Atherosclerosis
d) Formation of new blood vessels (angiogenesis)
e) Inflammation
f) Barrier function - the endothelium acts as a selective barrier between the vessel lumen and surrounding tissue, controlling the passage of materials and the transit of white blood cells into and out of the bloodstream. Excessive or prolonged increases in permeability of the endothelial monolayer, as in cases of chronic inflammation, may lead to tissue oedema/swelling.

In some organs, there are highly differentiated endothelial cells to perform specialized 'filtering' functions. Examples of such unique endothelial structures include the renal glomerulus and the blood-brain barrier.

Many substances can induce the contraction or relaxation of vascular smooth muscle. Many of these substances do so by acting directly on the arteriolar smooth muscle, but others act indirectly via the endothelial cells adjacent to the smooth muscle. Endothelial cells, in response to these latter substances as well as certain mechanical stimuli, secrete several paracrine agents that diffuse to the adjacent vascular smooth muscle and induce either relaxation or contraction, resulting in vasodilation or vasoconstriction, respectively.

One very important paracrine vasodilator released by endothelial cells is nitric oxide. Nitric oxide is released continuously in significant amounts by endothelial cells in the arterioles and contributes to arteriolar vasodilation in the basal state. In addition, its secretion rapidly and markedly increases in response to a large number of the chemical mediators involved in both reflex and local control of arterioles. For example, nitric oxide release is stimulated by bradykinin and histamine, substances produced locally during inflammation.

Another vasodilator the endothelial cells release is the eicosanoid protacyclin (PGI2). Unlike the case for nitric oxide, there is little basal secretion of PGI2, but secretion can increase markedly increases in response to various inputs.

One of the important vasoconstrictor paracrine agents that the endothelial cells release in response to certain mechanical and chemical stimuli is endothelin-1 (ET-1). ET-1 is a member of the endothelin family of peptide paracrine agents secreted by a variety of cells in diverse tissues and organs, including the brain, kidneys, and lungs. Not only does ET-1 serve as a hormone, causing widespread arteriolar vasoconstriction.

Endothelial cells in arteries can also secrete various paracrine agents that influence the arterie's smooth muscle, and thus, their diameters and resistances to flow. The force the flowing blood exerts on the inner surface of the arterial wall (the endothelial cells) is termed shear stress; it increases as the blood flow through the vessel increases. In response to this increased shear stress, arterial endothelium releases PGI2, increased amounts of nitric oxide, and less ET-1. All these changes cause the arterial vascular smooth muscle to relax and the artery to dilate. This flow-induced arterial vasodilation may be important in remodeling the arteries and in optimizing the blood supply to tissues under certain conditions.

<u>Endothelial exchange processes</u>

Nutrients and waste products are exchanged across the walls of the capillaries and postpapillary venules. Their endothelia can contain small (ca. 2–5 nm) or large (20–80 nm, especially in the kidneys and liver) functional pores: permeable, intercellular fissures or endothelial

fenestrae, respectively. The degree of endothelial permeability varies greatly from one organ to another. Virtually all endothelia allow water and inorganic ions to pass, but most are largely impermeable to blood cells and large protein molecules. Transcytosis and carriers allow for passage of certain larger molecules.

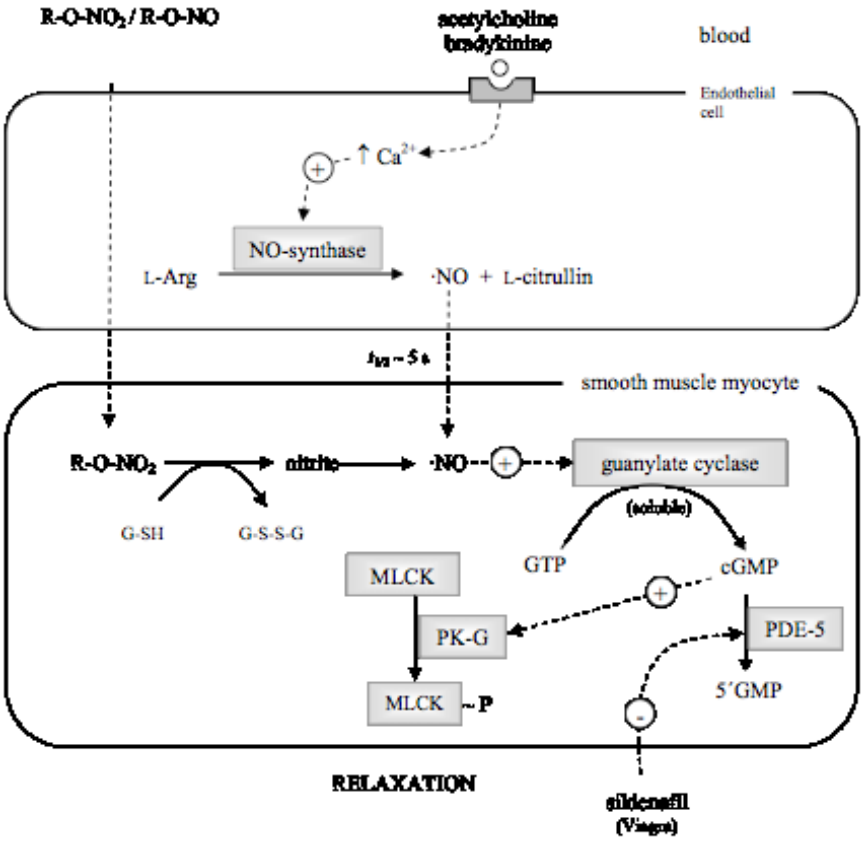
Filtration and reabsorption

About 20 L/day of fluid is filtered (excluding the kidneys) into the interstitium from the body's exchange vessels. About 18 L/day of this fluid is thought to be reabsorbed by the capillaries and venules. The remaining 2 L/day or so make up the lymph flow and thereby return to the bloodstream. The filtration or reabsorption rate Q_f is a factor of the endothelial filtration coefficient K_f (=water permeability k · exchange area A) and the effective filtration pressure P_{eff} ($Q_f = K_f \cdot P_{eff}$). P_{eff} is calculated as the hydrostatic pressure difference ΔP minus the oncotic pressure difference Δπ across the capillary wall (Starling's relationship), where ΔP = capillary pressure (P_{cap}) minus interstitial pressure (P_{int}, normally ≈ 0 mmHg).

In parts of the body below the heart, the effects of hydrostatic pressure from the blood column increase the pressure in the capillary lumen (in the feet 90 mmHg). The filtration rate in these regions therefore rise, especially when standing still. This is counteracted by two "self-regulatory" mechanisms:

(1) the outflow of water results in an increase in the luminal protein concentration (and thus Δπ) along the capillaries (normally the case in glomerular capillaries);

(2) increased filtration results in an increase in Pint and a consequent decrease in ΔP.



41. Vasoactive substances

Vasoactive hormones either have a direct effect on the vascular musculature (e.g., epinephrine) or lead to the local release of vasoactive substances (e.g., nitric oxide, endothelin) that exert local paracrine effects.

- Nitric (mon) oxide (NO) acts as a vasodilatory agent. NO is released from the endothelium when acetylcholine (M receptors), ATP, endothelin (ETB receptors), or histamine (H1 receptors) binds with an endothelial cell. NO then diffuses to and relaxes vascular myocytes in the vicinity.

- Endothelin-1 can lead to vasodilatation by inducing the release of NO from the endothelium by way of ETB receptors, or can cause vasoconstriction via ETA receptors in the vascular musculature. When substances such as angiotensin II or ADH (= vasopressin; V1 receptor) bind to an endothelial cell, they release endothelin-1, which diffuses to and constricts the adjacent vascular muscles with the aid of ETA receptors.

- Epinephrine (E): High concentrations of E from the adrenal medulla have a vasoconstrictive effect (α1 adrenoceptors), whereas low concentrations exert vasodilatory effects by way of β2 adrenoceptors in the myocardium, skeletal muscle and live. The effect of E mainly depends on which type of adrenoceptor is predominant in the organ. α1- adrenoceptors are predominant in the blood vessels of the kidney and skin.

- Eicosanoids: Prostaglandin (PG) F2α and the thromboxanes A2 (released from platelets) and B2 have vasoconstrictive effects, while PGI2 (= prostacyclin, e.g. released from endothelium) and PGE2 have vasodilatory effects. Another vasodilator released from the endothelium (e.g., by bradykinin) opens K+ channels in vascularmyocytes and hyperpolarizes them, leading to a drop in the cytosolic Ca2+ concentration. This endothelium-derived hyperpolarizing factor (EDHF), has been identified as a 11,12-epoxyeicosatrienoic acid (11,12-EET).

- Bradykinin and kallidin are vasodilatory agents cleaved from kininogens in blood plasma by the enzyme kallikrein. Histamine also acts as a vasodilator. All three substances influence also vessel permeability (e.g., during infection) and blood clotting.

42. Micro-circulation

Anatomy of the Capillary Network

Capillary structure varies considerably from organ to organ, but typical capillary is a thin-walled tube of endothelial cells one layer thick resting on a basement membrane, without any surrounding smooth muscle or elastic tissue. Capillaries in several organs have q second set of cells that surround the basement membrane and affect the ability of substances to penetrate the capillary wall.

The flat cells that constitute the endothelial tube are not attached tightly to each other but are separated by narrow, water-filled spaces termed intercellular clefts. The endothelial cells generally contain large numbers of endocytotic and exocytotic vesicles, and sometimes these fuse to form continuous fused-vesicle channels across the cell.

Blood flow through capillaries depends very much on the state of the other vessels that constitute the microcirculation. Thus, vasodilation of arterioles supplying the capillaries causes increased capillary flow, whereas arteriolar vasoconstriction reduces capillary flow, whereas arteriolar vasoconstriction reduces capillary flow.

In addition, in some tissues and organs, blood does not enter capillaries directly from arterioles but from vessels called metarterioles, which connect arterioles to venulles. Metarterioles, like arterioles, contain scattered smooth muscle cells. The site at which a capillary exits from a metarteriolle is surrounded by a ring of smooth muscle, a precapillary sphincter., which relaxes or contracts in response to local metabolic factors. When contracted, the precapillary sphincter closes the entry to the capillary completely. The more active the tissue, the more precapillary sphincters are open at any moment and the more capillaries in the network are receiving blood. Precapillary sphincters may also exist where the capillaries exit from arterioles.

Velocity of Capillary Blood Flow

When a continuous stream moves through consecutive sets of tubes, the velocity of flow decreases as the sum of the cross-sectional areas of the tubes increases. This is precisely the case in the cardiovascular system. The blood velocity is very great in the aorta, slows progressively in the arteries and arterioles, and then slows markedly as the blood passes through the huge cross-sectional area of the capillaries. Slow forward flow through the capillaries maximizes the time available for substances to exchange between the blood and interstitial fluid. The velocity of flow then progressively increases in the venules and veins because the cross-sectional area decreases. To reemphasize, flow velocity is not dependent on proximity to the heart, but rather on total cross-sectional area of the vessel type.

The cross-sectional area of the capillaries accounts for another important feature of capillaries: Because each capillary is very narrow, it offers considerable resistance flow, but the huge total number of capillaries provides such a large cross-sectional area that the total resistance of all the capillaries is much lower than that of the arterioles.

Diffusion Across the Capillary Wall: Exchanges of Nutrients and Metabolic End Products

The extremely slow forward movement of blood through the capillaries maximizes the time for substance exchange across the capillary wall. Three basic mechanisms allow substances to move between the interstitial fluid and the blood plasma: diffusion, vesicle transport, and bulk flow. Mediated transport constitutes a fourth mechanism in the capillaries of the brain.

In all capillaries, excluding those in the brain, diffusion is the only important means by which net movement of nutrients, oxygen, and metabolic end products occurs across the capillary walls. Lipid-soluble substances, including oxygen and carbon dioxide, easily diffuse through the plasma membranes of the capillary endothelial cells. In contrast, ion and polar molecules are poorly soluble in lipid and must pass through small water-filled channels in the endothelial lining.

The presence of water-filled channels in the capillary walls causes the permeability of ions and small polar molecules to be quite high, although still much lower than that of lipid-soluble molecules. One location where these channels exist is in the intercellular clefts - that is, te narrow water-filled spaces between adjacent cells. The fused-vesicle channels that penetrate the endothelial cells provide another set of water-filled channels.

The water-filled channels allow only very small amounts of protein to diffuse through them. Very small amounts of protein may also cross the endothelial cells by vesicle transport - endocytosis of plasma at the luminal border and exocytosis of the endocytotic vesicle at the interstitial side.

Variations in the size of the water-filled channels account for great differences in the “leakiness” of capillaries in different organs. At one extreme are the “tight” capillaries of the brain, which have no intercellular clefts, only tight junctions. Therefore, water-soluble substances, even those of low molecular weight, can gain access to or exit from the brain interstitial space only by carrier-mediated transport through the blood-brain barrier.

At the other end of the spectrum are liver capillaries, which have large intercellular clefts as well as large holes in the plasma membranes of the endothelial cells so that even protein molecules can readily pass across them. This is important because two of the major functions of the liver are the synthesis of plasma proteins and the metabolism of substances bound to plasma proteins.

The leakiness of capillaries in most organs and tissues lies between these extremes of brain and liver capillaries.

Nutrients diffuse first from the plasma across the capillary wall into the interstitial fluid, where they gain entry to cells. Conversely, metabolic end products from the tissues move across the cells’ plasma membranes into interstitial fluid, where they diffuse across the capillary endothelium into the plasma.

Transcapillary diffusion gradients for oxygen and nutrients occur as a result of cellular utilization of the substance. Those for metabolic end products arise as a result of cellular production of the substance. Consider two examples: glucose and carbon dioxide in muscle. Glucose is continuously transported from interstitial fluid into the muscle cell by carrier-mediated transport mechanisms. The removal of glucose from interstitial fluid lowers the interstitial fluid glucose concentration below the glucose concentration in capillary plasma and creates the gradient for glucose diffusion from the capillary into the interstitial fluid.

Simultaneously, carbon dioxide, which is continuously produced by muscle cells, diffuses into the interstitial fluid. This causes the carbon dioxide concentration in the interstitial fluid to be greater for carbon dioxide diffusion from the interstitial fluid into the capillary.

If a tissue is to increase its metabolic rate, is must obtain more nutrients from the blood and must eliminate more metabolic end products. One mechanism for achieving that is active hyperemia. The second important mechanism is increased diffusion gradients between plasma and tissue: increased cellular utilization of oxygen and nutrients lowers their tissue concentrations, whereas increased production of carbon dioxide and other end products raises their tissue concentrations. In both cases, the substance’s transcapillary concentration difference increases, which also increases the rate of diffusion.

43. Venous pressure

The factors determining pressure in any elastic tube are the volume of fluid within it and the compliance of its walls. Accordingly, total blood volume is one important determinant of venous pressure since, at any given moment most blood is in the veins. Also the walls of the veins are thinner and much more compliant than those of arteries. Thus, veins can accomodate large volumes of blood with a relatively small increase in internal pressure. Approximately 60% of the total blood volume is present in the systemic veins at any given moment, but the venous averages less than 10 mmHg. (In contrast, the systemic arteries contain less than 15% of the blood, at a pressure of nearly 100 mmHg).

The walls of the veins contain smooth muscle innervated by sympathetic neurons. Stimulation os these neurons releases norepinephrine, which causes contraction of the venous smooth muscle, decreasing the diameter and compliance of the vessels and raising the pressure within them. Increased venous pressure then drives more blood out of the veins into the right side of the heart. Although the sympathetic nerves are the most important input, venous smooth muscle, like arteriolar smooth muscle, also responds to hormonal and paracrine vasodilators and vasoconstrictors.

Two other mechanisms, in addition to contraction of venous smooth muscle, can increase venous pressure and facilitate venous return. These mechanisms are the skeletal muscle pump and te respiratory pump. During skeletal muscle contraction, the veins running through the muscle partially compressed, which reduces their diameter and forces more blood back the heart. Now we can describe a major function of the peripheral-vein valves: when the skeletal muscle pump raises venous pressure locally, the valves permit blood flow only toward the heart and prevent flow back toward the tissues.

The respiratory pump is somewhat more difficult to visualize. During inspiration of air, the diaphragm descends, pushing on the abdominal contents and increasing abdominal pressure. This pressure increase is transmitted passively to the intraabdominal veins. Simultaneously, the pressure in the thorax decreases, thereby decreasing the pressure in the intrathoracic veins and right atrium. The net effect of the pressure changes in the abdomen and thorax is to increase the pressure difference between the peripheral veins and the heart. Thus, venous return is enhanced during inspiration (expiration would reverse this effect in not for the venous valves). The larger the inspiration, the greater the effect. Thus, breathing deeply and frequently, as in exercise, helps blood flow toward the heart.

Any change in venous return almost immediately causes equivalent changes in cardiac output, largely through the Frank-Starling mechanism. Venous return and cardiac output therefore must be identical except for very brief periods of time.

44. Venous return. Venous stasis and embolism

The venous return to the heart is the sum of all the local blood flows through all the individual tissue segments of the peripheral circulation. Therefore, it follows that cardiac output regulation is the sum of all the local blood flow regulations. In most tissues, blood flow increases mainly in proportion to each tissue's metab- olism. cardiac output is determined by the sum of all the various factors throughout the body that control local blood flow. All the local blood flows summate to form the venous return, and the heart automatically pumps this returning blood back into the arteries to flow around the system again.

Three principal factors that affect venous return to the heart from the systemic circulation. They are as follows:

1. Right atrial pressure, which exerts a backward force on the veins to impede flow of blood from the veins into the right atrium.
2. Degree of filling of the systemic circulation (measured by the mean systemic filling pressure), which forces the systemic blood toward the heart (this is the pressure measured everywhere in the systemic circulation when all flow of blood is stopped—we discuss this in detail later).
3. Resistance to blood flow between the peripheral vessels and the right atrium. These factors can all be expressed quantitatively by the venous return curve.

Plateau in the Venous Return Curve at Negative Atrial Pressures—Caused by Collapse of the Large Veins.

When the right atrial pressure falls below zero—that is, below atmospheric pressure—further increase in venous return almost ceases. And by the time the right atrial pressure has fallen to about -2 mm Hg, the venous return will have reached a plateau. It remains at this plateau level even though the right atrial pressure falls to -20 mm Hg, -50 mm Hg, or even further. This plateau is caused by collapse of the veins entering the chest. Negative pressure in the right atrium sucks the walls of the veins together where they enter the chest, which prevents any additional flow of blood from the peripheral veins. Consequently, even very negative pressures in the right atrium cannot increase venous return significantly above that which exists at a normal atrial pressure of 0 mm Hg.

Mean Circulatory Filling Pressure and Mean Systemic Filling Pressure, and Their Effect on Venous Return

When heart pumping is stopped, flow of blood everywhere in the circulation ceases a few seconds later. Without blood flow, the pressures everywhere in the circulation become equal. This equilibrated pressure level is called the mean circulatory filling pressure.

Effect of Blood Volume on Mean Circulatory Filling Pressure.

The greater the volume of blood in the circulation, the greater is the mean circulatory filling pressure because extra blood volume stretches the walls of the vasculature.

Mean Systemic Filling Pressure and Its Relation to Mean Circulatory Filling Pressure.

The mean systemic filling pressure, Psf, is slightly different from the mean circulatory filling pressure. It is the pressure measured everywhere in the systemic circulation after blood flow has been stopped by clamping the large blood vessels at the heart, so that the pressures in the systemic circulation can be measured independently from those in the pulmonary circulation. The mean systemic pressure, although almost impossible to measure in the living animal, is the important pressure for determining venous return. The mean systemic filling pressure, however, is almost always nearly equal to the mean circulatory filling pressure because the pulmonary circulation has less than one eighth as much capacitance as the systemic circulation and only about one tenth as much blood volume.

Effect on the Venous Return Curve of Changes in Mean Systemic Filling Pressure.

The greater the mean systemic filling pressure (which also means the greater the “tightness” with which the circulatory system is filled with blood), the easier it is for blood to flow into the heart. The less the filling, the more difficult it is for blood to flow into the heart.

“Pressure Gradient for Venous Return”—When This Is Zero, There Is No Venous Return.

When the right atrial pressure rises to equal the mean systemic filling pressure, there is no longer any pressure difference between the peripheral vessels and the right atrium. Consequently, there can no longer be any blood flow from any peripheral vessels back to the right atrium. However, when the right atrial pressure falls progressively lower than the mean systemic filling pressure, the flow to the heart increases proportionately. That is, the greater the difference between the mean systemic filling pressure and the right atrial pressure, the greater becomes the venous return. Therefore, the difference between these two pressures is called the pressure gradient for venous return.

Resistance to Venous Return

In the same way that mean systemic filling pressure represents a pressure pushing venous blood from the periphery toward the heart, there is also resistance to this venous flow of blood. It is called the resistance to venous return. Most of the resistance to venous return occurs in the veins, although some occurs in the arterioles and small arteries as well.

Why is venous resistance so important in determining the resistance to venous return? The answer is that when the resistance in the veins increases, blood begins to be dammed up, mainly in the veins themselves. But the venous pressure rises very little because the veins are highly distensible. Therefore, this rise in venous pressure is not very effective in overcoming the resistance, and blood flow into the right atrium decreases drastically. Conversely, when arteriolar and small artery resistances increase, blood accumulates in the arteries, which have a capacitance only 1/30 as great as that of the veins. Therefore, even slight accumulation of blood in the arteries raises the pressure greatly—30 times as much as in the veins—and this high pressure does overcome much of the increased resistance. Mathematically, it turns out that about two thirds of the so-called “resistance to venous return” is determined by venous resistance, and about one third by the arteriolar and small artery resistance.

Venous return can be calculated by the following formula:

$$VR = \frac{Psf - PRA}{RVR}$$

in which VR is venous return, Psf is mean systemic filling pressure, PRA is right atrial pressure, and RVR is resistance to venous return. In the healthy human adult, the values for these are as follows: venous return equals 5 L/min, mean systemic filling pressure equals 7 mm Hg, right atrial pressure equals 0 mm Hg, and resistance to venous return equals 1.4 mm Hg per liter of blood flow.

Venous statis

Is a condition of slow blood flow in the veins, usually of the legs. A patient with venous stasis might be more vulnerable to the formation of blood clot, especially in the deep veins of the legs, called deep vein thrombosis (DVT). Causes include long periods of immobility such as when driving for long distances. It has been called the coach-class syndrome because of prevalence in long distance travel in cramped space. It also occurs in prolonged bed rest with an illness or after surgery.

Deep vein thrombosis

The most serious complication of a DVT is that the clot could dislodge and travel to the lungs, which is called a pulmonary embolism (PE).

According to Virchow's triad, venous thrombosis occurs via three mechanisms: (1) decreased flow rate of the blood, (2) damage to the blood vessel wall and (3) an increased tendency of the blood to clot (hypercoagulability). There are several factors which can increase a person's risk for DVT, including surgery, hospitalization, immobilization, smoking, obesity, age, certain drugs (such as estrogen or erythropoietin) and inborn tendencies to form clots known as thrombophilia (for

example, in carriers of factor V Leiden). Women have an increased risk during pregnancy and in the postnatal period.

45. Lymphatic system

The lymphatic system is a network of small organs (lymph nodes) and tubes (lymphatic vessels) through which lymph - a fluid derived from interstitial fluid - flows. The lymphatic system is not technically part of the cardiovascular system, but its vessels provide a route for the movement of interstitial fluid to the cardiovascular system.

Present in the interstitium of virtually all organs and tissues are numerous lymphatic capillaries that are completely distinct from blood vessel capillaries. Like the latter, they are tubes made of only a single layer of endothelial cells resting on a basement membrane, but they have large water-filled channels that are permeable to all interstitial fluid contituents, including protein. The lymphatic capillaries are the first of the lymphatic vessels, for unlike the blood vessel capillaries, no tubes flow into them.

Small amounts of interstital fluid continuously enter the lymphatic capillaries by bulk flow. The fluid flows from the lymphatic capillaries into the next set of lymphatic vessels, which converge to form larger and larger lymphatic vessels. At various point in the body - in particular the neck, armpits, groin, and around the intestines - the lymph flows through lymph nodes. Ultimately, the entire network ends in two large lymphatic ducts that drain into the veins near the junction of the jugular and subclavian veins in the upper chest. Valves at these junctions permit only one-way flow from lymphatic ducts into the veins. Thus, the lymphatic vessels carry interstitial fluid to the cardiovascular system.

The movement of interstitial fluid from the lymphatics to the cardiovascular system is very important because, as noted earlier, the amount of fluid filtered out of the all the blood vessel capillaries exceeds that absorbe by approximately 4 L each day. This 4 L is returned to the blood via the lymphatic system. In the process, the small amounts of protein that leak out of blood vessel capillaries into the interstitial fluid are also returned to the cardiovascular system.

Failure of the lymphatic system due, for example, to occlusion by infectious organisms (as in elephatiasis) allows the accumulation of excessive interstitial fluid. The result can be massive swelling of the involved area. Surgical removal of lymph nodes and vessels during the treatment of breast cancer can similarly allow interstitial fluid to pool in affected tissues. The accumulation of large amounts of interstitial fluid from whatever cause is termed edema.

In addition to draining excess interstitial fluid, the lymphatic system provides the pathway by which fat absorbed from the gastrointestinal tract reaches the blood. The lymphatics also, unfortunately, are often the route by which cancer cells spread from their area of origin to other parts of the body (which is why cancer treatment sometimes includes their removal).

Mechanism of Lymph Flow

In large part, the lymphatic vessels beyond the lymphatic capillaries propel the lymph within them by their own contractions. The smooth muscle in the wall of the lymphatics exerts a pumplike action by inherent rhythmical contractions. Since the lymphatic vessels have valves similar to those in veins, these contractions produce one-way flow toward the point at which the lymphatics enter the circulatory system. The lymphatic vessel smooth muscle is responsive to stretch, so when no interstitial fluid accumulates, and therefore no lymph enters the lymphatics, the smooth muscle is inactive. As lymph formation increases, however, like when there is increased fluid filtration out of blood vessel capilaries, the increased fluid entering the lymphatics stretches the walls and triggers rythmical contractions of the smooth muscle. This constitutes a negative feedback mechanism for adjusting the rate of lymph flow to the rate of lymph formation and thereby preventing edema.

In addition, the smooth muscle of the lymphatic vessels is innervated by sympathetic neurons, and excitation of these neurons in various physiological states such as exercise my contribute to increase lymph flow. Forces external to the lymphatic vessels also enhance lymph flow. These include the same external forces we described for veins - the skeletal muscle pump and respiratory pump.

46. Pulmonary circulation

The pulmonary circulation includes blood pumped from the right ventricle through the lungs and then to the left atrium. It is then pumped through the systemic circulation from the left ventricle through all the organs and tissues of he body and then to the right atrium.

In the pulmonary circulation blood leaves the right ventricle via a single large artery, the pulmonary trunk, which divides into the two pulmonary arteries, one supplying the right lung and the other the left. The pulmonary artery extends only 5 centimeters beyond the apex of the right ventricle and then divides into right and left main branches that supply blood to the two respective lungs.

The pulmonary artery is thin, with a wall thickness one third that of the aorta. The pulmonary arterial branches are very short, and all the pulmonary arteries, even the smaller arteries and arterioles, have larger diameters than their counterpart systemic arteries. This, combined with the fact that the vessels are thin and distensible, gives the pulmonary arterial tree a large compliance, averaging almost 7 ml/mm Hg, which is similar to that of the entire systemic arterial tree. This large compliance allows the pulmonary arteries to accommodate the stroke volume output of the right ventricle.In the lungs, the arteries continue to branch, ultimately forming capillaries that unite into venules and then veins. The blood leaves the lungs via four pulmonary veins, which empty into left atrium. The pulmonary veins, like the pulmonary arteries, are also short. They immediately empty their effluent blood into the left atrium, to be pumped by the left heart through the systemic circulation.

As blood flows through the lung capillaries, it picks up oxygen supplied to the lungs by breathing. Therefore, the blood in the pulmonary veins, left side of the heart, and systemic arteries has a oxygen content. As this blood flows through the capillaries of peripheral tisues and organs, some of this oxygen leaves the blood to enter and be used by cells, resulting in the lower oxygen content of systemic venous blood.

Note that the lungs receive all the blood pumped by the right side of the heart, whereas the branching pattern of the systemic arteries results in a parallel pattern so that eaach of the peripheral organs and tissues receives only fraction of the blood pumped by the left ventricle.

Bronchial Vessels

Blood also flows to the lungs through small bronchial arteries that originate from the systemic circulation, amounting to about 1 to 2 per cent of the total cardiac output. This bronchial arterial blood is oxygenated blood, in contrast to the partially deoxygenated blood in the pulmonary arteries. It supplies the supporting tissues of the lungs, including the connective tissue, septa, and large and small bronchi. After this bronchial and arterial blood has passed through the supporting tissues, it empties into the pulmonary veins and enters the left atrium, rather than passing back to the right atrium. Therefore, the flow into the left atrium and the left ventricular output are about 1 to 2 per cent greater than the right ventricular output.

Lymphatics

Lymph vessels are present in all the supportive tissues of the lung, beginning in the connective tissue spaces that surround the terminal bronchioles, coursing to the hilum of the lung, and thence mainly into the right thoracic lymph duct. Particulate matter entering the alveoli is partly removed by way of these channels, and plasma protein leaking from the lung capillaries is also removed from the lung tissues, thereby helping to prevent pulmonary edema.

47. Cerebral circulation

Cranial arteries

The brain is supplied by four large arteries: the two internal carotid arteries and the two vertebral arteries:

1) Internal carotid artery: These large arteries branches of the common carotid arteries in the neck which enter the skull (via external carotid aperture). The internal carotid artery branches into: the superior hypophysial artery, the ophtalmic artery, the posterior communicating artery and the anterior choroidal artery. It then divides into two large terminal branches, the anterial cerebral artery and the middle cerebral artery.
2) Vertebral arteries: These smaller arteries branch from the subclavian arteries an enter the cranial cavity through the foramen magnum. Within the cranium the two vertebral arteries fuse into the basilar artery, which supplies the midbrain, cerebellum, (via the posterior cerebellar artery, anterior inferior cerebellar artery, labyrinthine artery, pontine arteries amd the superior cerebellar artery) and usually branches into the posterior cerebral artery.

The circle of Willis - the posterior communicating arteries connect on both sides the posterior cerebral arteries with the internal carotid arteries so that the blood flow of the vertebral arteries can communicate with the carotid circulation. The anterior cerebral arteries are interconnected through the anterior communicating artery. This way, a closied cerebral arterial circle is created at the base of the brain. However, the anastomoses are often so thin that they do not allow for significant exchange of blood. Under conditions of normal intracranial pressure, each hemisphere is fed by the ipsilateral ineternal carotid artery and the ipsilateral posterial cerebral artery.

Cerebral venous drainage

The major veins lie on the surface of the brain in the subarachnoid space; some deep veins run beneath the ependyma. The cerebral veins do not possess valves. They exhibit considerable variations with respect to course and drainage. Quite often there are several small vessels instead of a single major vein. The cerebral veins are divided into two groups: the superficial cerebral veins which drain the blood into the sinuses of the dura mater, and the deep cerebral veins which drain the blood into the great cerebral vein.

Superficial Cerebral Veins

We distinguish between the group of superior cerebral veins and the group of inferior veins.

The superior cerebral veins, totaling about 10-15 veins, collect the blood from the frontal and parietal lobes and carry it into the superior sagittal sinus.

The inferior cerebral veins receive the blood from the temporal lobe and from the basal regions of the occipital lobe; they empty into the transverse sinus and the superior petrosals sinus. The most prominent of these sinuses is the superior sagittal sinus which flows in the sagittal plane under the midline of the cerebral vault, posteriorly and inferiorly to the torcula, forming the confluence of sinuses, where the superficial drainage joins with the sinus the primarily drains the deep venous system. From here, two transverse sinuses bifurcate and travel laterally and inferiorly in an S-shaped curve that form the sigmoid sinuses which go on to form the two jugular veins. In the neck, the jugular veins parallel the upward course of the carotid arteries and drain blood into the vena cava.

Deep Cerebral Veins

The deep venous drainage is primarily composed of traditional veins inside the deep structures of the brain, which join behind the midbrain to form the vein of Galen. This vein merges with the inferior sagittal sinus to form the straight sinus which then joins the superficial venous system mentioned above at the confluence of sinuses.

Cerebral Microcirculation

As is true for almost all other tissues of the body, the number of blood capillaries in the brain is greatest where the metabolic needs are greatest. The overall metabolic rate of the brain gray matter where the neuronal cell bodies lie is about four times as great as that of white matter;

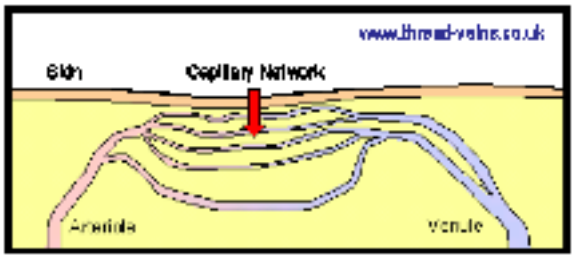
correspondingly, the number of capillaries and rate of blood flow are also about four times as great in the gray matter.

An important structural characteristic of the brain capillaries is that they are much less “leaky” than the blood capillaries in almost any other tissue of the body. One reason for this is that the capillaries are supported on all sides by “glial feet,” which are small projections from the surrounding glial cells that abut against all sur- faces of the capillaries and provide physical support to prevent overstretching of the capillaries in case of high capillary blood pressure.

The walls of the small arterioles leading to the brain capillaries become greatly thickened in people who develop high blood pressure, and these arterioles remain significantly constricted all the time to prevent transmission of the high pressure to the capillaries.

48. Skin circulation

Skin is a complex organ that covers almost all of the body surface. It has many functions but, as far as thread veins are concerned, its role as a regulator of body heat is important.



The skin has a blood supply from many small arterioles - these are small blood vessels that take blood at higher pressure into the capillary networks. The capillary networks are made up of a great many tiny vessels with very thin walls.

From these networks the blood flows back into venules - these are small veins that take the blood back to the larger veins and then ultimately the heart.

Blood flow in the capillary networks can be controlled by the body using both hormones and nerves (the sympathetic nervous system). When your body is too hot, more blood is allowed into the capillary networks and so more heat is lost to the air around the body. When this happens, the skin goes pink or red (often called flushing or blushing).
When your body is too cold, blood is not allowed into the capillary networks and so heat is kept in the body and the skin acts as insulation - this makes the skin look very white. Thread veins of the legs occur when the venules dilate (get bigger) and become big enough to be visible through the skin. Thread veins of the FACE are usually more related to increased flow in the feeding Arteriole end of the network.

Skin

- Has extensive sympathetic inervation. Cutaneous blood flow is under extrinsic control.
- Temperature regulation is the principal function of the cutaneous sympathetic nerves. Increased ambient temperatre leads to cutaneous vasodilation, allowing dissipation of excess body heat.
- Trauma produces the “triple response” in skin - a red line, a red flare, aand a wheal. A wheal is local edema that results from the local release of histamine, which increases capillary filtration.

49. Muscle and splanchnic circulation

Circulation in skeletal muscle

- Resting blood flow through the muscles is ~4ml/min/100g

- This can increase 20 fold during exercise. Why? Higher blood flow is needed in order to meet with O2/nutrient consumption and CO_2 removal demands.

- Contraction of muscle will slightly decrease blood flow due to mechanical contraction of the vessel caused by the surround contracting muscles, therefore blood flow increases between contractions (temporary).

- During contraction, metabolic rate of tissue increase, and therefore O2 concentration decreases causing a vasodilative reflex.

- Muscle exercise also releases vasodilators such as: adenosine, K+, H+, Lactic acid, and CO_2.

- Sympathetic stimulation can vastly reduce blood flow e.g., in circulatory shock. This is due postganglionic nerve release of NE/E and also adrenal release of NE/E in the blood acting on α1-adrenergenic receptors causing vasoconstriction.

- During exercise, we know that there are massive cardiovascular changes caused by sympathetic discharge and parasympathetic inhibition which results in: increase HR, increase heart strength, increase in heart conductance, arteriole and venous constriction (exception to this is the vasodilation in the vasculature of muscles, brain and coronary bed. How? E can stimulate β2-adrenogenic receptors causing vasodilation: vasodilation -> increases blood flow -> more efficient rate of O2/ CO_2 exchange -> increase mean systemic filling pressure -> increase venous return -> increases EDV (starlings hypothesis) -> increases CO up to 35L/min.

- Exercise also increases mean arterial pressure (to 20-80mmHg) due to arteriolar and small artery constriction, increased cardiac contractility, increase mean systemic filling pressure which helps to increase CO during exercise.

Splanchnic Circulation

The blood vessels of the gastrointestinal system are part of a more extensive system called the splanchnic circulation. It includes the blood flow through the gut itself plus blood flows through the spleen, pancreas, and liver. The design of this system is such that all the blood that courses through the gut, spleen, and pancreas then flows immediately into the liver by way of the portal vein. In the liver, the blood passes through millions of minute liver sinusoids and finally leaves the liver by way of hepatic veins that empty into the vena cava of the general circulation. This flow of blood through the liver, before it empties into the vena cava, allows the reticuloendothelial cells that line the liver sinusoids to remove bacteria and other particulate matter that might enter the blood from the gastrointestinal tract, thus preventing direct transport of potentially harmful agents into the remainder of the body.

The nonfat, water-soluble nutrients absorbed from the gut (such as carbohydrates and proteins) are transported in the portal venous blood to the same liver sinusoids. Here, both the reticuloendothelial cells and the principal parenchymal cells of the liver, the hepatic cells, absorb and store temporarily from one half to three quarters of the nutrients. Also, much chemical intermediary processing of these nutrients occurs in the liver cells. Almost all of the fats absorbed from the intestinal tract are not carried in the portal blood but instead are absorbed into the intestinal lymphatics and then conducted to the systemic circulating blood by way of the thoracic duct, bypassing the liver.

<u>Anatomy of the Gastrointestinal Blood Supply</u>

The arterial blood supply to the gut includes the superior mesenteric and inferior mesenteric arteries supplying the walls of the small and large intestines by way of an arching arterial system and the celiac artery, which provides a similar blood supply to the stomach. On entering the wall of the gut, the arteries branch and send smaller arteries circling in both directions around the gut, with the tips of these arteries meeting on the side of the gut wall opposite the mesenteric attachment. From the circling arteries, still much smaller arteries penetrate into the intestinal wall and spread (1) along the muscle bundles, (2) into the intestinal villi, and (3) into submucosal vessels beneath the epithelium to serve the secretory and absorptive functions of the gut.

Effect of Gut Activity and Metabolic Factors on Gastrointestinal Blood Flow

Under normal conditions, the blood flow in each area of the gastrointestinal tract, as well as in each layer of the gut wall, is directly related to the level of local activity. For instance, during active absorption of nutrients, blood flow in the villi and adjacent regions of the submucosa is increased as much as eightfold. Likewise, blood flow in the muscle layers of the intestinal wall increases with increased motor activity in the gut. For instance, after a meal, the motor activity, secretory 100 per cent; therefore, the increased mucosal and gut wall metabolic rate during gut activity probably lowers the oxygen concentration enough to cause much of the vasodilation.

"Countercurrent" Blood Flow in the Villi

Note that the arterial flow into the villus and the venous flow out of the villus are in directions opposite to each other, and that the vessels lie in close apposition to each other. Because of this vascular arrangement, much of the blood oxygen diffuses out of the arterioles directly into the adjacent venules without ever being carried in the blood to the tips of the villi. As much as 80 per cent of the oxygen may take this short-circuit route and therefore not be available for local metabolic functions of the villi.

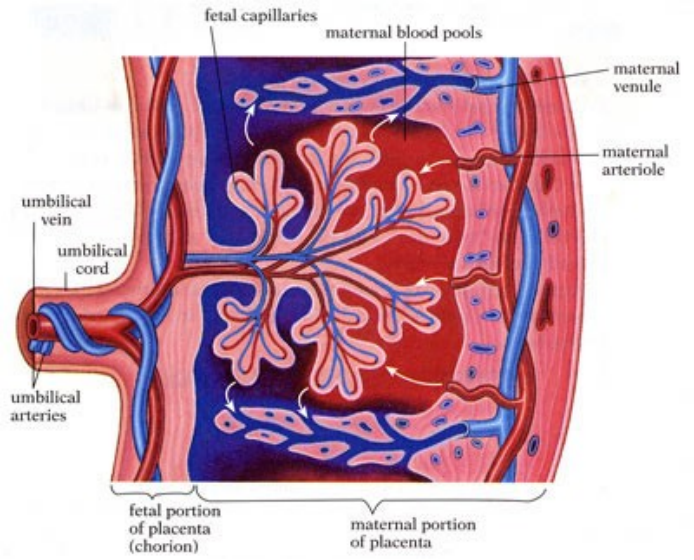
Under normal conditions, this shunting of oxygen from the arterioles to the venules is not harmful to the villi, but in disease conditions in which blood flow to the gut becomes greatly curtailed, such as in circulatory shock, the oxygen deficit in the tips of the villi can become so great that the villus tip or even the whole villus suffers ischemic death and can disintegrate.

Nervous Control of Gastrointestinal Blood Flow

Stimulation of the parasympathetic nerves going to the stomach and lower colon increases local blood flow at the same time that it increases glandular secretion. This increased flow probably results secondarily from the increased glandular activity and not as a direct effect of the nervous stimulation.

Sympathetic stimulation, by contrast, has a direct effect on essentially all the gastrointestinal tract to cause intense vasoconstriction of the arterioles with greatly decreased blood flow. After a few minutes of this vasoconstriction, the flow often returns almost to normal by means of a mechanism called "autoregulatory escape." That is, the local metabolic vasodilator mechanisms that are elicited by ischemia become prepotent over the sympathetic vasoconstriction and, therefore, redilate the arterioles, thus causing return of necessary nutrient blood flow to the gastrointestinal glands and muscle.

50. Placental and faetal circulation



Placental Circulation

The branch chorionic villi of the placenta provide a large surface area where materials may be exchanged across the very thin placental membrane ("barrier") interposed bwtween the fetal and maternal circulations. It is through the numerous branch villi that arise from the stem villi that the main exchange of material between the mother and the fetus takes place. The circulations of the fetus and the mother are separated by the placental membrane consisting of extrafetal tissues.

Fetal Placental Circulation

Poorly oxygenated blood leaves the fetus and passes through the umbilical arteries to the placenta. At the site of attachment of the umbilical cord to the placenta, these arteries divideinto several radially disposed chorionic arteries that branch freely in the chorionic plate before entering the chorionic villi. The blood vessels form an extensive anteriocapillary-venous system within the chorionic villi, which brings the fetal blood extremely close to the maternal blood. This system provides a very large surface area for the exchange of metabolic and gaseous products between the maternal and fetal bloodstreams. There is normally no intermingling of fetal and maternal blood; however, very small amounts of fetal blood may enter the maternal circulation when minute defects develop in the placental membrane. The well-oxygenated fetal blood in the fetal capillaries passes into thin-walled veins that follow the chorionic arteries to the site of attachment of the umbilical vein. This large vessel carries oxygen-rich blood to the fetus.

Maternal Placental Circulation

The maternal blood in the intervillous space is temporarily outside the maternal circulatory system. It enters the intervillous space through 80 to 100 spiral endometrial arteries in the decidua basalis. These vessels discharge into the intervillous space through gaps in the cytrotophoblastic shell. The blood flow from the spiral arteries is pulsatile and is propelled in jetlike fountains by the maternal blood pressure. The entering blood is at a considerably higher pressure than that in the intervillous space and spurts toward the chorionic plate forming the "roof" of the intervillous space. As the pressure dissipates, the blood flows slowly over the branch villi, allowing an exchange of metabolic and gaseous products with the fetal blood. the blood eventually returns through the endometrial veins to the maternal circulation.

The welfare of the embryo and fetus depends more on the adequate bathing of the branch villi with maternal blood than on any other factor. Reductions of uteroplacental circulation result in fetal hypoxia and intrauterine growth restriction (IUGR). Severe reductions of uteroplacental circulation may result in fetal death. The intervillous space of the mature placenta contains approximately 150 ml of blood that is replenished three or four times per minute. The intermittent contractions of the uterus during pregnancy decrease uteroplacental blood flow slightly; however, they do not force significant amounts of blood out of the intervillous space. Consequently, oxygen transfer to the fetus is decreased during uterine contractions, but does not stop.

Fetal circulation

The blood flows through the fetal body as follows: After being arterialized in the placenta, the blood passes into the fetus via the umbilical vein and part of it travels through the ductus venosus (Arantii), thereby bypassing the liver. When entering the inferior vena cava, the blood mixes with venous blood from the lower half of the body. Guided by special folds in the vena cava, the mixed blood passes directly from right atrium to the left atrium through an opening in the atrial septum (foramen ovale). From the left atrium, it then proceeds to the left ventricle. While in the right atrium, the blood mingles with venous blood from the superior vena cava (only slight mixing), which is

received by the right ventricle. Only about one-third of this blood reaches the lungs (due to high flow resistance since the lungs are not yet expanded, and due to hypoxic vasoconstriction). The other two-thirds of the blood travels through the ductus arteriosus (Botalli) to the aorta (right-to-left shunt). Due to the low peripheral resistance (placenta), the blood pressure in the aorta is relatively low—only about 65mmHg towards the end of pregnancy.

The arteries of the head and upper body are supplied with partly arterialized blood from the left ventricle. This is important since brain tissue is susceptible to hypoxia. The remaining blood leaves the aorta and mixes with venous blood from the ductus arteriosus. As a result, the blood supplied to the lower half of the body has a relatively low O2 concentration (O2 saturation = 0.3). The majority of this blood returns via the umbilical arteries to the placenta, where it is oxygenated again.

51. Circulatory adjustments at birth

Changes in the Fetal Circulation at Birth

Primary Changes in Pulmonary and Systemic Vascular Resistances at Birth

The primary changes in the circulation at birth are, first, loss of the tremendous blood flow through the placenta, which approximately doubles the systemic vascular resistance at birth. This increases the aortic pressure as well as the pressures in the left ventricle and left atrium.

Second, the pulmonary vascular resistance greatly decreases as a result of expansion of the lungs. In the unexpanded fetal lungs, the blood vessels are compressed because of the small volume of the lungs. Immediately on expansion, these vessels are no longer compressed and the resistance to blood flow decreases severalfold. Also, in fetal life, the hypoxia of the lungs causes considerable tonic vasoconstriction of the lung blood vessels, but vasodilation takes place when aeration of the lungs eliminates the hypoxia. All these changes together reduce the resistance to blood flow through the lungs as much as fivefold, which reduces the pulmonary arterial pressure, right ventricular pressure, and right atrial pressure.

Closure of the Foramen Ovale

The low right atrial pressure and the high left atrial pressure that occur secondarily to the changes in pulmonary and systemic resistances at birth cause blood now to attempt to flow backward through the foramen ovale; that is, from the left atrium into the right atrium, rather than in the other direction, as occurred during fetal life. Consequently, the small valve that lies over the foramen ovale on the left side of the atrial septum closes over this opening, thereby preventing further flow through the foramen ovale.

In two thirds of all people, the valve becomes adherent over the foramen ovale within a few months to a few years and forms a permanent closure. But even if permanent closure does not occur, the left atrial pressure throughout life normally remains 2 to 4 mm Hg greater than the right atrial pressure, and the backpressure keeps the valve closed.

Closure of the Ductus Arteriosus

The ductus arteriosus also closes, but for different reasons. First, the increased systemic resistance elevates the aortic pressure while the decreased pulmonary resistance reduces the pulmonary arterial pressure. As a consequence, after birth, blood begins to flow backward from the aorta into the pulmonary artery through the ductus arteriosus, rather than in the other direction as in fetal life. However, after only a few hours, the muscle wall of the ductus arteriosus constricts markedly, and within 1 to 8 days, the constriction is usually sufficient to stop all blood flow. This is called functional closure of the ductus arteriosus. Then, during the next 1 to 4 months, the ductus arteriosus ordinarily becomes anatomically occluded by growth of fibrous tissue into its lumen.

The cause of ductus arteriosus closure relates to the increased oxygenation of the blood flowing through the ductus. In fetal life the PO2 of the ductus blood is only 15 to 20 mm Hg, but it increases to about 100 mm Hg within a few hours after birth. Furthermore, many experiments have shown that the degree of contraction of the smooth muscle in the ductus wall is highly related to this availability of oxygen.

Closure of the Ductus Venosus

In fetal life, the portal blood from the fetus's abdomen joins the blood from the umbilical vein, and these together pass by way of the ductus venosus directly into the vena cava immediately below the heart but above the liver, thus bypassing the liver.

Immediately after birth, blood flow through the umbilical vein ceases, but most of the portal blood still flows through the ductus venosus, with only a small amount passing through the channels of the liver. However, within 1 to 3 hours the muscle wall of the ductus venosus contracts strongly and closes this avenue of flow. As a consequence, the portal venous pressure rises from near 0 to 6 to 10 mm Hg, which is enough to force portal venous blood flow through the liver sinuses. Although the ductus venosus rarely fails to close.

52. Intrapulmonary and pleural pressure. Pneumothorax

Pleural pressure is the pressure of the fluid in the thin space between the lung pleura and the chest wall pleura. As noted earlier, this is normally a slight suction, which means a slightly negative pressure. The normal pleural pressure at the beginning of inspiration is about –5 centimeters of water, which is the amount of suction required to hold the lungs open to their resting level. Then, during normal inspiration, expansion of the chest cage pulls outward on the lungs with greater force and creates more negative pressure, to an average of about –7.5 centimeters of water. Then, during expiration, the events are essentially reversed.

Alveolar pressure is the pressure of the air inside the lung alveoli. When the glottis is open and no air is flowing into or out of the lungs, the pressures in all parts of the respiratory tree, all the way to the alveoli, are equal to atmospheric pressure, which is considered to be zero reference pressure in the airways—that is, 0 centimeters water pressure. To cause inward flow of air into the alveoli during inspiration, the pressure in the alveoli must fall to a value slightly below atmospheric pressure (below 0). The second curve (labeled “alveolar pressure”) demonstrates that during normal inspiration, alveolar pressure decreases to about –1 centimeter of water. This slight negative pressure is enough to pull 0.5 liter of air into the lungs in the 2 seconds required for normal quiet inspiration. During expiration, opposite pressures occur: The alveolar pressure rises to about +1 centimeter of water, and this forces the 0.5 liter of inspired air out of the lungs during the 2 to 3 seconds of expiration.

Transpulmonary pressure is the difference between the alveolar pressure and the pleural pressure. It is the pressure difference between that in the alveoli and that on the outer surfaces of the lungs, and it is a measure of the elastic forces in the lungs that tend to collapse the lungs at each instant of res- piration, called the recoil pressure.

Pneumothorax

When air is admitted to the pleural space, through either a rupture in the lung or a hole in the chest wall, the lung on the affected side collapses because of its elastic recoil. Atmospheric air rushes through the wound into the intrapleural space and the intrapleural pressure goes from -4 mmHg to a 0 mmHg. The transpulmonary pressure acting to hold the lung open is thus eliminated,a nd the lung collapses. At the same time, the chest wall moves outward since its elastic recoil is also no longer opposed. If there is a flap of tissue over the hole in the lungs or chest wall that acts as a flutter valve, permitting air to enter during inspiration but preventing its exit during expiration, the pressure in the pleural space rises above atmospheric pressure (tension pneumothorax). The hypoxic stimulus to respiration causes deeper inspiratory efforts, which further increase the pressure in the pleural cavity, kinking the great veins and cause further hypoxia and shock. If the hole through which air enters the pleural space seals off (closed pneumothorax) respiratory distress is not great because, with each inspiration, air flows into the lung on the unaffected side rather than into the pleural space. Because the thoracic cavity is divided into right and left sides by a membrane called mediastinum, pneumothorax is often unilateral.

53. Alveolar surface tension. Surfactant

Principle of Surface Tension

When water forms a surface with air, the water molecules on the surface of the water have an especially strong attraction for one another. As a result, the water surface is always attempting to contract. This is what holds raindrops together: that is, there is a tight contractile membrane of water molecules around the entire surface of the raindrop. Now let us reverse these principles and see what happens on the inner surfaces of the alveoli. Here, the water surface is also attempting to contract. This results in an attempt to force the air out of the alveoli through the bronchi and, in doing so, causes the alveoli to try to collapse. The net effect is to cause an elastic contractile force of the entire lungs, which is called the surface tension elastic force.

Surfactant and Its Effect on Surface Tension

Surfactant is a surface active agent in water, which means that it greatly reduces the surface tension of water. It is secreted by special surfactant-secreting epithelial cells called type II alveolar epithelial cells, which constitute about 10 per cent of the surface area of the alveoli. These cells are granular, containing lipid inclusions that are secreted in the surfactant into the alveoli.

Surfactant is a complex mixture of several phospholipids, proteins, and ions. The most important components are the phospholipid dipalmitoylphosphatidylcholine, surfactant apoproteins, and calcium ions. The dipalmitoylphosphatidylcholine, along with several less important phospholipids, is responsible for reducing the surface tension. It does this by not dissolving uniformly in the fluid lining the alveolar surface. Instead, part of the molecule dissolves, while the remainder spreads over the surface of the water in the alveoli. This surface has from one twelfth to one half the surface tension of a pure water surface.

Pressure in Occluded Alveoli Caused by Surface Tension

If the air passages leading from the alveoli of the lungs are blocked, the surface tension in the alveoli tends to collapse the alveoli. This creates positive pressure in the alveoli, attempting to push the air out. The amount of pressure generated in this way in an alveolus can be calculated from the following formula:

$$\text{Pressure} = \frac{2 \times \text{Surface tension}}{\text{Radius of alveolus}}$$

For the average-sized alveolus with a radius of about 100 micrometers and lined with normal surfactant, this calculates to be about 4 centimeters of water pressure (3 mm Hg). If the alveoli were lined with pure water without any surfactant, the pressure would calculate to be about 18 centimeters of water pressure, 4.5 times as great. Thus, one sees how important surfactant is in reducing alveolar surface tension and therefore also reducing the effort required by the respiratory muscles to expand the lungs.

Effect of Alveolar Radius on the Pressure Caused by Surface Tension

Note from the preceding formula that the pressure generated as a result of surface tension in the alveoli is inversely affected by the radius of the alveolus, which means that the smaller the alveolus, the greater the alveolar pressure caused by the surface tension. Thus, when the alveoli have half the normal radius (50 instead of 100 micrometers), the pressures noted earlier are doubled. This is especially significant in small premature babies, many of whom have alveoli with radii less than one quarter that of an adult person. Further, surfactant does not normally begin to be secreted into the alveoli until between the sixth and seventh months of gestation, and in some cases, even later than that. Therefore, many premature babies have little or no surfactant in the alveoli when they are born, and their lungs have an extreme tendency to collapse, sometimes as great as six to eight times that in a normal adult person. This causes the condition called respiratory distress syndrome of the newborn. It is fatal if not treated with strong measures, especially properly applied continuous positive pressure breathing.

54. Compliance of lungs. Respiratory work

Compliance of the Lungs

The extent to which the lungs will expand for each unit increase in transpulmonary pressure (if enough time is allowed to reach equilibrium) is called the lung compliance. The total compliance of both lungs together in the normal adult human being averages about 200 milliliters of air per centimeter of water transpulmonary pressure. That is, every time the transpulmonary pressure increases 1 centimeter of water, the lung volume, after 10 to 20 seconds, will expand 200 milliliters.

Compliance Diagram of the Lungs

The characteristics of the compliance diagram are determined by the elastic forces of the lungs. These can be divided into two parts: (1) elastic forces of the lung tissue itself and (2) elastic forces caused by surface tension of the fluid that lines the inside walls of the alveoli and other lung air spaces.

The elastic forces of the lung tissue are determined mainly by elastin and collagen fibers interwoven among the lung parenchyma. In deflated lungs, these fibers are in an elastically contracted and kinked state; then, when the lungs expand, the fibers become stretched and unkinked, thereby elongating and exerting even more elastic force.

The tissue elastic forces tending to cause collapse of the air-filled lung represent only about one third of the total lung elasticity, whereas the fluid-air surface tension forces in the alveoli represent about two thirds.

The fluid-air surface tension elastic forces of the lungs also increase tremendously when the substance called surfactant is not present in the alveolar fluid.

"Work" of Breathing

During normal quiet breathing, all respiratory muscle contraction occurs during inspiration; expiration is almost entirely a passive process caused by elastic recoil of the lungs and chest cage. Thus, under resting conditions, the respiratory muscles normally perform "work" to cause inspiration but not to cause expiration.

The work of inspiration can be divided into three fractions:

(1) that required to expand the lungs against the lung and chest elastic forces, called compliance work or elastic work;
(2) that required to overcome the viscosity of the lung and chest wall structures, called tissue resistance work; and
(3) that required to overcome airway resistance to movement of air into the lungs, called airway resistance work.

Energy Required for Respiration

During normal quiet respiration, only 3 to 5 per cent of the total energy expended by the body is required for pulmonary ventilation. But during heavy exercise, the amount of energy required can increase as much as 50-fold, especially if the person has any degree of increased airway resistance or decreased pulmonary compliance. Therefore, one of the major limitations on the intensity of exercise that can be performed is the person's ability to provide enough muscle energy for the respiratory process alone.

55. Composition of atmospheric and alveolar air

Air is mainly composed of nitrogen, oxygen, and argon, which together constitute the major gases of the atmosphere. The remaining gases are often referred to as trace gases, among which are the greenhouse gases such as water vapor, carbon dioxide, methane, nitrous oxide, and ozone. Filtered air includes trace amounts of many other chemical compounds. Many natural substances may be present in tiny amounts in an unfiltered air sample, including dust, pollen and spores, sea spray, volcanic ash, and meteoroids. Various industrial pollutants also may be present, such as chlorine (elementary or in compounds), fluorine compounds, elemental mercury, and sulfur compounds such as sulfur dioxide [SO2].

Alveolar air does not have the same concentrations of gases as atmospheric air by any means, which can readily be seen by comparing the alveolar air composition in the table with that of atmospheric air. There are several reasons for the differences. First, the alveolar air is only partially replaced by atmospheric air with each breath. Second, oxygen is constantly being absorbed into the pulmonary blood from the alveolar air. Third, carbon dioxide is constantly diffusing from the pulmonary blood into the alveoli. And fourth, dry atmospheric air that enters the respiratory passages is humidified even before it reaches the alveoli.

Partial Pressures of Respiratory Gases as They Enter and Leave the Lungs (at Sea Level)

	Atmospheric Air* (mm Hg)		Humidified Air (mm Hg)		Alveolar Air (mm Hg)		Expired Air (mm Hg)	
N_2	597.0	(78.62%)	563.4	(74.09%)	569.0	(74.9%)	566.0	(74.5%)
O_2	159.0	(20.84%)	149.3	(19.67%)	104.0	(13.6%)	120.0	(15.7%)
CO_2	0.3	(0.04%)	0.3	(0.04%)	40.0	(5.3%)	27.0	(3.6%)
H_2O	3.7	(0.50%)	47.0	(6.20%)	47.0	(6.2%)	47.0	(6.2%)
TOTAL	760.0	(100.0%)	760.0	(100.0%)	760.0	(100.0%)	760.0	(100.0%)

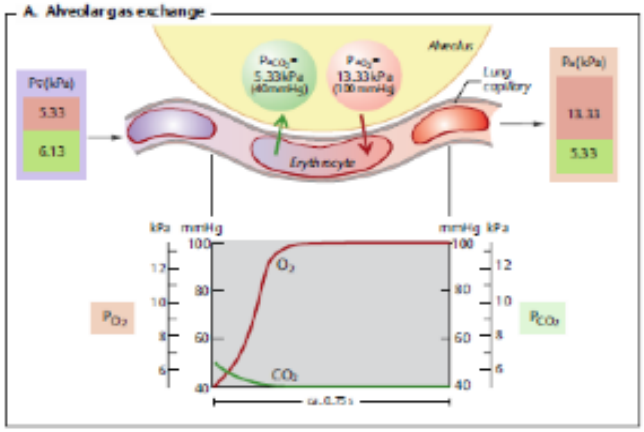
Humidification of the Air in the Respiratory Passages

The atmospheric air is composed almost entirely of nitrogen and oxygen; it normally contains almost no carbon dioxide and little water vapor. However, as soon as the atmospheric air enters the respiratory passages, it is exposed to the fluids that cover the respiratory surfaces. Even before the air enters the alveoli, it becomes (for all practical purposes) totally humidified.

The partial pressure of water vapor at a normal body temperature of 37°C is 47 mm Hg, which is therefore the partial pressure of water vapor in the alveolar air. Because the total pressure in the alveoli cannot rise to more than the atmospheric pressure (760 mm Hg at sea level), this water vapor simply dilutes all the other gases in the inspired air. The humidification of the air dilutes the oxygen partial pressure at sea level from an average of 159 mm Hg in atmospheric air to 149 mm Hg in the humidified air, and it dilutes the nitrogen partial pressure from 597 to 563 mm Hg.

56. Gas exchange in lungs and tissues

Gas Exchange Between Alveoli and Blood



The blood that enters the pulmonary capillaries is, of course, systemic venous blood pumped to the lungs via the pulmonary arteries. Having come from the tissues, it has relatively high PCO_2 (46 mmHg in a normal persons at rest) and a relatively low PO2 (40 mmHg). The differences in the partial pressures of oxygen and carbon dioxide on the two sides of the alveolar-capillary membrane result in the net diffusion of oxygen from alveoli to blood and of carbon dioxide from blood to alveoli. As this diffusion occurs, th PO2 falls. The net diffusion of these gases ceases when the capillary partial pressures become equal to those in the alveoli.

In a normal person, the rates at which oxygen and carbon dioxide diffuse are so rapid and the blood flow through the capillaries so slow that complete equilibrium is reached well before the blood reaches the end of the capillaries. Only during the most stenuous exercise, when blood flows through the lung capillaries very rapidly, is there insufficient time for complete equilibration.

Thus, the blood that leaves the pulmonary capillaries to return to the heart and be pumped into the systemic arteries has essentially the same PO_2 and PCO_2 as alveolar air. Accordingly, atmospheric PO2, cellular oxygen consumption and carbon dioxide production, and alveolar ventilation, determine the alveolar gas pressures, which then determine the systemic arterial gas pressures.

Given that diffusion between alveoli and pulmonary capillaries normally achieves complete equilibration, the more capillaries that participate in this process, the more total oxygen and carbon dioxide is exchanged. Many of the pulmonary capillaries at the apex of each lung are normally closed at rest.

During exercise, these capillaries open and receive blood, thereby enhancing gas exchange. The mechanism by which this occurs is a simple physical one; the pulmonary circulation at rest is at such a low blood pressure that the pressure in these apical capillaries is inadequate to keep them open, but the increased cardiac output of exercise raises pulmonary vascular pressures, which opens these capillaries.

The diffusion of gases between alveoli and capillaries may be impaired in a number of ways resulting in inadequate oxygen diffusion into the blood, particularly during exercise when the time the equilibration is reduced. For one thing, the surface area of the alveoli in contact with pulmonary capillaries may be decreased. In lung infections or pulmonary edema, for example, some of the alveoli may become filled with fluid. Diffusion may also be impaired if the alveolar walls become severely thickened with connective tissue, as, for example, in the disease called diffuse interstitial fibrosis. Pure diffusion problems of these types are restricted to oxygen and usually do not affect the elimination of carbon dioxide, which is much more diffusible than oxygen.

<u>Gas Exchange Between Tissues and Blood</u>

As the systemic arterial blood enters capillaries throughout the body, it is separated from the interstitial fluid by only the thin capillary wall, which is highly permeable to both oxygen and carbo dioxide. The interstitial fluid, in turn, is separated from the intracellular fluid by the plasma membranes of the cells, which are also quite permeable to oxygen and carbon dioxide. Metabolic reactions occuring within cells are constantly consuming oxygen and producing carbon dioxide. Therefore, intracellular PO2 is lower and PCO_2 higher than in blood. The lowest PO2 of all - less than 5 mmHg - is in the mitochondria, the site of oxygen utilization. As a result, a net diffusion of oxygen occurs from blood into cells (and, within the cells, into the mitochondria), and a net diffusion of carbon dioxide occurs from cells into blood. In this manner, as blood flows through systemic capillaries, its PO2, decreases and its PCO_2 increases. This accounts for the systemic venous blood values.

Using Fick's principle oxygen consumption of a given organ is given by the following formula:

$$VO_2 = Q([O_2]a - [O_2]v)$$

where Q is the blood flow in L/min

In summary, the supply of new oxygen to the alveoli and the consumption of oxygen in the cells create PO2, gradients that produce net diffusion of oxygen from alveoli to blood in the lungs and from blood to cells in the rest of the body. Conversely, the production pf carbon dioxide from cells to blood in the rest of the body and from blood to alveoli in the lungs.

57. Transport of O2. Oxygen – haemoglobin dissociation curve.

Diffusion of Oxygen from the Alveoli to the Pulmonary Capillary Blood

The PO2 of the gaseous oxygen in the alveolus averages 104 mm Hg, whereas the PO2 of the venous blood entering the pulmonary capillary at its arterial end averages only 40 mm Hg because a large amount of oxygen was removed from this blood as it passed through the peripheral tissues. Therefore, the initial pressure difference that causes oxygen to diffuse into the pulmonary capillary is 104–40, or 64 mm Hg.

Transport of Oxygen in the Arterial Blood

About 98 per cent of the blood that enters the left atrium from the lungs has just passed through the alveolar capillaries and has become oxygenated up to a PO2 of about 104 mm Hg. Another 2% of the blood has passed from the aorta through the bronchial circulation, which supplies mainly the deep tissues of the lungs and is not exposed to lung air. On leaving the lungs, the PO2 of the shunt blood is about that of normal systemic venous blood, about 40 mm Hg. When this blood combines in the pulmonary veins with the oxygenated blood from the alveolar capillaries, this so-called venous admixture of blood causes the PO2 of the blood entering the left heart and pumped into the aorta to fall to about 95 mm Hg.

Diffusion of Oxygen from the Peripheral Capillaries into the Tissue Fluid

When the arterial blood reaches the peripheral tissues, its PO2 in the capillaries is still 95 mm Hg. The PO2 in the interstitial fluid that surrounds the tissue cells averages only 40 mm Hg. Thus, there is a tremendous initial pressure difference that causes oxygen to diffuse rapidly from the capillary blood into the tissues—so rapidly that the capillary PO2 falls almost to equal the 40 mm Hg pressure in the interstitium. Therefore, the PO2 of the blood leaving the tissue capillaries and entering the systemic veins is also about 40 mm Hg.

Effect of Rate of Blood Flow on Interstitial Fluid PO2

If the blood flow through a particular tissue is increased, greater quantities of oxygen are transported into the tissue, and the tissue PO2 becomes correspondingly higher. Note that an increase in flow to 400% of normal increases the interstitial PO2 from 40 mm Hg to 66 mm Hg. However, the upper limit to which the PO2 can rise, even with maximal blood flow, is 95 mm Hg, because this is the oxygen pressure in the arterial blood. Conversely, if blood flow through the tissue decreases, the tissue PO2 also decreases.

Effect of Rate of Tissue Metabolism on Interstitial Fluid PO2

If the cells use more oxygen for metabolism than normally, this reduces the interstitial fluid PO2. Reduced interstitial fluid PO2 when the cellular oxygen consumption is increased, and increased PO2 when consumption is decreased. Tissue PO2 is determined by a balance between (1) the rate of oxygen transport to the tissues in the blood and (2) the rate at which the oxygen is used by the tissues.

Diffusion of Oxygen from the Peripheral Capillaries to the Tissue Cells

Oxygen is always being used by the cells. Therefore, the intracellular PO2 in the peripheral tissue cells remains lower than the PO2 in the peripheral capillaries. Also, in many instances, there is considerable physical distance between the capillaries and the cells. Therefore, the normal intracellular PO2 ranges from as low as 5 mm Hg to as high as 40 mm Hg, averaging 23 mm Hg.

Role of Hemoglobin in Oxygen Transport

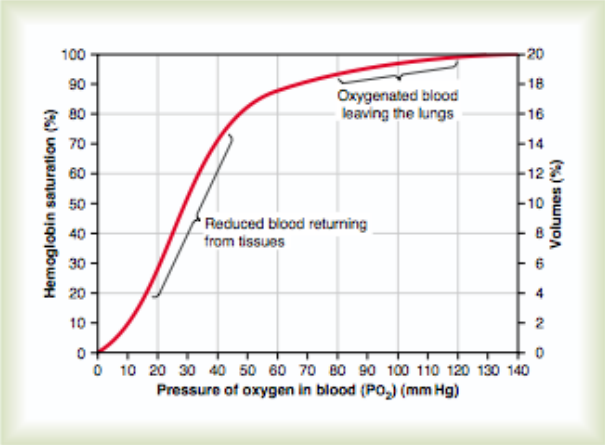
Normally, about 97 per cent of the oxygen transported from the lungs to the tissues is carried in chemical combination with hemoglobin in the red blood cells. The remaining 3 per cent is transported in the dissolved state in the water of the plasma and blood cells. Thus, under normal conditions, oxygen is carried to the tissues almost entirely by hemoglobin.

Reversible Combination of Oxygen with Hemoglobin

The oxygen molecule combines loosely and reversibly with the heme portion of hemoglobin. When PO2 is high, as in the pulmonary capillaries, oxygen binds with the hemoglobin, but when PO2 is low, as in the tissue capillaries, oxygen is released from the hemoglobin.

Oxygen-Hemoglobin Dissociation Curve

The figure shows the oxygen-hemoglobin dissociation curve, which demonstrates a progressive increase in the percentage of hemoglobin bound with oxygen as blood PO2 increases, which is called the per cent saturation of hemoglobin. Because the blood leaving the lungs and entering the systemic arteries usually has a PO2 of about 95 mm Hg, one can see from the dissociation curve that the usual oxygen saturation of systemic arterial blood averages 97%. Conversely, in normal venous blood returning from the peripheral tissues, the PO2 is about 40 mm Hg, and the saturation of hemoglobin averages 75%.



Factors That Shift the Oxygen- Hemoglobin Dissociation Curve— Their Importance for Oxygen Transport

A number of factors can displace the disso- ciation curve in one direction or the other. When the blood becomes slightly acidic, with the pH decreasing from the normal value of 7.4 to 7.2, the oxygen-hemoglobin dissociation curve shifts to the right. Conversely, an increase in pH from the normal 7.4 to 7.6 shifts the curve to the left.

In addition to pH changes, several other factors are known to shift the curve. Three of these, all of which shift the curve to the right, are (1) increased carbon dioxide concentration, (2) increased blood temperature, and (3) increased 2,3-biphosphoglycerate (BPG).

Increased Delivery of Oxygen to the Tissues When Carbon Dioxide and Hydrogen Ions Shift the Oxygen-Hemoglobin Dissociation Curve—The Bohr Effect.

A shift of the oxygen-hemoglobin dissociation curve to the right in response to increases in blood carbon dioxide and hydrogen ions has a significant effect by enhancing the release of oxygen from the blood in the tissues and enhancing oxygenation of the blood in the lungs. This is called the Bohr effect, which can be explained as follows: As the blood passes through the tissues, carbon dioxide diffuses from the tissue cells into the blood. This increases the blood PO2, which in turn raises the blood H2CO3 (carbonic acid) and the hydrogen ion concentration. These effects shift the oxygen-hemoglobin dissociation curve to the right and downward, forcing oxygen away from the hemoglobin and therefore delivering increased amounts of oxygen to the tissues.

Exactly the opposite effects occur in the lungs, where carbon dioxide diffuses from the blood into the alveoli. This reduces the blood PCO_2 and decreases the hydrogen ion concentration, shifting theoxygen-hemoglobin dissociation curve to the left. Therefore, the quantity of oxygen that binds with the hemoglobin at any given alveolar PO2 becomes considerably increased, thus allowing greater oxygen transport to the tissues.

Effect of BPG to Shift the Oxygen-Hemoglobin Dissociation Curve

The normal BPG in the blood keeps the oxygen-hemoglobin dissociation curve shifted slightly to the right all the time. In hypoxic conditions that last longer than a few hours, the quantity of BPG in the blood increases considerably, thus shifting the oxygen-hemoglobin dissociation curve even farther to the right. This causes oxygen to be released to the tissues at as much as 10 mm Hg higher tissue oxygen pressure than would be the case without this increased BPG. Therefore, under some conditions, the BPG mechanism can be important for adaptation to hypoxia, especially to hypoxia caused by poor tissue blood flow.

Shift of the Dissociation Curve During Exercise

During exercise, several factors shift the dissociation curve considerably to the right, thus delivering extra amounts of oxygen to the active, exercising muscle fibers. The exercising muscles, in turn, release large quantities of carbon dioxide; this and several other acids released by the muscles increase the hydrogen ion concentration in the muscle capillary blood. In addition, the temperature of the muscle often rises 2° to 3°C, which can increase oxygen delivery to the muscle fibers even more. The right-hand shift of the curve forces oxygen to be released from the blood hemoglobin to the muscle at Po2 levels as great as 40 mm Hg.

Transport of Oxygen in the Dissolved State

0.17 mL of oxygen is normally transported in the dissolved state to the tissues by each 100 mL of arterial blood flow. This compares with almost 5 mL of oxygen transported by the red cell hemoglobin. Therefore, the amount of oxygen transported to the tissues in the dissolved state is normally slight, only about 3 % of the total, as compared with 97 % transported by the hemoglobin.

58. Transport of CO2

Transport of CO_2 by the blood is not nearly as problematical as transport of O2 is, because even in the most abnormal conditions, CO_2 can usually be transported in far greater quantities than O2 can be. However, the amount of CO_2 in the blood has a lot to do with the acid-base balance of the body fluids. Under normal resting conditions, an average of 4 mL of CO_2 is transported from the tissues to the lungs in each 100 mL of blood.

Chemical Forms in Which Carbon Dioxide Is Transported

To begin the process of carbon dioxide transport, carbon dioxide diffuses out of the tissue cells in the dissolved molecular CO_2 form. On entering the tissue capillaries, the CO_2 initiates a host of almost instantaneous physical and chemical reactions which are essential for CO_2 transport.

Transport of Carbon Dioxide in the Dissolved State

A small portion of the carbon dioxide is transported in the dissolved state to the lungs. Recall that the PCO_2 of venous blood is 45 mm Hg and that of arterial blood is 40 mm Hg. The amount of CO2 dissolved in the fluid of the blood at 45 mm Hg is about 2.7 ml/dl. The amount dissolved at 40 mm Hg is about 2.4 mL, or a difference of 0.3 mL. Therefore, only about 0.3 mL of CO_2 is transported in the dissolved form by each 100 mL of blood flow. This is about 7% of all the CO_2 normally transported.

Transport of Carbon Dioxide in the Form of Bicarbonate Ion

Reaction of Carbon Dioxide with Water in the Red Blood Cells—Effect of Carbonic Anhydrase

The dissolved CO_2 in the blood reacts with water to form carbonic acid. This reaction is accelerated by carbonic anhydrase, which catalyzes the reaction between CO_2 and water and accelerates its reaction rate about 5000-fold. Therefore, instead of requiring many seconds or minutes to occur, as is true in the plasma, the reaction occurs so rapidly in the red blood cells that it reaches almost complete equilibrium within a very small fraction of a second. This allows tremendous amounts of CO_2 to react with the red blood cell water even before the blood leaves the tissue capillaries.

Dissociation of Carbonic Acid into Bicarbonate and Hydrogen Ions

In another fraction of a second, the carbonic acid formed in the red cells (H2CO3) dissociates into hydrogen and bicarbonate ions (H+ and HCO3–). Most of the hydrogen ions then combine with the hemoglobin in the red blood cells, because the hemoglobin protein is a powerful acid-base buffer. In turn, many of the bicarbonate ions diffuse from the red cells into the plasma, while chloride ions diffuse into the red cells to take their place. This is made possible by the presence of a special bicarbonate-chloride carrier protein in the red cell membrane that shuttles these two ions in opposite directions at rapid velocities. Thus, the chloride content of venous red blood cells is greater than that of arterial red cells, a phenomenon called the chloride shift.

The reversible combination of carbon dioxide with water in the red blood cells under the influence of carbonic anhydrase accounts for about 70 % of the CO_2 transported from the tissues to the lungs. Thus, this means of transporting carbon dioxide is by far the most important.

Transport of Carbon Dioxide in Combination with Hemoglobin and PlasmaProteins—Carbaminohemoglobin

In addition to reacting with water, carbon dioxide reacts directly with amine radicals of the hemoglobin molecule to form the compound carbaminohemoglobin (CO_2Hgb). This combination of carbon dioxide and hemoglobin is a reversible reaction that occurs with a loose bond, so that the carbon dioxide is easily released into the alveoli, where the PCO_2 is lower than in the pulmonary capillaries.

A small amount of carbon dioxide also reacts in the same way with the plasma proteins in the tissue capillaries. This is much less significant. The quantity of carbon dioxide that can be carried from the peripheral tissues to the lungs by carbamino combination with hemoglobin and plasma proteins is about 30% of the total quantity transported. However, because this reaction is much

slower than the reaction of CO_2 with water inside the red blood cells, it is doubtful that under normal conditions this carbamino mechanism transports more than 20% of the total CO_2.

59. Herring-Breuer reflexes

Lung Inflation Signals Limit Inspiration—The Hering-Breuer Inflation Reflex

In addition to the central nervous system respiratory control mechanisms operating entirely within the brain stem, sensory nerve signals from the lungs also help control respiration. Most important, located in the muscular portions of the walls of the bronchi and bronchioles throughout the lungs are stretch receptors that transmit signals through the vagi into the dorsal respiratory group of neurons when the lungs become overstretched. These signals affect inspiration in much the same way as signals from the pneumotaxic center; that is, when the lungs become overly inflated, the stretch receptors activate an appropriate feedback response that “switches off” the inspiratory ramp and thus stops further inspiration. This is called the Hering- Breuer inflation reflex. This reflex also increases the rate of respiration, as is true for signals from the pneu- motaxic center.

In human beings, the Hering-Breuer reflex probably is not activated until the tidal volume increases to more than three times normal (greater than about 1.5 liters per breath). Therefore, this reflex appears to be mainly a protective mechanism for preventing excess lung inflation rather than an important ingredient in normal control of ventilation.

60. Respiratory responses to irritants

Protective Reflexes

A group of responses protect the respiratory system from irritant materials. Most familiar are the cough and the sneeze reflexes, which originate in receptors located between airway epithelial cells. The receptors for the sneeze reflex are in the nose or pharynx, and those for cough are in larynx, trachea, and bronchi. When the receptors initiating a cough are stimulated, the medullary respiratory neurons reflexly cause a deep inspiration and a violent expiration. In this manner, particles and secretions are moved from smaller to larger airways, and aspiration of materials into the lungs is also prevented.

Alcohol inhibits the cough reflex, which may partially explain the susceptibility of aloholics to choking and pneumonia.

Another example of a protective reflex is the immediate cessation of respiration that is often triggered when noxious agents are inhaled. Chronic smoking may cause a loss of this reflex.

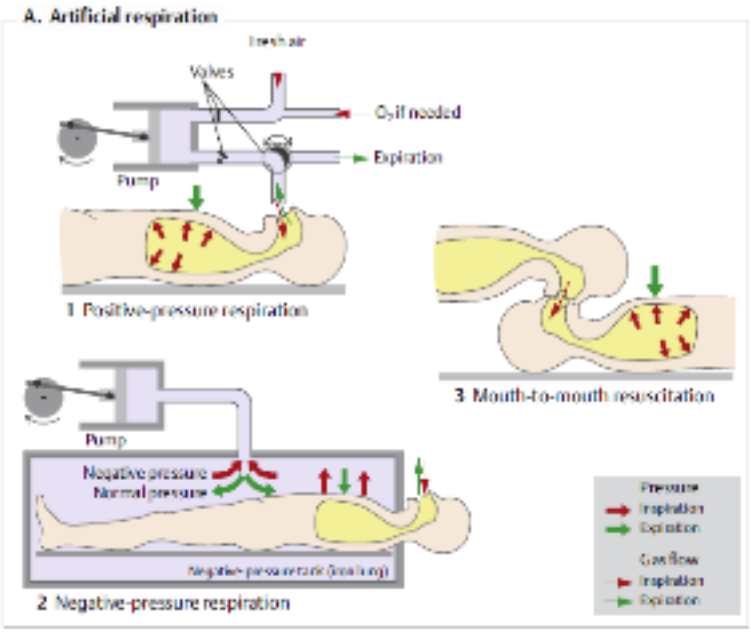
Responses mediated by receptors in the Airways & Lungs

Receptors in the air ways and lungs are innervated by myelinated and unmyelinated vagal fibers. The unmyelinated fibers are C fibers. The receptors innervated by myelinated fibers are commonly divided into slowly adapting receptors and rapidly adapting receptors. Because the rapidly adapting receptors are stimulated by chemicals such as histamine, they have been called irritant receptors. Activation of rapidly adapting receptors in the trachea causes coughing, bronchoconstriction, and mucus secretion, and activation of rapidly adapting receptors in the lung may produce hyperpnea.

Coughing & Sneezing

Coughing beings with a deep inspiration followed by forced expiration against a closed glottis. This increases the intrapleural pressure to 100 mm Hg or more. The glottis is the suddenly opened, producing an explosive outflow of air at velocities up to 965 km (600 miles) per hour. Sneezing is a similar expiratory effect with a continuously open glottis. These reflexes help expel irritants and keep airways clear.

61. Arteficial ventilation



Mouth-to-mouth resuscitation is an emergency measure performed when someone stops breathing. The patient is placed flat on the back. While pinching the patient's nostrils shut, the aid-giver places his or her mouth on the patient's mouth and blows forcefully into the patient's lungs (->A3). This raises the alveolar pressure in the patient's lungs relative to the atmospheric pressure outside the chest and causes the lungs and chest to expand (inspiration). The rescuer then removes his or her mouth to allowthe patient to exhale. Expulsion of the air blown into the lungs (expiration) occurs due to the intrinsic elastic recoil of the lungs and chest. This process can be accelerated by pressing down on the chest. The rescuer should ventilate the patient at a rate of about 16/min. The expiratory O2 fraction of the rescuer is high enough to adequately oxygenate the patient's blood. The color change in the patient's skin from blue (cyanosis) to pink indicates that a resuscitation attempt was successful.

Mechanical ventilation

Mechanical intermittent positive pressure ventilation (IPPV) works on the same principle. This technique is used when the respiratory muscles are paralyzed due to disease, anesthesia, etc. The pump of the respirator drives air into the patient's lung during inspiration (A1). The external inspiratory and expiratory pathways are separated by a valve (close to the patient's mouth as possible) to prevent enlargement of dead space. Ventilation frequency, tidal volume, inspiratory flow, as well as duration of inspiration and expiration can be preselected at the respirator. The drawback of this type of ventilation is that venous return to the heart is impaired to some extent. Today, the standard technique of mechanical respiration is continuous positive pressure ventilation (CPPV). In contrast to IPPV, the endexpiratory pressure is kept positive (PEEP) in CPPV.

In any case, all ventilated patients should be continuously monitored (expiratory gas fraction; blood gas composition, etc.).

The iron lung (Drinker respirator) makes use of negative-pressure respiration (A2). The patient's body is enclosed from the neck down in a metal tank. To achieve inhalation, pressure in the tank is decreased to a level below normal ambient pressure and, thus, below alveolar pressure. This pressure difference causes the chest to expand (inspiratory phase), and the cessation of negative pressure in the tank allows the patient to breathe out (expiratory phase).
This type of respirator is used to ventilate patients who require long-term mechanical ventilation due to paralytic diseases, such as polio.

62. Formation, composition and functions of saliva

Secretion of Saliva

Characteristics of Saliva

The principal glands of salivation are the parotid, submandibular, and sublingual glands; in addition, there are many very small buccal glands. Daily secretion of saliva normally ranges between 800 and 1500 mL.

Saliva contains two major types of protein secretion: (1) a serous secretion that contains a-amylase, which is an enzyme for digesting starches, and (2) mucus secretion that contains mucin for lubricating and for surface protective purposes.

The parotid glands secrete almost entirely the serous type of secretion, while the submandibular and sublingual glands secrete both serous secretion and mucus. The buccal glands secrete only mucus. Saliva has a pH between 6.0 and 7.0.

Secretion of Ions in Saliva

Saliva contains especially large quantities of potassium and bicarbonate ions. Conversely, the concentrations of both sodium and chloride ions are several times less in saliva than in plasma. One can understand these special concentrations of ions in the saliva from the following description of the mechanism for secretion of saliva.

Salivary secretion is a two-stage operation: the first stage involves the acini, and the second, the salivary ducts. The acini secrete a primary secretion that contains ptyalin and/or mucin in a solution of ions in concentrations not greatly different from those of typical extracellular fluid. As the primary secretion flows through the ducts, two major active transport processes take place that markedly modify the ionic composition of the fluid in the saliva.

First, sodium ions are actively reabsorbed from all the salivary ducts and potassium ions are actively secreted in exchange for the sodium. Therefore, the sodium ion concentration of the saliva becomes greatly reduced, whereas the potassium ion concentration becomes increased. However, there is excess sodium reabsorption over potassium secretion, and this creates electrical negativity of about -70 mV in the salivary ducts; this in turn causes Cl- ions to be reabsorbed passively. Therefore, the Cl- ion concentration in the salivary fluid falls to a very low level.

Second, bicarbonate ions are secreted by the ductal epithelium into the lumen of the duct. This is at least partly caused by passive exchange of bicarbonate for chloride ions, but it may also result partly from an active secretory process.

During maximal salivation, the salivary ionic concentrations change considerably because the rate of formation of primary secretion by the acini can increase as much as 20-fold. This acinar secretion then flows through the ducts so rapidly that the ductal reconditioning of the secretion is considerably reduced. Therefore, when copious quantities of saliva are being secreted, the sodium chloride concentration rises only to one half or two thirds that of plasma, and the potassium concentration rises to only four times that of plasma.

Function of Saliva for Oral Hygiene

Under basal awake conditions, about 0.5 mL of saliva, almost entirely of the mucous type, is secreted each minute; but during sleep, secretion becomes very little. This secretion plays an exceedingly important role for maintaining healthy oral tissues. The mouth is loaded with pathogenic bacteria that can easily destroy tissues and cause dental caries. Saliva helps prevent the deteriorative processes in several ways.

First, the flow of saliva itself helps wash away pathogenic bacteria as well as food particles that provide their metabolic support.

Second, saliva contains several factors that destroy bacteria. One of these is thiocyanate ions and another is several proteolytic enzymes—most important, lysozyme—that (a) attack the bacteria, (b) aid the thiocyanate ions in entering the bacteria where these ions in turn become bactericidal, and (c) digest food particles, thus helping further to remove the bacterial metabolic support.

Third, saliva often contains significant amounts of protein antibodies that can destroy oral bacteria, including some that cause dental caries. In the absence of salivation, oral tissues often become ulcerated and otherwise infected, and caries of the teeth can become rampant.

Nervous Regulation of Salivary Secretion

The salivary glands are controlled mainly by parasympathetic nervous signals all the way from the superior and inferior salivatory nuclei in the brain stem.

The salivatory nuclei are located approximately at the juncture of the medulla and pons and are excited by both taste and tactile stimuli from the tongue and other areas of the mouth and pharynx. Many taste stimuli, especially the sour taste (caused by acids), elicit copious secretion of saliva—often 8 to 20 times the basal rate of secretion. Also, certain tactile stimuli, such as the presence of smooth objects in the mouth, cause marked salivation, whereas rough objects cause less salivation and occasionally even inhibit salivation.

Salivation can also be stimulated or inhibited by nervous signals arriving in the salivatory nuclei from higher centers of the central nervous system. For instance, when a person smells or eats favorite foods, salivation is greater than when disliked food is smelled or eaten. The appetite area of the brain, which partially regulates these effects, is located in proximity to the parasympathetic centers of the anterior hypothalamus, and it functions to a great extent in response to signals from the taste and smell areas of the cerebral cortex or amygdala.

Salivation also occurs in response to reflexes originating in the stomach and upper small intestines—particularly when irritating foods are swallowed or when a person is nauseated because of some gastrointestinal abnormality. The saliva, when swallowed, helps to remove the irritating factor in the gastrointestinal tract by diluting or neutralizing the irritant substances.

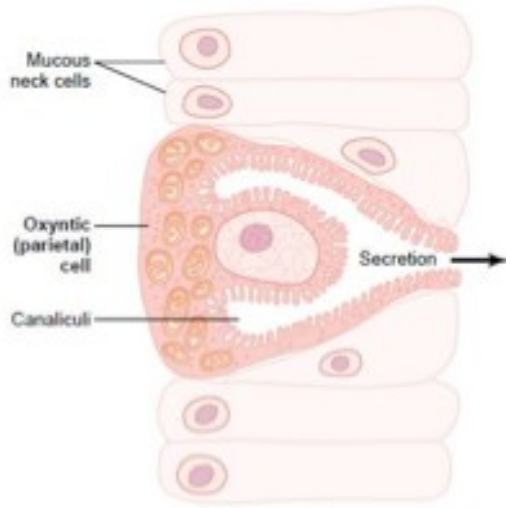
Sympathetic stimulation can also increase salivation a slight amount, much less so than does parasympathetic stimulation. The sympathetic nerves originate from the superior cervical ganglia and travel along the surfaces of the blood vessel walls to the salivary glands.

A secondary factor that also affects salivary secretion is the blood supply to the glands because secretion always requires adequate nutrients from the blood. The parasympathetic nerve signals that induce copious salivation also moderately dilate the blood vessels. In addition, salivation itself directly dilates the blood vessels, thus providing increased salivatory gland nutrition as needed by the secreting cells.

63. Gastric production of HCl

Basic Mechanism of Hydrochloric Acid Secretion

When stimulated, the parietal cells secrete an acid solution that contains about 160 mL of hydrochloric acid per liter, which is almost exactly isotonic with the body fluids. The pH of this acid is about 0.8, demonstrating its extreme acidity. At this pH, the hydrogen ion concentration is about 3 million times that of the arterial blood. To concentrate the hydrogen ions this tremendous amount requires more than 1500 calories of energy per liter of gastric juice.

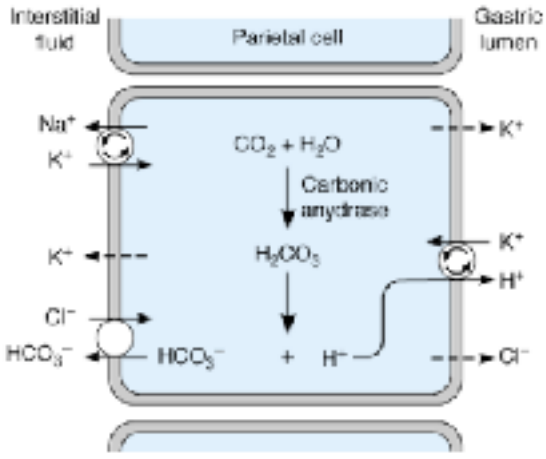


The parietal cell (also called oxyntic cell), contains large branching intracellular canaliculi. The hydrochloric acid is formed at the villus-like projections inside these canaliculi and is then conducted through the canaliculi to the secretory end of the cell.

Different suggestions for the chemical mechanism of hydrochloric acid formation have been offered. One of these, consists of the following steps:

1. Chloride ion is actively transported from the cytoplasm of the parietal cell into the lumen of the canaliculus, and sodium ions are actively transported out of the canaliculus into the cytoplasm of the parietal cell. These two effects together create a negative potential of -40 to -70 millivolts in the canaliculus, which in turn causes diffusion of positively charged potassium ions and a small number of sodium ions from the cell cytoplasm into the canaliculus. Thus, in effect, mainly potassium chloride and much smaller amounts of sodium chloride enter the canaliculus.

2. Water becomes dissociated into hydrogen ions and hydroxyl ions in the cell cytoplasm. The hydrogen ions are then actively secreted into the canaliculus in exchange for potassium ions: this active exchange process is catalyzed by H+,K+- ATPase. In addition, the sodium ions are actively reabsorbed by a separate sodium pump. Thus, most of the potassium and sodium ions that had diffused into the canaliculus are reabsorbed into the cell cytoplasm, and hydrogen ions take their place in the canaliculus, giving a strong solution of hydrochloric acid in the canaliculus. The hydrochloric acid is then secreted outward through the open end of the canaliculus into the lumen of the gland.



3. Water passes into the canaliculus by osmosis because of extra ions secreted into the canaliculus.

4.Finally, carbon dioxide, either formed duringmetabolism in the cell or entering the cell from the blood, combines under the influence of carbonic anhydrase with the hydroxyl ions (from step 2) to form bicarbonate ions. These then diffuse out of the cell cytoplasm into the extracellular fluid in exchange for chloride ions that enter the cell from the extracellular fluid and are later secreted into the canaliculus.

Stimulation of Gastric Acid Secretion

Parietal Cells of the Oxyntic Glands Are the Only Cells That Secrete Hydrochloric Acid

The parietal cells, located deep in the oxyntic glands of the main body of the stomach, are the only cells that secrete hydrochloric acid. Secretion of this acid is under continuous control by both endocrine and nervous signals. Furthermore, the parietal cells operate in close association with another type of cell called enterochromaffin-like cells (ECL cells), the primary function of which is to secrete histamine.

The ECL cells lie in the deep recesses of the oxyntic glands and therefore release histamine in direct contact with the parietal cells of the glands. The rate of formation and secretion of hydrochloric acid by the parietal cells is directly related to the amount of histamine secreted by the ECL cells. In turn, the ECL cells can be stimulated to secrete histamine in several different ways: (1) Probably the most potent mechanism for stimulating histamine secretion is by the hormonal substance gastrin, which is formed almost entirely in the antral portion of the stomach mucosa in response to proteins in the foods being digested. (2) In addition, the ECL cells can be stimulated by (a) acetylcholine released from stomach vagal nerve endings and (b) probably also by hormonal substances secreted by the enteric nervous system of the stomach wall.

Stimulation of Acid Secretion by Gastrin

Gastrin is itself a hormone secreted by gastrin cells, also called G cells. These cells are located in the pyloric glands in the distal end of the stomach. When meats or other protein-containing foods reach the antral end of the stomach, some of the proteins from these foods have a special stimulatory effect on the gastrin cells in the pyloric glands to cause release of gastrin into the digestive juices of the stomach. The vigorous mixing of the gastric juices transports the gastrin rapidly to the ECL cells in the body of the stomach, causing release of histamine directly into the deep oxyntic glands. The histamine then acts quickly to stimulate gastric hydrochloric acid secretion.

64. Functions of the stomach

Motor Functions of the Stomach

The motor functions of the stomach are threefold: (1) storage of large quantities of food until the food can be processed in the stomach, duodenum, and lower intestinal tract; (2) mixing of this food with gastric secretions until it forms a semifluid mixture called chyme; and (3) slow emptying of the chyme from the stomach into the small intestine at a rate suitable for proper digestion and absorption by the small intestine.

Anatomically, the stomach is usually divided into two major parts: (1) the body and (2) the antrum. Physiologically, it is more appropriately divided into (1) the "orad" portion, comprising about the first two thirds of the body, and (2) the "caudad" portion, comprising the remainder of the body plus the antrum.

Storage Function of the Stomach

As food enters the stomach, it forms concentric circles of the food in the orad portion of the stomach, the newest food lying closest to the esophageal opening and the oldest food lying nearest the outer wall of the stomach. Normally, when food stretches the stomach, a "vagovagal reflex" from the stomach to the brain stem and then back to the stomach reduces the tone in the muscular wall of the body of the stomach so that the wall bulges progressively outward, accommodating greater and greater quantities of food up to a limit in the completely relaxed stomach of 0.8 to 1.5 liters. The pressure in the stomach remains low until this limit is approached.

Mixing and Propulsion of Food in the Stomach—The Basic Electrical Rhythm of the Stomach Wall

The digestive juices of the stomach are secreted by gastric glands, which are present in almost the entire wall of the body of the stomach except along a narrow strip on the lesser curvature of the stomach. These secretions come immediately into contact with that portion of the stored food lying against the mucosal surface of the stomach. As long as food is in the stomach, weak peristaltic constrictor waves, called mixing waves, begin in the mid- to upper portions of the stomach wall and move toward the antrum about once every 15 to 20 seconds. These waves are initiated by the gut wall basic electrical rhythm, consisting of electrical "slow waves" that occur spontaneously in the stomach wall. As the constrictor waves progress from the body of the stomach into the antrum, they become more intense, some becoming extremely intense and providing powerful peristaltic action potential–driven constrictor rings that force the antral contents under higher and higher pressure toward the pylorus.

These constrictor rings also play an important role in mixing the stomach contents in the following way: Each time a peristaltic wave passes down the antral wall toward the pylorus, it digs deeply into the food contents in the antrum. Yet the opening of the pylorus is still small enough that only a few mL or less of antral contents are expelled into the duodenum with each peristaltic wave. Also, as each peristaltic wave approaches the pylorus, the pyloric muscle itself often contracts, which further impedes emptying through the pylorus. Therefore, most of the antral contents are squeezed upstream through the peristaltic ring toward the body of the stomach, not through the pylorus. Thus, the moving peristaltic constrictive ring, combined with this upstream squeezing action, called "retropulsion," is an exceedingly important mixing mechanism in the stomach.

Chyme

After food in the stomach has become thoroughly mixed with the stomach secretions, the resulting mixture that passes down the gut is called chyme. The degree of fluidity of the chyme leaving the stomach depends on the relative amounts of food, water, and stomach secretions and on the degree of digestion that has occurred. The appearance of chyme is that of a murky semifluid or paste.

Hunger Contractions

Besides the peristaltic contractions that occur when food is present in the stomach, another type of intense contractions, called hunger contractions, often occurs when the stomach has been empty for several hours or more. They are rhythmical peristaltic contractions in the body of the

stomach. When the successive contractions become extremely strong, they often fuse to cause a continuing tetanic contraction that sometimes lasts for 2 to 3 minutes.

Hunger contractions are most intense in young, healthy people who have high degrees of gastroin- testinal tonus; they are also greatly increased by the person's having lower than normal levels of blood sugar. When hunger contractions occur in the stomach, the person sometimes experiences mild pain in the pit of the stomach, called hunger pangs. Hunger pangs usually do not begin until 12 to 24 hours after the last ingestion of food; in starvation, they reach their greatest intensity in 3 to 4 days and gradually weaken in succeeding days.

Stomach Emptying

Stomach emptying is promoted by intense peristaltic contractions in the stomach antrum. At the same time, emptying is opposed by varying degrees of resistance to passage of chyme at the pylorus.

Intense Antral Peristaltic Contractions During Stomach Emptying—"Pyloric Pump."

Most of the time, the rhythmical stomach contractions are weak and function mainly to cause mixing of food and gastric secretions. However, for about 20% of the time while food is in the stomach, the contractions become intense, beginning in midstomach and spreading through the caudad stomach no longer as weak mixing contractions but as strong peristaltic, very tight ringlike constrictions that can cause stomach emptying. As the stomach becomes progressively more and more empty, these constric- tions begin farther and farther up the body of the stomach, gradually pinching off the food in the body of the stomach and adding this food to the chyme in the antrum. These intense peristaltic contractions often create 50 to 70 centimeters of water pressure, which is about six times as powerful as the usual mixing type of peristaltic waves.

When pyloric tone is normal, each strong peristaltic wave forces up to several milliliters of chyme into the duodenum. Thus, the peristaltic waves, in addition to causing mixing in the stomach, also provide a pumping action called the "pyloric pump."

Role of the Pylorus in Controlling Stomach Emptying

The distal opening of the stomach is the pylorus. Here the thickness of the circular wall muscle becomes 50 to 100% greater than in the earlier portions of the stomach antrum, and it remains slightly tonically contracted almost all the time. Therefore, the pyloric circular muscle is called the pyloric sphincter.

Despite normal tonic contraction of the pyloric sphincter, the pylorus usually is open enough for water and other fluids to empty from the stomach into the duodenum with ease. Conversely, the constriction usually prevents passage of food particles until they have become mixed in the chyme to almost fluid consistency. The degree of constriction of the pylorus is increased or decreased under the influence of nervous and humoral reflex signals from both the stomach and the duodenum.

Regulation of Stomach Emptying

The rate at which the stomach empties is regulated by signals from both the stomach and the duodenum. However, the duodenum provides by far the more potent of the signals, controlling the emptying of chyme into the duodenum at a rate no greater than the rate at which the chyme can be digested and absorbed in the small intestine.

Gastric Factors That Promote Emptying

Effect of Gastric Food Volume on Rate of Emptying

Increased food volume in the stomach promotes increased emptying from the stomach. But this increased emptying does not occur for the reasons that one would expect. It is not increased storage pressure of the food in the stomach that causes the increased emptying because, in the usual normal range of volume, the increase in volume does not increase the pressure much. However, stretching of the stomach wall does elicit local myenteric reflexes in the wall that greatly accentuate activity of the pyloric pump and at the same time inhibit the pylorus.

Effect of the Hormone Gastrin on Stomach Emptying

The stomach wall stretch and the presence of certain types of foods in the stomach—particularly digestive products of meat—elicit release of a hormone called gastrin from the antral mucosa. This has potent effects to cause secretion of highly acidic gastric juice by the stomach glands

Gastrin also has mild to moderate stimulatory effects on motor functions in the body of the stomach. Most important, it seems to enhance the activity of the pyloric pump. Thus, it, too, probably promotes stomach emptying.

Powerful Duodenal Factors That Inhibit Stomach Emptying

Inhibitory Effect of Enterogastric Nervous Reflexes from the Duodenum

When food enters the duodenum, multiple nervous reflexes are initiated from the duodenal wall that pass back to the stomach to slow or even stop stomach emptying if the volume of chyme in the duodenum becomes too much. These reflexes are mediated by three routes: (1) directly from the duodenum to the stomach through the enteric nervous system in the gut wall, (2) through extrinsic nerves that go to the prevertebral sympathetic ganglia and then back through inhibitory sympathetic nerve fibers to the stomach, and (3) probably to a slight extent through the vagus nerves all the way to the brain stem, where they inhibit the normal excitatory signals transmitted to the stomach through the vagi. All these parallel reflexes have two effects on stomach emptying: first, they strongly inhibit the “pyloric pump” propulsive contractions, and second, they increase the tone of the pyloric sphincter.

The types of factors that are continually monitored in the duodenum and that can initiate enterogastric inhibitory reflexes include the following: 1. The degree of distention of the duodenum 2. The presence of any degree of irritation of theduodenal mucosa 3. The degree of acidity of the duodenal chyme 4. The degree of osmolality of the chyme 5. The presence of certain breakdown products inthe chyme, especially breakdown products of proteins and perhaps to a lesser extent of fats The enterogastric inhibitory reflexes are especially sensitive to the presence of irritants and acids in the duodenal chyme, and they often become strongly activated within as little as 30 seconds. For instance, whenever the pH of the chyme in the duodenum falls below about 3.5 to 4, the reflexes frequently block further release of acidic stomach contents into the duodenum until the duodenal chyme can be neutralized by pancreatic and other secretions. Breakdown products of protein digestion also elicit inhibitory enterogastric reflexes; by slowing the rate of stomach emptying, sufficient time is ensured for ade- quate protein digestion in the duodenum and small intestine.

Finally, either hypotonic or hypertonic fluids (especially hypertonic) elicit the inhibitory reflexes. Thus, too rapid flow of nonisotonic fluids into the small intestine is prevented, thereby also preventing rapid changes in electrolyte concentrations in the whole-body extracellular fluid during absorption of the intestinal contents.

Hormonal Feedback from the Duodenum Inhibits Gastric Emptying—Role of Fats and the Hormone Cholecystokinin

Not only do nervous reflexes from the duodenum to the stomach inhibit stomach emptying, but hormones released from the upper intestine do so as well. The stimulus for releasing these inhibitory hormones is mainly fats entering the duodenum, although other types of foods can increase the hormones to a lesser degree.

On entering the duodenum, the fats extract several different hormones from the duodenal and jejunal epithelium, either by binding with “receptors” on the epithelial cells or in some other way. In turn, the hormones are carried by way of the blood to the stomach, where they inhibit the pyloric pump and at the same time increase the strength of contraction of the pyloric sphincter. These effects are important because fats are much slower to be digested than most other foods.
Precisely which hormones cause the hormonal feedback inhibition of the stomach is not fully clear. The most potent appears to be cholecystokinin (CCK), which is released from the mucosa of the jejunum in response to fatty substances in the chyme. This hormone acts as an inhibitor to block increased stomach motility caused by gastrin.

Other possible inhibitors of stomach emptying are the hormones secretin and gastric inhibitory peptide (GIP). Secretin is released mainly from the duodenal mucosa in response to

gastric acid passed from the stomach through the pylorus. GIP has a general but weak effect of decreasing gastrointestinal motility.

GIP is released from the upper small intestine in response mainly to fat in the chyme, but to a lesser extent to carbohydrates as well. Although GIP does inhibit gastric motility under some conditions, its effect at physiologic concentrations is probably mainly to stimulate secretion of insulin by the pancreas.

In summary, hormones, especially CCK, can inhibit gastric emptying when excess quantities of chyme, especially acidic or fatty chyme, enter the duodenum from the stomach.

Summary of the Control of Stomach Emptying

Emptying of the stomach is controlled only to a mod- erate degree by stomach factors such as the degree of filling in the stomach and the excitatory effect of gastrin on stomach peristalsis. Probably the more important control of stomach emptying resides in inhibitory feedback signals from the duodenum, including both enterogastric inhibitory nervous feed- back reflexes and hormonal feedback by CCK. These feedback inhibitory mechanisms work together to slow the rate of emptying when (1) too much chyme is already in the small intestine or (2) the chyme is excessively acidic, contains too much unprocessed protein or fat, is hypotonic or hypertonic, or is irritating. In this way, the rate of stomach emptying is limited to that amount of chyme that the small intestine can process.

65. Motility of gastrointestinal tract

Movements of the Small Intestine

The movements of the small intestine, like those elsewhere in the gastrointestinal tract, can be divided into mixing contractions and propulsive contractions. To a great extent, this separation is artificial because essencially all movements of the small intestine cause at least some degree of both mixing and propulsion.

Mixing Contractions (Segmentation Contractions)

When a portion of the small intestine becomes distended with chyme, stretching of the intestinal wall elicits localized concentric contractions spaced at intervals along the intestine and lasting a fraction of a minute. The contractions cause “segmentation” of the small intestine. That is, they divide the intestine into spaced segments. As one set of segmentation contractions relaxes, a new set often begins, but the contractions this time occur mainly at new points between the previous contractions. Therefore, the segmentation contractions “chop” the chyme two to three times per minute, in this way promoting progressive mixing of the food with secretions of the small intestine.

The maximum frequency of the segmentation contractions in the small intestine is determined by the frequency of electrical slow waves in the intestinal wall, which is the basic electrical rhythm. Because this frequency normally is not over 12 per minute in the duodenum and proximal jejunum, the maximum frequency of the segmentation contractions in these areas is also about 12 per minute, but this occurs only under extreme conditions of stim- ulation. In the terminal ileum, the maximum frequency is usually 8 to 9 contractions per minute.

The segmentation contractions become exceedingly weak when the excitatory activity of the enteric nervous system is blocked by the drug atropine. Therefore, even though it is the slow waves in the smooth muscle itself that cause the segmentation contractions, these contractions are not effective without background excitation mainly from the myenteric nerve plexus.

Propulsive Movements

Peristalsis in the Small Intestine

Chyme is propelled through the small intestine by peristaltic waves. These can occur in any part of the small intestine, and they move toward the anus at a velocity of 0.5 to 2.0 cm/sec, faster in the proximal intestine and slower in the terminal intestine. They normally are very weak and usually die out after traveling only 3 to 5 centimeters, very rarely farther than 10 centimeters, so that forward movement of the chyme is very slow, so slow in fact that net movement along the small intestine normallyaverages only 1 cm/min. This means that 3 to 5 hours are required for passage of chyme from the pylorus to the ileocecal valve.

Control of Peristalsis by Nervous and Hormonal Signals

Peristaltic activity of the small intestine is greatly increased after a meal. This is caused partly by the beginning entry of chyme into the duodenum causing stretch of the duodenal wall, but also by a so-called gastroenteric reflex that is initiated by distention of the stomach and conducted principally through the myenteric plexus from the stomach down along the wall of the small intestine.

In addition to the nervous signals that may affect small intestinal peristalsis, several hormonal factors also affect peristalsis. They include gastrin, CCK, insulin, motilin, and serotonin, all of which enhance intestinal motility and are secreted during various phases of food processing. Conversely, secretin and glucagon inhibit small intestinal motility.

The function of the peristaltic waves in the small intestine is not only to cause progression of chyme toward the ileocecal valve but also to spread out the chyme along the intestinal mucosa. As the chyme enters the intestines from the stomach and elicits peristalsis, this immediately spreads the chyme along the intestine; and this process intensifies as additional chyme enters the duodenum. On reaching the ileocecal valve, the chyme is sometimes blocked for several hours until the person eats another meal; at that time, a gastroileal reflex intensifies peristalsis in the

ileum and forces the remaining chyme through the ileocecal valve into the cecum of the large intestine.

Propulsive Effect of the Segmentation Movements

The segmentation movements, although lasting for only a few seconds at a time, often also travel 1 centimeter or so in the anal direction and during that time help propel the food down the intestine. The difference between the segmentation and the peristaltic movements is not as great as might be implied by their separation into these two classifications.

Peristaltic Rush

Although peristalsis in the small intestine is normally weak, intense irritation of the intestinal mucosa, as occurs in some severe cases of infectious diarrhea, can cause both powerful and rapid peristalsis, called the peristaltic rush. This is initiated partly by nervous reflexes that involve the autonomic nervous system and brain stem and partly by intrinsic enhancement of the myenteric plexus reflexes within the gut wall itself. The powerful peristaltic contractions travel long distances in the small intestine within minutes, sweeping the contents of the intestine into the colon and thereby relieving the small intestine of irritative chyme and excessive distention.

Movements Caused by the Muscularis Mucosae and Muscle Fibers of the Villi

The muscularis mucosae can cause short folds to appear in the intestinal mucosa. In addition, individual fibers from this muscle extend into the intestinal villi and cause them to contract intermittently. The mucosal folds increase the surface area exposed to the chyme, thereby increasing absorption. Also, contractions of the villi—shortening, elongating, and shortening again—"milk" the villi, so that lymph flows freely from the central lacteals of the villi into the lymphatic system. These mucosal and villous contractions are initiated mainly by local nervous reflexes in the submucosal nerve plexus that occur in response to chyme in the small intestine.

Movements of the Colon

The principal functions of the colon are (1) absorption of water and electrolytes from the chyme to form solid feces and (2) storage of fecal matter until it can be expelled. The proximal half of the colon, is concerned principally with absorption, and the distal half with storage. Because intense colon wall movements are not required for these functions, the movements of the colon are normally very sluggish. Yet in a sluggish manner, the movements still have characteristics similar to those of the small intestine and can be divided once again into mixing movements and propulsive movements.

Mixing Movements—"Haustrations."

In the same manner that segmentation movements occur in the small intestine, large circular constrictions occur in the large intestine. At each of these constrictions, about 2.5 centimeters of the circular muscle contracts, sometimes constricting the lumen of the colon almost to occlusion. At the same time, the longitudinal muscle of the colon, which is aggregated into three longitudinal strips called the teniae coli, contracts. These combined contractions of the circular and longitudinal strips of muscle cause the unstimulated portion of the large intestine to bulge outward into baglike sacs called haustrations.

Each haustration usually reaches peak intensity in about 30 seconds and then disappears during the next 60 seconds. They also at times move slowly toward the anus during contraction, especially in the cecum and ascending colon, and thereby provide a minor amount of forward propulsion of the colonic contents. After another few minutes, new haustral contractions occur in other areas nearby. Therefore, the fecal material in the large intestine is slowly dug into and rolled over. In this way, all the fecal material is gradually exposed to the mucosal surface of the large intestine, and fluid and dissolved substances are progressively absorbed until only 80 to 200 mL of feces are expelled each day.

Propulsive Movements—"Mass Movements."

Much of the propulsion in the cecum and ascending colon results from the slow but persistent haustral contractions, requiring as many as 8 to 15 hours to move the chyme from the

ileocecal valve through the colon, while the chyme itself becomes fecal in quality, a semisolid slush instead of semifluid.

From the cecum to the sigmoid, mass movements can, for many minutes at a time, take over the propulsive role. These movements usually occur only one to three times each day, in many people especially for about 15 minutes during the first hour after eating breakfast.

A mass movement is a modified type of peristalsis characterized by the following sequence of events: First, a constrictive ring occurs in response to a distended or irritated point in the colon, usually in the transverse colon. Then, rapidly, the 20 or more centimeters of colon distal to the constrictive ring lose their haustrations and instead contract as a unit, propelling the fecal material in this segment en masse further down the colon. The contraction develops progressively more force for about 30 seconds, and relaxation occurs during the next 2 to 3 minutes. Then, another mass movement occurs, this time perhaps farther along the colon.

A series of mass movements usually persists for 10 to 30 minutes. Then they cease but return perhaps a half day later. When they have forced a mass of feces into the rectum, the desire for defecation is felt.

Electrical Activity of Gastrointestinal Smooth Muscle

The smooth muscle of the gastrointestinal tract is excited by almost continual slow, intrinsic electrical activity along the membranes of the muscle fibers. This activity has two basic types of electrical waves: (1) slow waves and (2) spikes. In addition, the voltage of the resting membrane potential of the gastrointestinal smooth muscle can be made to change to different levels, and this too can have important effects in controlling motor activity of the gastrointestinal tract.

Slow Waves

Most gastrointestinal contractions occur rhythmically, and this rhythm is determined mainly by the frequency of so-called “slow waves” of smooth muscle membrane potential. These waves, are not action potentials. Instead, they are slow, undulating changes in the resting membrane potential. Their intensity usually varies between 5 and 15 mV, and their frequency ranges in different parts of the human gastrointestinal tract from 3 to 12 per minute: about 3 in the body of the stomach, as much as 12 in the duodenum, and about 8 or 9 in the terminal ileum.

The precise cause of the slow waves is not completely understood, although they appear to be caused by complex interactions among the smooth muscle cells and specialized cells, called the interstitial cells of Cajal, that are believed to act as electrical pacemakers for smooth muscle cells. These interstitial cells form a network with each other and are interposed between the smooth muscle layers, with synaptic-like contacts to smooth muscle cells. The interstitial cells of Cajal undergo cyclic changes in membrane potential due to unique ion channels that periodically open and produce inward (pacemaker) currents that may generate slow wave activity.

The slow waves usually do not by themselves cause muscle contraction in most parts of the gastrointestinal tract, except perhaps in the stomach. Instead, they mainly excite the appearance of intermittent spike potentials, and the spike potentials in turn actually excite the muscle contraction.

Spike Potentials

The spike potentials are true action potentials. They occur automatically when the resting membrane potential of the gastrointestinal smooth muscle becomes more positive than about -40 mV (the normal resting membrane potential in the smooth muscle fibers of the gut is between -50 and -60 mV). Thus, each time the peaks of the slow waves temporarily become more positive than -40 mV, spike potentials appear on these peaks. The higher the slow wave potential rises, the greater the frequency of the spike potentials, usually ranging between 1 and 10 spikes per second. The spike potentials last 10 to 40 times as long in gastrointestinal muscle as the action potentials in large nerve fibers, each gastrointestinal spike lasting as long as 10 to 20 milliseconds.

Another important difference between the action potentials of the gastrointestinal smooth muscle and those of nerve fibers is the manner in which they are generated. In nerve fibers, the action potentials are caused almost entirely by rapid entry of sodium ions through sodium channels to the interior of the fibers. In gastrointestinal smooth muscle fibers, the channels responsible for the action potentials are somewhat different; they allow especially large numbers of calcium ions to

enter along with smaller numbers of sodium ions and therefore are called calcium-sodium channels. These channels are much slower to open and close than are the rapid sodium channels of large nerve fibers. The slowness of opening and closing of the calcium-sodium channels accounts for the long duration of the action potentials. Also, the movement of large amounts of calcium ions to the interior of the muscle fiber during the action potential plays a special role in causing the intestinal muscle fibers to contract.

Changes in Voltage of the Resting Membrane Potential

In addition to the slow waves and spike potentials, the baseline voltage level of the smooth muscle resting membrane potential also can change. Under normal conditions, the resting membrane potential averages about -56 mV, but multiple factors can change this level.

Factors that depolarize the membrane—that is, make it more excitable—are (1) stretching of the muscle, (2) stimulation by acetylcholine, (3) stimulation by parasympathetic nerves that secrete acetylcholine at their endings, and (4) stimulation by several specific gastrointestinal hormones.

Important factors that make the membrane potential more negative—that is, hyperpolarize the membrane and make the muscle fibers less excitable—are (1) the effect of norepinephrine or epinephrine on the fiber membrane and (2) stimulation of the sympathetic nerves that secrete mainly norepinephrine at their endings.

Calcium Ions and Muscle Contraction

Smooth muscle contraction occurs in response to entry of calcium ions into the muscle fiber. Calcium ions, acting through a calmodulin control mechanism, activate the myosin filaments in the fiber, causing attractive forces to develop between the myosin filaments and the actin filaments, thereby causing the muscle to contract.

The slow waves do not cause calcium ions to enter the smooth muscle fiber (only sodium ions). Therefore, the slow waves by themselves usually cause no muscle contraction. Instead, it is during the spike potentials, generated at the peaks of the slow waves, that significant quantities of calcium ions do enter the fibers and cause most of the contraction.

Neural Control of Gastrointestinal Function— Enteric Nervous System

The gastrointestinal tract has a nervous system all its own called the enteric nervous system. It lies entirely in the wall of the gut, beginning in the esophagus and extending all the way to the anus. This highly developed enteric nervous system is especially important in controlling gastrointestinal movements and secretion.

The enteric nervous system is composed mainly of two plexuses: (1) an outer plexus lying between the longitudinal and circular muscle layers, called the myenteric plexus or Auerbach's plexus, and (2) an inner plexus, called the submucosal plexus or Meissner's plexus, that lies in the submucosa.

The myenteric plexus controls mainly the gastrointestinal movements, and the submucosal plexus controls mainly gastrointestinal secretion and local blood flow.

The extrinsic sympathetic and parasympathetic fibers connect to both the myenteric and submucosal plexuses. Although the enteric nervous system can function on its own, independently of these extrinsic nerves, stimulation by the parasympathetic and sympathetic systems can greatly enhance or inhibit gastrointestinal functions.

There are sensory nerve endings that originate in the gastrointestinal epithelium or gut wall and send afferent fibers to both plexuses of the enteric system, as well as (1) to the prevertebral ganglia of the sympathetic nervous system, (2) to the spinal cord, and (3) in the vagus nerves all the way to the brain stem. These sensory nerves can elicit local reflexes within the gut wall itself and still other reflexes that are relayed to the gut from either the prevertebral ganglia or the basal regions of the brain.

Autonomic Control of the Gastrointestinal Tract

Parasympathetic Innervation

The parasympathetic supply to the gut is divided into cranial and sacral divisions. Except for a few parasympathetic fibers to the mouth and pharyngeal regions of the alimentary tract, the cranial parasympathetic nerve fibers are almost entirely in the vagus nerves. These fibers provide

extensive innervation to the esophagus, stomach, and pancreas and somewhat less to the intestines down through the first half of the large intestine.

The sacral parasympathetics originate in the second, third, and fourth sacral segments of the spinal cord and pass through the pelvic nerves to the distal half of the large intestine and all the way to the anus. The sigmoidal, rectal, and anal regions are considerably better supplied with parasympathetic fibers than are the other intestinal areas. These fibers function especially to execute the defecation reflexes.

The postganglionic neurons of the gastrointestinal parasympathetic system are located mainly in the myenteric and submucosal plexuses. Stimulation of these parasympathetic nerves causes general increase in activity of the entire enteric nervous system. This in turn enhances activity of most gastrointestinal functions.

Sympathetic Innervation

The sympathetic fibers to the gastrointestinal tract originate in the spinal cord between segments T-5 and L-2. Most of the preganglionic fibers that innervate the gut, after leaving the cord, enter the sympathetic chains that lie lateral to the spinal column, and many of these fibers then pass on through the chains to outlying ganglia such as to the celiac ganglion and various mesenteric ganglia. Most of the postganglionic sympathetic neuron bodies are in these ganglia, and postganglionic fibers then spread through postganglionic sympathetic nerves to all parts of the gut.. The sympathetics innervate essentially all of the gastrointestinal tract, rather than being more extensive nearest the oral cavity and anus as is true of the parasympathetics. The sympathetic nerve endings secrete mainly norepinephrine but also small amounts of epinephrine.

In general, stimulation of the sympathetic nervous system inhibits activity of the gastrointestinal tract, causing many effects opposite to those of the parasympathetic system. It exerts its effects in two ways: (1) to a slight extent by direct effect of secreted norepinephrine to inhibit intestinal tract smooth muscle (except the mucosal muscle, which it excites) and (2) to a major extent by an inhibitory effect of norepinephrine on the neurons of the entire enteric nervous system.

Strong stimulation of the sympathetic system can inhibit motor movements of the gut so greatly that this literally can block movement of food through the gastrointestinal tract.

Afferent Sensory Nerve Fibers from the Gut

Many afferent sensory nerve fibers innervate the gut. Some of them have their cell bodies in the enteric nervous system itself and some in the dorsal root ganglia of the spinal cord. These sensory nerves can be stimulated by (1) irritation of the gut mucosa, (2) excessive distention of the gut, or (3) presence of specific chemical substances in the gut. Signals transmitted through the fibers can then cause excitation or, under other conditions, inhibition of intestinal move- ments or intestinal secretion.

In addition, other sensory signals from the gut go all the way to multiple areas of the spinal cord and even the brain stem.

Gastrointestinal Reflexes

The anatomical arrangement of the enteric nervous system and its connections with the sympathetic and parasympathetic systems support three types of gastrointestinal reflexes that are essential to gastrointestinal control. They are the following:

1. Reflexes that are integrated entirely within the gut wall enteric nervous system. These include reflexes that control much gastrointestinal secretion, peristalsis, mixing contractions, local inhibitory effects, and so forth. 2. Reflexes from the gut to the prevertebral sympathetic ganglia and then back to the gastrointestinal tract. These reflexes transmit signals long distances to other areas of the gastrointestinal tract, such as signals from the stomach to cause evacuation of the colon (the gastrocolic reflex), signals from the colon and small intestine to inhibit stomach motility and stomach secretion (the enterogastric reflexes), and reflexes from the colon to inhibit emptying of ileal contents into the colon (the colonoileal reflex).3. Reflexes from the gut to the spinal cord or brain stem and then back to the gastrointestinal tract. These include especially (1) reflexes from the stomach and duodenum to the brain stem and back to the stomach—by way of the vagus nerves—to control gastric motor and secretory activity; (2) pain reflexes that cause general inhibition of the entire gastrointestinal tract; and (3) defecation reflexes that travel from the colon

and rectum to the spinal cord and back again to produce the powerful colonic, rectal, and abdominal contractions required for defecation (the defecation reflexes).

Hormonal Control of Gastrointestinal Motility

Most of the hormones that control the secretion of digetive fluids also affect motility in some parts of the gastrointestinal tract. Although the motility effects are usually less important than the secretory effects of the hormones, some of the more important of them are the following.

Gastrin is secreted by the “G” cells of the antrum of the stomach in response to stimuli associated with ingestion of a meal, such as distention of the stomach. The primary actions of gastrin are (1) stimulation of gastric acid secretion and (2) stimulation of growth of the gastric mucosa.

Cholecystokinin is secreted by “I” cells in the mucosa of the duodenum and jejunum. This hormone strongly contracts the gallbladder, expelling bile into the small intestine where the bile in turn plays important roles in emulsifying fatty substances, allowing them to be digested and absorbed. Cholecystokinin also inhibits stomach contraction moderately. Therefore, at the same time that this hormone causes emptying of the gallbladder, it also slows the emptying of food from the stomach to give adequate time for digestion of the fats in the upper intestinal tract.

Secretin was the first gastrointestinal hormone dis- covered and is secreted by the “S” cells in the mucosa of the duodenum in response to acidic gastric juice emptying into the duodenum from the pylorus of the stomach. Secretin has a mild effect on motility of the gastrointestinal tract and acts to promote pancreatic secretion of bicarbonate which in turn helps to neutralize the acid in the small intestine.

Gastric inhibitory peptide is secreted by the mucosa of the upper small intestine. It has a mild effect in decreasing motor activity of the stomach and therefore slows emptying of gastric contents into the duodenum when the upper small intestine is already overloaded with food products.

Functional Types of Movements in the Gastrointestinal Tract

Two types of movements occur in the gastrointestinal tract: (1) propulsive movements, which cause food to move forward along the tract at an appropriate rate to accommodate digestion and absorption, and (2) mixing movements, which keep the intestinal contents thoroughly mixed at all times.

Propulsive Movements—Peristalsis

The basic propulsive movement of the gastrointestinal tract is peristalsis. A contractile ring appears around the gut and then moves forward; any material in front of the contractile ring is moved forward.

Peristalsis is an inherent property of many syncytial smooth muscle tubes; stimulation at any point in the gut can cause a contractile ring to appear in the circular muscle, and this ring then spreads along the gut tube.

The usual stimulus for intestinal peristalsis is distention of the gut. That is, if a large amount of food collects at any point in the gut, the stretching of the gut wall stimulates the enteric nervous system to contract the gut wall 2 to 3 centimeters behind this point, and a contractile ring appears that initiates a peristaltic movement. Other stimuli that can initiate peristalsis include chemical or physical irritation of the epithelial lining in the gut. Also, strong parasympathetic nervous signals to the gut will elicit strong peristalsis.

Function of the Myenteric Plexus in Peristalsis

Peristalsis occurs only weakly or not at all in any portion of the gastrointestinal tract that has congenital absence of the myenteric plexus. Also, it is greatly depressed or completely blocked in the entire gut when a person is treated with atropine to paralyze the cholinergic nerve endings of the myenteric plexus. Therefore, effectual peristalsis requires an active myenteric plexus.

Directional Movement of Peristaltic Waves Toward the Anus

Peristalsis, theoretically, can occur in either direction from a stimulated point, but it normally dies out rapidly in the orad direction while continuing for a considerable distance toward the anus. The exact cause of this directional transmission of peristalsis has never been ascertained,

although it probably results mainly from the fact that the myenteric plexus itself is “polar- ized” in the anal direction, which can be explained as follows.

Peristaltic Reflex and the “Law of the Gut.”

When a segment of the intestinal tract is excited by distention and thereby initiates peristalsis, the contractile ring causing the peristalsis normally begins on the orad side of the distended segment and moves toward the dis- tended segment, pushing the intestinal contents in the anal direction for 5 to 10 centimeters before dying out. At the same time, the gut sometimes relaxes several centimeters downstream toward the anus, which is called “receptive relaxation,” thus allowing the food to be propelled more easily anally than orally.

This complex pattern does not occur in the absence of the myenteric plexus. Therefore, the complex is called the myenteric reflex or the peristaltic reflex. The peristaltic reflex plus the anal direction of movement of the peristalsis is called the “law of the gut.”

Mixing Movements

Mixing movements differ in different parts of the alimentary tract. In some areas, the peristaltic contractions themselves cause most of the mixing. This is true especially true when forward progression of the intestinal contents is blocked by a sphincter, so that a peristaltic wave can then only churn the intestinal contents, rather than propelling them forward. At other times, local intermittent constrictive contractions occur every few centimeters in the gut wall. These constrictions usually last only 5 to 30 seconds; then new constrictions occur at other points in the gut, thus “chopping” and “shearing” the contents first here and then there. These peristaltic and constrictive movements are modified in different parts of the gastrointestinal tract for proper propulsion and mixing.

Initiation of Mass Movements by Gastrocolic and Duodenocolic Reflexes

Appearance of mass movements after meals is facilitated by gastrocolic and duodenocolic reflexes. These reflexes result from distention of the stomach and duodenum. They occur either not at all or hardly at all when the extrinsic autonomic nerves to the colon have been removed; therefore, the reflexes almost certainly are transmitted by way of the autonomic nervous system. Irritation in the colon can also initiate intense mass movements.

Defecation

Most of the time, the rectum is empty of feces. This results partly from the fact that a weak functional sphincter exists about 20 centimeters from the anus at the juncture between the sigmoid colon and the rectum. There is also a sharp angulation here that contributes additional resistance to filling of the rectum.

When a mass movement forces feces into the rectum, the desire for defecation occurs immediately, including reflex contraction of the rectum and relaxation of the anal sphincters.

Continual dribble of fecal matter through the anus is prevented by tonic constriction of (1) an internal anal sphincter, a several-centimeters-long thickening of the circular smooth muscle that lies immediately inside the anus, and (2) an external anal sphincter, composed of striated voluntary muscle that both surrounds the internal sphincter and extends distal to it. The external sphincter is controlled by nerve fibers in the pudendal nerve, which is part of the somatic nervous system and therefore is under voluntary, conscious or at least subconscious control; subconsciously, the external sphincter is usually kept continuously constricted unless conscious signals inhibit the constriction.

Defecation Reflexes

Ordinarily, defecation is initiated by defecation reflexes. One of these reflexes is an intrinsic reflex mediated by the local enteric nervous system in the rectal wall. This can be described as follows: When feces enter the rectum, distention of the rectal wall initiates afferent signals that spread through the myenteric plexus to initiate peristaltic waves in the descending colon, sigmoid, and rectum, forcing feces toward the anus. As the peristaltic wave approaches the anus, the internal anal sphincter is relaxed by inhibitory signals from the myenteric plexus; if the external anal sphincter is also consciously, voluntarily relaxed at the same time, defecation occurs.

The intrinsic myenteric defecation reflex functioning by itself normally is relatively weak. To be effective in causing defecation, it usually must be fortified by another type of defecation reflex, a parasympathetic defecation reflex that involves the sacral segments of the spinal cord. When the nerve endings in the rectum are stimulated, signals are transmitted first into the spinal cord and then reflexly back to the descending colon, sigmoid, rectum, and anus by way of parasympathetic nerve fibers in the pelvic nerves. These parasympathetic signals greatly intensify the peristaltic waves as well as relax the internal anal

Other Autonomic Reflexes That Affect Bowel Activity

Several other important nervous reflexes also can affect the overall degree of bowel activity. They are the peritoneointestinal reflex, renointestinal reflex, and vesicointestinal reflex.

The peritoneointestinal reflex results from irritation of the peritoneum; it strongly inhibits the excitatory enteric nerves and thereby can cause intestinal paralysis, especially in patients with peritonitis. The renointestinal and vesicointestinal reflexes inhibit intestinal activity as a result of kidney or bladder irritation.

66. Composition and function of pancreatic juice

Pancreatic Secretion

The pancreas, which lies parallel to and beneath the stomach, is a large compound gland with most of its internal structure similar to that of the salivary glands. The pancreatic digestive enzymes are secreted by pancreatic acini, and large volumes of sodium bicarbonate solution are secreted by the small ductules and larger ducts leading from the acini. The combined product of enzymes and sodium bicarbonate then flows through a long pancreatic duct that normally joins the hepatic duct immediately before it empties into the duodenum through the papilla of Vater, surrounded by the sphincter of Oddi.

Pancreatic juice is secreted most abundantly in response to the presence of chyme in the upper portions of the small intestine, and the characteristics of the pancreatic juice are determined to some extent by the types of food in the chyme.

Pancreatic Digestive Enzymes

Pancreatic secretion contains multiple enzymes for digesting all of the three major types of food: proteins, carbohydrates, and fats. It also contains large quantities of bicarbonate ions, which play an important role in neutralizing the acidity of the chyme emptied from the stomach into the duodenum.

The most important of the pancreatic enzymes for digesting proteins are trypsin, chymotrypsin, and carboxypolypeptidase. By far the most abundant of these is trypsin.

Trypsin and chymotrypsin split whole and partially digested proteins into peptides of various sizes but do not cause release of individual amino acids. However, carboxypolypeptidase does split some peptides into individual amino acids, thus completing digestion of some proteins all the way to the amino acid state.

The pancreatic enzyme for digesting carbohydrates is pancreatic amylase, which hydrolyzes starches, glycogen, and most other carbohydrates (except cellulose) to form mostly disaccharides and a few trisaccharides.

The main enzymes for fat digestion are (1) pancreatic lipase, which is capable of hydrolyzing neutral fat into fatty acids and monoglycerides; (2) cholesterol esterase, which causes hydrolysis of cholesterol esters; and (3) phospholipase, which splits fatty acids from phospholipids.

When first synthesized in the pancreatic cells, the proteolytic digestive enzymes are in the inactive forms trypsinogen, chymotrypsinogen, and procarboxypolypeptidase, which are all inactive enzymatically. They become activated only after they are secreted into the intestinal tract. Trypsinogen is activated by an enzyme called enterokinase, which is secreted by the intestinal mucosa when chyme comes in contact with the mucosa. Also, trypsinogen can be autocatalytically activated by trypsin that has already been formed from previously secreted trypsinogen. Chymotrypsinogen is activated by trypsin to form chymotrypsin, and procarboxypolypeptidase is activated in a similar manner.

Secretion of Trypsin Inhibitor Prevents Digestion of the Pancreas Itself

It is important that the proteolytic enzymes of the pancreatic juice not become activated until after they have been secreted into the intestine because the trypsin and the other enzymes would digest the pancreas itself. Fortunately, the same cells that secrete proteolytic enzymes into the acini of the pancreas secrete simultaneously another substance called trypsin inhibitor. This substance is formed in the cytoplasm of the glandular cells, and it prevents activation of trypsin both inside the secretory cells and in the acini and ducts of the pancreas. And, because it is trypsin that activates the other pancreatic proteolytic enzymes, trypsin inhibitor prevents activation of the others as well.

When the pancreas becomes severely damaged or when a duct becomes blocked, large quantities of pancreatic secretion sometimes become pooled in the damaged areas of the pancreas. Under these conditions, the effect of trypsin inhibitor is often overwhelmed, in which case the pancreatic secretions rapidly become activated and can literally digest the entire pancreas within a few hours, giving rise to the condition called acute pancreatitis.

Regulation of Pancreatic Secretion

Basic Stimuli That Cause Pancreatic Secretion

Three basic stimuli are important in causing pancreatic secretion:

1. Acetylcholine, which is released from the parasympathetic vagus nerve endings and from other cholinergic nerves in the enteric nervous system

2. Cholecystokinin, which is secreted by the duodenal and upper jejunal mucosa when food enters the small intestine

3. Secretin, which is also secreted by the duodenal and jejunal mucosa when highly acid food enters the small intestine

The first two of these stimuli, acetylcholine and cholecystokinin, stimulate the acinar cells of the pancreas, causing production of large quantities of pancreatic digestive enzymes but relatively small quantities of water and electrolytes to go with the enzymes. Without the water, most of the enzymes remain temporarily stored in the acini and ducts until more fluid secretion comes along to wash them into the duodenum. Secretin, in contrast to the first two basic stimuli, stimulates secretion of large quantities of water solution of sodium bicarbonate by the pancreatic ductal epithelium.

Multiplicative Effects of Different Stimuli.

When all the different stimuli of pancreatic secretion occur at once, the total secretion is far greater than the sum of the secretions caused by each one separately. Therefore, the various stimuli are said to “multiply,” or “potentiate,” one another. Thus, pancreatic secretion normally results from the combined effects of the multiple basic stimuli, not from one alone.

Phases of Pancreatic Secretion

Pancreatic secretion occurs in three phases, the same as for gastric secretion: the cephalic phase, the gastric phase, and the intestinal phase. Their characteristics are as follows.

Cephalic and Gastric Phases

During the cephalic phase of pancreatic secretion, the same nervous signals from the brain that cause secretion in the stomach also cause acetylcholine release by the vagal nerve endings in the pancreas. This causes moderate amounts of enzymes to be secreted into the pancreatic acini, accounting for about 20 per cent of the total secretion of pancreatic enzymes after a meal. But little of the secretion flows immediately through the pancreatic ducts into the intestine because only small amounts of water and electrolytes are secreted along with the enzymes.

During the gastric phase, the nervous stimulation of enzyme secretion continues, accounting for another 5 to 10 per cent of pancreatic enzymes secreted after a meal. But, again, only small amounts reach the duodenum because of continued lack of significant fluid secretion.

Intestinal Phase

After chyme leaves the stomach and enters the small intestine, pancreatic secretion becomes copious, mainly in response to the hormone secretin.

67. Liver functions

The various functions of the liver are carried out by the liver cells or hepatocytes. Currently, there is no artificial organ or device capable of emulating all the functions of the liver.

Synthesis

1. A large part of amino acid synthesis
2. The liver performs several roles in carbohydrate metabolism:

o *Gluconeogenesis* (the synthesis of glucose from certain amino acids, lactate or glycerol). Note that humans and some other mammals cannot synthesize glucose from glycerol.
o *Glycogenolysis* (the breakdown of glycogen into glucose)
o *Glycogenesis* (the formation of glycogen from glucose)(muscle tissues can also do this)

3. The liver is responsible for the mainstay of protein metabolism, synthesis as well as degradation
4. The liver also performs several roles in lipid metabolism:

o *Cholesterol synthesis*
o *Lipogenesis*, the production of triglycerides (fats).

5. The liver produces coagulation factors I (fibrinogen), II (prothrombin), V, VII, IX, X and XI, as well as protein C, protein S and antithrombin.
6. In the first trimester fetus, the liver is the main site of red blood cell production. By the 32nd week of gestation, the bone marrow has almost completely taken over that task.
7. The liver produces and excretes bile (a greenish liquid) required for emulsifying fats. Some of the bile drains directly into the duodenum, and some is stored in the gallbladder.
8. The liver also produces insulin-like growth factor 1 (IGF-1), a polypeptide protein hormone that plays an important role in childhood growth and continues to have anabolic effects in adults.
9. The liver is a major site of thrombopoietin production. Thrombopoietin is a glycoprotein hormone that regulates the production of platelets by the bone marrow.

Breakdown

1. The breakdown of insulin and other hormones
2. The liver breaks down hemoglobin, creating metabolites that are added to bile as pigment (bilirubin and biliverdin).
3. The liver breaks down or modifies toxic substances (e.g., methylation) and most medicinal products in a process called drug metabolism. This sometimes results in toxication, when the metabolite is more toxic than its precursor. Preferably, the toxins are conjugated to avail excretion in bile or urine.
4. The liver converts ammonia to urea. Review

Other functions

1. The liver stores a multitude of substances, including glucose (in the form of glycogen), vitamin A (1–2 years' supply), vitamin D (1–4 months' supply), vitamin B12 (1-3 years' supply), iron, and copper.
2. The liver is responsible for immunological effects- the reticuloendothelial system of the liver contains many immunologically active cells, acting as a 'sieve' for antigens carried to it via the portal system.
3. The liver produces albumin, the major osmolar component of blood serum.
4. The liver synthesizes angiotensinogen, a hormone that is responsible for raising the blood pressure when activated by renin, an enzyme that is released when the kidney senses low blood pressure.

68. Formation, composition and functions of bile

Physiologic Anatomy of Biliary Secretion

Bile is secreted in two stages by the liver: (1) The initial portion is secreted by the principal functional cells of the liver, the hepatocytes; this initial secretion contains large amounts of bile acids, cholesterol, and other organic constituents. It is secreted into minute bile canaliculi that originate between the hepatic cells. (2) Next, the bile flows in the canaliculi toward the interlobular septa, where the canaliculi empty into terminal bile ducts and then into progressively larger ducts, finally reaching the hepatic duct and common bile duct. From these the bile either empties directly into the duodenum or is diverted for minutes up to several hours through the cystic duct into the gallbladder.

In its course through the bile ducts, a second portion of liver secretion is added to the initial bile. This additional secretion is a watery solution of sodium and bicarbonate ions secreted by secretory epithelial cells that line the ductules and ducts. This second secretion sometimes increases the total quantity of bile by as much as an additional 100 per cent. The second secretion is stimulated especially by secretin, which causes release of additional quantities of bicarbonate ions to supplement the bicarbonate ions in pancreatic secretion (for neutralizing acid that empties into the duodenum from the stomach).

Storing and Concentrating Bile in the Gallbladder

Bile is secreted continually by the liver cells, but most of it is normally stored in the gallbladder until needed in the duodenum. The maximum volume that the gallbladder can hold is only 30 to 60 mL. Nevertheless, as much as 12 hours of bile secretion (usually about 450 mL) can be stored in the gallbladder because water, sodium, chloride, and most other small electrolytes are continually absorbed through the gallbladder mucosa, concentrating the remaining bile constituents that contain the bile salts, cholesterol, lecithin, and bilirubin.

Most of this gallbladder absorption is caused by active transport of sodium through the gallbladder epithelium, and this is followed by secondary absorp- tion of chloride ions, water, and most other diffusible constituents. Bile is normally concentrated in this way about 5-fold, but it can be concentrated up to a maximum of 20-fold.

Composition of Bile.

The table gives the compositionof bile when it is first secreted by the liver and then after it has been concentrated in the gallbladder. This table shows that by far the most abundant substances secreted in the bile are bile salts, which account for about one half of the total solutes also in the bile. Also secreted or excreted in large concentrations are bilirubin, cholesterol, lecithin, and the usual electrolytes of plasma.

Composition of Bile

	Liver Bile	Gallbladder Bile
Water	97.5 g/dl	92 g/dl
Bile salts	1.1 g/dl	6 g/dl
Bilirubin	0.04 g/dl	0.3 g/dl
Cholesterol	0.1 g/dl	0.3 to 0.9 g/dl
Fatty acids	0.12 g/dl	0.3 to 1.2 g/dl
Lecithin	0.04 g/dl	0.3 g/dl
Na^+	145.04 mEq/L	130 mEq/L
K^+	5 mEq/L	12 mEq/L
Ca^{++}	5 mEq/L	23 mEq/L
Cl^-	100 mEq/L	25 mEq/L
HCO_3^-	28 mEq/L	10 mEq/L

In the concentrating process in the gallbladder, water and large portions of the electrolytes (except calcium ions) are reabsorbed by the gallbladder mucosa; essentially all other constituents, especially the bile salts and the lipid substances cholesterol and lecithin, are not reabsorbed and, therefore, become highly concentrated in the gallbladder bile.

Emptying of the Gallbladder—Stimulatory Role of Cholecystokinin

When food begins to be digested in the upper gastrointestinal tract, the gallbladder begins to empty, especially when fatty foods reach the duodenum about 30 minutes after a meal. The mechanism of gallbladder emptying is rhythmical contractions of the wall of the gallbladder, but effective emptying also requires simultaneous relaxation of the sphincter of Oddi, which guards the exit of the common bile duct into the duodenum.

By far the most potent stimulus for causing the gallbladder contractions is the hormone cholecystokinin. The stimulus for cholecystokinin entry into the blood from the duodenal mucosa is mainly the presence of fatty foods in the duodenum.

In addition to cholecystokinin, the gallbladder is stimulated less strongly by acetylcholine-secreting nerve fibers from both the vagi and the intestinal enteric nervous system. They are the same nerves that promote motility and secretion in other parts of the upper gastrointestinal tract.

Function of Bile Salts in Fat Digestion and Absorption

The liver cells synthesize about 6 grams of bile salts daily. The precursor of the bile salts is cholesterol, which is either present in the diet or synthesized in the liver cells during the course of fat metabolism. The cholesterol is first converted to cholic acid or chenodeoxycholic acid in about equal quantities. These acids in turn combine principally with glycine and to a lesser extent with taurine to form glyco- and tauro- conjugated bile acids. The salts of these acids, mainly sodium salts, are then secreted in the bile.

The bile salts have two important actions in the intestinal tract:

First, they have a detergent action on the fat particles in the food. This decreases the surface tension of the particles and allows agitation in the intestinal tract to break the fat globules into minute sizes. This is called the emulsifying or detergent function of bile salts.

Second, and even more important than the emulsifying function, bile salts help in the absorption of (1) fatty acids, (2) monoglycerides, (3) cholesterol, and (4) other lipids from the intestinal tract. They do this by forming very small physical complexes with these lipids; the complexes are called micelles, and they are semi-soluble in the chyme because of the electrical charges of the bile salts. The intestinal lipids are absorbed in this form by the intestinal mucosa, where they are then absorbed into the blood. Without the presence of bile salts in the intestinal tract, up to 40% of the ingested fats are lost into the feces, and the person often develops a metabolic deficit because of this nutrient loss.

Enterohepatic Circulation of Bile Salts

About 94% of the bile salts are reabsorbed into the blood from the small intestine, about one half of this by diffusion through the mucosa in the early portions of the small intestine and the remainder by an active transport process through the intestinal mucosa in the distal ileum. They then enter the portal blood and pass back to the liver. On reaching the liver, on first passage through the venous sinusoids these salts are absorbed almost entirely back into the hepatic cells and then are resecreted into the bile.

In this way, about 94% of all the bile salts are recirculated into the bile, so that on the average these salts make the entire circuit some 17 times before being carried out in the feces. The small quantities of bile salts lost into the feces are replaced by new amounts formed continually by the liver cells. This recirculation of the bile salts is called the enterohepatic circulation of bile salts.

The quantity of bile secreted by the liver each day is highly dependent on the availability of bile salts—the greater the quantity of bile salts in the enterohepatic circulation (usually a total of only about 2.5 grams), the greater the rate of bile secretion.

If a bile fistula empties the bile salts to the exterior for several days to several weeks so that they cannot be reabsorbed from the ileum, the liver increases its production of bile salts 6- to 10-fold, which increases the rate of bile secretion most of the way back to normal.

Role of Secretin in Helping to Control Bile Secretion

In addition to the strong stimulating effect of bile acids to cause bile secretion, the hormone secretin that also stimulates pancreatic secretion increases bile secretion, sometimes more than doubling its secretion for several hours after a meal. This increase in secretion is almost entirely secretion of a sodium bicarbonate-rich watery solution by the epithelial cells of the bile ductules and ducts, and not increased secretion by the liver parenchymal cells themselves. The bicarbonate in turn passes into the small intestine and joins the bicarbonate from the pancreas in neutralizing the hydrochloric acid from the stomach. Thus, the secretin feedback mechanism for neutralizing duodenal acid operates not only through its effects on pancreatic secretion but also to a lesser extent through its effect on secretion by the liver ductules and ducts.

69. Digestion in the small intestine

Secretions of the Small Intestine

Secretion of Mucus by Brunner's Glands in the Duodenum

An extensive array of compound mucous glands, called Brunner's glands, is located in the wall of the first few centimeters of the duodenum, mainly between the pylorus of the stomach and the papilla of Vater. These glands secrete large amounts of alkaline mucus in response to (1) tactile or irritating stimuli on the duodenal mucosa; (2) vagal stimulation, which causes increased Brunner's glands secretion concurrently with increase in stomach secretion; and (3) gastrointestinal hormones, especially secretin.

The function of the mucus secreted by Brunner's glands is to protect the duodenal wall from digestion by the highly acid gastric juice emptying from the stomach. In addition, the mucus contains a large excess of bicarbonate ions, which add to the bicarbonate ions from pancreatic secretion and liver bile in neutralizing the hydrochloric acid entering the duodenum from the stomach.

Brunner's glands are inhibited by sympathetic stimulation; therefore, such stimulation in very excitable persons is likely to leave the duodenal bulb unprotected and is perhaps one of the factors that cause this area of the gastrointestinal tract to be the site of peptic ulcers in about 50% of ulcer patients.

Secretion of Intestinal Digestive Juices by the Crypts of Lieberkühn

Located over the entire surface of the small intestine are small pits called crypts of Lieberkühn. These crypts lie between the intestinal villi. The surfaces of both the crypts and the villi are covered by an epithelium composed of two types of cells: (1) a moderate number of goblet cells, which secrete mucus that lubricates and protects the intestinal surfaces, and (2) a large number of enterocytes, which, in the crypts, secrete large quantities of water and electrolytes and, over the surfaces of adjacent villi, reabsorb the water and electrolytes along with end products of digestion.

The intestinal secretions are formed by the enterocytes of the crypts at a rate of about 1800 ml/day. These secretions are almost pure extracellular fluid and have a slightly alkaline pH in the range of 7.5 to 8.0. The secretions also are rapidly reabsorbed by the villi. This flow of fluid from the crypts into the villi supplies a watery vehicle for absorption of substances from chyme when it comes in contact with the villi. Thus, the primary function of the small intestine is to absorb nutrients and their digestive products into the blood.

Mechanism of Secretion of the Watery Fluid.

The exact mechanism that controls the marked secretion of watery fluid by the crypts of Lieberkühn is not known. It is believed to involve at least two active secretory processes: (1) active secretion of chloride ions into the crypts and (2) active secretion of bicarbonate ions. The secretion of both of these ions causes electrical drag as well of positively charged sodium ions through the membrane and into the secreted fluid. Finally, all these ions together cause osmotic movement of water.

Digestive Enzymes in the Small Intestinal Secretion

When secretions of the small intestine are collected without cellular debris, they have almost no enzymes. The enterocytes of the mucosa, especially those that cover the villi, do contain digestive enzymes that digest specific food substances while they are being absorbed through the epithelium. These enzymes are the following: (1) several peptidases for splitting small peptides into amino acids, (2) four enzymes—sucrase, maltase, isomaltase, and lactase—for splitting disaccharides into monosaccharides, and (3) small amounts of intestinal lipase for splitting neutral fats into glycerol and fatty acids.

The epithelial cells deep in the crypts of Lieberkühn continually undergo mitosis, and new cells migrate along the basement membrane upward out of the crypts toward the tips of the villi, thus continually replacing the villus epithelium and also forming new digestive enzymes. As the villus cells age, they are finally shed into the intestinal secretions. The life cycle of an intestinal

epithelial cell is about 5 days. This rapid growth of new cells also allows rapid repair of excoriations that occur in the mucosa.

Regulation of Small Intestine Secretion—Local Stimuli

By far the most important means for regulating small intestine secretion are local enteric nervous reflexes, especially reflexes initiated by tactile or irritative stimuli from the chyme in the intestines.

70. Functions of colon

Secretions of the Large Intestine

Mucus secretion

The mucosa of the large intestine, like that of the small intestine, has many crypts of Lieberkühn; however, unlike the small intestine, there are no villi. The epithelial cells contain almost no enzymes. Instead, they consist mainly of mucous cells that secrete only mucus. The great preponderance of secretion in the large intestine is mucus. This mucus contains moderate amounts of bicarbonate ions secreted by a few non–mucus-secreting epithelial cells. The rate of secretion of mucus is regulated principally by direct, tactile stimulation of the epithelial cells lining the large intestine and by local nervous reflexes to the mucous cells in the crypts of Lieberkühn. Stimulation of the pelvic nerves from the spinal cord, which carry parasympathetic innervation to the distal one half to two thirds of the large intestine, also can cause marked increase in mucus secretion. This occurs along with increase in peristaltic motility of the colon.

During extreme parasympathetic stimulation, often caused by emotional disturbances, so much mucus can occasionally be secreted into the large intestine that the person has a bowel movement of ropy mucus as often as every 30 minutes; this mucus often contains little or no fecal material. Mucus in the large intestine protects the intestinal wall against excoriation, but in addition, it provides an adherent medium for holding fecal matter together. Furthermore, it protects the intestinal wall from the great amount of bacterial activity that takes place inside the feces, and, finally, the mucus plus the alkalinity of the secretion (pH of 8.0 caused by large amounts of sodium bicarbonate) provides a barrier to keep acids formed in the feces from attacking the intestinal wall.

Diarrhea Caused by Excess Secretion of Water and Electrolytes in Response to Irritation

Whenever a segment of the large intestine becomes intensely irritated, as occurs when bacterial infection becomes rampant during enteritis, the mucosa secretes extra large quantities of water and electrolytes in addition to the normal viscid alkaline mucus. This acts to dilute the irritating factors and to cause rapid movement of the feces toward the anus. The result is diarrhea, with loss of large quantities of water and electrolytes. But the diarrhea also washes away irritant factors, which promotes earlier recovery from the disease than might otherwise occur.

71. Resorption of lipids in the small intestine

Digestion of Fats

Fats of the Diet

By far the most abundant fats of the diet triglycerides, each molecule of which is composed of a glycerol nucleus and three fatty acid side chains.

In the usual diet are also small quantities of phospholipids, cholesterol, and cholesterol esters.

Digestion of Fats in the Intestine

A small amount of triglycerides is digested in the stomach by lingual lipase that is secreted by lingual glands in the mouth and swallowed with the saliva. This amount of digestion is less than 10% and generally unimportant.

Instead, essentially all fat digestion occurs in the small intestine as follows.

Emulsification of Fat by Bile Acids and Lecithin

The first step in fat digestion is physically to break the fat globules into very small sizes so that the water-soluble digestive enzymes can act on the globule surfaces. This process is called emulsification of the fat, and it begins by agitation in the stomach to mix the fat with the products of stomach digestion.

Then, most of the emulsification occurs in the duodenum under the influence of bile, the secretion from the liver that does not contain any digestive enzymes. However, bile does contain a large quantity of bile salts as well as the phospholipid lecithin. Both of these, but especially the lecithin, are extremely important for emulsification of the fat. These molecules decrease the interfacial tension of the fat and makes it soluble.

When the interfacial tension of a globule of nonmiscible fluid is low, this nonmiscible fluid, on agitation, can be broken up into many very minute particles far more easily than it can when the interfacial tension is great. Consequently, a major function of the bile salts and lecithin, especially the lecithin, in the bile is to make the fat globules readily fragmentable by agitation with the water in the small bowel.

The lipase enzymes are water-soluble compounds and can attack the fat globules only on their surfaces. Consequently, it can be readily understood how important this detergent function of bile salts and lecithin is for digestion of fats.

Digestion of Triglycerides by Pancreatic Lipase

By far the most important enzyme for digestion of the triglyc- erides is pancreatic lipase, present in enormous quantities in pancreatic juice, enough to digest within 1 minute all triglycerides that it can reach. In addition, the enterocytes of the small intestine contain still more lipase, known as enteric lipase, but this is usually not needed.

Role of Bile Salts to Accelerate Fat Digestion—Formation of Micelles

The hydrolysis of triglycerides is a highly reversible process; therefore, accumulation of monoglycerides and free fatty acids in the vicinity of digesting fats quickly blocks further digestion. But the bile salts play the additional important role of removing the monoglycerides and free fatty acids from the vicinity of the digesting fat globules almost as rapidly as these end products of digestion are formed. This occurs in the following way.

Bile salts, when in high enough concentration in water, have the propensity to form micelles. The micelle globule dissolves in the water of the digestive fluids and remains in stable solution until the fat is absorbed into the blood.

The bile salt micelles also act as a transport medium to carry the monoglycerides and free fatty acids, both of which would otherwise be relatively insoluble, to the brush borders of the intestinal epithelial cells.

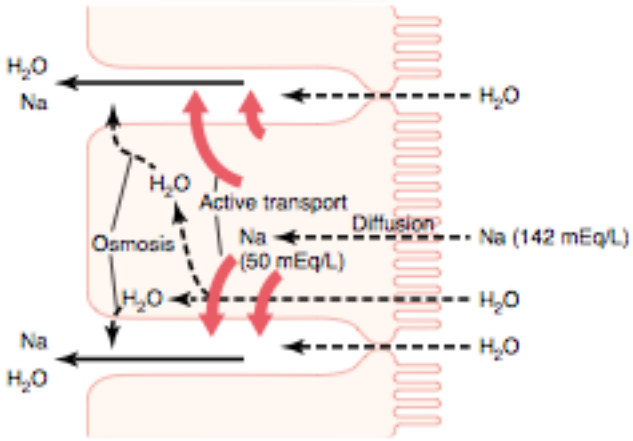
Digestion of Cholesterol Esters and Phospholipids

Most cholesterol in the diet is in the form of cholesterol esters, which are combinations of free cholesterol and one molecule of fatty acid. Phospholipids also contain fatty acid within their

molecules. Both the cholesterol esters and the phospholipids are hydrolyzed by two other lipases in the pancreatic secretion that free the fatty acids—the enzyme cholesterol ester hydrolase to hydrolyze the cholesterol ester, and phospholipase A2 to hydrolyze the phospholipid.

72. Resorption of minerals and water in small intestine

Absorption of Water



Isosmotic Absorption

Water is transported through the intestinal membrane entirely by diffusion. Furthermore, this diffusion obeys the usual laws of osmosis. Therefore, when the chyme is dilute enough, water is absorbed through the intestinal mucosa into the blood of the villi almost entirely by osmosis.

Conversely, water can also be transported in the opposite direction—from plasma into the chyme. This occurs especially when hyperosmotic solutions are discharged from the stomach into the duodenum. Within minutes, sufficient water usually will be transferred by osmosis to make the chyme isosmotic with the plasma.

Absorption of Ions

Active Transport of Sodium

The basic mechanism of sodium absorption from the intestine is shown in figure. The principles of this mechanism are also essentially the same as for absorption of sodium from the gallbladder and renal tubules.

The motive power for sodium absorption is pro- vided by active transport of sodium from inside the epithelial cells through the basal and side walls of these cells into paracellular spaces. This active transport obeys the usual laws of active transport: it requires energy, and the energy process is catalyzed by appropriate adenosine triphosphatase enzymes in the cell membrane. Part of the sodium is absorbed along with chloride ions; in fact, the negatively charged chloride ions are mainly passively “dragged” by the positive electrical charges of the sodium ions.

Active transport of sodium through the basolateral membranes of the cell reduces the sodium concentration inside the cell to a low value. Because the sodium concentration in the chyme is normally higher (that is, about equal to that in plasma), sodium moves down this steep electrochemical gradient from the chyme through the brush border of the epithelial cell into the epithelial cell cytoplasm. This provides still more sodium ions to be transported by the epithelial cells into the paracellular spaces.

Osmosis of the Water

The next step in the transport process is osmosis of water into the paracellular spaces. This occurs because a large osmotic gradient has been created by the elevated concentration of ions in the paracellular space. Much of this osmosis occurs through the tight junctions between the apical borders of the epithelial cells, but much also occurs through the cells themselves. And osmotic movement of water creates flow of fluid into and through the paracellular spaces and, finally, into the circulating blood of the villus.

Aldosterone Greatly Enhances Sodium Absorption

When a person becomes dehydrated, large amounts of aldosterone almost always are secreted by the cortices of the adrenal glands. Within 1 to 3 hours this aldosterone causes increased activation of the enzyme and transport mechanisms for all aspects of sodium absorption by the intestinal epithelium. And the increased sodium absorption in turn causes secondary increases in absorption of chloride ions, water, and some other substances.

This effect of aldosterone is especially important in the colon because it allows virtually no loss of sodium chloride in the feces and also little water loss. Thus, the function of aldosterone in the intestinal tract is the same as that achieved by aldosterone in the renal tubules.

Absorption of Chloride Ions in the Duodenum and Jejunum

In the upper part of the small intestine, chloride ion absorption is rapid and occurs mainly by diffusion— that is, absorption of sodium ions through the epithelium creates electronegativity in the chyme and electropositivity in the paracellular spaces between the epithelial cells. Then chloride ions move along this electrical gradient to “follow” the sodium ions.

Absorption of Bicarbonate Ions in the Duodenum and Jejunum

Often large quantities of bicarbonate ions must be reabsorbed from the upper small intestine because large amounts of bicarbonate ions have been secreted into the duodenum in both pancreatic secretion and bile. The bicarbonate ion is absorbed in an indirect way as follows: When sodium ions are absorbed, moderate amounts of hydrogen ions are secreted into the lumen of the gut in exchange for some of the sodium. These hydrogen ions in turn combine with the bicarbonate ions to form carbonic acid (H_2CO_3), which then dissociates to form water and carbon dioxide. The water remains as part of the chyme in the intestines, but the carbon dioxide is readily absorbed into the blood and subsequently expired through the lungs. Thus, this is so-called “active absorption of bicarbonate ions.” It is the same mechanism that occurs in the tubules of the kidneys.

Secretion of Bicarbonate Ions in the Ileum and Large Intestine—Simultaneous Absorption of Chloride Ions

The epithelial cells on the surfaces of the villi in the ileum as well as on all surfaces of the large intestine have a special capability of secreting bicarbonate ions in exchange for absorption of chloride ions. This is important because it provides alkaline bicarbonate ions that neutralize acid products formed by bacteria in the large intestine.

Absorption of Other Ions

Calcium ions are actively absorbed into the blood especially from the duode- num, and the amount of calcium ion absorption is very exactly controlled to supply exactly the daily need of the body for calcium. One important factor controlling calcium absorption is parathyroid hormone secreted by the parathyroid glands, and another is vitamin D. Parathyroid hormone activates vitamin D, and the activated vitamin D in turn greatly enhances calcium absorption.

Iron ions are also actively absorbed from the small intestine

The principles of iron absorption and regulation of its absorption in proportion to the body’s need for iron, especially for the formation of hemoglobin.

Potassium, magnesium, phosphate, and probably still other ions can also be actively absorbed through the intestinal mucosa. In general, the monovalent ions are absorbed with ease and in great quantities. Conversely, bivalent ions are normally absorbed in only small amounts; for example, maximum absorption of calcium ions is only 1/50 as great as the normal absorption of sodium ions. Fortunately, only small quantities of the bivalent ions are normally required daily by the body.

74. Nitrogen balance

There are two types of which the amino group is removed from amino acids. In the frst reaction, oxidative deamination, the amino group gives rise to a molecule of ammonia (NH_3) and is replaced by an oxygen atom derived from water to form a keto acid. The second means of removing an amino group is known as transamination and involves transfer of the amino group from an amino acid to a keto acid. Cells can also use the nitrogen derived from amino groups to synthesize other important nitrogen-containing molecules, such as the purine and pyrimidine bases found in nucleic acids.

Once formed, these keto acids can be metabolized to produce carbon dioxide and form ATP, or they can be used as intermediates in the synthetic pathway leading to the formation of glucose. As a third alternative, they can be used to synthesize fatty acids after their conversion to acetyl coenzyme A by way of pyruvic acid. Thus, amino acids can be used as a source of energy, and some can be converted into carbohydrate and fat.

The ammonia that oxidative deamination produces is highly toxic to cells if allowed to accumulate. Fortunately, it passes through cell membranes and enters the blood, which carries it to the liver. The liver contains enzymes that can link two molecules of ammonia with carbon dioxide to form urea. Thus, urea, which is relatively nontoxic, is the major nitrogenous waste product of protein catabolism. It enters the blood from the liver and is excreted by the kidneys into the urine.

The amino acid pools, which consist of the body's total free amino acids, are derived from (1) ingested protein, which is degraded to amino acids during digestion in the intestinal tract, (2) the synthesis of nonessential amino acids from the keto acids derived from carbohydrates and fat, (3) the continuous breakdown of body proteins. These pools are the source of amino acids for the resynthesis of body protein and a host of specialized amino acids derivatives, as well as for conversion to carbohydrate and fat. The body loses a very small quantity of amino acids and protein via the urine, skin, hair, fingernails, and in women, the menstrual fluid.

The terms negative nitrogen balance and positive nitrogen balance refer to whether there is net loss or gain, respectively, of amino acids in the body over any period of time.

If any of the essential amino acids are missing from the diet, a negative nitrogen balance - that is, loss greater than gain - always results. The proteins that require a missing essential amino acid cannot be synthesized, and the other amino acids that would have been incorporated into these proteins are metabolized. This explains why a dietary requirement for protein cannot be specified without regard to the amino acid composition of that protein. Protein is graded in terms of how closely its relative proportions of essential amino acids approximate those in the average body protein. The highest quality proteins are found in animal products, whereas the quality of most plant proteins is lower. Nevertheless, it is quite possible to obtain adequate quantities of all amino acids from a mixture of plant proteins alone

75. Metabolism of cholesterol. Aterosclerosis.

Formation of Cholesterol

Besides the cholesterol absorbed each day from the gastrointestinal tract, which is called exogenous cholesterol, an even greater quantity is formed in the cells of the body, called endogenous cholesterol. Essentially all the endogenous cholesterol that circulates in the lipoproteins of the plasma is formed by the liver, but all other cells of the body form at least some cholesterol.

The basic structure of cholesterol is a sterol nucleus. This is synthesized entirely from multiple molecules of acetyl-CoA. In turn, the sterol nucleus can be modified by means of various side chains to form (1) cholesterol; (2) cholic acid, which is the basis of the bile acids formed in the liver; and (3) many important steroid hormones secreted by the adrenal cortex, the ovaries, and the testes.

Factors That Affect Plasma Cholesterol Concentration—Feedback Control of Body Cholesterol

Among the important factors that affect plasma cholesterol concentration are the following: 1. An increase in the amount of cholesterol ingested each day increases the plasma concentration slightly. However, when cholesterol is ingested, the rising concentration of cholesterol inhibits the most essential enzyme for endogenous synthesis of cholesterol, 3-hydroxy-3-methylglutaryl CoA reductase, thus providing an intrinsic feedback control system to prevent an excessive increase in plasma cholesterol concentration. 2. A highly saturated fat diet increases blood cholesterol concentration 15 to 25 per cent. This results from increased fat deposition in the liver, which then provides increased quantities of acetyl-CoA in the liver cells for the production of cholesterol. 3. Ingestion of fat containing highly unsaturated fatty acids usually depresses the blood cholesterol concentration a slight to moderate amount. 4. Lack of insulin or thyroid hormone increases the blood cholesterol concentration, whereas excess thyroid hormone decreases the concentration.

Specific Uses of Cholesterol in the Body

By far the most abundant nonmembranous use of cholesterol in the body is to form cholic acid in the liver. As much as 80 per cent of cholesterol is converted into cholic acid. This is conjugated with other substances to form bile salts, which promote digestion and absorption of fats. A small quantity of cholesterol is used by (1) the adrenal glands to form adrenocortical hormones, (2) the ovaries to form progesterone and estrogen, and (3) the testes to form testosterone.

Atherosclerosis

Atherosclerosis is a disease of the large and intermediate- sized arteries in which fatty lesions called atheromatous plaques develop on the inside surfaces of the arterial walls.

One recent theory suggests that, for unknown reasons, leukocytes, such as monocytes or basophils, begin to attack the endothelium of the artery lumen in cardiac muscle. The ensuing inflammation leads to formation of atheromatous plaques in the arterial tunica intima, a region of the vessel wall located between the endothelium and the tunica media. The bulk of these lesions is made of excess fat, collagen, and elastin.

Increased Low-Density Lipoproteins

An important factor in causing atherosclerosis is a high blood plasma concentration of cholesterol in the form of low-density lipoproteins. The plasma concentration of these highcholesterol low-density lipoproteins is increased by several factors, including eating highly saturated fat in the daily diet, obesity, and physical inactivity.

76. Metabolism of iron

The total quantity of iron in the body averages 4 to 5 grams, about 65% of which is in the form of hemoglobin. About 4% is in the form of myoglobin, 1% is in the form of the various heme compounds that promote intracellular oxidation, 0.1% is combined with the protein transferrin in the blood plasma, and 15 to 30% is stored for later use, mainly in the reticuloendothelial system and liver parenchymal cells, principally in the form of ferritin.

Transport and Storage of Iron

Transport, storage, and metabolism of iron in the body can be explained as follows: When iron is absorbed from the small intestine, it immediately combines in the blood plasma with apotransferrin, to form transferrin, which is then transported in the plasma. The iron is loosely bound in the transferrin and, consequently, can be released to any tissue cell at any point in the body. Excess iron in the blood is deposited especially in the liver hepatocytes and less in the reticuloendothelial cells of the bone marrow.

In the cell cytoplasm, iron combines with apoferritin, to form ferritin.

Smaller quantities of the iron in the storage pool are in an extremely insoluble form called hemosiderin. This is especially true when the total quantity of iron in the body is more than the apoferritin storage pool can accommodate. When the quantity of iron in the plasma falls low, some of the iron in the ferritin storage pool is removed easily and transported in the form of transferrin in the plasma to the areas of the body where it is needed. A unique characteristic of the transferrin molecule is that it binds strongly with receptors in the cell membranes of erythroblasts in the bone marrow. Then, along with its bound iron, it is ingested into the erythroblasts by endocytosis. There the transferrin delivers the iron directly to the mitochondria, where heme is synthesized. In people who do not have adequate quantities of transferrin in their blood, failure to transport iron to the erythroblasts in this manner can cause severe hypochromic anemia—that is, red cells that contain much less hemoglobin than normal. When red blood cells have lived their life span and are destroyed, the hemoglobin released from the cells is ingested by monocyte-macrophage cells. There, iron is liberated and is stored mainly in the ferritin pool to be used as needed for the formation of new hemoglobin.

Daily Loss of Iron

Absorption of Iron from the Intestinal Tract

Iron is absorbed from all parts of the small intestine, mostly by the following mechanism. The liver secretes moderate amounts of apotransferrin into the bile, which flows through the bile duct into the duodenum. Here, the apotransferrin binds with free iron and also with certain iron compounds, such as hemoglobin and myoglobin from meat. This combination is called transferrin. It, in turn, is attracted to and binds with receptors in the membranes of the intestinal epithelial cells. Then, by pinocytosis, the transferrin molecule, carrying its iron store, is absorbed into the epithelial cells and later released into the blood capillaries beneath these cells in the form of plasma transferrin.

Iron absorption from the intestines is extremely slow. This means that even when tremendous quantities of iron are present in the food, only small proportions can be absorbed.

Regulation of Total Body Iron by Controlling Rate of Absorption

When the body has become saturated with iron so that essentially all apoferritin in the iron storage areas is already combined with iron, the rate of additional iron absorption from the intestinal tract becomes greatly decreased. Conversely, when the iron stores have become depleted, the rate of absorption can accelerate probably five or more times normal. Thus, total body iron is regulated mainly by altering the rate of absorption.

Life Span and Destruction of Red Blood Cells

When red blood cells are delivered from the bone marrow into the circulatory system, they normally circulate an average of 120 days before being destroyed. Even so, the metabolic systems

of old red cells become progressively less active, and the cells become more and more fragile, presumably because their life processes wear out.

Once the red cell membrane becomes fragile, the cell ruptures during passage through some tight spot of the circulation. Many of the red cells self-destruct in the spleen, where they squeeze through the red pulp of the spleen. There, the spaces between the structural trabeculae of the red pulp, through which most of the cells must pass, are only 3 micrometers wide, in comparison with the 8-micrometer diameter of the red cell. When the spleen is removed, the number of old abnormal red cells circulating in the blood increases considerably.

Destruction of Hemoglobin

When red blood cells burst and release their hemoglobin, the hemoglobin is phagocytized almost immediately by macrophages in many parts of the body, but especially by the Kupffer cells of the liver and macrophages of the spleen and bone marrow. During the next few hours to days, the macrophages release iron from the hemoglobin and pass it back into the blood, to be carried by transferrin either to the bone marrow for the production of new red blood cells or to the liver and other tissues for storage in the form of ferritin. The porphyrin portion of the hemoglobin molecule is converted by the macrophages, through a series of stages, into the bile pigment bilirubin, which is released into the blood and later removed from the body by secretion through the liver into the bile.

Anemias

Anemia means deficiency of hemoglobin in the blood, which can be caused by either too few red blood cells or too little hemoglobin in the cells. Some types of anemia and their physiologic causes are the following.

Blood Loss Anemia

After rapid hemorrhage, the body replaces the fluid portion of the plasma in 1 to 3 days, but this leaves a low concentration of red blood cells. If a second hemorrhage does not occur, the red blood cell concentration usually returns to normal within 3 to 6 weeks.

In chronic blood loss, a person frequently cannot absorb enough iron from the intestines to form hemoglobin as rapidly as it is lost. Red cells are then produced that are much smaller than normal and have too little hemoglobin inside them, giving rise to microcytic, hypochromic anemia.

Aplastic Anemia

Bone marrow aplasia means lack of functioning bone marrow.

Megaloblastic Anemia

The loss of vitamin B12, folic acid, and intrinsic factor from the stomach mucosa can lead to slow reproduction of erythroblasts in the bone marrow. As a result, the red cells grow too large, with odd shapes, and are called megaloblasts. Thus, atrophy of the stomach mucosa, as occurs in pernicious anemia, or loss of the entire stomach after surgical total gastrectomy can lead to megaloblastic anemia. Also, patients who have intestinal sprue, in which folic acid, vitamin B12, and other vitamin B compounds are poorly absorbed, often develop megaloblastic anemia. Because in these states the erythroblasts cannot proliferate rapidly enough to form normal numbers of red blood cells, those red cells that are formed are mostly oversized, have bizarre shapes, and have fragile membranes. These cells rupture easily, leaving the person in dire need of an adequate number of red cells.

Hemolytic Anemia

Different abnormalities of the red blood cells, many of which are hereditarily acquired, make the cells fragile, so that they rupture easily as they go through the capillaries, especially through the spleen. Even though the number of red blood cells formed may be normal, or even much greater than normal in some hemolytic diseases, the life span of the fragile red cell is so short that the cells are destroyed faster than they can be formed, and serious anemia results.

Some of these types of anemia are the following:

In hereditary spherocytosis, the red cells are very small and spherical rather than being biconcave discs. These cells cannot withstand compression forces because they do not have the

normal loose, baglike cell membrane structure of the biconcave discs. On passing through the splenic pulp and some other tight vascular beds, they are easily ruptured by even slight compression.

In sickle cell anemia, the cells have an abnormal type of hemoglobin called hemoglobin S, containing faulty beta chains in the hemoglobin molecule. When this hemoglobin is exposed to low concentrations of oxygen, it precipitates into long crystals inside the red blood cell. These crystals elongate the cell and give it the appearance of a sickle rather than a biconcave disc. The precipitated hemoglobin also damages the cell membrane, so that the cells become highly fragile, leading to serious anemia. Such patients frequently experience a vicious circle of events called a sickle cell disease “crisis,” in which low oxygen tension in the tissues causes sickling, which leads to ruptured red cells, which causes a further decrease in oxygen tension and still more sickling and red cell destruction. Once the process starts, it progresses rapidly, eventuating in a serious decrease in red blood cells within a few hours and, often, death.

In erythroblastosis fetalis, Rh-positive red blood cells in the fetus are attacked by antibodies from an Rh-negative mother. These antibodies make the Rh-positive cells fragile, leading to rapid rupture and causing the child to be born with serious anemia. The extremely rapid formation of new red cells to make up for the destroyed cells in erythroblastosis fetalis causes a large number of early blast forms of red cells to be released from the bone marrow into the blood.

77. Bone formation and resorption

Calcium Exchange Between Bone and Extracellular Fluid

If soluble calcium salts are injected intravenously, the calcium ion concentration may increase immediately to high levels. However, within 30 minutes to 1 hour or more, the calcium ion concentration returns to normal. Likewise, if large quantities of calcium ions are removed from the circulating body fluids, the calcium ion concentration again returns to normal within 30 minutes to about 1 hour. These effects result in great part from the fact that the bone contains a type of exchangeable calcium that is always in equilibrium with the calcium ions in the extracellular fluids.

A small portion of this exchangeable calcium is also the calcium found in all tissue cells, especially in highly permeable types of cells such as those of the li ver and the gastrointestinal tract. However, most of the exchangeable calcium is in the bone. It normally amounts to about 0.4 to 1 per cent of the total bone calcium. This calcium is deposited in the bones in a form of readily mobilizable salt such as $CaHPO_4$ and other amorphous calcium salts.

The importance of exchangeable calcium is that it provides a rapid buffering mechanism to keep the calcium ion concentration in the extracellular fluids from rising to excessive levels or falling to very low levels under transient conditions of excess or decreased availability of calcium.

Deposition and Absorption of Bone—Remodeling of Bone

Deposition of Bone by the Osteoblasts

Bone is continually being deposited by osteoblasts, and it is continually being absorbed where osteoclasts are active. Osteoblasts are found on the outer surfaces of the bones and in the bone cavities. A small amount of osteoblastic activity occurs continually in all living bones (on about 4% of all surfaces at any given time in an adult), so that at least some new bone is being formed constantly.

Absorption of Bone—Function of the Osteoclasts

Bone is also being continually absorbed in the presence of osteo- clasts, which are large phagocytic, multinucleated cells, derivatives of monocytes or monocyte-like cells formed in the bone marrow. The osteoclasts are normally active on less than 1 per cent of the bone surfaces of an adult. Later in the chapter we see that PTH controls the bone absorptive activity of osteoclasts. Histologically, bone absorption occurs immediately adjacent to the osteoclasts. The mechanism of this absorption is believed to be the following: The osteo- clasts send out villus-like projections toward the bone, forming a so-called ruffled border adjacent to the bone. The villi secrete two types of substances: (1) proteolytic enzymes, released from the lysosomes of the osteoclasts, and (2) several acids, including citric acid and lactic acid, released from the mitochondria and secretory vesicles. The enzymes digest or dissolve the organic matrix of the bone, and the acids cause solution of the bone salts. The osteoclastic cells also imbibe by phagocytosis minute particles of bone matrix and crystals, eventually also dis- soluting these and releasing the products into the blood.

Bone Deposition and Absorption Are Normally in Equilibrium

Normally, except in growing bones, the rates of bone deposition and absorption are equal to each other, so that the total mass of bone remains constant. Osteo- clasts usually exist in small but concentrated masses, and once a mass of osteoclasts begins to develop, it usually eats away at the bone for about 3 weeks, creating a tunnel that ranges in diameter from 0.2 to 1 millimeter and is several millimeters long. At the end of this time, the osteoclasts disappear and the tunnel is invaded by osteoblasts instead; then new bone begins to develop. Bone deposition then continues for several months, the new bone being laid down in successive layers of con- centric circles (lamellae) on the inner surfaces of the cavity until the tunnel is filled. Deposition of new bone ceases when the bone begins to encroach on the blood vessels supplying the area. The canal through which these vessels run, called the haversian canal, is all that remains of the original cavity. Each new area of bone deposited in this way is called an osteon, as shown in Figure 79–5. Value of Continual Bone Remodeling The continual deposi- tion and absorption of bone have several physiologically important functions. First, bone ordinarily adjusts its strength in proportion

to the degree of bone stress. Consequently, bones thicken when subjected to heavy loads. Second, even the shape of the bone can be rearranged for proper support of mechanical forces by deposition and absorption of bone in accordance with stress patterns. Third, because old bone becomes relatively brittle and weak, new organic matrix is needed as the old organic matrix degenerates. In this manner, the normal toughness of bone is maintained. Indeed, the bones of children, in whom the rates of deposition and absorption are rapid, show little brittleness in comparison with the bones of the elderly, in whom the rates of deposition and absorption are slow.

Control of the Rate of Bone Deposition by Bone "Stress."

Bone is deposited in proportion to the compressional load that the bone must carry. For instance, the bones of athletes become considerably heavier than those of nonathletes. Also, if a person has one leg in a cast but continues to walk on the opposite leg, the bone of the leg in the cast becomes thin and as much as 30 per cent decalcified within a few weeks, whereas the opposite bone remains thick and normally calcified. Therefore, continual physical stress stimulates osteoblastic deposi- tion and calcification of bone.

Bone stress also determines the shape of bones under certain circumstances. For instance, if a long bone of the leg breaks in its center and then heals at an angle, the compression stress on the inside of the angle causes increased deposition of bone, and increased absorption occurs on the outer side of the angle where the bone is not compressed. After many years of increased deposi- tion on the inner side of the angulated bone and absorp- tion on the outer side, the bone can become almost straight, especially in children because of the rapid remodeling of bone at younger ages.

Repair of a Fracture Activates Osteoblasts

Fracture of a bone in some way maximally activates all the periosteal and intraosseous osteoblasts involved in the break. Also, immense numbers of new osteoblasts are formed almost immediately from osteoprogenitor cells, which are bone stem cells in the surface tissue lining bone, called the "bone membrane." Therefore, within a short time, a large bulge of osteoblastic tissue and new organic bone matrix, followed shortly by the deposition of calcium salts, develops between the two broken ends of the bone. This is called a callus.

Many bone surgeons use the phenomenon of bone stress to accelerate the rate of fracture healing. This is done by use of special mechanical fixation apparatuses for holding the ends of the broken bone together so that the patient can continue to use the bone immediately. This causes stress on the opposed ends of the broken bones, which accelerates osteoblastic activity at the break and often shortens convalescence.

78. Hyperthermia and hypothermia

Fever

Fever, which means a body temperature above the usual range of normal, can be caused by abnormalities in the brain itself or by toxic substances that affect the temperature-regulating centers. Some causes include bacterial diseases, brain tumors, and environmental conditions that may terminate in heatstroke.

Resetting the Hypothalamic Temperature- Regulating Center in Febrile Diseases— Effect of Pyrogens

Many proteins, breakdown products of proteins, and certain other substances, especially lipopolysaccharide toxins released from bacterial cell membranes, can cause the set-point of the hypothalamic thermostat to rise. Substances that cause this effect are called pyrogens. Pyrogens released from toxic bacteria or those released from degenerating body tissues cause fever during disease conditions. When the set-point of the hypothalamic temperature-regulating center becomes higher than normal, all the mechanisms for raising the body temperature are brought into play, including heat conservation and increased heat production. Within a few hours after the set-point has been increased, the body temperature also approaches this level.

Mechanism of Action of Pyrogens in Causing Fever—Role of Interleukin-1

Some pyrogens can act directly and immediately on the hypothalamic temperature-regulating center to increase its set-point. Other pyrogens function indirectly and may require several hours of latency before causing their effects. This is true of many of the bacterial pyrogens, especially the endotoxins from gram-negative bacteria.

When bacteria or breakdown products of bacteria are present in the tissues or in the blood, they are phagocytized by the blood leukocytes, by tissue macrophages, and by large granular killer lymphocytes. All these cells digest the bacterial products and then release the substance interleukin-1—also called leukocyte pyrogen or endogenous pyrogen—into the body fluids. The interleukin-1, on reaching the hypothalamus, immediately activates the processes to produce fever, sometimes increasing the body temperature a noticeable amount in only 8 to 10 minutes. As little as one ten-millionth of a gram of endotoxin lipopolysaccharide from bacteria, acting in concert with the blood leukocytes, tissue macrophages, and killer lymphocytes, can cause fever. The amount of interleukin-1 that is formed in response to lipopolysaccharide to cause fever is only a few nanograms.

Several experiments have suggested that interleukin-1 causes fever by first inducing the formation of one of the prostaglandins, mainly prostaglandin E2, or a similar substance, which acts in the hypothalamus to elicit the fever reaction. When prostaglandin formation is blocked by drugs, the fever is either completely abrogated or at least reduced.

Fever Caused by Brain Lesions

When a brain surgeon operates in the region of the hypothalamus, severe fever almost always occurs. Another condition that frequently causes prolonged high temperature is compression of the hypothalamus by a brain tumor.

Characteristics of Febrile Conditions Chills

When the set-point of the hypothalamic temperature-control center is suddenly changed from the normal level to higher than normal (as a result of tissue destruction, pyrogenic substances, or dehydration), the body temperature usually takes several hours to reach the new temperature set-point.

Because the blood temperature is now less than the set-point of the hypothalamic temperature controller, the usual responses that cause elevation of body temperature occur. During this period, the person experiences chills and feels extremely cold, even though his or her body temperature may already be above normal. Also, the skin becomes cold because of vasoconstriction, and the person shivers. Chills can continue until the body temperature reaches the hypothalamic set-point. Then the person no longer experiences chills but instead feels neither cold nor hot. As long as the factor that is causing the higher set-point of the hypothalamic

temperature controller is present, the body temperature is regulated more or less in the normal manner, but at the high temperature set-point level.

Crisis, or "Flush."

If the factor that is causing the high temperature is removed, the set-point of the hypothalamic temperature controller will be reduced to a lower value—perhaps even back to the normal level. In this instance, the body temperature is still high, but the hypothalamus is attempting to regulate the temperature to lower values. This situation is analogous to excessive heating of the anterior hypothalamic-preoptic area, which causes intense sweating and the sudden development of hot skin because of vasodilation everywhere. This sudden change of events in a febrile state is known as the "crisis" or, more appropriately, the "flush." In the days before the advent of antibiotics, the crisis was always anxiously awaited, because once this occurred, the doctor assumed that the patient's temperature would soon begin falling.

Heatstroke

The upper limit of air temperature that one can stand depends almost entirely on whether the air is dry or wet. If the air is dry and sufficient convection air currents are flowing to promote rapid evaporation from the body, a person can withstand several hours of air temperature at 55°C. Conversely, if the air is 100% humidified or if the body is in water, the body temperature begins to rise whenever the environmental temperature rises above about 35°C. If the person is performing heavy work, the critical environmental temperature above which heatstroke is likely to occur may be as low as 30° to 32°C.

When the body temperature rises beyond a critical temperature, into the range of 40° to 42°C, the person is likely to develop heatstroke. The symptoms include dizziness, abdominal distress sometimes accompanied by vomiting, sometimes delirium, and eventually loss of consciousness if the body temperature is not soon decreased. These symptoms are often exacerbated by a degree of circulatory shock brought on by excessive loss of fluid and electrolytes in the sweat.

The hyperpyrexia itself is also exceedingly damaging to the body tissues, especially the brain, and is responsible for many of the effects. In fact, even a few minutes of very high body temperature can sometimes be fatal.

Harmful Effects of High Temperature

The pathological findings in a person who dies of hyperpyrexia are local hemorrhages and parenchymatous degeneration of cells throughout the entire body, but especially in the brain. Once neuronal cells are destroyed, they can never be replaced. Also, damage to the liver, kidneys, and other organs can often be severe enough that failure of one or more of these organs eventually causes death, but sometimes not until several days after the heatstroke.

Acclimatization to Heat

It can be extremely important to acclimatize people to extreme heat. Examples of people requiring acclimatization are soldiers on duty in the tropics and miners working in the 2-mile-deep gold mines of South Africa, where the temperature approaches body temperature and the humidity approaches 100%. A person exposed to heat for several hours each day while performing a reasonably heavy workload will develop increased tolerance to hot and humid conditions in 1 to 3 weeks.

Among the most important physiological changes that occur during this acclimatization process are an approximately twofold increase in the maximum rate of sweating, an increase in plasma volume, and diminished loss of salt in the sweat and urine to almost none; the last two effects result from increased secretion of aldosterone by the adrenal glands.

Exposure of the Body to Extreme Cold

Unless treated immediately, a person exposed to ice water for 20 to 30 minutes ordinarily dies because of heart standstill or heart fibrillation. By that time, the internal body temperature will have fallen to about 25°C. If warmed rapidly by the application of external heat, the person's life can often be saved.

Loss of Temperature Regulation at Low Temperatures

Once the body temperature has fallen below about 30°C, the ability of the hypothalamus to regulate temperature is lost; it is greatly impaired even when the body temperature falls below about 34°C. Part of the reason for this diminished temperature regulation is that the rate of chemical heat production in each cell is depressed. Also, sleepiness develops (later followed by coma), which depresses the activity of the central nervous system heat control mechanisms and prevents shivering.

Frostbite

When the body is exposed to extremely low temperatures, surface areas can freeze; the freezing is called frostbite. This occurs especially in the lobes of the ears and in the digits of the hands and feet. If the freeze has been sufficient to cause extensive formation of ice crystals in the cells, permanent damage usually results, such as permanent circulatory impairment as well as local tissue damage. Often gangrene follows thawing, and the frostbitten areas must be removed surgically.

Cold-Induced Vasodilation Is a Final Protection Against Frostbite at Almost Freezing Temperatures.

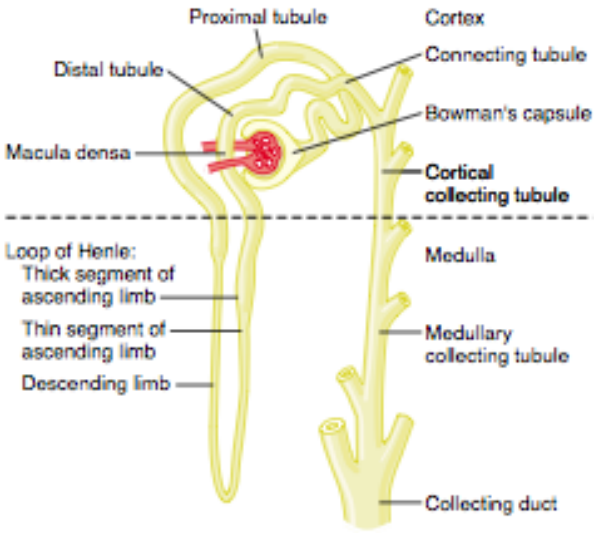
When the temperature of tissues falls almost to freezing, the smooth muscle in the vascular wall becomes paralyzed because of the cold itself, and sudden vasodilation occurs, often manifested by a flush of the skin. This mechanism helps prevent frostbite by delivering warm blood to the skin. This mechanism is far less developed in humans than in most lower animals that live in the cold all the time.

Artificial Hypothermia

It is easy to decrease the temperature of a person by first administering a strong sedative to depress the reactivity of the hypothalamic temperature controller and then cooling the person with ice or cooling blankets until the temperature falls. The temperature can then be maintained below 32°C for several days to a week or more by continual sprinkling of cool water or alcohol on the body. Such artificial cooling has been used during heart surgery so that the heart can be stopped artificially for many minutes at a time. Cooling to this extent does not cause tissue damage, but it does slow the heart and greatly depresses cell metabolism, so that the body's cells can survive 30 minutes to more than 1 hour without blood flow during the surgical procedure.

79. Functional morphology of nephron

Each kidney in the human contains about 1 million nephrons, each capable of forming urine. The kidney cannot regenerate new nephrons. Therefore, with renal injury, disease, or normal aging, there is a gradual decrease in nephron number. After age 40, the number of functioning nephrons usually decreases about 10 per cent every 10 years; thus, at age 80, many people have 40 per cent fewer functioning nephrons than they did at age 40. This loss is not life threatening because adaptive changes in the remaining nephrons allow them to excrete the proper amounts of water, electrolytes, and waste products. Each nephron contains (1) a tuft of glomerular cap- illaries called the glomerulus, through which large amounts of fluid are filtered from the blood, and (2) a long tubule in which the filtered fluid is converted into urine on its way to the pelvis of the kidney.



The glomerulus contains a network of branching and anastomosing glomerular capillaries that, compared with other capillaries, have high hydrostatic pressure (about 60 mm Hg). The glomerular capillaries are covered by epithelial cells, and the total glomerulus is encased in Bowman's capsule. Fluid filtered from the glomerular capillaries flows into Bowman's capsule and then into the proximal tubule, which lies in the cortex of the kidney.

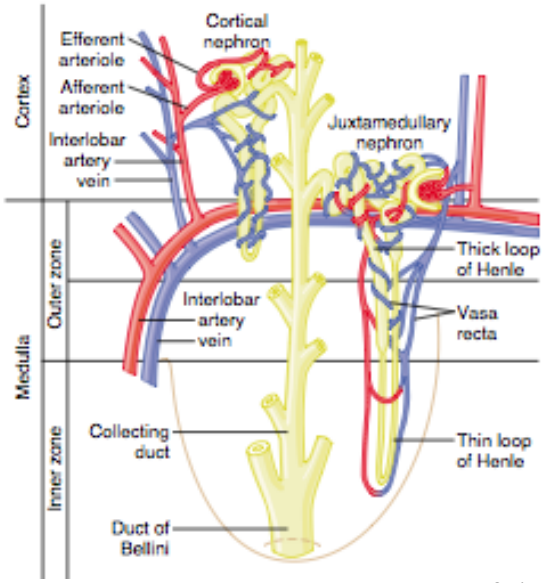
From the proximal tubule, fluid flows into the loop of Henle, which dips into the renal medulla. Each loop consists of a descending and an ascending limb. The walls of the descending limb and the lower end of the ascending limb are very thin and therefore are called the thin segment of the loop of Henle. After the ascend- ing limb of the loop has returned partway back to the cortex, its wall becomes much thicker, and it is referred to as the thick segment of the ascending limb.

At the end of the thick ascending limb is a short segment, which is actually a plaque in its wall, known as the macula densa. As we discuss later, the macula densa plays an important role in controlling nephron function. Beyond the macula densa, fluid enters the distal tubule, which, like the proximal tubule, lies in the renal cortex. This is followed by the connecting tubule and the cortical collecting tubule, which lead to the cortical collecting duct. The initial parts of 8 to 10 cortical collecting ducts join to form a single larger collecting duct that runs downward into the medulla and becomes the medullary collecting duct. The collecting ducts merge to form progressively larger ducts that eventually empty into the renal pelvis through the tips of the renal papillae. In each kidney, there are about 250 of the very large collecting ducts, each of which collects urine from about 4000 nephrons.

<u>Regional Differences in Nephron Structure: Cortical and Juxtamedullary Nephrons</u>.

Although each nephron has all the components described earlier, there are some differences, depending on how deep the nephron lies within the kidney mass. Those nephrons that have glomeruli located in the outer cortex are called cortical nephrons; they have short loops of Henle that penetrate only a short distance into the medulla (Figure 26–5).

About 20 to 30 per cent of the nephrons have glomeruli that lie deep in the renal cortex near the medulla and are called juxtamedullary nephrons. These nephrons have long loops of Henle that dip deeply into the medulla, in some cases all the way to the tips of the renal papillae.



The vascular structures supplying the jux- tamedullary nephrons also differ from those supplying the cortical nephrons. For the cortical nephrons, the entire tubular system is surrounded by an extensive network of peritubular capillaries. For the jux- tamedullary nephrons, long efferent arterioles extend from the glomeruli down into the outer medulla and then divide into specialized peritubular capillaries called vasa recta that extend downward into the medulla, lying side by side with the loops of Henle. Like the loops of Henle, the vasa recta return toward the cortex and empty into the cortical veins. This specialized network of capillaries in the medulla plays an essential role in the formation of a concentrated urine.

80. Urine formation

Urine Formation Results from Glomerular Filtration, Tubular Reabsorption, and Tubular Secretion

Urinary excretion rate = Filtration rate - Reabsorption rate + Secretion rate

Urine formation begins when a large amount of fluid that is virtually free of protein is filtered from the glomerular capillaries into Bowman's capsule. Most substances in the plasma, except for proteins, are freely filtered, so that their concentration in the glomerular filtrate in Bowman's capsule is almost the same as in the plasma. As filtered fluid leaves Bowman's capsule and passes through the tubules, it is modified by reabsorption of water and specific solutes back into the blood or by secretion of other substances from the peritubular capillaries into the tubules.

For each substance in the plasma, a particular combination of filtration, reabsorption, and secretion occurs. The rate at which the substance is excreted in the urine depends on the relative rates of these three basic renal processes.

Filtration, Reabsorption, and Secretion of Different Substances

In general, tubular reabsorption is quantitatively more important than tubular secretion in the formation of urine, but secretion plays an important role in determining the amounts of potassium and hydrogen ions and a few other substances that are excreted in the urine. Most substances that must be cleared from the blood, especially the end products of metabolism such as urea, creatinine, uric acid, and urates, are poorly reabsorbed and are therefore excreted in large amounts in the urine. Certain foreign substances and drugs are also poorly reabsorbed but, in addition, are secreted from the blood into the tubules, so that their excretion rates are high. Conversely, electrolytes, such as sodium ions, chloride ions, and bicarbonate ions, are highly reabsorbed, so that only small amounts appear in the urine. Certain nutritional substances, such as amino acids and glucose, are completely reabsorbed from the tubules and do not appear in the urine even though large amounts are filtered by the glomerular capillaries.

Each of the processes—glomerular filtration, tubular reabsorption, and tubular secretion—is regulated according to the needs of the body. For example, when there is excess sodium in the body, the rate at which sodium is filtered increases and a smaller fraction of the filtered sodium is reabsorbed, resulting in increased urinary excretion of sodium.

The First Step in Urine Formation = Glomerular Filtration

81. Renal blood flow and its autoregulation

Considering the fact that the two kidneys constitute only about 0.4% of the total body weight, one can readily see that they receive an extremely high blood flow compared with other organs.

As with other tissues, blood flow supplies the kidneys with nutrients and removes waste products. However, the high flow to the kidneys greatly exceeds this need. The purpose of this additional flow is to supply enough plasma for the high rates of glomerular filtration that are necessary for precise regulation of body fluid volumes and solute concentrations.

Renal Blood Flow and Oxygen Consumption

The kidneys normally consume oxygen at twice the rate of the brain but have almost seven times the blood flow of the brain. Thus, the oxygen delivered to the kidneys far exceeds their metabolic needs, and the arterial-venous extraction of oxygen is relatively low compared with that of most other tissues.

A large fraction of the oxygen consumed by the kidneys is related to the high rate of active sodium reabsorption by the renal tubules. If renal blood flow and GFR are reduced and less sodium is filtered, less sodium is reabsorbed and less oxygen is consumed. Therefore, renal oxygen consumption varies in proportion to renal tubular sodium reabsorption, which in turn is closely related to GFR and the rate of sodium filtered. If glomerular filtration completely ceases, renal sodium reabsorption also ceases, and oxygen consumption decreases to about one fourth normal. This residual oxygen consumption reflects the basic metabolic needs of the renal cells.

Determinants of Renal Blood Flow

Renal blood flow is determined by the pressure gradient across the renal vasculature (the difference between renal artery and renal vein hydrostatic pressures), divided by the total renal vascular resistance:

$$\frac{\text{(Renal artery pressure} - \text{Renal vein pressure)}}{\text{Total renal vascular resistance}}$$

Renal artery pressure is about equal to systemic arterial pressure, and renal vein pressure averages about 3 to 4 mm Hg under most conditions. As in other vascular beds, the total vascular resistance through the kidneys is determined by the sum of the resistances in the individual vasculature segments, including the arteries, arterioles, capillaries, and veins. Most of the renal vascular resistance resides in three major segments: interlobular arteries, afferent arterioles, and efferent arterioles. Resistance of these vessels is controlled by the sympathetic nervous system, various hormones, and local internal renal control mechanisms. An increase in the resistance of any of the vascular segments of the kidneys tends to reduce the renal blood flow, whereas a decrease in vascular resistance increases renal blood flow if renal artery and renal vein pressures remain constant.

Blood Flow in the Vasa Recta of the Renal Medulla Is Very Low Compared with Flow in the Renal Cortex

The outer part of the kidney, the renal cortex, receives most of the kidney's blood flow. Blood flow in the renal medulla accounts for only 1 to 2% of the total renal blood flow. Flow to the renal medulla is supplied by a specialized portion of the peritubular capillary system called the vasa recta. These vessels descend into the medulla in parallel with the loops of Henle and then loop back along with the loops of Henle and return to the cortex before emptying into the venous system. The vasa recta play an important role in allowing the kidneys to form a concentrated urine.

Physiologic Control of Glomerular Filtration and Renal Blood Flow

Sympathetic Nervous System Activation Decreases GFR

Essentially all the blood vessels of the kidneys, including the afferent and the efferent arterioles, are richly innervated by sympathetic nerve fibers. Strong activation of the renal

sympathetic nerves can constrict the renal arterioles and decrease renal blood flow and GFR. Moderate or mild sympathetic stimulation has little influence on renal blood flow and GFR. The renal sympathetic nerves seem to be most important in reducing GFR during severe, acute disturbances lasting for a few minutes to a few hours, such as those elicited by the defense reaction, brain ischemia, or severe hemorrhage. In the healthy resting person, sympathetic tone appears to have little influence on renal blood flow.

Hormonal and Autacoid Control of Renal Circulation

There are several hormones and autacoids that can influence GFR and renal blood flow.

Norepinephrine, Epinephrine, and Endothelin Constrict Renal Blood Vessels and Decrease GF

Hormones that constrict afferent and efferent arterioles, causing reductions in GFR and renal blood flow, include norepinephrine and epinephrine released from the adrenal medulla. In general, blood levels of these hormones parallel the activity of the sympathetic nervous system; thus, norepinephrine and epinephrine have little influence on renal hemodynamics except under extreme conditions, such as severe hemorrhage.

Another vasoconstrictor, endothelin, is a peptide that can be released by damaged vascular endothelial cells of the kidneys as well as by other tissues. The physiologic role of this autacoid is not completely understood. However, endothelin may contribute to hemostasis (minimizing blood loss) when a blood vessel is severed, which damages the endothelium and releases this powerful vasoconstrictor.

Angiotensin II Constricts Efferent Arterioles

A powerful renal vasoconstrictor, angiotensin II, can be considered a circulating hormone as well as a locally pro- duced autacoid because it is formed in the kidneys as well as in the systemic circulation. Because angiotensin II preferentially constricts efferent arterioles, increased angiotensin II levels raise glomerular hydrostatic pressure while reducing renal blood flow. It should be kept in mind that increased angiotensin II formation usually occurs in circumstances associated with decreased arterial pressure or volume depletion, which tend to decrease GFR. In these circumstances, the increased level of angiotensin II, by constricting efferent arterioles, helps prevent decreases in glomerular hydrostatic pressure and GFR; at the same time, though, the reduction in renal blood flow caused by efferent arteriolar constriction contributes to decreased flow through the peritubular capillaries, which in turn increases reabsorption of sodium and water.

Endothelial-Derived Nitric Oxide Decreases Renal Vascular Resistance and Increases GFR

An autacoid that decreases renal vascular resistance and is released by the vascular endothelium throughout the body is endothelial-derived nitric oxide. A basal level of nitric oxide production appears to be important for maintaining vasodilation of the kidneys. This allows the kidneys to excrete normal amounts of sodium and water. Therefore, administration of drugs that inhibit this normal formation of nitric oxide increases renal vascular resistance and decreases GFR and urinary sodium excretion, eventually causing high blood pressure. In some hypertensive patients, impaired nitric oxide production could be the cause of increased renal vasoconstriction and increased blood pressure.

Prostaglandins and Bradykinin Tend to Increase GFR

Hormones and autacoids that cause vasodilation and increased renal blood flow and GFR include the prostaglandins (PGE2 and PGI2) and bradykinin. Although these vasodilators do not appear to be of major importance in regulating renal blood flow or GFR in normal conditions, they may oppose the renal vasoconstrictor effects of the sympathetic nerves or angiotensin II, especially their effects to constrict the afferent arterioles.

PAH Clearance Can Be Used to Estimate Renal Plasma Flow

Theoretically, if a substance is completely cleared from the plasma, the clearance rate of that substance is equal to the total renal plasma flow. In other words, the amount of the substance delivered to the kidneys in the blood (renal plasma flow ¥ Ps) would be equal to the amount excreted in the urine (Us x V). Thus, renal plasma flow (RPF) could be calculated as

$$RPF = \frac{Us \times V}{Ps} = Cs$$

Because the GFR is only about 20% of the total plasma flow, a substance that is completely cleared from the plasma must be excreted by tubular secretion as well as glomerular filtration. There is no known substance that is completely cleared by the kidneys. One substance, however, PAH, is about 90% cleared from the plasma. Therefore, the clearance of PAH can be used as an approximation of renal plasma flow. To be more accurate, one can correct for the percentage of PAH that is still in the blood when it leaves the kidneys. The percentage of PAH removed from the blood is known as the extraction ratio of PAH and averages about 90% in normal kidneys.

The calculation of RPF can be demonstrated by the following example: Assume that the plasma concentration of PAH is 0.01 mg/ml, urine concentration is 5.85 mg/ml, and urine flow rate is 1 ml/min. PAH clearance can be calculated from the rate of urinary PAH excretion (5.85 mg/ml x 1 ml/min) divided by the plasma PAH concentration (0.01 mg/ml). Thus, clearance of PAH calculates to be 585 ml/min.

If the extraction ratio for PAH is 90%, the actual renal plasma flow can be calculated by dividing 585 ml/min by 0.9, yielding a value of 650 ml/min. Thus, total renal plasma flow can be calculated as

Total renal plasma flow = Clearance of PAH/Extraction ratio of PAH

The extraction ratio (EPAH) is calculated as the difference between the renal arterial PAH (PPAH) and renal venous PAH (VPAH) concentrations, divided by the renal arterial PAH concentration:

$$E_{PAH} = \frac{P_{PAH} - V_{PAH}}{P_{PAH}}$$

One can calculate the total blood flow through the kidneys from the total renal plasma flow and hematocrit (the percentage of red blood cells in the blood). If the hematocrit is 0.45 and the total renal plasma flow is 650 ml/min, the total blood flow through both kidneys is 650/(1 - 0.45), or 1182 ml/min.

Autoregulation of GFR and Renal Blood Flow

Feedback mechanisms intrinsic to the kidneys normally keep the renal blood flow and GFR relatively constant, despite marked changes in arterial blood pressure. These mechanisms still function independent of systemic influences. This relative constancy of GFR and renal blood flow is referred to as autoregulation.

The major function of autoregulation in the kidneys is to maintain a rela- tively constant GFR and to allow precise control of renal excretion of water and solutes.

The GFR normally remains autoregulated (that is, remains relatively constant), despite considerable arterial pressure fluctuations that occur during a person's usual activities. For instance, a decrease in arterial pressure to as low as 75 mm Hg or an increase to as high as 160 mm Hg changes GFR only a few percentage points. In general, renal blood flow is autoregulated in parallel with GFR, but GFR is more efficiently autoregulated under certain conditions.

82. Glomerular filtration

Composition of the Glomerular Filtrate

Urine formation begins with filtration of large amounts of fluid through the glomerular capillaries into Bowman's capsule. Like most capillaries, the glomerular capillaries are relatively impermeable to proteins, so that the filtered fluid (called the glomerular filtrate) is essentially protein-free and devoid of cellular elements, including red blood cells.

The concentrations of other constituents of the glomerular filtrate, including most salts and organic molecules, are similar to the concentrations in the plasma. Exceptions to this generalization include a few low-molecular-weight substances, such as calcium and fatty acids, that are not freely filtered because they are partially bound to the plasma proteins.

GFR Is About 20% of the Renal Plasma Flow

As in other capillaries, the GFR is determined by (1) the balance of hydrostatic and colloid osmotic forces acting across the capillary membrane and (2) the capillary filtration coefficient (Kf), the product of the permeability and filtering surface area of the capillaries. The glomerular capillaries have a much higher rate of filtration than most other capillaries because of a high glomerular hydrostatic pressure and a large Kf. In the average adult human, the GFR is about 180 L/day. The fraction of the renal plasma flow that is filtered (the filtration fraction) averages about 20% of the plasma flowing through the kidney is filtered through the glomerular capillaries. The filtration fraction is calculated as follows:

$$\text{Filtration fraction} = \text{GFR}/\text{Renal plasma flow}$$

Glomerular Capillary Membrane

The glomerular capillary membrane is similar to that of other capillaries, except that it has three (instead of the usual two) major layers: (1) the endothelium of the capillary, (2) a basement membrane, and (3) a layer of epithelial cells (podocytes) surrounding the outer surface of the capillary basement membrane. Together, these layers make up the filtration barrier, which, despite the three layers, filters several hundred times as much water and solutes as the usual capillary membrane.The glomerular capillary membrane normally prevents filtration of plasma proteins. The capillary endothelium is perforated by thousands of small holes called fenestrae, similar to the fenestrated capillaries found in the liver. Although the fenestrations are relatively large, endothelial cells are richly endowed with fixed negative charges that hinder the passage of plasma proteins.

Surrounding the endothelium is the basement membrane, which consists of a meshwork of collagen and proteoglycan fibrillae that have large spaces through which large amounts of water and small solutes can filter. The basement membrane effectively prevents filtration of plasma proteins, in part because of strong negative electrical charges associated with the proteoglycans.

The final part of the glomerular membrane is a layer of epithelial cells that line the outer surface of the glomerulus. These cells are not continuous but have long footlike processes (podocytes) that encircle the outer surface of the capillaries. The foot processes are separated by gaps called slit pores through which the glomerular filtrate moves. The epithelial cells, which also have negative charges, provide additional restriction to filtration of plasma proteins.

Filterability of Solutes Is Inversely Related to Their Size

Despite the high filtration rate, the glomerular filtration barrier is selective in determining which molecules will filter, based on their size and electrical charge.

Note that electrolytes such as sodium and small organic compounds such as glucose are freely filtered. As the molecular weight of the molecule approaches that of albumin, the filterability rapidly decreases, approach- ing zero.

Negatively Charged Large Molecules Are Filtered Less Easily Than Positively Charged Molecules of Equal Molecular Size.

The molecular diameter of the plasma protein albumin is only about 6 nm, whereas the pores of the glomerular membrane are thought to be about 8 nm. Albumin is restricted from filtration,

however, because of its negative charge and the electrostatic repulsion exerted by negative charges of the glomerular capillary wall proteoglycans.

For any given molecular radius, positively charged molecules are filtered much more readily than negatively charged molecules. The reason for these differences in filterability is that the negative charges of the basement membrane and the podocytes provide an important means for restricting large negatively charged molecules, including the plasma proteins.

Determinants of the GFR

The GFR is determined by (1) the sum of the hydro- static and colloid osmotic forces across the glomerular membrane, which gives the net filtration pressure, and (2) the glomerular capillary filtration coefficient, Kf. Expressed mathematically, the GFR equals the product of Kf and the net filtration pressure:

$$GFR = Kf \times \text{Net filtration pressure}$$

The net filtration pressure represents the sum of the hydrostatic and colloid osmotic forces that either favor or oppose filtration across the glomerular capillaries. These forces include

(1) hydrostatic pressure inside the glomerular capillaries (glomerular hydrostatic pressure, PG), which promotes filtration;

(2) the hydrostatic pressure in Bowman's capsule (PB) outside the capillaries, which opposes filtration;

(3) the colloid osmotic pressure of the glomerular capillary plasma proteins (pG), which opposes filtration;

(4) the colloid osmotic pressure of the proteins in Bowman's capsule (pB), which promotes filtration. (Under normal conditions, the concentration of protein in the glomerular filtrate is so low that the colloid osmotic pressure of the Bowman's capsule fluid is considered to be zero.)

The GFR can therefore be expressed as

$$GFR = Kf \times (PG - PB - pG + pB)$$

Based on the results in animals, the approximate normal forces favoring and opposing glomerular filtration in humans are believed to be as follows:

Forces Favoring Filtration (mm Hg)

Glomerular hydrostatic pressure 60
Bowman's capsule colloid osmotic pressure 0
Forces Opposing Filtration (mm Hg)
Bowman's capsule hydrostatic pressure 18
Glomerular capillary colloid osmotic pressure 32
Net filtration pressure = 60 – 18 – 32 = +10 mm Hg

Increased Glomerular Capillary Filtration Coefficient Increases GFR

The Kf is a measure of the product of the hydraulic conductivity and surface area of the glomerular capillaries. The Kf cannot be measured directly, but it is estimated experimentally by dividing the rate of glomerular filtration by net filtration pressure:

$$Kf = GFR/\text{Net filtration pressure}$$

Because total GFR for both kidneys is about 125 ml/ min and the net filtration pressure is 10 mm Hg, the normal Kf is calculated to be about 12.5 ml/min/mm Hg of filtration pressure. This high Kf for the glomerular capillaries contributes tremendously to their rapid rate of fluid filtration.

Although increased Kf raises GFR and decreased Kf reduces GFR, changes in Kf probably do not provide a primary mechanism for the normal day-to-day regulation of GFR. Some diseases, however, lower Kf by reducing the number of functional glomerular capillaries (thereby reducing the surface area for filtration) or by increasing the thickness of the glomerular capillary membrane and reducing its hydraulic conductivity.

83. Function of renal tubules

Tubular Reabsorption Is Selective and Quantitatively Large

The rate at which each of the substances are filtered is calculated as Filtration = Glomerular filtration rate x Plasma concentration

This calculation assumes that the substance is freely filtered and not bound to plasma proteins. The processes of glomerular filtration and tubular reabsorption are quantitatively very large relative to urinary excretion for many substances. This means that a small change in glomerular filtration or tubular reabsorption can potentially cause a relatively large change in urinary excretion. In reality, however, changes in tubular reabsorption and glomerular filtration are closely coordinated, so that large fluctuations in urinary excretion are avoided.

Second, unlike glomerular filtration, which is relatively nonselective (that is, essentially all solutes in the plasma are filtered except the plasma proteins or substances bound to them), tubular reabsorption is highly selective. Some sub- stances, such as glucose and amino acids, are almost completely reabsorbed from the tubules, so that the urinary excretion rate is essentially zero. Many of the ions in the plasma, such as sodium, chloride, and bicarbonate, are also highly reabsorbed, but their rates of reabsorption and urinary excretion are variable, depending on the needs of the body. Certain waste products, such as urea and creatinine, conversely, are poorly reabsorbed from the tubules and excreted in relatively large amounts.

Therefore, by controlling the rate at which they reabsorb different substances, the kidneys regulate the excretion of solutes independently of one another, a capability that is essential for precise control of the composition of body fluids.

Tubular Reabsorption Includes Passive and Active Mechanisms

For a substance to be reabsorbed, it must first be transported (1) across the tubular epithelial membranes into the renal interstitial fluid and then (2) through the peritubular capillary membrane back into the blood. Thus, reabsorption of water and solutes includes a series of transport steps. Reabsorption across the tubular epithelium into the interstitial fluid includes active or passive transport by way of the same basic mechanisms for transport across other membranes of the body. For instance, water and solutes can be transported either through the cell membranes themselves (transcellular route) or through the junctional spaces between the cells (paracellular route). Then, after absorption across the tubular epithelial cells into the interstitial fluid, water and solutes are transported the rest of the way through the peritubular capillary walls into the blood by ultrafiltration (bulk flow) that is mediated by hydrostatic and colloid osmotic forces. The peritubular capillaries behave very much like the venous ends of most other capillaries because there is a net reabsorptive force that moves the fluid and solutes from the interstitium into the blood.

Reabsorption and Secretion Along Different Parts of the Nephron

There are different characteristics of the individual tubular segments that enable them to perform their specific excretory functions. Only the tubular transport functions that are quantitatively most important are discussed, especially as they relate to the reabsorption of sodium, chloride, and water.

Proximal Tubular Reabsorption

Normally, about 65% of the filtered load of sodium and water and a slightly lower percentage of filtered chloride are reabsorbed by the proximal tubule before the filtrate reaches the loops of Henle.

Proximal Tubules Have a High Capacity for Active and Passive Reabsorption

The high capacity of the proximal tubule for reabsorption results from its special cellular characteristics. The proximal tubule epithelial cells are highly metabolic and have large numbers of mitochondria to support potent active transport processes. In addition, the proximal tubular cells have an extensive brush border on the luminal (apical) side of the membrane which provide an extensive membrane surface area on the luminal and basolateral sides of the epithelium for rapid transport of sodium ions and other substances.

The extensive membrane surface of the epithelial brush border is also loaded with protein carrier molecules that transport a large fraction of the sodium ions across the luminal membrane linked by way of the cotransport mechanism with multiple organic nutrients such as amino acids and glucose. The remainder of the sodium is transported from the tubular lumen into the cell by counter-transport mechanisms, which reabsorb sodium while secreting other substances into the tubular lumen, especially hydrogen ions. The secretion of hydrogen ions into the tubular lumen is an important step in the removal of bicarbonate ions from the tubule (by combining H+ with the HCO _ to form H2CO3 , which then dissociates into H2O and CO_2).

Although the sodium-potassium ATPase pump provides the major force for reabsorption of sodium, chloride, and water throughout the proximal tubule, there are some differences in the mechanisms by which sodium and chloride are transported through the luminal side of the early and late portions of the proximal tubular membrane.

In the first half of the proximal tubule, sodium is reabsorbed by co-transport along with glucose, amino acids, and other solutes. But in the second half of the proximal tubule, little glucose and amino acids remain to be reabsorbed. Instead, sodium is now reabsorbed mainly with chloride ions.

Concentrations of Solutes Along the Proximal Tubule

Although the amount of sodium in the tubular fluid decreases markedly along the proximal tubule, the concentration of sodium (and the total osmolarity) remains relatively constant because water permeability of the proximal tubules is so great that water reabsorption keeps pace with sodium reabsorption. Certain organic solutes, such as glucose, amino acids, and bicarbonate, are much more avidly reabsorbed than water, so that their concentrations decrease markedly along the length of the proximal tubule. Other organic solutes that are less permeant and not actively reabsorbed, such as creatinine, increase their concentration along the proximal tubule. The total solute concentration, as reflected by osmolarity, remains essentially the same all along the proximal tubule because of the extremely high permeability of this part of the nephron to water.

Secretion of Organic Acids and Bases by the Proximal Tubule

The proximal tubule is also an important site for secretion of organic acids and bases such as bile salts, oxalate, urate, and catecholamines. Many of these substances are the end products of metabolism and must be rapidly removed from the body. The secretion of these substances into the proximal tubule plus filtration into the proximal tubule by the glomerular capillaries and the almost total lack of reabsorption by the tubules, all combined, contribute to rapid excretion in the urine.

In addition to the waste products of metabolism, the kidneys secrete many potentially harmful drugs or toxins directly through the tubular cells into the tubules and rapidly clear these substances from the blood. In the case of certain drugs, such as penicillin and salicylates, the rapid clearance by the kidneys creates a problem in maintaining a therapeutically effective drug concentration.

Another compound that is rapidly secreted by the proximal tubule is para-aminohippuric acid (PAH). PAH is secreted so rapidly that the average person can clear about 90% of the PAH from the plasma flowing through the kidneys and excrete it in the urine. For this reason, the rate of PAH clearance can be used to estimate the renal plasma flow.

Solute and Water Transport in the Loop of Henle

The loop of Henle consists of three functionally distinct segments: the thin descending segment, the thin ascending segment, and the thick ascending segment. The thin descending and thin ascending segments, as their names imply, have thin epithelial membranes with no brush borders, few mitochondria, and minimal levels of metabolic activity.

The descending part of the thin segment is highly permeable to water and moderately permeable to most solutes, including urea and sodium. The function of this nephron segment is mainly to allow simple diffusion of substances through its walls. About 20% of the filtered water is reabsorbed in the loop of Henle, and almost all of this occurs in the thin descending limb. The ascending limb, including both the thin and the thick portions, is virtually impermeable to water, a characteristic that is important for concentrating the urine.

The thick segment of the loop of Henle, which begins about halfway up the ascending limb, has thick epithelial cells that have high metabolic activity and are capable of active reabsorption of

sodium, chloride, and potassium. About 25% of the filtered loads of sodium, chloride, and potassium are reabsorbed in the loop of Henle, mostly in the thick ascending limb. Considerable amounts of other ions, such as calcium, bicarbonate, and magnesium, are also reabsorbed in the thick ascending loop of Henle. The thin segment of the ascending limb has a much lower reabsorptive capacity than the thick segment, and the thin descending limb does not reabsorb significant amounts of any of these solutes.

An important component of solute reabsorption in the thick ascending limb is the sodium-potassium ATPase pump in the epithelial cell basolateral membranes. As in the proximal tubule, the reabsorption of other solutes in the thick segment of the ascending loop of Henle is closely linked to the reabsorptive capability of the sodium-potassium ATPase pump, which maintains a low intracellular sodium concentration. The low intracellular sodium concentration in turn provides a favorable gradient for movement of sodium from the tubular fluid into the cell. In the thick ascending loop, movement of sodium across the luminal membrane is mediated primarily by a 1-sodium, 2-chloride, 1-potassium co-transporter. This co-transport protein carrier in the luminal membrane uses the potential energy released by downhill diffusion of sodium into the cell to drive the reabsorption of potassium into the cell against a concentration gradient.

There is also significant paracellular reabsorption of cations, such as Mg++, Ca++, Na+, and K+, in the thick ascending limb owing to the slight positive charge of the tubular lumen relative to the interstitial fluid. Although the 1-sodium, 2-chloride, 1-potassium co-transporter moves equal amounts of cations and anions into the cell, there is a slight backleak of potassium ions into the lumen, creating a positive charge of about +8 millivolts in the tubular lumen. This positive charge forces cations such as Mg++ and Ca++ to diffuse from the tubular lumen through the paracellular space and into the interstitial fluid.

The thick ascending limb also has a sodium-hydrogen counter-transport mechanism in its luminal cell membrane that mediates sodium reabsorption and hydrogen secretion in this segment. The thick segment of the ascending loop of Henle is virtually impermeable to water. Therefore, most of the water delivered to this segment remains in the tubule, despite reabsorption of large amounts of solute. The tubular fluid in the ascending limb becomes very dilute as it flows toward the distal tubule, a feature that is important in allowing the kidneys to dilute or concentrate the urine under different conditions,.

Distal Tubule

The thick segment of the ascending limb of the loop of Henle empties into the distal tubule. The very first portion of the distal tubule forms part of the juxta-glomerular complex that provides feedback control of GFR and blood flow in this same nephron. The next part of the distal tubule is highly convoluted and has many of the same reabsorptive characteristics of the thick segment of the ascending limb of the loop of Henle. That is, it avidly reabsorbs most of the ions, including sodium, potassium, and chloride, but is virtually impermeable to water and urea.

Approximately 5% of the filtered load of sodium chloride is reabsorbed in the early distal tubule. The sodium-chloride co-transporter moves sodium chloride from the tubular lumen into the cell, and the sodium-potassium ATPase pump transports sodium out of the cell across the basolateral membrane. Chloride diffuses out of the cell into the renal interstitial fluid through chloride channels in the basolateral membrane.

Late Distal Tubule and Cortical Collecting Tubule

The second half of the distal tubule and the subsequent cortical collecting tubule have similar functional characteristics. Anatomically, they are composed of two distinct cell types, the principal cells and the intercalated cells. The principal cells reabsorb sodium and water from the lumen and secrete potassium ions into the lumen. The intercalated cells reabsorb potassium ions and secrete hydrogen ions into the tubular lumen.

Principal Cells Reabsorb Sodium and Secrete Potassium

Sodium reabsorption and potassium secretion by the principal cells depend on the activity of a sodium-potassium ATPase pump in each cell's basolateral membrane. This pump maintains a low sodium concentration inside the cell and, therefore, favors sodium diffusion into the cell through special channels. The secretion of potassium by these cells from the blood into the tubular lumen involves two steps: (1) Potassium enters the cell because of the sodium-potassium ATPase

pump, which maintains a high intracellular potassium concentration, and then (2) once in the cell, potassium diffuses down its concentration gradient across the luminal membrane into the tubular fluid.

Aldosterone antagonists compete with aldosterone for receptor sites in the principal cells and therefore inhibit the stimulatory effects of aldosterone on sodium reabsorption and potassium secretion.

Intercalated Cells Avidly Secrete Hydrogen and Reabsorb Bicarbonate and Potassium Ions

Hydrogen ion secretion by the intercalated cells is mediated by a hydrogen-ATPase transport mechanism. Hydrogen is generated in this cell by the action of carbonic anhydrase on water and carbon dioxide to form carbonic acid, which then dissociates into hydrogen ions and bicarbonate ions. The hydrogen ions are then secreted into the tubular lumen, and for each hydrogen ion secreted, a bicarbonate ion becomes available for reabsorption across the basolateral membrane. The intercalated cells can also reabsorb potassium ions.

The functional characteristics of the late distal tubule and cortical collecting tubule can be summarized as follows: 1. The tubular membranes of both segments are almost completely impermeable to urea, similar to the diluting segment of the early distal tubule; thus, almost all the urea that enters these segments passes on through and into the collecting duct to be excreted in the urine, although some reabsorption of urea occurs in the medullary collecting ducts. 2. Both the late distal tubule and the cortical collecting tubule segments reabsorb sodium ions, and the rate of reabsorption is controlled by hormones, especially aldosterone. At the same time, these segments secrete potassium ions from the peritubular capillary blood into the tubular lumen, a process that is also controlled by aldosterone and by other factors such as the concentration of potassium ions in the body fluids. 3. The intercalated cells of these nephron segments avidly secrete hydrogen ions by an active hydrogen-ATPase mechanism. This process is different from the secondary active secretion of hydrogen ions by the proximal tubule because it is capable of secreting hydrogen ions against a large concentration gradient, as much as 1000 to 1. 4. The permeability of the late distal tubule and cortical collecting duct to water is controlled by the concentration of ADH, which is also called vasopressin. With high levels of ADH, these tubular segments are permeable to water, but in the absence of ADH, they are virtually impermeable to water. This special characteristic provides an important mechanism for controlling the degree of dilution or concentration of the urine.

Medullary Collecting Duct

Although the medullary collecting ducts reabsorb less than 10% of the filtered water and sodium, they are the final site for processing the urine and, therefore, play an extremely important role in determining the final urine output of water and solutes.

The epithelial cells of the collecting ducts are nearly cuboidal in shape with smooth surfaces and relatively few mitochondria. Special characteristics of this tubular segment are as follows:

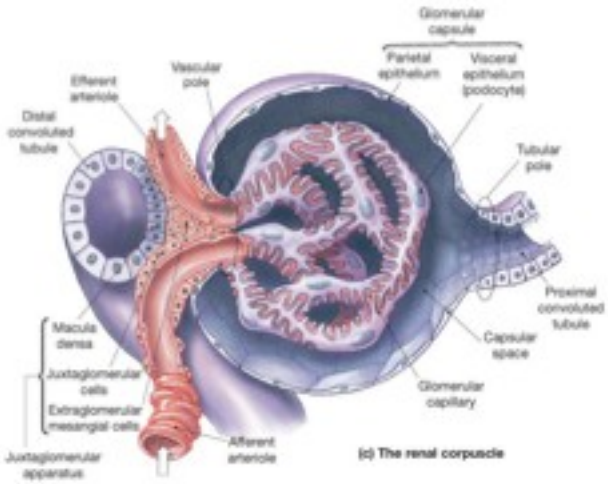
1. The permeability of the medullary collecting duct to water is controlled by the level of ADH. With high levels of ADH, water is avidly reabsorbed into the medullary interstitium, thereby reducing the urine volume and concentrating most of the solutes in the urine.

2. Unlike the cortical collecting tubule, the medullary collecting duct is permeable to urea. Therefore, some of the tubular urea is reabsorbed into the medullary interstitium, helping to raise the osmolality in this region of the kidneys and contributing to the kidneys' overall ability to form a concentrated urine.

3. The medullary collecting duct is capable of secreting hydrogen ions against a large concentration gradient, as also occurs in the cortical collecting tubule. Thus, the medullary collecting duct also plays a key role in regulating acid-base balance.

84. Juxtaglomerular apparatus

The juxtaglomerular apparatus is a microscopic structure in the kidney, which regulates the function of each nephron. The juxtaglomerular apparatus is named for its proximity to the glomerulus: it is found between the vascular pole of the renal corpuscle and the returning distal convoluted tubule of the same nephron. This location is critical to its function in regulating renal blood flow and glomerular filtration rate. The three cellular components of the apparatus are the macula densa, extraglomerular mesangial cells, and juxtaglomerular cells (also known as granular cells).



There are 3 different types of cells in the Juxtaglomerular Apparatus: Granular Cells, Mesangial Cells.

Granular Cells

These are modified pericytes of glomerular arterioles. They are also known as Juxtaglomerular cells.

The granular cells secrete renin in response to:

- Beta1 adrenergic stimulation
- Decrease in renal perfusion pressure (detected directly by the granular cells)
- Decrease in NaCl absorption in the Macula Densa (often due to a decrease in glomerular filtration rate, or GFR).

Macula Densa Cells

Macula densa cells are columnar epithelium thickening of the distal tubule. The macula densa senses sodium chloride concentration in the distal tubule of the kidney and secretes a locally active (paracrine) vasopressor which acts on the adjacent afferent arteriole to decrease glomerular filtration rate (GFR), as part of the tubuloglomerular feedback loop. Specifically, excessive filtration at the glomerulus or inadequate sodium uptake in the proximal tubule / thick ascending loop of Henle brings fluid to the distal convoluted tubule that has an abnormally high concentration of sodium.

Na/Cl cotransporters move sodium into the cells of the macula densa. The macula densa cells do not have enough basolateral Na/K ATPases to excrete this added sodium, so the cell's osmolarity increases. Water flows into the cell to bring the osmolarity back down, causing the cell to swell. When the cell swells, a stretch-activated non-selective anion channel is opened on the basolateral surface. ATP escapes through this channel and is subsequently converted to adenosine. Adenosine vasoconstricts the afferent arterioles via A1 receptors and vasodilates (to a lesser degree) efferent arterioles via A2 receptors which decreases GFR. Also, when macula densa cells detect higher concentrations of Na and Cl they inhibit Nitric Oxide Synthetase (decreasing renin release).

The macula densa cells detect lower concentrations in Na and Cl and upregulate Nitric Oxide Synthetase (NOS). NOS creates NO which catalyses the formation of prostaglandins. These prostaglandins diffuse to the granular cells and activate a prostaglandin specific Gs receptor. This receptor activates adenylate cyclase which increases levels of cAMP. cAMP augments renin release.

85. Renal sodium transport

In body electrolyte and water metabolism. In addition, Na+ transport is coupled to the movement of H+, other electrolyte, glucose, amino acids, organic acids, phosphate, and other substances across the tubule walls. In the proximal tubules, the thick portion of the ascending limb of Henle, the distal tubules, and the collecting ducts, Na+ moves by cotransport or exchange from the tubular lumen into the tubular epithelial cells down its conc. and electrical gradients and is actively pumped from these cells into the interstitial space. Thus, Na+ is actively transported out of all parts of the renal tubule except the thin portions of the loop of Henle. Na+ is pumped into the interstitium by Na+-K+ ATPase. It extrudes three Na+ in exchange for two K+ that are pumped into the cell.

The tubular cells are connected by tight junctions at their luminal edges, but there is space between the cells along the rest of their lateral borders. Much of the Na+ is actively transported into these extensions of the interstitial space, the lateral intercellular spaces.

Normally about 60% of the filtered Na+ is reabsorbed in the proximal tubule, primarily by the Na+/H+ exchange. Another 30% is absorbed via the Na+/2Cl/K+ cotransporter in the thick ascending limb of the loop of Henle, and about 7% is absorbed by the Na+/Cl- cotransport in the distal convoluted tubule. The remainder of the filtered Na+, about 3%, is absorbed via the ENaC (epithelial sodium channel) channels in the collecting ducts, and this is the portion that is regulated by aldosterone in the production of homeostatic adjustments in Na+ balance.

86. Transport of glucose in kidneys

The reabsorption rates of most organic nutrints, like glucose, are always very high and are not phisiologically regulated. Thus the filtered loads of these substances are normally completely reabsorbed, with none appearing in the urine. For these substances it is as though the kidneys do not exist since the kidneys do not eliminate these substances from the body at all. Therefore, the kidneys do not regulte the plasma concentrations of glucose - that is, they do not minimize changes from normal plasma levels. Rather, the kidneys merely maintain whatever plasma concentrations already exist.

The reabsorption of many substances is coupled to the reabsorption of sodium. The cotransported substance moves uphill into the cell via a secondary active cotransporter as sodium moves downhill into the cell via this same cotransporter. This is precisely how glucose, many amino acids, and other organic substances undergo tubular reabsorption. The reabsorption of several inorganic ions is also coupled in a variety of ways to the reabsorption of sodium.

Glucose is reabsorbed in the proximal tubule by secondaty active-transport. As noted earlier, glucose does not normally appear in the urine because all filtrated glucose is reabsorbed. However, glusose can appear in urine (glucosuria) when the concentration of glucose in the primary urine is so high that it excceeds the renal threshold (maximal reabsorptive capacity of glucose transporters).

88. Urea formation

Use of Proteins for Energy

Once the cells are filled to their limits with stored protein, any additional amino acids in the body fluids are degraded and used for energy or are stored mainly as fat or secondarily as glycogen. This degradation occurs almost entirely in the liver, and it begins with deamination, which is explained in the following section.

Deamination

Deamination means removal of the amino groups from the amino acids. This occurs mainly by transamination, which means transfer of the amino group to some acceptor substance, which is the reverse of the transamination explained earlier in relation to the synthesis of amino acids. Note from this schema that the amino group from the amino acid is transferred to a-ketoglutaric acid, which then becomes glutamic acid. The glutamic acid can then transfer the amino group to still other substances or release it in the form of ammonia (NH3). In the process of losing the amino group, the glutamic acid once again becomes a-ketoglutaric acid, so that the cycle can be repeated again and again. To initiate this process, the excess amino acids in the cells, especially in the liver, induce the activation of large quantities of aminotrans- ferases, the enzymes responsible for initiating most deamination.

Urea Formation by the Liver.

The ammonia released during deamination of amino acids is removed from the blood almost entirely by conversion into urea; two mol- ecules of ammonia and one molecule of carbon dioxide combine in accordance with the following net reaction:

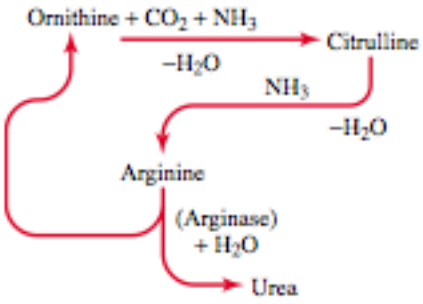
Essentially all urea formed in the human body is syn- thesized in the liver. In the absence of the liver or in serious liver disease, ammonia accumulates in the blood. This is extremely toxic, especially to the brain, often leading to a state called hepatic coma.

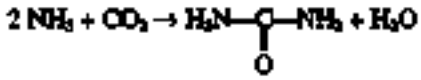
The stages in the formation of urea are essentially the following:

After its formation, the urea diffuses from the liver cells into the body fluids and is excreted by the kidneys.

Oxidation of Deaminated Amino Acids

Once amino acids have been deaminated, the resulting keto acids can, in most instances, be oxidized to release energy for metabolic purposes. This usually involves two successive processes: (1) the keto acid is changed into an appro- priate chemical substance that can enter the citric acid cycle, and (2) this substance is degraded by the cycle and used for energy in the same manner that acetyl coenzyme A (acetyl-CoA) derived from carbohydrate and lipid metabolism is used, as explained in Chapters 67 and 68. In general, the amount of adenosine triphos- phate (ATP) formed for each gram of protein that is oxidized is slightly less than that formed for each gram of glucose oxidized.

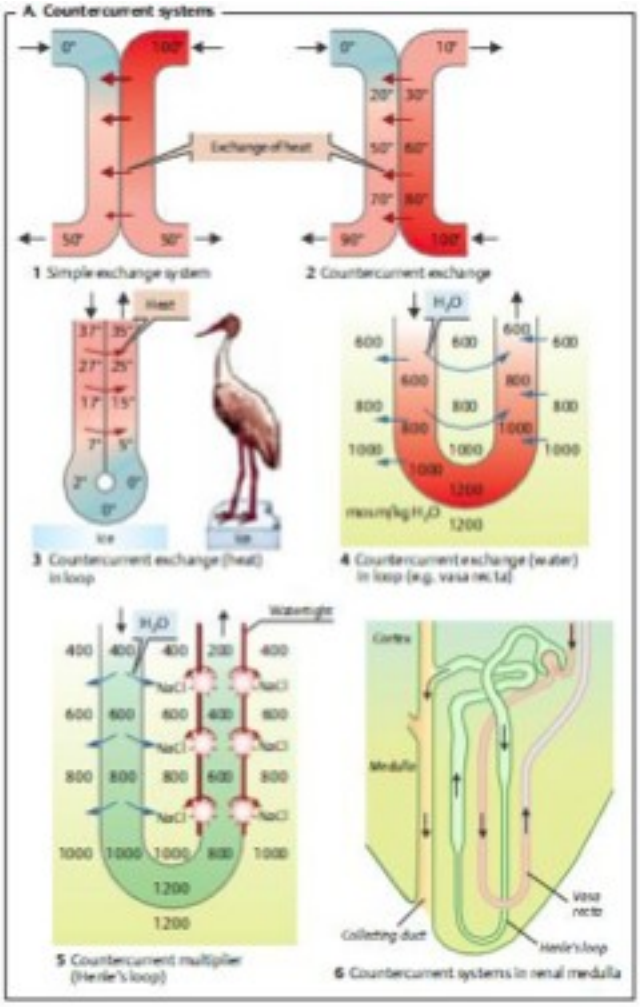




89. Hyper- and hypotonic urine. Counter-current system

Hyper- and hypotonic urine

The osmolality of plasma and glomerular filtrate is about 290 mOsm/kgH2O; that of the final urine (Uosm) ranges from 50 (hypotonic urine in extreme water diuresis) to about 1200 mOsm/kg H2O (hypertonic urine in maximally concentrated urine).



Countercurrent Systems

A simple exchange system A simple exchange system (->A1) can consist of two tubes in which parallel streams of water flow, one cold (0 ºC) and one hot (100 *C). Due to the exchange of heat between them, the water leaving the ends of both tubes will be about 50 *C, that is, the initially steep temperature gradient of 100 ºC will be offset.

In countercurrent exchange of heat (->A2), the fluid within the tubes flows in opposite directions. Since a temperature gradient is present in all parts of the tube, heat is exchanged along the entire length. Molecules can also be exchanged, provided the wall of the tube is permeable to them and that a concentration gradient exists for the substance. If the countercurrent exchange of heat occurs in a hairpin-shaped loop, the bend of which is in contact with an environment with a temperature different from that inside the tube (ice,->A3), the fluid exiting the loop will be only slightly colder than that entering it, because heat always passes from the warmer limb of the loop to the colder limb.

Countercurrent exchange of water in the vasa recta of the renal medulla (->A6) occurs if the medulla becomes increasingly hypertonic towards the papillae (see below) and if the vasa recta are permeable towater. Part of the water diffuses by osmosis from the descending vasa recta to the ascending ones, thereby “bypassing” the inner medulla (->A4).

Due to the extraction of water, the concentration of all other blood components increases as the blood approaches the papilla. The plasma osmolality in the vasa recta is therefore continuously adjusted to the osmolality of the surrounding interstitium, which rises towards the papilla. The hematocrit in the vasa recta also rises. Conversely, substances entering the blood in the renal medulla diffuse from the ascending to the descending vasa recta, provided the walls of both vessels are permeable to them (e.g., urea;->C). The countercurrent exchange in the vasa recta permits the necessary supply of blood to the renal medulla without significantly altering the high osmolality of the renal medulla and hence impairing the urine concentration capacity of the kidney.

In a countercurrent multiplier such as the loop of Henle, a concentration gradient between the two limbs is maintained by the expenditure of energy (A5). The countercurrent flow amplifies the relatively small gradient at all points between the limbs (local gradient of about 200 mOsm/kgH2O) to a relatively large gradient along the limb of the loop (about 1000 mOsm/kgH2O). The longer the loop and the higher the one-step gradient, the steeper the multiplied gradient. In addition, it is inversely proportional to (the square of) the flow rate in the loop.

91. Micturition

Micturition is the process by which the urinary bladder empties when it becomes filled. This involves two main steps: First, the bladder fills progressively until the tension in its walls rises above a threshold level; this elicits the second step, which is a nervous reflex called the micturition reflex that empties the bladder or, if this fails, at least causes a conscious desire to urinate. Although the micturition reflex is an autonomic spinal cord reflex, it can also be inhibited or facilitated by centers in the cerebral cortex or brain stem.

Physiologic Anatomy and Nervous Connections of the Bladder

The urinary bladder, is a smooth muscle chamber composed of two main parts: (1) the body, which is the major part of the bladder in which urine collects, and (2) the neck, which is a funnel-shaped extension of the body, passing inferiorly and anteriorly into the urogenital triangle and connecting with the urethra. The lower part of the bladder neck is also called the posterior urethra because of its relation to the urethra.

The smooth muscle of the bladder is called the detrusor muscle. Its muscle fibers extend in all directions and, when contracted, can increase the pressure in the bladder to 40 to 60 mm Hg. Thus, contraction of the detrusor muscle is a major step in emptying the bladder. Smooth muscle cells of the detrusor muscle fuse with one another so that low-resistance electrical pathways exist from one muscle cell to the other. Therefore, an action potential can spread throughout the detrusor muscle, from one muscle cell to the next, to cause contraction of the entire bladder at once.

On the posterior wall of the bladder, lying immediately above the bladder neck, is a small triangular area called the trigone. At the lowermost apex of the trigone, the bladder neck opens into the posterior urethra, and the two ureters enter the bladder at the uppermost angles of the trigone. The trigone can be identified by the fact that its mucosa, the inner lining of the bladder, is smooth, in contrast to the remaining bladder mucosa, which is folded to form rugae. Each ureter, as it enters the bladder, courses obliquely through the detrusor muscle and then passes another 1 to 2 centimeters beneath the bladder mucosa before emptying into the bladder.

The bladder neck (posterior urethra) is 2 to 3 cm long, and its wall is composed of detrusor muscle interlaced with a large amount of elastic tissue. The muscle in this area is called the internal sphincter. Its natural tone normally keeps the bladder neck and posterior urethra empty of urine and, therefore, prevents emptying of the bladder until the pressure in the main part of the bladder rises above a critical threshold.

Beyond the posterior urethra, the urethra passes through the urogenital diaphragm, which contains a layer of muscle called the external sphincter of the bladder. This muscle is a voluntary skeletal muscle, in contrast to the muscle of the bladder body and bladder neck, which is entirely smooth muscle. The external sphincter muscle is under voluntary control of the nervous system and can be used to consciously prevent urination even when involuntary controls are attempting to empty the bladder.

Innervation of the Bladder

The principal nerve supply of the bladder is by way of the pelvic nerves, which connect with the spinal cord through the sacral plexus, mainly connecting with cord segments S-2 and S-3. Coursing through the pelvic nerves are both sensory nerve fibers and motor nerve fibers. The sensory fibers detect the degree of stretch in the bladder wall. Stretch signals from the posterior urethra are especially strong and are mainly responsible for initiating the reflexes that cause bladder emptying.

The motor nerves transmitted in the pelvic nerves are parasympathetic fibers. These terminate on ganglion cells located in the wall of the bladder. Short postganglionic nerves then innervate the detrusor muscle.

In addition to the pelvic nerves, two other types of innervation are important in bladder function. Most important are the skeletal motor fibers transmitted through the pudendal nerve to the external bladder sphincter. These are somatic nerve fibers that innervate and control the

voluntary skeletal muscle of the sphincter. Also, the bladder receives sympathetic innervation from the sympathetic chain through the hypogastric nerves, connecting mainly with the L-2 segment of the spinal cord. These sympathetic fibers stimulate mainly the blood vessels and have little to do with bladder contraction. Some sensory nerve fibers also pass by way of the sympathetic nerves and may be important in the sensation of fullness and, in some instances, pain.

Transport of Urine from the Kidney Through the Ureters and into the Bladder

Urine that is expelled from the bladder has essentially the same composition as fluid flowing out of the collecting ducts; there are no significant changes in the composition of urine as it flows through the renal calyces and ureters to the bladder.

Urine flowing from the collecting ducts into the renal calyces stretches the calyces and increases their inherent pacemaker activity, which in turn initiates peristaltic contractions that spread to the renal pelvis and then downward along the length of the ureter, thereby forcing urine from the renal pelvis toward the bladder. The walls of the ureters contain smooth muscle and are innervated by both sympathetic and parasympathetic nerves as well as by an intramural plexus of neurons and nerve fibers that extends along the entire length of the ureters. The ureters enter the bladder through the detrusor muscle in the trigone region of the bladder. Normally, the ureters course obliquely for several centimeters through the bladder wall. The normal tone of the detrusor muscle in the bladder wall tends to compress the ureter, thereby preventing backflow of urine from the bladder when pressure builds up in the bladder during micturition or bladder compression. Each peristaltic wave along the ureter increases the pressure within the ureter so that the region passing through the bladder wall opens and allows urine to flow into the bladder.

Filling of the Bladder and Bladder Wall Tone; the Cystometrogram

When there is no urine in the bladder, the intravesicular pres- sure is about 0, but by the time 30 to 50 milliliters of urine has collected, the pressure rises to 5 to 10 cm of water. Additional urine—200 to 300 milli- liters—can collect with only a small additional rise in pressure; this constant level of pressure is caused by intrinsic tone of the bladder wall itself. Beyond 300 to 400 milliliters, collection of more urine in the bladder causes the pressure to rise rapidly.

Superimposed on the tonic pressure changes during filling of the bladder are periodic acute increases in pressure that last from a few seconds to more than a minute. The pressure peaks may rise only a few cen- timeters of water or may rise to more than 100

Micturition Reflex

As the bladder fills, many superimposed micturition contractions begin to appear. They are the result of a stretch reflex initiated by sensory stretch receptors in the bladder wall, especially by the receptors in the posterior urethra when this area begins to fill with urine at the higher bladder pressures. Sensory signals from the bladder stretch receptors are conducted to the sacral segments of the cord through the pelvic nerves and then reflexively back again to the bladder through the parasympathetic nerve fibers by way of these same nerves.

When the bladder is only partially filled, these micturition contractions usually relax spontaneously after a fraction of a minute, the detrusor muscles stop contracting, and pressure falls back to the baseline. As the bladder continues to fill, the micturition reflexes become more frequent and cause greater contractions of the detrusor muscle.

Once a micturition reflex begins, it is “self-regenerative.” That is, initial contraction of the bladder activates the stretch receptors to cause a greater increase in sensory impulses to the bladder and posterior urethra, which causes a further increase in reflex contraction of the bladder; thus, the cycle is repeated again and again until the bladder has reached a strong degree of contraction. Then, after a few seconds to more than a minute, the self-regenerative reflex begins to fatigue and the regenerative cycle of the micturition reflex ceases, permitting the bladder to relax.

Once the micturition reflex becomes powerful enough, it causes another reflex, which passes through the pudendal nerves to the external sphincter to inhibit it. If this inhibition is more potent in the brain than the voluntary constrictor signals to the external sphincter, urination will occur. If not, urination will not occur until the bladder fills still further and the micturition reflex becomes more powerful.

Facilitation or Inhibition of Micturition by the Brain

The micturition reflex is a completely autonomic spinal cord reflex, but it can be inhibited or facilitated by centers in the brain. These centers include (1) strong facilitative and inhibitory centers in the brain stem, located mainly in the pons, and (2) several centers located in the cerebral cortex that are mainly inhibitory but can become excitatory.

The micturition reflex is the basic cause of micturition, but the higher centers normally exert final control of micturition as follows: 1. The higher centers keep the micturition reflex partially inhibited, except when micturition is desired. 2. The higher centers can prevent micturition, even if the micturition reflex occurs, by continual tonic contraction of the external bladder sphincter until a convenient time presents itself. 3. When it is time to urinate, the cortical centers can facilitate the sacral micturition centers to help initiate a micturition reflex and at the same time inhibit the external urinary sphincter so that urination can occur.

Voluntary urination is usually initiated in the following way: First, a person voluntarily contracts his or her abdominal muscles, which increases the pressure in the bladder and allows extra urine to enter the bladder neck and posterior urethra under pressure, thus stretching their walls. This stimulates the stretch receptors, which excites the micturition reflex and simultaneously inhibits the external urethral sphincter. Ordinarily, all the urine will be emptied, with rarely more than 5 to 10 mL left in the bladder.

92. Effects of thyroid hormones

Physiologic Functions of the Thyroid Hormones

Thyroid Hormones Increase the Transcription of Large Numbers of Genes

The general effect of thyroid hormone is to activate nuclear transcription of large numbers of genes. Therefore, in virtually all cells of the body, great numbers of protein enzymes, structural proteins, transport proteins, and other substances are synthesized. The net result is generalized increase in functional activity throughout the body.

Most of the Thyroxine Secreted by the Thyroid Is Converted to Triiodothyronine

Before acting on the genes to increase genetic transcription, one iodide is removed from almost all the T4, thus forming T3.

Thyroid Hormones Activate Nuclear Receptors

The thyroid hormone receptors are either attached to the DNA genetic strands or located in proximity to them. The thyroid hormone receptor usually binds to a specific thyroid hormone response elements on the DNA. On binding with thyroid hormone, the receptors become activated and initiate the transcription process. Then large numbers of different types of messenger RNA are formed, followed within another few minutes or hours by RNA translation on the cytoplasmic ribosomes to form hundreds of new intracellular proteins.

Thyroid Hormones Increase Cellular Metabolic Activity

The thyroid hormones increase the metabolic activities of almost all the tissues of the body. The basal metabolic rate can increase to 60 to 100% above normal when large quantities of the hormones are secreted. The rate of utilization of foods for energy is greatly accelerated. Although the rate of protein synthesis is increased, at the same time the rate of protein catabolism is also increased. The growth rate of young people is greatly accelerated. The mental processes are excited, and the activities of most of the other endocrine glands are increased.

Thyroid Hormones Increase the Number and Activity of Mitochondria

When T3 or T4 is given, the mitochondria in most cells increase in size as well as number which in turn increases the rate of formation of adenosine triphosphate (ATP) to energize cellular function. Furthermore, the total membrane surface area of the mitochondria increases almost directly in proportion to the increased metabolic rate.

Thyroid Hormones Increase Active Transport of Ions Through Cell Membranes

One of the enzymes that increases its activity in response to thyroid hormone is Na+/K+-ATPase. This in turn increases the rate of transport of both sodium and potassium ions through the cell membranes of some tissues. Because this process uses energy and increases the amount of heat produced in the body, it has been suggested that this might be one of the mechanisms by which thyroid hormone increases the body's metabolic rate.

Effect of Thyroid Hormone on Growth

Thyroid hormone has both general and specific effects on growth.

In humans, the effect of thyroid hormone on growth is manifested mainly in growing children. In those who are hypothyroid, the rate of growth is greatly retarded. In those who are hyperthyroid, excessive skeletal growth often occurs, causing the child to become considerably taller at an earlier age. However, the bones also mature more rapidly and the epiphyses close at an early age, so that the duration of growth and the eventual height of the adult may actually be shortened.

An important effect of thyroid hormone is to promote growth and development of the brain during fetal life and for the first few years of postnatal life. If the fetus does not secrete sufficient quantities of thyroid hormone, growth and maturation of the brain both before birth and afterward are greatly retarded, and the brain remains smaller than normal.

Effects of Thyroid Hormone on Specific Bodily Mechanisms

Stimulation of Carbohydrate Metabolism

Thyroid hormone stimulates almost all aspects of carbohydrate metabolism, including rapid uptake of glucose by the cells, enhanced glycolysis, enhanced gluconeogenesis, increased rate of absorption from the gastrointestinal tract, and even increased insulin secretion with its resultant secondary effects on carbohydrate metabolism.

Stimulation of Fat Metabolism

Essentially all aspects of fat metabolism are also enhanced under the influence of thyroid hormone. In particular, lipids are mobilized rapidly from the fat tissue, which decreases the fat stores of the body to a greater extent than almost any other tissue element. This also increases the free fatty acid concentration in the plasma and greatly accelerates the oxidation of free fatty acids by the cells.

Effect on Plasma and Liver Fats

Increased thyroid hormone decreases the concentrations of cholesterol, phospholipids, and triglycerides in the plasma, even though it increases the free fatty acids. Conversely, decreased thyroid secretion greatly increases the plasma concentrations of cholesterol, phospholipids, and triglycerides and almost always causes excessive deposition of fat in the liver as well. The large increase in circulating plasma cholesterol in prolonged hypothyroidism is often associated with severe atherosclerosis.

One of the mechanisms by which thyroid hormone decreases the plasma cholesterol concentration is to increase significantly the rate of cholesterol secretion in the bile and consequent loss in the feces. A possible mechanism for the increased cholesterol secretion is that thyroid hormone induces increased numbers of low-density lipoprotein receptors on the liver cells, leading to rapid removal of LDL from the plasma by the liver and subsequent secretion of cholesterol in these lipoproteins by the liver cells.

Increased Requirement for Vitamins

Because thyroid hormone increases the quantities of many bodily enzymes and because vitamins are essential parts of some of the enzymes or coenzymes, thyroid hormone causes increased need for vitamins. Therefore, a relative vitamin deficiency can occur when excess thyroid hormone is secreted, unless at the same time increased quantities of vitamins are made available.

Increased Basal Metabolic Rate

Because thyroid hormone increases metabolism in almost all cells of the body, excessive quantities of the hormone can occasionally increase the basal metabolic rate 60 to 100% above normal. Conversely, when no thyroid hormone is produced, the basal metabolic rate falls almost to one-half normal.

Decreased Body Weight

Greatly increased thyroid hormone almost always decreases the body weight, and greatly decreased hormone almost always increases the body weight; these effects do not always occur, because thyroid hormone also increases the appetite, and this may counterbalance the change in the metabolic rate.

Effect of Thyroid Hormones on the Cardiovascular System

Increased Blood Flow and Cardiac Output

Increased metabolism in the tissues causes more rapid utilization of oxygen than normal and release of greater than normal quantities of metabolic end products from the tissues. These effects cause vasodilation in most body tissues, thus increasing blood flow. The rate of blood flow in the skin especially increases because of the increased need for heat elimination from the body. As a consequence of the increased blood flow, cardiac output also increases, sometimes rising to 60%

or more above normal when excessive thyroid hormone is present and falling to only 50% of normal in very severe hypothyroidism.

Increased Heart Rate

The heart rate increases considerably more under the influence of thyroid hormone than would be expected from the increase in cardiac output. Therefore, thyroid hormone seems to have a direct effect on the excitability of the heart, which in turn increases the heart rate.

Increased Heart Strength

The increased enzymatic activity caused by increased thyroid hormone production apparently increases the strength of the heart when only a slight excess of thyroid hormone is secreted. However, when thyroid hormone is increased markedly, the heart muscle strength becomes depressed because of long-term excessive protein catabolism.

Normal Arterial Pressure

The mean arterial pressure usually remains about normal after administration of thyroid hormone. Because of increased blood flow through the tissues between heartbeats, the pulse pressure is often increased, with the systolic pressure elevated in hyperthyroidism 10 to 15 mm Hg and the diastolic pressure reduced a corresponding amount.

Increased Respiration

The increased rate of metabolism increases the utilization of oxygen and formation of carbon dioxide; these effects activate all the mechanisms that increase the rate and depth of respiration.

Increased Gastrointestinal Motility

In addition to increased appetite and food intake, thyroid hormone increases both the rates of secretion of the digestive juices and the motility of the gastrointestinal tract. Hyperthyroidism often results in diarrhea. Lack of thyroid hormone can cause constipation.

Excitatory Effects on the Central Nervous System

In general, thyroid hormone increases the rapidity of cerebration; conversely, lack of thyroid hormone decreases this function. The hyper- thyroid individual is likely to have extreme nervousness and many psychoneurotic tendencies, such as anxiety complexes, extreme worry, and paranoia.

Effect on the Function of the Muscles

Slight increase in thyroid hormone usually makes the muscles react with vigor, but when the quantity of hormone becomes excessive, the muscles become weakened because of excess protein catabolism. Conversely, lack of thyroid hormone causes the muscles to become sluggish, and they relax slowly after a contraction.

Effect on Sleep

Because of the exhausting effect of thyroid hormone on the musculature and on the central nervous system, the hyperthyroid subject often has a feeling of constant tiredness, but because of the excitable effects of thyroid hormone on the synapses, it is difficult to sleep. Conversely, extreme somnolence is characteristic of hypothyroidism, with sleep sometimes lasting 12 to 14 hours a day.

Effect on Other Endocrine Glands

Increased thyroid hormone increases the rates of secretion of most other endocrine glands, but it also increases the need of the tissues for the hormones. For instance, increased thyroxine secretion increases the rate of glucose metabolism everywhere in the body and therefore causes a corresponding need for increased insulin secretion by the pancreas. Also, thyroid hormone increases many metabolic activities related to bone formation and, as a consequence, increases the need for parathyroid hormone. Thyroid hormone also increases the rate at which adrenal glucocorticoids are inactivated by the liver. This leads to feedback increase in adrenocorticotropic hormone production by the anterior pituitary and, therefore, increased rate of glucocorticoid secretion by the adrenal glands.

Effect of Thyroid Hormone on Sexual Function

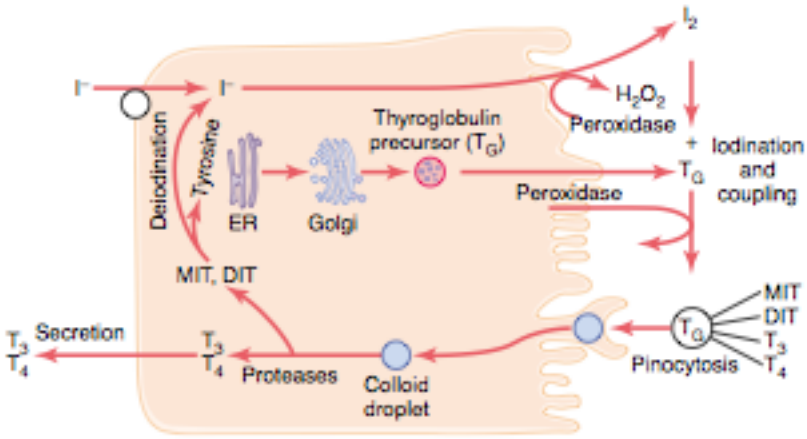
For normal sexual function, thyroid secretion needs to be approximately normal. In men, lack of thyroid hormone is likely to cause loss of libido; great excesses of the hormone, however, sometimes cause impotence.

In women, lack of thyroid hormone often causes menorrhagia and polymenorrhea— that is, respectively, excessive and frequent menstrual bleeding. In other women thyroid lack may cause irregular periods and occasionally even amenorrhea.

A hypothyroid woman, like a man, is likely to have greatly decreased libido.

93. Metabolism of iodine; Thyroid hormones synthesis

Within the thyroid gland are numerous follicles, each composed by an enclosed sphere of highly specialized cells surrounding a protein-rich core. The follicular cells participate in almost all phases of thyroid hormone synthesis and secretion. Synthesis begins when circulating iodide is cotransported with sodium ions across the follicular cell plasma membrane. Once inside the follicular cell, the bulky iodide ion cannot diffuse back into the interstitial fluid; this is known as iodide trapping. The sodium is eventually pumped back out of the cell by Na+/K+-ATPases.



The trapped, negatively charged iodide ions diffuse down their electrical and concentration gradients to the lumenal border of the follicular cells. The follicles are filled with a substance known as the colloid, which contains large amounts of a protein called thyroglobulin. The iodide that diffuses to the colloid is rapidly oxidized at the lumenal surface of the follicular cells to iodine free radicals; these are then attached to the phenolic rings of tyrosine molecules within the amino acid structure of thyroglobulin. Thyroglobulin itself is synthesized by the follicular cells and secreted by exocytosis into the follicle lumen. The enzyme responsible for oxidizing iodides and attaching them to tyrosines on thyroglobulin in the colloid is called thyroid peroxidase, and it, too, is synthesized by follicular cells. Iodines may be added to either of two positions on a given tyrosine within thyroglobulin. A tyrosine with one iodine attached is called monoiodotyrosine (MIT); it two iodines are attached, the product is diiodotyrosine (DIT). The precise mechanism of what happens next is still somewhat unclear. The phenolic ring of a molecule of MIT or DIT is removed from the remainder of its tyrosine and coupled to another DIT on the thyroglobulin molecule. This reaction may also be mediated by thyroid peroxidase. If two DIT molecules are coupled, the result is thyroxine (T4). If one MIT and one DIT are coupled, the result is T3.

Finally, when thyroid hormone is needed in the blood, extensions on the colloid-facing membranes of follicular cells engulf portions of the colloid (with its iodinated thyroglobulin) by endocytosis. The thyroglobulin, with its coupled MITs and DITs, is brought into contact with lysosomes in the cell interior. Proteolysis of thyroglobulin releases T3, and T4 which then diffuse out of the follicular cell into the interstitial fluid and from there to the blood.

94. Hyper- and hypothyroidism

Hyperthyroidism

Most effects of hyperthyroidism are obvious from the various physiologic effects of thyroid hormone. However, some specific effects should be mentioned in connection especially with the development, diagnosis, and treatment of hyperthyroidism.

Causes of Hyperthyroidism (Toxic Goiter, Thyrotoxicosis, Graves' Disease)

In most patients with hyperthyroidism, the thyroid gland is increased to two to three times normal size, with tremendous hyperplasia and infolding of the follicular cell lining into the follicles, so that the number of cells is increased greatly. Also, each cell increases its rate of secretion severalfold; radioactive iodine uptake studies indicate that some of these hyperplastic glands secrete thyroid hormone at rates 5 to 15 times normal.

The changes in the thyroid gland in most instances are similar to those caused by excessive TSH. However, plasma TSH concentrations are less than normal rather than enhanced in almost all patients and often are essentially zero. However, other substances that have actions similar to those of TSH are found in the blood of almost all these patients. These substances are immunoglobulin antibodies that bind with the same membrane receptors that bind TSH. They induce continual activation of the cAMP system of the cells, with resultant development of hyperthyroidism. These antibodies are called thyroid-stimulating immunoglobulin and are designated TSI. They have a prolonged stimulating effect on the thyroid gland, lasting for as long as 12 hours, in contrast to a little over 1 hour for TSH. The high level of thyroid hormone secretion caused by TSI in turn suppresses anterior pituitary formation of TSH.

The antibodies that cause hyperthyroidism almost certainly occur as the result of autoimmunity that has developed against thyroid tissue.

Thyroid Adenoma

Hyperthyroidism occasionally results from a localized adenoma (a tumor) that develops in the thyroid tissue and secretes large quantities of thyroid hormone. This is different from the more usual type of hyperthyroidism, in that it usually is not associated with evidence of any autoimmune disease. An interesting effect of the adenoma is that as long as it continues to secrete large quantities of thyroid hormone, secretory function in the remainder of the thyroid gland is almost totally inhibited because the thyroid hormone from the adenoma depresses the production of TSH by the pituitary gland.

Symptoms of Hyperthyroidism

The symptoms of hyperthyroidism are obvious from the preceding discussion of the physiology of the thyroid hormones: (1) a high state of excitability, (2) intolerance to heat, (3) increased sweating, (4) mild to extreme weight loss (sometimes as much as 45Kg), (5) varying degrees of diarrhea, (6) muscle weakness, (7) nervousness or other psychic disorders, (8) extreme fatigue but inability to sleep, and (9) tremor of the hands.

Exophthalmos

Most people with hyperthyroidism develop some degree of protrusion of the eyeballs. This condition is called exophthalmos. A major degree of exophthalmos occurs in about one third of hyperthyroid patients, and the condition sometimes becomes so severe that the eyeball protrusion stretches the optic nerve enough to damage vision. Much more often, the eyes are damaged because the eyelids do not close completely when the person blinks or is asleep. As a result, the epithelial surfaces of the eyes become dry and irritated and often infected, resulting in ulceration of the cornea.

The cause of the protruding eyes is edematous swelling of the retroorbital tissues and degenerative changes in the extraocular muscles. In most patients, immunoglobulins can be found in the blood that react with the eye muscles.

Diagnostic Tests for Hyperthyroidism

For the usual case of hyperthyroidism, the most accurate diagnostic test is direct measurement of the concentration of "free" thy- roxine (and sometimes triiodothyronine) in the plasma, using appropriate radioimmunoassay procedures.

Other tests that are sometimes used are as follows: 1. The basal metabolic rate is usually increased to +30 to +60 in severe hyperthyroidism. 2. The concentration of TSH in the plasma is measured by radioimmunoassay. In the usual type of thyrotoxicosis, anterior pituitary secretion of TSH is so completely suppressed by the large amounts of circulating thyroxine and triiodothyronine that there is almost no plasma TSH. 3. The concentration of TSI is measured by radioimmunoassay. This is usually high in thyrotoxicosis but low in thyroid adenoma.

Physiology of Treatment in Hyperthyroidism

The most direct treatment for hyperthyroidism is surgical removal of most of the thyroid gland.

Treatment of the Hyperplastic Thyroid Gland with Radioactive Iodine

80 to 90% of an injected dose of iodide is absorbed by the hyperplastic, toxic thyroid gland within 1 day after injection. If this injected iodine is radioactive, it can destroy most of the secretory cells of the thyroid gland.

Hypothyroidism

The effects of hypothyroidism, in general, are opposite to those of hyperthyroidism, but there are a few physiologic mechanisms peculiar to hypothyroidism. Hypothyroidism, like hyperthyroidism, probably is initiated by autoimmunity against the thyroid gland, but immunity that destroys the gland rather than stimulates it. The thyroid glands of most of these patients first have autoimmune "thyroiditis," which means thyroid inflammation. This causes progressive deterioration and finally fibrosis of the gland, with resultant diminished or absent secretion of thyroid hormone. Several other types of hypothyroidism also occur, often associated with development of enlarged thyroid glands, called thyroid goiter.

Endemic Colloid Goiter Caused by Dietary Iodide Deficiency

The term "goiter" means a greatly enlarged thyroid gland. As pointed out in the discussion of iodine metabolism, about 50 milligrams of iodine are required each year for the formation of adequate quantities of thyroid hormone. In certain areas of the world, notably in the Swiss Alps, the Andes, and the Great Lakes region of the United States, insufficient iodine is present in the soil for the foodstuffs to contain even this minute quantity.

The mechanism for development of large endemic goiters is the following: Lack of iodine prevents production of both thyroxine and triiodothyronine. As a result, no hormone is available to inhibit production of TSH by the anterior pituitary; this causes the pituitary to secrete excessively large quantities of TSH. The TSH then stimulates the thyroid cells to secrete tremendous amounts of thyroglobulin colloid into the follicles, and the gland grows larger and larger. But because of lack of iodine, thyroxine and triiodothyronine production does not occur in the thyroglobulin molecule and therefore does not cause the normal suppression of TSH production by the anterior pituitary. The follicles become tremendous in size, and the thyroid gland may increase to 10 to 20 times normal size.

Idiopathic Nontoxic Colloid Goiter

Enlarged thyroid glands similar to those of endemic colloid goiter can also occur in people who do not have iodine deficiency. These goitrous glands may secrete normal quantities of thyroid hormones, but more frequently, the secretion of hormone is depressed, as in endemic colloid goiter.

The exact cause of the enlarged thyroid gland in patients with idiopathic colloid goiter is not known, but most of these patients show signs of mild thyroiditis; therefore, it has been suggested that the thyroiditis causes slight hypothyroidism, which then leads to increased TSH secretion and progressive growth of the noninflamed portions of the gland. This could explain why these glands usually are nodular, with some por- tions of the gland growing while other portions are being destroyed by thyroiditis.

In some persons with colloid goiter, the thyroid gland has an abnormality of the enzyme system required for formation of the thyroid hormones. Among the abnormalities often encountered are the following: 1. Deficient iodide-trapping mechanism, in which iodine is not pumped adequately into the thyroidcells 2. Deficient peroxidase system, in which the iodides are not oxidized to the iodine state 3. Deficient coupling of iodinated tyrosines in the thyroglobulin molecule, so that the final thyroid hormones cannot be formed 4. Deficiency of the deiodinase enzyme, which prevents recovery of iodine from the iodinated tyrosines that are not coupled to form the thyroid hormones (this is about two thirds of the iodine), thus leading to iodine deficiency

PhysiologicCharacteristics of Hypothyroidism

They include fatigue and extreme somnolence with sleeping up to 12 to 14 hours a day, extreme muscular sluggishness, slowed heart rate, decreased cardiac output, decreased blood volume, sometimes increased body weight, constipation, mental sluggishness, failure of many trophic functions in the body evidenced by depressed growth of hair and scaliness of the skin, development of a froglike husky voice, and, in severe cases, development of an edematous appearance throughout the body called myxedema.

Myxedema

Myxedema develops in the patient with almost total lack of thyroid hormone function. Such a patient demonstrates bagginess under the eyes and swelling of the face. In this condition, for reasons not explained, the total quantity of interstitial fluid is increased. Because of the gel nature of the excess fluid, it is mainly immobile, and the edema is the nonpitting type.

Atherosclerosis in Hypothyroidism

Lack of thyroid hormone increases the quantity of blood cholesterol because of altered fat and cholesterol metabolism and diminished liver excretion of cholesterol in the bile. The increase in blood cholesterol is usually associated with increased atherosclerosis.

Diagnostic Tests in Hypothyroidism

The tests already described for diagnosis of hyperthyroidism give oppo- site results in hypothyroidism.

Treatment of Hypothyroidism

It is easy to maintain a steady level of thyroid hormone activity in the body by daily oral ingestion of a tablet or more containing thyroxine.

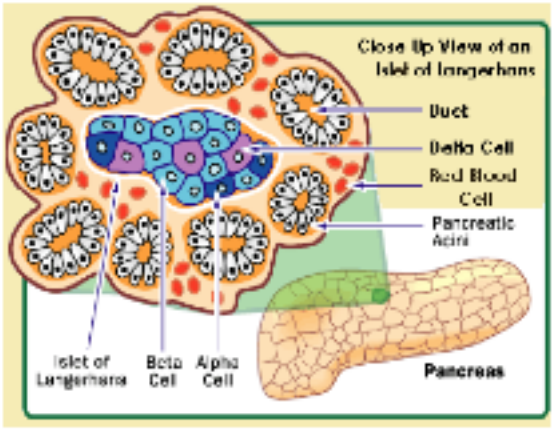
Cretinism

Cretinism is caused by extreme hypothyroidism during fetal life, infancy, or childhood. This condition is characterized especially by failure of body growth and by mental retardation. It results from congenital lack of a thyroid gland (congenital cretinism), from failure of the thyroid gland to produce thyroid hormone because of a genetic defect of the gland, or from iodine lack in the diet (endemic cretinism).

A neonate without a thyroid gland may have normal appearance and function because it was supplied with some (but usually not enough) thyroid hormone by the mother while in utero, but a few weeks after birth, the neonate's movements become sluggish and both physical and mental growth begin to be greatly retarded. Treatment of the neonate with cretinism at any time with adequate iodine or thyroxine usually causes normal return of physical growth, but unless the cretinism is treated within a few weeks after birth, mental growth remains permanently retarded. This results from retardation of the growth, branching, and myelination of the neuronal cells of the central nervous system at this critical time in the normal development of the mental powers.

Skeletal growth in the child with cretinism is characteristically more inhibited than is soft tissue growth. As a result of this disproportionate rate of growth, the soft tissues are likely to enlarge excessively, giving the child with cretinism an obese, stocky, and short appearance. Occasionally the tongue becomes so large in relation to the skeletal growth that it obstructs swallowing and breathing, inducing a characteristic guttural breathing that sometimes chokes the child.

95. Endocrine pancreas



The pancreas is composed of two major types of tissues: (1) the acini, which secrete digestive juice into the duodenum, and (2) the islets of Langerhans, which secrete insulin and glucagon directly into the blood.

1 to 2 million cellular islets of Langerhans are distributed throughout the pancreas. They consist of endocrine cells and are known as the islet organ.

The islets produce at least 2 antagonistic hormones: Insulin promotes glycogen synthesis in the liver and thereby lowers the blood sugar level. Glucagon leads to glycogenolysis in the liver and so raises the blood sugar level.

Using immunohistochemistry and special staining techniques, three major types of cells can be distinguished. A-cells about 20% of all cells, produce glucagon and a gastrin inhibitory polypeptide (GIP). β-cells constituting about 60% of all cells, secrete insulin and amylin, a hormone that is often secreted in parallel to insulin, although its function is unclear. D-cells are about 10% and secrete somatostatin, which regulates insulin release (inhibitory). In addition D-cells contain β-endorphin. In addition, at least one other type of cell, the PP-cell. is present in small numbers in the islets and secretes a hormone of uncertain function, called pancreatic polypeptide.

The close interrelations among these cell types in the islets of Langerhans allow cell-to-cell communication and direct control of secretion of some of the hormones by the other hormones. For instance, insulin inhibits glucagon secretion, amylin inhibits insulin secretion and somatostatin inhibits the secretion of both insulin and glucagon.

The islets are permeated by wide capillaries. A microcirculation exists between the individual islet and the surrounding exocrine tissue through small insuloacinar portal vessels (influence, for example of the D-cells on the activity of the exocrine pancreas).

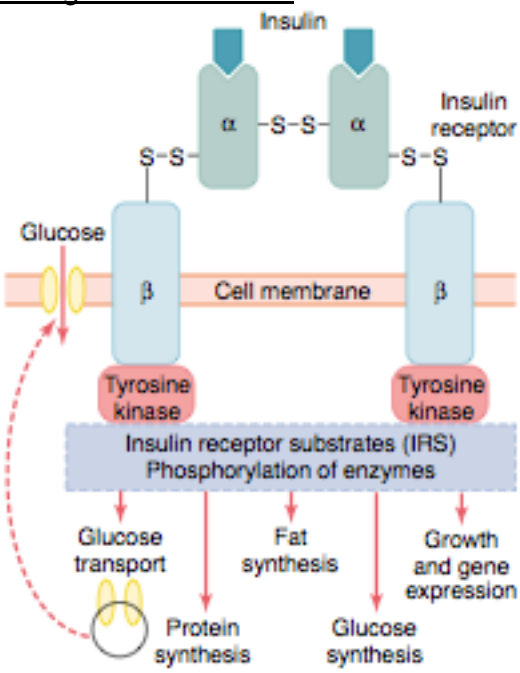
Sympathetic fibers stimulate the secretion of glucagon and inhibit that of insulin, which is stimulated by the vagus nerve. Serotininergic nerve fibers inhibit the release of insulin.

96. Insulin – mechanism of action

Insulin secretion is associated with energy abundance. That is, when there is great abundance of energy-giving foods in the diet, especially excess amounts of carbohydrates, insulin is secreted in great quantity. In turn, the insulin plays an important role in storing the excess energy. In the case of excess carbohydrates, it causes them to be stored as glycogen mainly in the liver and muscles. Also, all the excess carbohydrates that cannot be stored as glycogen are converted under the stimulus of insulin into fats and stored in the adipose tissue. In the case of proteins, insulin has a direct effect in promoting amino acid uptake by cells and conversion of these amino acids into protein. In addition, it inhibits the break-down of the proteins that are already in the cells. Insulin is synthesized in the beta cells by the usual cell machinery for protein synthesis, beginning with translation of the insulin RNA by ribosomes attached to the endoplasmic reticulum to form an insulin preprohormone. It is then cleaved in the endoplasmic reticulum to form a proinsulin; most of this is further cleaved in the Golgi apparatus to form insulin and peptide fragments before being packaged in the secretory granules. When insulin is secreted into the blood, it circulates almost entirely in an unbound form; it has a plasma half-life that averages only about 6 minutes. Except for that portion of the insulin that combines with receptors in the target cells, the remainder is degraded by the enzyme insulinase mainly in the liver.

Activation of Target Cell Receptors by Insulin and the Resulting Cellular Effects

To initiate its effects on target cells, insulin first binds with and activates a membrane receptor protein. It is the activated receptor, not the insulin, that causes the subsequent effects.



The insulin receptor is a combination of four subunits held together by disulfide linkages: two alpha subunits that lie entirely outside the cell membrane and two beta subunits that penetrate through the membrane, protruding into the cell cytoplasm. The insulin binds with the alpha subunits on the outside of the cell, but because of the linkages with the beta subunits, the portions of the beta subunits protruding into the cell become autophosphorylated. Autophosphorylation of the beta subunits of the receptor activates a local tyrosine kinase, which in turn causes phosphorylation of multiple other intracellular enzymes including a group called insulin-receptor substrates (IRS). The net effect is to activate some of these enzymes while inactivating others. In this way, insulin directs the intracellular metabolic machinery to produce the desired effects on carbohydrate, fat, and protein metabolism. The end effects of insulin stimulation are the following:

1. Within seconds after insulin binds with its membrane receptors, the membranes of about 80% of the body's cells markedly increase their uptake of glucose. This is especially true of muscle cells and adipose cells but is not true of most neurons in the brain. The increased glucose transported into the cells is immediately phosphorylated and becomes a substrate for all the usual carbohydrate metabolic functions.

2. The cell membrane becomes more permeable to many of the amino acids, potassium ions, and phosphate ions, causing increased transport of these substances into the cell.

3. Slower effects occur during the next 10 to 15 minutes to change the activity levels of many more intracellular metabolic enzymes. These effects result mainly from the changed states of phosphorylation of the enzymes.

4. Much slower effects continue to occur for hours and even several days. They result from changed rates of translation of messenger RNAs at the ribosomes to form new proteins and still slower effects from changed rates of transcription of DNA in the cell nucleus. In this way, insulin remolds much of the cellular enzymatic machinery to achieve its metabolic goals.

Effect of Insulin on Carbohydrate Metabolism

Immediately after a high-carbohydrate meal, the glucose that is absorbed into the blood causes rapid secretion of insulin. The insulin in turn causes rapid uptake, storage, and use of glucose by almost all tissues of the body, but especially by the muscles, adipose tissue, and liver.

Insulin Promotes Muscle Glucose Uptake and Metabolism

During much of the day, muscle tissue depends not on glucose for its energy but on fatty acids. The principal reason for this is that the normal resting muscle membrane is only slightly permeable to glucose, except when the muscle fiber is stimulated by insulin; between meals, the amount of insulin that is secreted is too small to promote significant amounts of glucose entry into the muscle cells.

However, under two conditions the muscles do use large amounts of glucose. One of these is during moderate or heavy exercise. This usage of glucose does not require large amounts of insulin, because exercising muscle fibers become more permeable to glucose even in the absence of insulin because of the contraction process itself.

The second condition for muscle usage of large amounts of glucose is during the few hours after a meal. At this time the blood glucose concentration is high and the pancreas is secreting large quantities of insulin. The extra insulin causes rapid transport of glucose into the muscle cells. This causes the muscle cell during this period to use glucose preferentially over fatty acids.

Storage of Glycogen in Muscle

If the muscles are not exercising after a meal and yet glucose is transported into the muscle cells in abundance, then most of the glucose is stored in the form of muscle glycogen, up to a limit of 2 to 3% concentration. The glycogen can later be used for energy by the muscle. It is especially useful for short periods of extreme energy use by the muscles.

Insulin Promotes Liver Uptake, Storage, and Use of Glucose

One of the most important of all the effects of insulin is to cause most of the glucose absorbed after a meal to be stored almost immediately in the liver in the form of glycogen.

The mechanism by which insulin causes glucose uptake and storage in the liver includes several almost simultaneous steps: 1. Insulin inactivates liver phosphorylase, the principal enzyme that causes liver glycogen to split into glucose. This prevents breakdown of the glycogen that has been stored in the liver cells. 2. Insulin causes enhanced uptake of glucose from the blood by the liver cells. It does this by increasing the activity of the enzyme glucokinase, which is one of the enzymes that causes the initial phosphorylation of glucose after it diffuses into the liver cells. Once phosphorylated, the glucose is temporarily trapped inside the liver cells because phosphorylated glucose cannot diffuse back through the cell membrane. 3. Insulin also increases the activities of the enzymes that promote glycogen synthesis, including especially glycogen synthase.

Effect of Insulin on Fat Metabolism

Although not quite as visible as the acute effects of insulin on carbohydrate metabolism, insulin's effects on fat metabolism are, in the long run, equally important. Especially dramatic is the long-term effect of insulin lack in causing extreme atherosclerosis, often leading to heart attacks, cerebral strokes, and other vascular accidents.

Insulin Promotes Fat Synthesis and Storage

Insulin has several effects that lead to fat storage in adipose tissue. First, insulin increases the utilization of glucose by most of the body's tissues, which automatically decreases the utilization of fat, thus functioning as a fat sparer. However, insulin also promotes fatty acid synthesis. This is especially true when more carbohydrates are ingested than can be used for immediate energy, thus providing the substrate for fat synthesis. Almost all this synthesis occurs in the liver cells, and the fatty acids are then transported from the liver by way of the blood lipoproteins to the adipose cells to be stored. The different factors that lead to increased fatty acid synthesis in the liver include the following:

1. Insulin increases the transport of glucose into the liver cells. Then all the additional glucose entering the liver cells becomes available to form fat. The glucose is first split to pyruvate

in the glycolytic pathway, and the pyruvate subsequently is converted to acetyl-CoA, the substrate from which fatty acids are synthesized.

2. An excess of citrate and isocitrate ions is formed by the citric acid cycle when excess amounts of glucose are being used for energy. These ions then have a direct effect in activating acetyl-CoA carboxylase, the enzyme required to carboxylate acetyl-CoA to form malonyl-CoA, the first stage of fatty acid synthesis.

3. Most of the fatty acids are then synthesized within the liver itself and used to form triglycerides, the usual form of storage fat. They are released from the liver cells to the blood in the lipoproteins. Insulin activates lipoprotein lipase in the capillary walls of the adipose tissue, which splits the triglycerides again into fatty acids, a requirement for them to be absorbed into the adipose cells, where they are again converted to triglycerides and stored.

Role of Insulin in Storage of Fat in the Adipose Cells

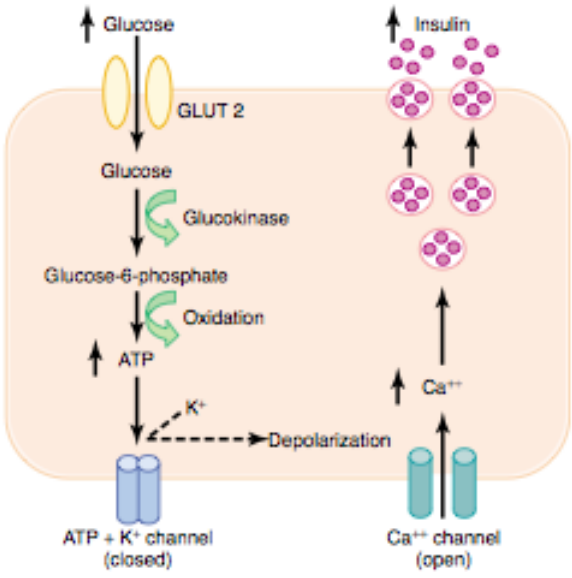
Insulin has two other essential effects that are required for fat storage in adipose cells: 1. Insulin inhibits the action of hormone-sensitive lipase. This is the enzyme that causes hydrolysis of the triglycerides already stored in the fat cells. Therefore, the release of fatty acids from the adipose tissue into the circulating blood is inhibited. 2. Insulin promotes glucose transport through the cell membrane into the fat cells in exactly the same ways that it promotes glucose transport into muscle cells. It also forms large quantities of a-glycerol phosphate. This substance supplies the glycerol that combines with fatty acids to form the triglycerides that are the storage form of fat in adipose cells. Therefore, when insulin is not available, even storage of the large amounts of fatty acids transported from the liver in the lipoproteins is almost blocked.

Effect of Insulin on Protein Metabolism and on Growth

Insulin Promotes Protein Synthesis and Storage

The manner in which insulin causes protein storage is not as well understood as the mechanisms for both glucose and fat storage. Some of the facts follow.

1. Insulin stimulates transport of many of the amino acids into the cells. 2. Insulin increases the translation of messenger RNA, thus forming new proteins. Insulin “turns on” the ribosomal machinery. 3. Insulin inhibits the catabolism of proteins.



Mechanisms of Insulin Secretion

The beta cells have a large number of glucose transporters (GLUT-2) that permit a rate of glucose influx that is propor- tional to the blood concentration in the physiologic range. Once inside the cells, glucose is phosphorylated to glucose-6-phosphate by glucokinase. The glucose-6-phosphate is subsequently oxidized to form adenosine triphosphate (ATP), which inhibits the ATP-sensitive potassium channels of the cell. Closure of the potassium channels depolarizes the cell membrane, thereby opening voltage-gated calcium channels, which are sensitive to changes in membrane voltage. This produces an influx of calcium that stimulates fusion of the docked insulin-containing vesicles with the cell membrane and secretion of insulin into the extracellular fluid by exocytosis.

Control of Insulin Secretion

Formerly, it was believed that insulin secretion was controlled almost entirely by the blood glucose concentration. However, as more has been learned about the metabolic functions of insulin for protein and fat metabolism, it has become apparent that blood amino acids and other factors also play important roles in controlling insulin secretion.

97. Hyper- and hypoglycaemia. Diabetes mellitus.

Hyperglycemia

Or high blood sugar is a condition in which an excessive amount of glucose circulates in the blood plasma. This is generally a blood glucose level higher than 10 mmol/l (180 mg/dl), but symptoms may not start to become noticeable until even higher values such as 15-20 mmol/l (270-360 mg/dl). However, chronic levels exceeding 7 mmol/l (125 mg/dl) can produce organ damage.

In diabetes mellitus, hyperglycemia is usually caused by low insulin levels (Diabetes mellitus type 1) and/or by resistance to insulin at the cellular level (Diabetes mellitus type 2), depending on the type and state of the disease. Low insulin levels and/or insulin resistance prevent the body from converting glucose into glycogen (a starch-like source of energy stored mostly in the liver), which in turn makes it difficult or impossible to remove excess glucose from the blood.

Hypoglycemia

Develops when the insulin concentration is too high. Glucose levels of <2 mmol/L (35 mg/dL) produce glucose deficiencies in the brain, which can lead to coma and hypoglycemic shock.
The excessive intake of carbohydrates can overload glycogen stores. The liver therefore starts to convert glucose into fatty acids, which are transported to and stored in fatty tissues in the form of triacylglycerols.

Diabetes Mellitus

Diabetes mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin. There are two general types of diabetes mellitus:

1. Type I diabetes, also called insulin-dependent diabetes mellitus (IDDM), is caused by lack of insulin secretion.

2. Type II diabetes, also called non–insulin-dependent diabetes mellitus (NIDDM), is caused by decreased sensitivity of target tissues to the metabolic effect of insulin. This reduced sensitivity to insulin is often called insulin resistance.

In both types of diabetes mellitus, metabolism of all the main foodstuffs is altered. The basic effect of insulin lack or insulin resistance on glucose metabolism is to prevent the efficient uptake and utilization of glucose by most cells of the body, except those of the brain. As a result, blood glucose concentration increases, cell utilization of glucose falls increasingly lower, and utilization of fats and proteins increases.

Type I Diabetes—Lack of Insulin Production by Beta Cells of the Pancreas

Injury to the beta cells of the pancreas or diseases that impair insulin production can lead to type I diabetes. Viral infections or autoimmune disorders may be involved in the destruction of beta cells in many patients with type I diabetes, although heredity also plays a major role in determining the susceptibility of the beta cells to destruction by these insults.

The usual onset of type I diabetes occurs at about 14 years of age, and for this reason it is often called juvenile diabetes mellitus. Type I diabetes may develop very abruptly, over a period of a few days or weeks, with three principal sequelae: (1) increased blood glucose, (2) increased utilization of fats for energy and for formation of cholesterol by the liver, and (3) depletion of the body's proteins.

<u>Blood Glucose Concentration Rises to Very High Levels in Diabetes Mellitus</u>

The lack of insulin decreases the efficiency of peripheral glucose utilization and augments glucose production, raising plasma glucose.

<u>Increased Blood Glucose Causes Loss of Glucose in the Urine</u>

The high blood glucose causes more glucose to filter into the renal tubules than can be reabsorbed, and the excess glucose spills into the urine. This normally occurs when the blood glucose concentration rises above 180 mg/100 ml, a level that is called the blood "thresh- old" for the appearance of glucose in the urine. When the blood glucose level rises to 300 to 500 mg/100

ml— common values in people with severe untreated dia- betes—100 or more grams of glucose can be lost into the urine each day.

Increased Blood Glucose Causes Dehydration

The very high levels of blood glucose (sometimes as high as 8 to 10 times normal in severe untreated diabetes). This occurs partly because glucose does not diffuse easily through the pores of the cell membrane, and the increased osmotic pressure in the extracellular fluids causes osmotic transfer of water out of the cells.

In addition to the direct cellular dehydrating effect of excessive glucose, the loss of glucose in the urine causes osmotic diuresis. Thus, polyuria (excessive urine excretion), intracellular and extracellular dehydration, and increased thirst are classic symptoms of diabetes.

Chronic High Glucose Concentration Causes Tissue Injury

When blood glucose is poorly controlled over long periods in diabetes mellitus, blood vessels in multiple tissues throughout the body begin to function abnormally and undergo structural changes that result in inadequate blood supply to the tissues. This in turn leads to increased risk for heart attack, stroke, end-stage kidney disease, retinopathy and blindness, and ischemia and gangrene of the limbs.

The precise mechanisms that cause tissue injury in diabetes are not well understood but probably involve multiple effects of high glucose concentrations and other metabolic abnormalities on proteins of endothelial and vascular smooth muscle cells, as well as other tissues.

Diabetes Mellitus Causes Increased Utilization of Fats and Metabolic Acidosis

The shift from carbohydrate to fat metabolism in diabetes increases the release of keto acids into the plasma more rapidly than they can be taken up and oxidized by the tissue cells. As a result, the patient develops severe metabolic acidosis from the excess keto acids, which, in association with dehydration due to the excessive urine formation, can cause severe acidosis. This leads rapidly to diabetic coma and death unless the condition is treated immediately with large amounts of insulin.

All the usual physiologic compensations that occur in metabolic acidosis take place in diabetic acidosis. They include rapid and deep breathing, which causes increased expiration of carbon dioxide; the kidneys compensate by decreasing bicarbonate excretion.

Diabetes Causes Depletion of the Body's Proteins

Failure to use glucose for energy leads to increased utilization and decreased storage of proteins as well as fat. Therefore, a person with severe untreated diabetes mellitus suffers rapid weight loss and asthenia (lack of energy).

Type II Diabetes—Resistance to the Metabolic Effects of Insulin

Type II diabetes is far more common than type I, accounting for about 90% of all cases of diabetes mellitus. In most cases, the onset of type II diabetes occurs after age 30, often between the ages of 50 and 60 years, and the disease develops gradually. It is realated to increasing prevalence of obesity, the most important risk factor for type II diabetes in children as well as in adults.

Obesity, Insulin Resistance, and "Metabolic Syndrome" Usually Precede Development of Type II Diabetes

Type II diabetes, in contrast to type I, is associated with increased plasma insulin concentration (hyperinsulinemia). This occurs as a compensatory response by the pancreatic beta cells for diminished sensitivity of target tissues to the metabolic effects of insulin, a condition referred to as insulin resistance. Development of insulin resistance and impaired glucose metabolism is usually a gradual process, beginning with excess weight gain and obesity. The mechanisms that link obesity with insulin resistance, however, are still uncertain. Some studies suggest that there are fewer insulin receptors, especially in the skeletal muscle, liver, and adipose tissue, in obese than in lean subjects.

Insulin resistance is part of a cascade of disorders that is often called the "metabolic syndrome." Some of the features of the metabolic syndrome include: (1) obesity, especially

accumulation of abdominal fat; (2) insulin resistance; (3) fasting hyperglycemia; (4) lipid abnormalities such as increased blood triglycerides and decreased blood high-density lipoprotein-cholesterol; and (5) hypertension.

Development of Type II Diabetes During Prolonged Insulin Resistance

With prolonged and severe insulin resistance, even the increased levels of insulin are not sufficient to maintain normal glucose regulation. As a result, moderate hyperglycemia occurs after ingestion of carbohydrates in the early stages of the disease. In the later stages of type II diabetes, the pancreatic beta cells become “exhausted” and are unable to produce enough insulin to prevent more severe hyperglycemia, especially after the person ingests a carbohydrate-rich meal.

In many instances, type II diabetes can be effectively treated, at least in the early stages, with exercise, caloric restriction, and weight reduction, and no exogenous insulin administration is required. Drugs that increase insulin sensitivity, or drugs that cause additional release of insulin by the pancreas may also be used. However, in the later stages of type II diabetes, insulin administration is usually required to control plasma glucose.

Physiology of Diagnosis of Diabetes Mellitus

The usual methods for diagnosing diabetes are based on various chemical tests of the urine and the blood.

Urinary Glucose

To determine the quantity of glucose lost in the urine. In general, a normal person loses undetectable amounts of glucose, whereas a person with diabetes loses glucose in small to large amounts, in proportion to the severity of disease and the intake of carbohydrates.

Insulin Levels

In type I diabetes, plasma insulin levels are very low or undetectable during fasting and even after a meal. In type II diabetes, plasma insulin concentration may be severalfold higher than normal and usually increases to a greater extent after ingestion of a standard glucose load during a glucose tolerance test.

Glucose Tolerance Test

When a normal, fasting person ingests 75 gram of glucose in 300 ml of water, the blood glucose level rises from about 6 mmol/l to 11 mmol/l and falls back to below normal in about 2 hours.

In a person with diabetes, the fasting blood glucose concentration is almost always above 6 mmol/L. Also, the glucose tolerance test is almost always abnormal. On ingestion of glucose, these people exhibit a much greater than normal rise in blood glucose level and the glucose level falls back to the control value only after 4 to 6 hours; furthermore, it fails to fall below the control level. This demonstrates that either (1) the normal increase in insulin secretion after glucose ingestion does not occur or (2) there is decreased sensitivity to insulin. A diagnosis of diabetes mellitus can usually be established on the basis of such test, and type I and type II diabetes can be distinguished from each other by measurements of plasma insulin, with plasma insulin being low or undetectable in type I diabetes and increased in type II diabetes.

Acetone Breath

Small quantities of acetoacetic acid in the blood, which increase greatly in severe diabetes, are converted to acetone. This is volatile and vaporized into the expired air. Consequently, one can frequently make a diagnosis of type I diabetes mellitus simply by smelling acetone on the breath of a patient.

Treatment of Diabetes

The treatment of type I diabetes mellitus is to administer enough insulin so that the patient will have carbohydrate, fat, and protein metabolism that is as normal as possible.

In persons with type II diabetes, dieting and exercise are usually recommended in an attempt to induce weight loss and to reverse the insulin resistance. If this fails, drugs may be administered

to increase insulin sensitivity or to stimulate increased production of insulin by the pancreas. In many persons, however, exogenous insulin must be used to regulate blood glucose.

Relation of Treatment to Arteriosclerosis

Diabetic patients, mainly because of their high levels of circulating cholesterol and other lipids, develop atherosclerosis, arteriosclerosis, severe coronary heart disease, and multiple microcirculatory lesions far more easily than do normal people. Indeed, those who have poorly controlled diabetes throughout childhood are likely to die of heart disease in early adulthood.

Because the complications of diabetes—such as atherosclerosis, greatly increased susceptibility to infection, diabetic retinopathy, cataracts, hypertension, and chronic renal disease—are closely associated with the level of blood lipids as well as the level of blood glucose, most physicians also use lipid-lowering drugs to help prevent these disturbances.

98. Adrenal cortex. Functions, malfunctions

The two adrenal glands, lie at the superior poles of the two kidneys. Each gland is composed of two distinct parts, the adrenal medulla and the adrenal cortex. The adrenal medulla, the central 20% of the gland, is functionally related to the sympathetic nervous system; it secretes the hormones epinephrine and norepinephrine in response to sympathetic stimulation.

The adrenal cortex secretes an entirely different group of hormones, called corticosteroids. These hormones are all synthesized from the steroid cholesterol, and they all have similar chemical formulas. However, slight differences in their molecular structures give them several different but very important functions.

Corticosteroids Mineralo corticoids,Glucocorticoids, and Androgens

Two major types of adrenocortical hormones, the mineralocorticoids and the glucocorticoids, are secreted by the adrenal cortex. In addition to these, small amounts of sex hormones are secreted, especially androgenic hormones, which exhibit about the same effects in the body as the male sex hormone testosterone. The mineralocorticoids have gained this name because they especially affect the electrolytes (the “minerals”) of the extracellular fluids-sodium and potassium, in particular. The glucocorticoids have gained their name because they exhibit important effects that increase blood glucose concentration. They have additional effects on both protein and fat metabolism that are equally as impor- tant to body function as their effects on carbohydrate metabolism.

Synthesis and Secretion of Adrenocortical Hormones

The Adrenal Cortex Has Three Distinct Layers

The adrenal cortex is composed of three relatively distinct layers: 1. The zona glomerulosa, a thin layer of cells that lies just underneath the capsule. These cells are the only ones in the adrenal gland capable of secreting significant amounts of aldosterone because they contain the enzyme aldosterone synthase. The secretion of these cells is controlled mainly by the extracellular fluid concentrations of angiotensin II and potassium, both of which stimulate aldosterone secretion. 2. The zona fasciculata, the middle and widest layer and secretes the glucocorticoids cortisol and corticosterone, as well as small amounts of adrenal androgens and estrogens. The secretion of these cells is controlled in large part by the hypothalamic-pituitary axis via adrenocorticotropic hormone (ACTH). 3. The zona reticularis, the deep layer of the cortex, secretes the adrenal androgens dehydroepiandrosterone (DHEA) and androstenedione. ACTH also regulates secretion of these cells.

Aldosterone and cortisol secretion are regulated by independent mechanisms. Factors such as angiotensin II that specifically increase the output of aldosterone and cause hypertrophy of the zona glomerulosa have no effect on the other two zones. Similarly, factors such as ACTH that increase secretion of cortisol and adrenal androgens and cause hypertrophy of the zona fasciculata and zona reticularis have little or no effect on the zona glomerulosa.

Adrenocortical Hormones Are Steroids Derived from Cholesterol

All human steroid hormones, including those produced by the adrenal cortex, are synthesized from cholesterol. For example, ACTH, which stimulates adrenal steroid synthesis, increases the number of adrenocortical cell receptors for LDL, as well as the activity of enzymes that liberate cholesterol from LDL.

Once the cholesterol enters the cell, it is delivered to the mitochondria, where it is cleaved by the enzyme cholesterol desmolase to form pregnenolone; In all three zones of the adrenal cortex, this initial step in steroid synthesis is stimulated by the different factors that control secretion of the major hormone products aldosterone and cortisol. For example, both ACTH, which stimulates cortisol secretion, and angiotensin II, which stimulates aldosterone secretion, increase the conversion of cholesterol to pregnenolone.

Synthetic Pathways for Adrenal Steroids

In addition to aldosterone and cortisol, other steroids having glucocorticoid or mineralocorticoid activities, or both, are normally secreted in small amounts by the adrenal cortex. And several additional potent steroid hormones not normally formed in the adrenal glands have been synthesized and are used in various forms of therapy. Some of the more important of the corticos- teroid hormones, including the synthetic ones:

Mineralocorticoids

- Aldosterone
- Desoxycorticosterone
- Corticosterone
- Cortisol
- Cortisone (synthetic, slight mineralocorticoid activity)

Glucocorticoids

- Cortisol
- Corticosterone
- Cortisone
- Prednisone
- Methylprednisone
- Dexamethasone

Adrenocortical Hormones Are Bound to Plasma Proteins

Approximately 90 to 95% of the cortisol in the plasma binds to plasma proteins, especially a globulin called cortisol-binding globulin or transcortin and, to a lesser extent, to albumin. This high degree of binding to plasma proteins slows the elimination of cortisol from the plasma. Only about 60 per cent of circulating aldosterone combines with the plasma proteins, so that about 40% is in the free form. In both the combined and free forms, the hor- mones are transported throughout the extracellular fluid compartment.

Binding of adrenal steroids to the plasma proteins may serve as a reservoir to lessen rapid fluctuations in free hormone concentrations.

Adrenocortical Hormones Are Metabolized in the Liver

The adrenal steroids are degraded mainly in the liver and conjugated especially to glucuronic acid and, to a lesser extent, sulfates. About 25% of these conjugates are excreted in the bile and then in the feces. The remaining conjugates formed by the liver enter the circulation but are not bound to plasma proteins, are highly soluble in the plasma, and are therefore filtered readily by the kidneys and excreted in the urine.

99. Metabolic and anti-inflammatory affects of glucocorticoids

At least 95% of the glucocorticoid activity of the adrenocortical secretions results from the secretion of cortisol. In addition to this, a small but significant amount of glucocorticoid activity is provided by corticosterone.

Effects of Cortisol on Carbohydrate Metabolism

Stimulation of Gluconeogenesis

The metabolic effect of cortisol and other glucocorticoids on metabolism is their ability to stimulate gluconeogenesis by the liver, often increasing the rate of gluconeogenesis. This results mainly from two effects of cortisol. 1. Cortisol increases the enzymes required to convert amino acids into glucose in the liver cells. This results from the effect of the glucocorticoids to activate DNA transcription in the liver cell nuclei with formation of messenger RNAs that in turn lead to the array of enzymes required for gluconeogenesis. 2. Cortisol causes mobilization of amino acids from the extrahepatic tissues mainly from muscle. As a result, more amino acids become available in the plasma to enter into the gluconeogenesis process of the liver and thereby to promote the formation of glucose.

One of the effects of increased gluconeogenesis is a marked increase in glycogen storage in the liver cells.

Decreased Glucose Utilization by Cells

Cortisol also causes a moderate decrease in the rate of glucose utilization by most cells in the body. A suggested mechanism is based on the observation that glucocorticoids depress the oxidation of nicotinamide-adenine dinucleotide (NADH) to form NAD+. Because NADH must be oxidized to allow glycolysis, this effect could account for the diminished utilization of glucose by the cells.

Elevated Blood Glucose Concentration and “Adrenal Diabetes.”

Both the increased rate of gluconeogenesis and the moderate reduction in the rate of glucose utilization by the cells cause the blood glucose concentrations to rise. The rise in blood glucose in turn stimulates secretion of insulin. The increased plasma levels of insulin, however, are not as effective in maintaining plasma glucose as they are under normal conditions. In this way, excess secretion of glucocorticoids may produce disturbances of carbohydrate metabolism very similar to those found in patients with excess levels of growth hormone.

The increase in blood glucose concentration is occasionally great enough (50% or more above normal) that the condition is called adrenal diabetes. Administration of insulin lowers the blood glucose concentration only a moderate amount in adrenal diabetes-not nearly as much as it does in pancreatic diabetes because the tissues are resistant to the effects of insulin.

Effects of Cortisol on Protein Metabolism

Reduction in Cellular Protein

One of the principal effects of cortisol on the metabolic systems of the body is reduction of the protein stores in essentially all body cells except those of the liver. This is caused by both decreased protein synthesis and increased catabolism of protein already in the cells.

In the presence of great excesses of cortisol, the muscles can become so weak that the person cannot rise from the squatting position. And the immunity functions of the lymphoid tissue can be decreased to a small fraction of normal.

Cortisol Increases Liver and Plasma Proteins

Coincidentally with the reduced proteins elsewhere in the body, the liver proteins become enhanced. Furthermore, the plasma proteins (which are produced by the liver and then released into the blood) are also increased. These increases are exceptions to the protein depletion that occurs elsewhere in the body. It is believed that this difference results from a possible effect of

cortisol to enhance amino acid transport into liver cells (but not into most other cells) and to enhance the liver enzymes required for protein synthesis.

Effects of Cortisol on Fat Metabolism

Mobilization of Fatty Acids

Cortisol promotes amino acid mobilization from muscle, it promotes mobilization of fatty acids from adipose tissue. This increases the concentration of free fatty acids in the plasma, which also increases their utilization for energy.

The increased use of fatty acids for metabolic energy is an important factor for long-term conservation of body glucose and glycogen.

Obesity Caused by Excess Cortisol

Cortisol can cause a moderate degree of fatty acid mobilization from adipose tissue, many people with excess cortisol secretion develop a peculiar type of obesity, with excess deposition of fat in the chest and head regions of the body, and a rounded “moon face.” It has been suggested that this obesity results from excess stimulation of food intake, with fat being generated in some tissues of the body more rapidly than it is mobilized and oxidized.

Cortisol is Important in Resisting Stress and Inflammation

Almost any type of stress, causes an immediate and marked increase in ACTH secretion by the anterior pituitary gland, followed within minutes by greatly increased adrenocortical secretion of cortisol. Corticosteroid formation and secretion increased sixfold in a rat within 4 to 20 minutes after fracture of two leg bones.

Cortisol secretion often increases greatly in stressful situations. One possibility is that the glucocorticoids cause rapid mobilization of amino acids and fats from their cellular stores, making them immediately available both for energy and for synthesis of other compounds, including glucose, needed by the different tissues of the body.

Anti-inflammatory Effects of High Levels of Cortisol

When tissues are damaged by trauma, by infection with bacteria, or in other ways, they almost always become “inflamed.” The administration of large amounts of cortisol can usually block this inflammation or even reverse many of its effects once it has begun.

There are five main stages of inflammation: (1) release from the damaged tissue cells of chemical substances that activate the inflammation process- chemicals such as histamine, bradykinin, proteolytic enzymes, prostaglandins, and leukotrienes; (2) an increase in blood flow in the inflamed area caused by some of the released products from the tissues, an effect called erythema; (3) leakage of large quantities of almost pure plasma out of the capillaries into the damaged areas because of increased capillary perme- ability, followed by clotting of the tissue fluid, thus causing a nonpitting type of edema; (4) infiltration of the area by leukocytes; and (5) after days or weeks, ingrowth of fibrous tissue that often helps in the healing process.

When large amounts of cortisol are secreted or injected into a person, the cortisol has two basic anti-inflammatory effects: (1) it can block the early stages of the inflammation process before inflammation even begins, or (2) if inflammation has already begun, it causes rapid resolution of the inflammation and increased rapidity of healing.

Cortisol Prevents the Development of Inflammation by Stabilizing Lysosomes and by Other Effects

Cortisol has the following effects in preventing inflammation: 1. Cortisol stabilizes the lysosomal membranes. This is one of its most important anti-inflammatory effects, because it is much more difficult than normal for the membranes of the intracellular lysosomes to rupture. Therefore, most of the proteolytic enzymes that are released by damaged cells to cause inflammation, which are mainly stored in the lysosomes, are released in greatly decreased quantity. 2. Cortisol decreases the permeability of the capillaries. This prevents loss of plasma into the tissues. 3. Cortisol decreases both migration of white blood cells into the inflamed area and phagocytosis of the damaged cells. These effects probably result from the fact that cortisol diminishes the formation of prostaglandins and leukotrienes that otherwise would increase vasodilation, capillary permeability, and mobility of white blood cells. 4. Cortisol suppresses the

immune system, causing lymphocyte reproduction to decrease markedly. The T lymphocytes are especially suppressed. In turn, reduced amounts of T cells and antibodies in the inflamed area lessen the tissue reactions that would otherwise promote the inflammation process. 5. Cortisol attenuates fever mainly because it reduces the release of interleukin-1 from the white blood cells, which is one of the principal excitants to the hypothalamic temperature control system. The decreased temperature in turn reduces the degree of vasodilation.

Cortisol Causes Resolution of Inflammation

Even after inflammation has become well established, the administration of cortisol can often reduce inflammation within hours to a few days. The immediate effect is to block most of the factors that are promoting the inflammation. But in addition, the rate of healing is enhanced.

Other Effects of Cortisol

Cortisol Blocks the Inflammatory Response to Allergic Reactions

The basic allergic reaction between antigen and anti-body is not affected by cortisol, and even some of the secondary effects of the allergic reaction still occur. However, because the inflammatory response is responsible for many of the serious and sometimes lethal effects of allergic reactions, administration of cortisol, followed by its effect in reducing inflammation and the release of inflammatory products, can be lifesaving.

Effect on Blood Cells and on Immunity in Infectious Diseases.

Cortisol decreases the number of eosinophils and lymphocytes in the blood; this effect begins within a few minutes after the injection of cortisol and becomes marked within a few hours. Indeed, a finding of lymphocytopenia or eosinopenia is an important diagnostic criterion for overproduction of cortisol by the adrenal gland.

As a result, the level of immunity for almost all foreign invaders of the body is decreased. This occasionally can lead to fulminating infection and death from diseases that would otherwise not be lethal. Conversely, this ability of cortisol and other glucocorticoids to suppress immunity makes them useful drugs in preventing immunological rejection of transplanted hearts, kidneys, and other tissues.

100. Adrenal medulla. Synthesis of catecholamines.

Function of the Adrenal Medullae

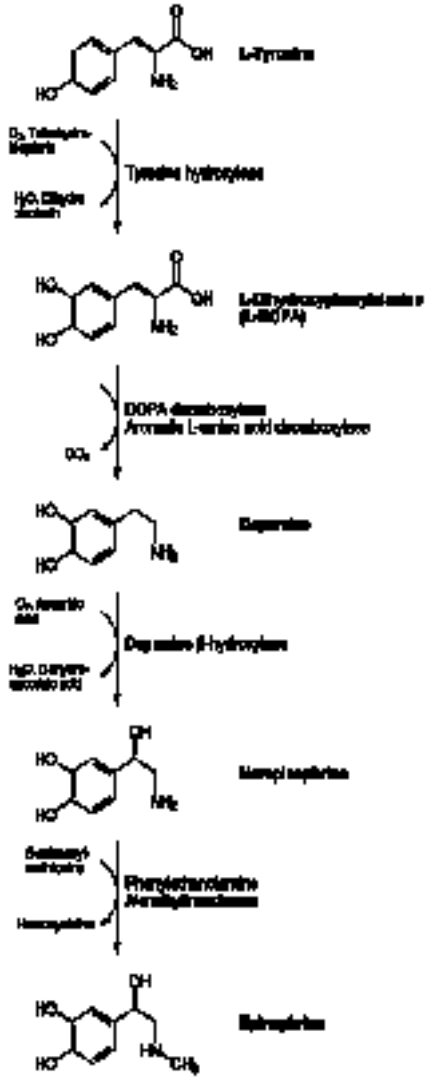
Stimulation of the sympathetic nerves to the adrenal medullae causes large quantities of epinephrine and norepinephrine to be released into the circulating blood, and these two hormones in turn are carried in the blood to all tissues of the body.

The circulating epinephrine and norepinephrine have almost the same effects on the different organs as the effects caused by direct sympathetic stimulation, except that the effects last 5 to 10 times as long because both of these hormones are removed from the blood slowly.

The circulating norepinephrine causes constriction of essentially all the blood vessels of the body; it also causes increased activity of the heart, inhibition of the gastrointestinal tract, dilation of the pupils of the eyes, and so forth.

Epinephrine causes almost the same effects as those caused by norepinephrine, but the effects differ in the following respects: First, epinephrine, because of its greater effect in stimulating the beta receptors, has a greater effect on cardiac stimulation than does norepinephrine. Second, epinephrine causes only weak constriction of the blood vessels in the muscles, in comparison with much stronger constriction caused by norepinephrine.

A third difference between the actions of epinephrine and norepinephrine relates to their effects on tissue metabolism. Epinephrine has 5 to 10 times as great a metabolic effect as norepinephrine. Indeed, the epinephrine secreted by the adrenal medullae can increase the metabolic rate of the whole body often to as much as 100% above normal. It also increases the rates of other metabolic activities, such as glycogenolysis in the liver and muscle, and glucose release into the blood.



<u>Value of the Adrenal Medullae to the Function of the Sympathetic Nervous System</u>

Epinephrine and norepinephrine are almost always released by the adrenal medullae at the same time that the different organs are stimulated directly by generalized sympathetic activation. Therefore, the organs are actually stimulated in two ways: directly by the sympathetic nerves and indirectly by the adrenal medullary hormones. The two means of stimulation support each other, and either can, in most instances, substitute for the other. Another important value of the adrenal medullae is the capability of epinephrine and norepinephrine to stimulate structures of the body that are not innervated by direct sympathetic fibers.

Synthesis of cathecholamines

Dopamine is the first catecholamine to be synthesized from steps shown. Norepinephrine and epinephrine, in turn, are derived from further modifications of dopamine. Synthesis of norepinephrine begins in the axoplasm of the terminal nerve endings of adrenergic nerve fibers but is completed inside the secretory vesicles. It is important to note that the enzyme dopamine hydroxylase requires copper as a cofactor and DOPA decarboxylase requires PLP . The rate limiting step in the biosynthesis is hydroxylation of tyrosine.

101. Hypothalamo-pituitary system

Hypothalamus Controls Pituitary Secretion

Almost all secretion by the pituitary is controlled by either hormonal or nervous signals from the hypothalamus.

Secretion from the posterior pituitary is controlled by nerve signals that originate in the hypothalamus and terminate in the posterior pituitary. In contrast, secretion by the anterior pituitary is controlled by hormones called hypothalamic releasing and hypothalamic inhibitory hormones (or factors) secreted within the hypothalamus itself and then conducted, to the anterior pituitary through minute blood vessels called hypothalamic-hypophysial portal vessels. In the anterior pituitary, these releasing and inhibitory hormones act on the glandular cells to control their secretion.

The hypothalamus receives signals from many sources in the nervous system. Even the concentrations of nutrients, electrolytes, water, and various hormones in the blood excite or inhibit various portions of the hypothalamus. Thus, the hypothalamus is a collecting center for information concerning the internal well-being of the body, and much of this information is used to control secretions of the many globally important pituitary hormones.

Physiological Actions

- Stimulates body growth; stimulates secretion of IGF-1; stimulates lipolysis; inhibits actions of insulin on carbohydrate and lipid metabolism
- Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
- Stimulates production of thyroid hormones by thyroid follicular cells; maintains size of follicular cells
- Stimulates development of ovarian follicles; regulates spermatogenesis in the testis
- Causes ovulation and formation of the corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
- Stimulates milk secretion and production

Hypothalamic-Hypophysial Portal Blood Vessels of the Anterior Pituitary Gland

The anterior pituitary is a highly vascular gland with extensive capillary sinuses among the glandular cells. Almost all the blood that enters these sinuses passes first through another capillary bed in the lower hypothalamus. The blood then flows through small hypothalamic-hypophysial portal blood vessels into the anterior pituitary sinuses. The median eminence connects inferiorly with the pituitary stalk. Small arteries penetrate into the substance of the median eminence and then additional small vessels return to its surface, coalescing to form the hypothalamic-hypophysial portal blood vessels. These pass downward along the pituitary stalk to supply blood to the anterior pituitary sinuses.

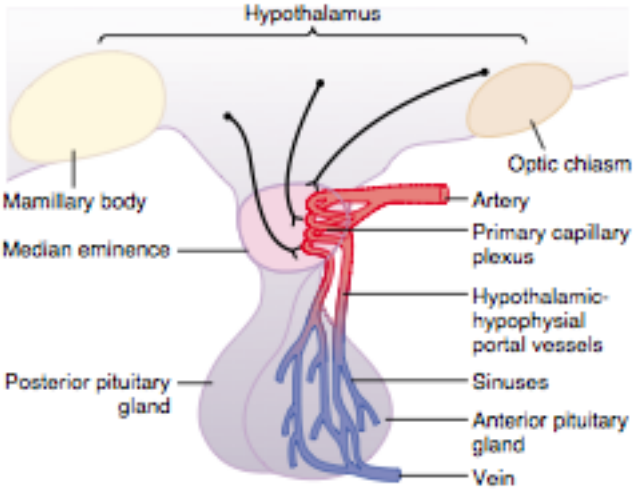
Hypothalamic Releasing and Inhibitory Hormones Are Secreted into the Median Eminence

Special neurons in the hypothalamus synthesize and secrete the hypothalamic releasing and inhibitory hormones that control secretion of the anterior pituitary hormones. These neurons originate in various parts of the hypothalamus and send their nerve fibers to the median eminence and tuber cinereum, an extension of hypothalamic tissue into the pituitary stalk.

The endings of these fibers are different from most endings in the central nervous system, in that their function is not to transmit signals from one neuron to another but rather to secrete the hypothalamic releasing and inhibitory hormones into the tissue fluids. These hormones are immediately absorbed into the hypothalamic-hypophysial portal system and carried directly to the sinuses of the anterior pituitary gland.

102. Glandotropic hormones of anterior pituitary gland

Anterior Pituitary Gland Contains Several Different Cell Types That Synthesize and Secrete Hormones



Usually, there is one cell type for each major hormone formed in the anterior pituitary gland.

There are five cell types in the anterior pituitary cells:

1. Somatotropes—human growth hormone (hGH)
2. Corticotropes—adrenocorticotropin (ACTH)
3. Thyrotropes—thyroid-stimulating hormone (TSH)
4. Gonadotropes—gonadotropic hormones, which include both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) 5. Lactotropes—prolactin (PRL)

About 30 to 40% of the anterior pituitary cells are somatotropes that secrete growth hormone, and about 20% are corticotropes that secrete ACTH. Each of the other cell types accounts for only 3 to 5% of the total; nevertheless, they secrete powerful hormones for controlling thyroid function, sexual functions, and milk secretion by the breasts.

Cells and Hormones of the Anterior Pituitary Gland and Their Physiological Functions

Cell	Hormone	Chemistry	Physiological Action
Somatotropes	Growth hormone (GH; somatotropin)	Single chain of 191 amino acids	Stimulates body growth; stimulates secretion of IGF-1; stimulates lipolysis; inhibits action of insulin on carbohydrate and lipid metabolism
Corticotropes	Adrenocorticotropic hormone (ACTH; corticotropin)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (TSH; thyrotropin)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acid)	Stimulates production of thyroid hormones by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acid)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis
	Luteinizing hormone (LH)	Glycoprotein of two subunits, α (89 amino acids) and β (115 amino acid)	Causes ovulation and formation of the corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Lactotropes, Mammotropes	Prolactin (PRL)	Single chain of 198 amino acids	Stimulates milk secretion and production

IGF, insulin-like growth factor

103. Growth hormone and growth factors (IGF)

Physiological Functions of Growth Hormone

Growth hormone, does not function through a target gland but exerts its effects directly on all or almost all tissues of the body.

Growth Hormone Promotes Growth of Many Body Tissues

Growth hormone, also called somatotropic hormone or somatotropin causes growth of almost all tissues of the body that are capable of growing. It promotes increased sizes of the cells and increased mitosis, with development of greater numbers of cells and specific differentiation of certain types of cells such as bone growth cells and early muscle cells.

Growth Hormone Has Several Metabolic Effects

Aside from its general effect in causing growth, growth hormone has multiple specific metabolic effects, including (1) increased rate of protein synthesis in most cells of the body; (2) increased mobilization of fatty acids from adipose tissue, increased free fatty acids in the blood, and increased use of fatty acids for energy; and (3) decreased rate of glucose utilization throughout the body. Thus, in effect, growth hormone enhances body protein, uses up fat stores, and conserves carbohydrates.

Growth Hormone Promotes Protein Deposition in Tissues

Enhancement of Amino Acid Transport Through the Cell Membranes

Growth hormone directly enhances transport of at least some and perhaps most amino acids through the cell membranes to the interior of the cells. This increases the amino acid concentrations in the cells and is presumed to be at least partly responsible for the increased protein synthesis. This control of amino acid transport is similar to the effect of insulin in controlling glucose transport through the membrane.

Enhancement of RNA Translation to Cause Protein Synthesis by the Ribosomes

Even when the amino acid concentrations are not increased in the cells, growth hormone still increases RNA translation, causing protein to be synthesized in greater amounts by the ribosomes in the cytoplasm.

Increased Nuclear Transcription of DNA to Form RNA

Over more prolonged periods (24 to 48 hours), growth hormone also stimulates the transcription of DNA in the nucleus, causing the formation of increased quantities of RNA. This promotes more protein synthesis and promotes growth if sufficient energy, amino acids, vitamins, and other requisites for growth are available. In the long run, this may be the most important function of growth hormone.

Decreased Catabolism of Protein and Amino Acids

In addition to the increase in protein synthesis, there is a decrease in the breakdown of cell protein. A probable reason for this is that growth hormone also mobilizes large quantities of free fatty acids from the adipose tissue, and these are used to supply most of the energy for the body's cells, thus acting as a potent "protein sparer."

Growth Hormone Enhances Fat Utilization for Energy

Growth hormone has a specific effect in causing the release of fatty acids from adipose tissue and, therefore, increasing the concentration of fatty acids in the body fluids. In addition, in tissues throughout the body, growth hormone enhances the conversion of fatty acids to acetyl coenzyme A (acetyl-CoA) and its subsequent utilization for energy. Therefore, under the influence of growth hormone, fat is used for energy in preference to the use of carbohydrates and proteins.

Growth hormone's ability to promote fat utilization, together with its protein anabolic effect, causes an increase in lean body mass. However, mobilization of fat by growth hormone requires

several hours to occur, whereas enhancement of protein synthesis can begin in minutes under the influence of growth hormone.

"Ketogenic" Effect of Growth Hormone

Under the influence of excessive amounts of growth hormone, fat mobilization from adipose tissue sometimes becomes so great that large quantities of acetoacetic acid are formed by the liver and released into the body fluids, thus causing ketosis. This excessive mobilization of fat from the adipose tissue also frequently causes a fatty liver.

Growth Hormone Decreases Carbohydrate Utilization

Growth hormone causes multiple effects that influence carbohydrate metabolism, including (1) decreased glucose uptake in tissues such as skeletal muscle and fat, (2) increased glucose production by the liver, and (3) increased insulin secretion.

Each of these changes results from growth hormone–induced "insulin resistance," which attenuates insulin's actions. For these reasons, growth hormone's effects are called diabetogenic, and excess secretion of growth hormone can produce metabolic disturbances very similar to those found in patients with type II (non-insulin-dependent) diabetes, who are also very resistant to the metabolic effects of insulin.

We do not know the precise mechanism by which growth hormone causes insulin resistance and decreased glucose utilization by the cells. However, growth hormone–induced increases in blood concentrations of fatty acids may impair insulin's actions on tissue glucose utilization.

Necessity of Insulin and Carbohydrate for the Growth-Promoting Action of Growth Hormone

Adequate insulin activity and adequate availability of carbohydrates are necessary for growth hormone to be effective. Part of this requirement for carbohydrates and insulin is to provide the energy needed for the metabolism of growth, but there seem to be other effects as well. Especially important is insulin's ability to enhance the transport of some amino acids into cells, in the same way that it stimulates glucose transport.

Growth Hormone Stimulates Cartilage and Bone Growth

Although growth hormone stimulates increased deposition of protein and increased growth in almost all tissues of the body, its most obvious effect is to increase growth of the skeletal frame. This results from multiple effects of growth hormone on bone, including (1) increased deposition of protein by the chondrocytic and osteogenic cells that cause bone growth, (2) increased rate of reproduction of these cells, and (3) a specific effect of converting chondrocytes into osteogenic cells, thus causing deposition of new bone.

There are two principal mechanisms of bone growth. First, in response to growth hormone stimulation, the long bones grow in length at the epiphyseal cartilages, where the epiphyses at the ends of the bone are separated from the shaft. This growth first causes deposition of new cartilage, followed by its conversion into new bone, thus elongating the shaft and pushing the epiphyses farther and farther apart. At the same time, the epiphyseal cartilage itself is progressively used up, so that by late adolescence, no additional epiphyseal cartilage remains to provide for further long bone growth. At this time, bony fusion occurs between the shaft and the epiphysis at each end, so that no further lengthening of the long bone can occur.

Second, osteoblasts in the bone periosteum and in some bone cavities deposit new bone on the surfaces of older bone. Simultaneously, osteoclasts in the bone remove old bone. When the rate of deposition is greater than that of resorption, the thickness of the bone increases.

Growth Hormone Exerts Much of Its Effect Through Intermediate Substances Called "Somatomedins" (Also Called "Insulin-Like Growth Factors")

It has been found that growth hormone causes the liver (and, to a much less extent, other tissues) to form several small proteins called somatomedins that have the potent effect of increasing all aspects of bone growth. Many of the somatomedin effects on growth are similar to the effects of insulin on growth. Therefore, the somatomedins are also called insulin-like growth factors (IGFs).

At least four somatomedins have been isolated, but by far the most important of these is somatomedin C.

It has been postulated that most, if not all, of the growth effects of growth hormone result from somatomedin C and other somatomedins, rather than from direct effects of growth hormone on the bones and other peripheral tissues.

Short Duration of Action of Growth Hormone but Prolonged Action of Somatomedin C

Growth hormone attaches only weakly to the plasma proteins in the blood. Therefore, it is released from the blood into the tissues rapidly. By contrast, somatomedin C attaches strongly to a carrier protein in the blood that, like somatomedin C, is produced in response to growth hormone.

As a result, somatomedin C is released only slowly from the blood to the tissues. This greatly prolongs the growth-promoting effects of the bursts of growth hormone secretion.

Regulation of Growth Hormone Secretion

After adolescence, secretion decreases slowly with aging, finally falling to about 25% of the adolescent level in very old age.

Growth hormone is secreted in a pulsatile pattern, increasing and decreasing. The precise mechanisms that control secretion of growth hormone are not fully understood, but several factors related to a person's state of nutrition or stress are known to stimulate secretion: (1) starvation, especially with severe protein deficiency; (2) hypoglycemia or low concentration of fatty acids in the blood; (3) exercise; (4) excitement; and (5) trauma. Growth hormone also characteristically increases during the first 2 hours of deep sleep.

Role of the Hypothalamus, Growth Hormone–Releasing Hormone, and Somatostatin in the Control of Growth Hormone Secretion

It is known that growth hormone secretion is controlled by two factors secreted in the hypothalamus and then transported to the anterior pituitary gland through the hypothalamic-hypophysial portal vessels. They are growth hormone–releasing hormone and growth hormone inhibitory hormone (also called somatostatin).

The part of the hypothalamus that causes secretion of GHRH is the ventromedial nucleus; this is the same area of the hypothalamus that is sensitive to blood glucose concentration, causing satiety in hyperglycemic states and hunger in hypoglycemic states. The secretion of somatostatin is controlled by other nearby areas of the hypothalamus. Therefore, it is reasonable to believe that some of the same signals that modify a person's behavioral feeding instincts also alter the rate of growth hormone secretion.

In a similar manner, hypothalamic signals depicting emotions, stress, and trauma can all affect hypothalamic control of growth hormone secretion.

Most of the control of growth hormone secretion is probably mediated through GHRH rather than through the inhibitory hormone somatostatin. GHRH stimulates growth hormone secretion by attaching to specific cell membrane receptors on the outer surfaces of the growth hormone cells in the pituitary gland. The receptors activate the adenylyl cyclase system inside the cell membrane, increasing the intracellular level of cyclic adenosine monophosphate (cAMP).

104. Formation and secretion of posterior pituitary hormones

Posterior Pituitary Gland and Its Relation to the Hypothalamus

The posterior pituitary gland, also called the neurohypophysis, is composed mainly of glial-like cells called pituicytes. The pituicytes do not secrete hormones; they act simply as a supporting structure for large numbers of terminal nerve fibers and terminal nerve endings from nerve tracts that originate in the supraoptic and paraventricular nuclei of the hypothalamus. These tracts pass to the neurohypophysis through the pituitary stalk (hypophysial stalk). The nerve endings are bulbous knobs that contain many secretory granules. These endings lie on the surfaces of capillaries, where they secrete two posterior pituitary hormones: (1) antidiuretic hormone (ADH), also called vasopressin, and (2) oxytocin. The hormones are initially synthesized in the cell bodies of the supraoptic and paraventricular nuclei and are then transported in combination with "carrier" proteins called neurophysins down to the nerve endings in the posterior pituitary gland, requiring several days to reach the gland.

ADH is formed primarily in the supraoptic nuclei, whereas oxytocin is formed primarily in the paraventricular nuclei. When nerve impulses are transmitted downward along the fibers from the supraoptic or paraventricular nuclei, the hormone is immediately released from the secretory granules in the nerve endings by the usual secretory mechanism of exocytosis and is absorbed into adjacent capillaries. Both the neurophysin and the hormone are secreted together, but because they are only loosely bound to each other, the hormone separates almost immediately.

The neurophysin has no known function after leaving the nerve terminals.

Physiological Functions of ADH

The injection of extremely minute quantities of ADH—as small as 2 nanograms—can cause decreased excretion of water by the kidneys (antidiuresis). Briefly, in the absence of ADH, the collecting tubules and ducts become almost impermeable to water, which prevents significant reabsorption of water and therefore allows extreme loss of water into the urine, also causing extreme dilution of the urine. Conversely, in the presence of ADH, the permeability of the collecting ducts and tubules to water increases greatly and allows most of the water to be reabsorbed as the tubular fluid passes through these ducts, thereby conserving water in the body and producing very concentrated urine.

The precise mechanism by which ADH acts on the collecting ducts to increase their permeability is only partially known. Without ADH, the luminal membranes of the tubular epithelial cells of the collecting ducts are almost impermeable to water. However, immediately inside the cell membrane are a large number of special vesicles that have highly waterpermeable pores called aquaporins. When ADH acts on the cell, it first combines with membrane receptors that activate adenylyl cyclase and cause the formation of cAMP inside the tubular cell cytoplasm. This causes phosphorylation of elements in the special vesicles, which then causes the vesicles to insert into the apical cell membranes, thus providing many areas of high water permeability. Then, in the absence of ADH, the entire process reverses in another 5 to 10 minutes.

Regulation of ADH Production

<u>Osmotic Regulation</u>

The concentration of ADH in the body fluids can change from small amounts to large amounts, or vice versa, in only a few minutes. The precise way that the osmotic concentration of the extracellular fluid controls ADH secretion is not clear. Yet somewhere in or near the hypothalamus are modified neuron receptors called osmoreceptors. When the extracellular fluid becomes too concentrated, fluid is pulled by osmosis out of the osmoreceptor cell, decreasing its size and initiating appropriate nerve signals in the hypothalamus to cause additional ADH secretion. Conversely, when the extracellular fluid becomes too dilute, water moves by osmosis in the opposite direction, into the cell, and this decreases the signal for ADH secretion. Although some researchers place these osmoreceptors in the hypothalamus itself (possibly even in the supraoptic nuclei), others believe that they are located in the organum vasculosum, a highly vascular structure in the anteroventral wall of the third ventricle.

Regardless of the mechanism, concentrated body fluids stimulate the supraoptic nuclei, whereas dilute body fluids inhibit them. A feedback control system is available to control the total osmotic pressure of the body fluids.

Vasoconstrictor and Pressor Effects of ADH, and Increased ADH Secretion Caused by Low Blood Volume

Higher concentrations of ADH have a potent effect of constricting the arterioles throughout the body and therefore increasing the arterial pressure. For this reason, ADH has another name, vasopressin.

One of the stimuli for causing intense ADH secretion is decreased blood volume. The atria have stretch receptors that are excited by overfilling. When excited, they send signals to the brain to inhibit ADH secretion. Conversely, when the receptors are unexcited as a result of underfilling, the opposite occurs, with greatly increased ADH secretion. Decreased stretch of the baroreceptors of the carotid, aortic, and pulmonary regions also stimulates ADH secretion.

Oxytocic Hormone

Oxytocin Causes Contraction of the Pregnant Uterus

The hormone oxytocin, in accordance with its name, powerfully stimulates contraction of the pregnant uterus, especially toward the end of gestation. Therefore, many obstetricians believe that this hormone is at least partially responsible for causing birth of the baby.

Oxytocin Aids in Milk Ejection by the Breasts

Oxytocin also plays an especially important role in lactation—a role that is far better understood than its role in delivery. In lactation, oxytocin causes milk to be expressed from the alveoli into the ducts of the breast so that the baby can obtain it by suckling.

This mechanism works as follows: The suckling stimulus on the nipple of the breast causes signals to be transmitted through sensory nerves to the oxytocin neurons in the paraventricular and supraoptic nuclei in the hypothalamus, which causes release of oxytocin by the posterior pituitary gland. The oxytocin is then carried by the blood to the breasts, where it causes contraction of myoepithelial cells that lie outside of and form a latticework surrounding the alveoli of the mammary glands. In less than a minute after the beginning of suckling, milk begins to flow. This mechanism is called milk letdown or milk ejection.

105. Hypothalamic releasing hormones

Almost all secretion by the pituitary is controlled by either hormonal or nervous signals from the hypothalamus. Secretion by the anterior pituitary is controlled by hormones called hypothalamic releasing and hypothalamic inhibitory hormones (or factors) secreted within the hypothalamus itself and then conducted, to the anterior pituitary through minute blood vessels called hypothalamic-hypophysial portal vessels. In the anterior pituitary, these releasing and inhibitory hormones act on the glandular cells to control their secretion. The hypothalamus receives signals from many sources in the nervous system. Even the concentrations of nutrients, electrolytes, water, and various hormones in the blood excite or inhibit various portions of the hypo- thalamus. Thus, the hypothalamus is a collecting center for information concerning the internal well-being of the body, and much of this information is used to control secretions of the many globally important pituitary hormones.

Hypothalamic Releasing and Inhibitory Hormones Control Anterior Pituitary Secretion

The function of the releasing and inhibitory hormones is to control secretion of the anterior pituitary hormones. For most of the anterior pituitary hormones, it is the releasing hormones that are important, but for prolactin, a hypothalamic inhibitory hormone probably exerts more control. The major hypothalamic releasing and inhibitory hormones are the following:

1. Thyrotropin-releasing hormone (TRH), which causes release of thyroid-stimulating hormone
2. Corticotropin-releasing hormone (CRH), which causes release of adrenocorticotropin
3. Growth hormone–releasing hormone (GHRH), which causes release of growth hormone, and growth hormone inhibitory hormone (GHIH), also called somatostatin, which inhibits release of growth hormone
4. Gonadotropin-releasing hormone (GnRH), which causes release of the two gonadotropic hormones, luteinizing hormone and follicle-stimulating hormone.
5. Prolactin inhibitory hormone (PIH), which causes inhibition of prolactin secretion

There are some additional hypothalamic hormones, including one that stimulates prolactin secretion and perhaps others that inhibit release of the anterior pituitary hormones.

Specific Areas in the Hypothalamus Control Secretion of Specific Hypothalamic Releasing and Inhibitory Hormones

All or most of the hypothalamic hormones are secreted at nerve endings in the median eminence before being transported to the anterior pituitary gland. Electrical stimulation of this region excites these nerve endings and, therefore, causes release of essentially all the hypothalamic hormones. However, the neuronal cell bodies that give rise to these median eminence nerve endings are located in other discrete areas of the hypothalamus or in closely related areas of the basal brain. The specific loci of the neuronal cell bodies that form the different hypothalamic releasing or inhibitory hormones are still poorly known, so that it would be misleading to attempt delineation here.

106. Parathormone, vitamin D and calcitonin

Three hormones are primarily concerned with the regulation of calcium. 1,25-Dihydroxycholecalciferol is a steroid hormone formed from vitamin D by successive hydroxylation in the liver and kidneys. Its primary action is to increase calcium absorption from the intestine.

Parathyroid hormone (PTH) is secreted by the parathyroid glands. Its main action is to mobilize calcium from bone and increase urinary phosphate excretion. Calcitonin, a calcium-lowering hormone that in mammals is secreted primarily by cells in the thyroid gland, inhibits bone reabsorption.

Parathyroid hormone (PTH)

- Is the major hormone for the regulation of serum [Ca2+].
- Is synthesized and secreted by the chief cells of the parathyroid glands.

1. Secretion of PTH

- is controlled by serum [Ca2+] through negative feedback. Decreased serum [Ca2+] increases PTH secretion.
- Mild decreases in serum [Mg2+] stimulate PTH secretion.
- Severe secretion in serum [Mg2+] inhibit PTH secretion and produce symptoms of hypoparathyroidism (e.g., hypocalcemia).
- The second messenger for PTH secretion by the parathyroid gland is cAMP.

2. Actions of PTH

- Is coordinated to produce an increase in serum [Ca2+] and a decrease in serum [phosphate].
- The second messenger for PTH actions on its target tissues is cAMP.

a. PTH increases bone resorption, which brings both Ca2+ and phosphate from the bone mineral into the ECF. Alone, this effect on bone would not increase the serum ionized [Ca2+] because phosphate complexes Ca2+.

- Resorption of the organic matrix of bone is reflected in increased hydroxyproline excretion.

b. PTH inhibits renal phosphate reabsorption in the proximal tubule and, therefore, increases phosphate excretion (phosphaturic effect). As a result, the phosphate resorbed from bone is excreted in the urine, allowing the serum ionized [Ca2+] to increase.

- cAMP generated as a result of the action of PTH on the proximal tubule is excreted in the urine (urinary cAMP).

c. PTH increases renal Ca2+ reabsorption in the distal tubule. Which also increases the serum [Ca2+].

d. PTH increases intestinal Ca2+ absorption indirectly by stimulating the production of 1.25-dihydrocholecalciferol in the kidney.

Vitamin D

- Provides Ca2+ and phosphate to ECF for bone mineralization
- In children, vitamin D deficiency causes rickets.
- In adults, vitamin D deficiency causes osteomalacia.

1. Vitamin D metabolism

- The active form of vitamin D is 1,25-dihydroxycholecalciferol.
- The production of 1,25-dihydroxycholecalciferol in the kidney is catalyzed by the enzyme 1α-hydroxylase.
- 1α-hydroxylase activity is increased by the following:

a. decreased serum [Ca2+]
b. increased PTH levels
c. decreased serum [phosphate]

2. Actions of 1,25-dihydroxycholecalciferol

- are coordinated to increase both [Ca2+] and [phosphate] in ECF to mineralize new bone.

a. Increases intestinal Ca2+ absorption. Vitamin D-dependent Ca2+-binding protein (calbindin D-28K) is induced by 1,25-dihydroxycholecalciferol. > PTH increases intestinal Ca2+ absorption indirectly by stimulating 1α-hydroxylase and increasing production of the active form of vitamin D.
b. Increases intestinal phosphate absorption.
c. Increases renal reabsorption of Ca2+ and phosphate
d. Increase bone resorption, which provides Ca2+ and phosphate from “old” bone to mineralize “new” bone.

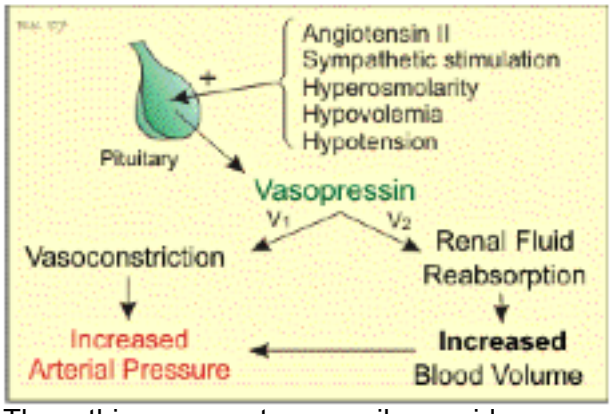
Calcitonin

- is synthesized and secreted by the parafollicular cells of the thyroid.
- secretion is stimulated by an increase in serum [Ca2+]
- acts primarily to inhibit bone resorption. can be used to treat hypercalcemia.

107. Vasopressin and natriuretic hormone

Physiological Functions of ADH

The injection of extremely minute quantities of ADH—as small as 2 nanograms—can cause decreased excretion of water by the kidneys (antidiuresis). Briefly, in the absence of ADH, the collecting tubules and ducts become almost impermeable to water, which prevents significant reabsorption of water and therefore allows extreme loss of water into the urine, also causing extreme dilution of the urine. Conversely, in the presence of ADH, the permeability of the collecting ducts and tubules to water increases greatly and allows most of the water to be reabsorbed as the tubular fluid passes through these ducts, thereby conserving water in the body and producing very concentrated urine.



Immediately inside the cell membrane are a large number of special vesicles that have highly water-permeable pores called aquaporins. When ADH acts on the cell, it first combines with membrane receptors that activate adenylyl cyclase and cause the formation of cAMP inside the tubular cell cytoplasm. This causes phosphorylation of elements in the special vesicles, which then causes the vesicles to insert into the apical cell membranes, thus providing many areas of high water permeability. Then, in the absence of ADH, the entire process reverses. Thus, this process temporarily provides many new pores that allow free diffusion of water from the tubular fluid through the tubular epithelial cells and into the renal interstitial fluid. Water is then absorbed from the collecting tubules and ducts by osmosis.

Regulation of ADH Production

Osmotic Regulation

The concentration of ADH in the body fluids can change from small amounts to large amounts, or vice versa, in only a few minutes.

Tubular Fluid in Distal and Collecting Tubules Is Further Diluted in the Absence of ADH

As the dilute fluid in the early distal tubule passes into the late distal convoluted tubule, cortical collecting duct, and collecting duct, there is additional reabsorption of sodium chloride. In the absence of ADH, this portion of the tubule is also impermeable to water, and the additional reabsorption of solutes causes the tubular fluid to become even more dilute. The failure to reabsorb water and the con- tinued reabsorption of solutes lead to a large volume of dilute urine.

The basic requirements for forming a concentrated urine are (1) a high level of ADH, which increases the permeability of the distal tubules and collecting ducts to water, thereby allowing these tubular segments to avidly reabsorb water, and (2) a high osmolarity of the renal medullary interstitial fluid, which provides the osmotic gradient necessary for water reabsorption to occur in the presence of high levels of ADH. The renal medullary interstitium surrounding the collecting ducts normally is very hyperosmotic, so that when ADH levels are high, water moves through the tubular membrane by osmosis into the renal intersti- tium; from there it is carried away by the vasa recta back into the blood.

Natriuretic Peptides

Two of these are secreted by the heart. The muscle cells in the atria and, to a much lesser extent, in the ventricles contain secretory granules. The granules increase in number when NaCl intake is increased and extracellular fluid expanded, and extracts of arterial tissue cause natriuresis.

The first natriuretic hormone isolated from the heart was atrial natriuretic peptide (ANP), a polypeptide with 17-amino-acid ring formed by a disulfide bond between two cysteines. The

circulating form of this polypeptide has 28 amino acid residues. ANP was subsequently isolated from other tissues, including the brain, where it exists in two forms that are smaller than the circulating ANP. A second natriuretic polypeptide was isolated from the porcine brain and named brain natriuretic peptide (BNP; also known as B-type natriuretic peptide). It is also present in the brain in humans, but more is present in the heart. A third member of this family has been named C-type natriuretic peptide (CNP) because it was the third in the sequence to be isolated. CNP is present in the brain, the pituitary, the kidneys, and vascular endothelial cells. However, very little is present in the heart and the circulation, and it appears to be primarily a paracrine mediator.

Actions ANP and BNP in the circulation act on the kidneys to increase Na+ excretion, and injected CNP has a similar effect. They appear to produce this effect by dilating afferent arterioles ad relaxing mesangial cells. Both of this actions increase the glomerular filtration. In addition, they act on the renal tubules to inhibit Na+ reabsorption. Other actions include an increase in capillary permeability, leading to extravasation of fluid and a decline in blood pressure. CNP has the greatest dilator effect on veins. These peptides also inhibit rennin secretion and counteract the pressor effects of cathecholamines and angiotensin II.

In the brain, ANP is present in neurons. In general, the effects of ANP in the brain are opposite to those of angiotensin II, and ANP-containing neural circuits appear to be involved in lowering blood pressure and promoting natriuresis.

Natriuretic Peptide Receptors

Three different natriuretic peptide receptors (NPR) have been isolated and characterized. The NPR-A and NPR-B receptors both span the cell membrane and have cytoplasmic domains that are guanylyl cyclases. ANP has greatest affinity for the NPR-A receptor, and CNP has the greatest affinity for the NPR-B receptor. The third receptor, NPR-C, binds all three peptides but has a markedly shortened cytoplasmic domain. Some evidence suggests that it acts via G-proteins to activate phospholipase C and inhibit adenylyl cyclase. However, it has also been argued that this receptor does not trigger any intracellular change and instead a clearance receptor that removes natriuretic peptides from the blood stream and then releases them later, helping to maintain a steady blood level of the hormones.

Secretion & Metabolism

ANP secretion is increased when the ECF volume is increased by infusion of isotonic saline and when atria are stretched. BNP secretion is increased when ventricles are stretched. ANP secretion is also increased by immersion in water up to the neck, a procedure that counteracts the effect of gravity on the circulation and increases central venous and consequently atrial pressure. Plasma levels of both hormones are elevated in congestive heart failure.

Circulating ANP has a short half-life. It is metabolized by neutral endopeptidase (NEP), which is inhibited by thiorphan. Therefore, administration of thiorphan increases circulating ANP.

108. Endorphins and enkephalins

Pro-opimelanocortin

Intermediate lobe cells and corticotropes of the anterior lobe both synthesize a large percursor protein that is cleaved to form a family of hormones. After removal of the signal peptide, this prohormone is known as pro-opiomelanocortin (POMC). This molecule is also synthesized in the hypothalamus and other parts of the nervous system, the lungs, the gastrointestinal tract, and the placenta. In the corticotropes, it is hydrolyzed to ACTH and a small amount of β-endorphin. In the intermediate lobe, POMC is further hydrolyzed to α-MSH (melanocyte stimulating hormone) and corticotropinlike intermediate-lobe peptide (CLIP).

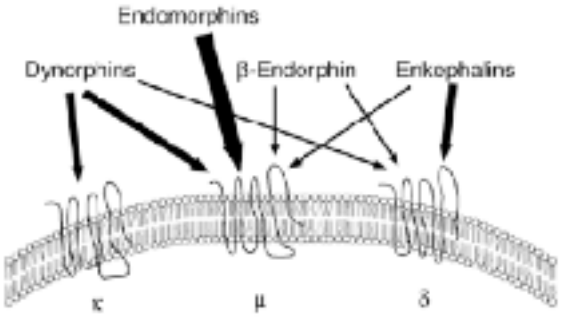
Brain's Opiate System—Endorphins and Enkephalins

About a dozen such opiate-like substances have now been found at different points of the nervous system; all are breakdown products of three large protein molecules: pro-opiomelanocortin, proenkephalin, and prodynorphin. Among the more important of these opiate-like substances are β-endorphin, met-enkephalin, leuenkephalin, and dynorphin.

The two enkephalins are found in the brain stem and spinal cord, in the portions of the analgesia system, and β-endorphin is present in both the hypothalamus and the pituitary gland. Dynorphin is found mainly in the same areas as the enkephalins, but in much lower quantities.

Thus, although the fine details of the brain's opiate system are not understood, activation of the analgesia system by nervous signals entering the periaqueductal gray and periventricular areas, or inactivation of pain pathways by morphine-like drugs, can almost totally suppress many pain signals entering through the peripheral nerves.

<u>Opioid Peptides</u>



The brain and the gastrointestinal tract contain receptors that bind morphine. The search for endogenous ligands for these receptors led to the discovery of two closely related pentapeptides, called enkephalins, that bind to these opioid receptors. One contains methionine (met-enkephalin), and one contains leucine (leu-enkephalin). These and other peptides that bind to opioid receptors are called opioid peptides. The enkephalins are found in nerve endings in the gastrointestinal tract and many different part of the brain, and they appear to function as synaptic transmitters. They have analgesic activity when injected into the brain stem. They also decrease intestinal motility.

Opioid receptors There are 3 opioid receptors: μ, κ, and δ. They differ in physiological effects, distribution, and affinity for various opioid peptides. All three are serpentine receptors coupled to Gq, and all inhibit adenylyl cyclase.

109. Pineal gland. Circadian rhythm.

The pineal is known to secrete melatonin, and there is speculation that it may function as a timing device to keep internal events synchronized with the light-dark cycle in the environment.

Anatomy

The pineal arises from the roof of the third ventricular under the posterior end of the corpus callosum and is connected by a stalk to the posterior commisure and habenular commisure. The pineal stroma contains neuroglia and parenchymal cells with features suggesting that they have a secretory function.

Melatonin

It is a derivative of tryptophan. Melatonin synthesis and secretion is increased during the dark period of the day and maintained at a low level during daylight hours. This remarkable diurnal variation of secretion is brought about by norepinephrine secreted by the postganglionic sympathetic nerves (nervi coranii) that innervate the pineal. The norepinephrine acts via β-adrenergic receptors in the pineal to increase intracellular cAMP, and the cAMP in turn produces a marked increase in N-acetyltransferase activity. This results in increased melatonin synthesis and secretion.

This discharge of the sympathetic nerves to the pineal is entrained to the light-dark cycle in the environment via the retinohypothalamic nerve fibers to the suprachiasmatic nuclei.

Function of the Pineal

Injected melatonin has effects on the gonads, but at least in some species these effects are sometimes stimulating and sometimes inhibitor, depending on the time of day the hormone is injected. This observation led to the hypothesis that the diurnal change in melatonin secretion functions as a timing signal that coordinates endocrine and other internal events with the light-dark cycle environment. Evidence supporting this timing function of melatonin includes the observation that in blind people with free-circadian rhythms, melatonin injections entrain the rhythms.

110. Ovarian cycle and its control

The normal reproductive years of the female are characterized by monthly rhythmical changes in the rates of secretion of the female hormones and corresponding physical changes in the ovaries and other sexual organs. There are two significant results of the female sexual cycle. First, only a single ovum is normally released from the ovaries each month, so that normally only a single fetus will begin to grow at a time. Second, the uterine endometrium is prepared in advance for implantation of the fertilized ovum at the required time of the month.

Gonadotropic Hormones and Their Effects on the Ovaries

The ovarian changes that occur during the sexual cycle depend completely on the gonadotropic hormones FSH and LH, secreted by the anterior pituitary gland. In the absence of these hormones, the ovaries remain inactive, which is the case throughout childhood, when almost no pituitary gonadotropic hormones are secreted. At age 9 to 12 years, the pituitary begins to secrete progressively more FSH and LH, which leads to onset of normal monthly sexual cycles beginning between the ages of 11 and 15 years. This period of change is called puberty, and the time of the first menstrual cycle is called menarche.

During each month of the female sexual cycle, there is a cyclical increase and decrease of both FSH and LH. Both FSH and LH stimulate their ovarian target cells by combining with highly specific FSH and LH receptors in the ovarian target cell membranes. In turn, the activated receptors increase the cells' rates of secretion and usually the growth and proliferation of the cells as well. Almost all these stimulatory effects result from activation of the cyclic adenosine monophosphate second messenger system in the cell cytoplasm, which causes the formation of protein kinase and multiple phosphorylations of key enzymes that stimulate sex hormone synthesis.

Ovarian Follicle Growth— "Follicular" Phase of the Ovarian Cycle

When a female child is born, each ovum is surrounded by a single layer of granulosa cells; the ovum, with this granulosa cell sheath, is called a primordial follicle. Throughout childhood, the granulosa cells are believed to provide nourishment for the ovum and to secrete an oocyte maturation-inhibiting factor that keeps the ovum suspended in its primordial state in the prophase stage of meiotic division. Then, after puberty, when FSH and LH from the anterior pituitary gland begin to be secreted in significant quantities, the ovaries, together with some of the follicles within them, begin to grow.

The first stage of follicular growth is moderate enlargement of the ovum itself, which increases in diameter twofold to threefold. Then follows growth of additional layers of granulosa cells in some of the fol- licles; these follicles are known as primary follicles.

<u>Development of Antral and Vesicular Follicles</u>

During the first few days of each monthly female sexual cycle, the concentrations of both FSH and LH secreted by the anterior pituitary gland increase slightly to moderately, with the increase in FSH slightly greater than that of LH and preceding it by a few days. These hormones, especially FSH, cause accelerated growth of 6 to 12 primary follicles each month. The initial effect is rapid proliferation of the granulosa cells, giving rise to many more layers of these cells. In addition, spindle cells derived from the ovary interstitium collect in several layers outside the granulosa cells, giving rise to a second mass of cells called the theca. This is divided into two layers. In the theca interna, the cells take on epithelioid characteristics similar to those of the granulosa cells and develop the ability to secrete additional steroid sex hormones (estrogen and progesterone). The outer layer, the theca externa, develops into a highly vascular connective tissue capsule that becomes the capsule of the developing follicle.

After the early proliferative phase of growth, lasting for a few days, the mass of granulosa cells secretes a follicular fluid that contains a high concentration of estrogen, one of the important female sex hormones. Accumulation of this fluid causes an antrum to appear within the mass of granulosa cells.

The early growth of the primary follicle up to the antral stage is stimulated mainly by FSH alone. Then greatly accelerated growth occurs, leading to still larger follicles called vesicular

follicles. This accelerated growth is caused by the following: (1) Estrogen is secreted into the follicle and causes the granulosa cells to form increasing numbers of FSH receptors; this causes a positive feedback effect, because it makes the granulosa cells even more sensitive to FSH. (2) The pituitary FSH and the estrogens combine to promote LH receptors on the original granulosa cells, thus allowing LH stimulation to occur in addition to FSH stimulation and creating an even more rapid increase in follicular secretion. (3) The increasing estrogens from the follicle plus the increasing LH from the anterior pituitary gland act together to cause proliferation of the follicular thecal cells and increase their secretion as well.

As the follicle enlarges, the ovum itself remains embedded in a mass of granulosa cells located at one pole of the follicle.

Only One Follicle Fully Matures Each Month, and the Remainder Undergo Atresia

After a week or more of growth— but before ovulation occurs—one of the follicles begins to outgrow all the others; the remaining 5 to 11 developing follicles involute (a process called atresia). The cause of the atresia is unknown, but it has been postulated to be the following: The large amounts of estrogen from the most rapidly growing follicle act on the hypothalamus to depress further enhancement of FSH secretion by the anterior pituitary gland, in this way blocking further growth of the less well developed follicles. Therefore, the largest follicle continues to grow because of its intrinsic positive feedback effects, while all the other follicles stop growing and actually involute.

Ovulation

Ovulation in a woman who has a normal 28-day female sexual cycle occurs 14 days after the onset of menstruation. Shortly before ovulation, the protruding outer wall of the follicle swells rapidly, and a small area in the center of the follicular capsule, called the stigma, protrudes like a nipple. Fluid begins to ooze from the follicle through the stigma, and the stigma ruptures widely, allowing a more viscous fluid, which has occupied the central portion of the follicle, to evaginate outward. This viscous fluid carries with it the ovum surrounded by a mass of several thousand small granulosa cells, called the corona radiata.

Surge of LH Is Necessary for Ovulation

LH is necessary for final follicular growth and ovulation. Without this hormone, even when large quantities of FSH are available, the follicle will not progress to the stage of ovulation.

About 2 days before ovulation, the rate of secretion of LH by the anterior pituitary gland increases markedly. FSH also increases about 2-fold to 3-fold at the same time, and the FSH and LH act synergistically to cause rapid swelling of the follicle during the last few days before ovulation. The LH also has a specific effect on the granulosa and theca cells, converting them mainly to progesterone-secreting cells. Therefore, the rate of secretion of estrogen begins to fall about 1 day before ovulation, while increasing amounts of progesterone begin to be secreted.

It is in this environment of (1) rapid growth of the follicle, (2) diminishing estrogen secretion after a prolonged phase of excessive estrogen secretion, and (3) initiation of secretion of progesterone that ovulation occurs. Without the initial preovulatory surge of LH, ovulation will not take place.

Initiation of Ovulation

LH causes rapid secretion of follicular steroid hormones that contain progesterone. Within a few hours, two events occur, both of which are necessary for ovulation: (1) The theca externa (the capsule of the follicle) begins to release proteolytic enzymes from lysosomes, and these cause dissolution of the follicular capsular wall and consequent weakening of the wall, resulting in further swelling of the entire follicle and degeneration of the stigma. (2) Simultaneously, there is rapid growth of new blood vessels into the follicle wall, and at the same time, prostaglandins (local hormones that cause vasodilation) are secreted into the follicular tissues. These two effects cause plasma transudation into the follicle, which contributes to follicle swelling. Finally, the combination of follicle swelling and simultaneous degeneration of the stigma causes follicle rupture, with discharge of the ovum.

Corpus Luteum—"Luteal" Phase of the Ovarian Cycle

During the first few hours after expulsion of the ovum from the follicle, the remaining granulosa and theca interna cells change rapidly into lutein cells. This process is called luteinization, and the total mass of cells together is called the corpus luteum. A well-developed vascular supply also grows into the corpus luteum.

The granulosa cells in the corpus luteum develop extensive intracellular smooth endoplasmic reticula that form large amounts of the female sex hormones progesterone and estrogen (more progesterone than estrogen). In the normal female, the corpus luteum grows, then it begins to involute and eventually loses its secretory function as well as its yellowish, lipid characteristic about 12 days after ovulation, becoming the corpus albicans; during the ensuing few weeks, this is replaced by connective tissue and over months is absorbed.

Luteinizing Function of LH

The change of granulosa and theca interna cells into lutein cells is dependent mainly on LH secreted by the anterior pituitary gland. In fact, this function gives LH its name—"luteinizing". Luteinization also depends on extrusion of the ovum from the follicle. A yet uncharacterized local hormone in the follicular fluid, called luteinization-inhibiting factor, seems to hold the luteinization process in check until after ovulation.

Secretion by the Corpus Luteum: An Additional Function of LH

The corpus luteum is a highly secretory organ, secreting large amounts of both progesterone and estrogen. Once LH (mainly that secreted during the ovulatory surge) has acted on the granulosa and theca cells to cause luteinization, the newly formed lutein cells seem to be programmed to go through a preordained sequence of (1) proliferation, (2) enlargement, and (3) secretion, followed by (4) degeneration. All this occurs in about 12 days. Another hormone with has almost exactly the same properties as LH, chorionic gonadotropin, which is secreted by the placenta, can act on the corpus luteum to prolong its life—usually maintaining it for at least the first 2 to 4 months of pregnancy.

Involution of the Corpus Luteum and Onset of the Next Ovarian Cycle

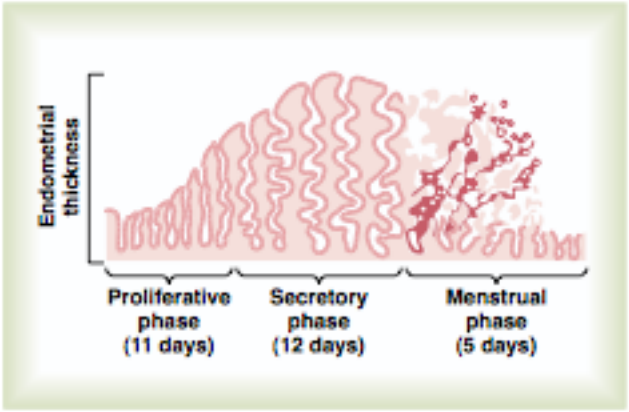
Estrogen in particular and progesterone to a lesser extent, secreted by the corpus luteum during the luteal phase of the ovarian cycle, have strong feedback effects on the anterior pituitary gland to maintain low secretory rates of both FSH and LH.

In addition, the lutein cells secrete small amounts of the hormone inhibin, the same as the inhibin secreted by the Sertoli cells of the male testes. This hormone inhibits secretion by the anterior pituitary gland, especially FSH secretion. Low blood concentrations of both FSH and LH result, and loss of these hormones finally causes the corpus luteum to degenerate completely, a process called involution of the corpus luteum.

Final involution and thus the sudden cessation of secretion of estrogen, progesterone, and inhibin by the corpus luteum removes the feedback inhibition of the anterior pituitary gland, allowing it to begin secreting increasing amounts of FSH and LH again. FSH and LH initiate the growth of new follicles, beginning a new ovarian cycle.

111. Uterine cycle

Associated with the monthly cyclical production of estrogens and progesterone by the ovaries is an endometrial cycle in the lining of the uterus that operates through the following stages: (1) proliferation of the uterine endometrium; (2) development of secretory changes in the endometrium; and (3) desquamation of the endometrium, which is known as menstruation.



Proliferative Phase (Estrogen Phase) of the Endometrial Cycle, Occurring Before Ovulation

At the beginning of each monthly cycle, most of the endometrium has been desquamated by menstruation. After menstruation, only a thin layer of endometrial stroma remains. Under the influence of estrogens, secreted in increasing quantities by the ovary during the first part of the monthly ovarian cycle, the stromal cells and the epithelial cells proliferate rapidly. The endometrial surface is reepithelialized within 4 to 7 days after the beginning of menstruation.

Then, during the next week and a half—that is, before ovulation occurs—the endometrium increases greatly in thickness, owing to increasing numbers of stromal cells and to progressive growth of the endometrial glands and new blood vessels into the endometrium. The endometrial glands, especially those of the cervical region, secrete a thin, stringy mucus.

Secretory Phase (Progestational Phase) of the Endometrial Cycle, Occurring After Ovulation

During most of the latter half of the monthly cycle, after ovulation has occurred, progesterone and estrogen together are secreted in large quantities by the corpus luteum. The estrogens cause slight additional cellular proliferation in the endometrium during this phase of the cycle, whereas progesterone causes marked swelling and secretory development of the endometrium. The glands increase in tortuosity; an excess of secretory substances accumulates in the glandular epithelial cells. Also, the cytoplasm of the stromal cells increases; lipid and glycogen deposits increase greatly in the stromal cells; and the blood supply to the endometrium further increases in proportion to the developing secretory activity, with the blood vessels becoming highly tortuous. At the peak of the secretory phase, about 1 week after ovulation, the endometrium has a thickness of 5 to 6 millimeters.

The whole purpose of all these endometrial changes is to produce a highly secretory endometrium that contains large amounts of stored nutrients to provide appropriate conditions for implantation of a fertilized ovum during the latter half of the monthly cycle.

Menstruation

If the ovum is not fertilized, about 2 days before the end of the monthly cycle, the corpus luteum in the ovary suddenly involutes, and the ovarian hormones (estrogens and progesterone) decrease to low levels of secretion. Menstruation follows.

Menstruation is caused by the reduction of estrogens and progesterone, especially progesterone, at the end of the monthly ovarian cycle. The first effect is decreased stimulation of the endometrial cells by these two hormones, followed rapidly by involution of the endometrium itself to about 65% of its previous thickness. Then, during the 24 hours preceding the onset of menstruation, the tortuous blood vessels leading to the mucosal layers of the endometrium become vasospastic.

The vasospasm, the decrease in nutrients to the endometrium, and the loss of hormonal stimulation initiate necrosis in the endometrium, especially of the blood vessels.Gradually, the necrotic outer layers of the endometrium separate from the uterus at the sites of the hemorrhages until, about 48 hours after the onset of menstruation, all the superficial layers of the endometrium have desquamated.

Within 4 to 7 days after menstruation starts, the loss of blood ceases because, by this time, the endometrium has become re-epithelialized.

112. Physiology of pregnancy

Transport of the Fertilized Ovum in the Fallopian Tube

After fertilization has occurred, an additional 3 to 5 days is normally required for transport of the fertilized ovum through the remainder of the fallopian tube into the cavity of the uterus. Movements of teh cilia, fluid secreted by the epithelial cells and weak contractions of the fallopian tube aid the ovum passage.

This delayed transport of the fertilized ovum through the fallopian tube allows several stages of cell division to occur before the dividing ovum—now called a blastocyst—enters the uterus. During this time, the fallopian tube secretory cells produce large quantities of secretions used for the nutrition of the developing blastocyst.

Implantation of the Blastocyst in the Uterus

After reaching the uterus, the developing blastocyst usually remains in the uterine cavity an additional 1 to 3 days before it implants in the endometrium; thus, implantation ordinarily occurs on about the fifth to seventh day after ovulation. Before implantation, the blastocyst obtains its nutrition from the uterine endometrial secretions, called “uterine milk.”

Implantation results from the action of trophoblast cells that develop over the surface of the blastocyst. These cells secrete proteolytic enzymes that digest and liquefy the adjacent cells of the uterine endometrium. Some of the fluid and nutrients released are actively transported by the same trophoblast cells into the blas- tocyst, adding more sustenance for growth. Figure 82–3 shows an early implanted human blastocyst, with a small embryo. Once implantation has taken place, the trophoblast cells and other adjacent cells (from the blastocyst and the uterine endometrium) proliferate rapidly, forming the placenta and the various mem- branes of pregnancy.

Early Nutrition of the Embryo

The progesterone secreted by the ovarian corpus luteum during the latter half of each monthly sexual cycle has an effect on the uterine endometrium, converting the endometrial stromal cells into large swollen cells containing extra quantities of glycogen, proteins, lipids, and even some minerals necessary for development of the conceptus. Then, when the conceptus implants in the endometrium, the continued secretion of progesterone causes the endometrial cells to swell further and to store even more nutrients. These cells are now called decidual cells, and the total mass of cells is called the decidua.

As the trophoblast cells invade the decidua, digesting and imbibing it, the stored nutrients in the decidua are used by the embryo for growth and development. This trophoblastic period of nutrition gives way to placental nutrition.

Function of the Placenta

Developmental and Physiologic Anatomy of the Placenta

Blood sinuses supplied with blood from the mother develop around the outsides of the trophoblastic cords. The trophoblast cells send out more and more projections, which become placental villi into which fetal capillaries grow. Thus, the villi, carrying fetal blood, are surrounded by sinuses that contain maternal blood.

The fetus’s blood flows through two umbilical arteries, then into the capillaries of the villi, and finally back through a single umbilical vein into the fetus.

Placental Permeability and Membrane Diffusion Conductance

The major function of the placenta is to provide for diffusion of foodstuffs and oxygen from the mother’s blood into the fetus’s blood and diffusion of excretory products from the fetus back into the mother.

Diffusion of Oxygen Through the Placental Membrane

The dissolved oxygen in the blood of the large maternal sinuses passes into the fetal blood by simple diffusion, driven by an oxygen pressure gradient from the mother’s blood to the fetus’s blood. The hemoglobin of the fetus is mainly fetal hemoglobin, a type of hemoglobin synthesized in

the fetus before birth. The fetal hemoglobin can carry 20 to 50% more oxygen than maternal hemoglobin can.

Second, the hemoglobin concentration of fetal blood is about 50% greater than that of the mother; this is an even more important factor in enhancing the amount of oxygen transported to the fetal tissues.

Third, the fetal blood entering the placenta carries large amounts of carbon dioxide, but much of this carbon dioxide diffuses from the fetal blood into the maternal blood. Loss of the carbon dioxide makes the fetal blood more alkaline, whereas the increased carbon dioxide in the maternal blood makes it more acidic. These changes cause the capacity of fetal blood to combine with oxygen to increase and that of maternal blood to decrease. This forces still more oxygen from the maternal blood, while enhancing oxygen uptake by the fetal blood.

Diffusion of Carbon Dioxide Through the Placental Membrane.

Carbon dioxide is continually formed in the tissues of the fetus in the same way that it is formed in maternal tissues, and the only means for excreting the carbon dioxide from the fetus is through the placenta into the mother's blood. The PCO_2 of the fetal blood is higher than that of the maternal blood. This small pressure gradient for carbon dioxide across the membrane is more than sufficient to allow adequate diffusion of carbon dioxide.

Diffusion of Foodstuffs Through the Placental Membrane.

Other metabolic substrates needed by the fetus diffuse into the fetal blood in the same manner as oxygen does. For instance, in the late stages of pregnancy, the fetus often uses as much glucose as the entire body of the mother uses.The glucose is transported by carrier molecules in the trophoblast cells of the membrane. Because of the high solubility of fatty acids in cell membranes, these also diffuse from the maternal blood into the fetal blood, but more slowly than glucose, so that glucose is used more easily by the fetus for nutrition.

Excretion of Waste Products Through the Placental Membrane

In the same manner that carbon dioxide diffuses from the fetal blood into the maternal blood, other excretory products formed in the fetus also diffuse through the placental membrane into the maternal blood and are then excreted along with the excretory products of the mother.

Hormonal Factors in Pregnancy

In pregnancy, the placenta forms especially large quantities of human chorionic gonadotropin, estrogens, progesterone, and human chorionic somatomammotropin, the first three of which, and probably the fourth as well, are all essential to a normal pregnancy.

Human Chorionic Gonadotropin and Its Effect to Cause Persistence of the Corpus Luteum and to Prevent Menstruation

Menstruation is prevented by the secretion of human chorionic gonadotropin by the newly developing embryonic tissues in the following manner.

Coincidental with the development of the trophoblast cells from the early fertilized ovum, the hormone human chorionic gonadotropin is secreted by the syncytial trophoblast cells into the fluids of the mother. The secretion of this hormone can first be measured in the blood 8 to 9 days after ovulation, shortly after the blastocyst implants in the endometrium. Then the rate of secretion rises rapidly to reach a maximum at about 10 to 12 weeks of pregnancy and decreases back to a lower value by 16 to 20 weeks. It continues at this level for the remainder of pregnancy.

Function of Human Chorionic Gonadotropin

Human chorionic gonadotropin's most important function is to prevent involution of the corpus luteum at the end of the monthly female sexual cycle. Instead, it causes the corpus luteum to secrete even larger quantities of its sex hormones—progesterone and estrogens—for the next few months. These sex hormones prevent menstruation and cause the endometrium to continue to grow and store large amounts of nutrients rather than being shed in the menstruum. As a result, the decidua-like cells that develop in the endometrium during the normal female sexual cycle become actual decidual cells—greatly swollen and nutritious—at about the time that the blastocyst implants.

Under the influence of human chorionic gonadotropin, the corpus luteum in the mother's ovary grows to about twice its initial size by a month or so after pregnancy begins, and its continued secretion of estrogens and progesterone maintains the decidual nature of the uterine endometrium, which is necessary for the early development of the fetus. The corpus luteum involutes slowly after the 13th to 17th week of gestation.

Effect of Human Chorionic Gonadotropin on the Fetal Testes

Human chorionic gonadotropin also exerts an interstitial cell–stimulating effect on the testes of the male fetus, resulting in the production of testosterone in male fetuses until the time of birth. This small secretion of testosterone during gestation is what causes the fetus to grow male sex organs instead of female organs. Near the end of pregnancy, the testosterone secreted by the fetal testes also causes the testes to descend into the scrotum.

Secretion of Estrogens by the Placenta

The placenta, like the corpus luteum, secretes both estrogens and progesterone. Toward the end of pregnancy, the daily production of placental estrogens increases to about 30 times the mother's normal level of production.

Function of Estrogen in Pregnancy

These hormones exert mainly a proliferative function on most reproductive and associated organs of the mother. During pregnancy, the extreme quantities of estrogens cause (1) enlargement of the mother's uterus, (2) enlargement of the mother's breasts and growth of the breast ductal structure, and (3) enlargement of the mother's female external genitalia.

The estrogens also relax the pelvic ligaments of the mother, so that the sacroiliac joints become relatively limber and the symphysis pubis becomes elastic. These changes allow easier passage of the fetus through the birth canal.

Secretion of Progesterone by the Placenta

Progesterone is also essential for a successful pregnancy—in fact, it is just as important as estrogen. In addition to being secreted in moderate quantities by the corpus luteum at the beginning of pregnancy, it is secreted later in tremendous quantities by the placenta. The special effects of progesterone that are essential for the normal progression of pregnancy are as follows: 1. Progesterone causes decidual cells to develop in the uterine endometrium, and these cells play an important role in the nutrition of the early embryo. 2. Progesterone decreases the contractility of the pregnant uterus, thus preventing uterine contractions from causing spontaneous abortion. 3. Progesterone contributes to the development of the conceptus even before implantation, because it specifically increases the secretions of the mother's fallopian tubes and uterus to provide appropriate nutritive matter for the developing morula and blastocyst. There is also reason to believe that progesterone affects cell cleavage in the early developing embryo. 4. The progesterone secreted during pregnancy helps the estrogen prepare the mother's breasts for lactation, which is discussed later in this chapter.

Other Hormonal Factors in Pregnancy

Almost all the nonsexual endocrine glands of the mother also react markedly to pregnancy. This results mainly from the increased metabolic load on the mother but also, to some extent, from the effects of placental hormones on the pituitary and other glands. Some of the most notable effects are the following.

Pituitary Secretion

The anterior pituitary gland of the mother enlarges at least 50% during pregnancy and increases its production of corticotropin, thyrotropin, and prolactin. Conversely, pituitary secretion of follicle-stimulating hormone and luteinizing hormone is almost totally suppressed as a result of the inhibitory effects of estrogens and progesterone from the placenta.

Corticosteroid Secretion

The rate of adrenocortical secretion of the glucocorticoids is moderately increased throughout pregnancy. It is possible that these glucocorticoids help mobilize amino acids from the mother's tissues so that these can be used for synthesis of tissues in the fetus.

Secretion by the Thyroid Gland

The mother's thyroid gland ordinarily enlarges up to 50% during pregnancy and increases its production of thyroxine a corresponding amount. The increased thyroxine production is caused at least partly by a thyrotropic effect of human chorionic gonadotropin secreted by the placenta and by small quantities of a specific thyroid-stimulating hormone, human chorionic thyrotropin, also secreted by the placenta.

Secretion by the Parathyroid Glands

The mother's parathyroid glands usually enlarge during pregnancy; this is especially true if the mother is on a calcium-deficient diet. Enlargement of these glands causes calcium absorption from the mother's bones, thereby maintaining normal calcium ion concentration in the mother's extracellular fluid even while the fetus removes calcium to ossify its own bones. This secretion of parathyroid hormone is even more intensified during lactation after the baby's birth.

Secretion of "Relaxin" by the Ovaries and Placenta.

A hormone called relaxin, is secreted by the corpus luteum of the ovary and by placental tissues. Its secretion is increased by a stimulating effect of human chorionic gonadotropin at the same time that the corpus luteum and the placenta secrete large quantities of estrogens and progesterone. Relaxin softens the cervix of the pregnant woman at the time of delivery.

Response of the Mother's Body to Pregnancy

Most apparent among the many reactions of the mother to the fetus and to the excessive hormones of pregnancy is the increased size of the various sexual organs. For instance, the uterus and the breasts, the vagina enlarges and the introitus opens more widely. Also, the various hormones can cause marked changes in a pregnant woman's appearance, sometimes resulting in the development of edema, acne, and masculine or acromegalic features.

The average weight gain during pregnancy is about 11Kg, with most of this gain occurring during the last two trimesters. Of this, about 3 Kg is fetus and 2 Kg is amniotic fluid, placenta, and fetal membranes.

During pregnancy, a woman often has a greatly increased desire for food, partly as a result of removal of food substrates from the mother's blood by the fetus and partly because of hormonal factors.

113. Physiology of parturition and lactation

Increased Uterine Excitability Near Term

Toward the end of pregnancy, the uterus becomes progressively more excitable, until finally it develops such strong rhythmical contractions that the baby is expelled. The exact cause of the increased activity of the uterus is not known, but at least two major categories of effects lead up to the intense contractions responsible for parturition: (1) progressive hormonal changes that cause increased excitability of the uterine musculature, and (2) progressive mechanical changes.

Hormonal Factors That Increase Uterine Contractility

Increased Ratio of Estrogens to Progesterone

Progesterone inhibits uterine contractility during pregnancy, thereby helping to prevent expulsion of the fetus. Conversely, estrogens have a definite tendency to increase the degree of uterine contractility, partly because estrogens increase the number of gap junctions between the adjacent uterine smooth muscle cells, but also because of other poorly understood effects. Both progesterone and estrogen are secreted in progressively greater quantities throughout most of pregnancy, but from the seventh month onward, estrogen secretion continues to increase while progesterone secretion remains constant or perhaps even decreases slightly. Therefore, it has been postulated that the estrogen-to-progesterone ratio increases sufficiently toward the end of pregnancy to be at least partly responsible for the increased contractility of the uterus.

Effect of Oxytocin on the Uterus

Oxytocin is a hormone secreted by the neurohypophysis that specifically causes uterine contraction. There are four reasons to believe that oxytocin might be important in increasing the contractility of the uterus near term: (1) The uterine muscle increases its oxytocin receptors and, therefore, increases its responsiveness to a given dose of oxytocin during the latter few months of pregnancy. (2) The rate of oxytocin secretion by the neurohypophysis is considerably increased at the time of labor. (3) Hypophysectomized animals have longer labor. (4)Irritation or stretching of the uterine cervix, as occurs during labor, can cause a neurogenic reflex through the paraventricular and supraoptic nuclei of the hypothalamus that causes the posterior pituitary gland to increase its secretion of oxytocin.

Effect of Fetal Hormones on the Uterus

The fetus's pituitary gland secretes increasing quantities of oxytocin, which might play a role in exciting the uterus. Also, the fetus's adrenal glands secrete large quantities of cortisol, another possible uterine stimulant. In addition, the fetal membranes release prostaglandins in high concentration at the time of labor. These, too, can increase the intensity of uterine contractions.

Mechanical Factors That Increase Uterine Contractility

Stretch of the Uterine Musculature

Simply stretching smooth muscle organs usually increases their contractility. Further, intermittent stretch, as occurs repeatedly in the uterus because of fetal movements, can also elicit smooth muscle contraction.

Stretch or Irritation of the Cervix

There is reason to believe that stretching or irritating the uterine cervix is particularly important in eliciting uterine contractions. For instance, the obstetrician frequently induces labor by rupturing the membranes so that the head of the baby stretches the cervix more forcefully than usual or irritates it in other ways.

It has been suggested that stretching or irritation of nerves in the cervix initiates reflexes to the body of the uterus, but the effect could also result simply from myogenic transmission of signals from the cervix to the body of the uterus.

Onset of Labor—A Positive Feedback Mechanism for Its Initiation

During most of the months of pregnancy, the uterus undergoes periodic episodes of weak and slow rhythmical contractions called Braxton Hicks contractions. These contractions become progressively stronger toward the end of pregnancy; then they change suddenly, within hours, to become exceptionally strong contractions that start stretching the cervix and later force the baby through the birth canal, thereby causing parturition.

The positive feedback theory suggests that stretching of the cervix by the fetus's head finally becomes great enough to elicit a strong reflex increase in contractility of the uterine body. This pushes the baby forward, which stretches the cervix more and initiates more positive feedback to the uterine body. Thus, the process repeats until the baby is expelled. Second, two known types of positive feedback increase uterine contractions during labor: (1) Stretching of the cervix causes the entire body of the uterus to contract, and this contraction stretches the cervix even more because of the downward thrust of the baby's head. (2) Cervical stretching also causes the pituitary gland to secrete oxytocin, which is another means for increasing uterine contractility.

Abdominal Muscle Contractions During Labor

Once uterine contractions become strong during labor, pain signals originate both from the uterus itself and from the birth canal. These signals, in addition to causing suffering, elicit neurogenic reflexes in the spinal cord to the abdominal muscles, causing intense contractions of these muscles. The abdominal contractions add greatly to the force that causes expulsion of the baby.

Mechanics of Parturition

The uterine contractions during labor begin mainly at the top of the uterine fundus and spread downward over the body of the uterus. Also, the intensity of contraction is great in the top and body of the uterus but weak in the lower segment of the uterus adjacent to the cervix. Therefore, each uterine contraction tends to force the baby downward toward the cervix.

In the early part of labor, the contractions might occur only once every 30 minutes. As labor progresses, the contractions finally appear as often as once every 1 to 3 minutes, and the intensity of contraction increases greatly, with only a short period of relaxation between contractions.

It is fortunate that the contractions of labor occur intermittently, because strong contractions impede or sometimes even stop blood flow through the placenta and would cause death of the fetus if the contractions were continuous.

In about 95% of births, the head is the first part of the baby to be expelled.

The first major obstruction to expulsion of the fetus is the uterine cervix. Toward the end of pregnancy, the cervix becomes soft, which allows it to stretch when labor contractions begin in the uterus. The so-called first stage of labor is a period of progressive cervical dilation, lasting until the cervical opening is as large as the head of the fetus. This stage usually lasts for 8 to 24 hours in the first pregnancy but often only a few minutes after many pregnancies.

Once the cervix has dilated fully, the fetal membranes usually rupture and the amniotic fluid is lost suddenly through the vagina. Then the fetus's head moves rapidly into the birth canal, and with additional force from above, it continues to wedge its way through the canal until delivery is effected.

Separation and Delivery of the Placenta

For 10 to 45 minutes after birth of the baby, the uterus continues to contract to a smaller and smaller size, which causes a shearing effect between the walls of the uterus and the placenta, thus separating the placenta from its implantation site. Separation of the placenta opens the placental sinuses and causes bleeding. The amount of bleeding is limited to an average of 350 mL by the following mechanism: The smooth muscle fibers of the uterine musculature are arranged in figures of eight around the blood vessels as the vessels pass through the uterine wall. Therefore, contraction of the uterus after delivery of the baby constricts the vessels that had previously supplied blood to the placenta. In addition, it is believed that vasoconstrictor prostaglandins formed at the placental separation site cause additional blood vessel spasm.

Lactation

Development of the Breasts

The breasts, begin to develop at puberty. This development is stimulated by the estrogens of the monthly female sexual cycle; estrogens stimulate growth of the breasts' mammary glands plus the deposition of fat to give the breasts mass. In addition, far greater growth occurs during the high- estrogen state of pregnancy, and only then does the glandular tissue become completely developed for the production of milk.

Growth of the Ductal System—Role of the Estrogens

All through pregnancy, the large quantities of estrogens secreted by the placenta cause the ductal system of the breasts to grow and branch. Simultaneously, large quantities of fat are laid down in the stroma.

Also important for growth of the ductal system are at least four other hormones: growth hormone, prolactin, the adrenal glucocorticoids, and insulin. Each of these is known to play at least some role in protein metabolism, which presumably explains their function in the development of the breasts.

Development of the Lobule-Alveolar System—Role of Progesterone

Final development of the breasts into milk-secreting organs also requires progesterone. Once the ductal system has developed, progesterone causes additional growth of the breast lobules, with budding of alveoli and development of secretory characteristics in the cells of the alveoli. These changes are analogous to the secretory effects of progesterone on the endometrium of the uterus during the latter half of the female menstrual cycle.

Initiation of Lactation—Function of Prolactin

Both estrogen and progesterone inhibit the actual secretion of milk. Conversely, the hormone prolactin has exactly the opposite effect on milk secretion—promoting it. This hormone is secreted by the mother's anterior pituitary gland, and its concentration in her blood rises steadily from the fifth week of pregnancy until birth of the baby, at which time it has risen to 10 to 20 times the normal nonpregnant level. In addition, the placenta secretes large quantities of human chorionic somatomammotropin, which probably has lactogenic properties, thus supporting the prolactin. Even so, because of the suppressive effects of estrogen and progesterone, no more than a few milliliters of fluid are secreted each day until after the baby is born. The fluid secreted during the last few days before and the first few days after parturition is called colostrum; it contains essentially the same concentrations of proteins and lactose as milk, but it has almost no fat, and its maximum rate of production is about 1/100 the subsequent rate of milk production.

Immediately after the baby is born, the sudden loss of both estrogen and progesterone secretion from the placenta allows the lactogenic effect of prolactin from the mother's pituitary gland to assume its natural milk-promoting role, and over the next 1 to 7 days, the breasts begin to secrete copious quantities of milk instead of colostrum.

After birth of the baby, the basal level of prolactin secretion returns to the nonpregnant level over the next few weeks. However, each time the mother nurses her baby, nervous signals from the nipples to the hypothalamus cause a surge in prolactin secretion that lasts for about 1 hour. This prolactin acts on the mother's breasts to keep the mammary glands secreting milk into the alveoli for the subsequent nursing periods.

Hypothalamic Control of Prolactin Secretion

The hypothalamus mainly stimulates production of all the other hormones, but it mainly inhibits prolactin production. Consequently, damage to the hypothalamus or blockage of the hypothalamic-hypophysial portal system often increases prolactin secretion while it depresses secretion of the other anterior pituitary hormones.

Suppression of the Female Ovarian Cycles in Nursing Mothers for Many Months After Delivery

In most nursing mothers, the ovarian cycle (and ovulation) does not resume until a few weeks after cessation of nursing. The reason seems to be that the same nervous signals from the breasts to the hypothalamus that cause prolactin secretion during suckling inhibit secretion of

gonadotropin-releasing hormone by the hypothalamus. This, in turn, suppresses formation of the pituitary gonadotropic hormones—luteinizing hormone and follicle-stimulating hormone.

Ejection (or "Let-Down") Process in Milk Secretion—Function of Oxytocin

Milk is secreted continuously into the alveoli of the breasts, but milk does not flow easily from the alveoli into the ductal system and, therefore, does not continually leak from the breast nipples. Instead, the milk must be ejected from the alveoli into the ducts before the baby can obtain it. This is caused by a combined neurogenic and hormonal reflex that involves the posterior pituitary hormone oxytocin, as follows.

When the baby suckles, it receives virtually no milk for the first half minute or so. Sensory impulses must first be transmitted through somatic nerves from the nipples to the mother's spinal cord and then to her hypothalamus, where they cause nerve signals that promote oxytocin secretion at the same time that they cause prolactin secretion. The oxytocin is carried in the blood to the breasts, where it causes myoepithelial cells to contract, thereby expressing the milk from the alveoli into the ducts. Then the baby's suckling becomes effective in removing the milk. Thus, within 30 seconds to 1 minute after a baby begins to suckle, milk begins to flow. This process is called milk ejection or milk let-down.

Suckling on one breast causes milk flow not only in that breast but also in the opposite breast.

114. Endocrine functions of testes

Secretion, Metabolism, and Chemistry of the Male Sex Hormone

Secretion of Testosterone by the Interstitial Cells of Leydig in the Testes

The testes secrete several male sex hormones, which are collectively called androgens, including testosterone, dihydrotestosterone, and androstenedione. Testosterone is consider it to be the significant testicular hormone, much, if not most of which is eventually converted into the more active hormone dihy- drotestosterone in the target tissues.

Testosterone is formed by the interstitial cells of Leydig, which lie in the interstices between the seminiferous tubules. Leydig cells are almost nonexistent in the testes during childhood when the testes secrete almost no testosterone, but they are numerous in the newborn male infant for the first few months of life and in the adult male any time after puberty; at both these times the testes secrete large quantities of testosterone.

Secretion of Androgens Elsewhere in the Body

Adrenal glands secrete at least five androgens, although the total masculinizing activity of all these is normally so slight (less than 5% of the total in the adult male) that even in women they do not cause significant masculine characteristics, except for causing growth of pubic and axillary hair.

Metabolism of Testosterone

After secretion by the testes, about 97% of the testosterone becomes either loosely bound with plasma albumin or more tightly bound with a β-globulin called sex hormone–binding globulin. By that time, the testosterone either is transferred to the tissues or is degraded into inactive products that are subsequently excreted.

Much of the testosterone that becomes fixed to the tissues is converted within the tissue cells to dihy-drotestosterone, especially in certain target organs such as the prostate gland in the adult and the external gen- italia of the male fetus.

Degradation and Excretion of Testosterone

The testosterone that does not become fixed to the tissues is rapidly converted, mainly by the liver and simultaneously conjugated as either glucuronides or sulfates. These are excreted either into the gut by way of the liver bile or into the urine through the kidneys.

Production of Estrogen in the Male

In addition to testosterone, small amounts of estrogens are formed in the male, and a reasonable quantity of estrogens can be recovered from a man's urine. The exact source of estrogens in the male is unclear, but the following are known: (1) the concentration of estrogens in the fluid of the seminiferous tubules is quite high and probably plays an important role in spermiogenesis. This estrogen is believed to be formed by the Sertoli cells by converting testosterone to estradiol. (2) Much larger amounts of estrogens are formed from testosterone and androstanediol in other tissues of the body, especially the liver, probably accounting for as much as 80% of the total male estrogen production.

Functions of Testosterone

In general, testosterone is responsible for the distinguishing characteristics of the masculine body. Even during fetal life, the testes are stimulated by chorionic gonadotropin from the placenta to produce moderate quantities of testosterone throughout the entire period of fetal development and for 10 or more weeks after birth; thereafter, essentially no testosterone is produced during childhood until about the ages of 10 to 13 years. Then testosterone production increases rapidly under the stimulus of anterior pituitary gonadotropic hormones at the onset of puberty and lasts throughout most of the remainder of life, dwindling rapidly beyond age 50 to become 20 to 50%t of the peak value by age 80.

Functions of Testosterone During Fetal Development

Testosterone begins to be elaborated by the male fetal testes at about the seventh week of embryonic life.

Thus, testosterone secreted first by the genital ridges and later by the fetal testes is responsible for the development of the male body characteristics, including the formation of a penis and a scrotum rather than formation of a clitoris and a vagina. Also, it causes formation of the prostate gland, seminal vesicles, and male genital ducts, while at the same time suppressing the formation of female genital organs.

Effect of Testosterone to Cause Descent of the Testes

The testes usually descend into the scrotum during the last 2 to 3 months of gestation when the testes begin secreting reasonable quantities of testosterone.

Effect of Testosterone on Development of Adult Primary and Secondary Sexual Characteristics

After puberty, the increasing amounts of testosterone secretion cause the penis, scrotum, and testes to enlarge about eightfold before the age of 20 years. In addition, testosterone causes the secondary sexual characteristics of the male to develop, beginning at puberty and ending at maturity. These secondary sexual characteristics, in addition to the sexual organs themselves, distinguish the male from the female as follows.

Effect on the Distribution of Body Hair

Testosterone causes growth of hair (1) over the pubis, (2) upward along the linea alba of the abdomen sometimes to the umbilicus and above, (3) on the face, (4) usually on the chest, and (5) less often on other regions of the body, such as the back.

Baldness

Testosterone decreases the growth of hair on the top of the head; a man who does not have functional testes does not become bald. However, many virile men never become bald because baldness is a result of two factors: first, a genetic background for the development of baldness and, second, superimposed on this genetic background, large quantities of androgenic hormones.

Effect on the Voice

Testosterone secreted by the testes causes hypertrophy of the laryngeal mucosa and enlargement of the larynx. The effects cause at first a relatively discordant, “cracking” voice, but this gradually changes into the typical adult masculine voice.

Testosterone Increases Thickness of the Skin and Can Contribute to Development of Acne

Testosterone increases the thickness of the skin over the entire body and increases the ruggedness of the subcutaneous tissues. Testosterone also increases the rate of secretion by some or perhaps all the body’s sebaceous glands.

Testosterone Increases Protein Formation and Muscle Development

One of the most important male characteristics is development of increasing musculature after puberty, averaging about a 50% increase in muscle mass over that in the female. This is associated with increased protein in the nonmuscle parts of the body as well.

Because of the great effect that testosterone and other androgens have on the body musculature, synthetic androgens are widely used by athletes to improve their muscular performance.

Testosterone Increases Bone Matrix and Causes Calcium Retention

After the great increase in circulating testosterone that occurs at puberty, the bones grow considerably thicker and deposit considerable additional calcium salts. Thus, testosterone increases the total quantity of bone matrix and causes calcium retention. The increase in bone matrix is believed to result from the general protein anabolic function of testosterone plus deposition of calcium salts in response to the increased protein.

Testosterone Increases Basal Metabolism

Large quantities of testosterone can increase the basal metabolic rate by as much as 15%. Also, even the usual quantity of testosterone secreted by the testes during adolescence and early adult life increases the rate of metabolism some 5 to 10% above the value that it would be were the testes not active. This increased rate of metabolism is possibly an indirect result of the effect of testosterone on protein anabolism, the increased quantity of proteins—the enzymes especially—increasing the activities of all cells.

Effect on Red Blood Cells

The average man has about 700,000 more red blood cells per cubic millimeter than the average woman. This difference may be due partly to the increased metabolic rate that occurs after testosterone administration rather than to a direct effect of testosterone on red blood cell production.

Effect on Electrolyte and Water Balance

Many steroid hormones can increase the reabsorption of sodium in the distal tubules of the kidneys. Testosterone also has such an effect, but only to a minor degree in comparison with the adrenal mineralocorticoids. Nevertheless, after puberty, the blood and extracellular fluid volumes of the male in relation to body weight increase as much as 5 to 10%.

115. Sex reflexes

Neuronal Stimulus for Performance of the Male Sexual Act

The most important source of sensory nerve signals for initiating the male sexual act is the glans penis. The glans contains an especially sensitive sensory end-organ system that transmits into the central nervous system that special modality of sensation called sexual sensation. The slippery massaging action of intercourse on the glans stimulates the sensory end-organs, and the sexual signals in turn pass through the pudendal nerve, then through the sacral plexus into the sacral portion of the spinal cord, and finally up the cord to undefined areas of the brain.

Impulses may also enter the spinal cord from areas adjacent to the penis to aid in stimulating the sexual act. For instance, stimulation of the scrotum, and perineal structures in general can send signals into the cord that add to the sexual sensation.

Psychic Element of Male Sexual Stimulation

Appropriate psychic stimuli can greatly enhance the ability of a person to perform the sexual act.

Integration of the Male Sexual Act in the Spinal Cord

Although psychic factors usually play an important part in the male sexual act and can initiate or inhibit it, brain function is probably not necessary for its performance because appropriate genital stimulation can cause ejaculation in in humans after their spinal cords have been cut above the lumbar region. The male sexual act results from inherent reflex mechanisms integrated in the sacral and lumbar spinal cord, and these mechanisms can be initiated by either psychic stimulation from the brain or actual sexual stimulation from the sex organs, but usually it is a combination of both.

Female Sexual Act

Stimulation of the Female Sexual Act

Successful performance of the female sexual act depends on both psychic stimulation and local sexual stimulation. Thinking sexual thoughts can lead to female sexual desire, and this aids greatly in the performance of the female sexual act. Sexual desire does increase in proportion to the level of sex hormones secreted. Desire also changes during the monthly sexual cycle, reaching a peak near the time of ovulation, probably because of the high levels of estrogen secretion during the preovulatory period.

Local sexual stimulation in women occurs in more or less the same manner as in men because massage and other types of stimulation of the vulva, vagina, and other perineal regions can create sexual sensations. The glans of the clitoris is especially sensitive for initiating sexual sensations.

As in the male, the sexual sensory signals are transmitted to the sacral segments of the spinal cord through the pudendal nerve and sacral plexus. Once these signals have entered the spinal cord, they are transmitted to the cerebrum. Also, local reflexes integrated in the sacral and lumbar spinal cord are at least partly responsible for some of the reactions in the female sexual organs.

116. Regulation of body fluid volume

Fluid Intake and Output Are Balanced During Steady-State Conditions

The relative constancy of the body fluids is remarkable because there is continuous exchange of fluid and solutes with the external environment as well as within the different compartments of the body.

Daily Intake of Water

Water is added to the body by two major sources: (1) it is ingested in the form of liquids or water in the food, which together normally add about 2100 ml/day to the body fluids, and (2) it is synthesized in the body as a result of oxidation of carbohydrates, adding about 200 ml/day. This provides a total water intake of about 2300 ml/day.

Daily Loss of Body Water Insensible Water Loss

Some of the water losses cannot be precisely regulated. For example, there is a continuous loss of water by evaporation from the respiratory tract and diffusion through the skin, which together account for about 700 ml/day of water loss under normal conditions. This is termed insensible water loss because we are not consciously aware of it, even though it occurs continually in all living humans.

The average water loss by diffusion through the skin is about 300 to 400 ml/day. This loss is minimized by the cholesterol-filled cornified layer of the skin, which provides a barrier against excessive loss by diffusion.

Insensible water loss through the respiratory tract averages about 300 to 400 ml/day. As air enters the respiratory tract, it becomes saturated with moisture, to a vapor pressure of about 47 mm Hg, before it is expelled. Because the vapor pressure of the inspired air is usually less than 47 mm Hg, water is continuously lost through the lungs with respiration. In cold weather, the atmospheric vapor pressure decreases to nearly 0, causing an even greater loss of water from the lungs as the temperature decreases.

Fluid Loss in Sweat

The volume of sweat normally is about 100 ml/day, but in very hot weather or during heavy exercise, water loss in sweat occasionally increases to 1 to 2 L/hour.

Water Loss in Feces

Only a small amount of water (100 ml/day) normally is lost in the feces. This can increase to several liters a day in people with severe diarrhea. For this reason, severe diarrhea can be life threatening if not corrected within a few days.

Water Loss by the Kidneys

The remaining water loss from the body occurs in the urine excreted by the kidneys. There are multiple mechanisms that control the rate of urine excretion. In fact, the most important means by which the body maintains a balance between water intake and output, as well as a balance between intake and output of most electrolytes in the body, is by controlling the rates at which the kidneys excrete these substances.

Regulation of Fluid Exchange and Osmotic Equilibrium Between Intracellular and Extracellular Fluid

The relative amounts of extracellular fluid distributed between the plasma and interstitial spaces are determined mainly by the balance of hydrostatic and colloid osmotic forces across the capillary membranes. The distribution of fluid between intracellular and extracellular compartments, in contrast, is determined mainly by the osmotic effect of the smaller solutes—especially sodium, chloride, and other electrolytes— acting across the cell membrane. The reason for this is that the cell membranes are highly permeable to water but relatively impermeable to even small ions such as sodium and chloride. Therefore, water moves across the cell membrane rapidly, so that the intracellular fluid remains isotonic with the extracellular fluid.

117. Regulation of constant osmotic pressure

Osmoregulation

The osmolality of most body fluids is about 290mOsm/kg H2O, so that the intracellular fluid (ICF) and extracellular fluid (ECF) are generally in osmotic balance. Any increase in the osmolality of ECF due, for example, to NaCl absorption or water loss, results in an outflow of water from the intracellular space (cell shrinkage). A fall in extracellular osmolality due to drinking or infusion of large volumes of water or to sodium loss (e.g. in aldosterone deficit) results in an inflow of water to the cells from the ECF (cell expansion). Both volume fluctuations endanger the cell's functioning, but the cell can protect against them.

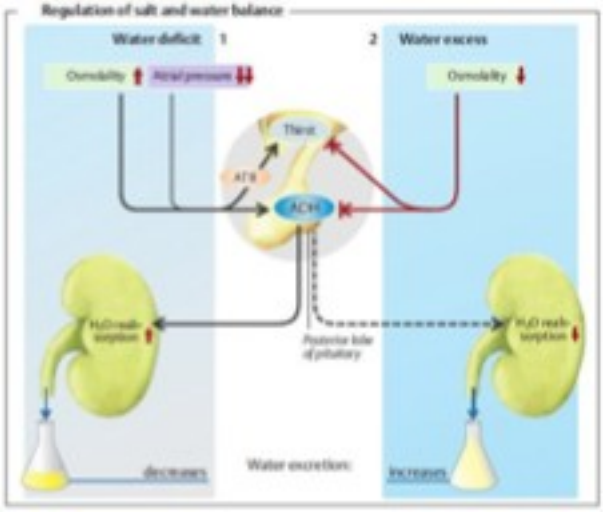
The osmolality of the ECF as a whole must be tightly regulated to protect cells from large volume fluctuations. Osmoregulation is controlled by central osmosensors (or osmoreceptors) located in circumventricular organs (SFO and OVLT, see below). H2O fluctuations in the gastrointestinal tract are monitored by peripheral osmosensors in the portal vein region and communicated to the hypothalamus by vagal afferent neurons.

Water deficit

Net water losses (hypovolemia) due, for example, to sweating make the ECF hypertonic. Osmolality rises of only 1–2% are sufficient to increase the secretion of ADH (antidiuretic hormone = vasopressin), from the posterior lobe of the pituitary. ADH decreases urinary H2O excretion.
Fluid intake from outside the body is also required, however. The likewise hypertonic cerebrospinal fluid (CSF), via osmosensors in the OVLT (organum vasculosum laminae terminalis) and SFO (subfornical organ) stimulates the secretion of (central) angiotensin II (AT II) which trigger hyperosmotic thirst.

Isotonic hypovolemia, for example following blood loss or secondarily following hyponatremia also stimulates thirst (hypovolemic thirst). The sensors for hypovolemia are primarily the atrial volume sensors. Via their afferent pathways and the nucleus tractus solitarii (NTS) secretion of central AT II is triggered in the SFO and via the sympathetic nervous system and β1-adrenoceptors in the kidney the peripheral renin-AT-II system (RAS) is activated. A drop in mean blood pressure below approx. 85mmHg triggers very high renin secretion directly in the kidney.

Thirst is a subjective perception and motivation to search for fluids and drink. The thirst that is a homeostatic response to hyperosmolality or hypovolemia (_0.5% of body weight: thirst threshold) triggers primary drinking. Drinking quenches the thirst before osmolality has completely normalized. This pre-resorptive thirst quenching is astonishingly accurate as regards the estimate of volume, due to afferent signals from volume sensors and osmosensors in the throat, gastrointestinal tract, and liver.



Relaxin, a peptide hormone produced by the corpus luteum in pregnant women, binds to receptors in the SFO and OVLT. It causes thirst and stimulates ADH secretion. Despite the reduced plasma osmolality during pregnancy, which would suppress thirst and ADH secretion, relaxin evidently provides for normal or even increased fluid intake during pregnancy.

118. Regulation of calcium metabolism

Parathormone, vitamin D and calcitonin

Three hormones are primarily concerned with the regulation of calcium. 1,25-Dihydroxycholecalciferol is a steroid hormone formed from vitamin D by successive hydroxylation in the liver and kidneys. Its primary action is to increase calcium absorption from the intestine. Parathyroid hormone (PTH) is secreted by the parathyroid glands. Its main action is to mobilize calcium from bone and increase urinary phosphate excretion. Calcitonin, a calcium-lowering hormone that in mammals is secreted primarily by cells in the thyroid gland, inhibits bone reabsorption.

Parathyroid hormone (PTH)

- Is the major hormone for the regulation of serum [Ca2+].
- Is synthesized and secreted by the chief cells of the parathyroid glands.

1. Secretion of PTH

- is controlled by serum [Ca2+] through negative feedback. Decreased serum [Ca2+] increases PTH secretion.
- Mild decreases in serum [Mg2+] stimulate PTH secretion.
- Severe secretion in serum [Mg2+] inhibit PTH secretion and produce symptoms of hypoparathyroidism (e.g., hypocalcemia).
- The second messenger for PTH secretion by the parathyroid gland is cAMP.

2. Actions of PTH

- Is coordinated to produce an increase in serum [Ca2+] and a decrease in serum [phosphate].
- The second messenger for PTH actions on its target tissues is cAMP.
- PTH increases bone resorption, which brings both Ca2+ and phosphate from the bone mineral into the ECF. Alone, this effect on bone would not increase the serum ionized [Ca2+] because phosphate complexes Ca2+.
- PTH inhibits renal phosphate reabsorption in the proximal tubule and, therefore, increases phosphate excretion (phosphaturic effect). As a result, the phosphate resorbed from bone is excreted in the urine, allowing the serum ionized [Ca2+] to increase.
- PTH increases renal Ca2+ reabsorption in the distal tubule. Which also increases the serum [Ca2+].
- PTH increases intestinal Ca2+ absorption indirectly by stimulating the production of 1.25-dihydrocholecalciferol in the kidney.

Vitamin D

Provides Ca2+ and phosphate to ECF for bone mineralization In children, vitamin D deficiency causes rickets. In adults, vitamin D deficiency causes osteomalacia.

Actions of 1,25-dihydroxycholecalciferol are coordinated to increase both [Ca2+] and [phosphate] in ECF to mineralize new bone.

Increases intestinal Ca2+ absorption. Vitamin D-dependent Ca2+-binding protein (calbindin D-28K) is induced by 1,25-dihydroxycholecalciferol. > PTH increases intestinal Ca2+ absorption indirectly by stimulating 1α-hydroxylase and increasing production of the active form of vitamin D.

Increases intestinal phosphate absorption. c. Increases renal reabsorption of Ca2+ and phosphate d. Increase bone resorption, which provides Ca2+ and phosphate from “old” bone to mineralize “new” bone.

Calcitonin

- is synthesized and secreted by the parafollicular cells of the thyroid.
- secretion is stimulated by an increase in serum [Ca2+]
- acts primarily to inhibit bone resorption.
- can be used to treat hypercalcemia.

119. Regulation of glycemia

Blood sugar regulation is the process by which the levels of blood sugar, primarily glucose, are maintained by the body.

Blood sugar levels are regulated by negative feedback in order to keep the body in homeostasis. The levels of glucose in the blood are monitored by the cells in the pancreas's Islets of Langerhans. If the blood glucose level falls to dangerous levels, the Alpha cells of the pancreas release glucagon, a hormone whose effects on liver cells act to increase blood glucose levels. They convert glycogen into glucose (this process is called glycogenolysis). The glucose is released into the bloodstream, increasing blood sugar levels. H_2O

When levels of blood sugar rise, whether as a result of glycogen conversion, or from digestion of a meal, a different hormone is released from beta cells found in the Islets of Langerhans in the pancreas. This hormone, insulin, causes the liver to convert more glucose into glycogen (this process is called glycogenesis), and to force about 2/3 of body cells (primarily muscle and fat tissue cells) to take up glucose from the blood through the GLUT4 transporter, thus decreasing blood sugar. When insulin binds to the receptors on the cell surface, vesicles containing the GLUT4 transporters come to the plasma member and fuse together by the process of exocytosis and thus enabling a facilitated diffusion of glucose into the cell. As soon as the glucose enters the cell, it is phosphorylated into Glucose-6-Phosphate in order to preserve the concentration gradient so glucose will continue to enter the cell. Insulin also provides signals to several other body systems, and is the chief regulatory metabolic control in humans.

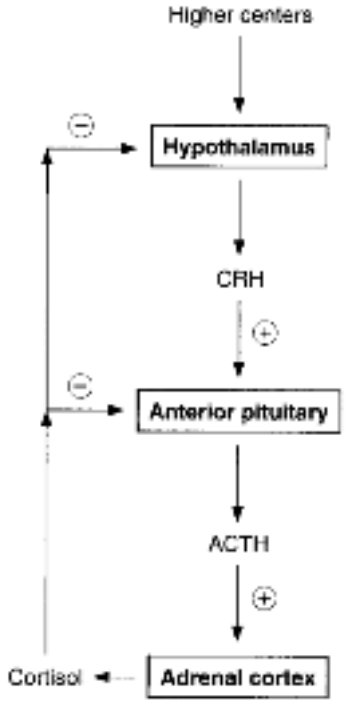
Hormone	Tissue of Origin	Metabolic Effect	Effect on Blood Glucose
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

120. Regulation of adrenal cortex

Regulation of secretion of adrenocortical hormones

a. Glucocorticoid secretion

- oscillates with a 24-hour periodicity, or circadian rhythm.
- for those who sleep at night, cortisol levels are highest just before waking (=8 a.m.) and lowest in the evening (= 12 mid-night).



(1) Hypothalamic control - corticotropin-releasing hormone (CRH)

- CRH-containing neurons are located in the paraventricular nuclei of the hypothalamus.
- When these neurons are stimulated, CRH is released into hypothalamic-hypophysial portal blood and delivered to the anterior pituitary.
- CRH binds to receptors on corticotrophs of the anterior pituitary and directs them to synthesize POMC (the percursor to ACTH).
- The second messenger for CRH is cAMP.

(2) Anterior lobe of the pituitary - ACTH

- ACTH increases steroid hormone synthesis in all zones of the adrenal cortex by stimulating cholesterol desmolase and increasing the conversion of cholesterol to pregnenolone.
- ACTH also up-regulates its own receptor so that the sensitivity of te adrenal cortex to ACTH is increased.
- Chronically increased levels of ACTH cause hypertrophy of the adrenal cortex.
- The second messenger for ACTH is cAMP.

(3) Negative feedback control.cortisol

- Cortisol inhibits the secretion of CRH from the hypothalamus and the secretion of ACTH fromt he anterior pituitary.
- When cortisol (glucocorticoid) levels are chronically elevated, the secretion of CRH and ACTH is inhibited by negative feedback.
- The dexamethasome supressions test is based on the ability of dexamethasome (a potent synthetic glucocorticoid) to inhibit ACTH secretion. If the hypothalamic-pituitary-adrenocortical axis is normal, then the administration of dexamethasome inhibits the secretion of ACTH and cortisol.

b. Aldosterone secretion

- is under tonic control by ACTH, but is separately regulated by the renin-angiotensin system and by potassium.

(1) Renin-angiotensin-aldosterone system

(a) Decreases in blood volume cause a decrease in renal perfusion pressure, which in turn increases renin secretion. Renin, an enzyme, catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin-converting enzyme (ACE).

(b) Angiotensin II acts on the zona glomerulosa of the adrenal cortex to increase the conversion of corticosterone to aldosterone.

(c) Aldosterone increases renal Na+ reabsorption, thereby restoring extracellular fluid (ECF) volume and blood volume to normal.

(2) Hyperkalemia increases aldosterone secretion. Aldosterone increases renal concentration of K+ to normal.